

von Willebrand Disease

From platelet adhesion to factor VIII protection



Inheritance • quantitative and qualitative defects • clinicopathologic interpretation

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Learning outcomes

- Explain why vWF participates in both primary and secondary hemostasis.
- Distinguish quantitative deficiency from qualitative vWF dysfunction.
- Connect type-specific mechanisms to bleeding patterns and laboratory findings.
- Interpret focused clinical scenarios and treatment principles.

Hemostasis requires coordinated components

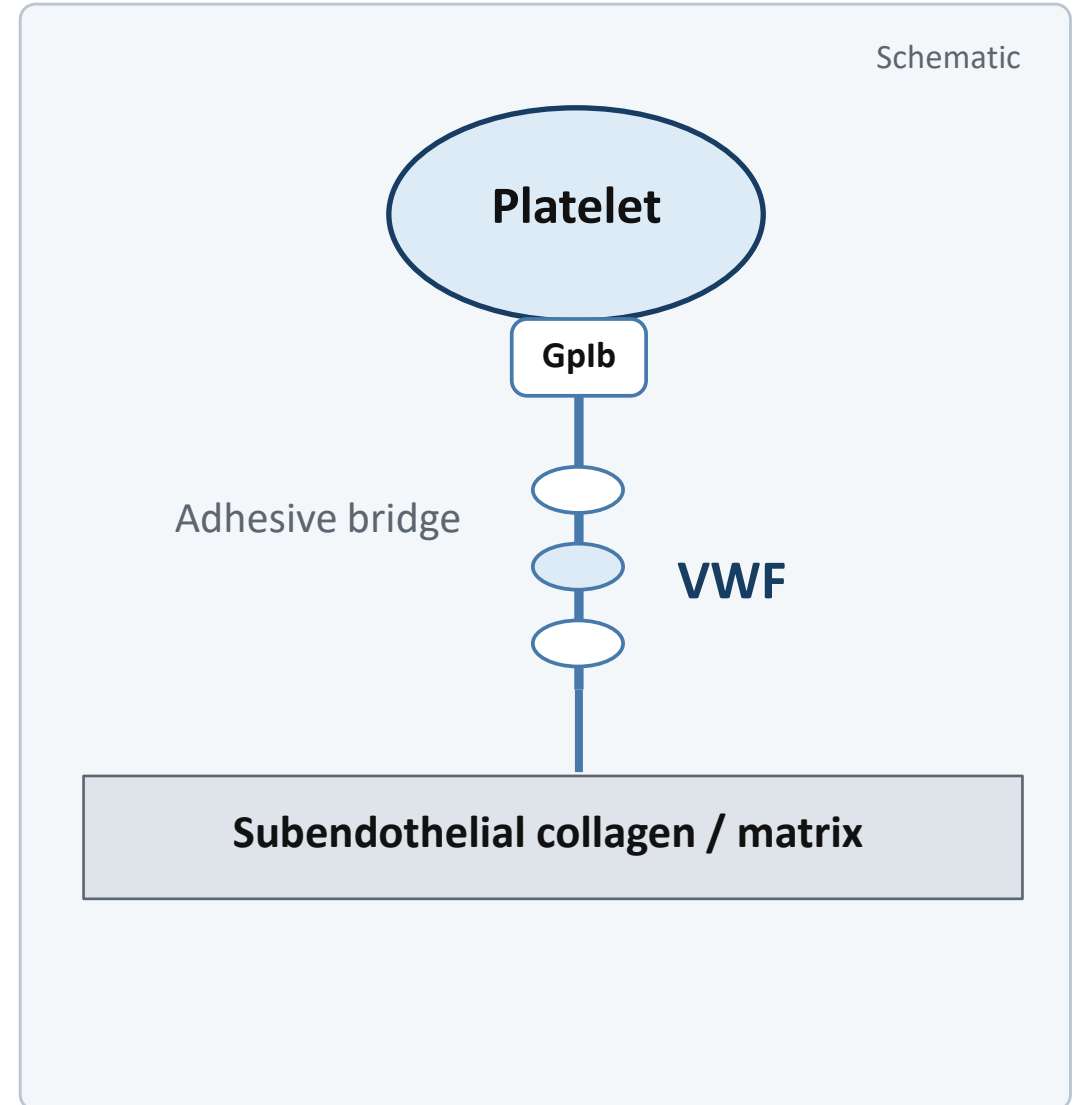
- Endothelium and subendothelial matrix define the injured vessel surface.
- Platelets form the initial, mechanically fragile hemostatic plug.
- Coagulation deposits fibrin to consolidate the platelet plug.
- Von Willebrand factor connects the vessel wall, platelets, and factor VIII.

Schematic



Primary hemostasis begins with adhesion

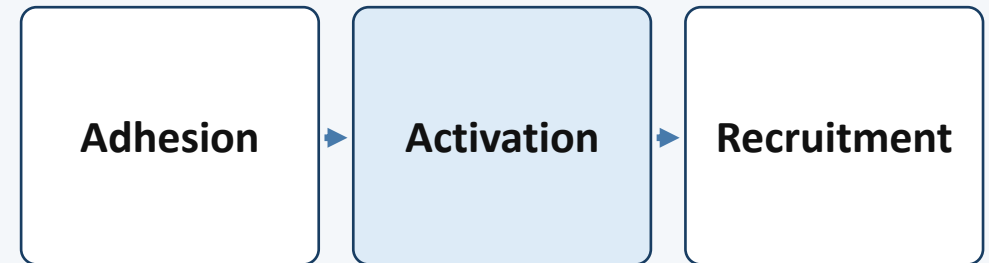
- Vascular injury exposes subendothelial collagen and matrix-bound vWF.
- Platelet GpIb/IX engages vWF anchored to the matrix.
- This adhesive interaction recruits platelets to the injured surface.



Platelet activation amplifies recruitment

- Adherent platelets undergo shape change and granule release.
- ADP and thromboxane A₂ recruit and activate additional platelets.
- Activation increases the ability of GpIIb/IIIa to bind fibrinogen.

Schematic



Aggregation uses a different molecular bridge

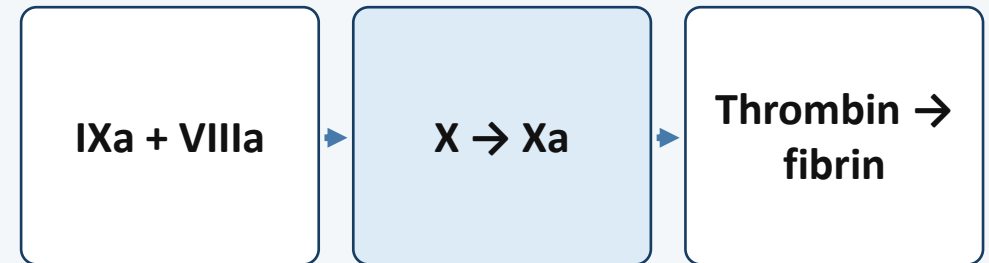
- Fibrinogen links GpIIb/IIIa receptors on adjacent activated platelets.
- This interaction produces platelet–platelet aggregation.
- VWF-mediated adhesion and fibrinogen-mediated aggregation are complementary, not synonymous.

Feature	Adhesion	Aggregation
Bridge	VWF	Fibrinogen
Platelet receptor	GpIb/IX	GpIIb/IIIa
Target	Exposed matrix	Adjacent platelets

Secondary hemostasis stabilizes the plug

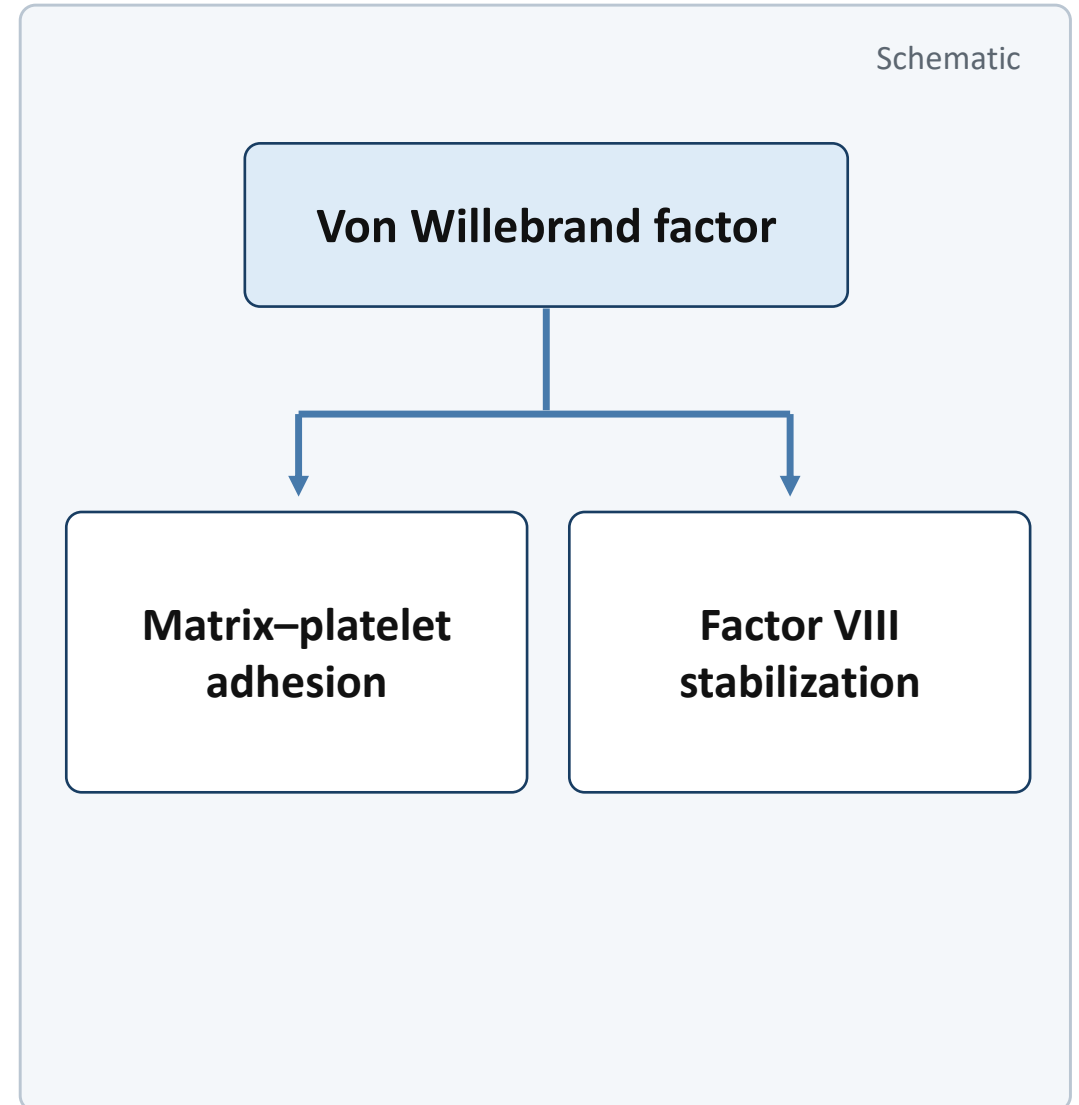
- Activated platelet surfaces support assembly of coagulation-factor complexes.
- The factor IXa–VIIIa complex promotes activation of factor X.
- Thrombin generation and fibrin deposition strengthen the initial plug.

Schematic



VWF operates across two hemostatic pathways

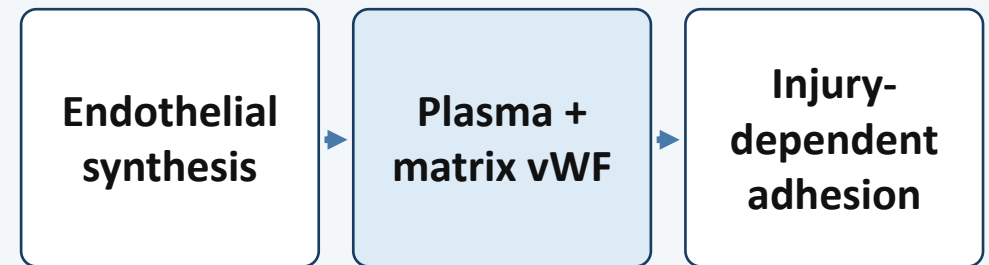
- Adhesive function: Links platelets to exposed subendothelial matrix.
- Carrier function: Binds and protects circulating factor VIII.
- Disease may therefore display platelet-type bleeding with an altered intrinsic-pathway test.



Endothelial cells synthesize vWF

- Endothelial cells release vWF into the circulation.
- A fraction is deposited in the subendothelial matrix.
- Deposited vWF is positioned to act immediately when the endothelial lining is disrupted.

Schematic



Megakaryocytes supply platelet vWF

- Megakaryocytes produce vWF stored in platelet α -granules.
- Activation releases granule vWF near an injured vessel.
- Released vWF can contribute to the local adhesive response.



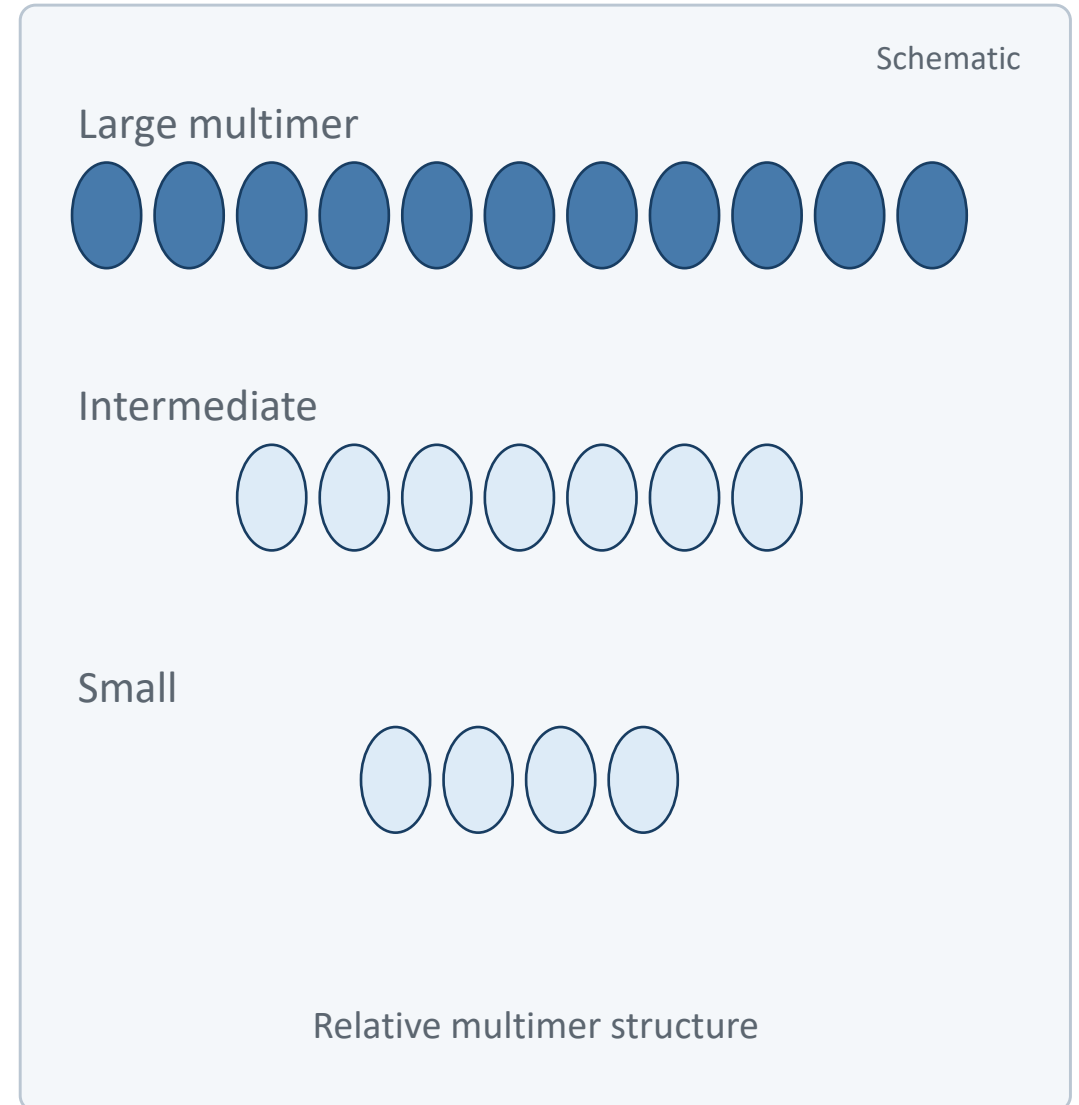
Circulating and matrix vWF have distinct locations

- Circulating vWF carries factor VIII and can interact with exposed matrix.
- Subendothelial vWF provides a ready-made adhesive interface.
- The same protein consequently supports both plasma and vessel-wall functions.

Feature	Circulating pool	Subendothelial pool
Location	Plasma	Extracellular matrix
Key function	Factor VIII protection	Platelet attachment
Access	Continuous	Exposed by injury

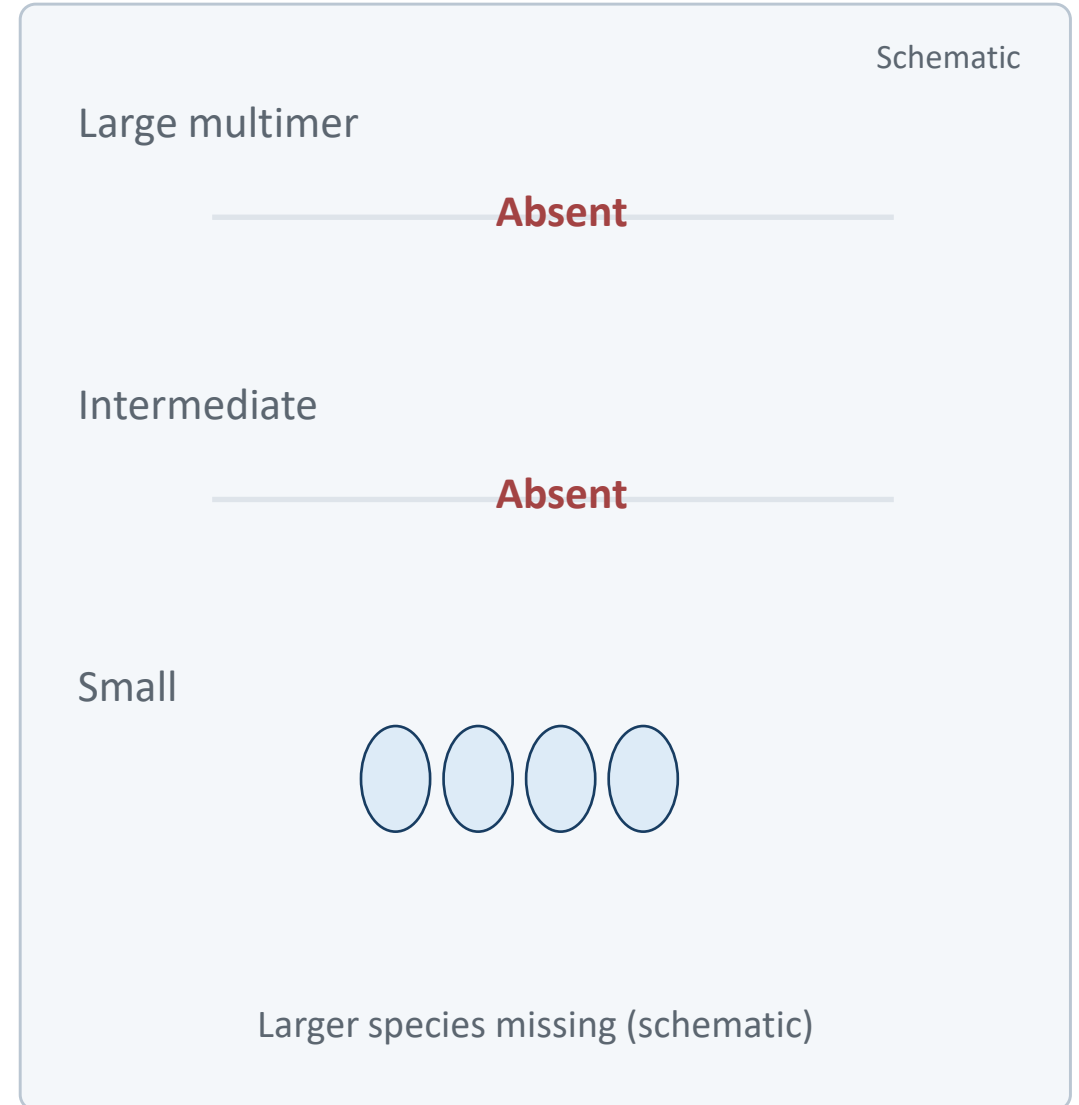
VWF is assembled into multimers

- Individual vWF subunits are assembled into very large multimeric structures.
- The largest forms provide particularly effective multivalent platelet interactions.
- Disrupted assembly can impair function despite continued protein expression.



Multimer size matters for platelet capture

- Multiple binding sites make high-molecular-weight vWF functionally effective.
- Multivalent vWF helps form stable interactions under high shear stress.
- Loss of large multimers diminishes efficient platelet adhesion.



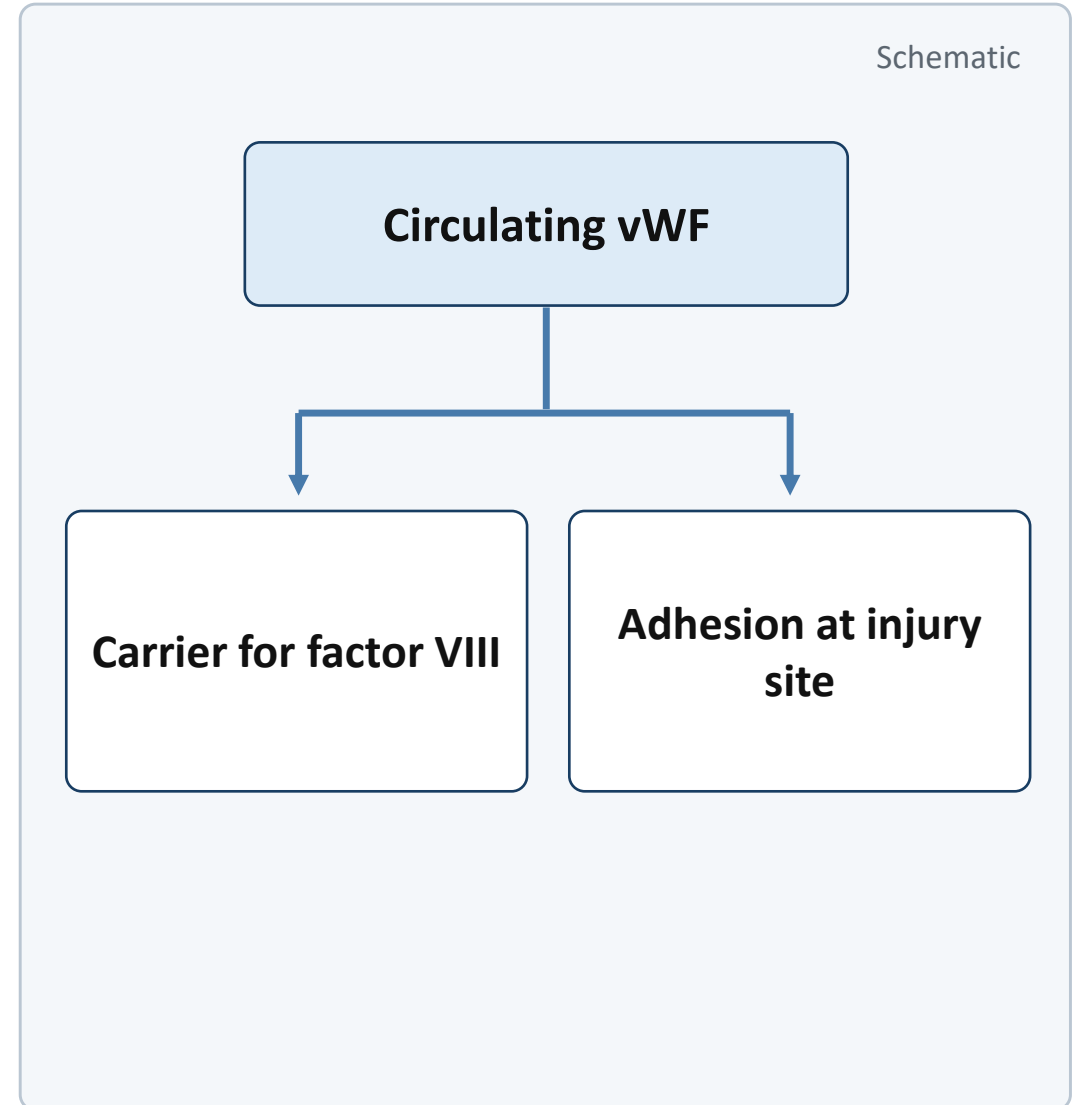
VWF is not a substitute for platelet receptors

- GpIb deficiency prevents normal engagement with vWF.
- GpIIb/IIIa deficiency disrupts a later aggregation step.
- These inherited receptor disorders help localize the site of the defect.

Feature	GpIb defect	GpIIb/IIIa defect
Affected step	Adhesion	Aggregation
Ligand interaction	VWF	Fibrinogen
Named disorder	Bernard–Soulier	Glanzmann thrombasthenia

VWF carries factor VIII in the bloodstream

- Factor VIII and vWF associate in a large plasma complex.
- Binding stabilizes factor VIII after secretion into the circulation.
- Loss of vWF shortens factor VIII survival and may lower its measurable activity.



Factor VIII binding greatly extends survival

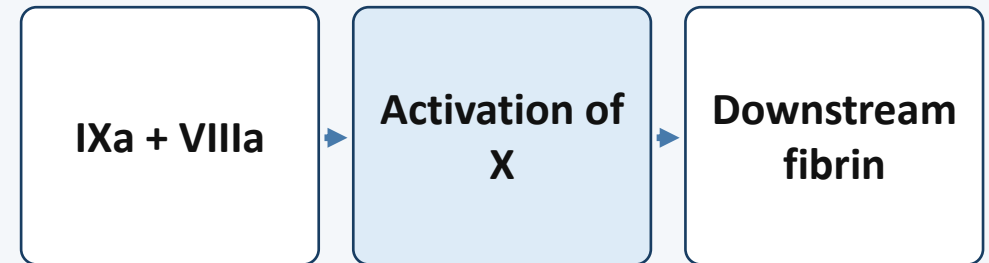
- A factor VIII half-life of approximately 2.4 hours without vWF protection.
- Association with vWF increases the half-life to approximately 12 hours.
- This explains why severe vWF deficiency can also resemble a coagulation-factor deficiency.

Feature	Without vWF protection	With vWF protection
Factor VIII half-life	≈ 2.4 hours	≈ 12 hours
Mechanism	Rapid loss	Binding and stabilization

Factor VIII supports factor X activation

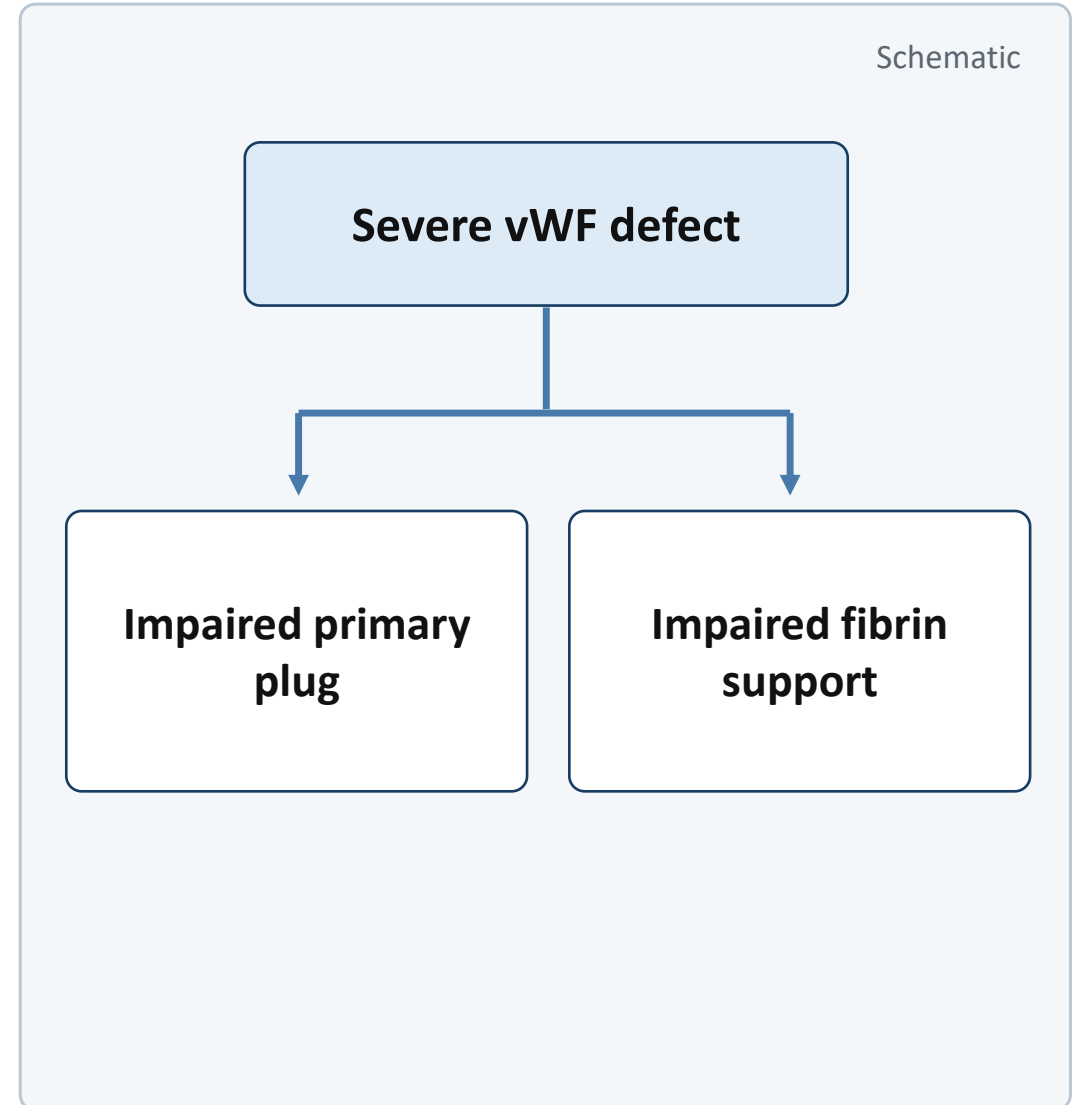
- Factor VIII is a cofactor for factor IXa.
- Their complex converts factor X toward factor Xa on activated platelet surfaces.
- Fibrin generation is compromised when functional factor VIII is markedly reduced.

Schematic



Two defects explain a severe phenotype

- Primary defect: Fewer effective platelet–matrix interactions.
- Secondary contribution: Reduced factor VIII stability.
- Severe forms can combine mucocutaneous bleeding with deeper hemorrhage.



VWD is a common inherited bleeding disorder

- VWD as the most common inherited human bleeding disorder.
- The text gives an approximate prevalence of 1% among United States adults.
- Many affected persons have a relatively mild phenotype.

Mild disease may remain unrecognized

- Baseline hemostatic capacity may be sufficient for everyday minor injuries.
- Surgery, tooth extraction, or other hemostatic stress can reveal the deficit.
- Clinical recognition therefore depends on both baseline phenotype and challenge history.

Schematic

**Mild baseline
phenotype**



**Hemostatic
challenge**



**Unexpected
bleeding**

Epistaxis reflects mucosal vulnerability

- Spontaneous nasal bleeding is a characteristic presentation.
- The phenotype is consistent with impaired formation of the primary platelet plug.
- Recurrent mucosal bleeding should prompt assessment beyond the platelet count.

Excessive wound bleeding is an important clue

- Persistent bleeding after cuts or tissue injury may be disproportionate.
- The problem is defective hemostatic plugging rather than simply low platelet numbers.
- A history of recurrent wound bleeding supports a primary hemostatic disorder.

Schematic



Heavy menstrual bleeding may be the first clue

- Menorrhagia is a typical manifestation listed.
- A mucosal bleeding history can be more informative than dramatic spontaneous deep hemorrhage.
- Bleeding history should include menstrual and reproductive contexts when relevant.

Inheritance is usually autosomal dominant

- Most cases show autosomal dominant inheritance.
- Autosomal recessive disease occurs in rarer, severe variants.
- Pedigree patterns require interpretation alongside incomplete penetrance.

Feature	Often dominant	Rarely recessive
Common examples	Type 1; Type 2	Type 3
Typical expression	Variable	Often severe
Family pattern	Vertical transmission possible	Affected siblings possible

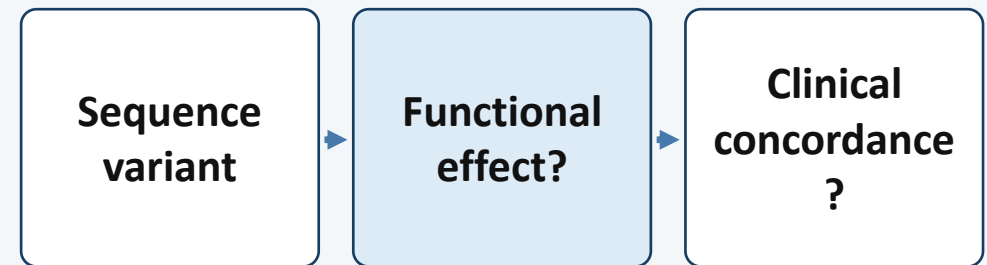
Clinical severity varies among relatives

- A single defective vWF allele may produce different bleeding phenotypes within a family.
- Expression is influenced by circulating vWF concentrations.
- A mildly affected relative does not exclude meaningful disease in another family member.

Molecular heterogeneity complicates attribution

- Hundreds of vWF sequence variants have been described.
- Only a minority have been formally shown to cause disease.
- A molecular finding must be interpreted in the context of phenotype and functional results.

Schematic



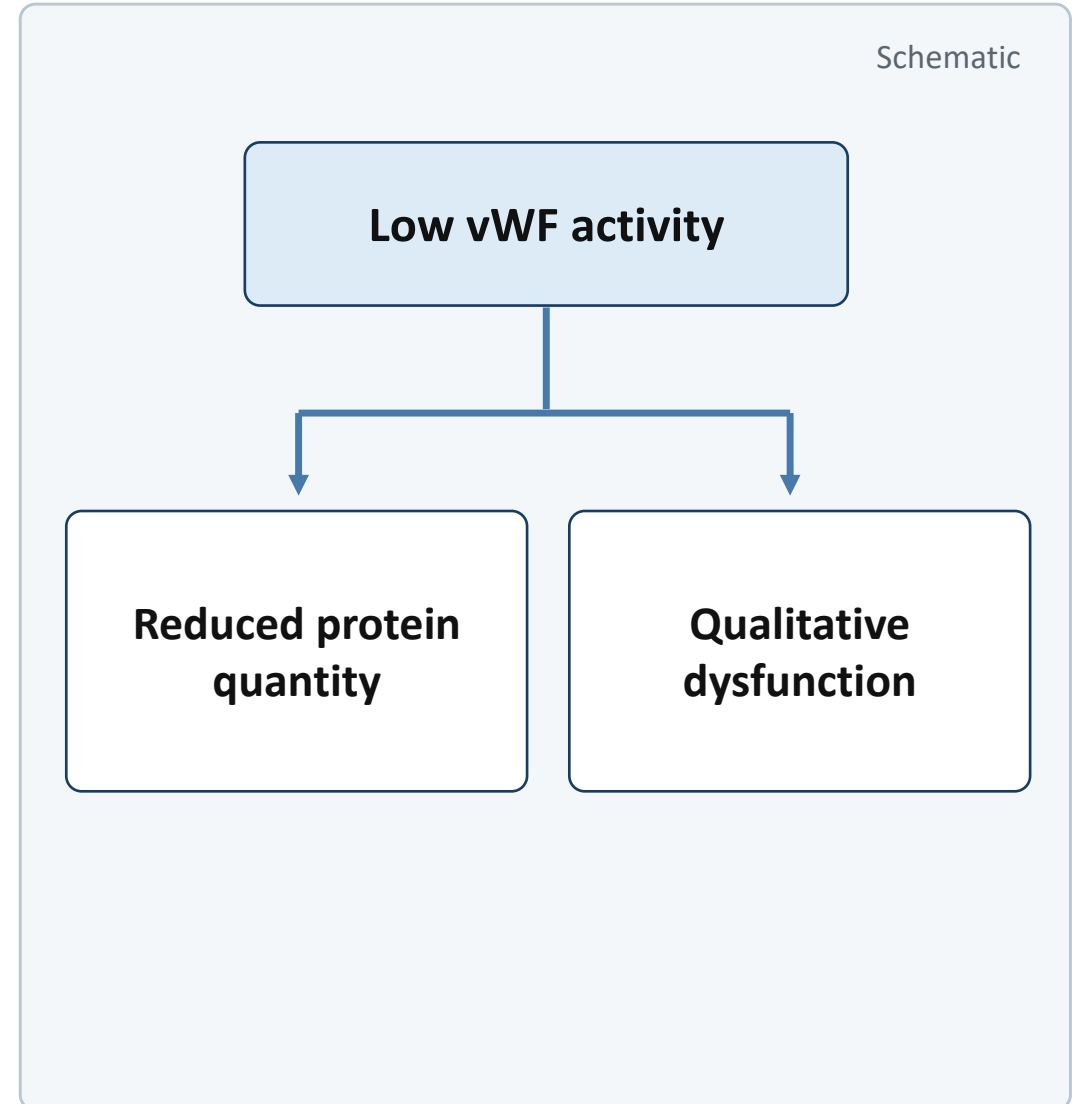
Three broad vWD types organize diagnosis

- Type 1: Quantitative, partial loss of vWF.
- Type 2: Qualitative vWF dysfunction, with recognized subtypes.
- Type 3: Quantitative, near-complete vWF loss.
- Approximately 70% type 1 cases and 25% type 2 cases.

Feature	Type 1	Type 2	Type 3
Primary defect	Partial quantity	Function	Near-absent quantity
General phenotype	Usually mild	Mild–moderate	Often severe
Inheritance	Usually AD	Usually AD	AR

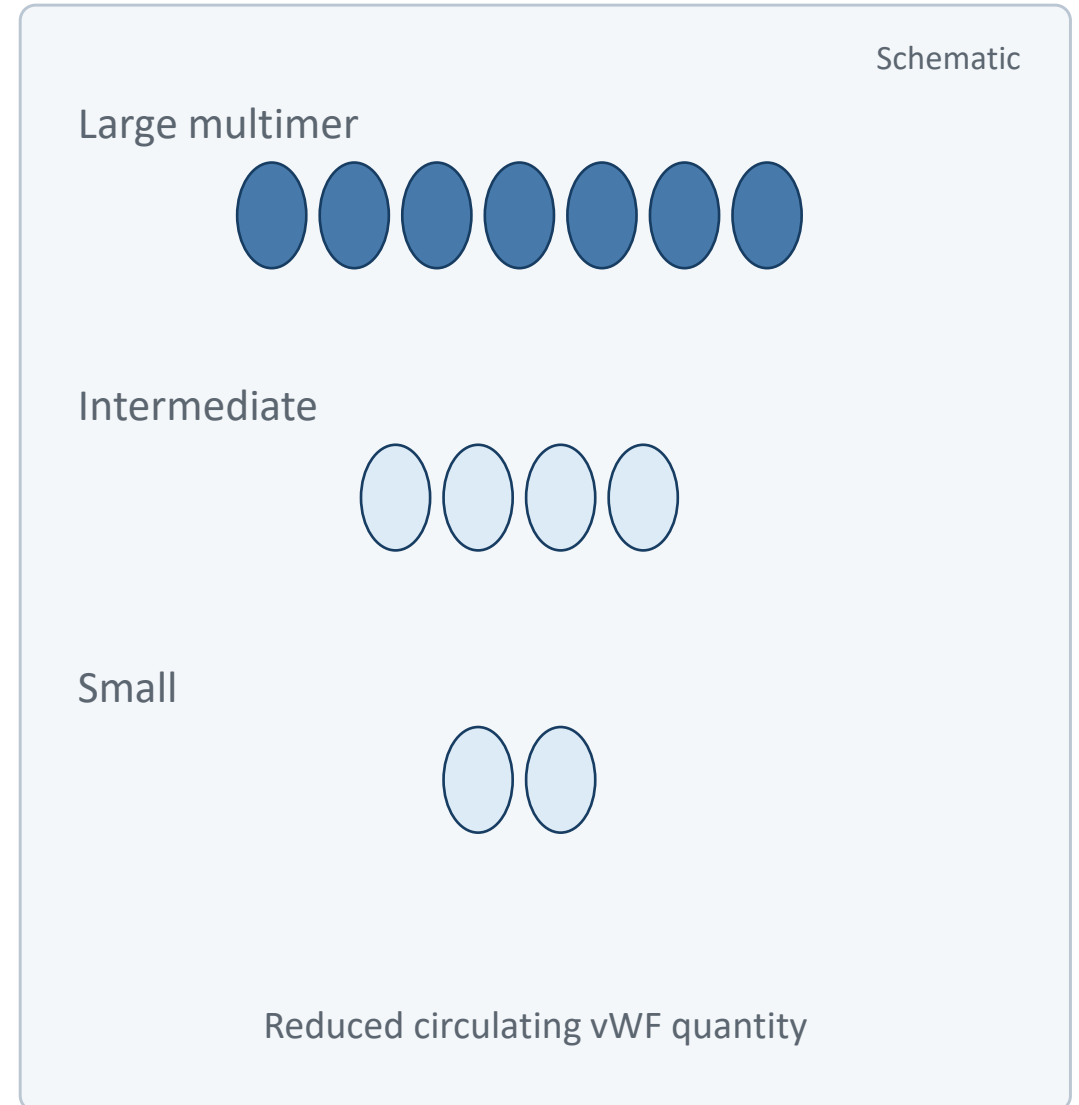
Quantity and quality must be distinguished

- A low amount of protein can reduce total functional activity.
- A normal amount of structurally abnormal protein may also show low activity.
- Antigen and functional assays therefore address different diagnostic questions.



Type 1: Partial quantitative deficiency

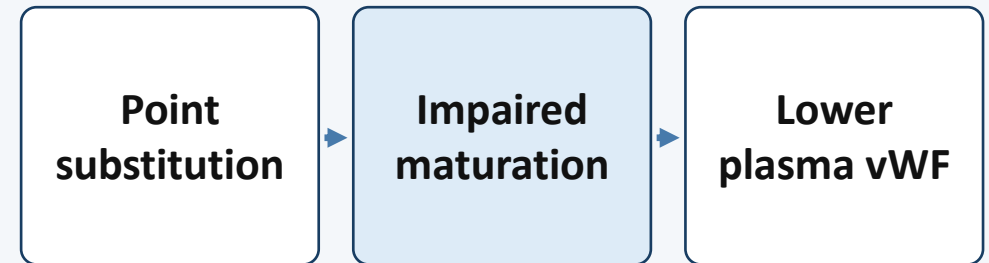
- Type 1 has a mild to moderate reduction in circulating vWF.
- It is generally associated with mild bleeding.
- It accounts for about 70% of vWD cases.



Type 1 can impair vWF maturation

- Some point substitutions interfere with normal maturation of the protein.
- The resulting reduction in available circulating vWF weakens platelet adhesion.
- This is a production/processing explanation for a quantitative phenotype.

Schematic



Type 1 can accelerate plasma clearance

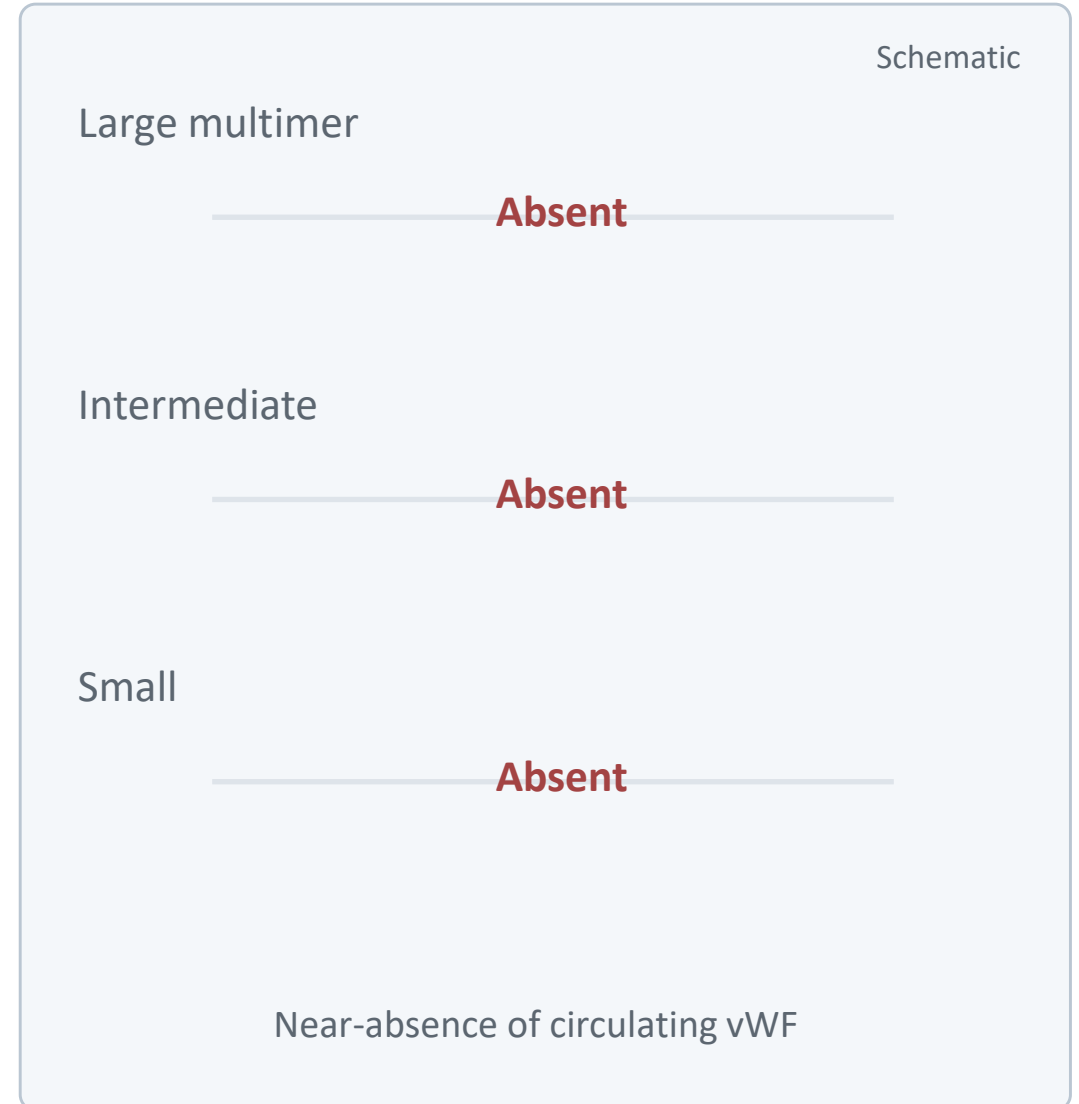
- Other mutations allow vWF production but shorten its time in circulation.
- Accelerated clearance produces a low steady-state vWF concentration.
- Different molecular mechanisms can converge on the same type 1 phenotype.

Schematic



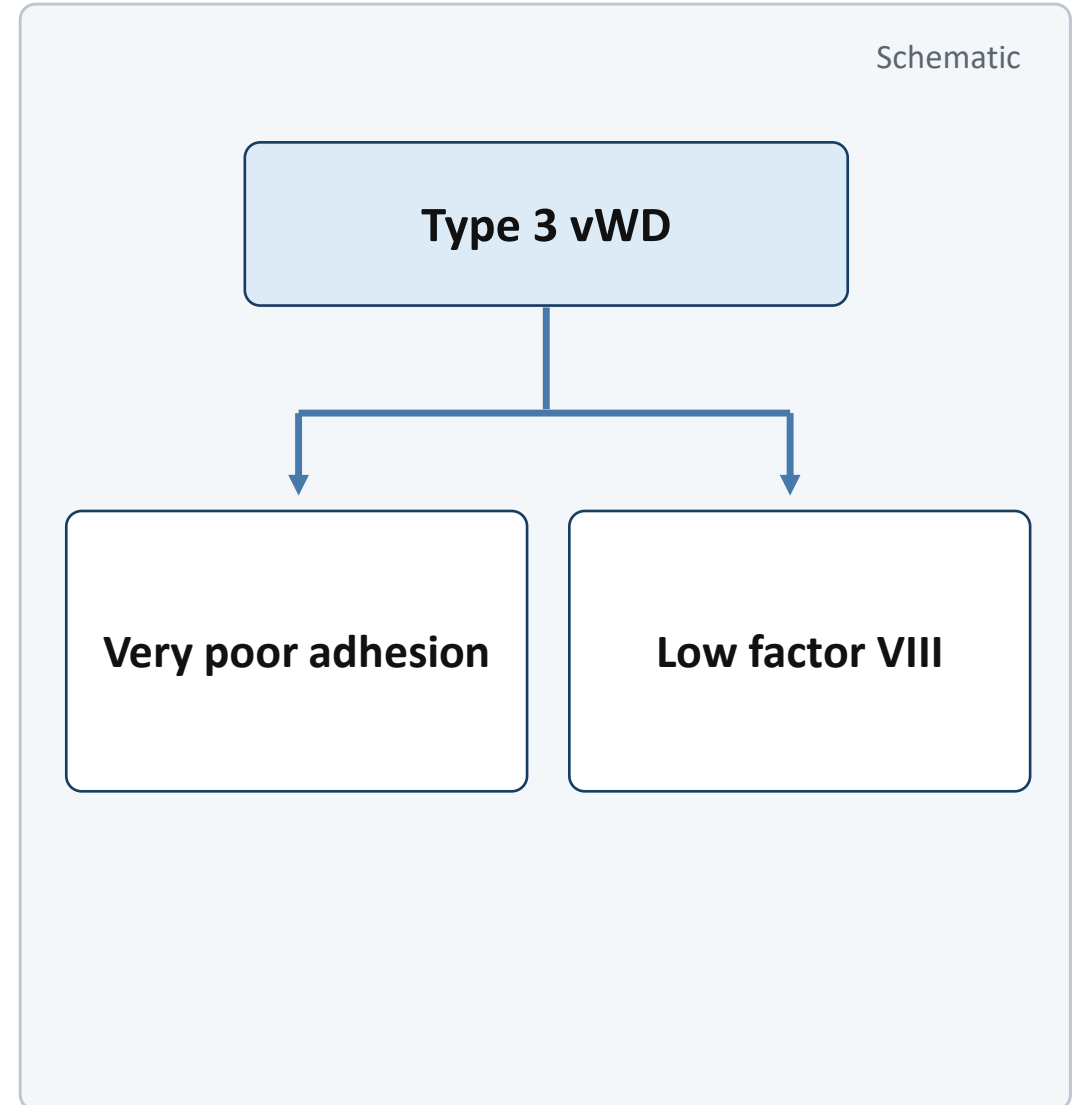
Type 3: Recessive, near-absent vWF

- Type 3 is usually autosomal recessive.
- Deletions or frameshift variants involving both alleles can prevent meaningful synthesis.
- Little or no vWF remains to support adhesion or factor VIII stability.



Type 3 also produces factor VIII deficiency

- Without vWF, factor VIII is poorly stabilized in plasma.
- Reduced factor VIII can impair the coagulation contribution to clot formation.
- The combination explains the severe, hemophilia-like phenotype.



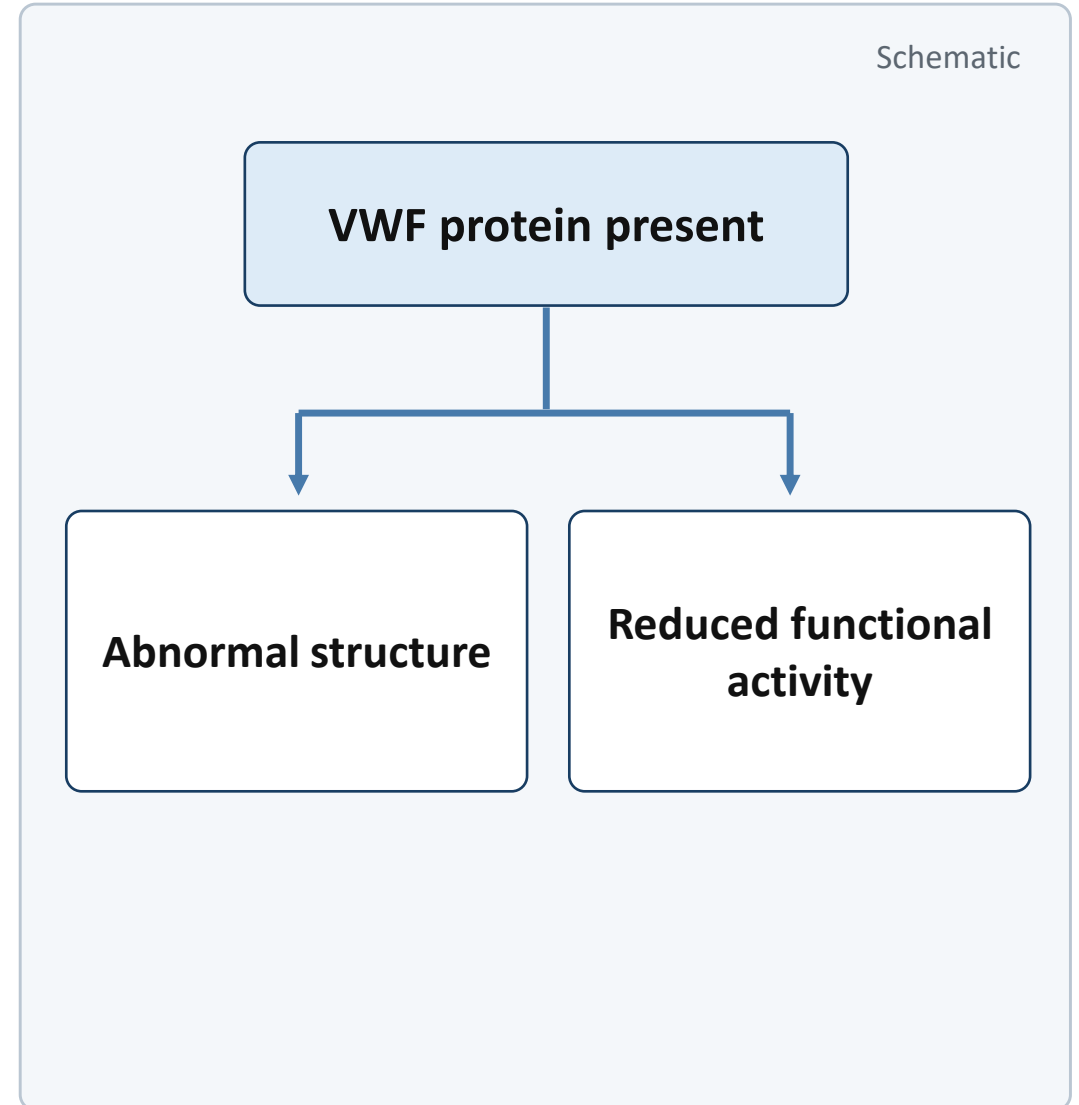
Severe vWD is not simply thrombocytopenia

- Type 3 severity arises from extreme vWF loss and secondary factor VIII reduction.
- Platelet counts may remain normal despite defective adhesion.
- A normal count must not be interpreted as normal platelet-mediated hemostasis.

Feature	Measured quantity	Hemostatic function
Platelet count	Often normal	Adhesion impaired
VWF	Nearly absent	Adhesive bridge lost
Factor VIII	Reduced	Fibrin support reduced

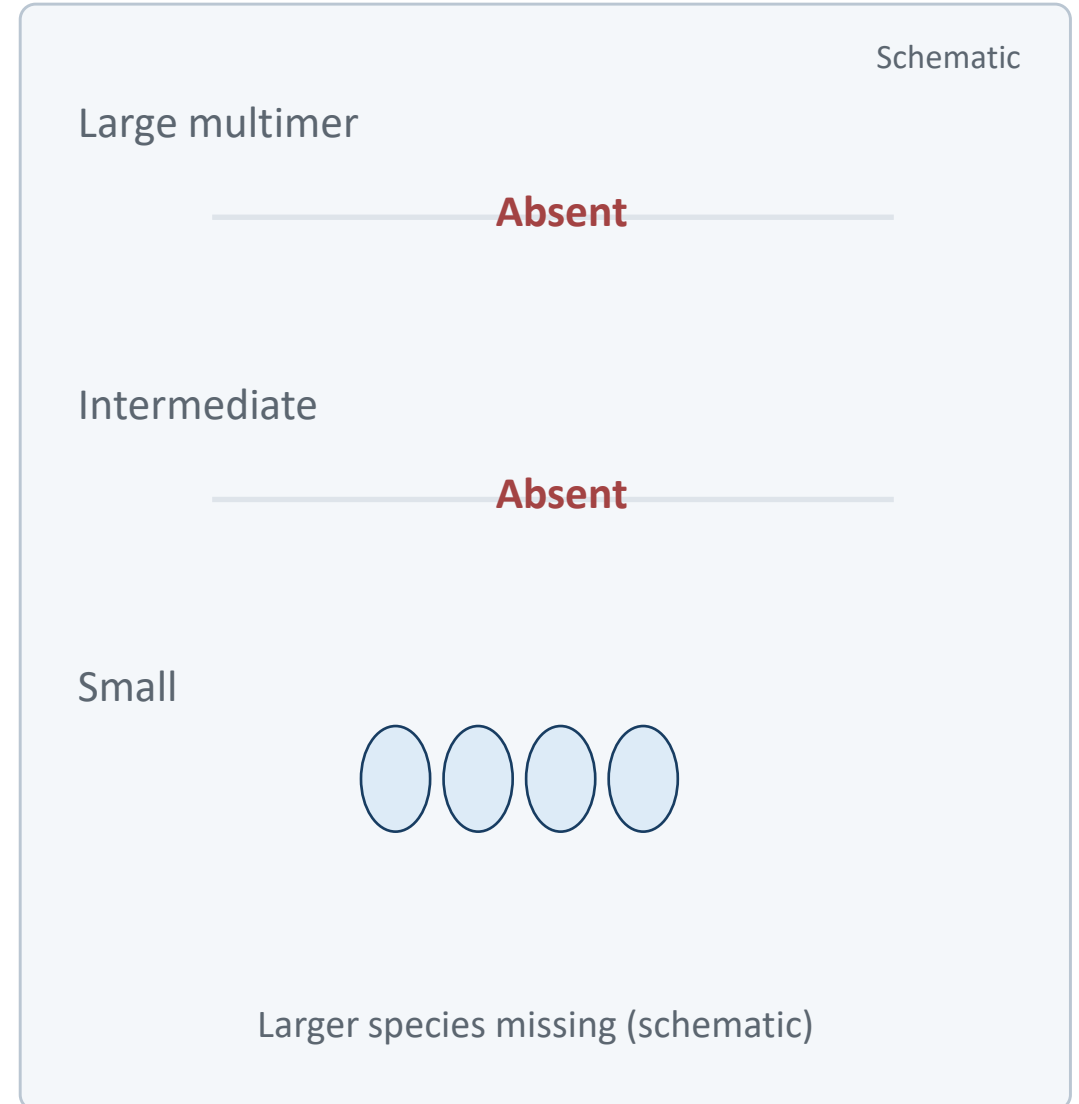
Type 2: Qualitative vWF dysfunction

- Type 2 denotes defective function rather than simple lack of protein.
- Some affected proteins are expressed but cannot perform normal adhesive tasks.
- The type includes several molecular and functional subtypes.



Type 2A involves abnormal multimer assembly

- Type 2A as the most common type 2 subtype.
- Missense changes interfere with assembly of functional multimers.
- Large and intermediate multimers are missing from plasma.



Type 1 and type 2 need different interpretation

- Type 1 mainly reduces the amount of available vWF.
- Type 2 chiefly reduces the functional quality of vWF.
- Activity alone may be decreased in both; Protein quantity helps distinguish them.

Feature	Type 1	Type 2
Mechanism	Quantitative	Qualitative
VWF quantity	Reduced	May be preserved
VWF activity	Reduced	Reduced
Clinical range	Usually mild	Mild–moderate

Type 1 and type 3 differ in depth of loss

- Both are quantitative disorders, but the magnitude of deficiency differs markedly.
- Type 1 generally retains enough vWF for a milder phenotype.
- Type 3 may leave negligible vWF and consequently substantial factor VIII deficiency.

Feature	Type 1	Type 3
Deficiency	Partial	Near-complete
Inheritance	Usually AD	AR
Severity	Usually mild	Often severe
Factor VIII	May decline	Often markedly reduced

A focused bleeding history guides testing

- Characterize epistaxis, wound bleeding, menorrhagia, and postoperative bleeding.
- Ask whether bleeding occurred only after a substantial hemostatic challenge.
- Document similar symptoms in relatives while accounting for variable expression.

Normal platelet count does not exclude vWD

- VWD produces a functional platelet-adhesion defect.
- Platelet counts are typically normal.
- Platelet counting and platelet-function assessment answer different questions.

Feature	Count	Function
Question	How many platelets?	Can platelets adhere?
In vWD	Usually normal	Abnormal
Why	Production preserved	VWF bridge defective

PT and PTT evaluate different pathways

- Prothrombin time (PT) evaluates extrinsic and common coagulation pathways.
- Partial thromboplastin time (PTT) evaluates intrinsic and common pathways.
- A vWF-related fall in factor VIII can affect PTT without requiring PT prolongation.

Feature	PT	PTT
Primary pathway	Extrinsic + common	Intrinsic + common
Factor VIII sensitive?	Not directly	Yes
Relevance to vWD	Usually not altered	Can be prolonged

Why factor VIII loss can prolong PTT

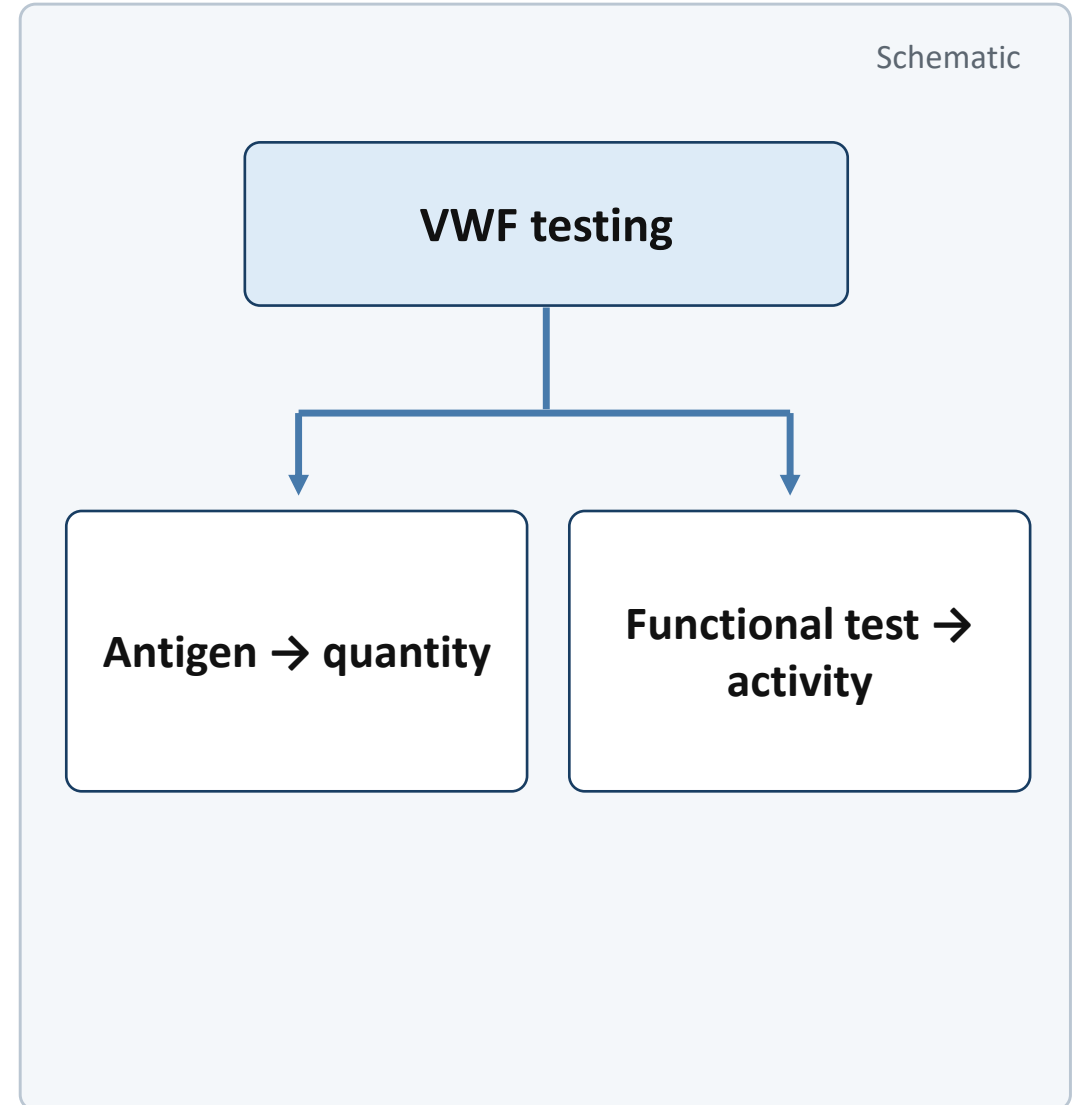
- The intrinsic coagulation assay depends on factor VIII activity.
- VWF normally prolongs the circulating survival of factor VIII.
- Marked vWF deficiency can reduce factor VIII sufficiently to prolong PTT.

Schematic



Antigen tests measure protein abundance

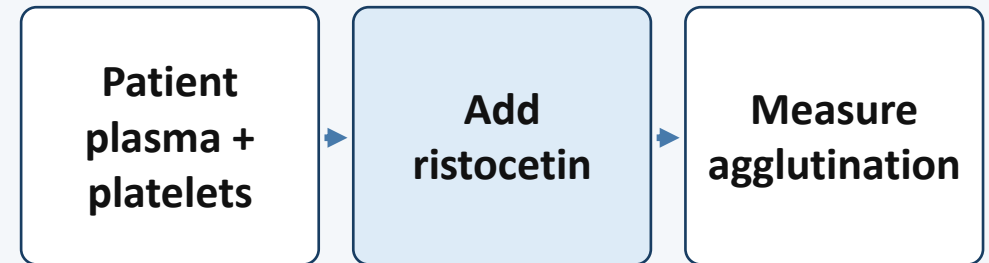
- Immunologic assays quantify factor VIII and vWF protein levels.
- VWF antigen addresses quantity rather than adhesive performance.
- A quantitative result alone cannot fully classify a qualitative defect.



Ristocetin testing probes vWF function

- Patient plasma is combined with reagent platelets and ristocetin.
- Ristocetin activates vWF-mediated binding to platelet GpIb/IX.
- The extent of agglutination reflects functional plasma vWF activity.

Schematic



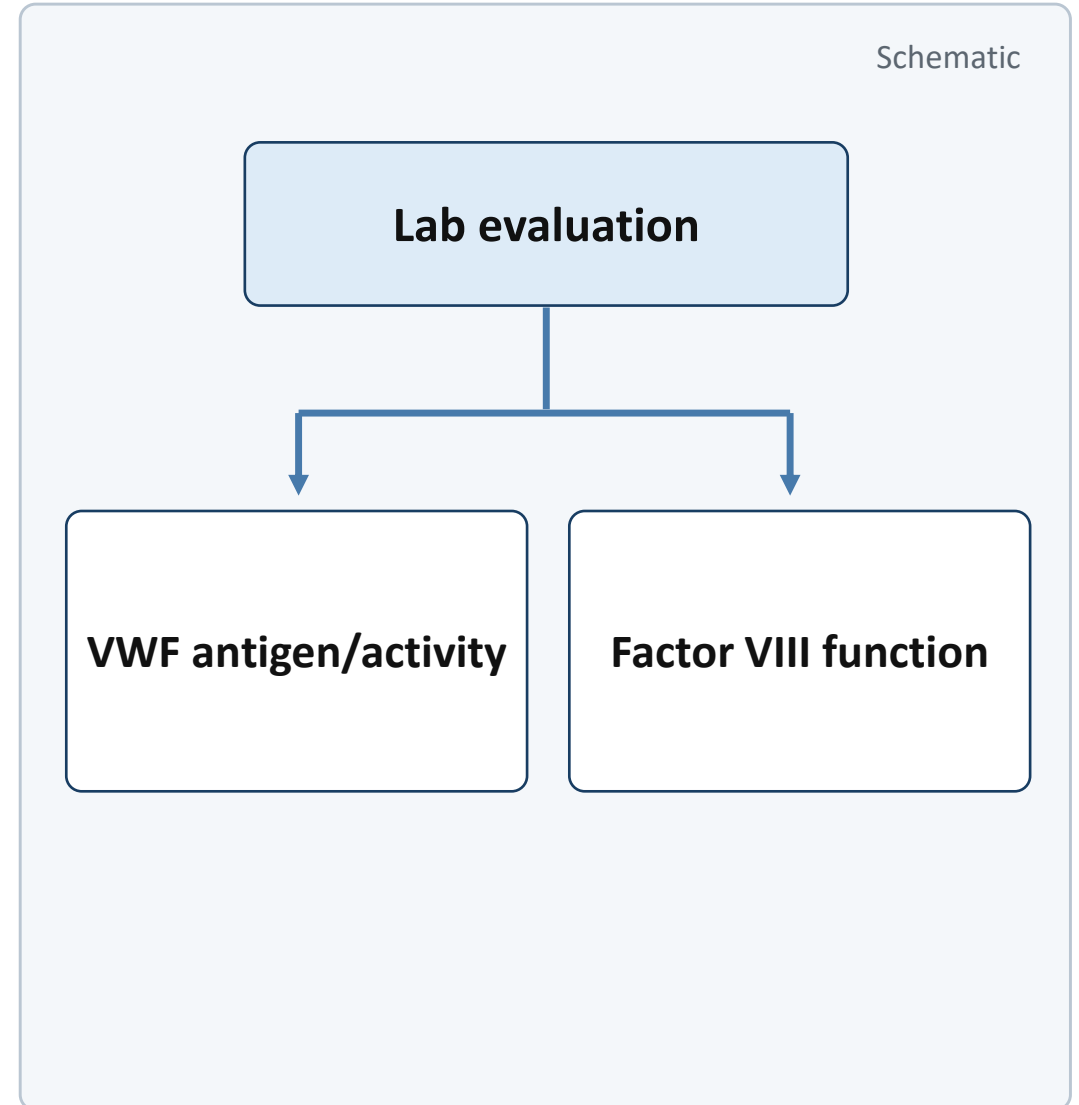
Reduced activity links the disease subtypes

- Both reduced quantity and qualitative dysfunction can lower active vWF.
- Reduced ristocetin cofactor activity as a characteristic finding.
- Subtype interpretation requires combining activity with protein quantity and clinical context.

Feature	Type 1 / type 3	Type 2
Reason activity falls	Insufficient protein	Dysfunctional protein
Count	Normal platelets possible	Normal platelets possible
Next interpretation	Severity of deficiency	Quality of multimers

Factor VIII assays add a second dimension

- Coagulation-based factor VIII testing measures the factor's functional capacity.
- Low factor VIII may be secondary to loss of its vWF carrier.
- This is particularly important when severe vWD resembles hemophilia.



Laboratory interpretation is multidimensional

- Platelet number evaluates thrombocytopenia, not adhesive competence.
- VWF antigen and function evaluate quantity and biological activity.
- Factor VIII activity and PTT assess the secondary-coagulation contribution.

Schematic



Distinguish vWD from hemophilia A

- VWD affects vWF-dependent platelet adhesion and may secondarily reduce factor VIII.
- Hemophilia A arises from a primary factor VIII gene defect.
- Mucosal predominance versus hemarthrosis and the vWF panel help localize the defect.

Feature	Von Willebrand disease	Hemophilia A
Primary defect	VWF	Factor VIII
Hemostatic limb	Adhesion ± coagulation	Coagulation
Clinical clue	Mucocutaneous	Deep tissue / joints
Inheritance	Usually autosomal	X-linked

Acquired platelet dysfunction is another branch

- Aspirin inhibits cyclooxygenase-mediated platelet responses.
- Uremia may impair platelet adhesion, secretion, and aggregation.
- These acquired mechanisms differ from inherited vWF quantitative or qualitative defects.

Feature	VWD	Acquired dysfunction
Example	Inherited vWF defect	Aspirin; Uremia
Primary mechanism	VWF adhesion impaired	Platelet signaling/response
Use in differential	Family + vWF assays	Exposure/comorbidity

Desmopressin mobilizes endogenous vWF

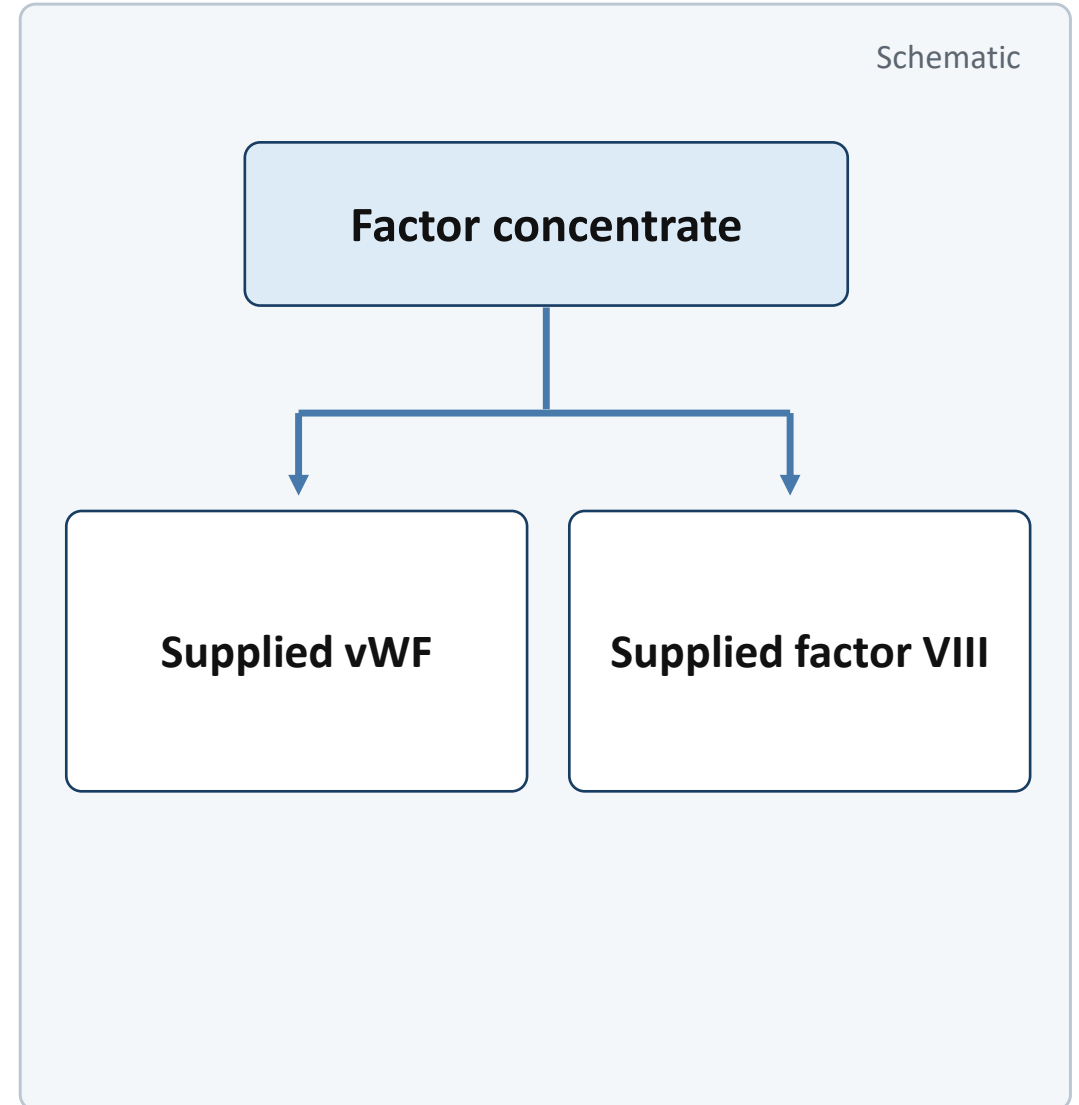
- Desmopressin as a stimulus for vWF release.
- It may help selected individuals with type 1 or type 2 disease around procedures.
- Its utility depends on the patient retaining a releasable functional vWF pool.

Schematic



Concentrates directly replace deficient proteins

- Plasma-derived concentrates can contain both vWF and factor VIII.
- They may support platelet adhesion and secondary coagulation.
- Use is described for hemostatic challenges in selected type 1 or 2 disease.



Recombinant vWF is a replacement option

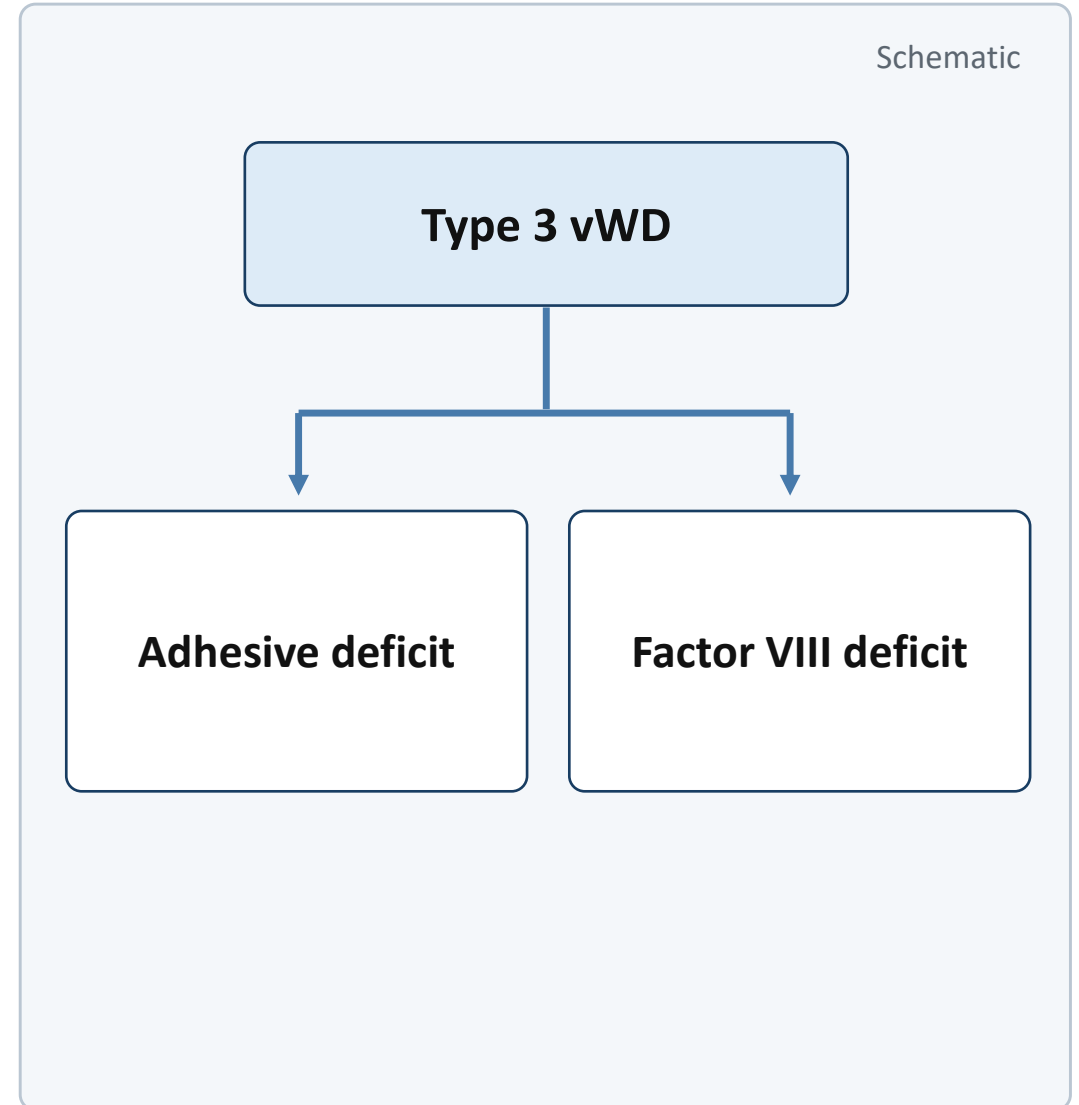
- The source identifies recombinant vWF as an alternative replacement product.
- This strategy replaces the defective adhesive protein rather than releasing stores.
- Therapy must be individualized rather than inferred from the type label alone.

Schematic



Type 3 requires sustained hemostatic protection

- Severe type 3 disease has little or no endogenous vWF available.
- Prophylactic replacement with plasma concentrates and factor VIII.
- Prophylaxis addresses the risk of severe hemophilia-like bleeding.



Clinical case: Bleeding after dental extraction

- A young adult reports prolonged bleeding after a tooth extraction.
- There is recurrent epistaxis; Platelet count is reported as normal.
- What shared defect could explain the mucosal and procedural bleeding?

Schematic

Clinical reasoning

?

Phenotype

?

Mechanism

?

Most likely subtype

Answer and reasoning on following slide

Case interpretation: Investigate vWF function

- A normal platelet count does not test the vWF–GpIb adhesive bridge.
- Assess vWF activity and quantity rather than relying only on platelet number.
- If factor VIII is reduced, intrinsic-pathway testing may also be abnormal.

Schematic



Clinical case: Severe bleeding in siblings

- Two siblings have severe bleeding and no detectable functional vWF.
- Factor VIII activity is also reduced.
- Which vWD category best explains both abnormalities?

Schematic

Clinical reasoning

?

Phenotype

?

Mechanism

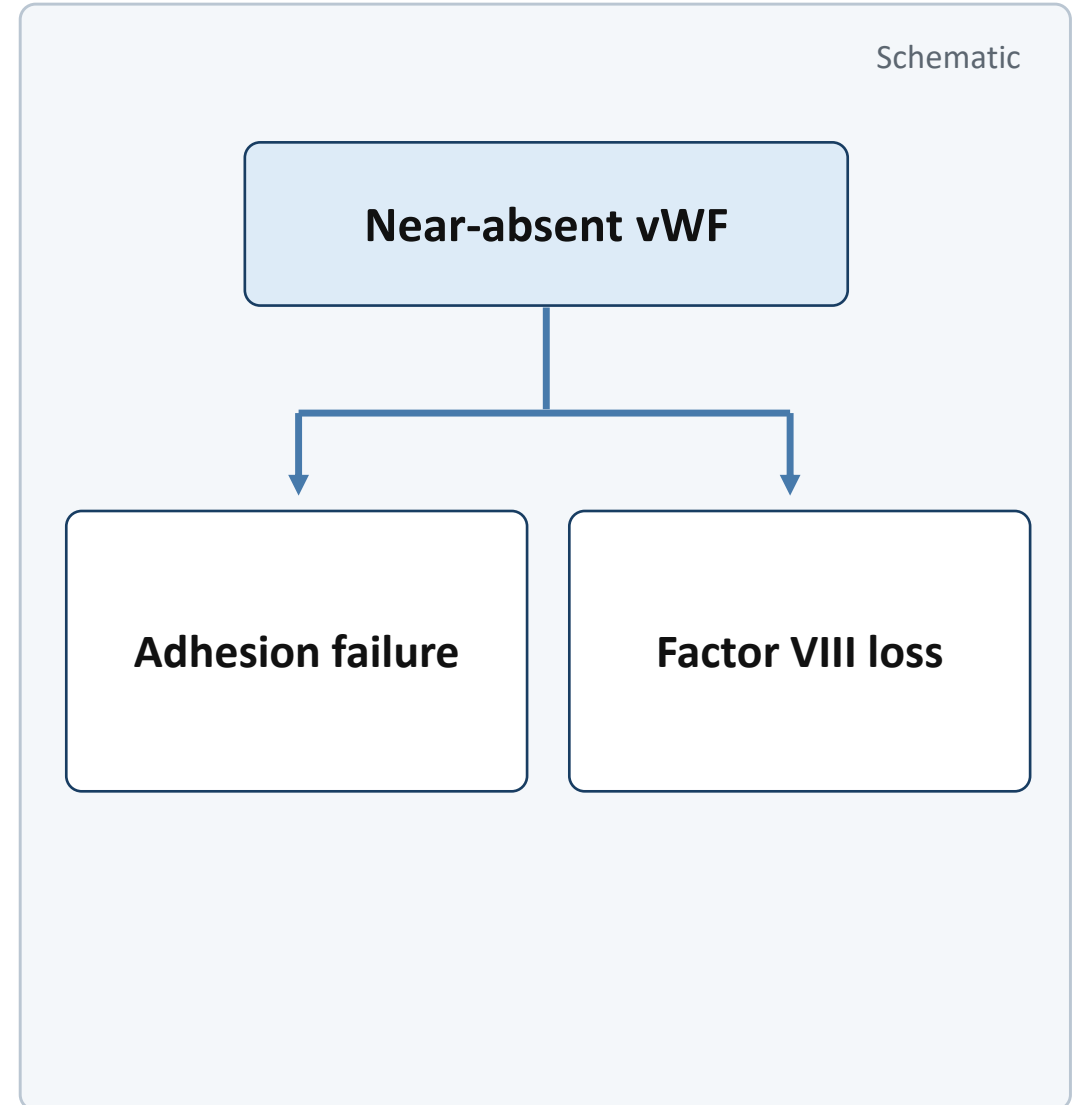
?

Most likely subtype

Answer and reasoning on following slide

Case interpretation: Near-absent vWF

- Near-absent vWF supports a profound quantitative defect.
- Reduced factor VIII follows from loss of plasma stabilization.
- This mechanism supports the severe, hemophilia-like bleeding pattern of type 3.



Clinical case: Protein present but not effective

- A patient has mild to moderate mucosal bleeding and reduced functional vWF.
- Substantial protein is present, but larger multimers are lacking.
- Which mechanistic type is most consistent with these findings?

Schematic

Clinical reasoning

?

Phenotype

?

Mechanism

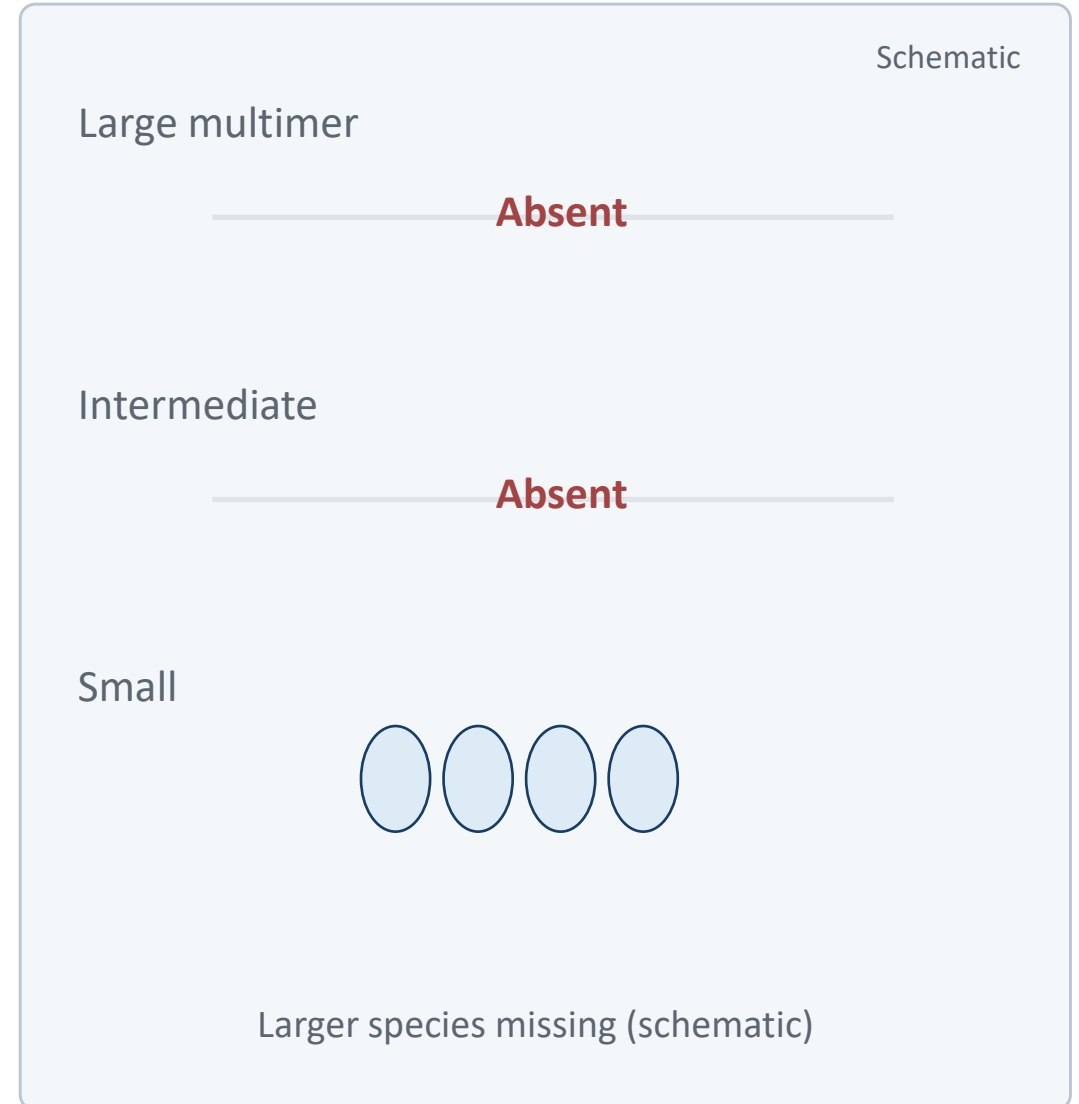
?

Most likely subtype

Answer and reasoning on following slide

Case interpretation: Type 2A multimer defect

- Protein abundance alone does not establish functional adequacy.
- Loss of large and intermediate multimers indicates abnormal assembly in the source description.
- Activity and multimer pattern clarify why the adhesive system underperforms.



Integrate type, phenotype, and laboratory results

- Type 1: Partial deficiency, variable expression, usually mild phenotype.
- Type 2: Qualitative dysfunction, including type 2A multimer defects.
- Type 3: Near-absence, low factor VIII, often severe phenotype.
- A normal platelet count does not contradict any of these mechanisms.

Feature	Type 1	Type 2	Type 3
Core problem	Low quantity	Poor quality	Near-zero quantity
Clinical pattern	Usually mild	Mild–moderate	Often severe
Mechanistic clue	Maturation/clearance	Multimer defect	Biallelic loss

Essential clinicopathologic synthesis

- VWF is the adhesive bridge between matrix and platelet GpIb/IX.
- Its binding to factor VIII explains the coagulation component of severe disease.
- Quantitative versus qualitative defects underlie the three major vWD types.
- Clinical history, vWF activity/antigen, and factor VIII testing must be interpreted together.

Source and further textbook context

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 14: Red Blood Cell and Bleeding Disorders — factor VIII–vWF complex and vWD.
- Chapter 4: Hemodynamic Disorders — platelet adhesion, aggregation, and hemostasis.