# **Blood** in Context

## The Dynamic **Pathology** of Acquired **von Willebrand Syndrome**

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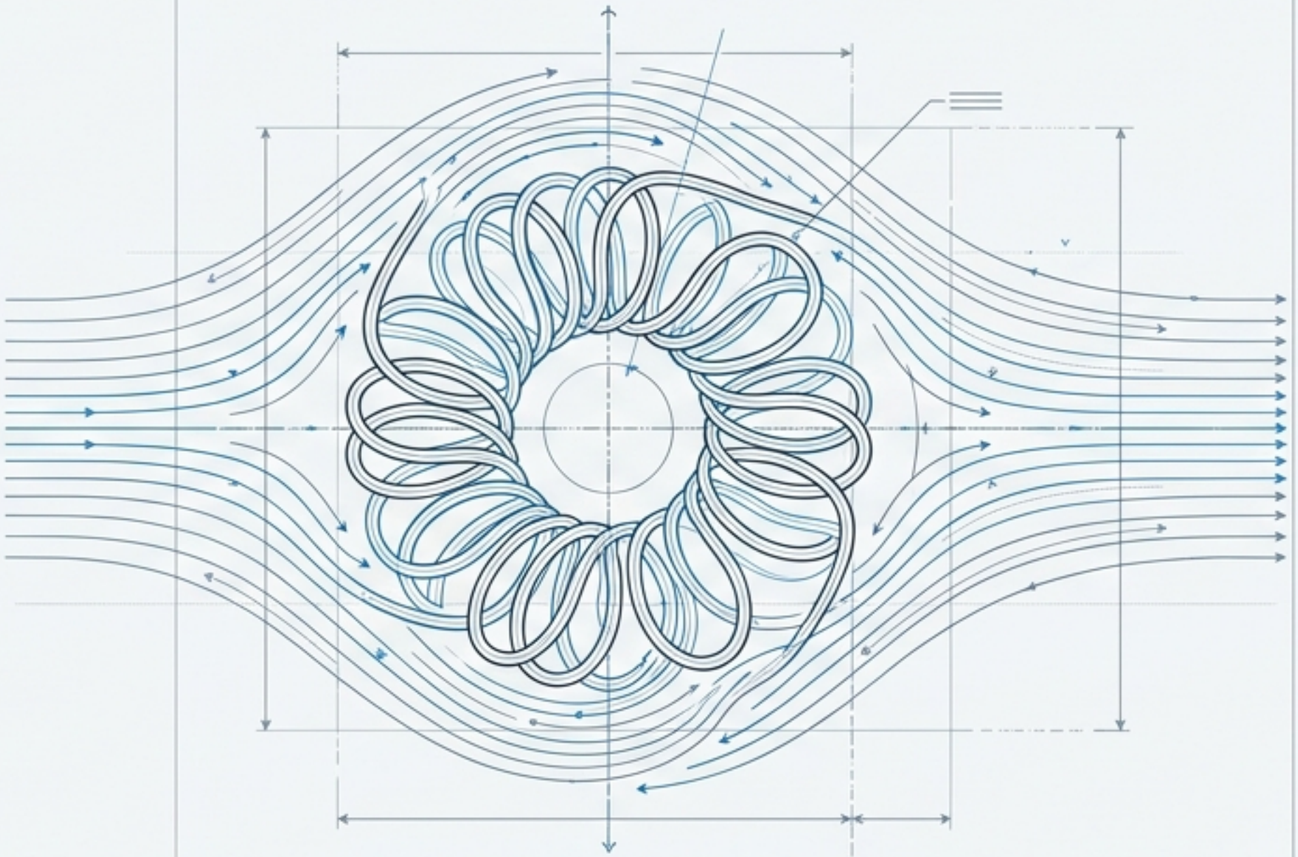
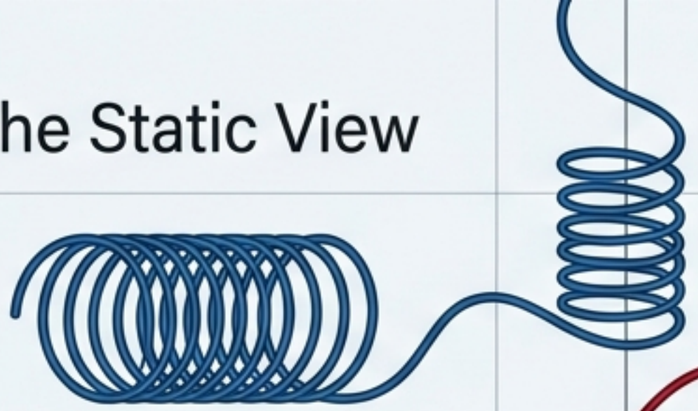
When hemostasis is disrupted by disease, flow, or clearance.



## **Inherited VWD** - The Static View

The healthy VWF multimer, is advanced medical diagnostic aesthetic.

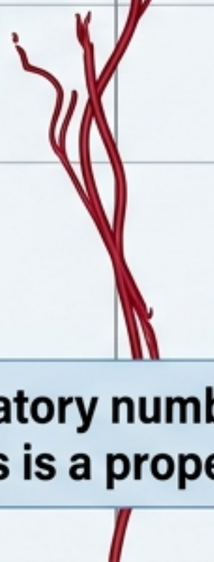


| | |
|---|---|
| **Genetic Origin** | Present at birth; DNA-level defect. |
| **Onset Timing** | Usually early childhood. |
| **Family History** | Often positive. |
| **Laboratory Meaning** | Reflects fixed biology of the VWF gene. |
| **Core Biological Question** | What did the patient inherit? |

## **Acquired VWS** - The Dynamic View

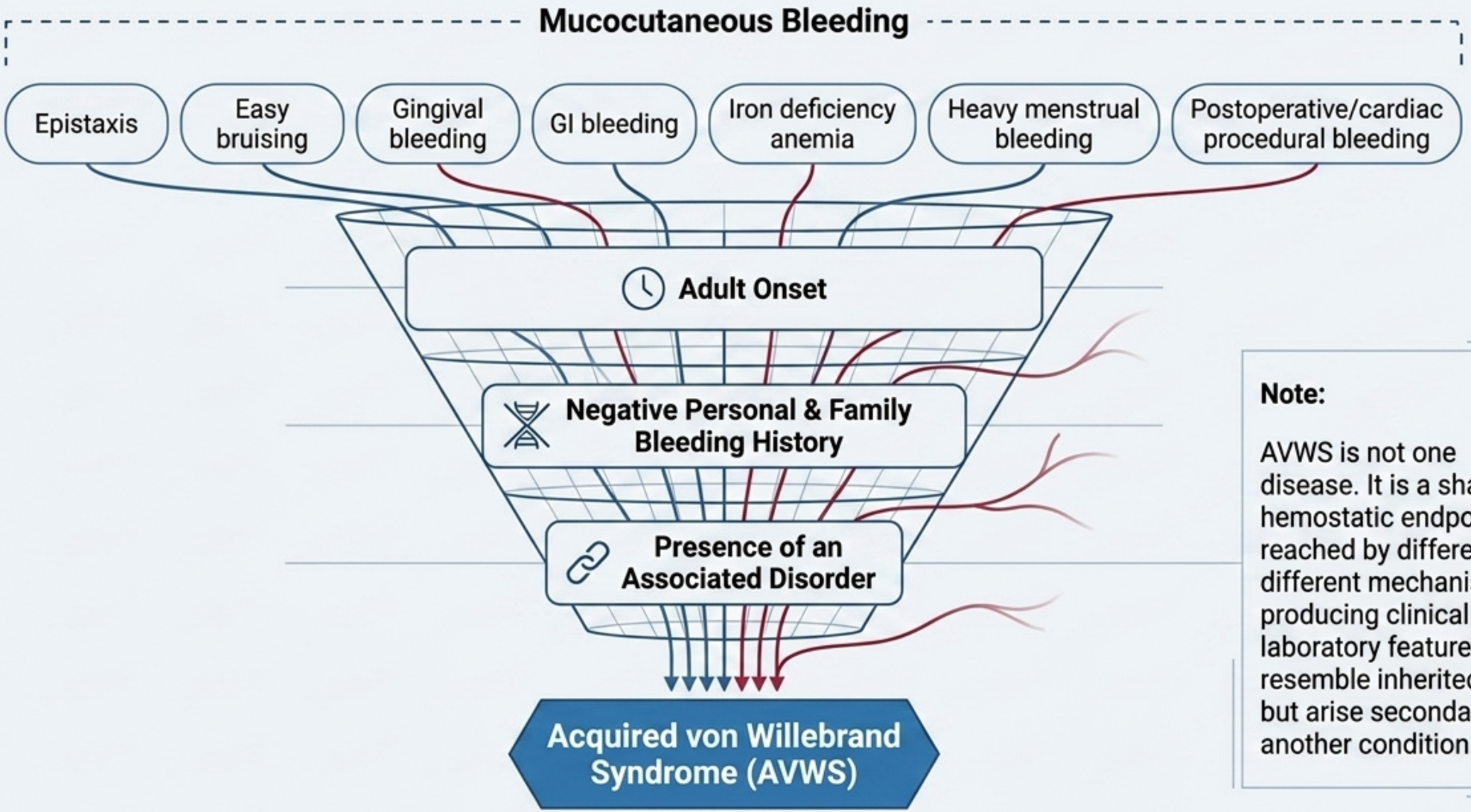
Damaged VWF natit damaged and vulnerable VWF under systimic systemic stress.

| | |
|---|---|
| **Genetic Origin** | Normal VWF genes; secondary to environmental conditions. |
| **Onset Timing** | Adult onset. |
| **Family History** | Negative. |
| **Laboratory Meaning** | Reflects a vulnerable, circulating structure being damaged or cleared. |
| **Question** | What is happening to VWF now? |



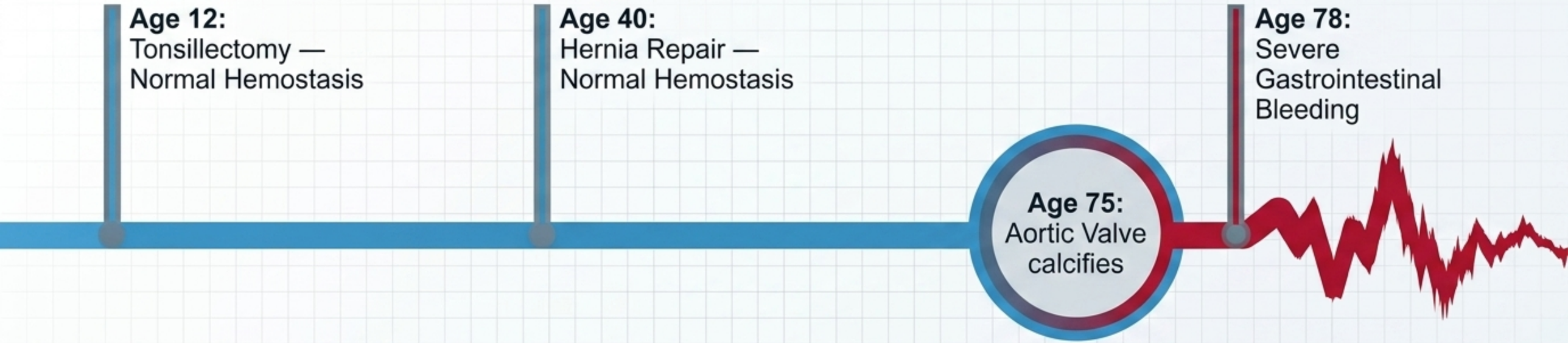
**Insight: VWF is not simply a fixed laboratory number. It is a vulnerable, moving participant in disease. Hemostasis is a property of blood in context.**

# Symptoms to Syndrome Funnel




**Note:**

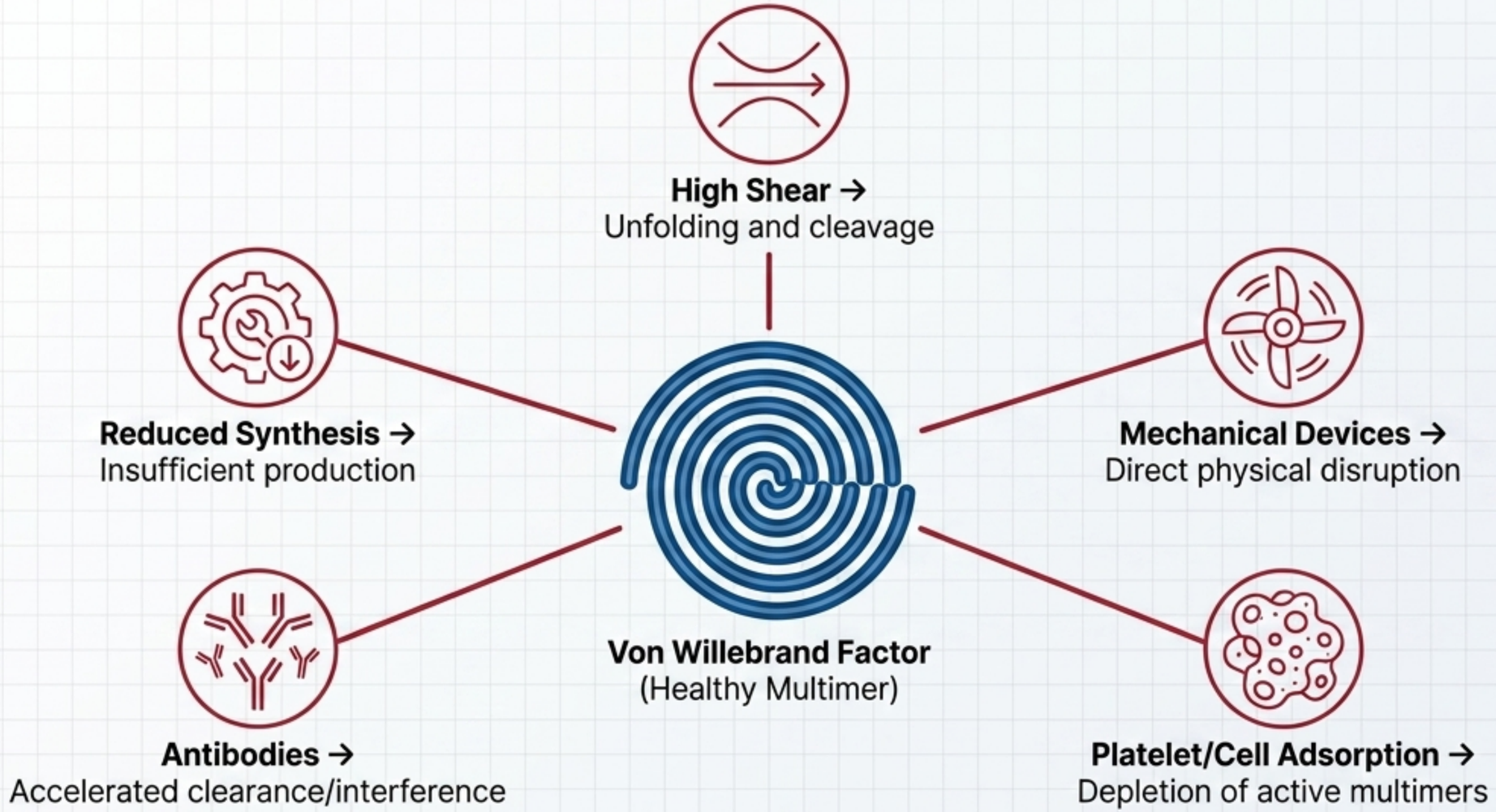
AVWS is not one disease. It is a shared hemostatic endpoint reached by different different mechanisms, producing clinical and laboratory features that resemble inherited VWD but arise secondary to another condition.




## Core Takeaway:

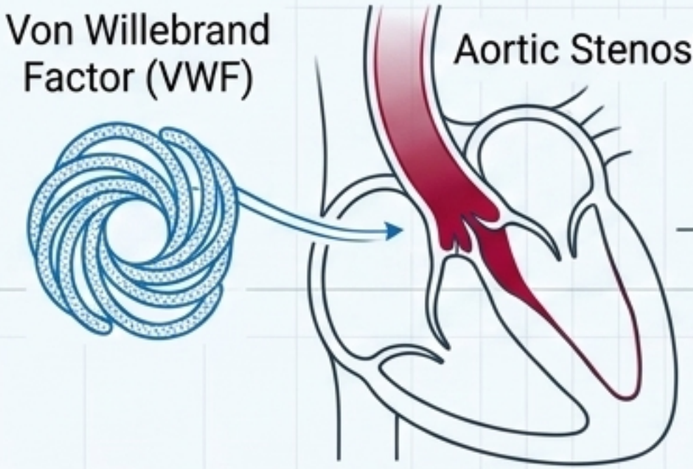
The **most important clinical clue** is timing. A patient who successfully underwent surgery or trauma earlier in life without bleeding should not be assumed to have newly discovered inherited VWD. The clinical task is to investigate what changed in their circulation, immune system, or endocrine state.

# Mechanism Ecosystem Map



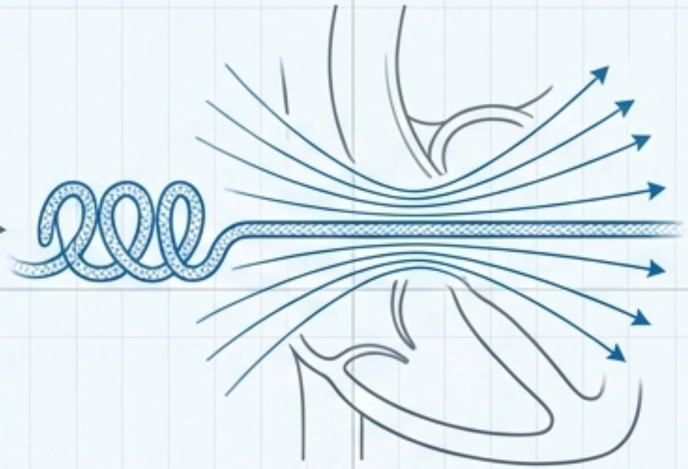

**The common mistake is to think of associated diseases as a list.**
**They are better understood as mechanisms.**

## Phase 1: Normal Flow & Stenosis Entry



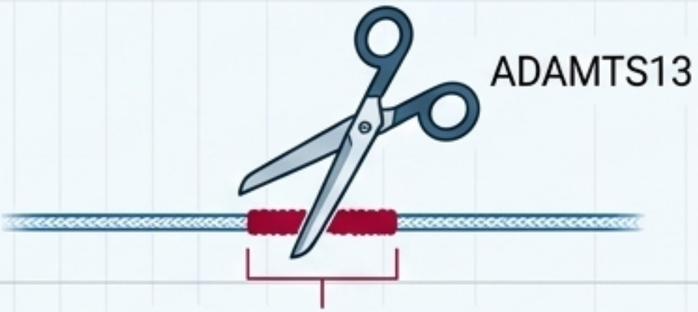

Normal Flow

## Phase 2: Velocity Acceleration & VWF Stretching



Velocity accelerates. VWF stretches.

## Phase 3: Cleavage & Loss of Function




Selective loss of the largest, most hemostatically active multimers.

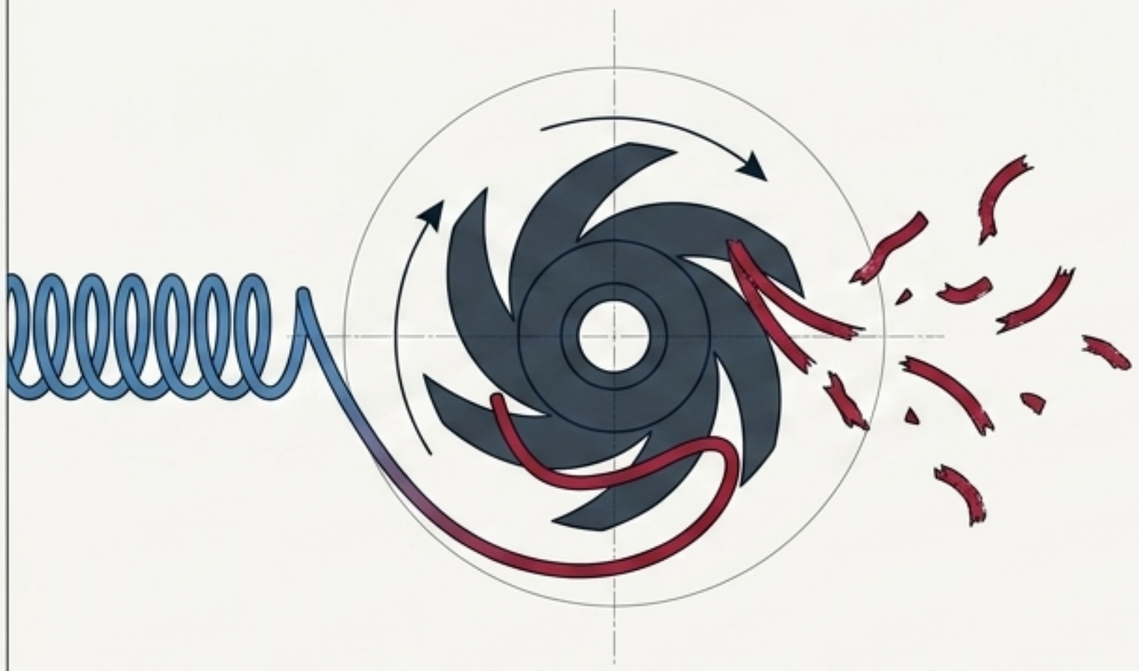
### Clinical Link (Heyde Syndrome)

Aortic Stenosis + Loss of high-molecular-weight multimers + GI bleeding (often from angiodysplasia).

**Note**: Angiogenesis impairment may contribute to fragile mucosal vascular beds in the GI tract.

**Teaching Point**: Hemostasis can improve not because hematology changed the blood, but because cardiology changed the flow (e.g., via TAVI/AVR).

## The Mechanical Threat



**Culprits:** Left ventricular assist devices (LVADs), Extracorporeal membrane oxygenation (ECMO).

**Pathophysiology:** Shear-mediated unfolding + direct mechanical disruption. Laboratory multimer abnormalities are near-universal in these patients.

## The Bleeding Context Formula

# Multimer Loss ≠ Guaranteed Bleeding

**AVWS** + Anticoagulation + Antiplatelet therapy + Renal function + Mucosal lesions + Procedural exposures = **True Bleeding Risk**

**Insight:** AVWS is part of the bleeding biology; it is not the whole story.

# The MPN Paradox: Platelet Adsorption

**Associated Conditions:** Myeloproliferative Neoplasms (MPN) — specifically Essential Thrombocythemia (ET) and Polycythemia Vera (PV).

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**The Paradox:** The patient has too many platelets, but platelet-dependent hemostasis is impaired because the high-molecular-weight VWF structures have been consumed. Laboratory phenotype resembles Type 2A VWD.

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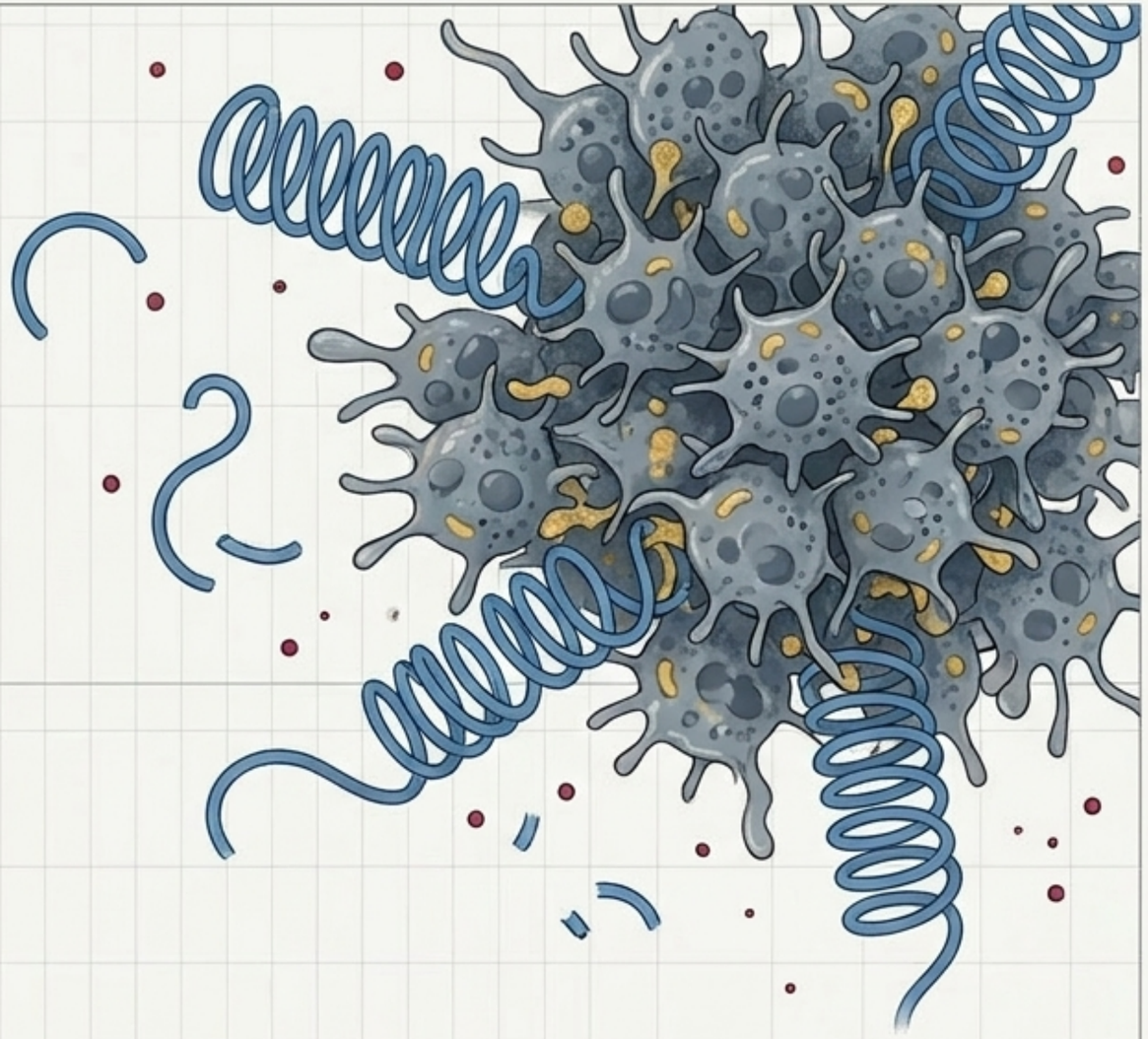
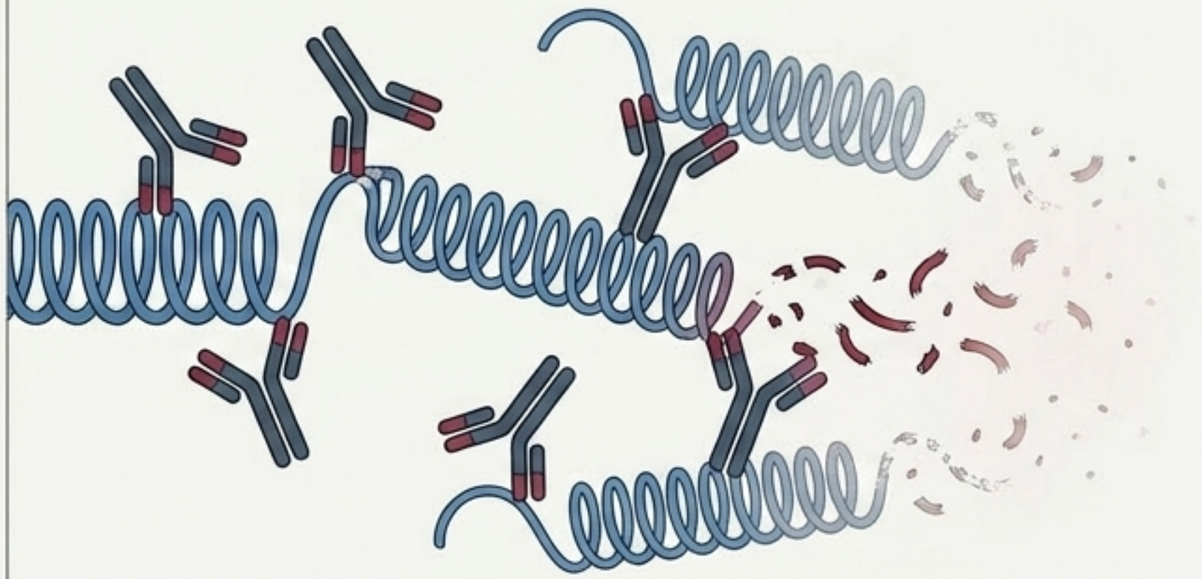
**Clinical Impact:** This is why AVWS must influence decisions about prescribing aspirin in extreme thrombocytosis. Platelet thresholds alone are imperfect predictors of bleeding.



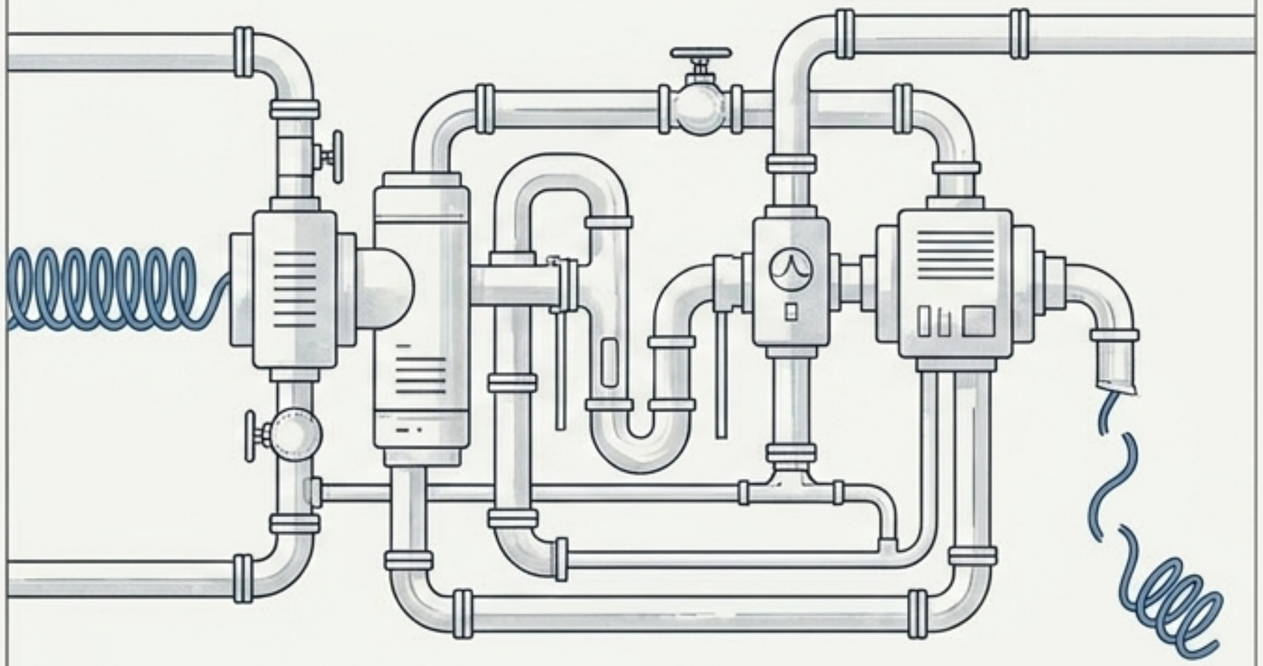
# Mechanism 4: Antibodies & Accelerated Clearance



**Associations:** Lymphoproliferative disorders (Lymphoma), Plasma cell dyscrasias (Multiple Myeloma, Waldenström macroglobulinemia), MGUS.

**Key Insight:** Testing for anti-VWF antibodies is imperfect; negative testing does not exclude immune-mediated AVWS. Rapid clearance means standard VWF replacement therapies may be short-lived.

# Mechanism 5: Reduced Synthesis



**Associations:** Hypothyroidism.

**Key Insight:** Conceptually different from shear-mediated AVWS. The problem is not destruction of large multimers; it is insufficient production, producing a Type 1-like pattern. Correctable with thyroid replacement.

# The Master Mechanism Matrix

| Mechanism Category | Primary Culprits | Pathophysiology | Key Lab Signature | Definitive Treatment |
|---|---|---|---|---|
| High Shear | Aortic stenosis | Flow unfolds VWF, exposing A2 to ADAMTS13 | Loss of HMW multimers | Valve replacement |
| Mechanical Support | LVAD, ECMO | Shear unfolding + direct mechanical disruption | Loss of HMW multimers | Device removal or optimization |
| Cell Adsorption | Essential thrombocythemia, PV | Multimers adsorbed onto massive platelet burdens | Type 2A-like (low activity-to-antigen) | Cytoreduction |
| Antibodies/Clearance | MGUS, Lymphoma, Waldenström | Immune-mediated clearance or functional block | Variable; poor response to VWF replacement | IVIG, Plasmapheresis, Clone-directed therapy |
| Reduced Synthesis | Hypothyroidism | Insufficient VWF production | Type 1-like pattern | Thyroid replacement |

# The Diagnostic Discipline

~~Flawed Question: Does this patient have low VWF?~~

**Better Question:** Why does this patient have a VWD-like pattern now?

**Step 1:** Clinical Relational Linking

Age of onset + Bleeding phenotype + Negative family history.

**Step 2:** The Testing Panel

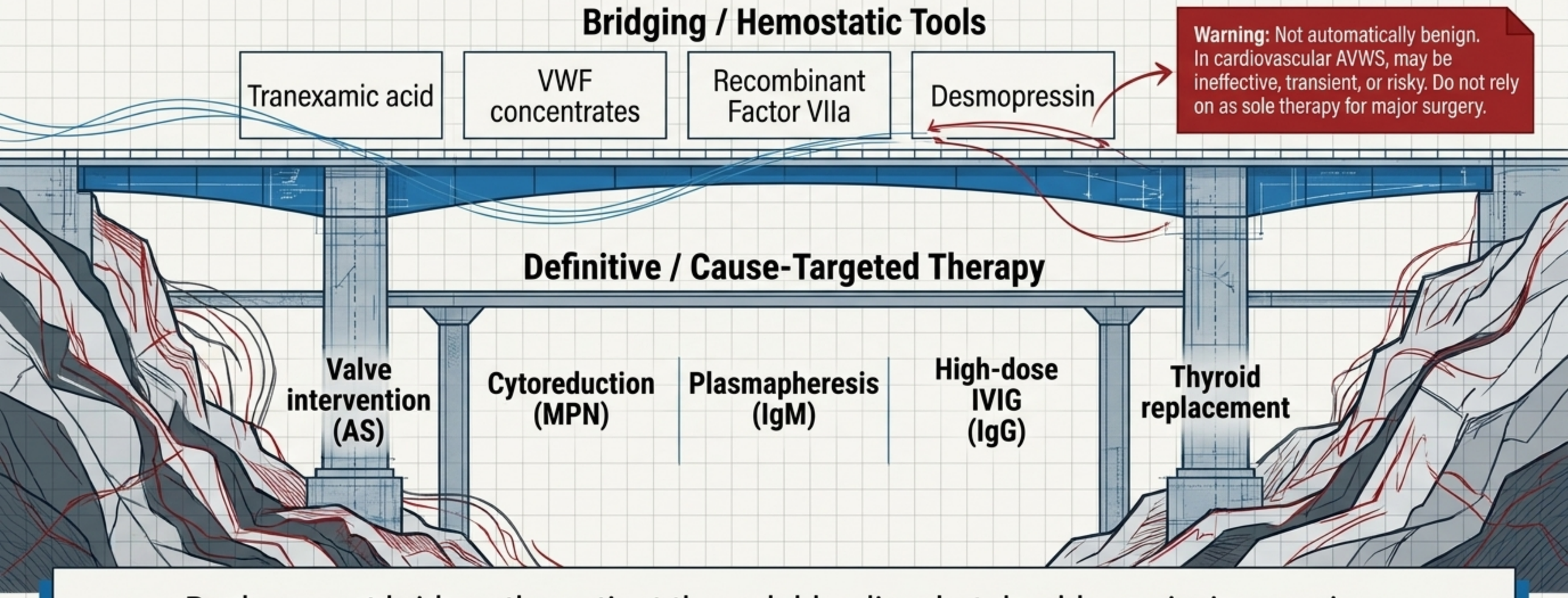
Integration of: VWF antigen, platelet-dependent activity, Factor VIII, Activity-to-antigen ratios, Collagen-binding, Multimers. (No single test proves AVWS).

**Step 3:** Mechanism Hunt

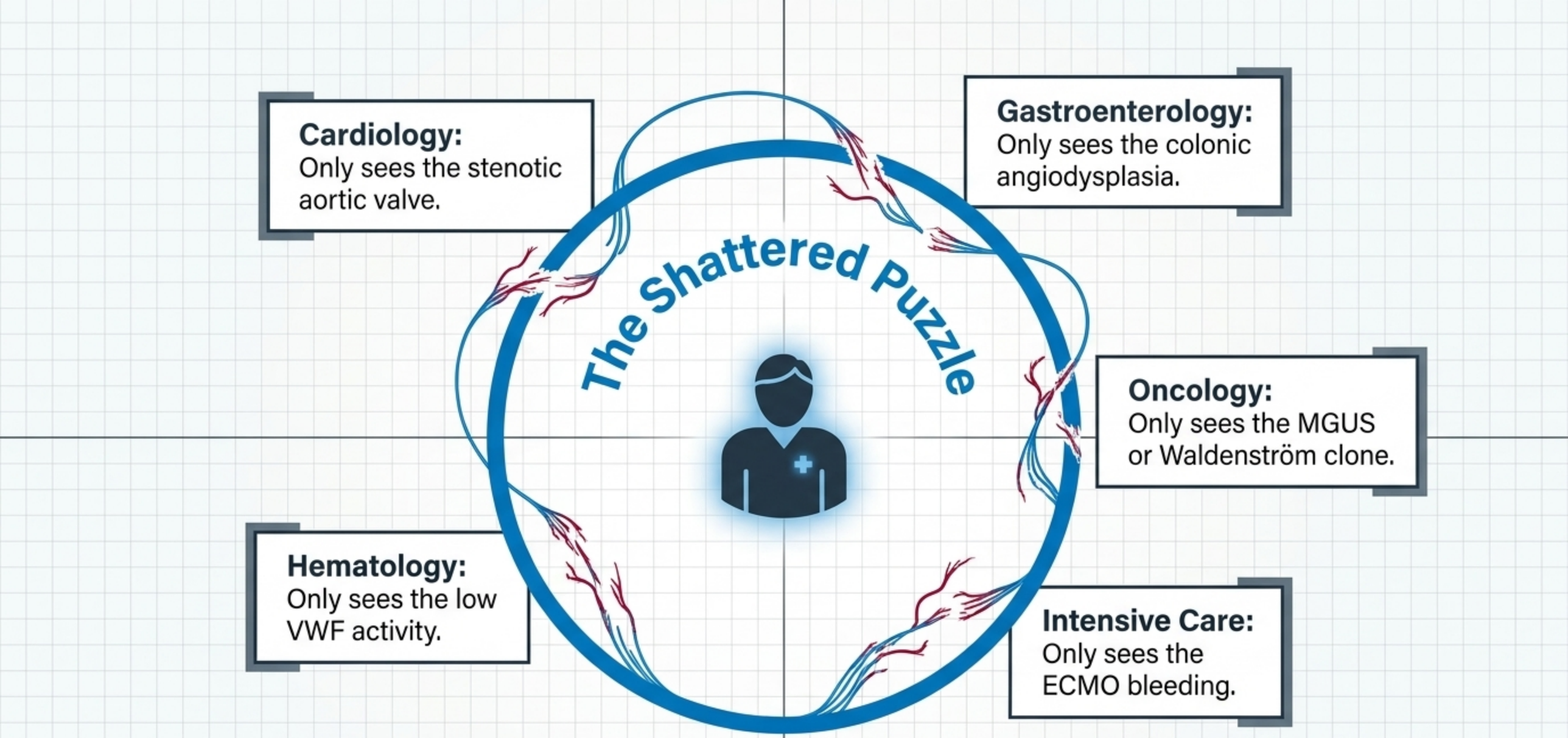
Force the search for: Aortic stenosis, extreme thrombocytosis, monoclonal gammopathy, hypothyroidism.

AVWS should not become a diagnostic shortcut. It should become a diagnostic discipline. The lab pattern identifies that VWF function is abnormal; the clinical task is to determine why.

# The Treatment Bridge

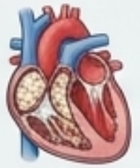



Replacement bridges the patient through bleeding, but durable remission requires rebuilding the structural foundation by addressing the biology destroying VWF.




VWS is easy to miss because each specialty sees only part of the syndrome. The definitive diagnosis emerges only when the pieces are connected. Inherited VWD and AVWS are not mutually exclusive—acquired disease can unmask previously mild genetic susceptibility.

# The Final Case Study: Acquired Von Willebrand Syndrome (AVWS)

| | |
|---|---|
| **Patient:** | 78-year-old man. |
| **Symptoms:** | Recurrent iron deficiency anemia, intermittent melena. |
| **History:** | Normal hernia repair 25 years ago. No family bleeding history. |
| **Findings:** | Multiple colonic angiodysplastic lesions + harsh systolic ejection murmur (severe calcific aortic stenosis).  |
| **Labs:** | Mildly reduced VWF antigen, disproportionately reduced activity, decreased activity-to-antigen ratio, loss of high-molecular-weight multimers.  |

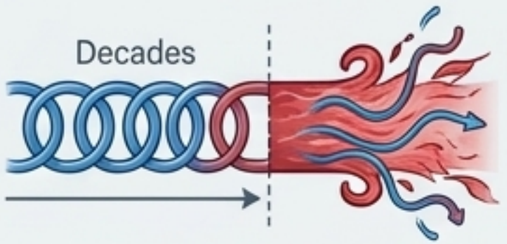
# The Resolution & Application: Unmasking the Mechanism

### ⚠ The Trap

Diagnosing VWD and simply prescribing VWF replacement.

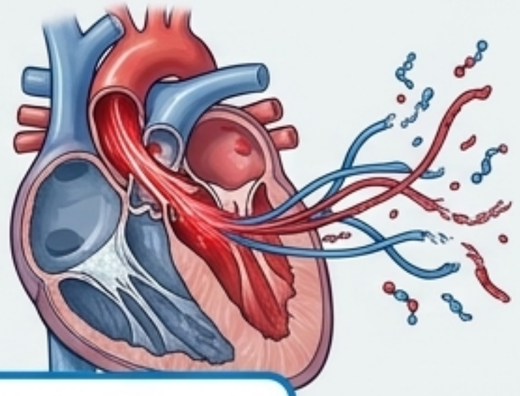
### → The Shift

What has changed? Decades of normal hemostasis means the issue is flow, not genetics.




### 🔍 The Conclusion

The abnormal blood flow across the severely stenotic valve created a high-shear environment, unfolding VWF and promoting multimer loss.



**Final Pearl:** In AVWS, the laboratory pattern tells you that VWF is failing. Mechanism, not the VWF level alone, guides definitive management. **(Fix the valve, fix the bleeding).**