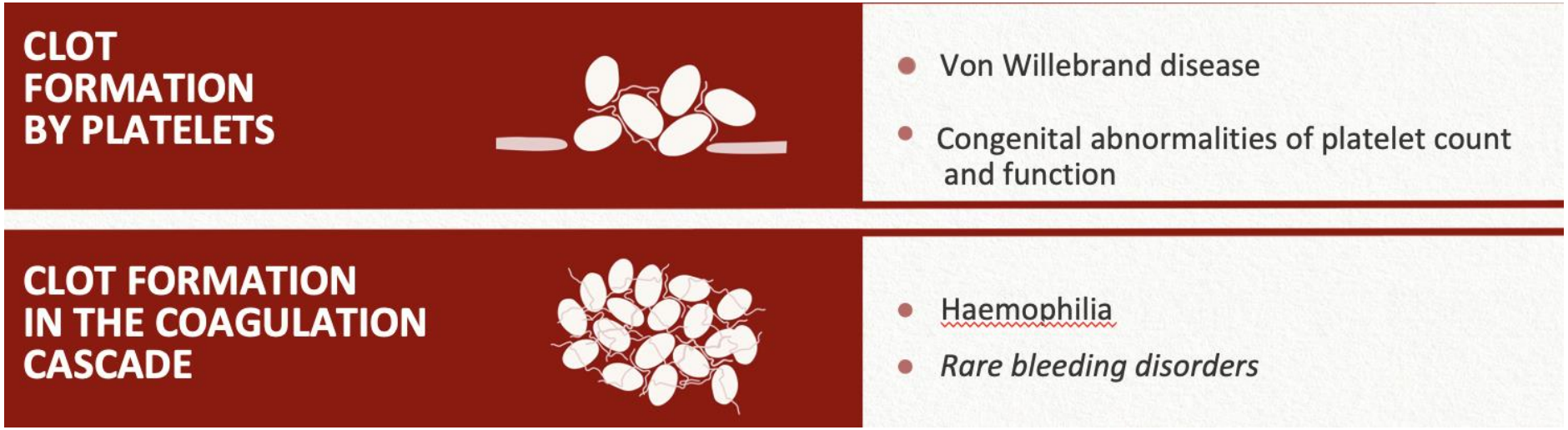
CONGENITAL BLEEDING DISORDERS

Pr Catherine LAMBERT
Hemostasis and Thrombosis Unit
Division of Hematology
Catherine.lambert@uclouvain.be

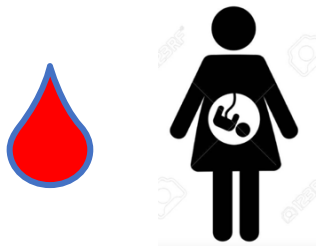
AGENDA

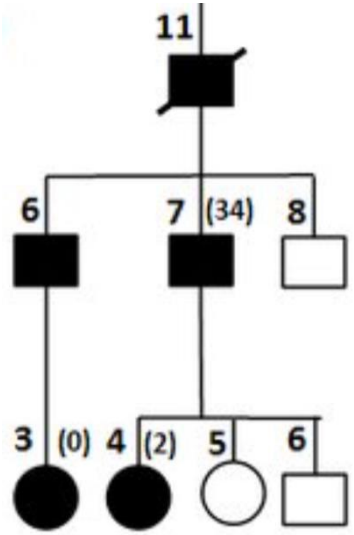
- Recognition and diagnosis of congenital bleeding disorders
- Von willebrand disease - Rare inherited bleeding disorders – inherited platelet disorders
- Principles of hemostatic management

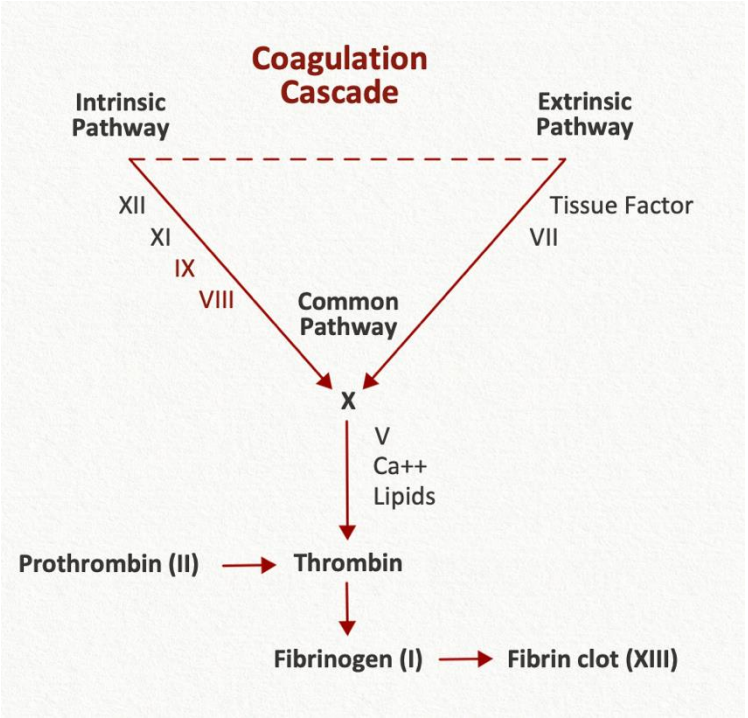


DIAGNOSIS OF BLEEDING DISORDERS

- 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

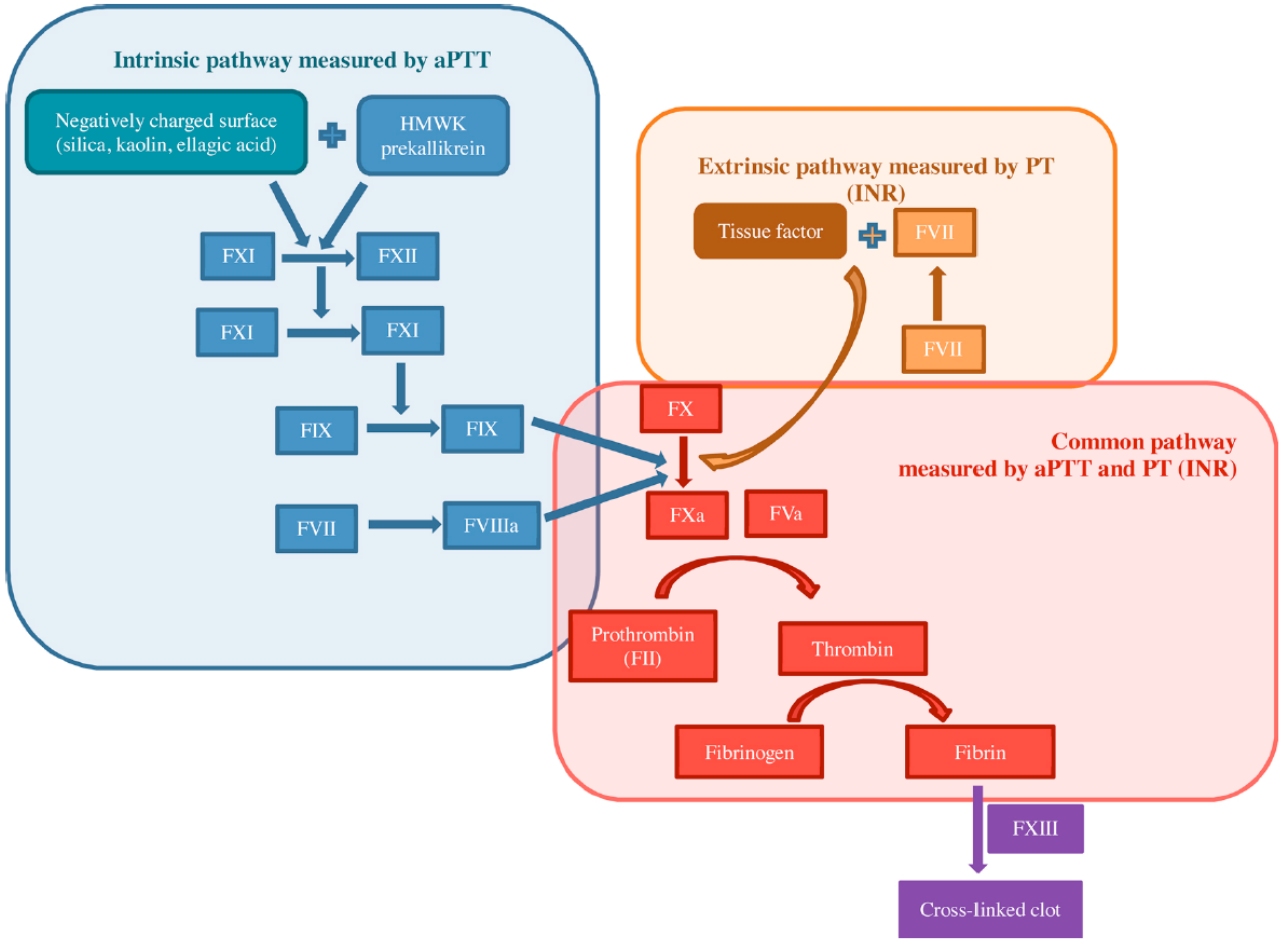
aPTT, Prothrombin Time, Thrombin Time, Fibrinogen
Full Blood count
Blood smear

- 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)

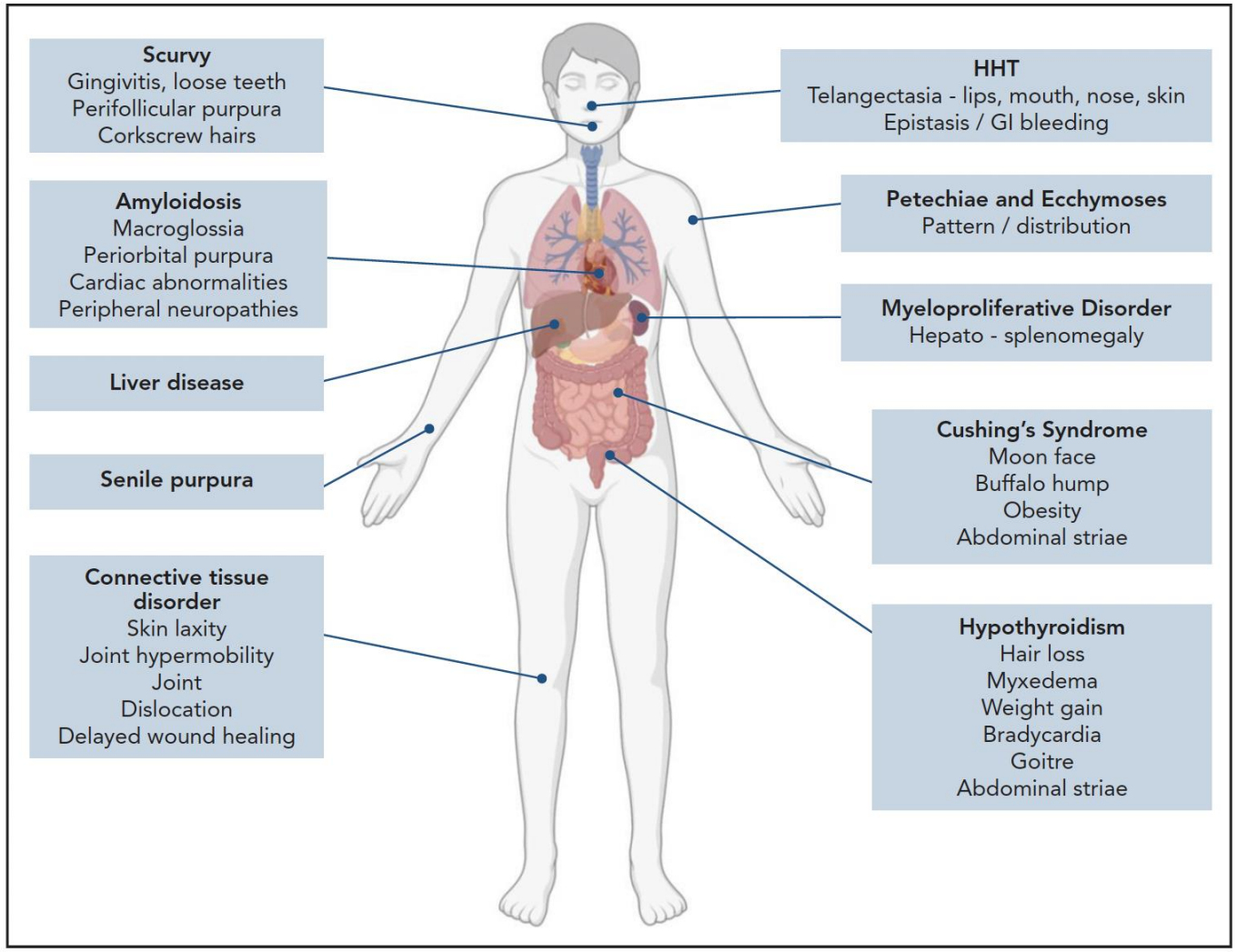


Figure 1. Clinical features associated with inherited and acquired causes of mild to moderate mucocutaneous bleeding. HHT, hereditary hemorrhagic telangiectasia.

- 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

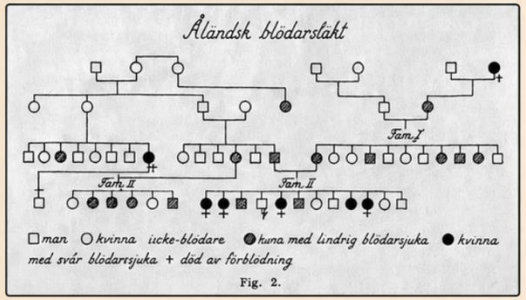
100 YEARS *of*
VON WILLEBRAND DISEASE

HISTORY

Hjördis Sundblom was the first person described in the medical literature with what is now known as von Willebrand disease (VWD).

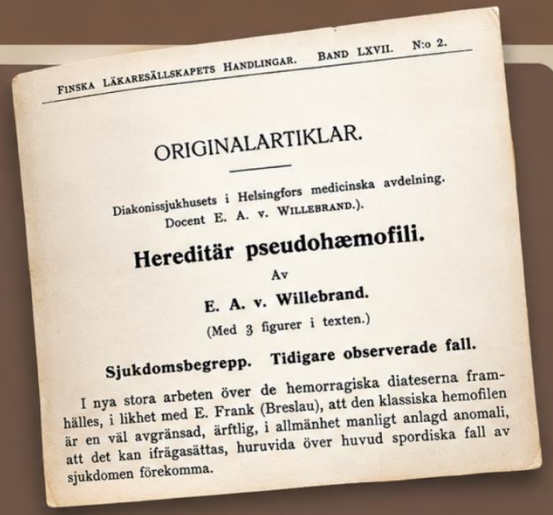
She lived in the **Åland Islands** and had frequent bleeding from early childhood, now thought to reflect severe (Type 3) VWD.





Several family members were affected. **Three sisters died** from severe bleeding.

She died at age 14 after heavy menstrual bleeding during her fourth menstrual period.


FINSKA LÄKARESÄLLSKAPETS HANDLINGAR. BAND LXVII. N:o 2.

ORIGINALARTIKLAR.

Diakonissjukhusets i Helsingfors medicinska avdelning.
Docent E. A. v. WILLEBRAND.).

Hereditär pseudohæmofili.

Av

E. A. v. Willebrand.

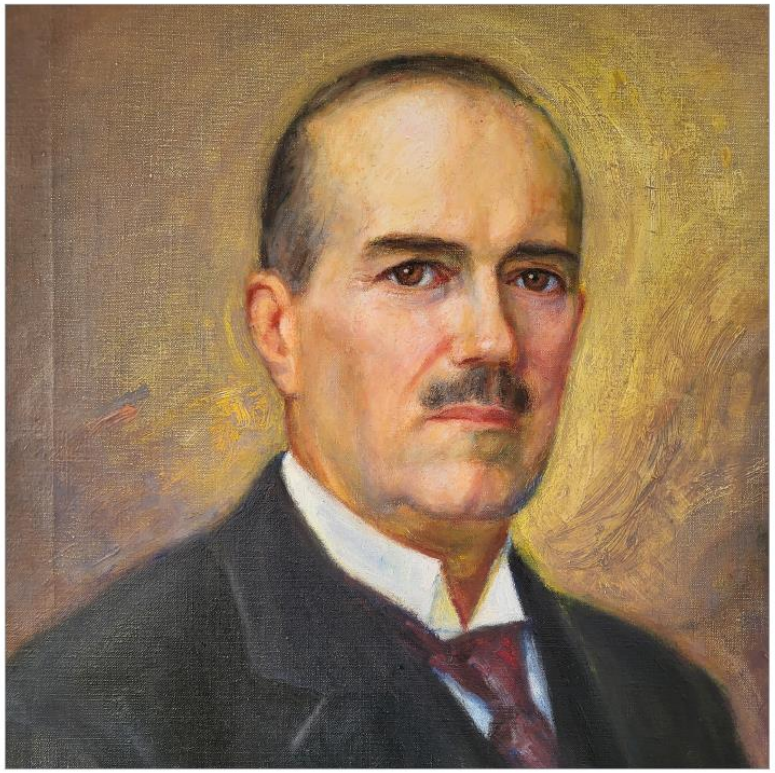
(Med 3 figurer i texten.)

Sjukdomsbegrepp. Tidigare observerade fall.

I nya stora arbeten över de hemorragiska diateserna framhålles, i likhet med E. Frank (Breslau), att den klassiska hemofilen är en väl avgränsad, ärftlig, i allmänhet manligt anlagd anomali, att det kan ifrågasättas, huruvida över huvud spordiska fall av sjukdomen förekomma.

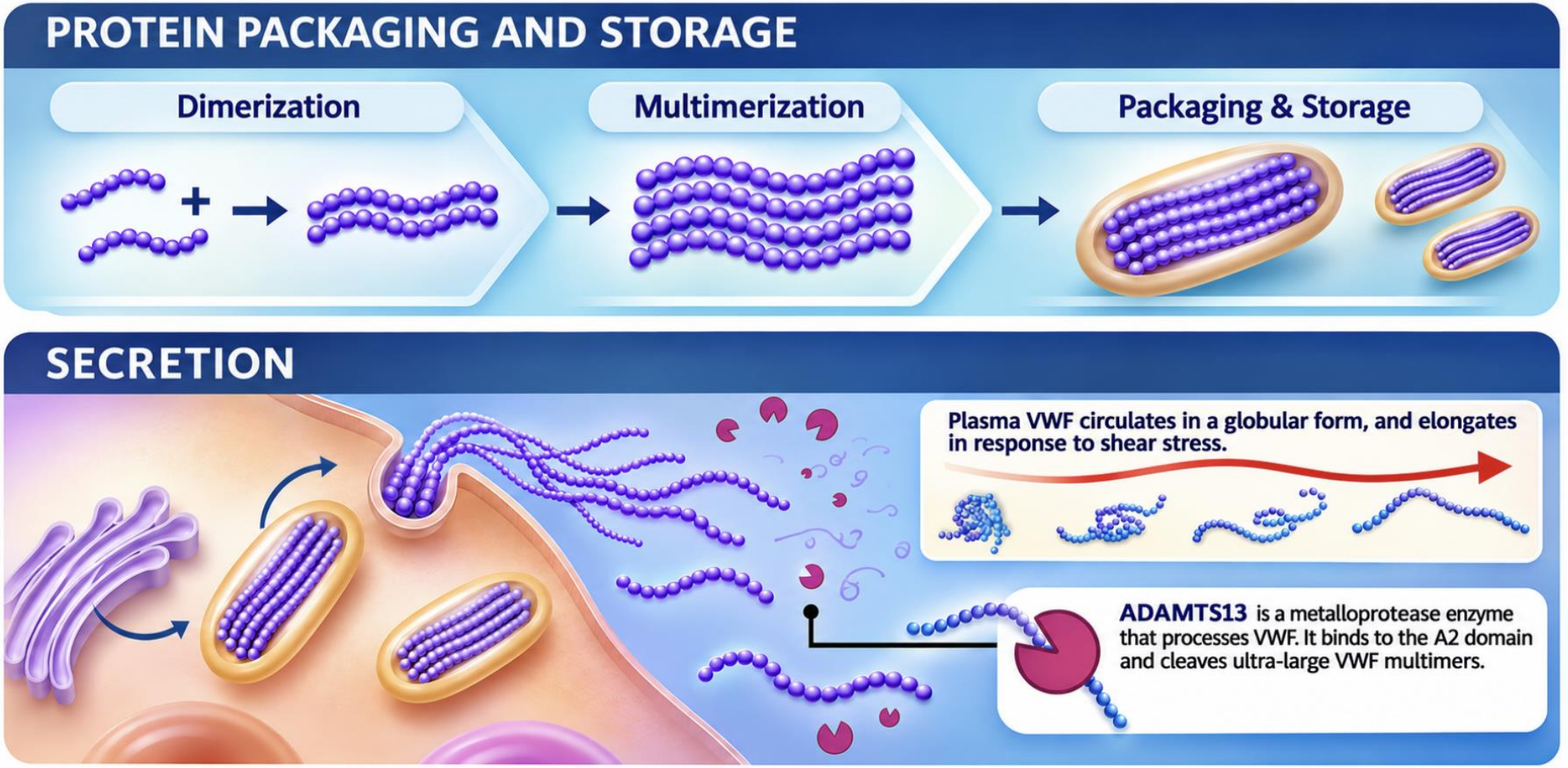
Erik Adolf von Willebrand investigated Hjördis and her family.

In 1926, he published the landmark paper that first described the disorder, titled **"Hereditär pseudohæmofili"** ("hereditary pseudohemophilia").



Lassila R and Berntorp E, Haematologica 2026

VON WILLEBRAND FACTOR



VON WILLEBRAND FACTOR

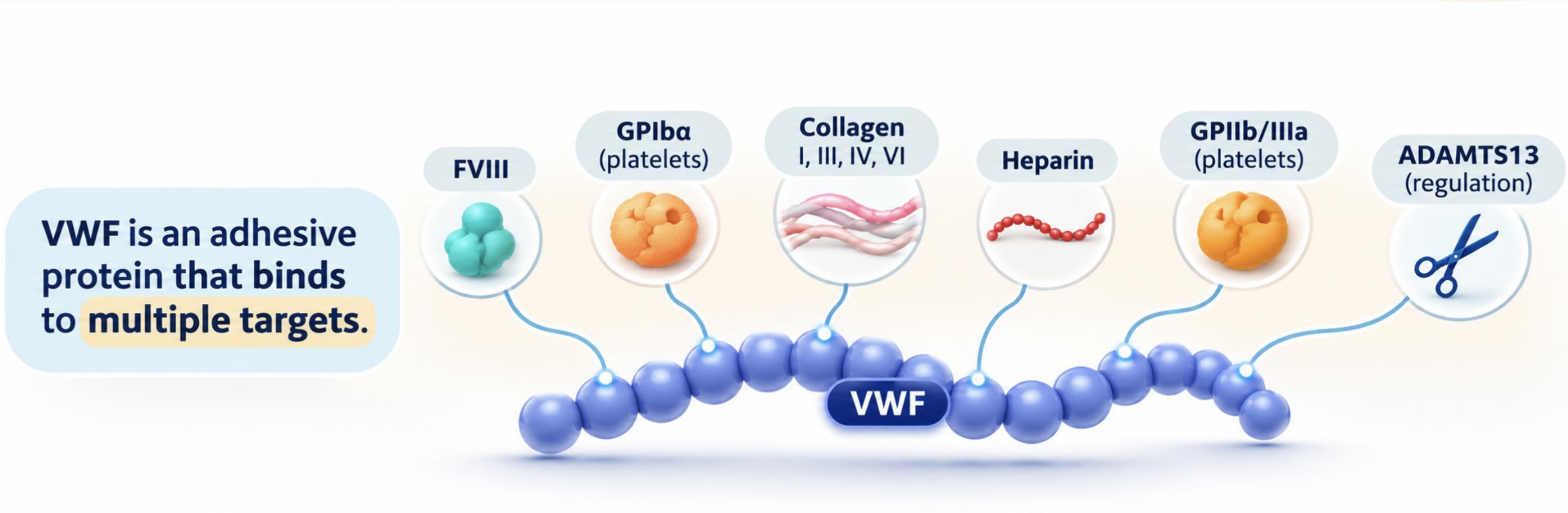
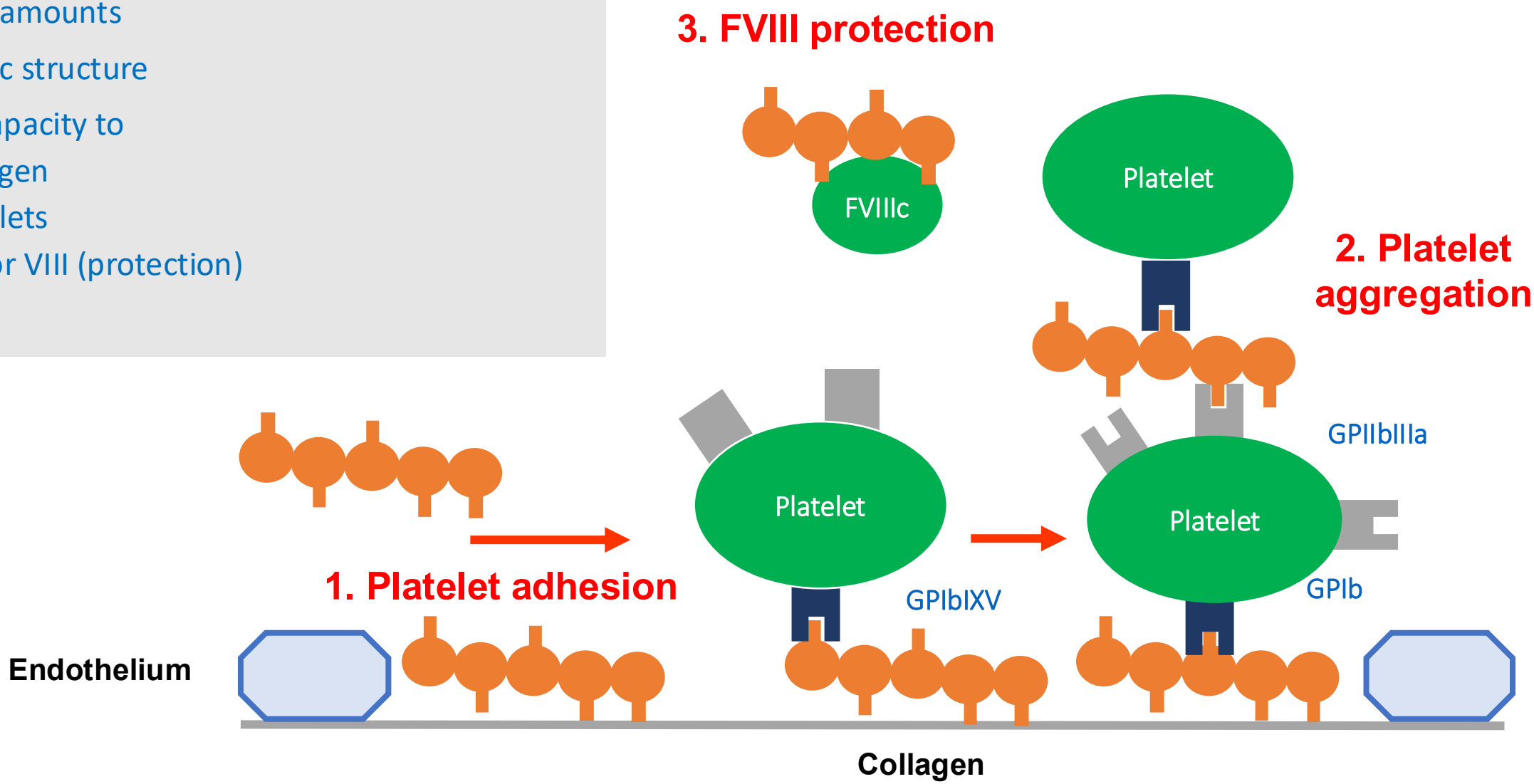


Image created with ChatGPT

THE MULTIPLE FUNCTIONS OF VWF

Required properties of VWF to be fully effective

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



PHYSIOLOGICAL VARIATIONS OF VWF

In ~20–30% of Type 1 VWD patients, VWF may normalize with age due to physiological increases in VWF.

? It remains unclear whether this ameliorates bleeding symptoms or not.

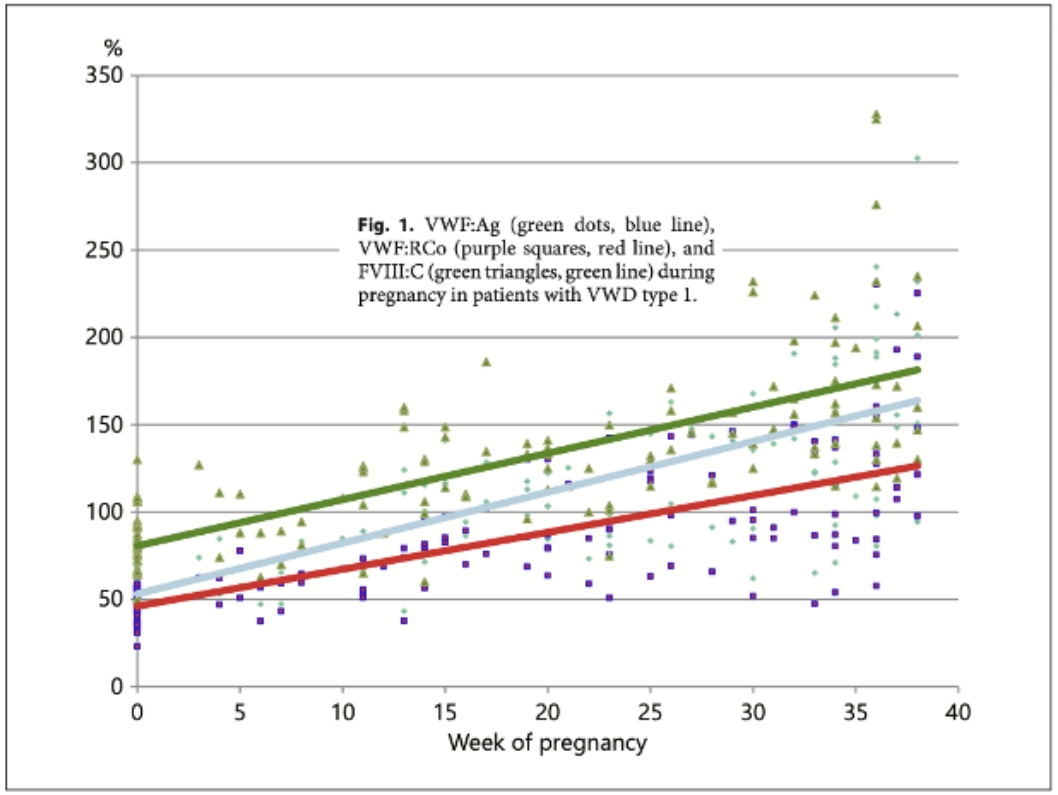


Fig. 1. VWF:Ag (green dots, blue line), VWF:RCo (purple squares, red line), and FVIII:C (green triangles, green line) during pregnancy in patients with VWD type 1.

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.

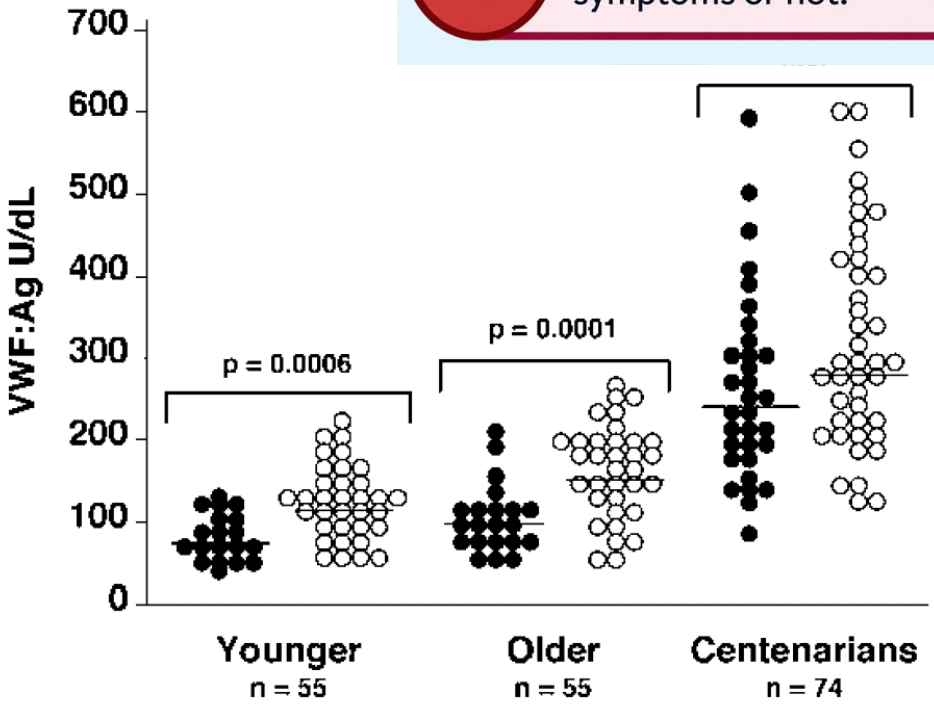


Figure 1. von Willebrand factor (U/dL) related to blood groups in younger, older, and centenarian individuals. Closed circles represent blood group type O, open circles type non-O.

PHYSIOLOGICAL LOW VWF IN BLOOD GROUP O

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

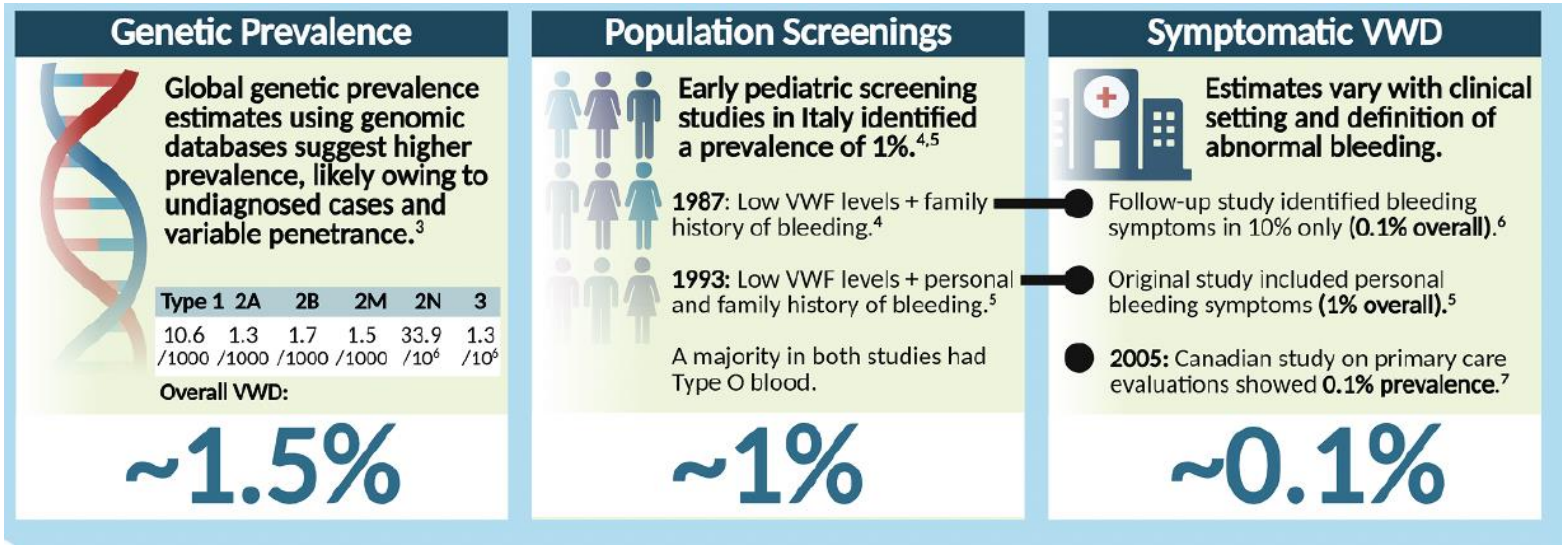
ABO Type	n	vWF:AG Geometric Mean	vWF:Ag Geometric Mean ± 2 SD
O	456	74.8	35.6-157.0
A	340	105.9	48.0-233.9
B	196	116.9	56.8-241.0
AB	109	123.3	63.8-238.2

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

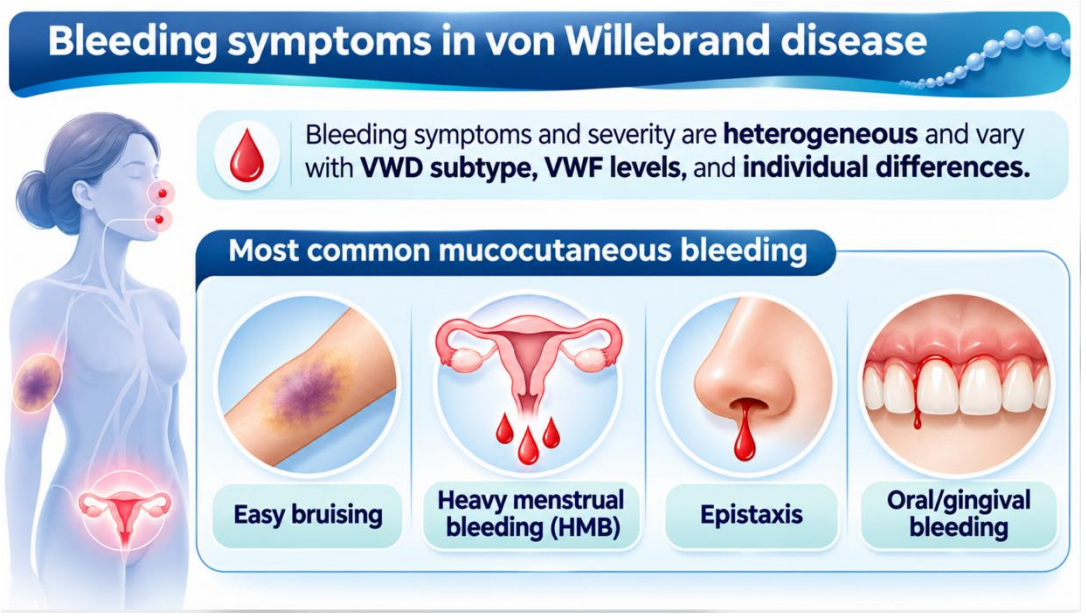
VON WILLEBRAND DISEASE

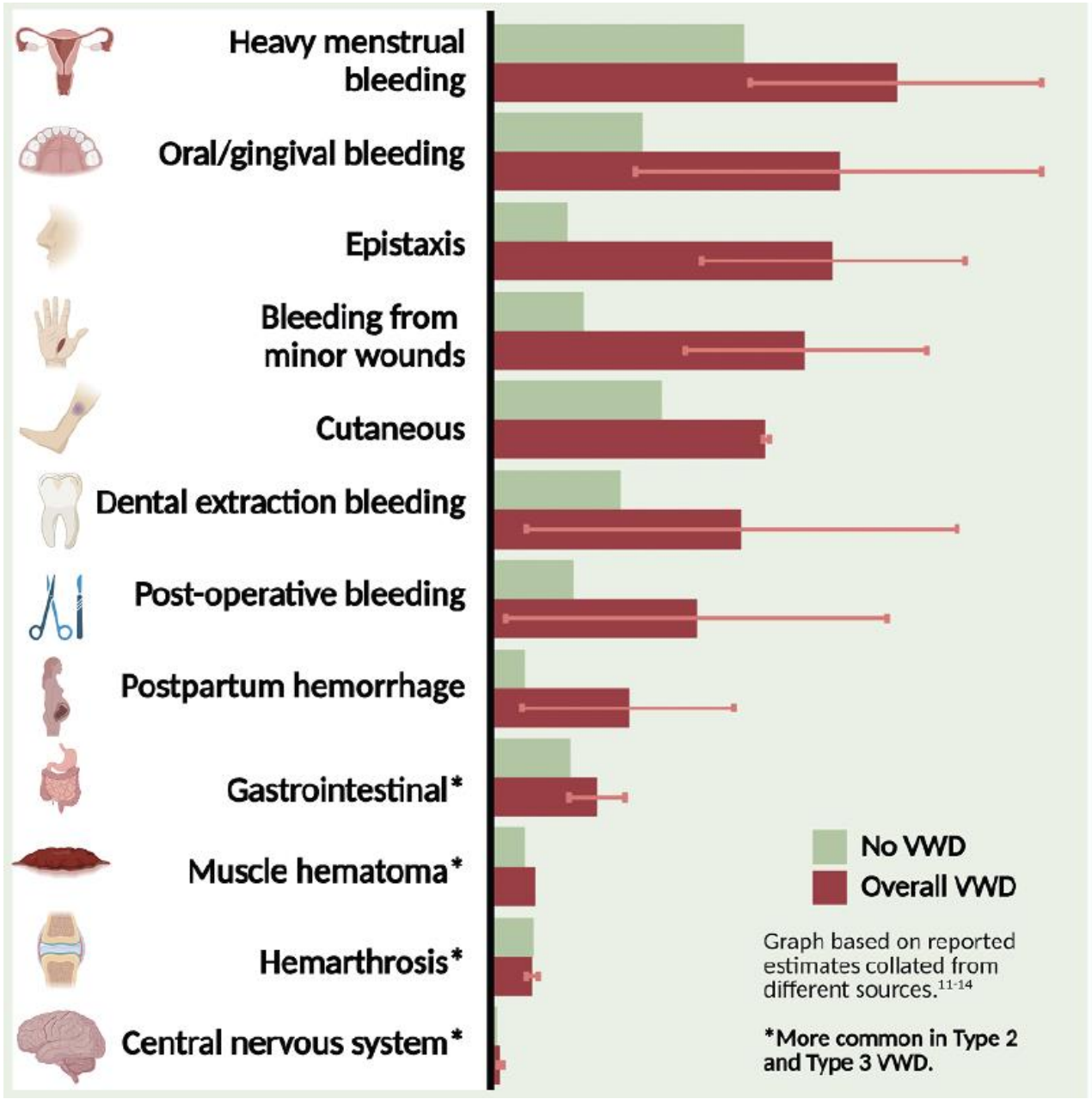
- The **most common inherited bleeding disorder**.
- Affects men and women
- Estimated to occur in 1 in 1000 people
- Heterogeneous disease



- 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





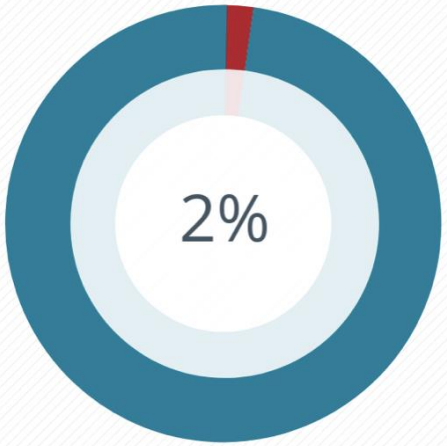
Leebeek *N Engl J Med*. 2016 ;375(21):2067-2080

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

VWD is more frequently diagnosed among females due to the unique challenges related to:

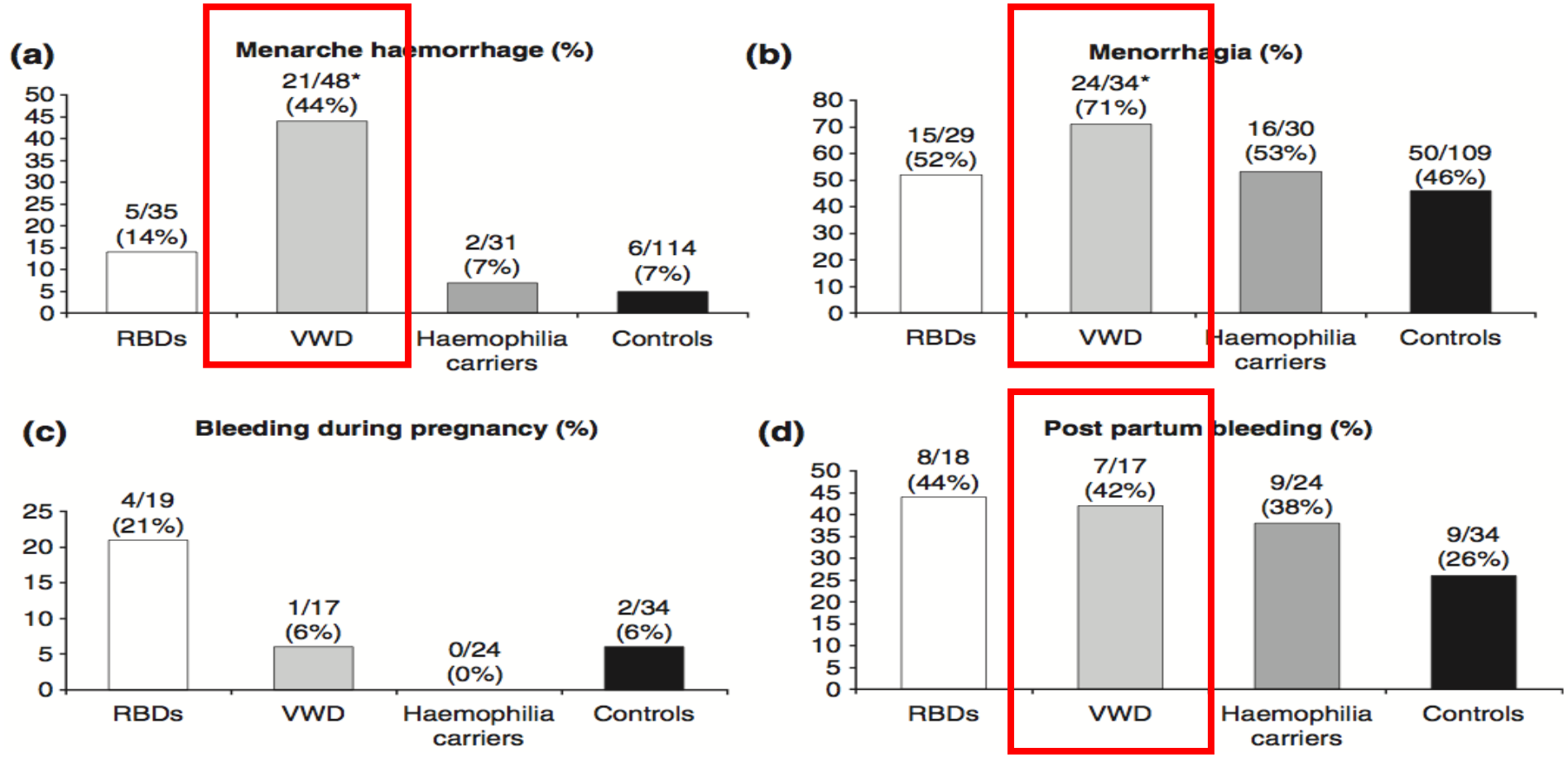


Heavy Menstrual Bleeding



Childbirth

GYNAECOLOGICAL BLEEDS IN VWD

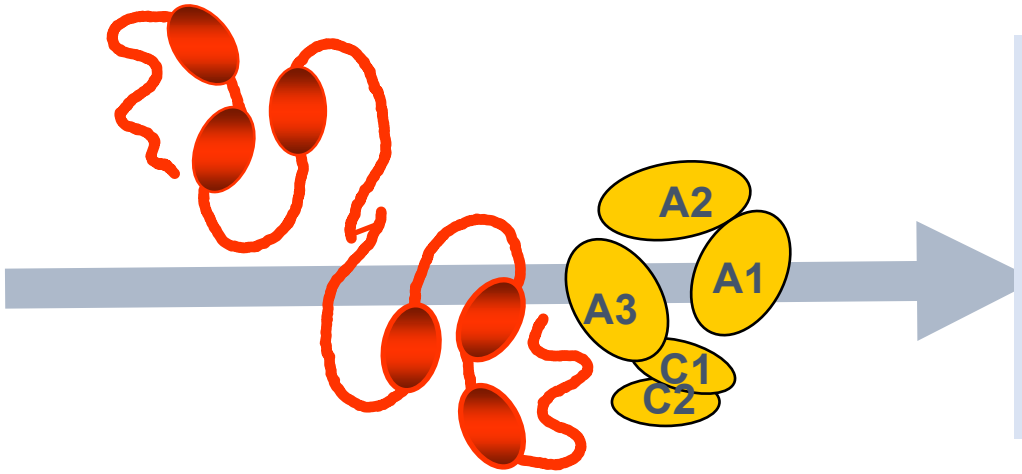


- 32 -70% of women with VWD experience heavy menstrual bleeding
- Low VWF patients also experience significant bleeding phenotype despite mild plasma VWF reduction.

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

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

CLASSIFICATION AND TRANSMISSION OF VWD

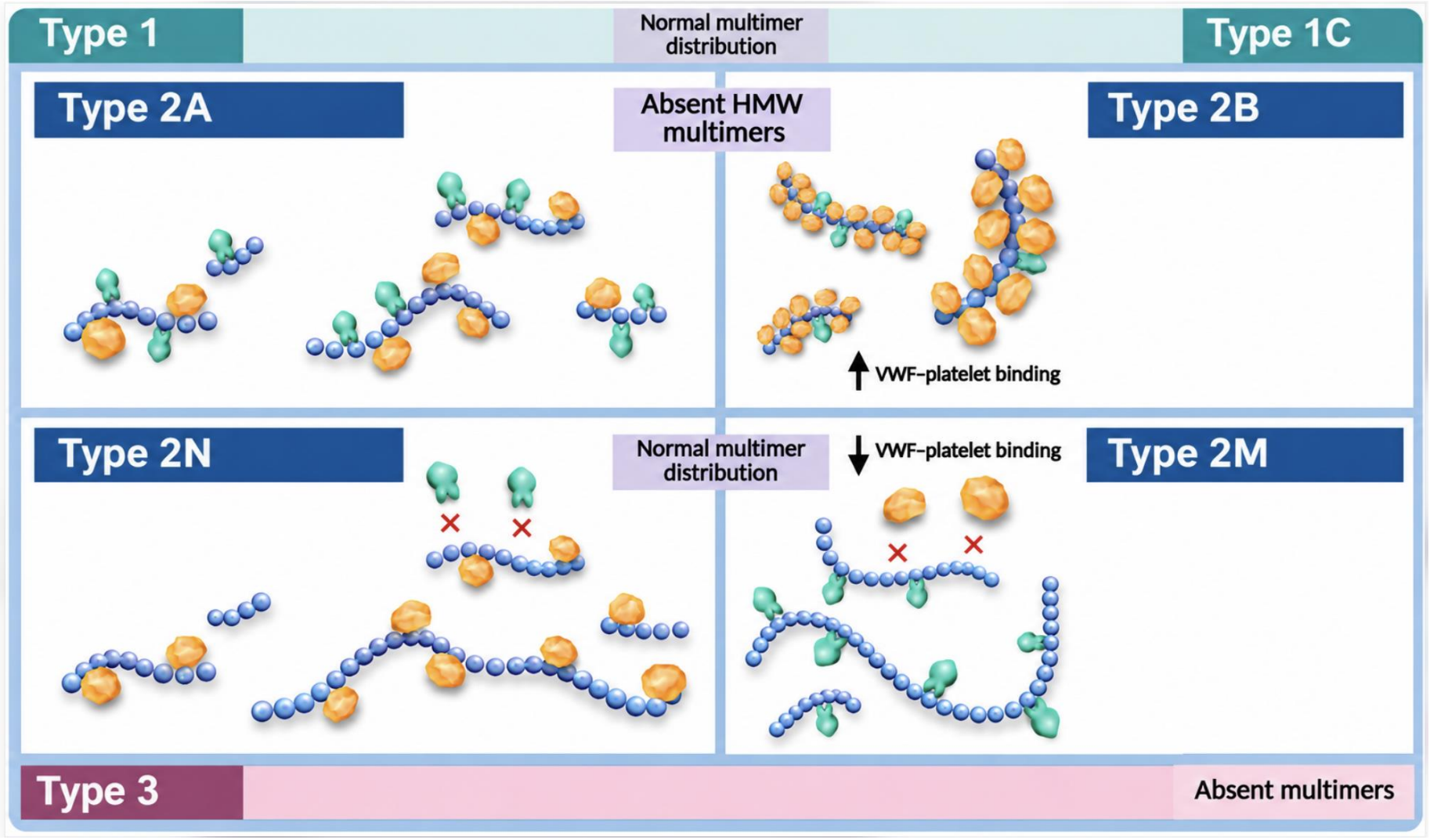
TABLE 1. Classification and inheritance of von Willebrand disease.

Type	Subtype	Mechanism	Mode of Inheritance
Type 1	1	Partial quantitative deficiency of VWF	Autosomal dominant - incomplete penetrance
	Vicenza	Accelerated clearance of VWF (often due to p.R1205H mutation)	Autosomal dominant
Type 2	2A	Decreased platelet-dependent function associated with loss of high and intermediate molecular weight VWF multimers	Autosomal dominant
	2B	Increased affinity for platelets Glycoprotein Ib	Autosomal dominant (some rare recessive forms)
	2M	Decreased platelet-dependent function associated without loss of high molecular weight VWF multimers	Autosomal dominant
	2N	Defective binding to FVIII	Autosomal recessive
Type 3	–	Virtually complete absence of VWF	Autosomal recessive

Adapted from Castaman G. 2020.[6]

Lambert C. BJH 2025

CLASSIFICATION OF VWD



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

	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.

ALGORITHM FOR TESTING VWD

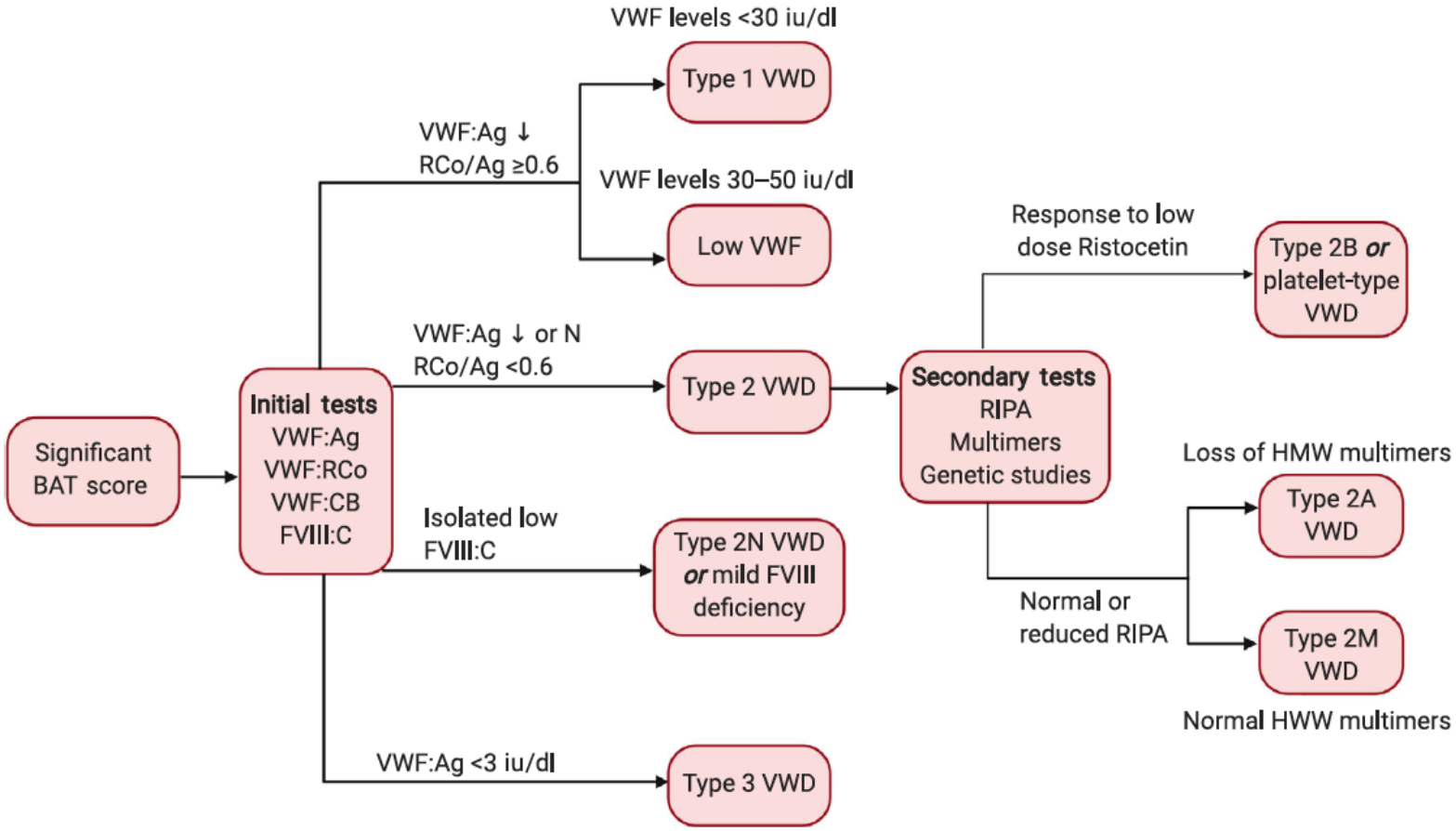
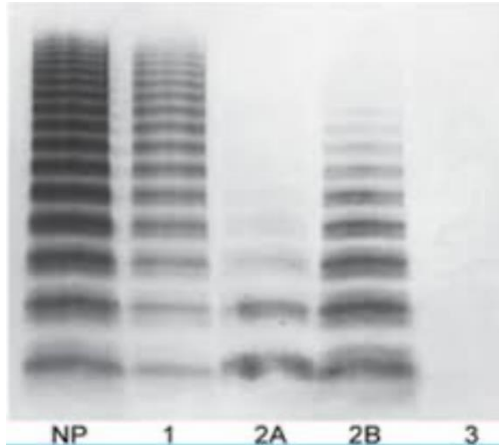


Fig 3. Suggested VWD diagnostic algorithm with defined threshold cut-offs. Adapted from UKHCDO guidelines.[11]



GENETIC TESTING

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

ALGORITHM FOR TESTING VWD

CONFIRMING THE DIAGNOSIS OF VWD

To make a diagnosis of VWD, The ASH ISTH NHF WFH 2021 guidelines[13] require:

VWF:Ag or platelet-dependent VWF activity (IU/dL) <30 OR <50 + bleeding symptoms*

*Objective assessment can be performed using bleeding assessment tools, such as the ISTH-BAT.[29]



Physiologic Factors

	May increase VWF levels	May decrease VWF levels
Normal Physiology	**Exercise** **Normal aging** **Stress** eg. phlebotomy, stress in children, psychological stress **Estrogen rise** eg. pregnancy, menstrual cycle changes	**Blood Type O**
Exogenous Causes	**Estrogen** eg. contraceptives, hormonal replacement **Cigarette Smoking**	**Medications** eg. ciprofloxacin, valproic acid **Mechanical Devices** eg. ECMO, LVAD
Pathologic Causes	**Atherosclerosis** **Liver Disease** **Inflammation** e.g. trauma, infections, acute illness, obesity, inflammatory conditions **Anemia** eg. acute blood loss from HMB	**Hypothyroidism** **Autoimmune Disease** **Cardiac Disease** eg. aortic stenosis, severe mitral regurgitation **Neoplasms** Acquired VWS may occur secondary to MPNs, Wilms tumor, paraneoplastic antibodies. Conversely, other neoplasms may elevate VWF due to inflammation.

Abou-Ismail et al. RPTH 2026

TREATMENT OF VWD



Available Treatment Options

- Desmopressin
- VWF Concentrate
- Tranexamic acid

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

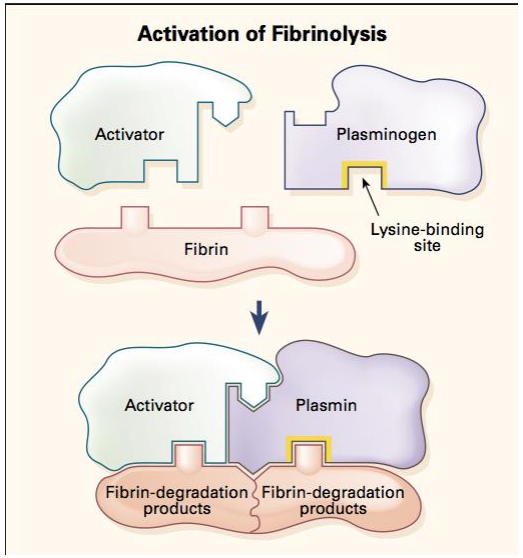
- Antifibrinolytics (+++)
- Estroprogestative contraception/ IUD releasing levogenestrel
- Iron supplementation
- Avoidance of drugs interfering with the platelet function

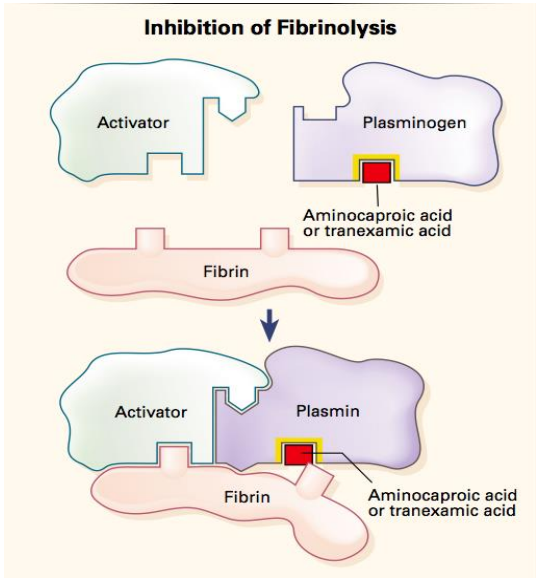
SPECIFIC

- DDAVP
- Pd-VWF/FVIII concentrates
- Recombinant vWF concentrates
- Platelet transfusion (Type 2B)

ANTIFIBRINOLYTICS

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

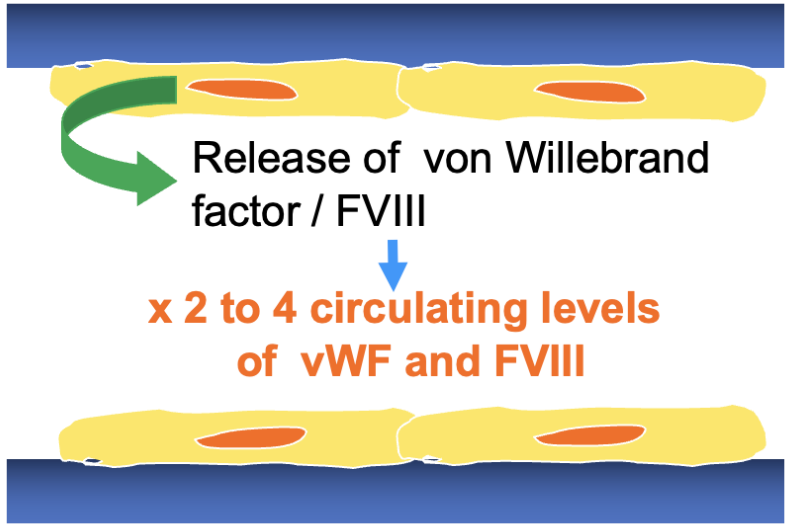




Manucci, NEJM 1998

DESMOPRESSIN (DDAVP) – MINIRIN®

DDAVP: 1-deamino-8-arginin vasopressin



Intravenous
0.3µg/kg

Notable Side Effects:

- **Hyponatremia**
- **Seizures**
- **Cardiac disease exacerbation** (contraindicated)
- **Tachyphylaxis** (drug may become ineffective after 3-5 consecutive days)

In most HTCs, DDAVP is avoided in patients age ≤2 or ≥60.

A DDAVP trial is recommended to document response prior to use. However, it may not be necessary in mild Type 1 VWD as the majority typically respond.

DDAVP response definition:

- ≥ 2× VWF/FVIII increase from baseline **AND**
- Sustained increase to > 0.50 IU/mL for ≥ 4 hours

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.

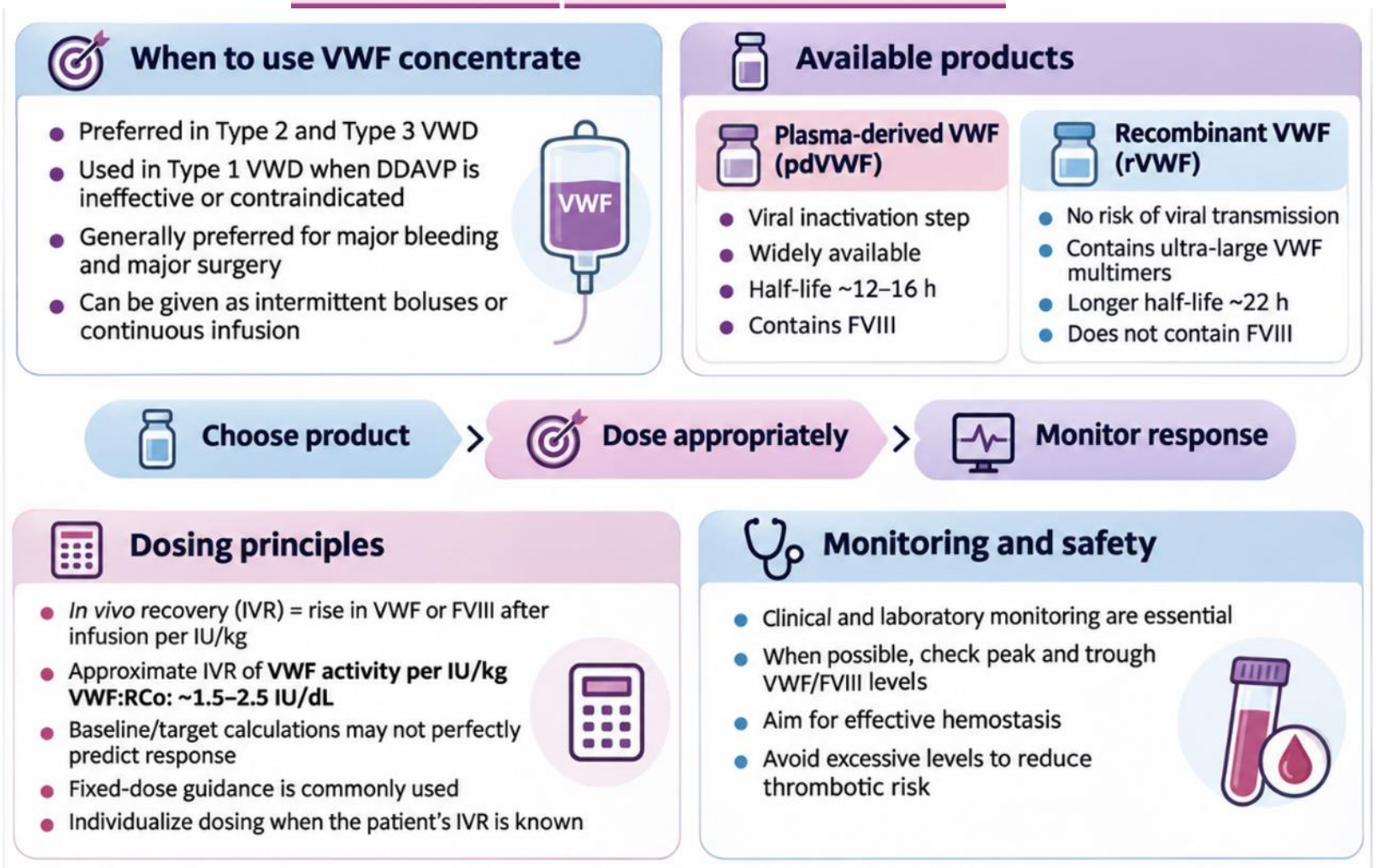
ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Adv. 2021

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

VWF:RCo/FVIII ratio	VWF:RCo half-life* (median hours, range)

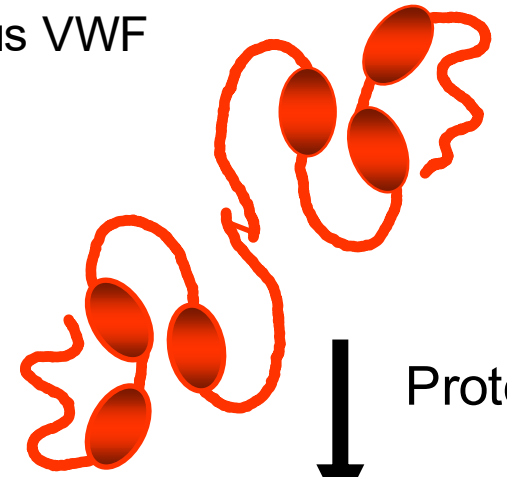


Abou-Ismail et al. RPTH 2026

REPLACEMENT THERAPY IN VWD

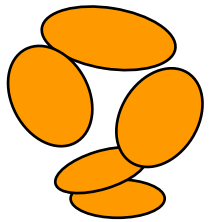
Monotherapy (Pure exogenous VWF)

Exogenous VWF



Wilfactin
(1000U VWF)

Protection

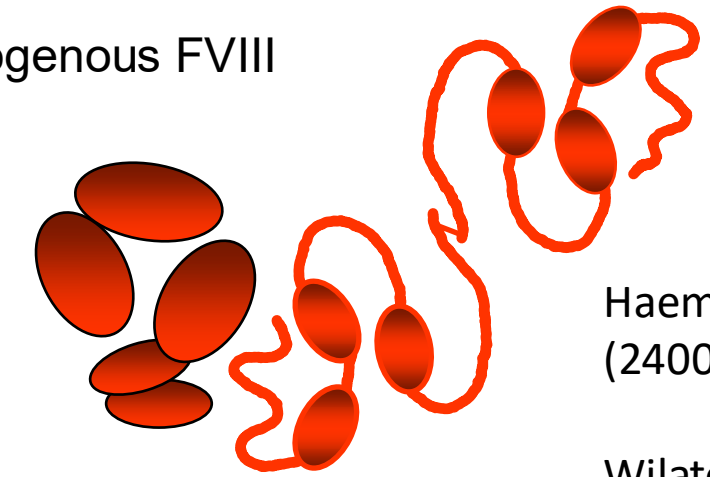


Endogenous FVIII

Dual therapy (Exogenous FVIII-VWF)

Exogenous VWF

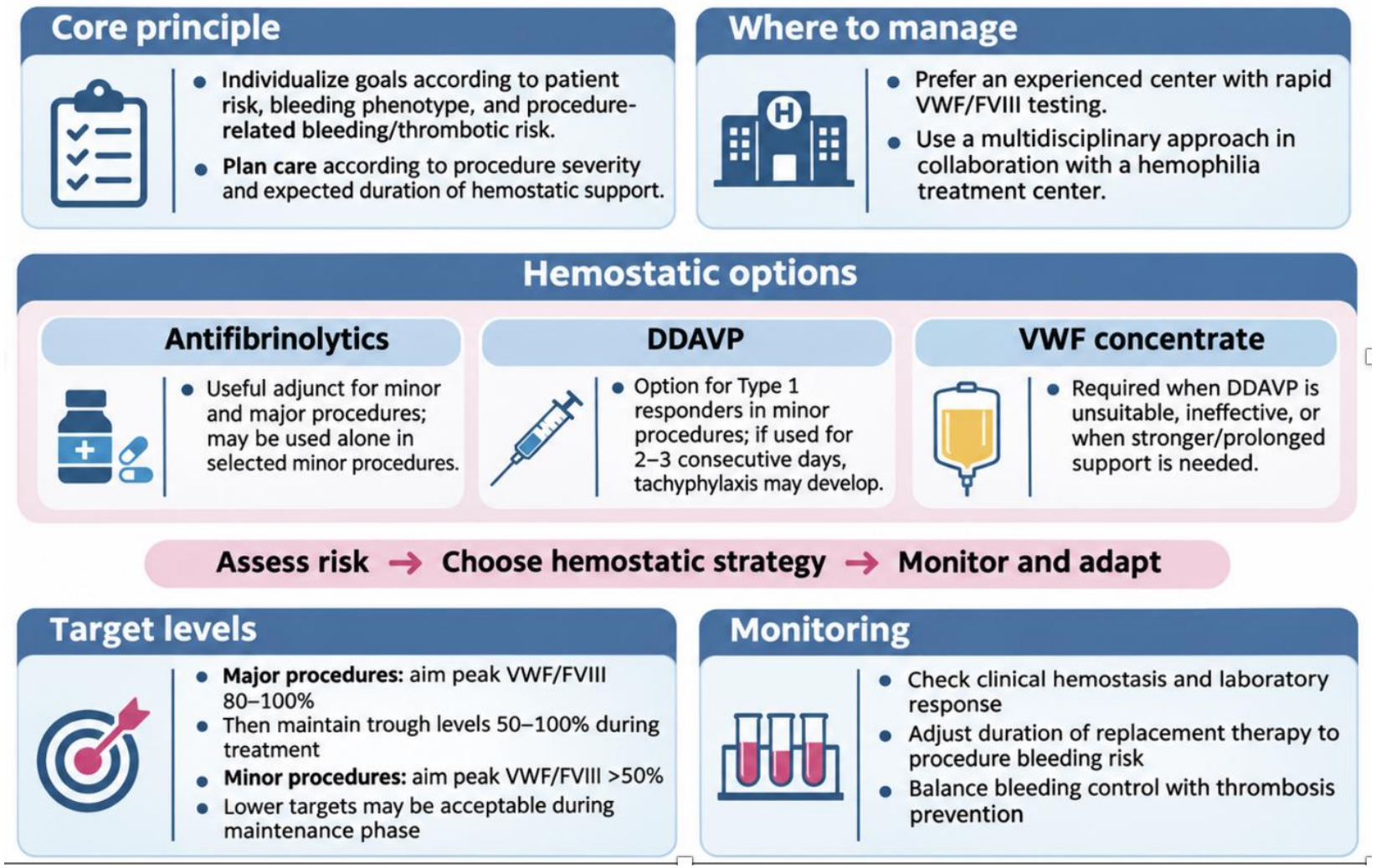
Exogenous FVIII



Haemate P
(2400VWF/1000 FVIII)

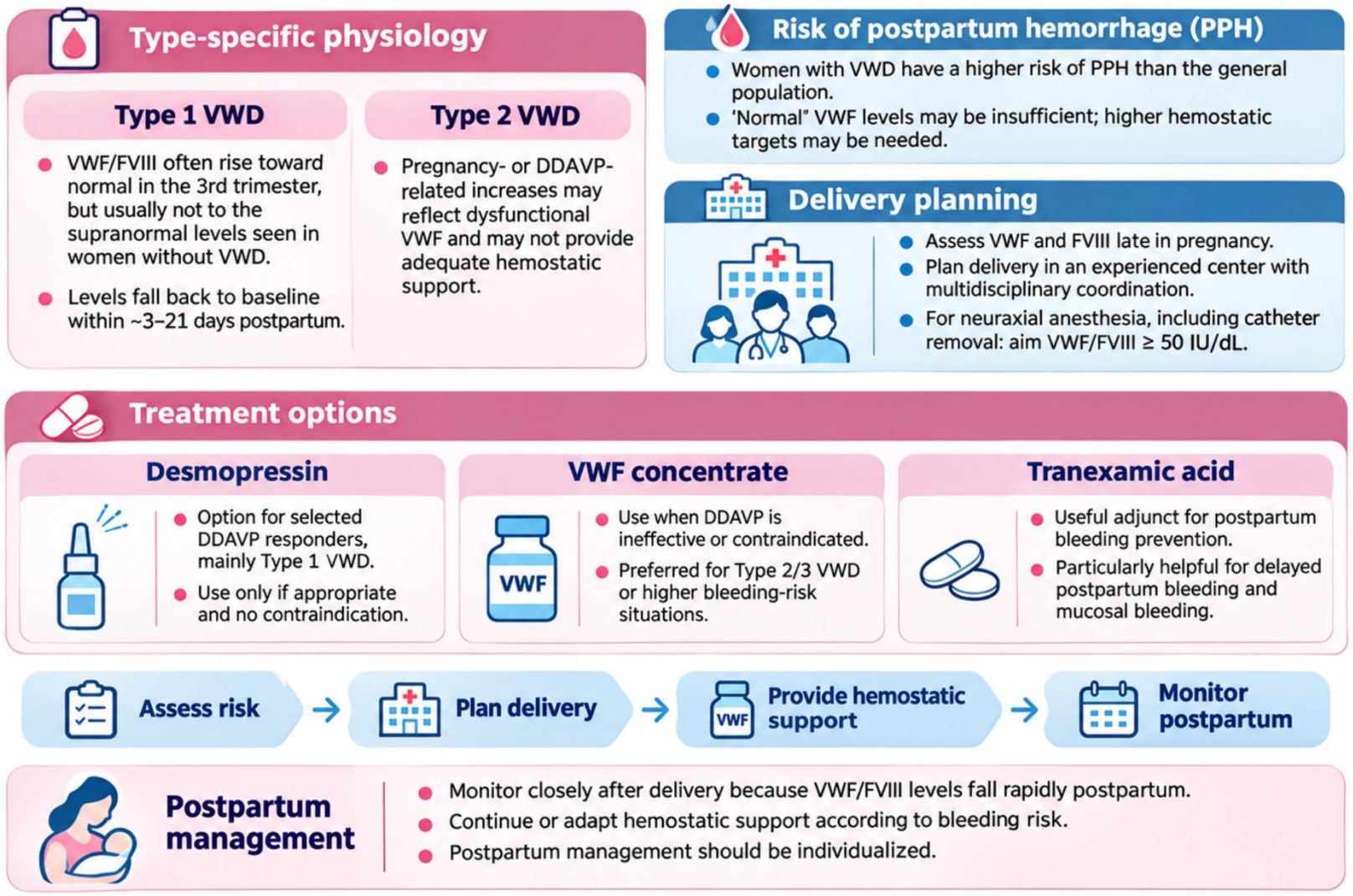
Wilate
(1000vWF/1000 FVIII)

SURGERY IN VWD



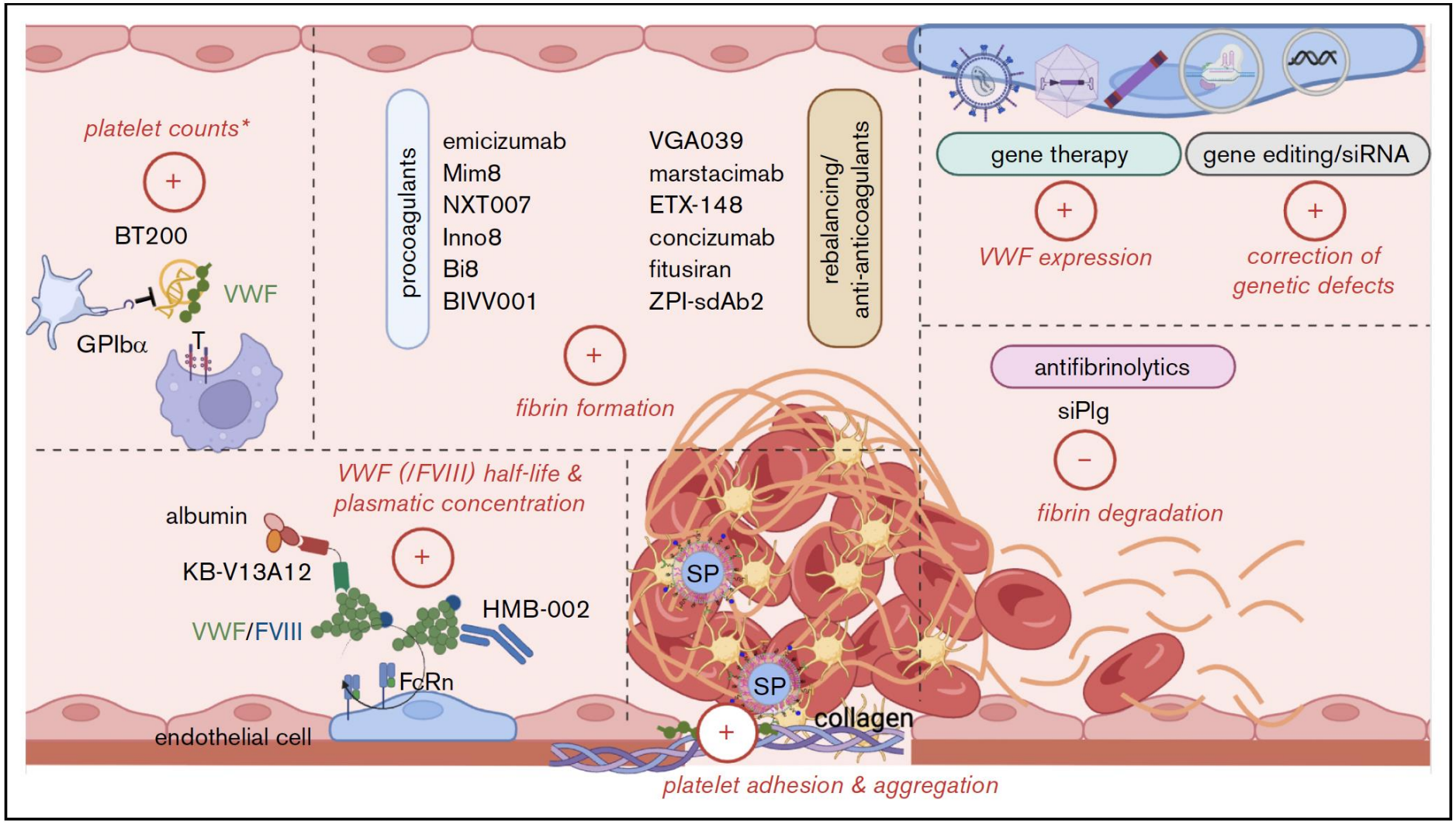
Abou-Ismail et al. RPTH 2026

DELIVERY AND POST-PARTUM IN VWD



Abou-Ismail et al. RPTH 2026

FUTURE THERAPIES IN SEVERE VWD



Denis C et al. Blood Advances 2026

INHERITED RARE BLEEDING DISORDERS

TABLE 2. Summary of rare inherited bleeding disorders.

Deficiency	Estimated prevalence of severe form*‡	Minimal haemostatic levels†	Available products
Fibrinogen	1 : 50 - 1.000.000	>1 g/L	PDC, Cryoprecipitate, FFP
Prothrombin	1 : 2.000.000	>10%	PCC, FFP
Factor V	1 :1,000.000	>10%	FFP, Platelet concentrates
Combined Factor V + VIII	1 :1.000.000	>40%	Desmopressin + FFP Factor VIII concentrate + FFP
Factor VII	1 : 500,000	>20%	Recombinant FVIIa, PDC, PCC, FFP
Factor X	1 :1.000.000	>40%	PDC, PCC
Factor XI	1 : 1.000.000	>20%	PDC, FFP, Antifibrinolytics
Factor XIII	1 : 2.000.000	>30%	PDC, Recombinant FXIII, Cryoprecipitate, FFP

*Prevalence is higher in countries with consanguinity.
†Asymptomatic levels based on EN-RBD study.
‡Mild (heterozygous) forms are more frequent.

PDC, plasma derived concentrate; FFP, fresh frozen plasma, PCC, prothrombin complex concentrate.
Adapted from Cassini A, et al. 2024 and Peyvandi F, et al. 2012.[9,15]

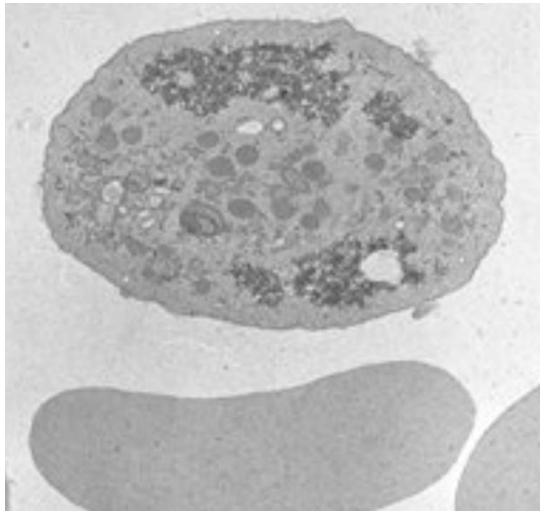
Lambert C. BJH 2025

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.

INHERITED PLATELET DISORDERS (IPD)



Three Major Categories of Inherited Thrombocytopenias

Isolated thrombocytopenias

Mainly low platelets, often with platelet dysfunction.

- **Bernard-Soulier syndrome**
- **Gray platelet syndrome**
- ***FLI1*-related thrombocytopenia**

Syndromic thrombocytopenias

Thrombocytopenia associated with extra-hematologic or systemic features.

- **Jacobsen syndrome / Paris-Trousseau thrombocytopenia**
- **TAR syndrome** (thrombocytopenia with absent radii)
- **Wiskott-Aldrich syndrome** (immunodeficiency, eczema)

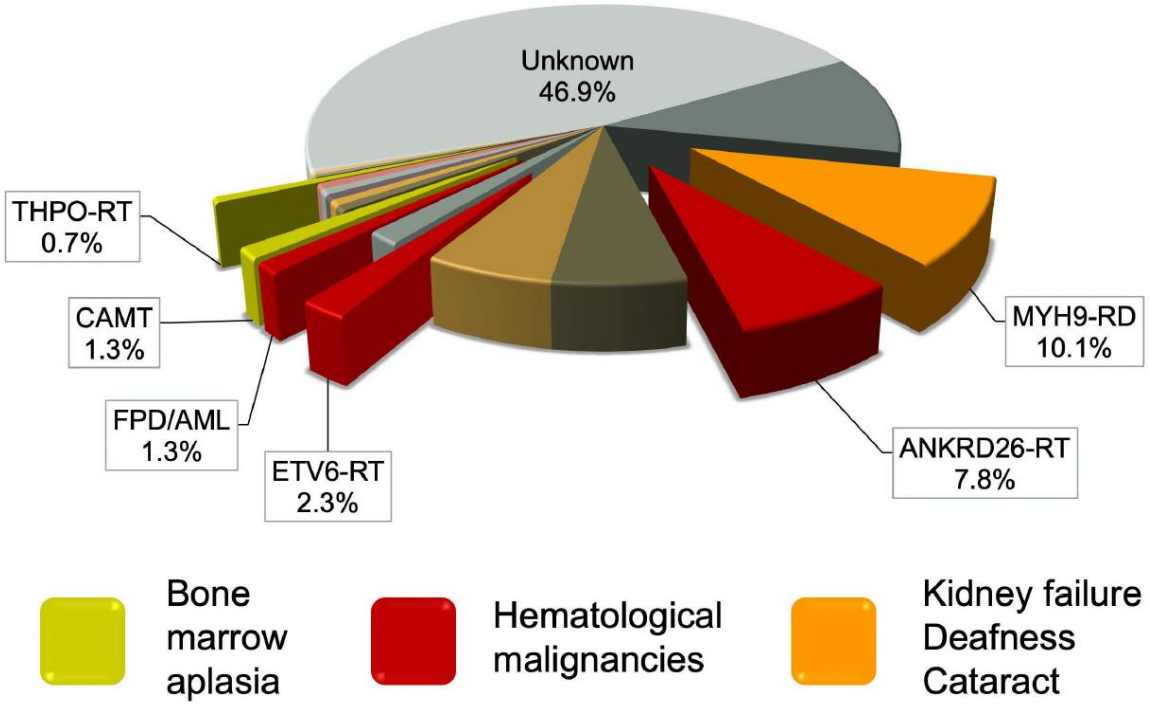
Thrombocytopenias predisposing to additional diseases

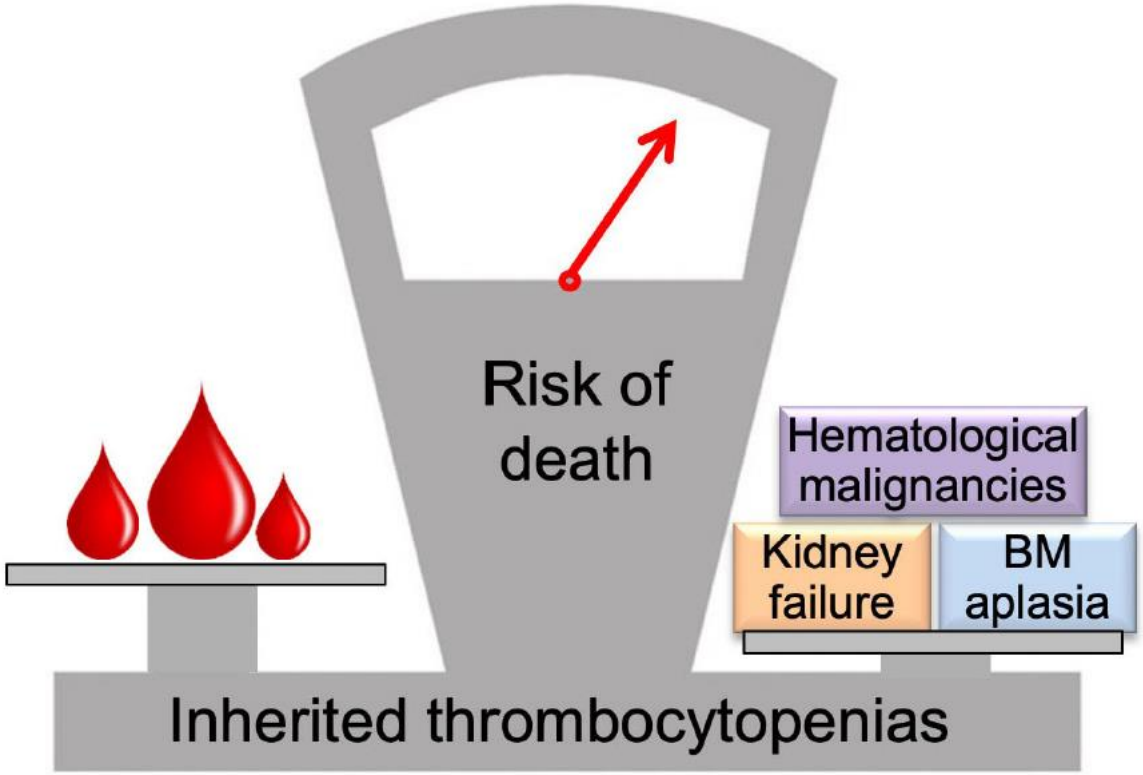
Associated with risk of organ disease or hematologic malignancy.

- ***MYH9*-related disease** (e.g., kidney/hearing involvement)
- ***RUNX1*-related familial platelet disorder** (leukemia predisposition)
- ***ETV6*-related thrombocytopenia** (risk of hematologic malignancy, particularly in childhood)

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INHERITED PLATELET DISORDERS





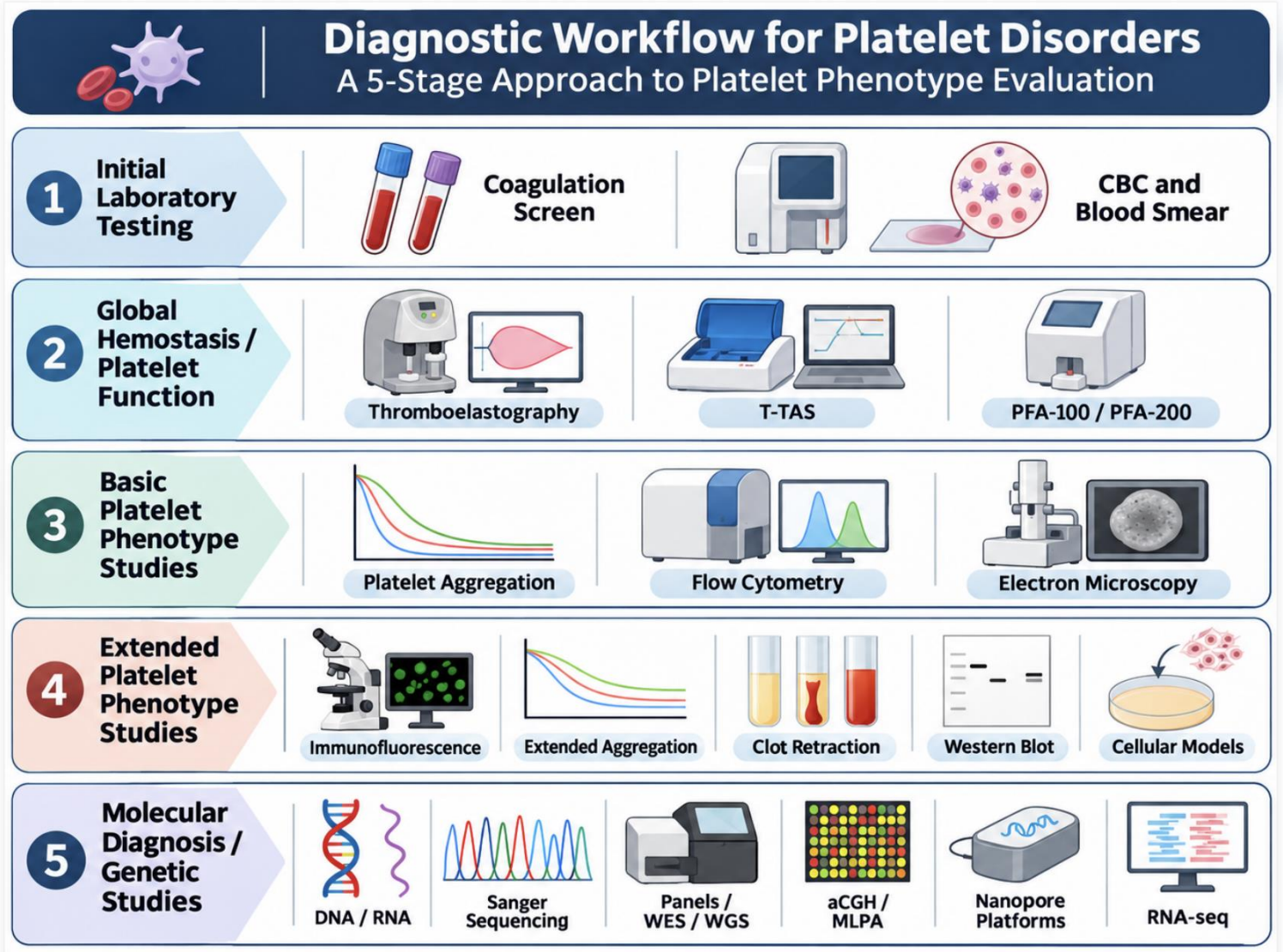
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TREATMENT OPTIONS FOR IPD

	Indications
Platelet transfusions	All inherited thrombocytopenias. To stop bleedings when local measures failed. To prepare patients for surgery
Splenectomy	-Wiskott–Aldrich syndrome -X-linked thrombocytopenia
TPO-receptor agonists	Preparation for hemostatic challenges of patients with: - *MYH9*-related disease - Wiskott–Aldrich syndrome/X-linked thrombocytopenia - monoallelic Bernard-Soulier syndrome - *ANKRD26*-related thrombocytopenia
	Variant of congenital amegakaryocytic thrombocytopenia (*THPO* mutation)
Hematopoietic stem cell transplantation	-Wiskott–Aldrich syndrome -Congenital amegakaryocytic thrombocytopenia (*MPL* mutation) -Severe Bernard-Soulier syndrome -*MECOM*-associated syndrome
Gene therapy	-Wiskott–Aldrich syndrome

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DIAGNOSIS OF INHERITED PLATELET DISORDERS

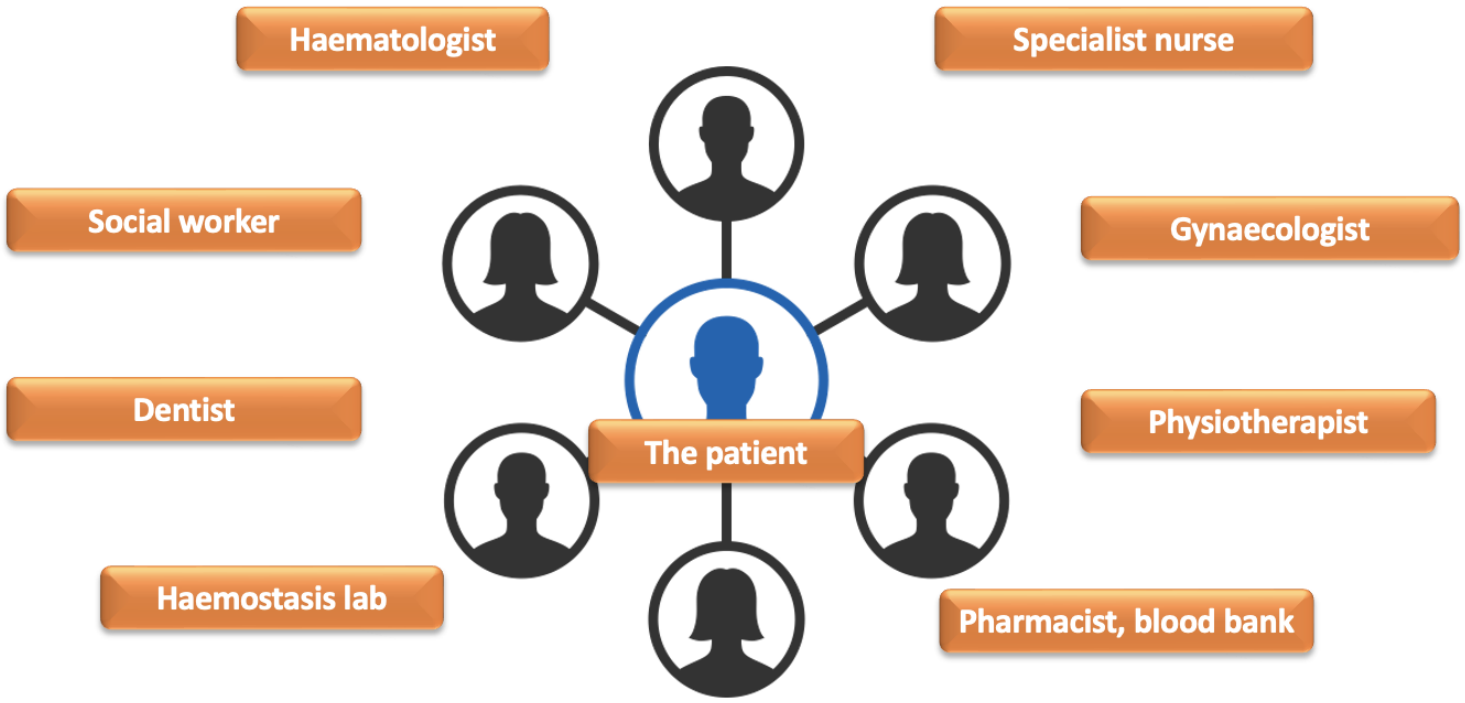


Ana Sánchez-Fuentes, et al. Biomolecules 2025, *15*(6), 846

PRINCIPLES OF CARE IN INHERITED BLEEDING DISORDERS

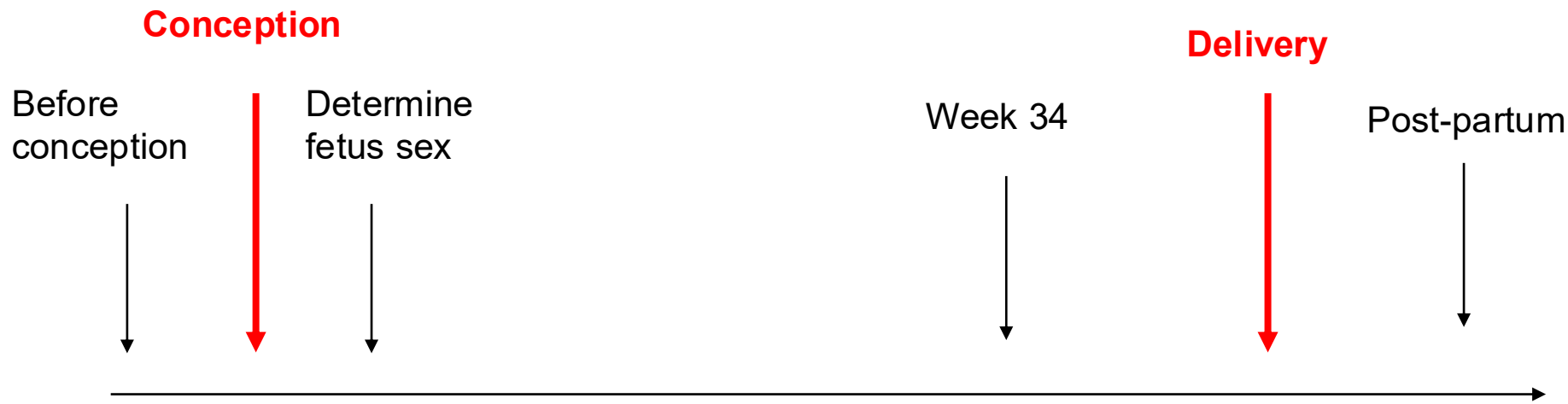
Comprehensive and multidisciplinary care – individualized care plan

- 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
- Neuraxial analgesia ?

- Control post-partum bleeds
- Screen neonate

Image developed by the speaker

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Thank you for your attention