CONGENITAL BLEEDING DISORDERS

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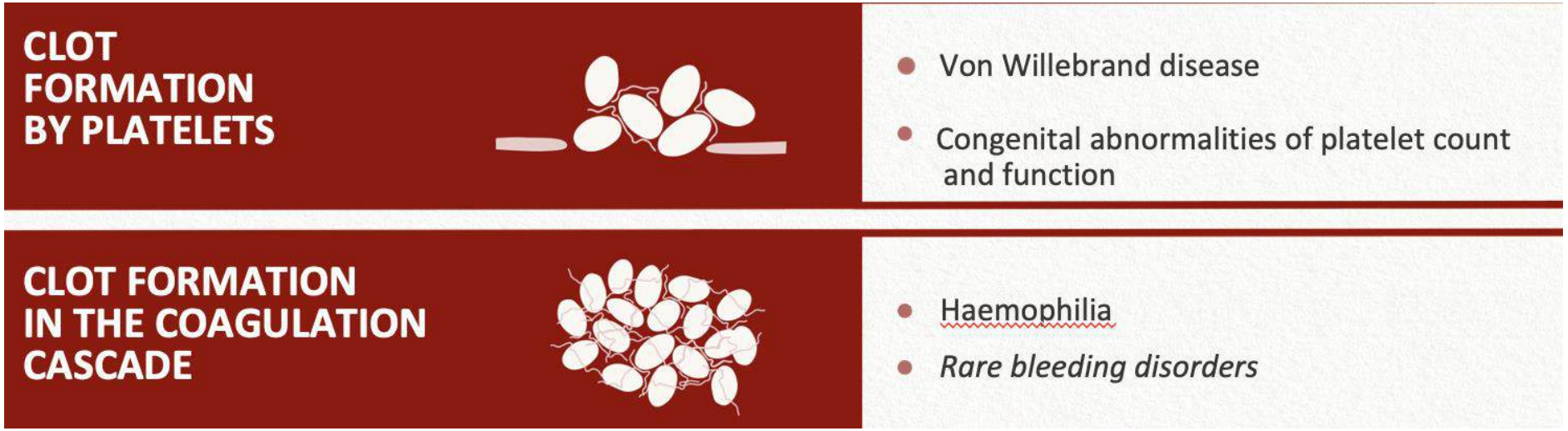
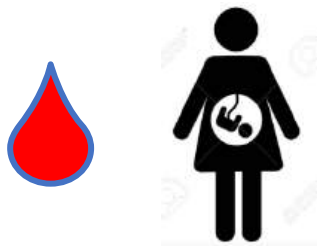
AGENDA

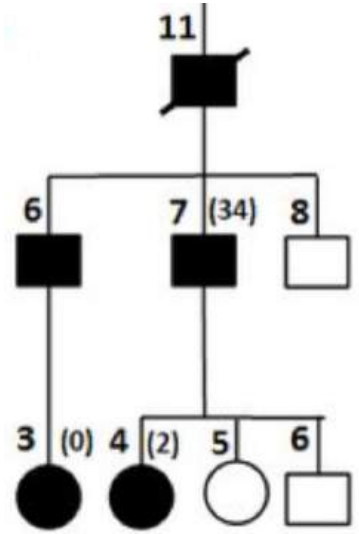
- Recognition and diagnosis of congenital bleeding disorders
- Von willebrand disease – Hemophilia - Rare inherited bleeding disorders
- Principles of hemostatic management

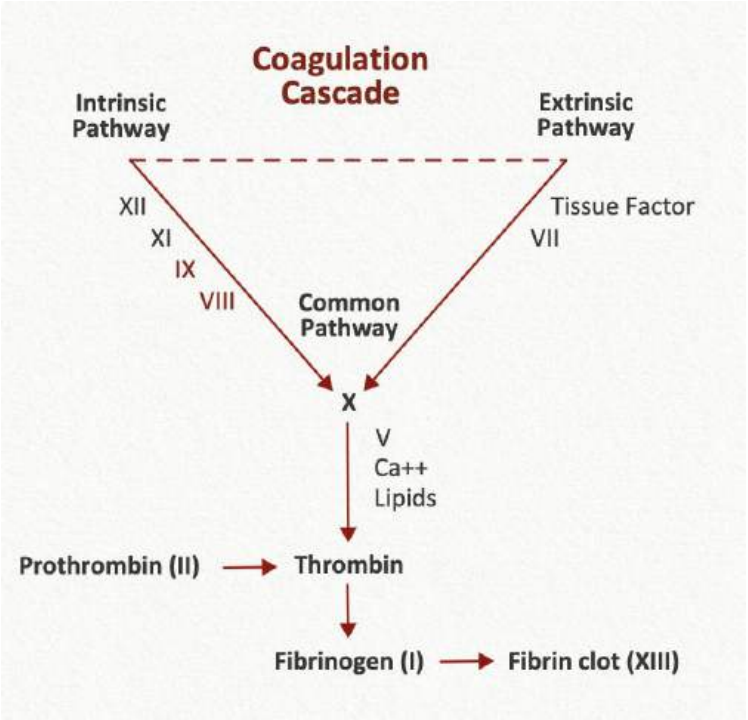


DIAGNOSIS

- Personal and familial bleeding history - consanguinity
- Clinical pattern
- Biological abnomalities
- Genetic testing







BLEEDING ASSESSMENT TOOLS

The ISTH-SSC bleeding assessment tool scores the following symptoms

1. Epistaxis
2. Cutaneous bruising
3. Bleeding from minor wounds
4. Oral cavity bleeding
5. Gastrointestinal bleeding
6. Haematuria
7. Dental extraction bleeds
8. Surgical bleeding
9. Menorrhagia
10. Post-partum haemorrhage
11. Muscle haematomas
12. Haemarthrosis
13. Central-nervous system bleeding
14. Other bleeding problems

A score of ≥ 6 in women, ≥ 4 in men and ≥ 3 in children required further testing.

An online version of the ISTH bleeding assessment tool is available at https://bleedingscore.certe.nl

ISTH, International Society on Thrombosis and Haemostasis; SSC, Scientific and Standardization Committee
Rodeghiero F, et al. J Thromb Haemost. 2010;8:2063-5

BLEEDING ASSESSMENT

Personal and familial anamnesis

Clinical examination

Bleeding score

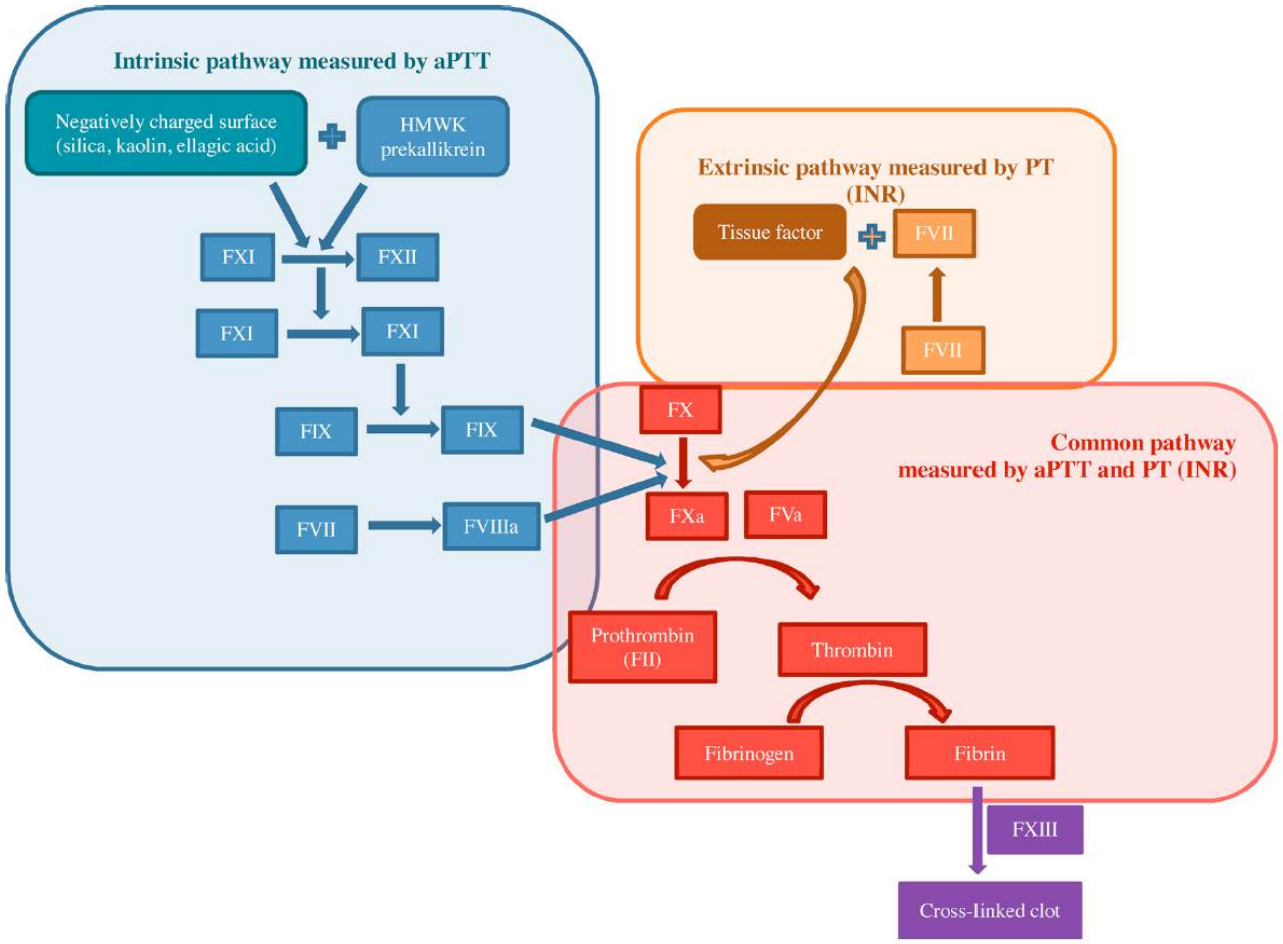
aPTT, Prothrombin Time, Thrombin Time, Fibrinogen
Full Blood count
Blood smear

- Factor XI, VIII, IX
- Factor XIII

- PFA-100 (ADP)
- Von Willebrand
- Platelet function (aggregation, secretion…)

- Fibrinolysis

- Whole blood (TG, TEG)



- Platelet microscopy and cytometry
- Molecular testing

Lee A. Transfus Apher Sci. 2019

BLEEDING OF UNKNOWN CAUSE (BDUC)

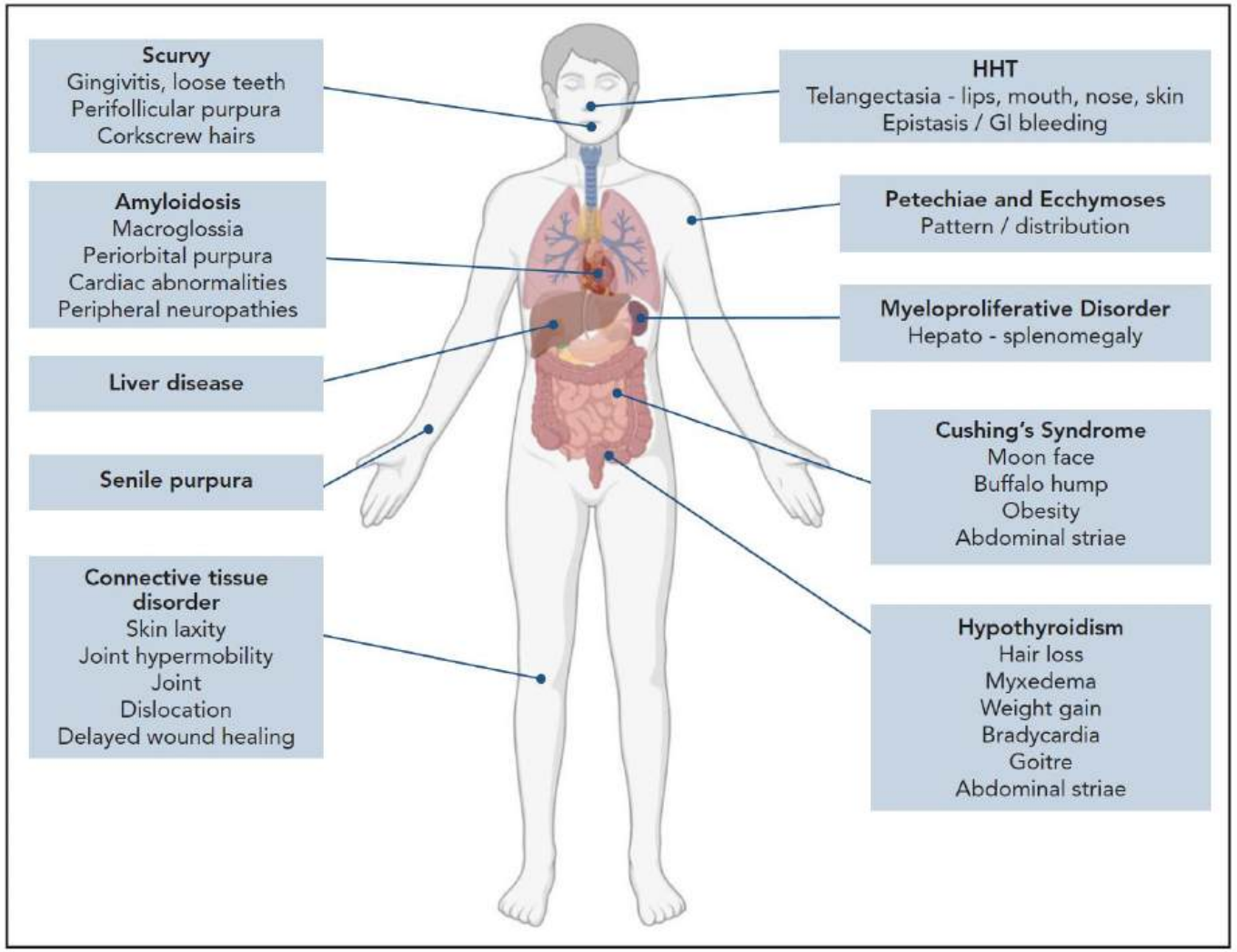
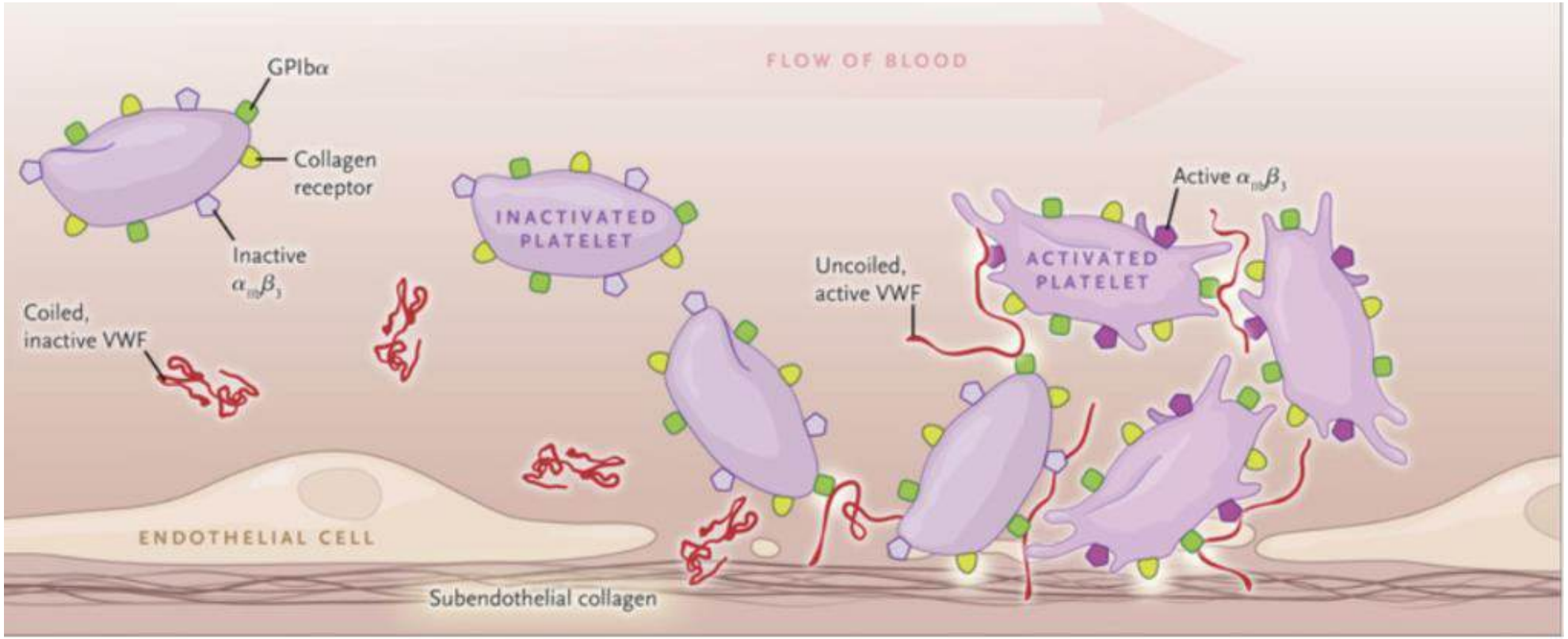


Figure 1. Clinical features associated with inherited and acquired causes of mild to moderate mucocutaneous bleeding. HHT, hereditary hemorrhagic telangiectasia.

- BDUC: quite **frequent**
- 30-40% of hemostasis work-up
- **Contrast** : positive hemorragic anamnesis and the few biological abnomalities

Baker RI, *Blood*. 2021;138(19):1795-1804.

VON WILLEBRAND DISEASE

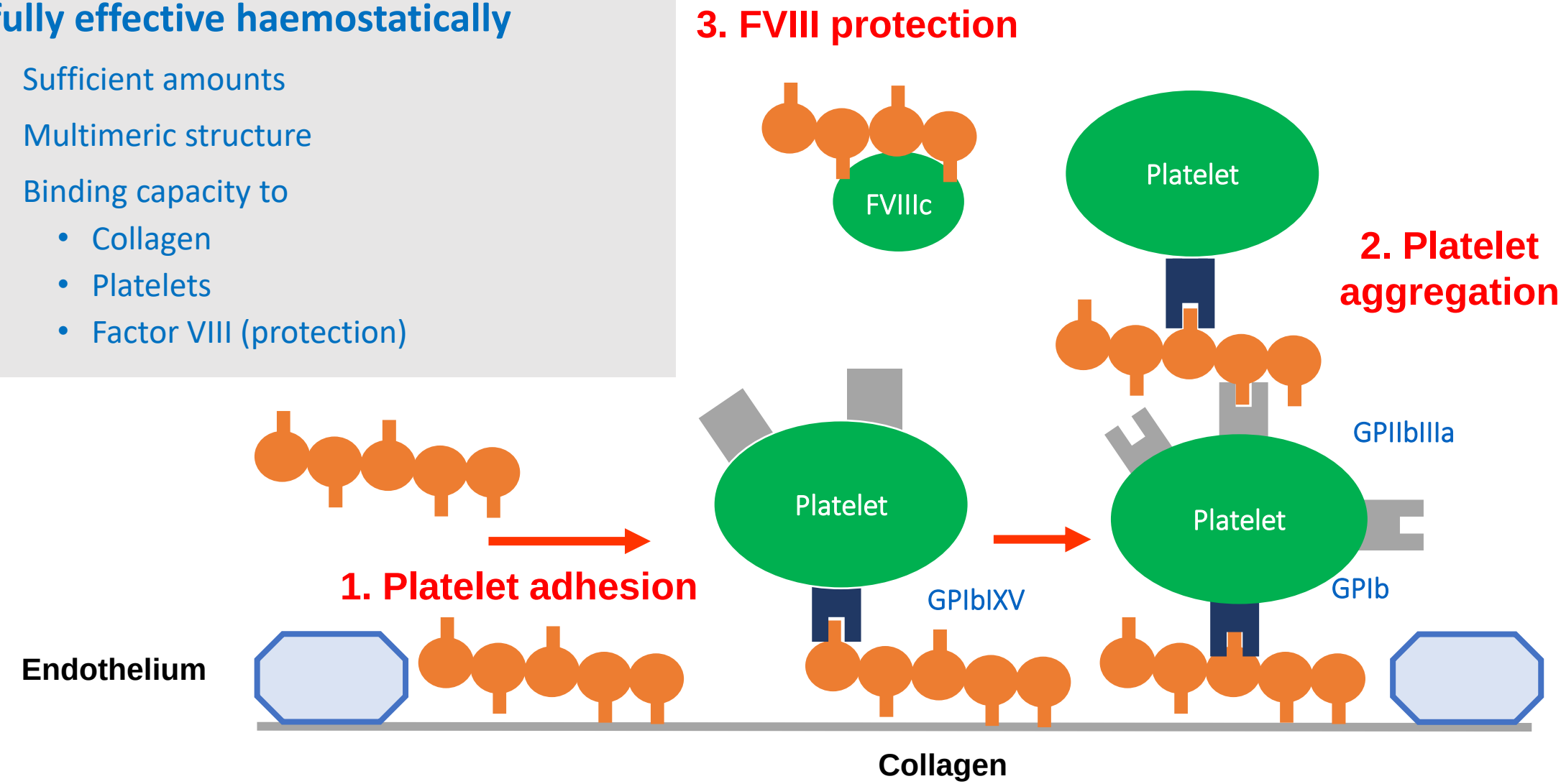


Leebeeck NEJM 2016

THE MULTIPLE FUNCTIONS OF VWF

Required properties of VWF to be fully effective haemostatically

- Sufficient amounts
- Multimeric structure
- Binding capacity to
  - Collagen
  - Platelets
  - Factor VIII (protection)



PHYSIOLOGICAL VARIATIONS OF VWF

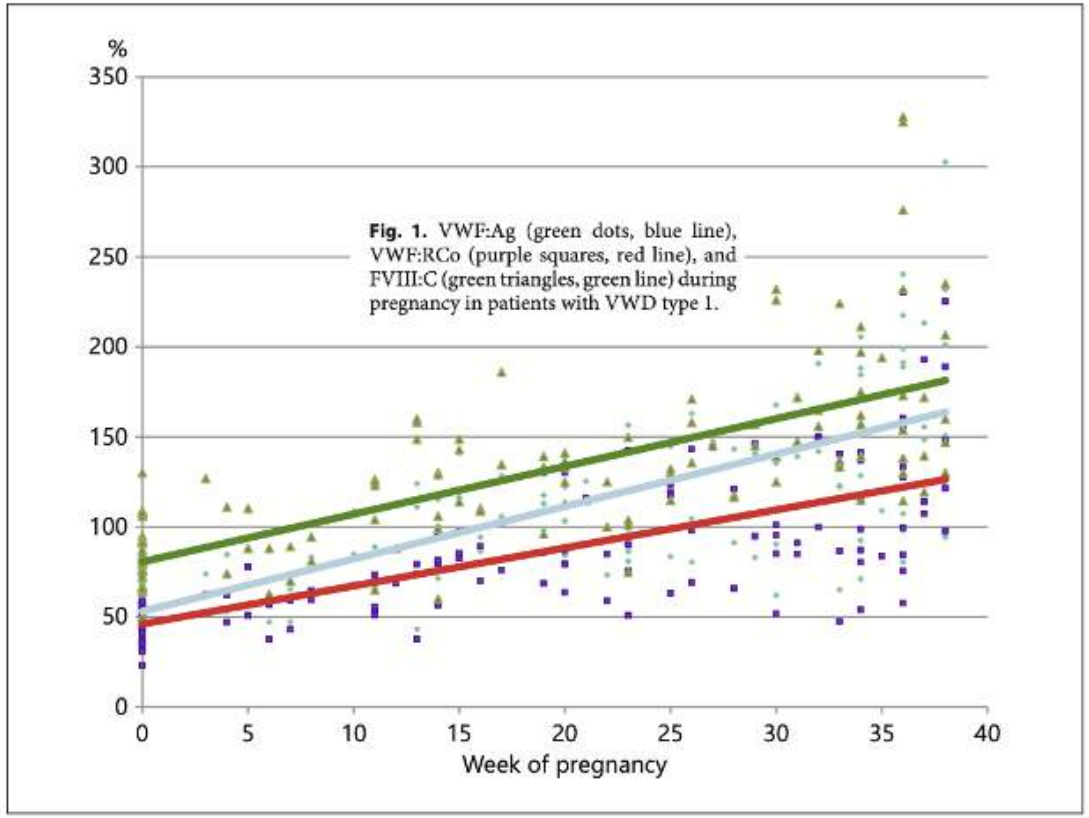


Fig. 1. VWF:Ag (green dots, blue line), VWF:RCo (purple squares, red line), and FVIII:C (green triangles, green line) during pregnancy in patients with VWD type 1.

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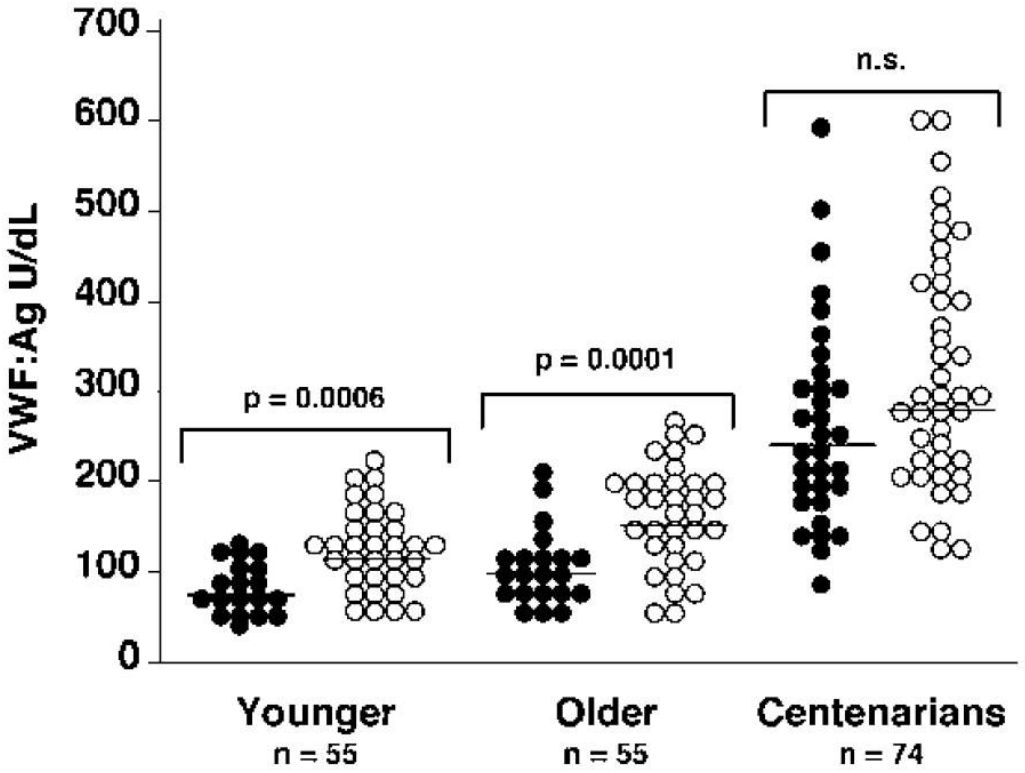


Figure 1. von Willebrand factor (U/dL) related to blood groups in younger, older, and centenarian individuals. Closed circles represent blood group type O, open circles type non-O.

PHYSIOLOGICAL LOW VWF IN BLOOD GROUP O

Table 1. Influence of ABO Blood Group on vWF:Ag Values in Volunteer Blood Donors

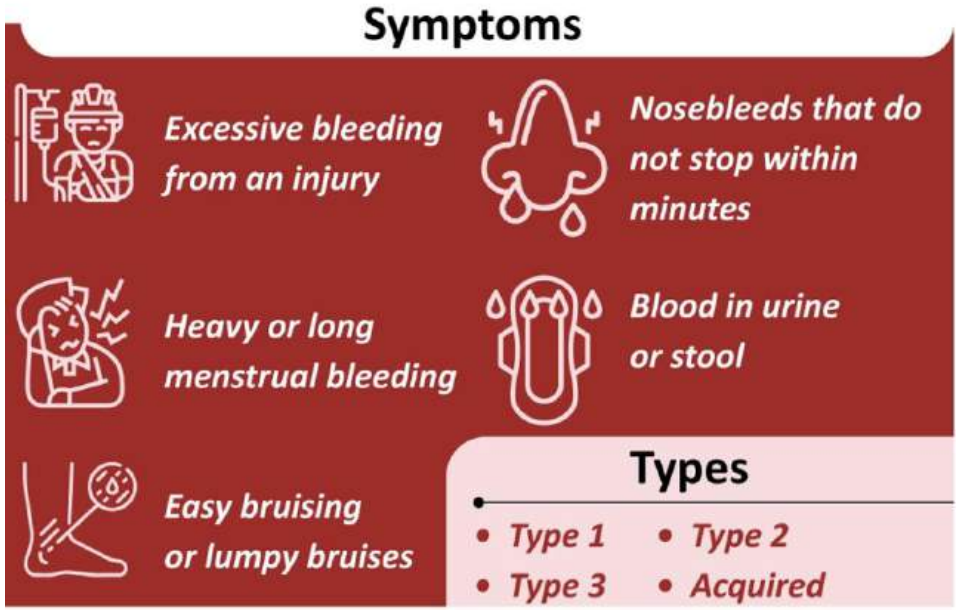
ABO Type	n	vWF:AG Geometric Mean	vWF:Ag Geometric Mean ± 2 SD
O	456	74.8	35.6-157.0
A	340	105.9	48.0-233.9
B	196	116.9	56.8-241.0
AB	109	123.3	63.8-238.2

The groups were statistically significantly different from each other as follows: O *v* A, B, and AB, $P < .01$; A *v* AB, $P < .01$; B *v* A, $P < .05$.

Gill et al. Blood 1987

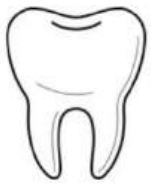
VON WILLEBRAND DISEASE

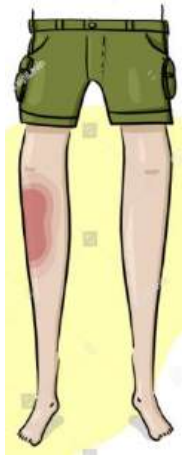
- The **most common inherited bleeding disorder**.
- Affects men and women
- Estimated to occur in 1 in 1000 people (probably less frequent)
- Heterogeous disease

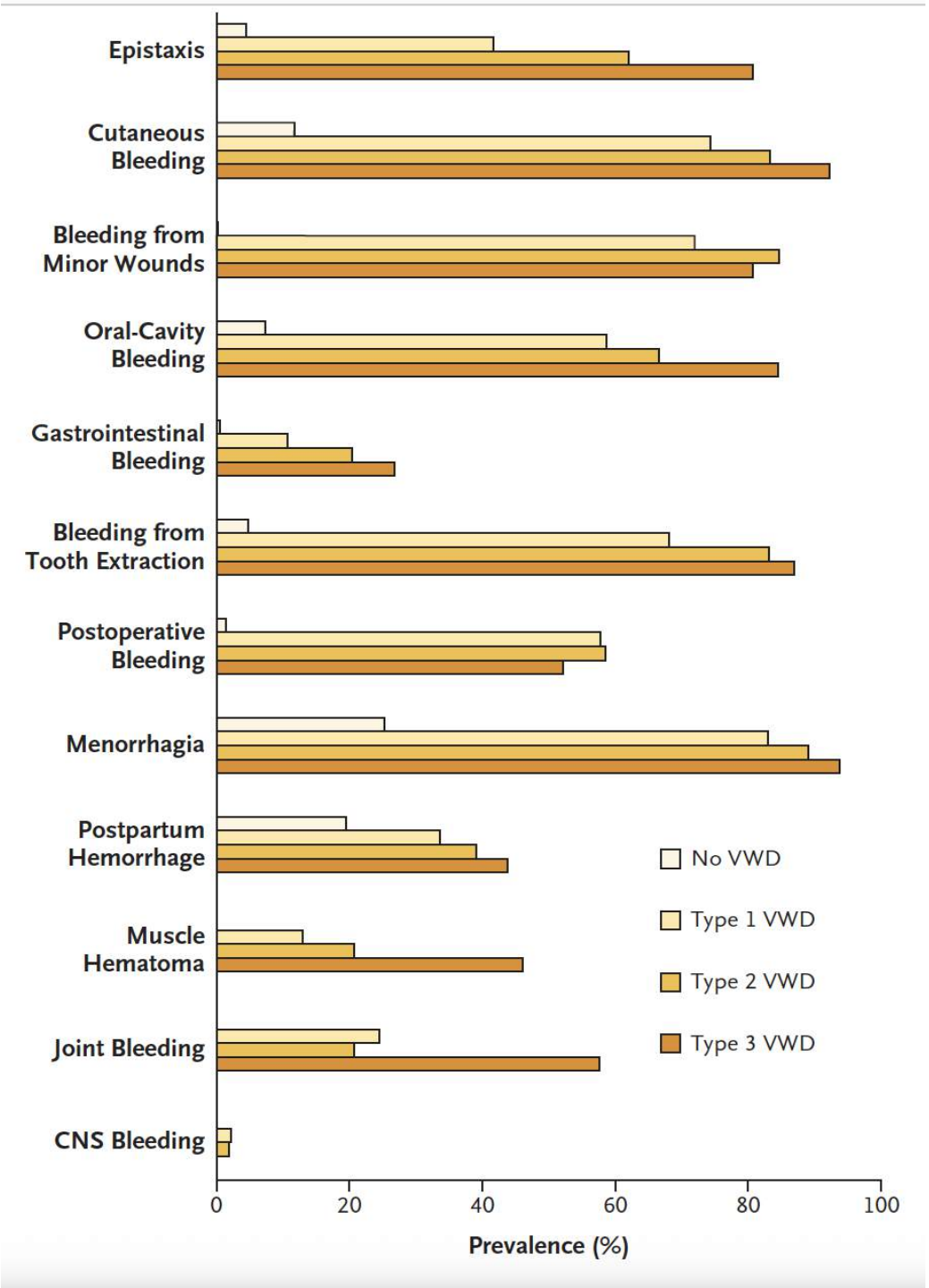


- Bleeding symptoms ranging from mild bruising to severe hemorrhage
- Complexity of tests leading it to be under-diagnosed, over-diagnosed and misdiagnosed

SYMPTOMS OF VWD





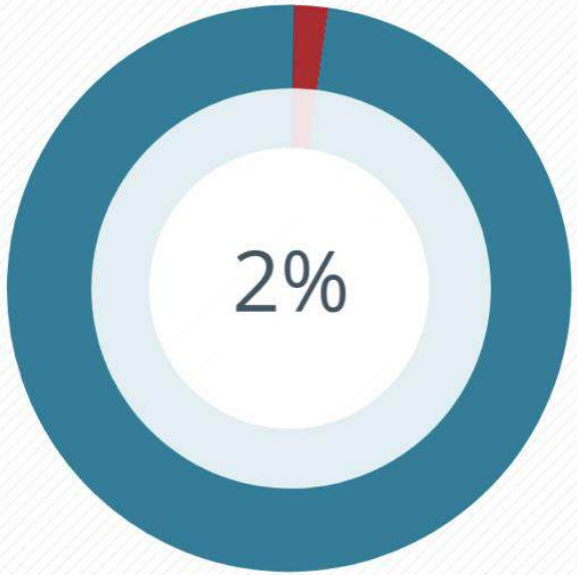


Leebeek *N Engl J Med*. 2016 ;375(21):2067-2080

WOMEN and bleeding disorders

1 in 10

10% of women with heavy menstrual periods may have a bleeding disorder

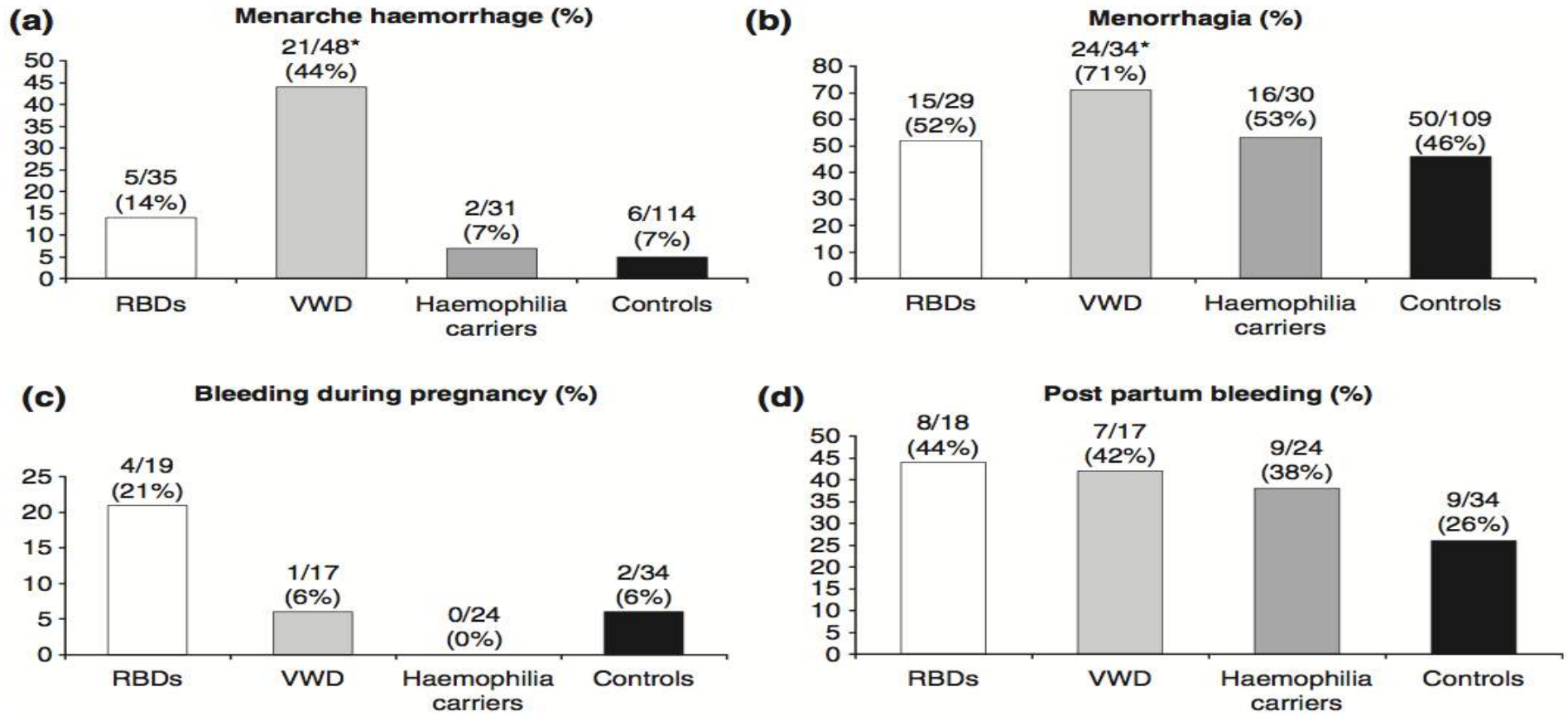


women who get tested for bleeding disorders

Von Willebrand Disease (VWD)

Most common bleeding disorder in women

GYNECOLOGICAL BLEEDS IN VWD



- 32 -70% of women with VWD experience heavy menstrual bleeding
- Low VWF patients also experience significant bleeding phenotype despite mild plasma VWF reduction.

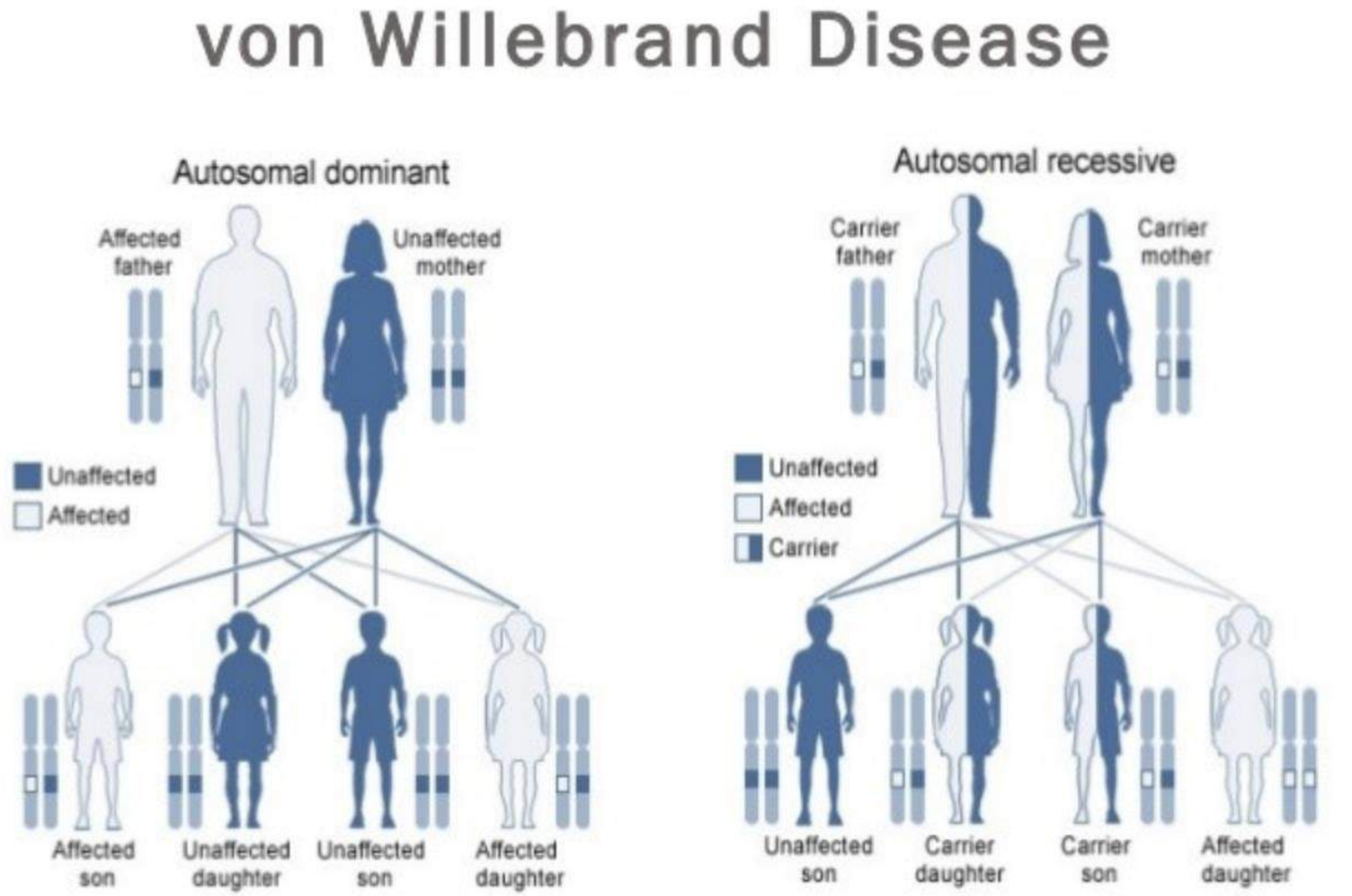
Siboni et al. Haemophilia 2009;15:1291–1299, James P, Hematology Am Soc Hematol Educ Program 2020; 2020 (1): 547–552

CLASSIFICATION OF VWD

Type 1	Partial quantitative deficiency of VWF Accounts for ~85% cases Autosomal dominant pattern of inheritance
Type 1C [Vicenza]	Increased clearance of VWF leading to Type 1 Phenotype Poor response to DDAVP Autosomal dominant pattern of inheritance
Type 2A	Qualitative deficiency of VWF Decreased VWF-dependent adhesion due to a loss of HMWM Autosomal dominant pattern of inheritance
Type 2B	Qualitative deficiency of VWF Increased affinity of VWF for platelet GpIb Autosomal dominant pattern of inheritance
Type 2M	Qualitative deficiency of VWF Decreased VWF-dependent adhesion but without a loss of HMWM Autosomal dominant pattern of inheritance
Type 2N	Qualitative deficiency of VWF Decreased binding of Factor VIII - may 'mimic' mild-moderate Haemophilia A Autosomal recessive pattern of inheritance
Type 3	Virtual complete absence of VWF and Factor VIII Rare Autosomal recessive pattern of inheritance Patients with Type 3 VWD due to major gene deletions may form inhibitory antibodies following treatment
Platelet-Type vWD	Gain of function mutation in the platelet membrane platelet GpIb receptor Autosomal dominant pattern of inheritance

ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Adv 2021; 5 (1): 280–300

MODE OF TRANSMISSION OF VWD

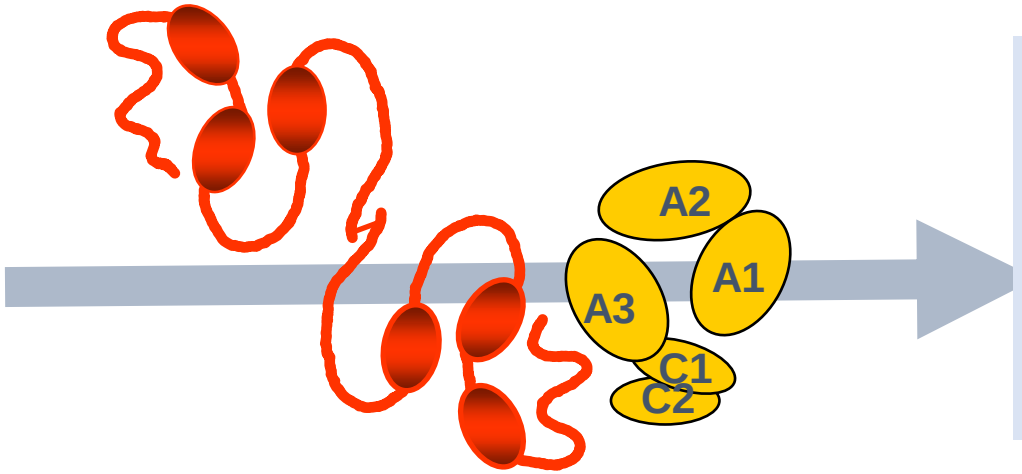


	Low VWF	Type 1 VWD
Diagnosis	Plasma VWF levels consistently 30-50 IU/dL	Plasma VWF levels consistently <30 IU/dL
VWF gene sequence variations	Detected in 40% to 64% of patients	Detected in majority of patients (up to 91.8%)
Pathogenic mechanism	Predominantly due to reduced VWF synthesis/ secretion within EC. Subtle enhanced clearance in some cases.	Depending upon *VWF* gene mutation, can be attributable to a major impairment in VWF synthesis and/or markedly enhanced VWF clearance (type 1C VWD)
Response to DDAVP	Consistent and reproducible plasma VWF responses, with levels sustained >50 IU/dL at 4 h	Variable responses, related to the nature of the underlying *VWF* mutation. Complete response, partial response, or failure to respond may be seen. In patients with type 1C VWD, VWF half-life may be <4 h.
Need for DDAVP trial	No need for routine DDAVP trial but confirm plasma VWF:Ag levels and duration of response at time of first therapeutic use	DDAVP trial should be performed and should include plasma samples at 4 h post-DDAVP to ensure no rapid fall-off in plasma VWF levels
Plasma VWF half-life	Some low VWF patients have elevated VWF:pp/ VWF:Ag ratios consistent with subtly increased VWF clearance	Related to underlying *VWF* mutation, but patients with type 1C VWD may have markedly enhanced VWF clearance with half-lives <4 h
ABO effect	Blood group O is strongly overrepresented	The effect of ABO blood group is less significant
Impact of aging	Plasma VWF levels increase with age and often correct into the normal range (>50 IU/dL)	Depending on underlying VWF gene mutation, plasma VWF levels may increase with age, but often remain <50 IU/dL
	Not clear whether age-related VWF correction necessarily equates to resolution of bleeding phenotype	Unknown whether age-related increase in plasma VWF levels attenuates bleeding risk

Lavin M. *Blood*. 2019 Feb 21;133(8):795-804.

PATHOPHYSIOLOGY OF VWD

Primary quantitative or qualitative defect of VWF



Secondary quantitative deficiency of FVIIIc not efficiently protected

FVIII deficiency in patients with VWD results from an ineffective protection by VWF

Mucosal and cutaneous bleeding symptoms

Joint and muscle bleeds
Post-op bleeds

ALGORITHM FOR TESTING VWD

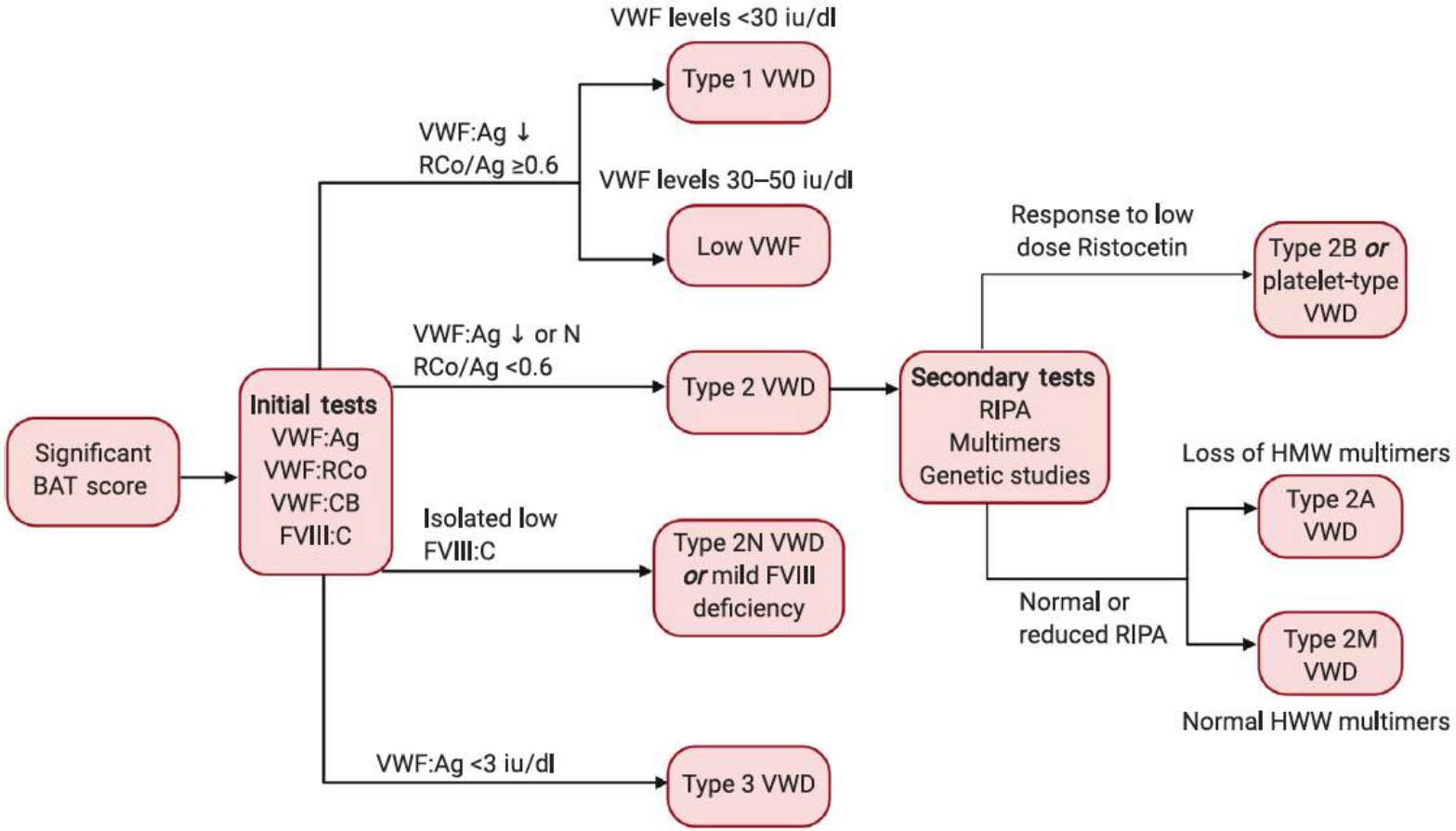
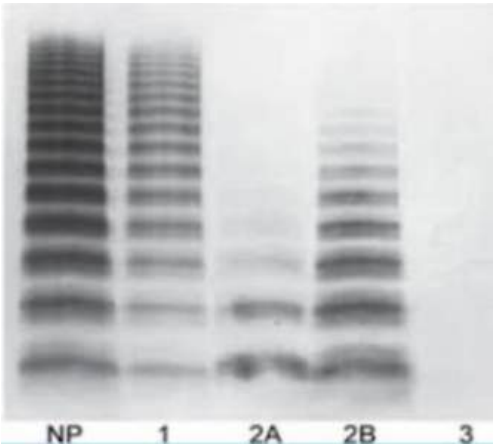


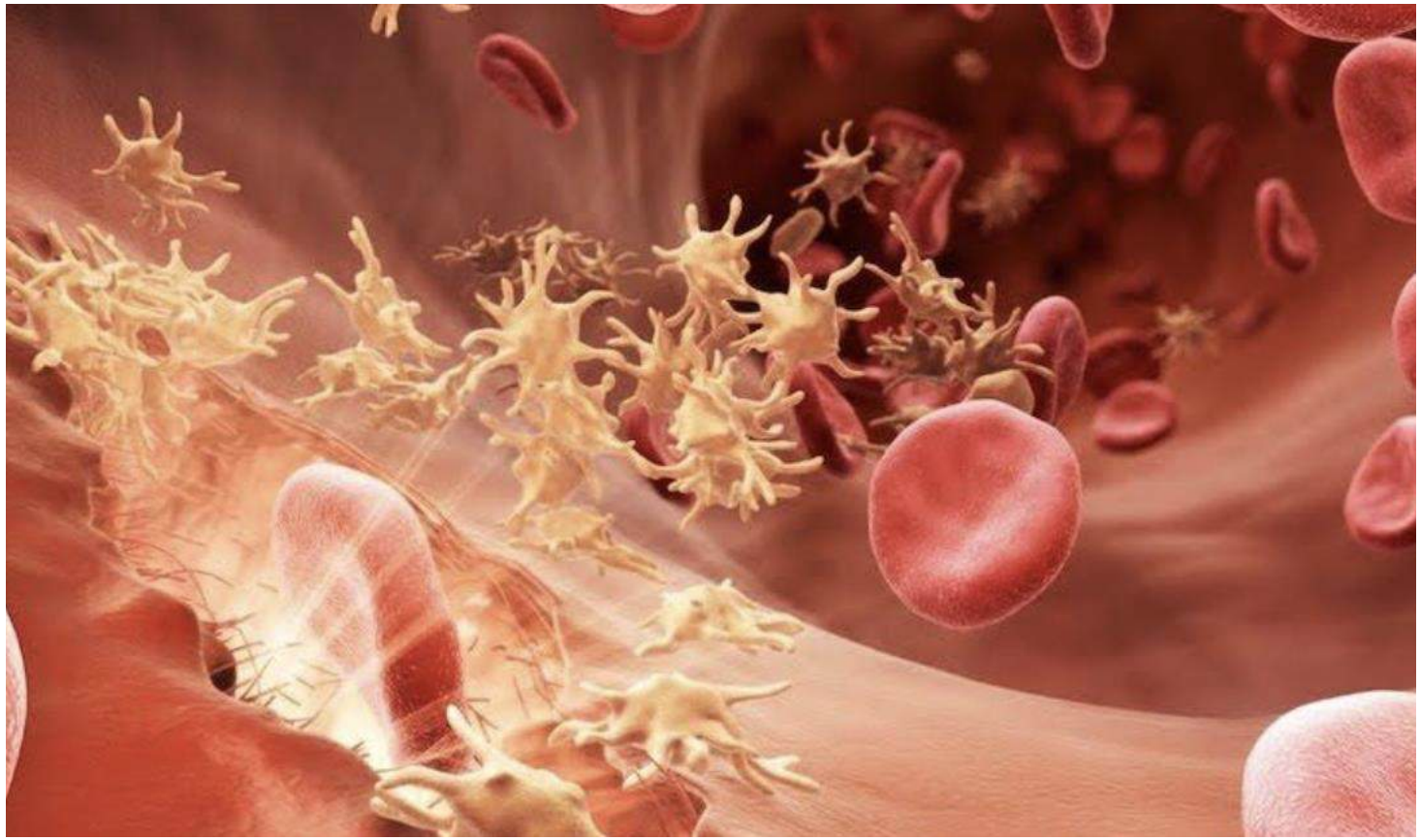
Fig 3. Suggested VWD diagnostic algorithm with defined threshold cut-offs. Adapted from UKHCDO guidelines.[11]



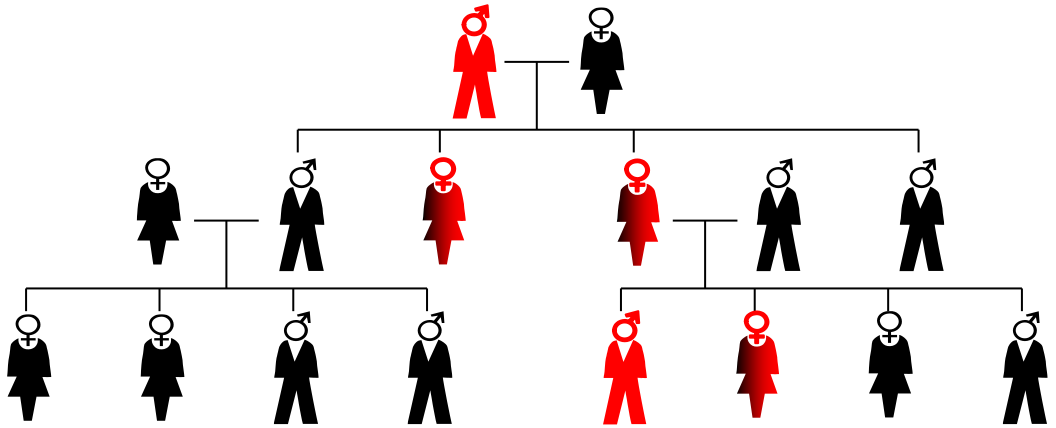
MOLECULAR TESTING

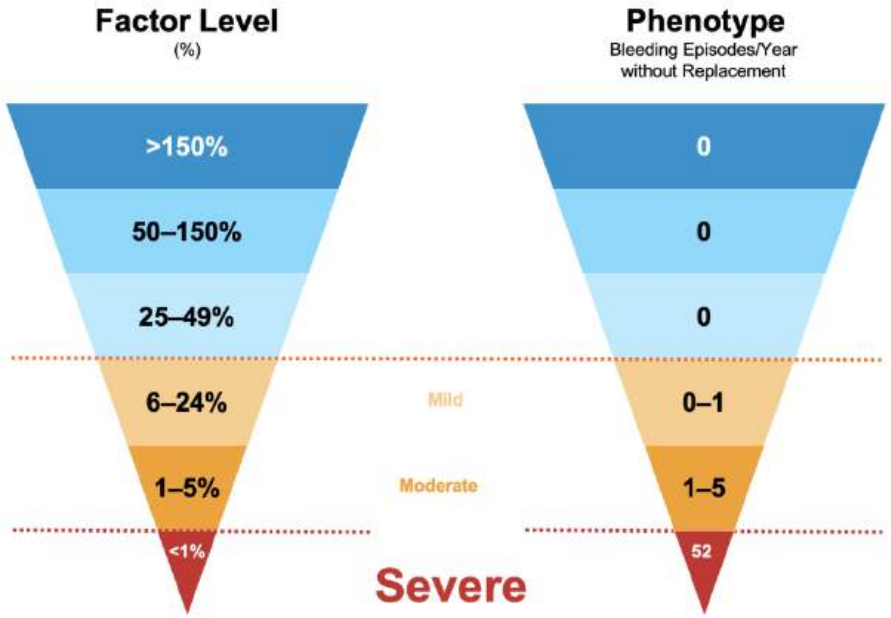
Fogarty H, et al. *Br J Haematol*. 2020 Nov;191(3):329-339.

HAEMOPHILIA



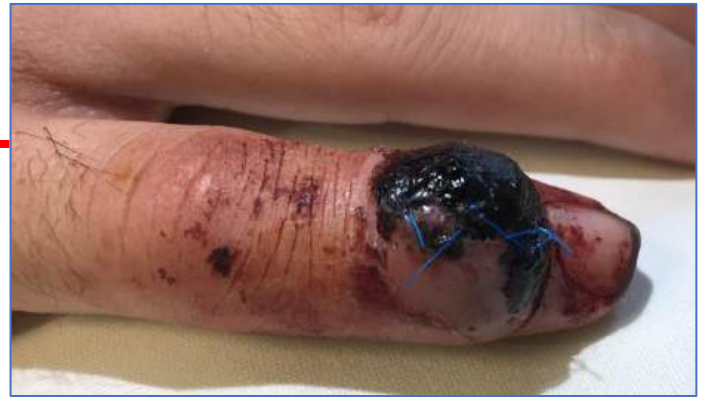
HAEMOPHILIA IS AN X-LINKED DISORDER RESULTING IN LOW FVIII (HA) OR FIX (HB)



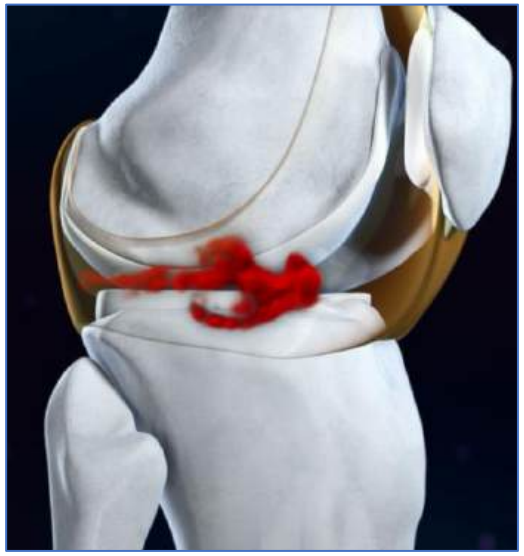


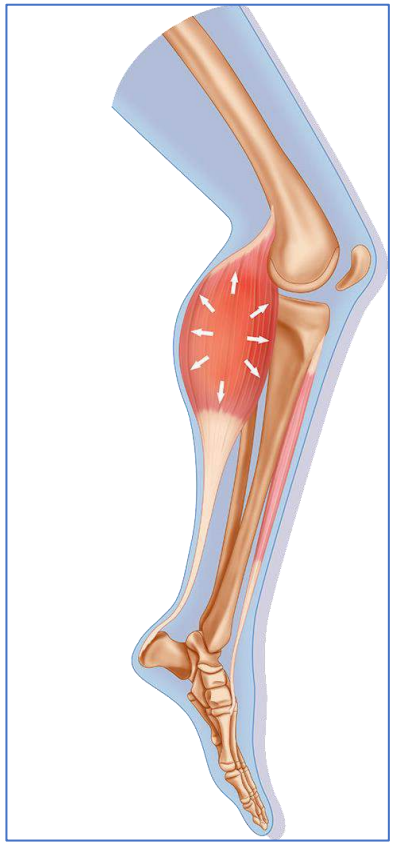
- Prolonged aPTT
- Correction with mixing study
- Measurement of FVIII/IX
- Genetic testing

CLINICAL SIGNS OF HAEMOPHILIA

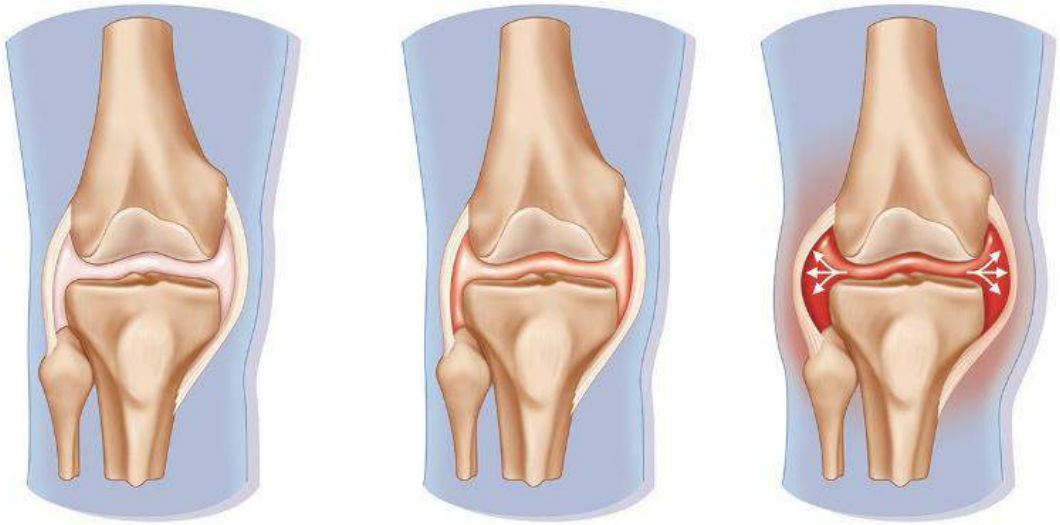


- Prolonged bleeding
- Spontaneous, post surgery, trauma or injury
- Bleeds in joints and muscles (severe)
- Intracranial haemorrage





MUSKULOSKELETAL CONSEQUENCES



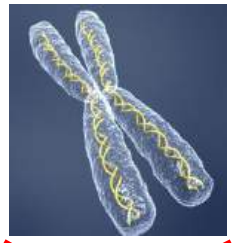
CARRIERS OF HAEMOPHILIA

Transmission

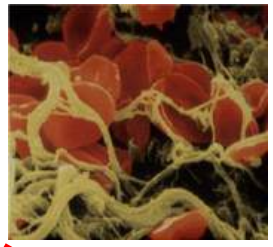
?

Bleeding risk

Genetic testing



Coagulation assessment



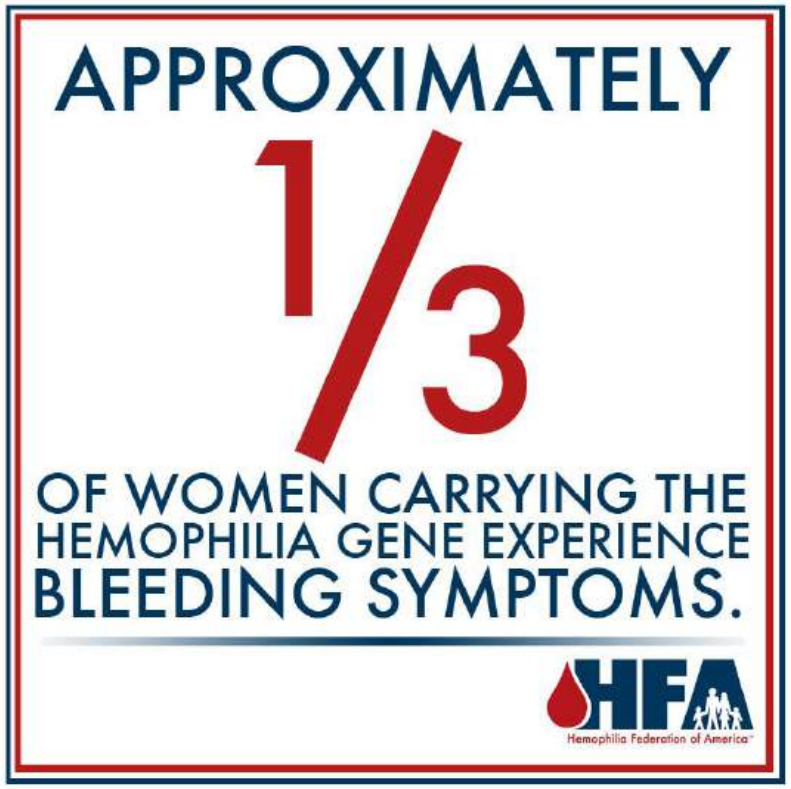
Carrier

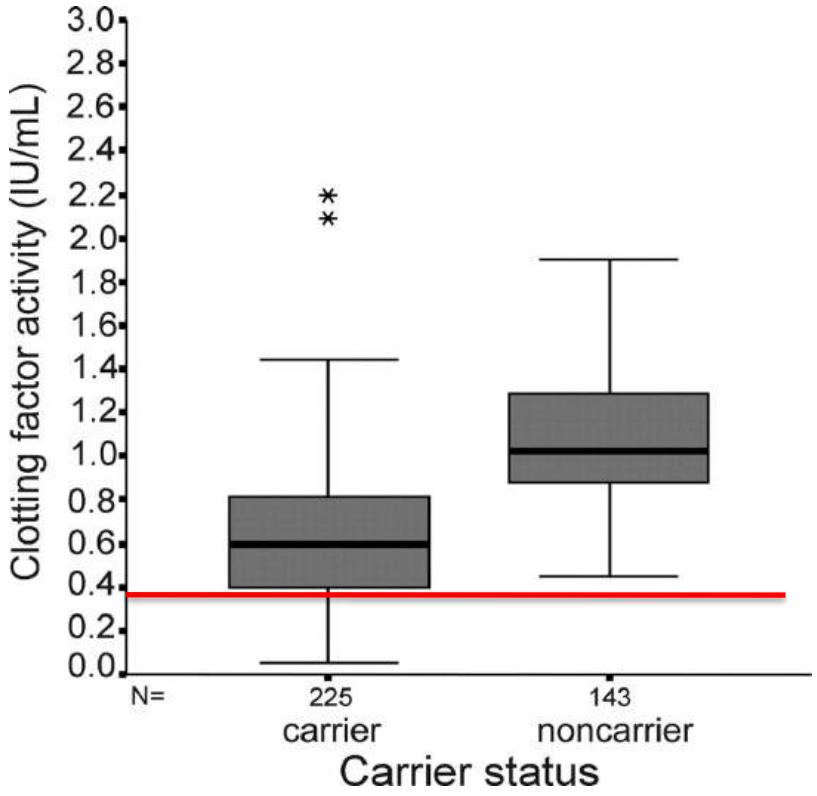
Non carrier

With haemophilia

Without haemophilia

CARRIERS OF HAEMOPHILIA





Carriers with low clotting factor levels may have bleeding manifestations commensurate with their degree of clotting factor deficiency, particularly during trauma and surgery.
Carriers often have increased bleeding tendency, even if the factor level is normal.[1]

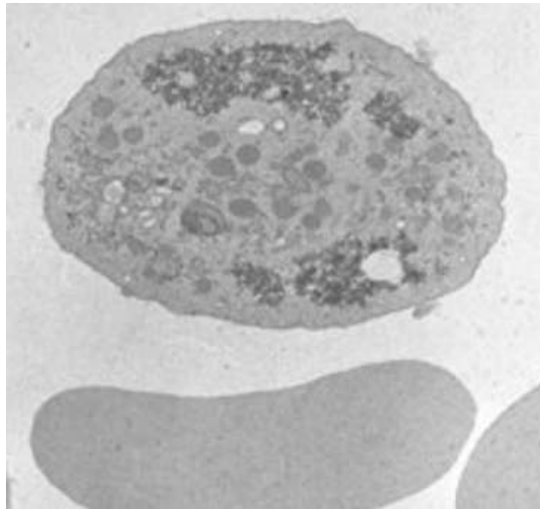
1. Plug I *et al. Blood* 2006;108:52–6.

INHERITED RARE BLEEDING DISORDERS

Deficiency	Prevalence	Gene on chromosome	Clinical features
Fibrinogen	1:1,000,000	4 (three separate genes)	Usually mild, except in afibrinogenemia
Prothrombin	1:2,000,000	11	Usually mild (severe in homozygotes)
Factor V	1:1,000,000	1	Usually mild
Combined factor V + VIII	1:1,000,000	2 (*MCFD2*), 18 (*LMAN1*)	Usually mild
Factor VII	1:500,000	13	Severe (when factor levels are low)
Factor X	1:1,000,000	13	Moderate to severe (when factor levels are low)
Factor XI	1:1,000,000	4	Mild to moderate
Factor XIII	1:2,000,000	6 (*F13A*), 1 (*F13B*)	Severe

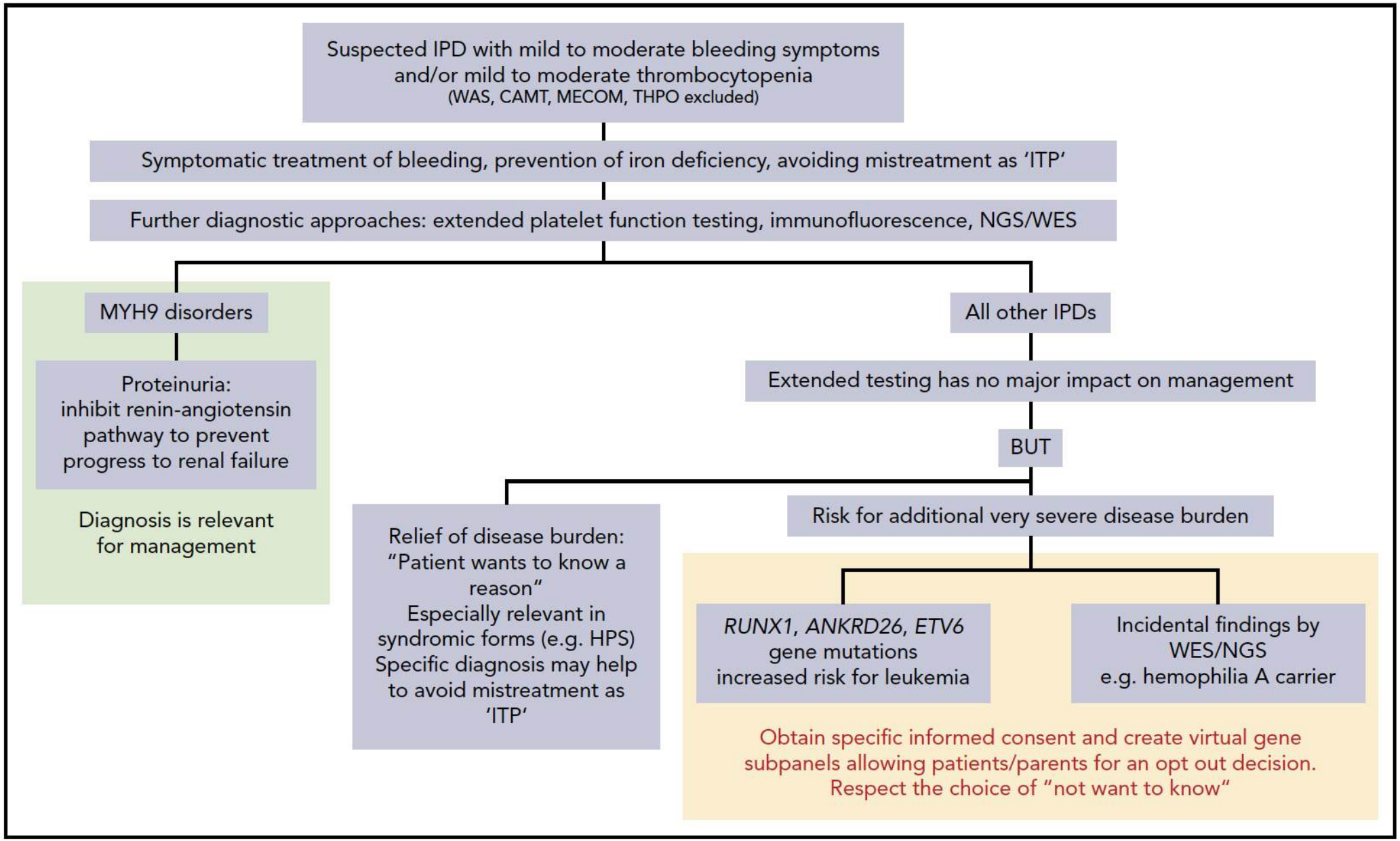
Franchini M, Marano G, Pupella S, et al. Rare congenital bleeding disorders. *Ann Transl Med*. 2018;6(17):331.

INHERITED PLATELET DISORDERS



Platelet Function Disorders with Thrombocytopenia	Platelet count reduction	Platelet size
Bernard–Soulier syndrome	Moderate to severe	Giant
Filaminopathy-related macrothrombocytopenia	Mild to moderate	Large
Familial platelet disorder associated with acute myeloid leukemia	Mild to moderate	Normal
GATA1-related disease	Severe	Large
Gray platelet syndrome	Mild	Large
Glanzmann thrombasthenia variant	Mild to moderate	Large
Medich platelet syndrome	Mild	Large
Paris–Trousseau syndrome	Moderate to severe	Normal or slightly increased
Platelet type von Willebrand disease	Mild	Normal or slightly increased
Stormorken syndrome	Mild to moderate	Normal
Velocardiofacial syndrome	Mild	Large
Wiskott–Aldrich	Severe	Small
White platelet syndrome	Mild	Large

INHERITED PLATELET DISORDERS

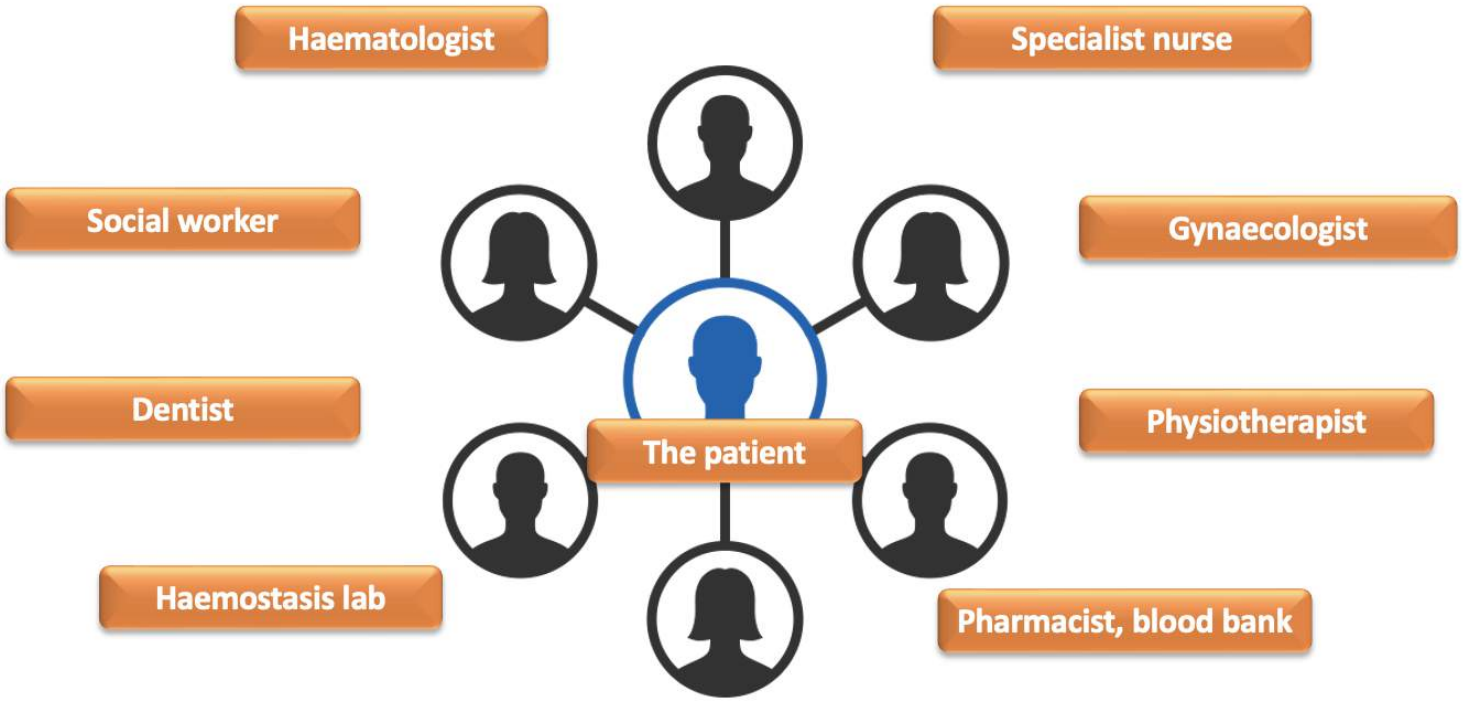


Greinacher A, Blood. 2019 Jun 6;133(23):2478-2483

GENERAL PRINCIPLES OF CARE

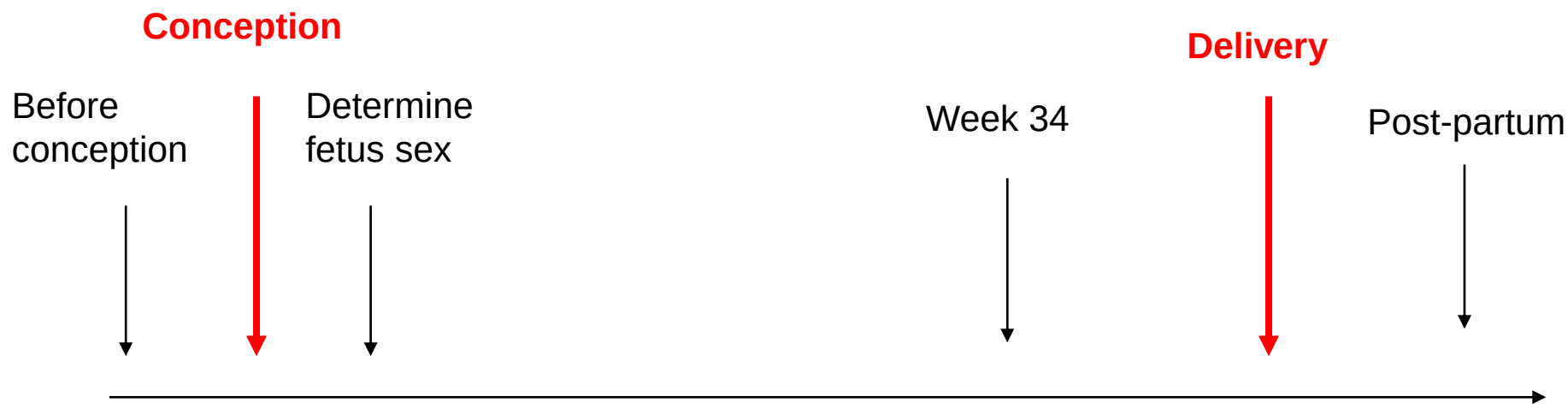
Comprehensive and multidisciplinary care – individualized care plan

- Specialized haemostasis laboratory
- Haemostatic treatment
- Identification card
- Information and education
- Genetic counseling
- Patients' association



Pai M, et al. *Haemophilia* 2016;22(Suppl. 3):6–16.

MANAGEMENT OF PREGNANCY AND DELIVERY IN WOMEN WITH INHERITED BLEEDING DISORDERS



Accurate diagnosis

- Genetic counseling
- Risk of transmission

Prenatal diagnosis

- Control haemostasis
- Prepare management plan with anesthestist, gynaecologist and pediatrician
-Epidural analgesia ?

- Control post-partum bleeds
- Screen neonate

HEMOSTATIC TREATMENT

ON DEMAND: in case on bleeding events, trauma

PREVENTIVE : before surgery, invasive procedures, delivery, high bleeding risk

PROPHYLAXIS: regular hemostatic treatment in severe bleeding phenotype

THERAPEUTIC OPTIONS

GENERAL

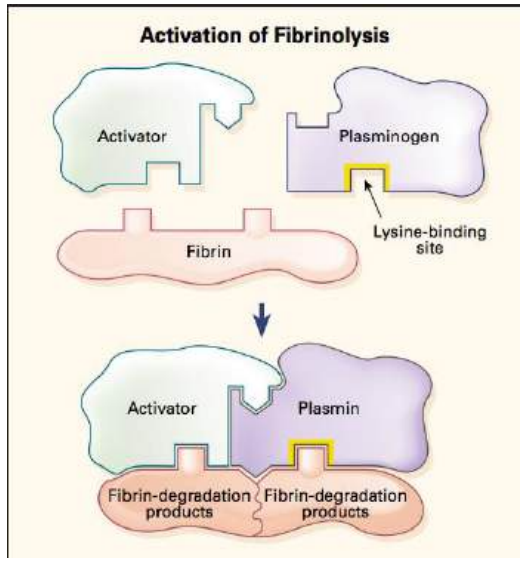
- Antifibrinolytics (+++)
- Estroprogestative contraception/ intrauterine device releasinglevogenestrel
- Iron supplementation
- Avoidance of drugs interfering with the platelet function

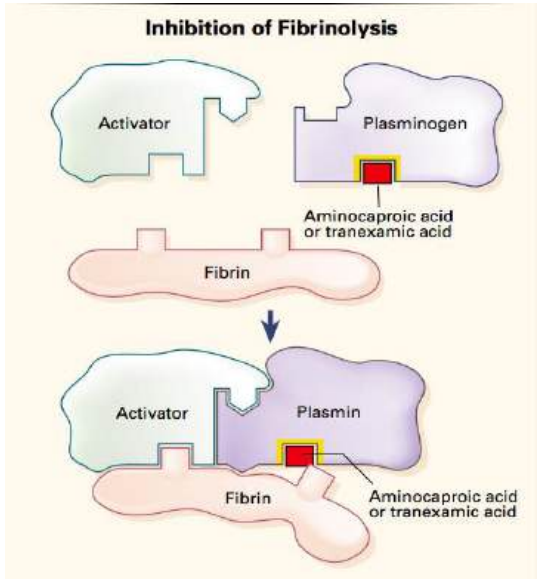
SPECIFIC (not exhaustive)

- DDAVP
- Pd-VWF/FVIII - rvWF concentrates
- Factor VIII/Factor IX
- rFVIIa
- Fresh frozen plasma, platelets

ANTIFIBRINOLYTICS

- Efficient in muco-cutaneous bleeds
- Cheap
- Dosage: 15-20mg/kg 3-4 times/day
- IV, orally, mouth wash
- Contra-indicated in urinary tract bleeding
- Duration adapted to the hemostatic challenge

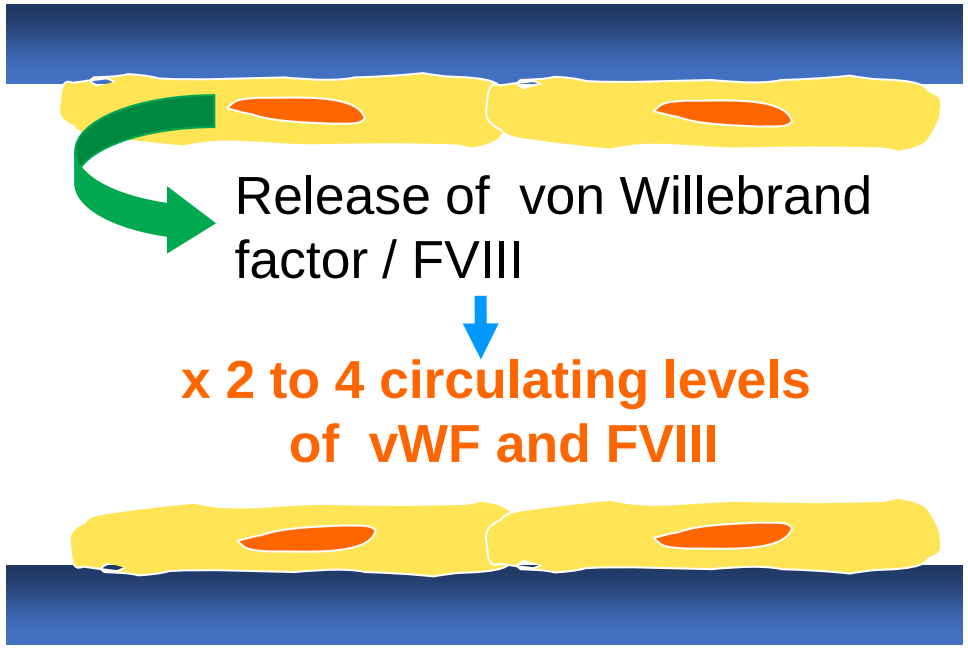




Manucci, NEJM 1998

DESMOPRESSIN (DDAVP) – MINIRIN®

DDAVP: 1-deamino-8-arginin vasopressin



Intravenous
0.3µg/kg

- Synthetic analogue of vasopressin
- Induces a release of endothelial FVIII
- Dosage: 0.2 - 0.3 µg/kg iv (subcutaneous)
- Response and tolerance should be evaluated!
- Side-effects: flush, fluid retention, hyponatremia
- Contra-indicated in elderly patients or with uncontrolled hypertension

DDAVP TESTING

Table 5. Practical considerations for desmopressin trial/challenge and administration

Domain	Description
Route	Desmopressin trials may be performed with either IV or intranasal desmopressin, but intranasal desmopressin trials may not be successful because of issues with administration and/or absorption. Subcutaneous administration has also been used.
Dose	IV desmopressin is given as 0.3 μg/kg, with a maximum dose of 20 μg. The desmopressin nasal spray (150 μg per spray) is given as 1 spray for individuals weighing <50 kg and 2 sprays for individuals weighing ≥50 kg.
Timing of laboratory testing	VWF antigen, VWF activity, and FVIII activity levels should be determined immediately before administration of desmopressin, ~30-60 min after administration of desmopressin, and ~4 h postadministration, because in type 1C VWD, there is a rapid decrease in VWF levels.
Responsiveness	There are multiple definitions of desmopressin responsiveness.[128-130] The panel considered that an increase of at least 2 times the baseline VWF level and the ability to achieve both VWF and FVIII levels of >0.50 IU/mL were required to consider the patient responsive to desmopressin. Desmopressin responsiveness does not guarantee, however, that the level achieved is adequate to prevent bleeding in all procedures (eg, higher levels may be indicated based on type of procedure).
Precautions	Because of the risk of hyponatremia, desmopressin should not be given on >3 concurrent days and is generally not administered to children age <2 y. In addition, tachyphylaxis occurs after repeated infusions. Caution is advised when desmopressin is used in patients with active cardiovascular disease. Additionally, desmopressin trials should be avoided in pregnancy.

ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Adv. 2021

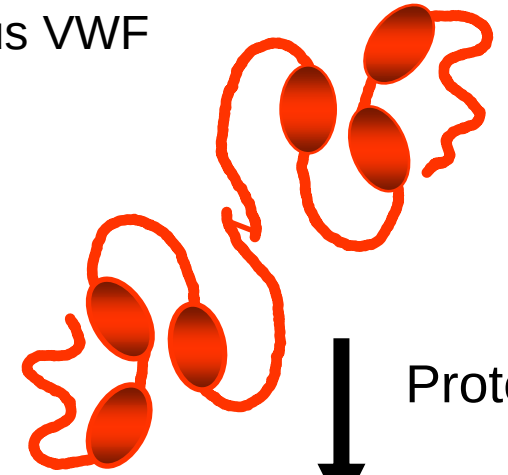
DDAVP testing is not needed when lowest historical VWF:Act ≥ 0.30 IU/ml.

The OPTI-CLOT Study Group, RPTH 2022

REPLACEMENT THERAPY IN VWD

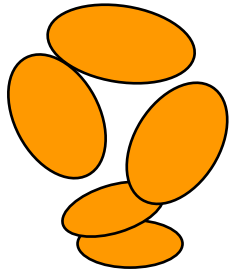
Monotherapy (Pure exogenous VWF)

Exogenous VWF



Wilfactin
(1000U VWF)

Protection

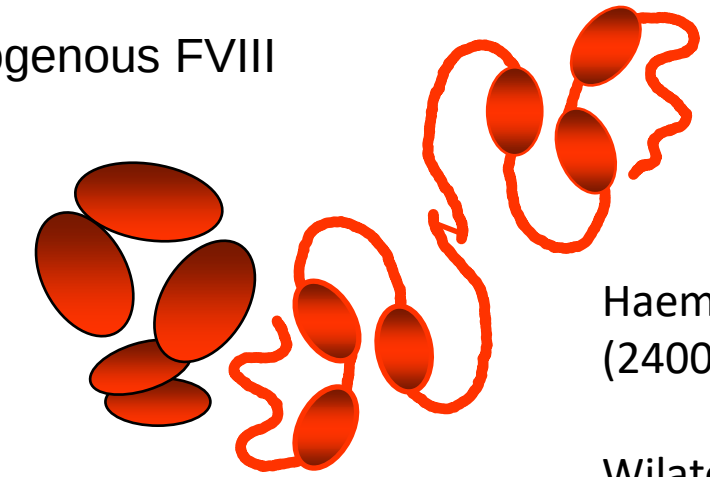


Endogenous FVIII

Dual therapy (Exogenous FVIII-VWF)

Exogenous VWF

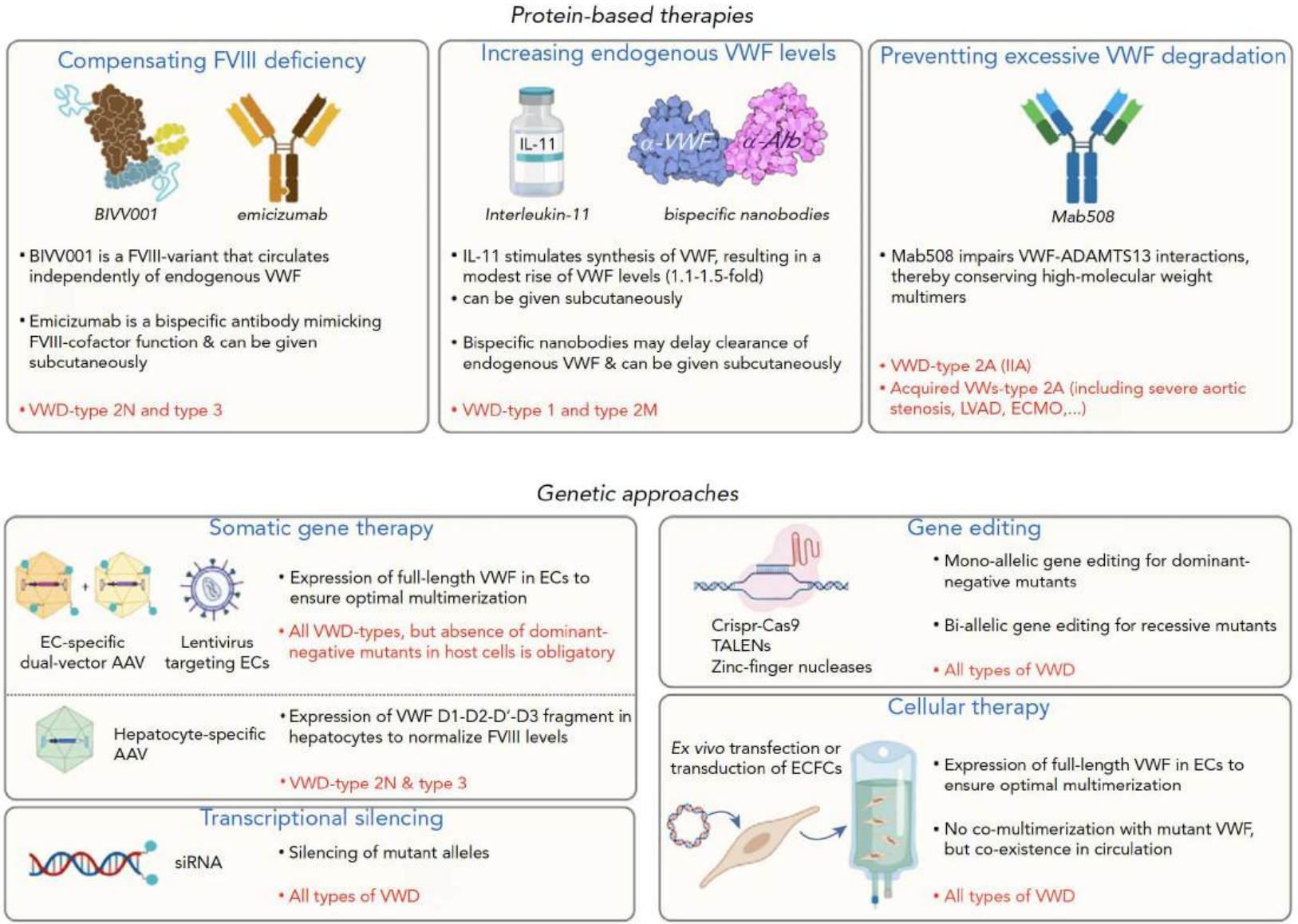
Exogenous FVIII



Haemate P
(2400VWF/1000 FVIII)

Wilate
(1000vWF/1000 FVIII)

FUTURE THERAPIES IN SEVERE VWD



Denis C et al. Blood 2021

CURRENT THERAPEUTIC STRATEGIES OF HEMOPHILIA

Replacement therapy **of the missing protein**

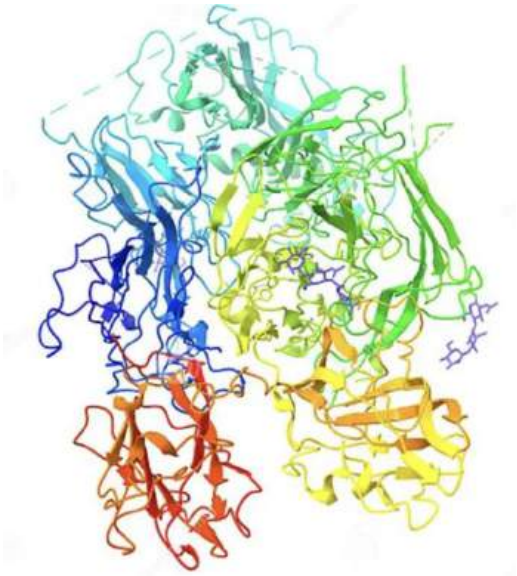
- SHL and EHL FVIII
- XTEN FVIII
- SHL and EHL FIX

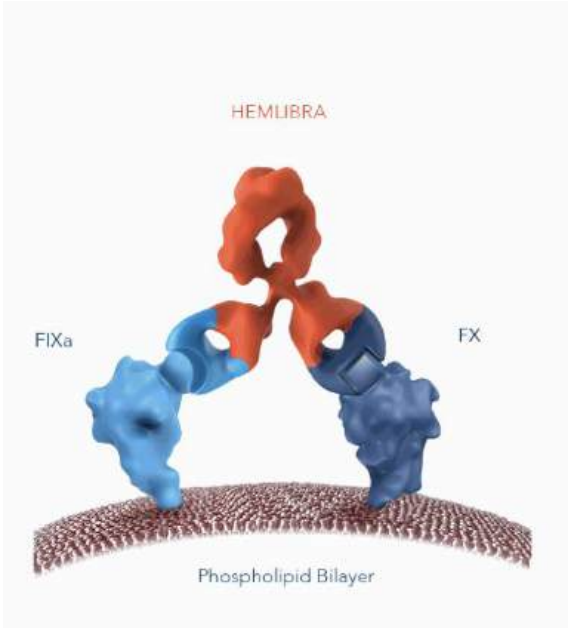
Modulation of the balance of pro-coagulant and anticoagulant proteins

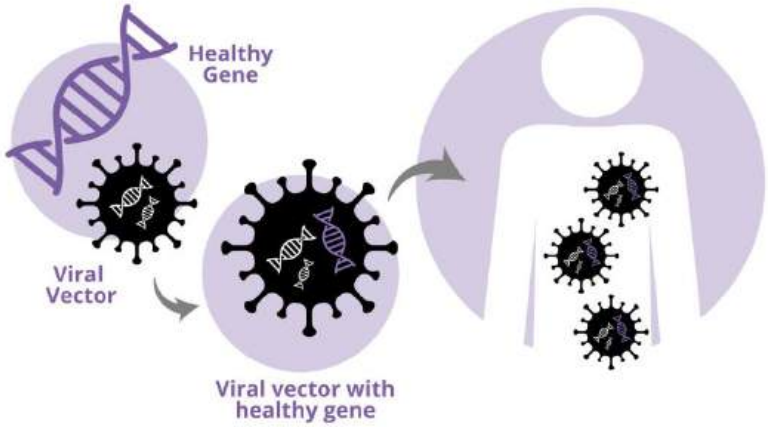
- Non-replacement therapy (HA)
- Small molecules

Gene therapy **to restore endogenous expression of the missing protein**

Possible cure of the disease







Croteau S et al. Am J Hematol. 2021

Plasma half-life, therapeutic target levels, available treatment, and therapeutic dosages for each RCD (on demand and prophylaxis)

Deficient factor	Plasma half-life	Trough levels		Available treatment	On-demand dosages	Long-term prophylaxis dosages
		Previously reported	EN-RBD*			
Fibrinogen	2-4 d	0.5-1 g/L	1 g/L	Cryoprecipitate	15-20 mL/kg	1 bag/10 kg/7-10 d
				FFP†	15-30 mL/kg	—
				Fibrinogen concentrate	50-100 mg/kg	20-30 mg/kg/wk
Prothrombin	3-4 d	20%-30%	>10%	FFP†	15-25 mL/kg	—
				PCC	20-40 U/kg	20-40 U/kg once/wk
FV	36 h	10%-20%	10%	FFP†	15-25 mL/kg	20 mL/kg 2 times/wk
				Platelet transfusions could be considered, with particular attention on alloimmunization		—
FV and FVIII	FVIII 10-14 h	10%-15%	40%	FV deficiency: (see above) mild FVIII deficiency: DDAVP moderate and severe FVIII deficiency: pd- or rFVIII concentrates		Usually no need for prophylaxis
FVII	4-6 h	10%-15%	>20%	FFP†	—	10-15 mL/kg 2 times/wk
				pd-FVII concentrate	30-40 U/kg	30-40 U/kg 3 times/wk
				rFVIIa	15-30 µg/kg every 4-6 h	20-40 mg/kg 2-3 times/wk
FX	40-60 h	10%-20%	>40%	FFP†	10-20 mL/kg	—
				PCC	20-30 U/kg	20-40 U/kg 2 times/wk
				pd-FX/FIX concentrate	10-20 U/kg	20 U/kg/weekly
				pd-FX	25 U/kg	25 U weekly
FXI	50 h	15%-20%	—	FFP†	15-20 mL/kg	Not indicated
				pd-FXI concentrate	15-20 U/kg	
FXIII	9-12 d	2%-5%	30%	Cryoprecipitate	2-3 bags	1 bag/10 kg/3 wk
				FFP†	3-5 mL/kg	—
				pd-FXIII concentrate	20-40 U/kg	20-40 U/kg/4 wk‡
				rFXIII-A	35 U/kg	35 U/kg/4 wk (2-3 wk in pregnant women)
Vitamin K dependent	Prothrombin, FVII, FIX, FX (see specific factors)			Vitamin K1	10 mg for minor bleeding	5-20 mg/daily (orally) 5-20 mg/wk (parenteral)
				4-factor PCC	20-30 U/kg	—
				FFP†	15-25 mL/kg	—

Menegatti et al. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019 31;133(5):415-424.

Thank you for your attention

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