

100 YEARS OF VON WILLEBRAND DISEASE- Past, Present and Future

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2021 Von Willebrand disease guidelines

11 diagnosis recommendations covering-

- The role of bleeding assessment tools (BAT) in the assessment of patients suspected of VWD
- Diagnostic laboratory cut-offs for type 1 and type 2 VWD
- The role of genetic testing vs. phenotypic assays for types 2B and 2N
- The reconsideration, rather than simple removal, of a type 1 VWD diagnosis, should VWF levels normalize over time

8 management recommendations covering-

- Prophylaxis for severe and frequent bleeds
- Desmopressin (DDAVP) trials to determine therapy
- Use of antithrombotic therapy (antiplatelet agents and anticoagulant therapy)
- Target VWF and factor VIII activity levels for major surgery
- Strategies to reduce bleeding during minor surgery or invasive procedures
- Management options for heavy menstrual bleeding
- Management of VWD in the context of neuraxial anaesthesia during labour and delivery
- Management in the postpartum setting with tranexamic acid



Portrait of Erik von Willebrand (1870–1949).
Reproduced with permission from John Wiley and Sons [2].

ORIGINALARTIKLAR.

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

Hereditär pseudohemofili.

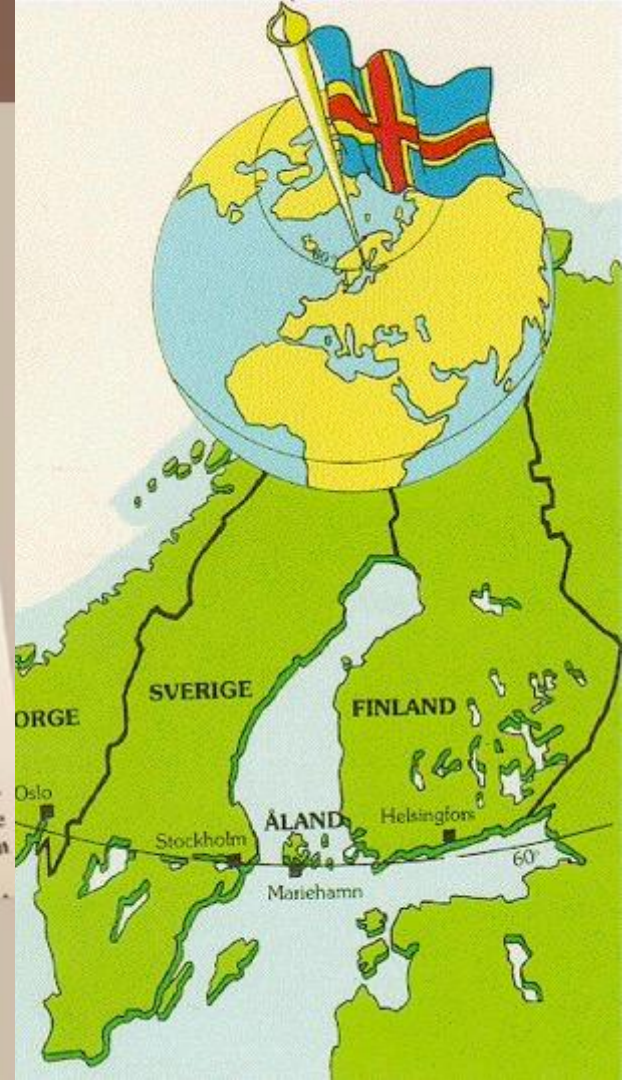
Av

E. A. v. Willebrand.

(Med 3 figurer i texten.)

Sjukdomsbegrepp. Tidigare observerade fall.

En nya stora arbete över de hemorragiska diateserna fram-
E. FRANK (Breslau), att den klassiska hemofilien är en
visit hereditär—familjär anomal, att det kan ifråga-
huruvida över huvud sporadiska fall av sjukdomen
ra. Däremot är, säger han, den klassiska trombopenien
räglat sporadisk, att man kan diskutera, om en familjär
av densamma alls förekommer. Med trombopeni avses
en sjukdom, som sedan gammalt bär namnet morbus macu-
WERLHOPI eller purpura haemorrhagica och som på senaste
v FRANK och en del andra forskare betecknats såsom
entiell trombopeni.



100 YEARS of VON WILLEBRAND DISEASE

TIMELINE

1926

First VWD patient reported

1950s

FVIII assay becomes available

1971

VWF purified by Zimmerman et al.

1977

Desmopressin first used for hemostasis

1985

VWF gene sequenced

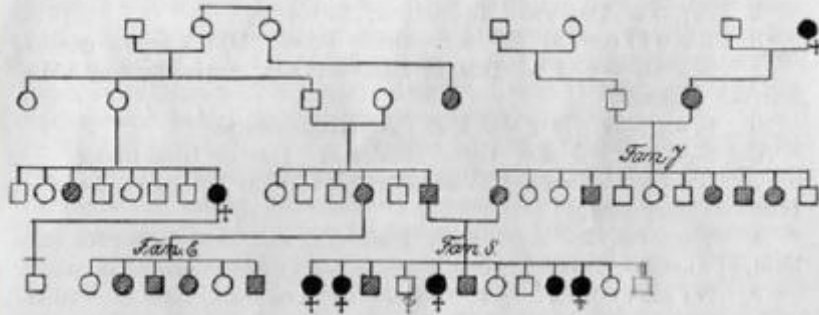
1999

First plasma-derived VWF product licensed for VWD treatment

2015

First recombinant VWF licensed in the US

Ätändsk blödersläkt



□ man, ○ kvinna, icke-blödersjuk, ■ man, ● kvinna med lindrig blödersjuk, ● kvinna med svår blödersjuk, + död av förblödning

Fig. 2.

► 1924- a 5 y/o girl Hjordis Sundblom, 9th of 11 children referred to Erk von Willebrand with bleeding time of 2 hours!

► 1993- researchers identified a single cytosine deletion in exon 18 of VWF in surviving family members



VON WILLEBRAND DISEASE

An Illustrated Review

Mouhamed Yazan Abou-Ismaïl, Peter Kouides, Paula James, Nathan Connell

INTRODUCTION



Von Willebrand disease (VWD) is the most common hereditary bleeding disorder, characterized by a quantitative or qualitative deficiency in von Willebrand factor (VWF), a large, multimeric glycoprotein that plays an essential role in hemostasis. **This comprehensive illustrated review covers the pathophysiology, evaluation, diagnosis, management, challenges, and evolving therapeutics in VWD.**



Abou-Ismaïl MY, Kouides PA, James PD, Connell NT. von Willebrand disease: an illustrated review. Res Pract Thromb Haemost. 2026 Jul 11;10(5):106838. PMID: 42598104; PMCID: PMC13471213.

The Past: 1957-Marie Inge Nissen and Margreta Blomback described a plasma fraction that corrected both FVIII and bleeding time

The Present:

VWF has 3 major binding partners involved in the primary and secondary stage of hemostasis. Which of the following is not a binding partner?

A. Platelets

B. FVIII

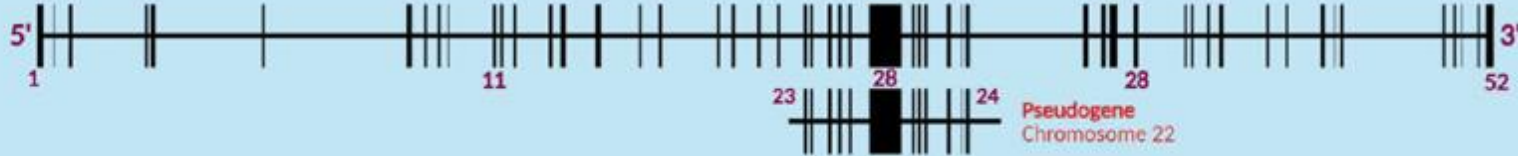
C. Collagen

D. Fibronectin

The Present Understanding of VWF from Gene to Protein

VWF GENE

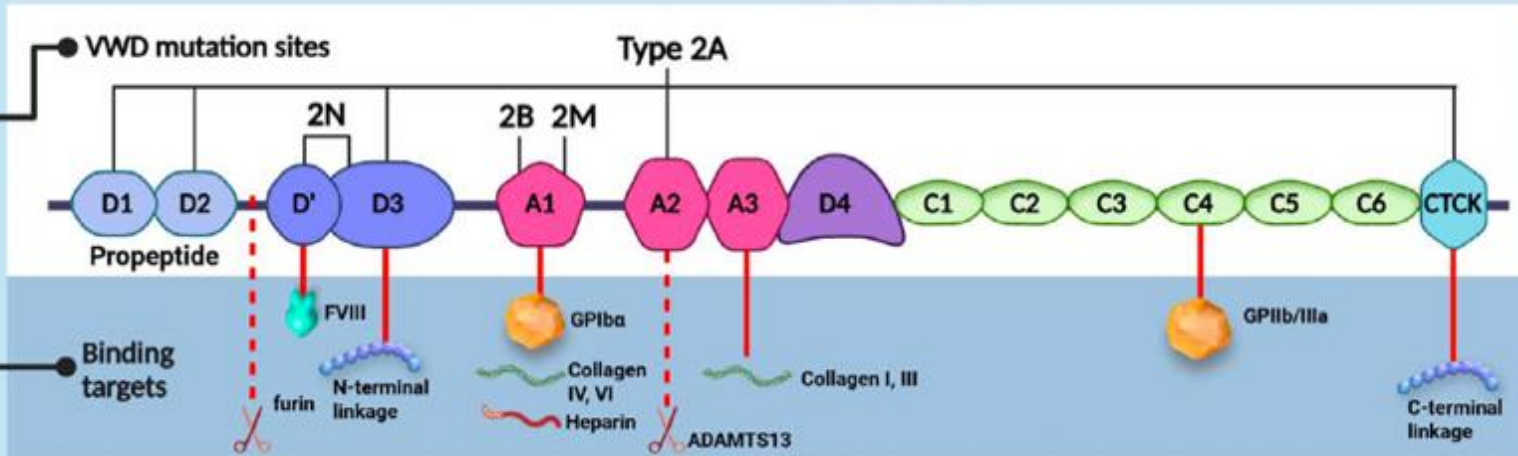
The *VWF* gene is located on chromosome 12p13.3, and spans around 178 kb.



It is highly polymorphic, with >4,000 estimated polymorphisms and >900 pathogenic variants.

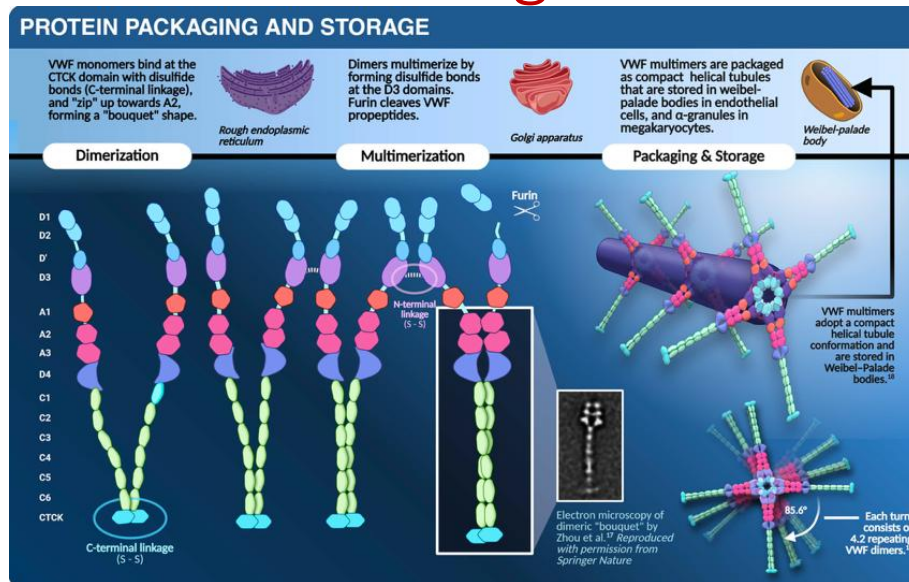
It contains 52 exons coding a polypeptide protein of 2813 amino acids.

VWF is fundamentally an adhesive protein that binds multiple targets.



The Present Understanding of the VWF life cycle

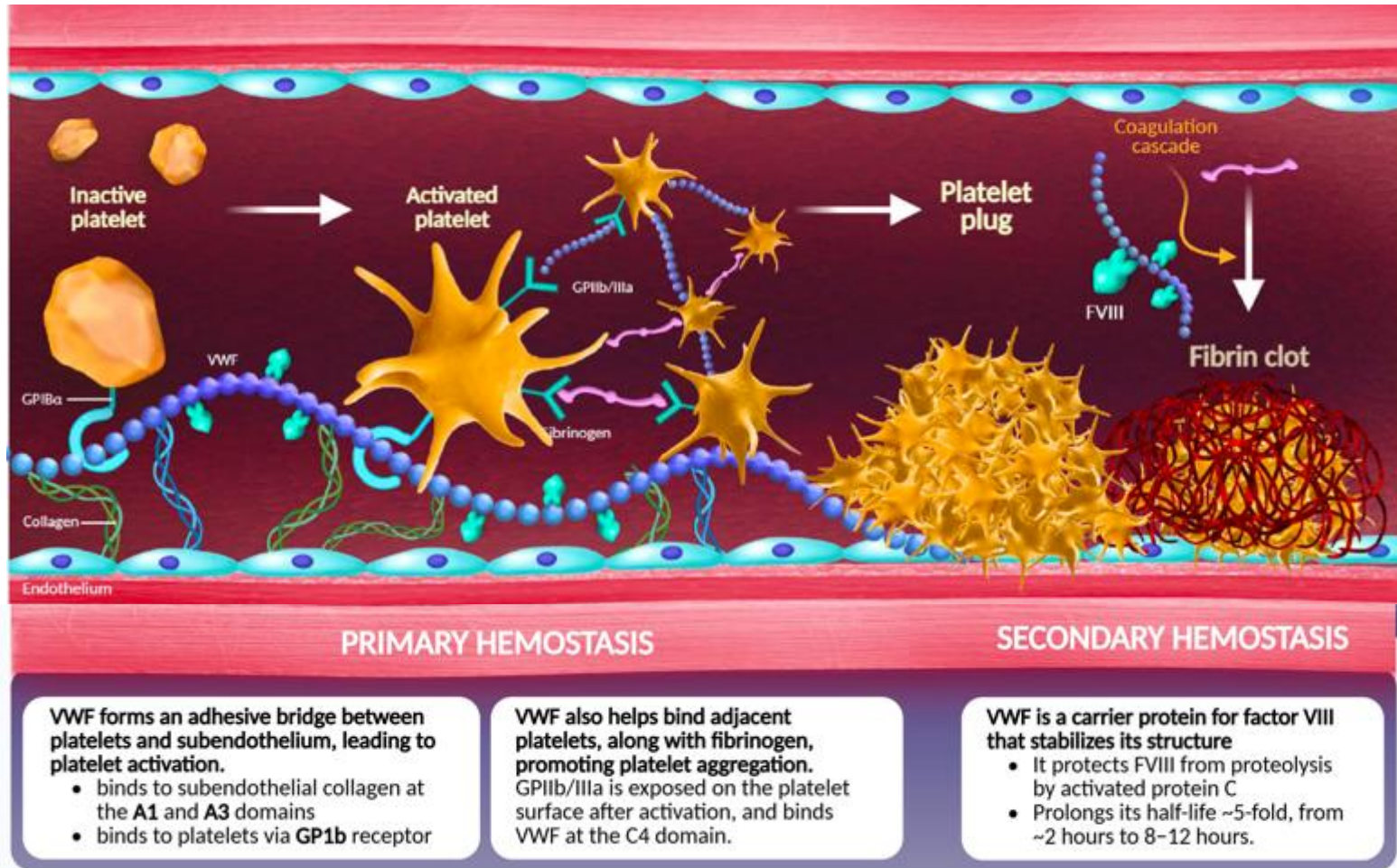
1. Synthesis
2. Protein packaging and storage
3. Secretion
4. Clearance



SECRETION



The Present Understanding of the Physiology of VWF in Hemostasis



The Past: 1994 International Society of Hemostasis and Thrombosis proposed a classification of VWD

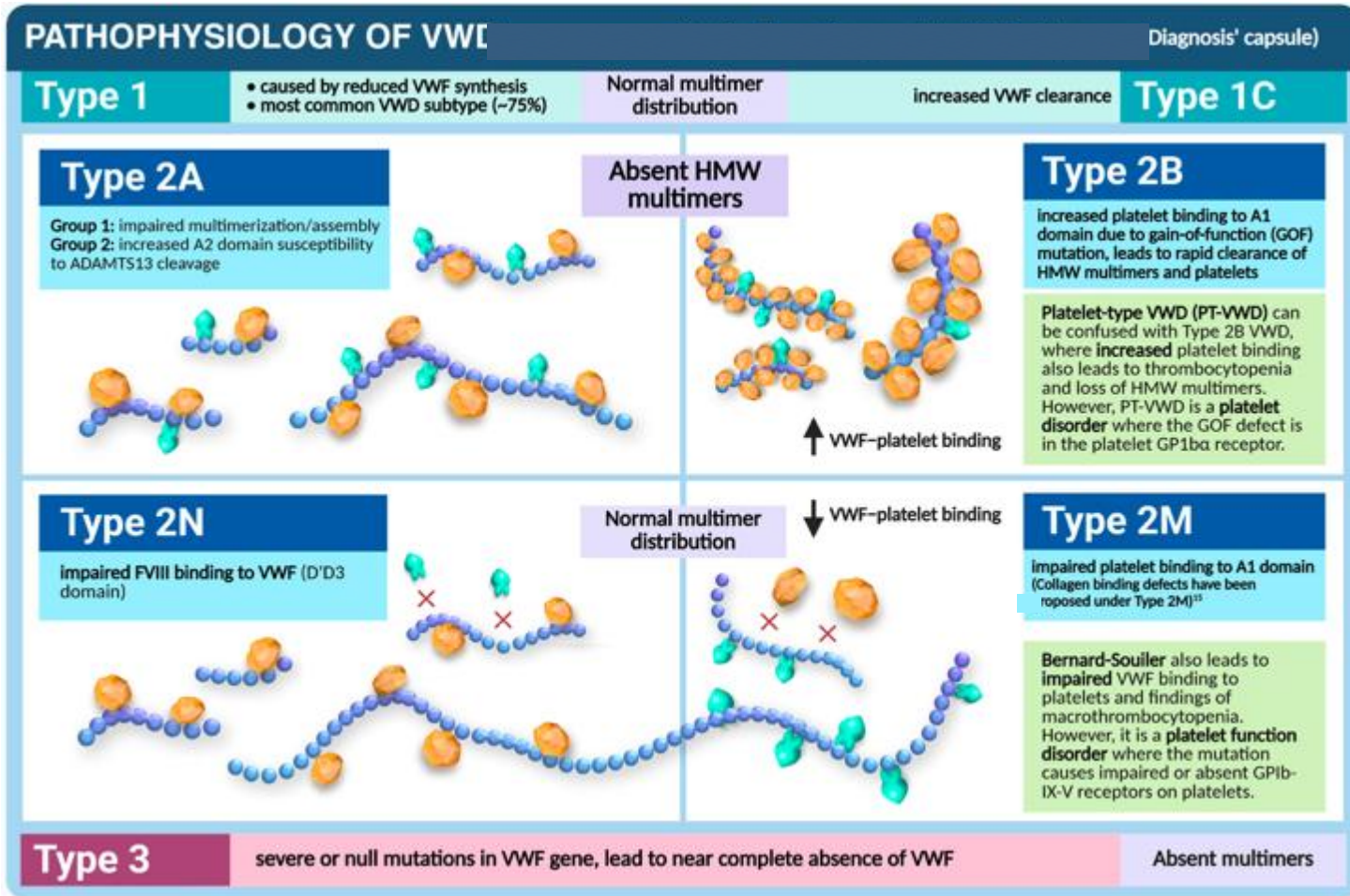
Present Concept: VWD is an Absolute or Functional deficiency

i.e. Quantitative or Qualitative i.e.. Hypo/aproteinemia (Type1/3) or Dysproteinemia (Type 2)

Type 1	Partial quantitative VWF deficiency (75% of symptomatic patients with VWD)	Reduction in all multimers but normal function & composition of multimers
Type 2A	Decreased VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers	
Type 2B	Increased affinity for platelet GP1b	Qualitative deficiency due to loss of HMW multimers or loss of function despite normal multimer #
Type 2M	VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight ↓ multimers	
Type 2N	Markedly decreased binding affinity for FVIII	
Type 3	Virtually complete deficiency of VWF (severe, rare)	Complete reduction of multimers

The Present Understanding of the VWD Subtypes

- **A** = **A**bsent multimers
- **B** = increased platelets **b**inding
- **M** = **M**ad at the platelets
- **N** = **N**o binding to factor VIII



The Past: 6 subtypes of VWD

The Future....is now!- a 7th was added- Type 1C

Received: 31 July 2025 | Revised: 29 January 2026 | Accepted: 5 February 2026

<https://doi.org/10.1016/j.jth.2026.02.010>

ISTH SSC COMMUNICATIONS

jth

Recommendation to adopt the type 1C VWD nomenclature into the classification of von Willebrand disease: communication from the ISTH Scientific and Standardisation Subcommittee on von Willebrand Factor

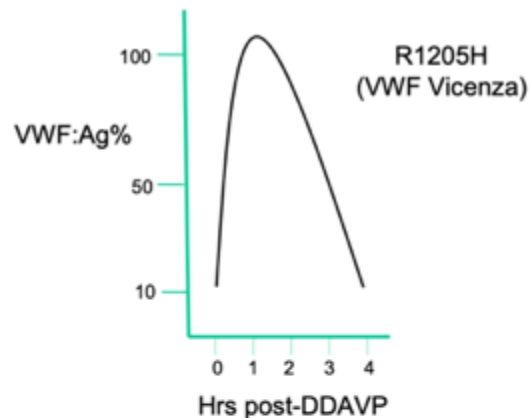
Christopher J. Ng¹ | Ross I. Baker^{2,3,4} | Michelle Lavin^{5,6} | Sandra L. Haberichter⁷

J Thromb Haemost. 2026 Jul;24(7):2656-2660.

PMID: 41786033.

Type 1C

- Dominant (highly penetrant)
- ~10-15% of Type 1 VWD
- Missense mutations (eg. R1205H)
- VWF:Ag <30% often <15%
- VWF:pp to VWF:Ag ratio >3 up to >10
- Subtly abnormal VWF multimer profiles



- Exaggerated DDAVP response >4-fold up to 10-fold
- Short term benefit from DDAVP (2-4 hrs)
- Plasma VWF half-lives <3 hrs

The Past: VWD was termed pseudohemophilia

The Present: We Now Know Its 5-10 times more common than hemophilia

PREVALENCE

VWD is considered the most common hereditary bleeding disorder, with an estimated prevalence of 1% based on population screening studies. However, its true prevalence remains difficult to ascertain; different analysis methods show largely different estimates:

Genetic Prevalence



Global estimates of genetic prevalence using genomic databases suggest higher prevalence, likely owing to undiagnosed cases and variable penetrance.³

Type 1	2A	2B	2M	2N	3
10.6 /1000	1.3 /1000	1.7 /1000	1.5 /1000	33.9 /10 ⁴	1.3 /10 ⁴

Overall VWD

~1.5%

Population Screenings



Early screening studies in pediatric subjects identified a prevalence of 1% in Italy.^{4,5} A majority in both studies had Type O blood.

1987: Based on low VWF levels + family history of bleeding.⁴ A follow-up identified personal bleeding symptoms in 10% only.⁶

1993: Low VWF levels + personal history of bleeding symptoms + family history.³

~1%

Symptomatic VWD

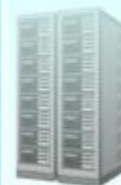


Estimates vary due to variable settings and definitions of abnormal bleeding.

The aforementioned Italian studies reported rates of 0.1% and 1%^{5,6}. A Canadian study evaluating estimates based on primary care setting evaluations also showed 0.1% prevalence.⁷

~0.1%

Worldwide Registries



Global registries likely grossly underestimate the prevalence of VWD due to undiagnosed and underreported cases, as well as resource limitations.

Prevalence varies widely by income status and geographic location,^{8,9} ranging between:

~1-60 /million

DIAGNOSTIC BARRIERS

VWD likely remains grossly underdiagnosed worldwide owing to several challenges:¹⁰



Under-recognition



Access to resources



Complex diagnosis



Limited awareness



Wolfgang Miesbach · 1st

To address the complexity of coagulation disorder...

1w ·

🔴 In 1924 a five-year-old girl, Hjördis Sundblom, was brought from Föglö in the Åland archipelago to Erik von Willebrand. Ninth of eleven children; three siblings had already bled to death. Her bleeding time: two hours. 📖 In 1926 he published "Hereditär pseudohemofili". Finska Läkaresällskapets Handlingar, 26 pages.

🕒 Hjördis died at fourteen, during her fourth menstrual period.

🧬 Her cause of death took another 60 years to name: a single cytosine deletion in exon 18 of VWF, found in the surviving family in 1993.

📄 A century on, VWD is the most common inherited bleeding disorder — yet Europe registers ~51 patients per million against an expected ~1,000. Roughly one in twenty is found.

🕒 In a CDC survey, women with VWD waited an average of 16 years from first symptoms to diagnosis — most first told they had heavy periods or iron deficiency.

🕒 Von Willebrand described the disease before he could treat it. We can treat it and still fail to find it. Which story will 2126 tell about us?

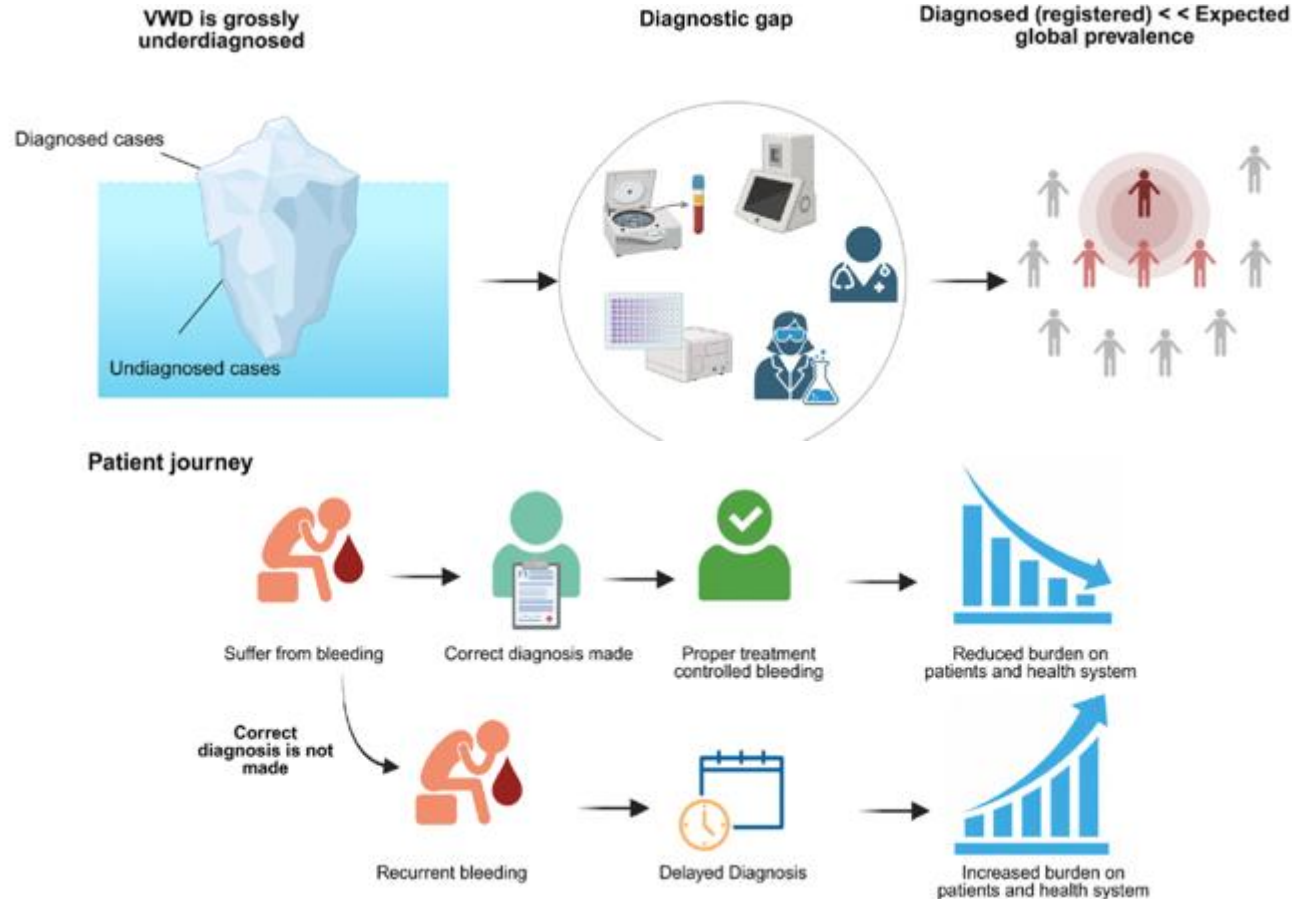
[#VWD](#) [#vonWillebrandDisease](#) [#BleedingDisorders](#)

[#WomenWithBleedingDisorders](#) [#Haemostasis](#)

[#Haematology](#) [#RareDisease](#)

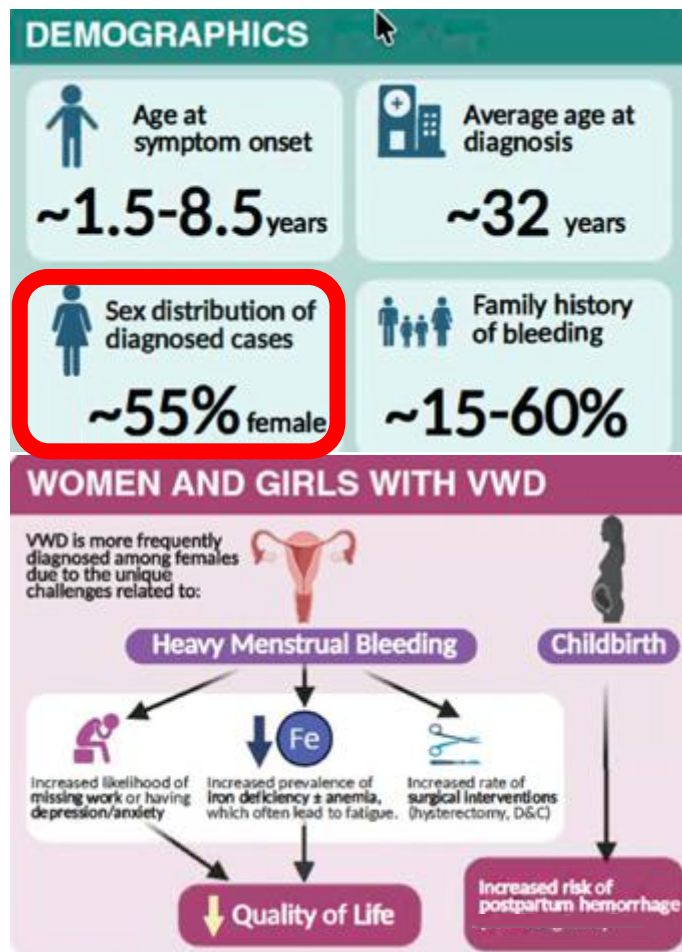
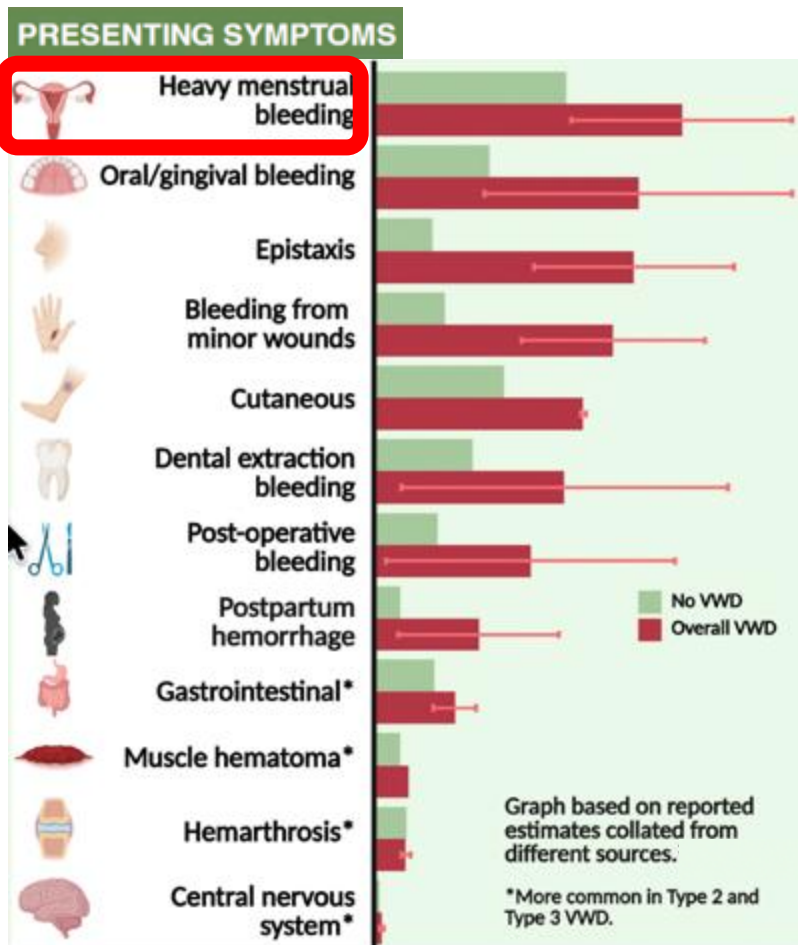


The Future: Increasing Awareness of VWD



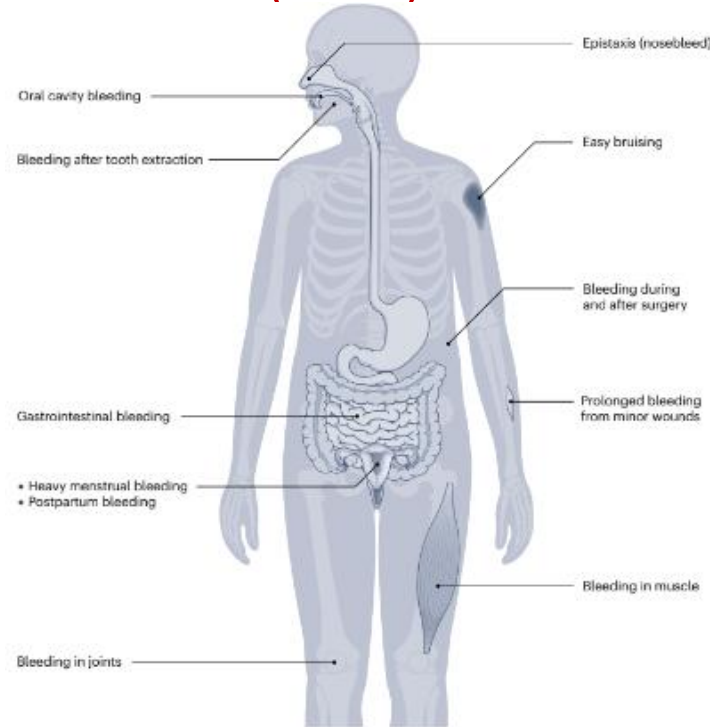
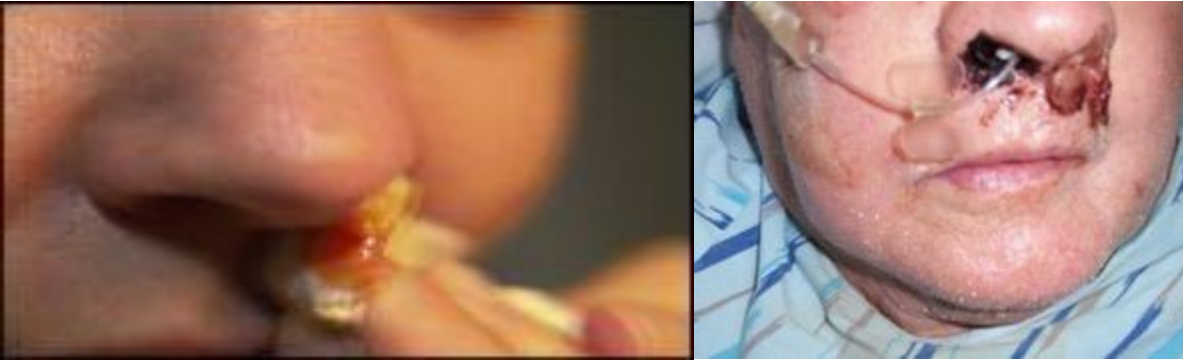
*Seidizadeh O et al
Beyond a century of
discovery: the global
and persistent burden
of underdiagnosis in
von Willebrand
disease. Res Pract
Thromb Haemost.
2026 Jan
20;10(1):103359.
PMID: 41732305;*

The Present Clinical Landscape of VWD



The Recent Past: Subsequent development of a standardized ISTH bleeding assessment tool (BAT)

- Well defined symptom (eg. epistaxis 5/year or > 10 min)
- Summing the symptoms/cumulative score
- Grading the symptom based on degree of intervention



Evolution of the ISTH Bleeding Assessment Tool (BAT)

<https://bleedingscore.certe.nl/>

Also available in MedCalc

Epistaxis	
0	No or trivial (<5)
1	>5 or more than 10
2	CONSULTATION ONLY
3	Packing or cauterization or antifibrinolytics
4	Blood transfusion or replacement therapy or desmopressin

Cutaneous	
0	No or trivial (<1 cm)
1	>1 cm and no trauma
2	CONSULTATION ONLY

Bleeding From Minor Wounds	
0	No or trivial (<5)
1	>5 or more than 5
2	CONSULTATION ONLY
3	Surgical hemostasis
4	Blood transfusion or replacement therapy or desmopressin

Oral Cavity	
0	No
1	Reported at least one
2	CONSULTATION ONLY
3	Surgical hemostasis or antifibrinolytics
4	Blood transfusion or replacement therapy or desmopressin

GI Bleeding	
0	No
1	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia
2	Spontaneous
3	Surgical hemostasis or blood transfusion or replacement therapy or desmopressin or antifibrinolytics

Tooth Extraction	
-1	No bleeding in at least 2 extractions
0	Not done or no bleeding in 1 extraction
1	Reported in <25% of all procedures
2	Reported in >25% of all procedures, no intervention
3	Resuturing or packing
4	Blood transfusion or replacement therapy or desmopressin

Surgery	
-1	No bleeding in at least 2 surgeries
0	Not done or no bleeding in 1 surgery
1	Reported in <25% of all surgeries
2	Reported in >25% of all surgeries, no intervention
3	Surgical hemostasis or antifibrinolytics
4	Blood transfusion or replacement therapy or desmopressin

Menorrhagia	
0	No
1	CONSULTATION ONLY
2	Antifibrinolytics or pill use
3	Curettage or iron therapy
4	Blood transfusion or replacement therapy or desmopressin or hysterectomy

Postpartum Hemorrhage	
-1	No bleeding in at least 2 deliveries
0	No deliveries or no bleeding in 1 delivery
1	CONSULTATION ONLY
2	Curettage or iron therapy or antifibrinolytics
3	Blood transfusion or replacement therapy or desmopressin
4	Hysterectomy

Muscle Hematoma	
0	Never
1	Post-trauma no therapy
2	Spontaneous no therapy
3	Spontaneous or traumatic requiring desmopressin or replacement therapy
4	Spontaneous or traumatic requiring surgical intervention or blood transfusion

Hemarthrosis	
0	Never
1	Post-trauma no therapy
2	Spontaneous no therapy
3	Spontaneous or traumatic requiring desmopressin or replacement therapy
4	Spontaneous or traumatic requiring surgical intervention or blood transfusion

CNS Bleeding	
0	Never
1	—
2	—
3	Subdural, any intervention
4	Intracerebral, any intervention

1 pt= symptom (rigorously defined)



2 pts= sought provider attention



3 pts= underwent provider intervention



4 pts= underwent transfusion or surgery

Rodeghiero et al, JTH 2005; 3:1-9

A 15 year old female is referred from the Emergency Room for suspected VWD after presenting with epistaxis requiring packing. She also reports heavy menses changing her sanitary pad every 90 minutes since menarche at age 13. She also reports “easy” bruising throughout childhood and prolonged bleeding from cuts. What is her bleeding score per the ISTH Bleeding Assessment Tool?

A. 3 points

B. 5 points

C. 8 points

D. 10 points

Answer C:

• Bleeding score can be calculated as follows:

- ☐ 1 point for easy bruising,
- ☐ 1 point for prolonged bleeding from cuts,
- ☐ 3 points for epistaxis requiring packing,
- ☐ 3 points for heavy periods since menarche.

Normal bleeding score for adult females is 0-5.
Such patients should undergo VWF testing.

The Present:

Initial evaluation of patient 1: My Clinical Pearls

- Be able to do bleeding score in your sleep
 - And short version in parents and sibs
- Ask for s/s in consideration of Hypothyroidism
 - Low thyroid hormone can decrease VWF biosynthesis
- Take good history for superimposed medications/OTCs causing platelet dysfunction

"A > H"

- **A**SA
- **B**eta lactams
- **C**lopidogrel
- anti-**D**epressants
- Vitamin **E**
- **F**lavinoids
- **G**ingko
- and other **H**erbs: garlic, birberry, ginger,ding quai, ginseng, turmeric, meadowsweet, willow
 - Besides anti-platelet meds and herbs, know about coumarin containing herbs-motherwort, chamomile, horse chestnut,red clover, fenugrek

The Present: The initial “core” tests of someone with suspected VWD (at Rochester General Hospital)

- A. CBC, PT, PTT, fibrinogen, VWF:RCo, VWF antigen, FII, FV, FVIII, closure time
- B. CBC, PT, PTT, fibrinogen, VWF:RCo , VWF antigen, FVIII, bleeding time
- C. CBC, PT, PTT, fibrinogen, VWF:RCo, VWF antigen, FVIII, closure time
- D. CBC, PT, PTT, fibrinogen, VWF:RCo, VWF antigen, FVIII, closure time, VWF multimers

Laboratory testing of VWF activity over the years

Past (poor coefficient of variation)- VWF:RCo

- Patient Plasma plus
- ~~Lyophilized Platelets~~ as as Gp1b source plus
- Ristocetin (to promote platelet agglutination) then measure agglutination

Present- VWF-Gp1bR

- Patient Plasma plus
- recombinant GP1b immunologically bound to latex or magnetic particles
- Add ~~ristocetin~~ and patient plasma, measure agglutination

Present/Future (now NYS approved)- VWF-Gp1bM

- Patient Plasma plus
- recombinant gain of function GP1b immunologically bound to latex or magnetic particles

LOWEST COEFFICIENT OF VARIATION

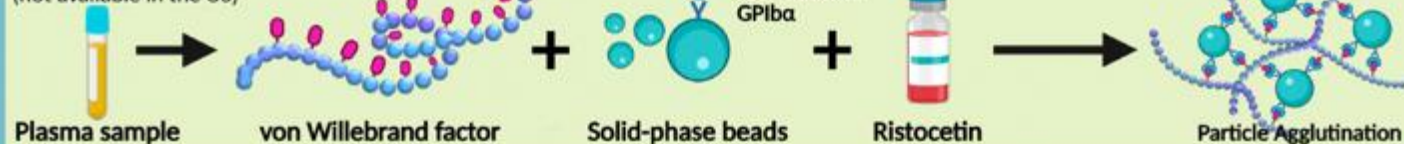
The Present Evolution of VWF-Platelet Binding Assays: “VWF activity”

VWF platelet-binding activity

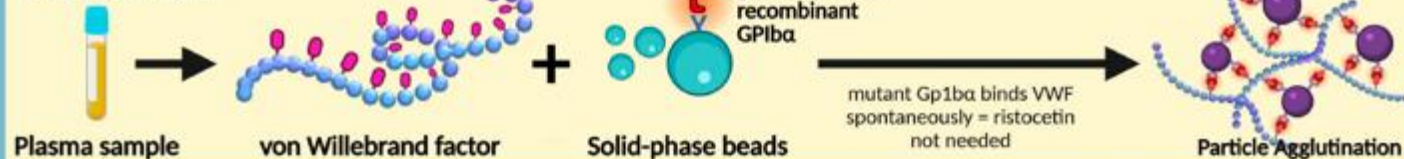
VWF:RCo



VWF:GPIbR (not available in the US)



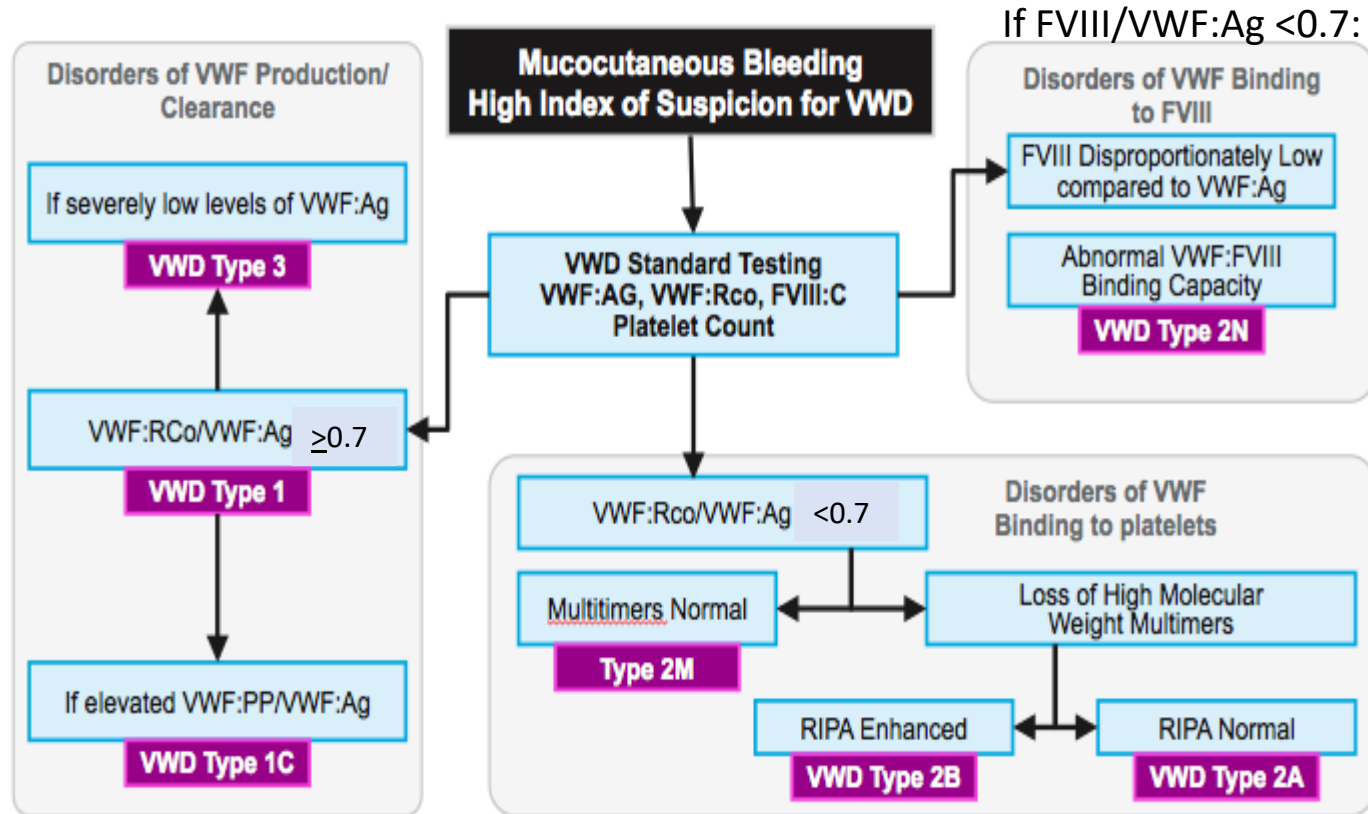
VWF:GPIbM



VWF:GPIbM & VWF:GPIbR are preferred over VWF:RCo whenever available

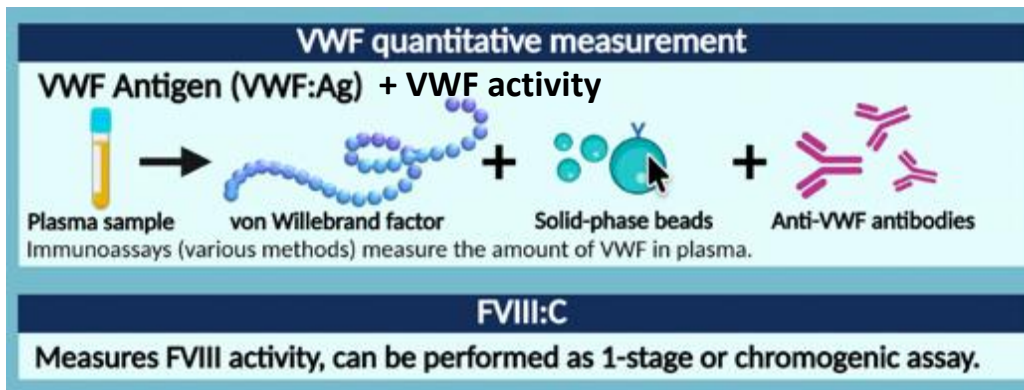
- excellent coefficient of variation = 5.6%
- greater precision
- more sensitive lower limit of detection (0.2 IU/mL)
- unaffected by p.D1472H variant

The Present algorithmic approach to laboratory testing- if VWF level < 50% then calculate 2 ratios- VWF activity(VWF RCo)/ VWF:Ag and FVIII/VWF:Ag...

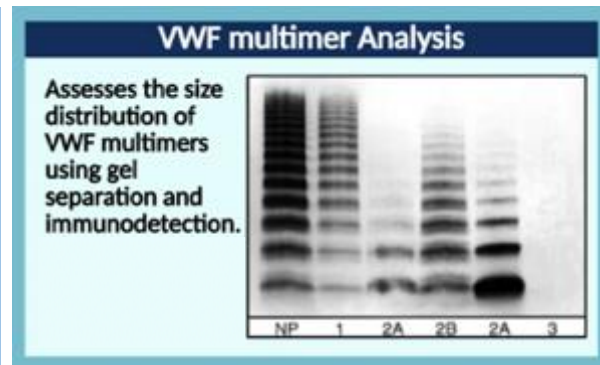


VWF testing sequence: VWF profile>multimers>CB activity> RIPA etc.

First Line



If VWF act/Ag <0.7



If VWF act/Ag <0.7

Collagen-binding activity (VWF:CB)

VWF:CB/VWF:Ag ratio can serve as a surrogate for **multimer analysis**.
VWF:CB testing may also identify **collagen binding defects**:



Variants that impair the ability of VWF to bind collagen have been identified, and may cause abnormal bleeding.^{27,28}

- **VWF A1 domain binding variant** (more common): may be detected using type IV/VI collagen assays
- **VWF A3 domain binding variant** (less common): may be detected using type I/III collagen assays

What if VWF:CB is the only abnormality, while VWF:Ag and platelet-binding activity are normal?

There is currently no consensus on whether this constitutes VWD, but some consider it to be a unique subtype within Type 2M VWD.

Ancillary Tests

- Useful in specific scenarios**
- **Ristocetin-Induced Platelet Aggregation (RIPA)**: positive aggregation to low-dose ristocetin helps identify Type 2B VWD.
 - **VWF:FVIII binding**: decreased FVIII binding helps identify Type 2N VWD.
 - **VWF propeptide (VWF:pp)**: elevated VWF:pp/VWF:Ag ratio reflects increased clearance, seen in Type 1C VWD.

My Clinical Pearls of VWD Testing

- Do not stop COC as present formulations are too low of a dose to raise VWF levels to any degree of clinical significance
- We need to convince insurers to cover on site testing and have them stop trying to save money by sending it to national laboratories 3000 miles away!
- Remember VWF is an acute phase reactant so be aware of present state of health when testing
- Consequently, if levels $>50\%$ but $<100\%$ we and others have shown that there is only 5% chance on re-resting levels may be $< 50\%$ so in general we do not test if levels $> 100\%$

The Present Understanding of Variables Affecting VWF levels

AGING: 5 studies, N=461 total Type 1/Low VWF

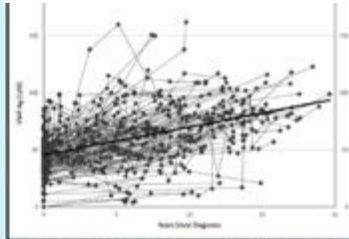
In ~20-30% of Type 1 VWD patients, VWF may normalize with age due to physiological increases in VWF

?

It remains unclear whether this ameliorates bleeding symptoms or not.

- The diagnosis may be reconsidered in some patients, and they may no longer require hemostatic interventions.
- Other patients may still have bleeding symptoms, potentially requiring hemostatic interventions or supranormal VWF levels.

2018 Rochester NY study AJH.
2018 Feb;93(2):232-237



VWF:Ag rise with age. Abou-Ismaïl et al.⁶⁸ Reproduced with permission from John Wiley and Sons.

	↑ 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 Inflammation eg. trauma, infections, acute illness, obesity, inflammatory conditions	Liver Disease Anemia eg. acute blood loss from HMB Hypothyroidism Cardiac Disease eg. aortic stenosis, severe mitral regurgitation Autoimmune Disease Neoplasms* Acquired VWS may occur secondary to MPNs, Wilms tumor, paraneoplastic antibodies. *Conversely, other neoplasms may elevate VWF due to inflammation

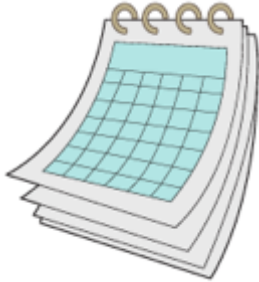
Schaefer BA, Cheng D, Kouides P. Impact of obesity on factor VIII and von Willebrand factor levels in patients with Type 1 von Willebrand disease and low von Willebrand factor: An analysis of the ATHN dataset. *Haemophilia*. 2022 Jan;28(1):109-116. PMID: 34874087

Moving Forward into the Future....



So how often should we check VWF levels in type 1 VWD and low VWF?

And to reiterate, stop insurers from mandating send out laboratory testing!! Insist on lab app't at WNY Hemophilia Center!!



Consider repeating VWF panel every 3-5 years, and reconsider treatment plan based on the levels especially in older patients pre-operatively



Preanalytical process

Preanalytical problem



Sample collection

- Identification errors
- Inappropriate procedure
- Inappropriate device
- Inappropriate volume

Sample handling

- Sample mixing

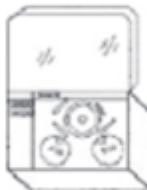


Sample transportation

- Temperature
- Time
- Conditions

Sample storage

- Temperature
- Time
- Thawing



Sample preparation

- Centrifuge temperature
- Centrifuge time
- Centrifuge speed
- Plasma stratification

*Preston et al, Quality issues in laboratory haemostasis, Haemophilia 2010;
Favaloro et al., Am J Clin Pathol 2004; Favaloro et al, Semin Thrombo Hemost 2008
Lipton R Haemophilia (2003), 9:235-236
Jaffray J, Am J Hematol. 2020; 95(9)1022-1029.*

Ideal VWD testing environment- On-site Coagulation Lab

- Phlebotomy, processing and analysis occurring in a timely manner
 - **Most important aspect is prompt processing**
- Most insurers necessitate testing be performed at outside laboratories
 - Increased likelihood of inappropriate processing
 - False positive VWD diagnosis
- Multi-center study in 2020 showed assays increased within normal range in 30-50% of subjects when re-tested at on-site laboratories
- Consequences of misdiagnosing VWD-
 - Inappropriate interventions
 - Inadequate therapy
 - Increased healthcare costs
 - Unnecessary stress to patients and families
 - Repetitive VWD testing

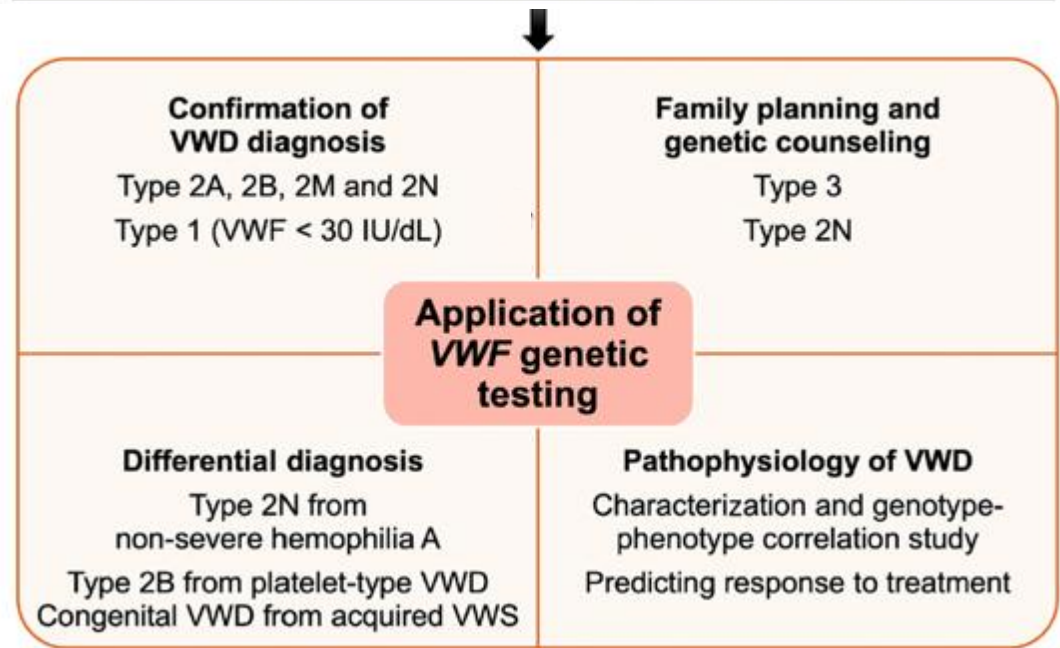
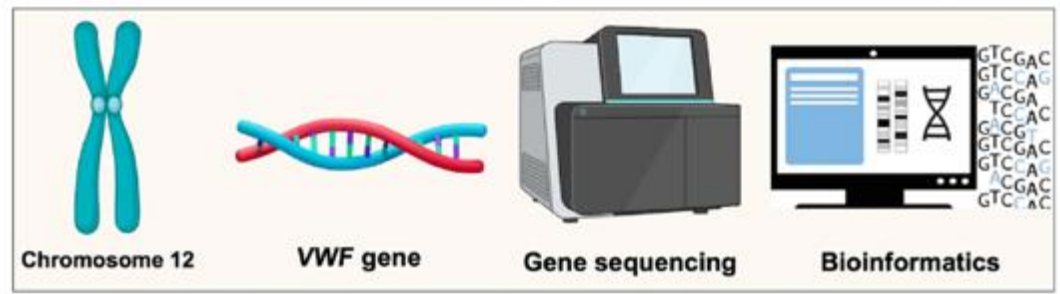


- *Lipton R Misdiagnosis by Milkbox Haemophilia* 2003, 9:235-236
- *Coyle T, et al. Milk Box Misdiagnosis of Von Willebrand Disease Is Common. Blood.* 2008;112(11):2266..
- *Jaffray J, Laboratory misdiagnosis of von Willebrand disease in post-menarchal females: A multi-center study Am J Hematol.* 2020; 95(9)1022-1029.

The Future: Expanding role of genetic testing

Challenges
VWF gene is highly polymorphic. >4,000 polymorphisms and >900 pathogenic variants - difficult to distinguish pathogenic vs. benign variants
Reduced penetrance, variable expressivity, incomplete knowledge of gene, and ethnic-specific mutations.

Utility
Limited utility in routine VWD evaluation. Only ~62% of Type 1 VWD have identifiable sequence variants



Seidizadeh O, Lillicrap D. Molecular genetic testing in von Willebrand disease: past, present, and beyond. *Haematologica*. 2026 Jan 1;111(1):44-53. PMID: 41496703.

Case 1 continued- 15 y/o with BAT of 8 presenting to ED with epistaxis needing packing and heavy menses since menarche

- The patient undergoes testing for VWD:
 - Ristocetin cofactor AKA VWF activity = 26% (normal 40%-120%)
 - VWF antigen = 28% (normal 50%-150%)
 - FVIII level = 47% (normal 50%-150%).
 - VWF multimers are slightly reduced but in normal pattern.
- A presumptive diagnosis of Type 1 VWD was made (definitive diagnosis was then made when a second set of levels returned subnormal).

CONFIRMING THE DIAGNOSIS OF VWD

To make a diagnosis of VWD, The ASH ISTH NHF WFH 2021 guidelines¹³ require:

VWF:Ag or
platelet-dependent
VWF activity (IU/dL)



OR



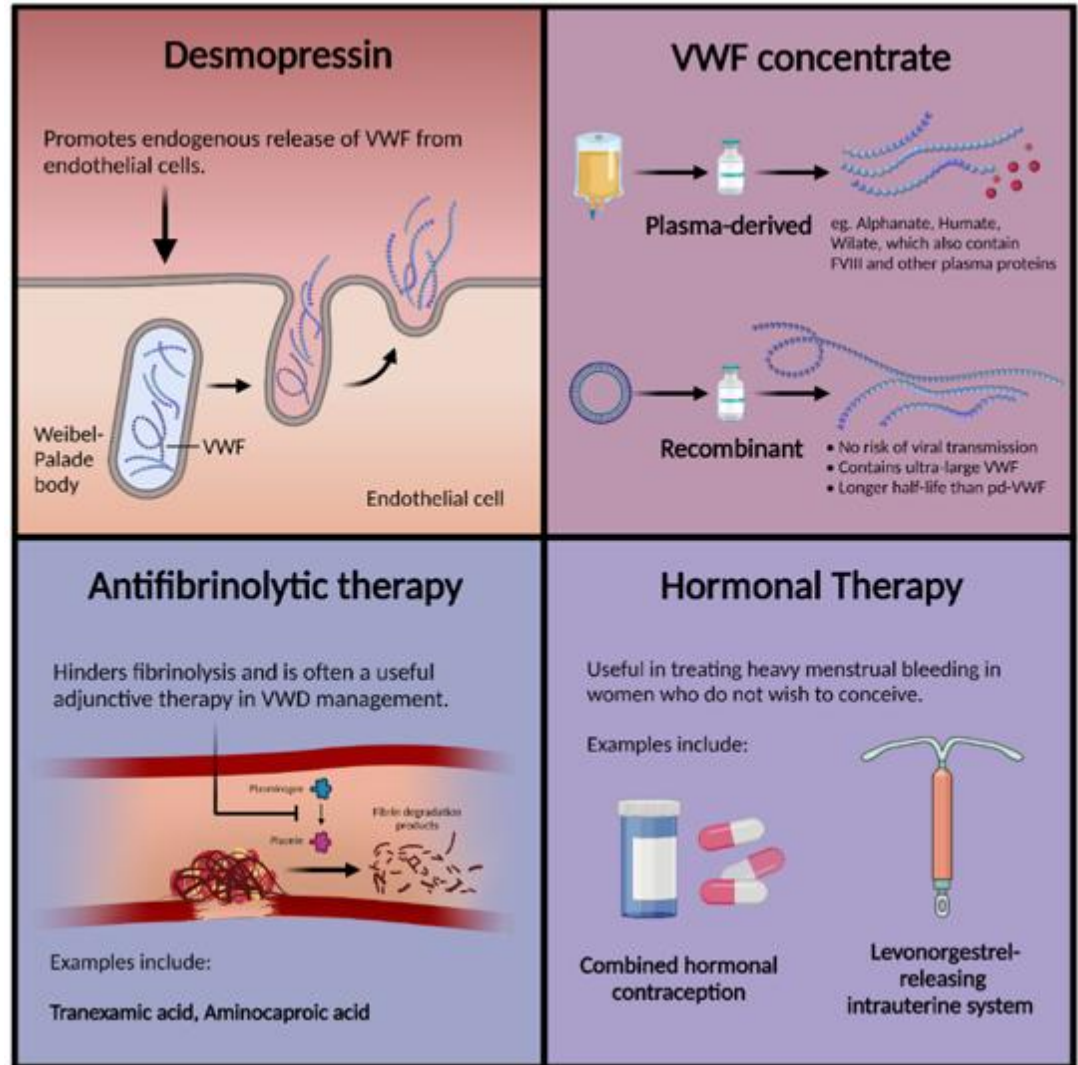
+



bleeding
symptoms*

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

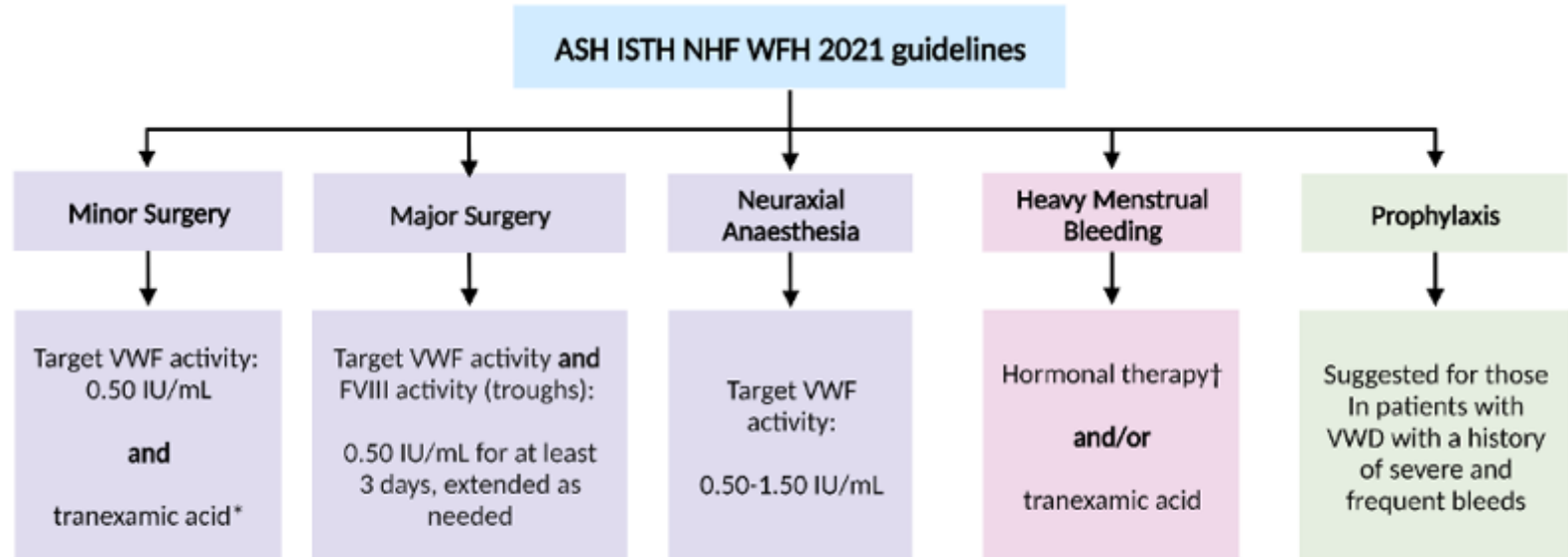
The Present: VWD Management Options



The Present: Management of VWD by subtype

Condition	Prevalence	Treatment (± Aminocaproic Acid or Tranexamic Acid for Mucosal Bleeding)
Type 1	75%-85%	Desmopressin usually works in majority of cases For major surgery, VWF replacement may be preferable
Type 2A	10%-15%	Desmopressin rarely effective Infuse VWF (plasma-derived FVIII concentrate or rVWF)
Type 2B	5%	Desmopressin maybe deleterious (may lower platelets, cause clots) Infuse VWF (plasma-derived FVIII concentrate or rVWF)
Type 2M	Rare	Desmopressin rarely effective Infuse VWF (plasma-derived FVIII concentrate or rVWF)
Type 2N	Rare	Infuse VWF (plasma-derived FVIII concentrate or rVWF)
Type 3	1 in 1,000,000	Infuse VWF (plasma-derived FVIII concentrate or rVWF)

The Present: Management of VWD by guidelines

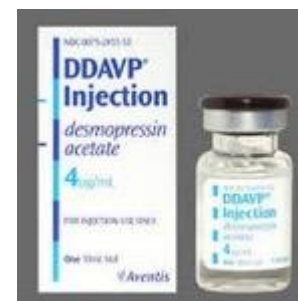


* Tranexamic acid alone can be considered for minor procedures in Type 1 VWD patients with baseline VWF activity levels of >0.30 IU/mL and mild bleeding phenotype.

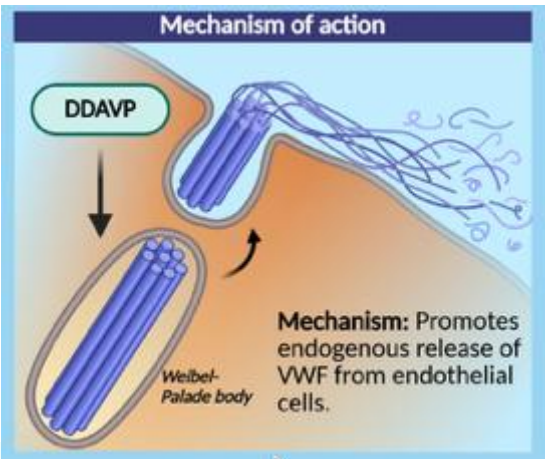
† For those who do not wish to conceive.

ASH: American Society of Hematology, ISTH: International Society on Thrombosis and Haemostasis, NHF: National Hemophilia Foundation, WFH: World Federation of Hemophilia, VWF: von Willebrand Factor

Desmopressin-1-deamino-8-D-arginine vasopressin (DDAVP)



Mechanism of action



Notable Side Effects:



Hyponatremia



Seizures



Cardiac disease exacerbation
(contraindicated)



Tachyphylaxis (drug may become ineffective after consecutive 3-5 days)

In most HTC's, DDAVP is avoided in patients age ≤ 5 or ≥ 60 .

Suggested use:

Treatment of minor bleeds or minor procedures in Type 1 VWD (known responders).

Response definition

- $\geq 2x$ increase from baseline **AND**
- sustained VWF/FVIII increase to >0.50 IU/mL for at least 4 hours

Doses and routes:

- **intravenous:** 0.3mcg/kg (max 20-30mcg)
- **subcutaneous:** 0.3mcg/kg (max 20-30mcg)
- **intranasal:** 300mcg, 1 spray (150mcg) per nostril
(limited availability since 2020 product recall)

2021 VWD guidelines panel- Patients for whom desmopressin is a valid treatment option (primarily type 1 VWD) and who have a baseline VWF level of <0.30 IU/mL, the panel *suggests* performing a trial of desmopressin and treating based on the results over not performing a trial and

The Present at the Mary M. Gooley HTC: Lower Dose DDAVP

- Standard recommended dose of DDAVP based on 5 (!!) healthy controls treated with varying doses of DDAVP ranging from 0.1 to 0.4 mg/kg.
- A dose-response relationship was observed for FVIII:C up to 0.3 mg/kg, for VWF Ag up to 0.2 mcg/kg



1. Mary M. Gooley Hemophilia Center experience – “Sham dosing”
 - a) Cap at 25 mcg IVSS if weight >80 kg
 - b) Lower dose 0.15 mcg/kg IVSS in patients with mild VWF deficiency if adequate DDAVP trial **and prothrombotic risks present and/or worried about hyponatremia especially if on SSRI or Ob-Gyn case including childbirth**
2. Recent low dose studies with 0.15 mcg/kg sc show adequate fold rise

	N	VWF:RCO	VWF Ag	FVIII
Denzili, Turkey 2013	14	3.6	4.0	4.0
Ontario, Canada 2014	40	5.5	3.4	5.3

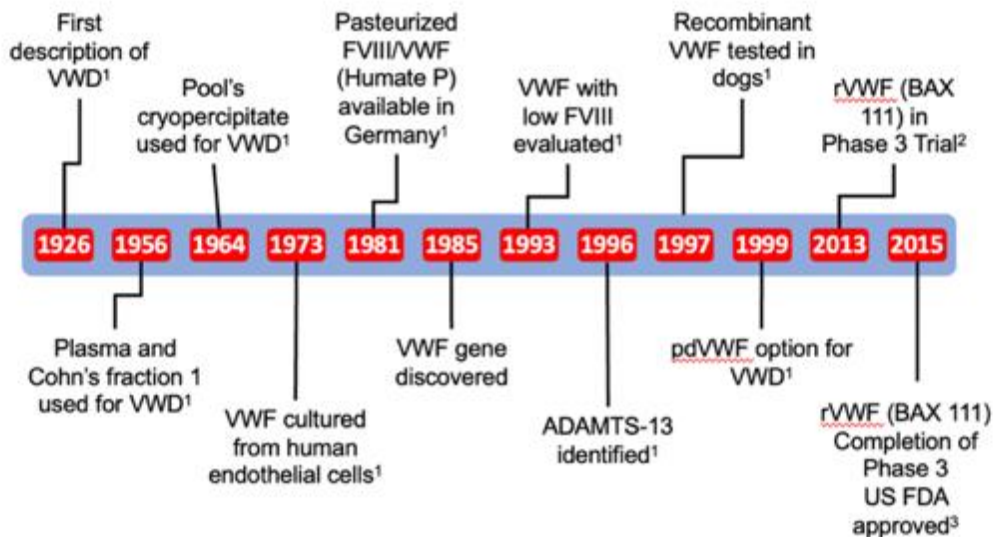
Akin M, *Hematology* 2013;18(2):155-118

Siew DA, et al. *Blood Coag Fibrinol* 2014 on-line

Furqan F, Sham R, Kouides P. Efficacy and safety of half-dose desmopressin for bleeding prophylaxis in bleeding disorder patients undergoing predominantly low to moderate risk invasive procedures. Am J Hematol. 2020 Oct;95(10):E285-E287.. PMID: 32628278.

The Past to Present: Evolution of VWF replacement therapy

Beyond DDAVP: Milestones in VWF replacement therapy



1. Federici AB, et al. *Haemophilia*. 2006; 12:563-572. 2. Baxter. News Release: October 13, 2011. Available at:

PROPHYLAXIS

Prophylaxis using VWF concentrate may be indicated in certain patients to prevent or minimize bleeding and improve QoL.



Definition:

VWF replacement ≥ 1 /week, or dosed for HMB, for a period of 3–6 months.

- No consensus on standard dosing (e.g. 1-3x/ week)
- pd-VWF or rVWF are appropriate options

RCT evidence shows efficacy in annualized bleeding rates (ABR) with pdVWF or rVWF

A phase III prospective randomized study showed 91% reduction in spontaneous ABR with rVWF prophylaxis compared to on-demand therapy.

When to consider:

- Frequent/recurrent chronic bleeding, despite appropriate on-demand therapy.
- Bleeding that interferes with daily activities, school attendance, work, or QoL
- Type 3 VWD
- Need for antithrombotic treatment (e.g. cardiovascular procedures)

In patients with VWD with a history of severe and frequent bleeds, the guideline panel *suggests* using long-term prophylaxis rather than no prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Past: Plasma VWF Replacement...Present: also rVWF



Plasma-derived (pd-VWF)

- Undergoes viral inactivation
- More readily available
- Half-life (~12-16hr)
- Contains FVIII



Recombinant VWF (rVWF)

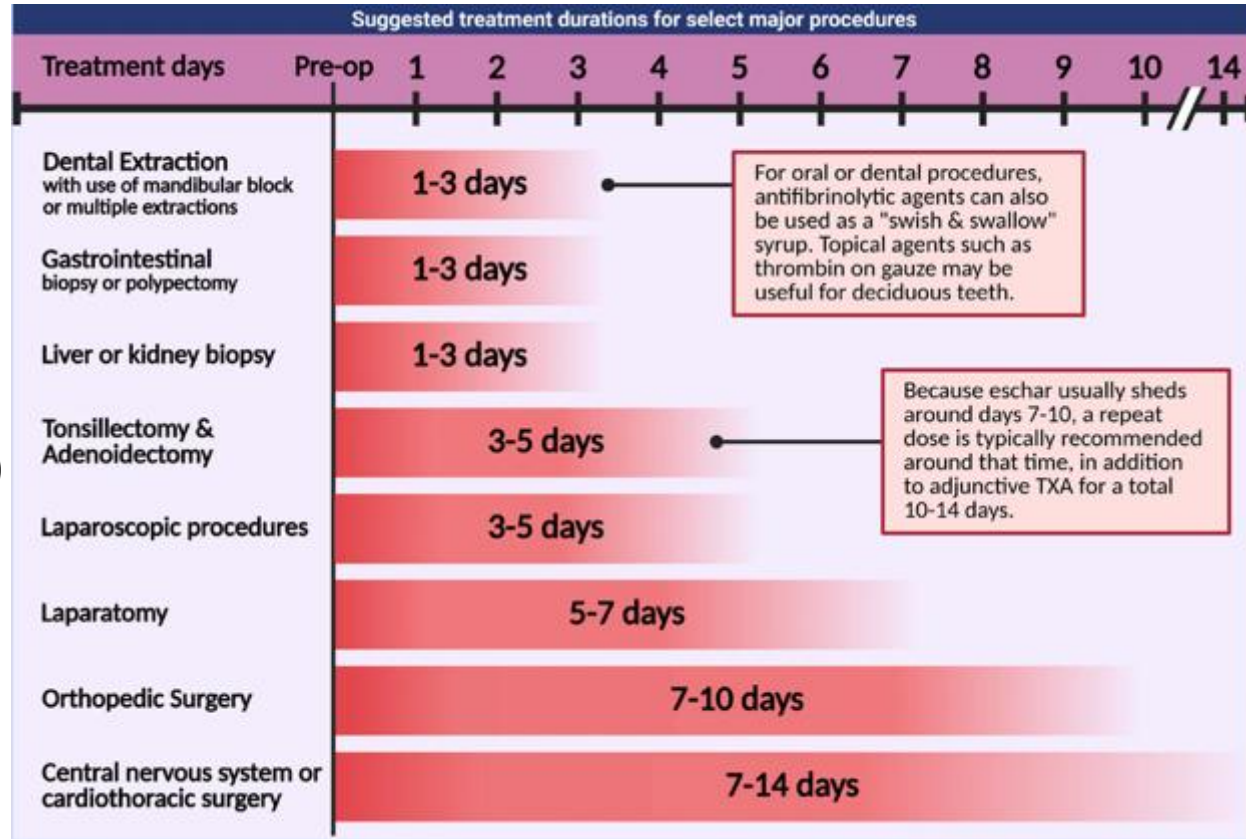
- No risk of viral transmission
- Contains ultra-large VWF
- Longer half-life (~22hr)
- Does not contain FVIII

Select examples of VWF concentrates	Licensing	VWF:RCO/FVIII ratio	VWF:RCO half-life* (median hours, range or SD)
 Alphanate/Fanhdi	 	~0.5–1.0 (varies by lot)	7.7 ± 3.3
 Humate-P/Haemate-P	 	~2.4	11 (3.5–34)
 Wilate	 	~1.0	15.8 (6–49)
 Voncento		~2.4	11.5 (6–35)
 Wilfactin		~50	12.4 (8–14)
 Vonvendi/Veyvondi	 	contains no FVIII	~22.6 (17–37)

The Present: Surgical Management

My Clinical Pearls:

- Individualize treatment goals based on patient levels, bleeding phenotype, site of surgery and surgical bleed/thrombotic risk
- Communicate orally and with care of plan letter
- Low threshold for overnight stay
- We are spoiled and in house check levels daily (cost-effective!!)
- Liberal use of anti-fibrinolytics
- Reserve DDAVP for minor procedures
 - For moderate/major bleeding risk procedures in Type 1 patients we prefer VWF replacement d/t to hyponatremia, tachyphylaxis and CV risk (in older patients)



Case continued 15 y/o Type 1 VWD

• You counsel the patient and her parents on her new diagnosis. Which of the following is not a clinical manifestation/complication of VWD in females?

- A. Iron deficiency anemia
- B. Increased rate of gynecological surgical interventions (dilatation and curettage, hysterectomy)
- C. Decreased quality of life
- D. Increased rate of miscarriage**
- E. Postpartum vulvar hematoma

Skeith L and the VWD Pregnancy Loss Study Group. Pregnancy loss in individuals with von Willebrand disease and unspecified mucocutaneous bleeding disorders: a multicenter cohort study. J Thromb Haemost. 2025 Feb;23(2):429-439. PMID: 39454883.

Female with VWD

Kouides PA. Females with von Willebrand disease: 72 years as the silent majority. *Haemophilia* 1998; 4: 665-76.

Childbirth

Post-partum hemorrhage

Menstruation

Menorrhagia

Other menstrual issues:

- Increased prevalence of mid-cycle pain (Mittlesmerz) and dysmenorrhea
- Risk of hemoperitoneum
- ? Increased incidence of endometriosis, polyps, fibroids

Psychosocial complications (Quality-of-life impact)

- Increased prevalence of anxiety (-depressive) disorders
- 1/3rd to 1/2 have lost time from work/school in the past year
- In one study QOL impairment was equivalent to a HIV + severe hemophiliac

Medical and Surgical complications

- Iron deficiency anemia
- Increased rate of surgical interventions: D&C, hysterectomy

Case continued (15 y/o Type 1 VWD) The patient, and her parents are informed that there are numerous treatment options for managing her heavy menses.

• All the following are front-line options to control heavy menses in this patient except?

A. Tranexamic acid (Lysteda TM) 1.3 gram po tid first 5 days of menses

B. MIRENA IUD

C. Combined oral contraceptive (COC)

D. Plasma-derived VWF containing FVIII concentrate



Armour
**ANTI-MENORRHAGIC
FACTOR
GLANULES**

Oral contraceptive



Levonorgestrel IUD



Endometrial ablation



Hemostatic Therapies:

Intranasal DDAVP (Stimate®)



The panel suggests using either hormonal therapy (CHC or levonorgestrel-releasing intrauterine system) or tranexamic acid over desmopressin to treat women with VWD with heavy menstrual bleeding who do not wish to conceive (conditional recommendation)

VWF/FVIII concentrate



Antifibrinolytic therapy



Hysterectomy



Brignardello-Petersen R et al :
Blood Adv. 2021
Oct 21:Blood
Advances. PMID:
34673921.

Back to our 15 y/o patient, a year later (age 16)

- Patient undergoes DDAVP trial with robust response
- Parents opt for Intranasal DDAVP for daughter's heavy periods
- Follow-up PBAC score showed decrease from 320 to 60
- One year later, patient's pediatrician calls me and tells me that she is now pregnant
- Asks why did I not prescribe COC instead of IN DDAVP as she was sexually active then
 - A long silence ensued at my end of the phone call
- Family and patient are concerned about delivery-
 - Can she have an epidural ?
 - Won't she bleed after delivery b/c of her VWD?

	Ristocetin cofactor (nl= 40% to 120%)	VWF antigen (nl = 50% to 150%)	Factor 8 level (nl = 50% to 150%)
Preintra-nasal DDAVP	20%	27%	52%
60 min postintra-venous DDAVP	103%	105%	185%
4 hr post	99%	100%	166%

N.B. She initially underwent 1 and 4 hr IV DDAVP trial with <30% decrease from the peak VWF level so ruling out Type 1C

Case continued- regarding her pregnancy-

- **All the following statements are correct except:**

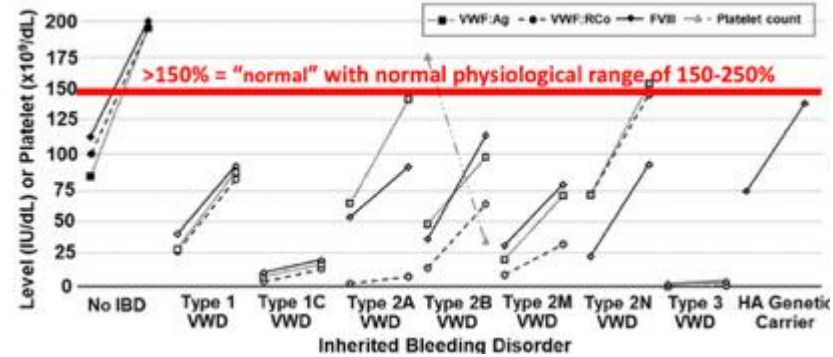
- A. A VWF level $> 50\%$ in the third trimester would clear her for an epidural
- B. The VWF levels can begin to fall 3 days post-partum placing the patient at risk of post-partum hemorrhage
- C. Tranexamic acid can be prescribed prophylactically post-partum to reduce risk of hemorrhage

D. Patient should be advised to have an induction to reduce risk of PPH

Pregnancy in VWD

- von Willebrand factor (VWF) and factor VIII (FVIII) levels increase in healthy pregnancy by 200-250%¹
- VWF increases are much less pronounced (or absent) in pregnant women with VWD²
- Women with VWD have high rates of postpartum hemorrhage (PPH), even with treatment for VWD^{3,4}
 - 5-40% prevalence of PPH compared to 2-10% prevalence in general population

VWF changes in pregnancy in normal patients and patients with VWD

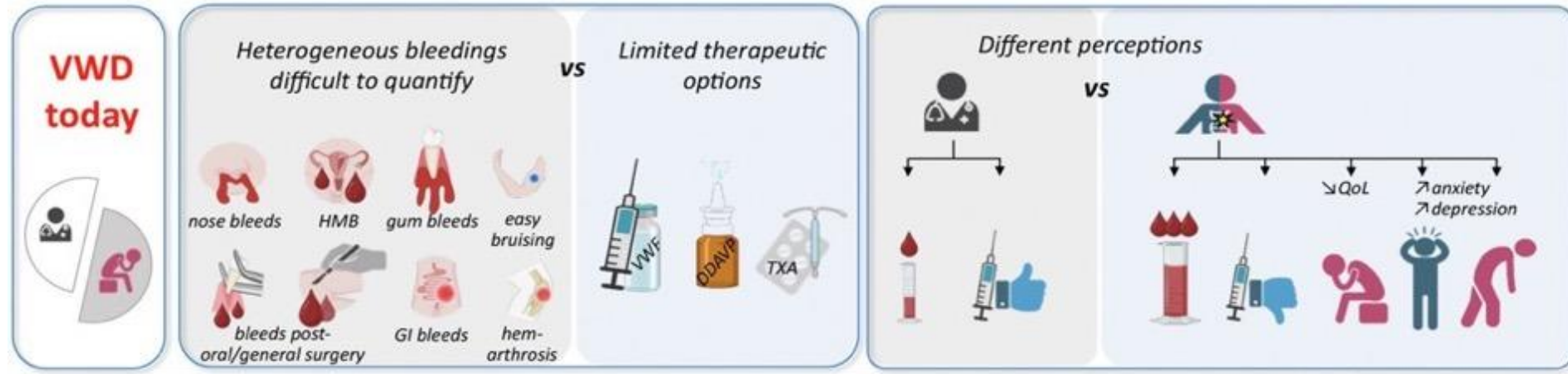


Present Issues in VWD related pregnancy:

1. How best to raise level in Type 1 VWD- DDAVP or VWF? >Prefer VWF replacement
2. Optimal target VWF level for epidural? >50%, >100%, > 150%? >Prefer >50%
3. Optimal target VWF level for delivery? >50%, >100%, > 150%? >Prefer 100-150%
4. How long to maintain levels? >3-7 d
3. Role of tranexamic acid > For 7-14 d PP

¹ Drury-Stewart et al. PLoS One. 2014 Nov 19;9(11):e112935; ²Castaman G. Mediterr J Hematol Infect Dis. 2013; 5(1): e2013052; ³James et al. Haemophilia. 2015 Jan;21(1):81-7; ⁴Machin & Ragni. Blood Adv. 2020 Jul 28;4(14):3234-3238.

Present Challenges for VWD Patients



- Despite greater awareness in screening women and girls:
 - Diagnostic delay for women with VWD still persists since CDC report 22 years ago of 16 years average delay
 - 2024 Alberta Canada study- 14 years diagnostic delay in 178 women
 - Many do not have adequate control of heavy menses once diagnosed-
 - 2023 Kingston Ontario Women's BD Clinic- N=109: only 74 (68%) were satisfied with medical management, and only 18 (17%) with first-line therapy
- No agreement on how best to manage peri-partum in terms of target VWF level and how to raise it (DDAVP or VWF product and in turn bolus or continuous)
- No consensus on defining severe VWD to warrant prophylaxis or how best to manage AVM-related GI bleeding
- The past decade has seen an explosion of new hemophilia products but not VWD products yet

Present Challenges in Improving Care at our Own HTC's!!!

Lack of awareness among PCPs and Ob-Gyns and lack of clarity on VWD nomenclature & management historically has led inadvertently to distress and limited access to the Hemophilia Treatment Centers

Our HTC's were created to largely support males with moderate and severe hemophilia



*Slide courtesy of Dr. Robert Sidonio,
Emory HTC, Atlanta GA*

Present and Future: Improving Care at Our Own HTC's and beyond Western NY!

- Rochester and Buffalo, in progress
- Through supporting various organizations: e.g. NBDF, WFH, WGBD



Multidisciplinary VWD clinics

Integration within bleeding disorder centers or women-focused bleeding programs to provide coordinated diagnosis, treatment, and counseling.



Diagnostic infrastructure

Expanding laboratory capacity and access to standardized assays in low-resource areas. Improving regional reference laboratories can reduce diagnostic delays and variability in care.



Structured outcome measurement

Standardized bleeding scores, QoL metrics, health-economic modeling to evaluate care models and guide resource allocation by identify health care gaps and outcome disparities.



Data-driven policy and advocacy:

Global registries (WFH, WHO) and surveillance data can identify health care gaps and inform policy decisions and advocacy efforts aimed at expanding access to specialized care and essential therapies.

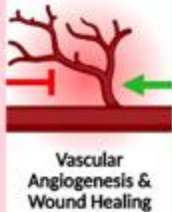
Lim MY, Anguiano KC, Carpenter SL, Funkhouser KB. Building access to care for Women and Girls⁺ with Bleeding Disorders: the WGBD Clinic of Excellence Model. Res Pract Thromb Haemost. 2025 Sep 30;9(7):103203. PMID: 41208943

The Present & Future of Angiogenesis and Gene Therapy

Antiangiogenic therapy

VWF may have varying **anti-angiogenic** and **pro-angiogenic** effects in different conditions and tissues.

Endothelial VWF may act as a **negative regulator of angiogenesis**. VWF deficiency has been associated with angiodysplasia, and increased/abnormal vascular proliferation and density, suggesting an **inhibitory** role.



Paradoxically, VWF may assist in **wound healing and local angiogenesis** in other settings, suggesting a role in **promoting** angiogenesis which has been associated with tumor growth and metastasis.

Antiangiogenic therapy (e.g. bevacizumab) may be useful in cases of refractory GI bleeding related to **angiodysplasia in VWD**, although specific clinical trials evaluating the efficacy and safety of this approach are needed.²⁴

Gene Therapy now and beyond



Large gene size
At ~178 kb and 52 exons, the **VWF** gene exceeds AAV capacity.



Complex post-translational biology
Dimerization, multimerization, glycosylation, helical tubule formation, and Weibel-Palade packaging complicate processing.



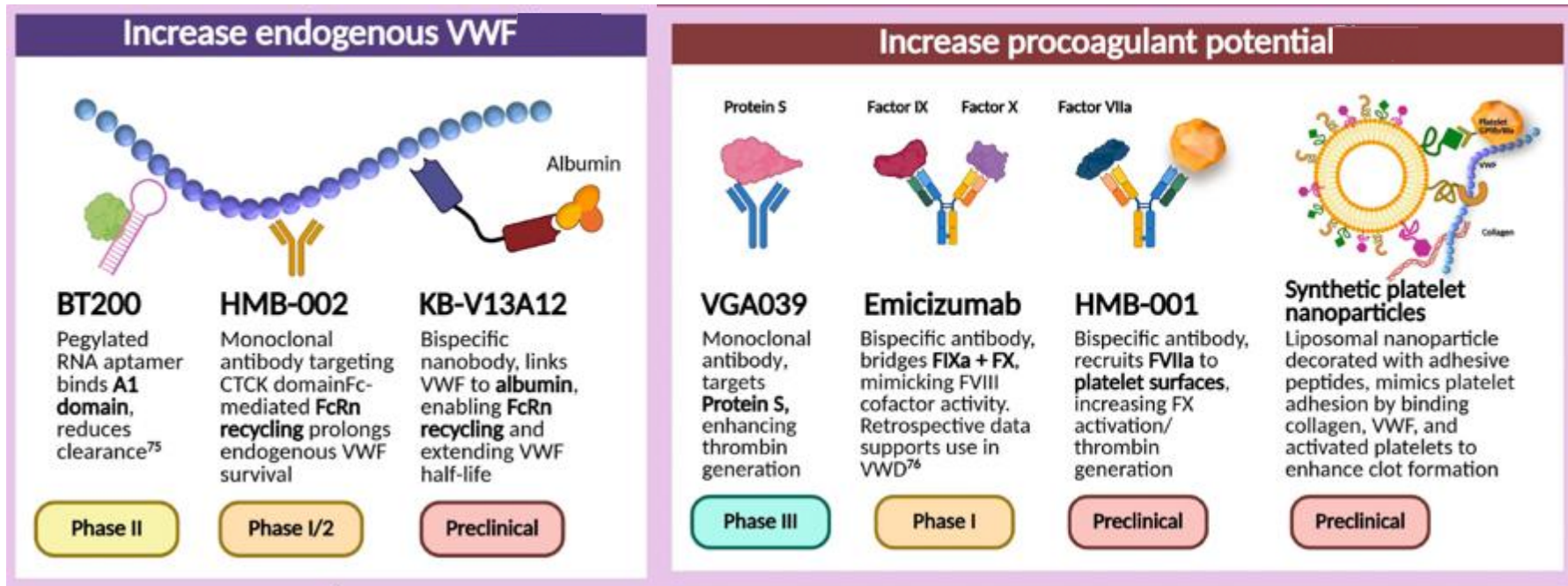
Cell-specific expression
Many vectors target hepatocytes, which may not replicate normal storage and regulated secretion of native VWF that occurs in endothelial cells and megakaryocytes.

→ Future directions
Dual-vector systems, CRISPR repair, or mRNA-based endothelial editing approaches.

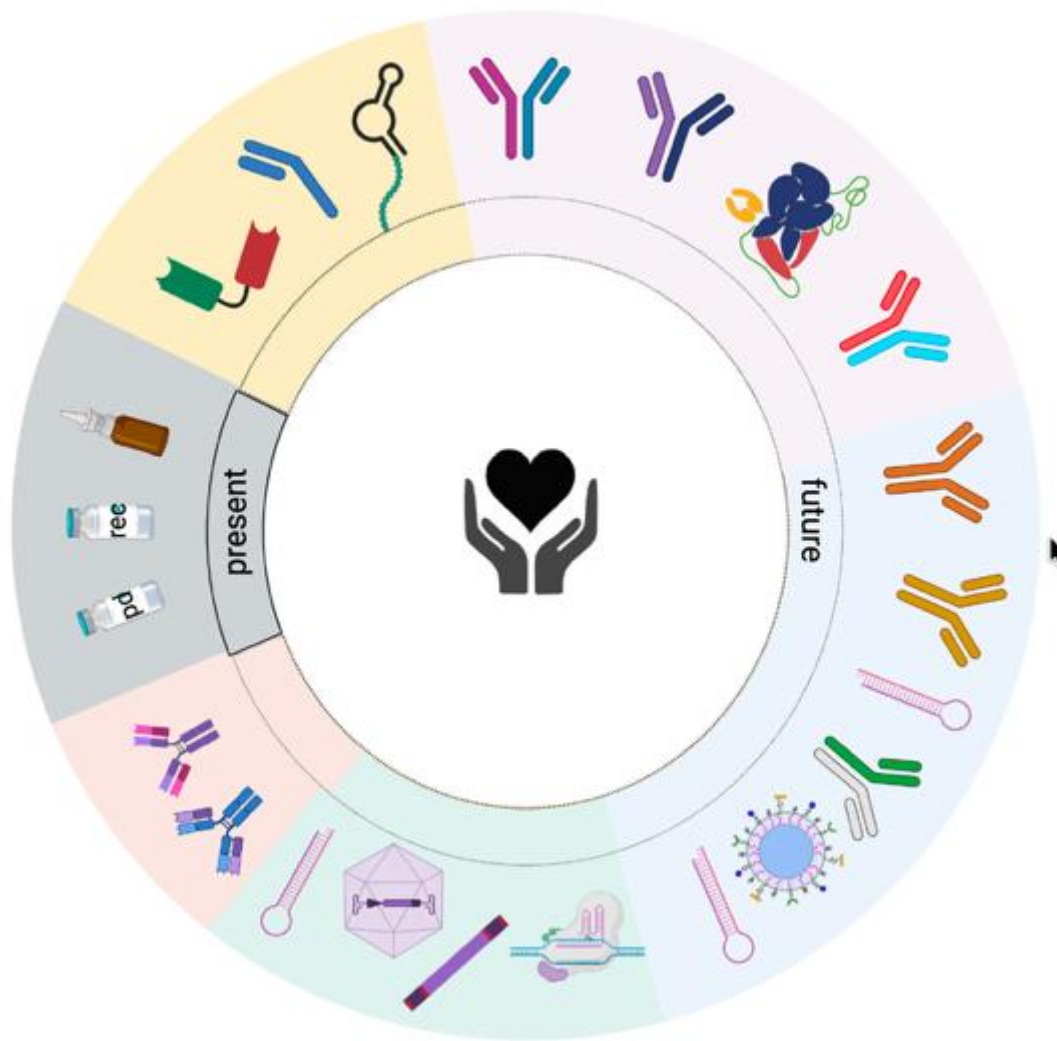
The Bright Future of VWD Research and Care!!....

The Great Promise of the Next Decade for VWD Patients-

Novel Therapeutic Strategies!!!!..aptamers, bispecifics, MoAbs, Nanoparticles



Casari C, Leebeek FWG, Peyvandi F. Historical, current and future treatments for von Willebrand disease. Haematologica. 2026 Jan 1;111(1):54-66. Dec 11. PMID: 41496704



Casari C et al
Haematologica.
2026 Jan
1;111(1):54-66.
PMID: 41496704