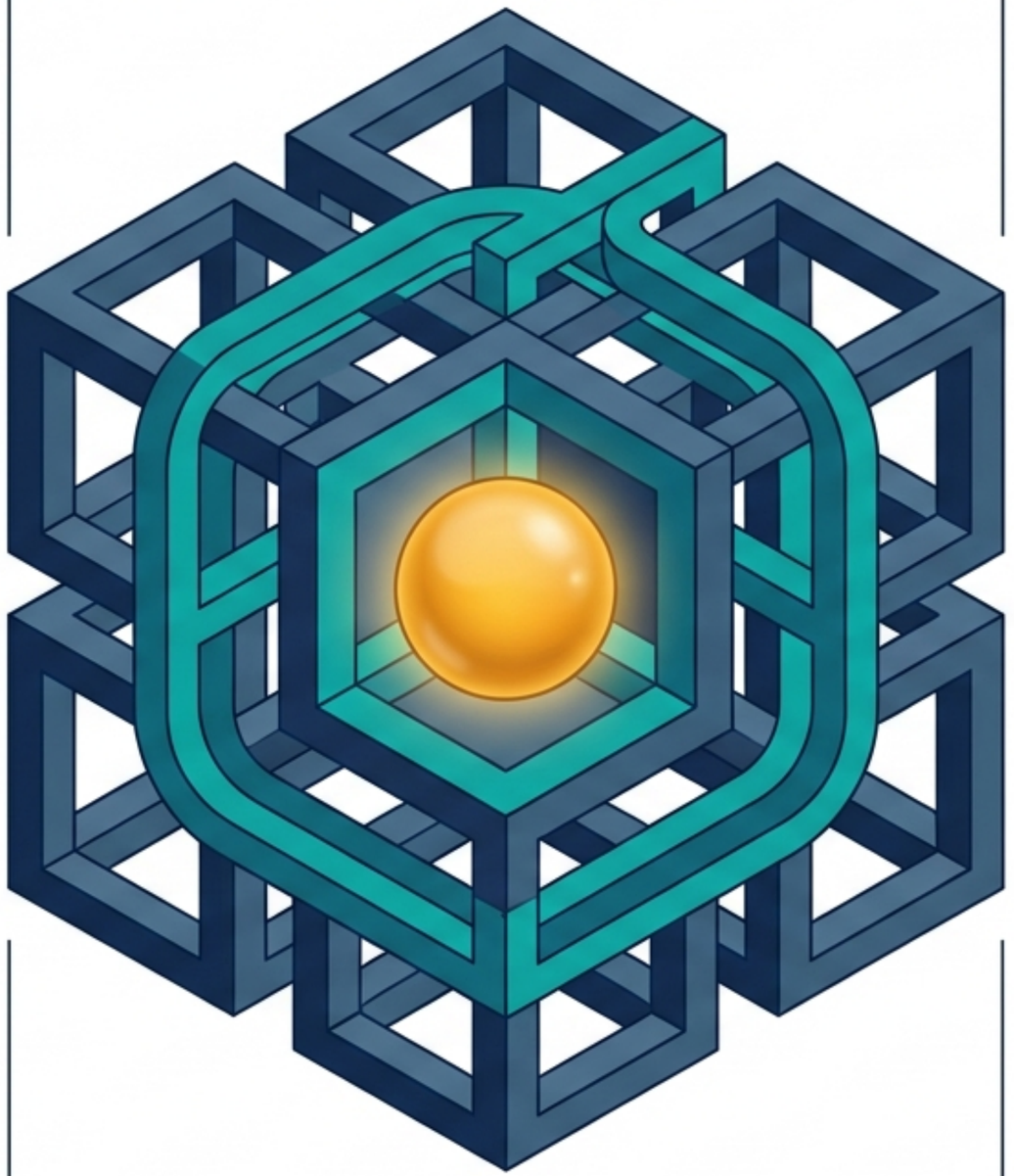


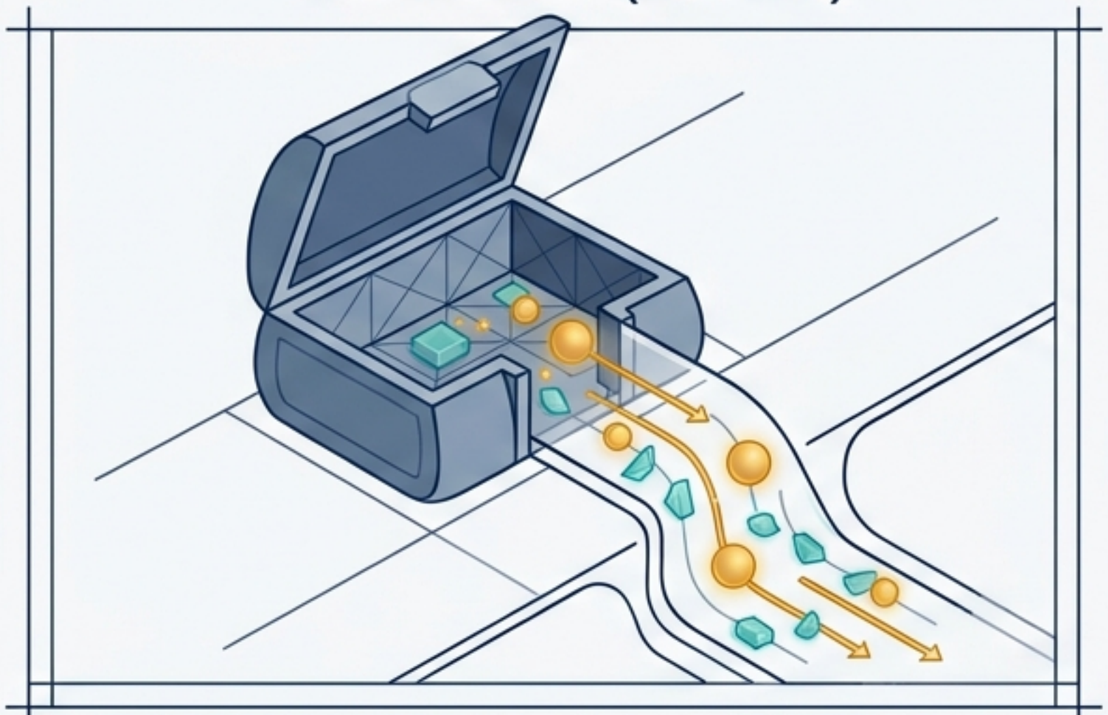
Strategic VWF Replacement

Principles, Kinetics, and Clinical Management

The challenge is not only to replace.
It is to replace wisely.

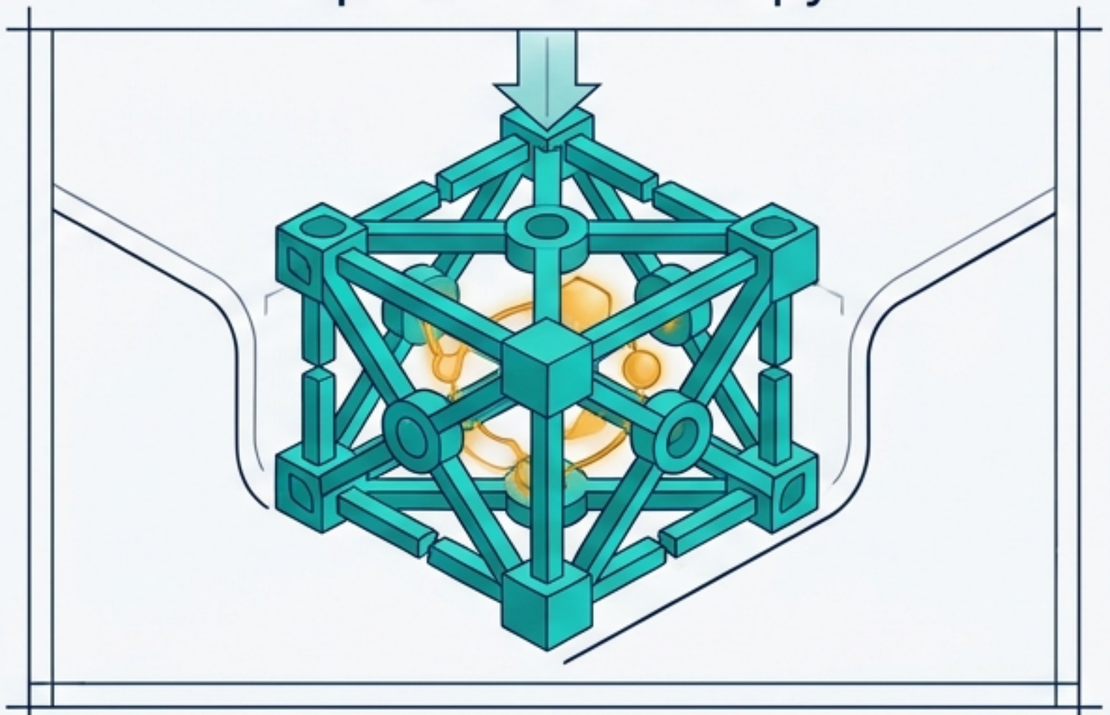
Borrowing from the Endothelium vs. Supplying the Scaffold

Mobilization (DDAVP)



- Transiently mobilizes endogenous VWF.
- Requires a **stored, releasable, functional reserve.**
- Limited by tachyphylaxis & hyponatremia.

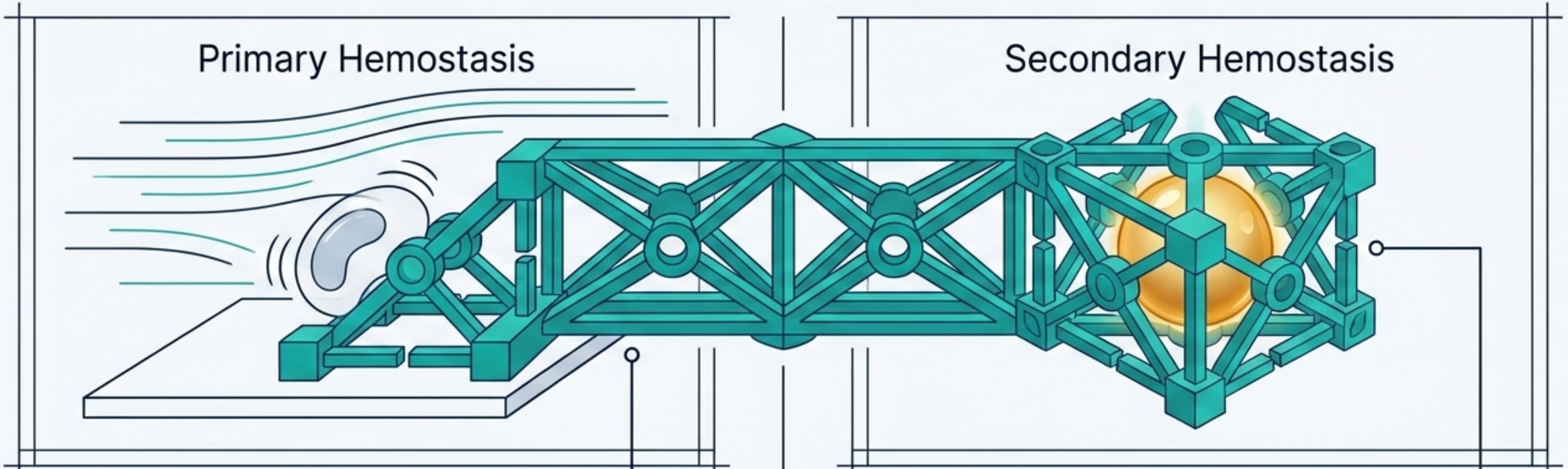
Replacement Therapy



- Supplies exogenous VWF directly.
- Required when endogenous VWF is **absent, dysfunctional**, or **unsafe to mobilize.**
- Provides **direct hemostatic support.**

The Dual Defect of von Willebrand Disease

The Hemostatic Scaffold



Defect 1: Primary Hemostasis

Platelets cannot adhere to the injured vessel wall under flow without the VWF bridge.

Defect 2: Secondary Hemostasis

Without the VWF shield, endogenous Factor VIII is unprotected in circulation and rapidly degrades.

Explicit Triggers for Exogenous Replacement

Patient Profiles

- ✓ Type 3 VWD (total absence)
- ✓ Severe Type 1
- ✓ Many Type 2 variants
- ✓ Type 1C (accelerated clearance)
- ✓ DDAVP non-response or contraindication

Procedural Demands

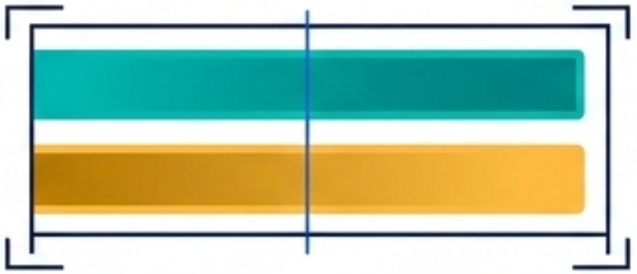
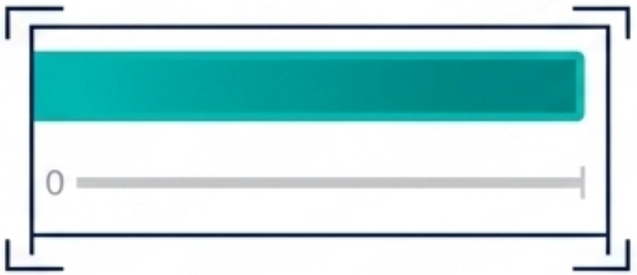
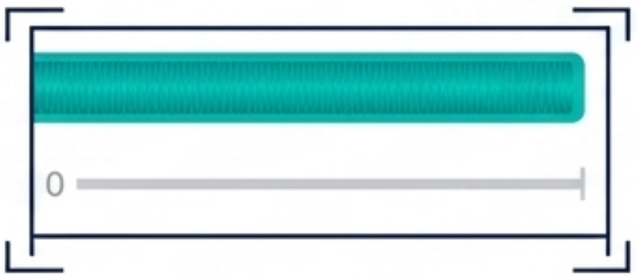
- ✓ Major or critical-site surgery
- ✓ Severe active bleeding
- ✓ Recurrent gastrointestinal bleeding
- ✓ Long-term prophylaxis

Replacement is never deployed simply because the number is low. It is used when bleeding risk requires support that endothelial release cannot reliably provide.

Matching Therapeutic Logic to Disease Subtype

Type 1 (Severe)	Type 2 (Variants)	Type 3
		
Quantitative defect.	**Qualitative defect (2A, 2B, 2M, 2N).**	**Total absence.**
Sustained volumetric support exceeding endothelial capacity.	Quality correction: supplying a protein engineered to do what the patient's VWF cannot.	Absolute replacement (VWF + immediate FVIII support), alongside vigilant management of alloantibody/anaphylaxis risks

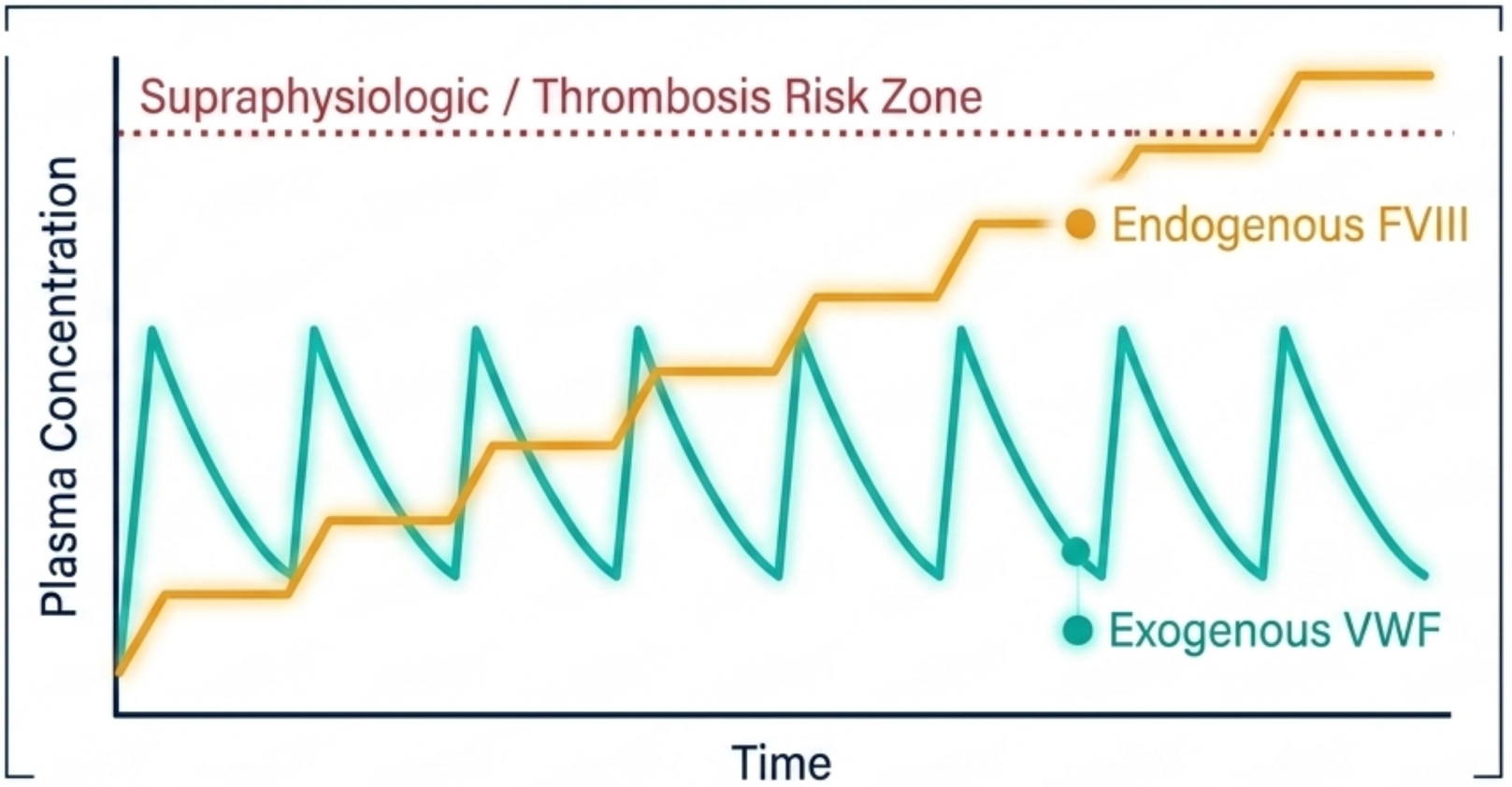
The Biologic Arsenal is Not Interchangeable

THERAPY PROFILE		CLINICAL IMPLICATION & TRADE-OFF
Plasma-Derived VWF/FVIII		Contains both. Corrects primary and secondary defects instantly. **Trade-off:** Highest risk of FVIII accumulation with repeated dosing.
Plasma-Derived VWF-Only		Replaces VWF, allows endogenous FVIII to rise secondarily. Excellent for repeated dosing. **Trade-off:** May require initial FVIII co-administration if baseline is critical.
Recombinant VWF		Distinct multimer/pharmacokinetic profile. Zero human plasma exposure. Zero baseline FVIII.

Strategic Product Selection Pathway

The product is not just a brand. It is a biologic preparation with a distinct **VWF/FVIII composition**.

The Hidden Kinetic: FVIII Accumulation



- Infused VWF binds and protects endogenous FVIII.
- With repeated dosing, FVIII levels can rise substantially, independently of the VWF dose administered.

The Goal: Adequate hemostasis. Not maximal FVIII.

The Bleeding vs. Thrombosis Balancing Act

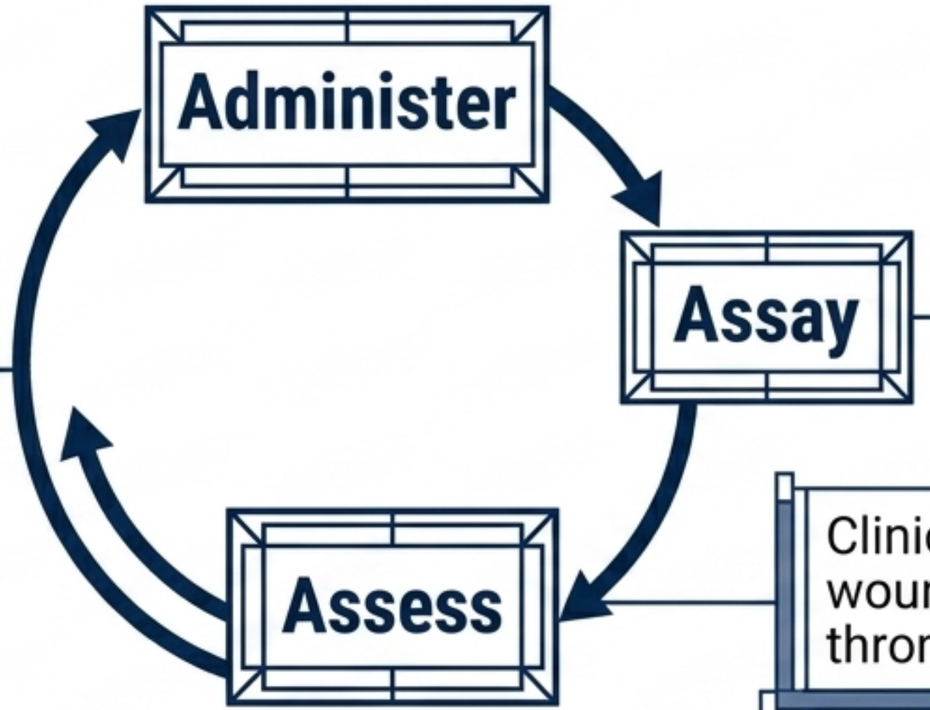
Replacement therapy is biologically active.
It intentionally shifts the patient toward a procoagulant state.

High-Risk Settings for Thrombosis:

- Older age
- Immobility
- Cardiovascular disease
- Cancer surgery
- Orthopedic surgery
- Concurrent antifibrinolytic use

Clinical Action: Avoid extended periods of excessively high VWF and FVIII levels in high-risk patients. Monitor both under-correction and over-correction.

Monitoring as an Active Treatment Strategy



VWF activity, **FVIII** activity. (Trough levels are just as critical as peak levels for prolonged coverage).

Clinical bleeding status, wound/procedural-site assessment, thrombotic risk evaluation.

The Mindset Shift

- **Diagnosis asks:** “What disorder is this?”
- **Treatment asks:** “Have we created enough hemostatic function without unnecessary excess?”

Perioperative Guideline Targets

ASH/ISTH/NHF/WFH 2021

The Standard Target:

Maintain VWF activity AND FVIII activity at ≥0.50 IU/mL.

Duration: For at least 3 days in major surgery (individualized by procedure and bleeding risk).

Prophylaxis Note: Long-term prophylaxis can shift care from episodic rescue to prevention in patients with severe, frequent bleeding (e.g., recurrent GI bleeds).

Beyond the Factor: Combined Therapy

Clinical Application: Reflect & Apply

Patient Profile Card

- 46yo woman
- Type 2A VWD
- Major abdominal surgery
- Baseline:
  - VWF Ag 48%
  - VWF Act 14%
  - FVIII 42%
- Loss of high-molecular-weight multimers.
- DDAVP non-responder.

Why Replacement?

Needs quality correction (functional multimers) and sustained surgical coverage. DDAVP cannot fix the multimer defect.

The Kinetic Risk

She already produces FVIII (42%). Providing VWF will stabilize her endogenous FVIII, causing a secondary rise.

The Plan

Closely monitor for FVIII accumulation and thrombotic risk over the multi-day surgical recovery.

The Risk of Treating the Number

Replacement therapy can encourage dangerous numeric thinking:
VWF is low -> give VWF.

The Strategic Question:

What level is needed for this patient, this bleed, this duration, and this risk profile?

Final Takeaway: The goal of VWF replacement is not to normalize a number.
It is to provide the right hemostatic function for the right duration in the right patient.