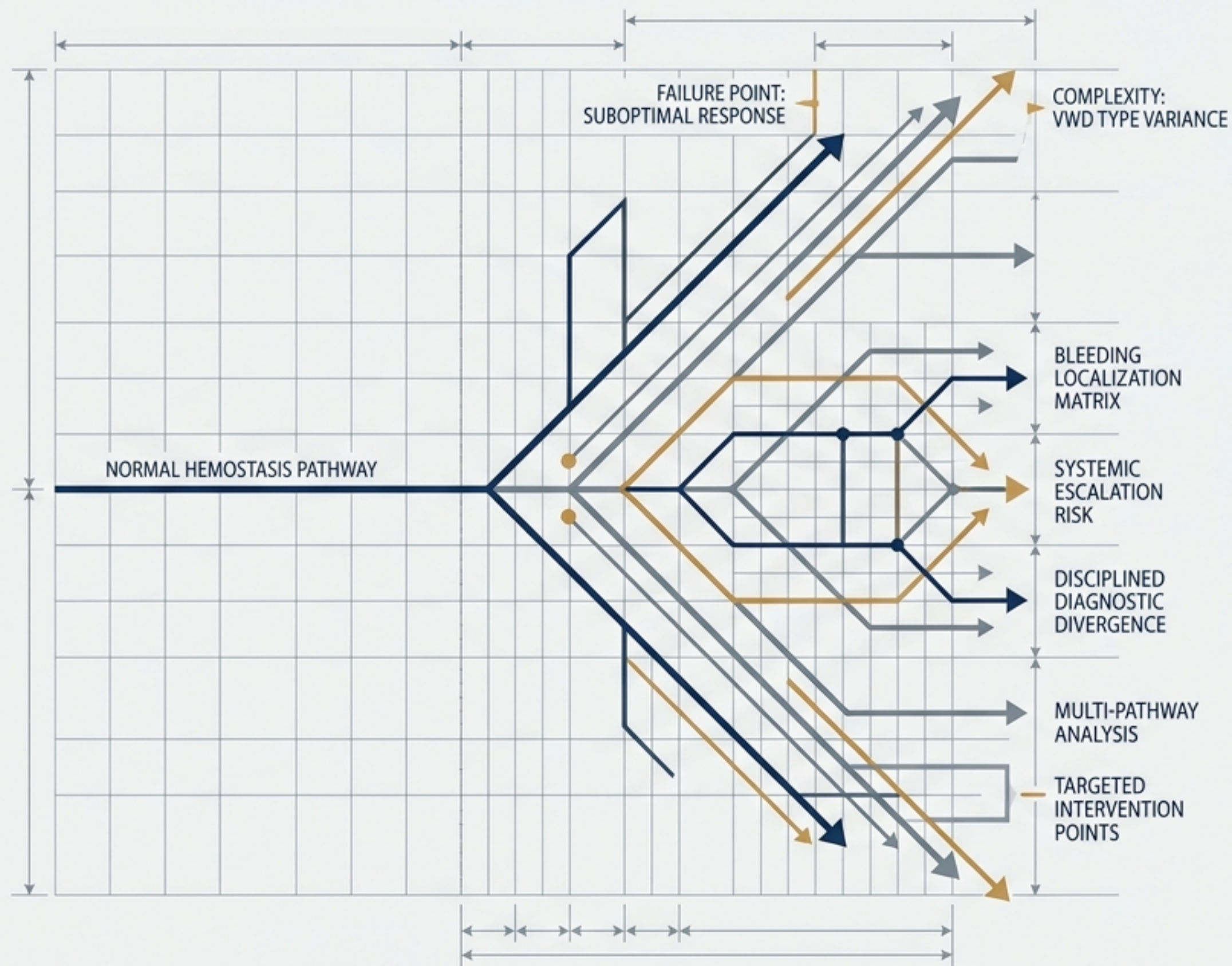




# WHEN TREATMENT FAILS IN VON WILLEBRAND DISEASE

Shifting from reflex escalation to disciplined localization.

Persistent bleeding is a **diagnostic event**, not just a dosing problem.



# Persistent bleeding requires a change in strategy, not just a change in dose

## Reflex Escalation

**Action: Do more of the same.**

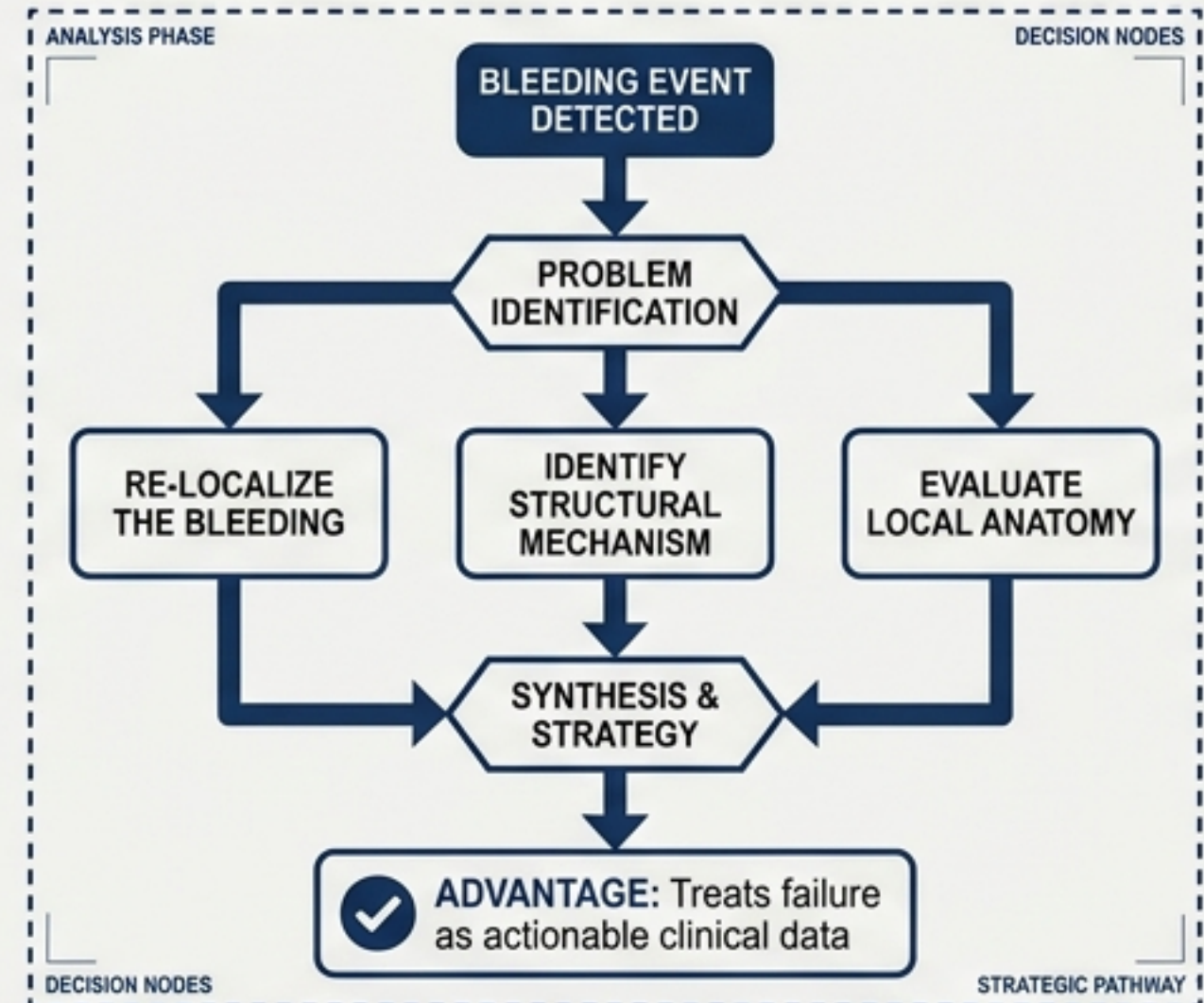
- Tactics: Higher targets, more factor, longer coverage, frequent doses



## Disciplined Escalation

**Action: What part of the plan failed?**

- Tactics: Re-localize the bleeding, identify the structural mechanism, evaluate local anatomy





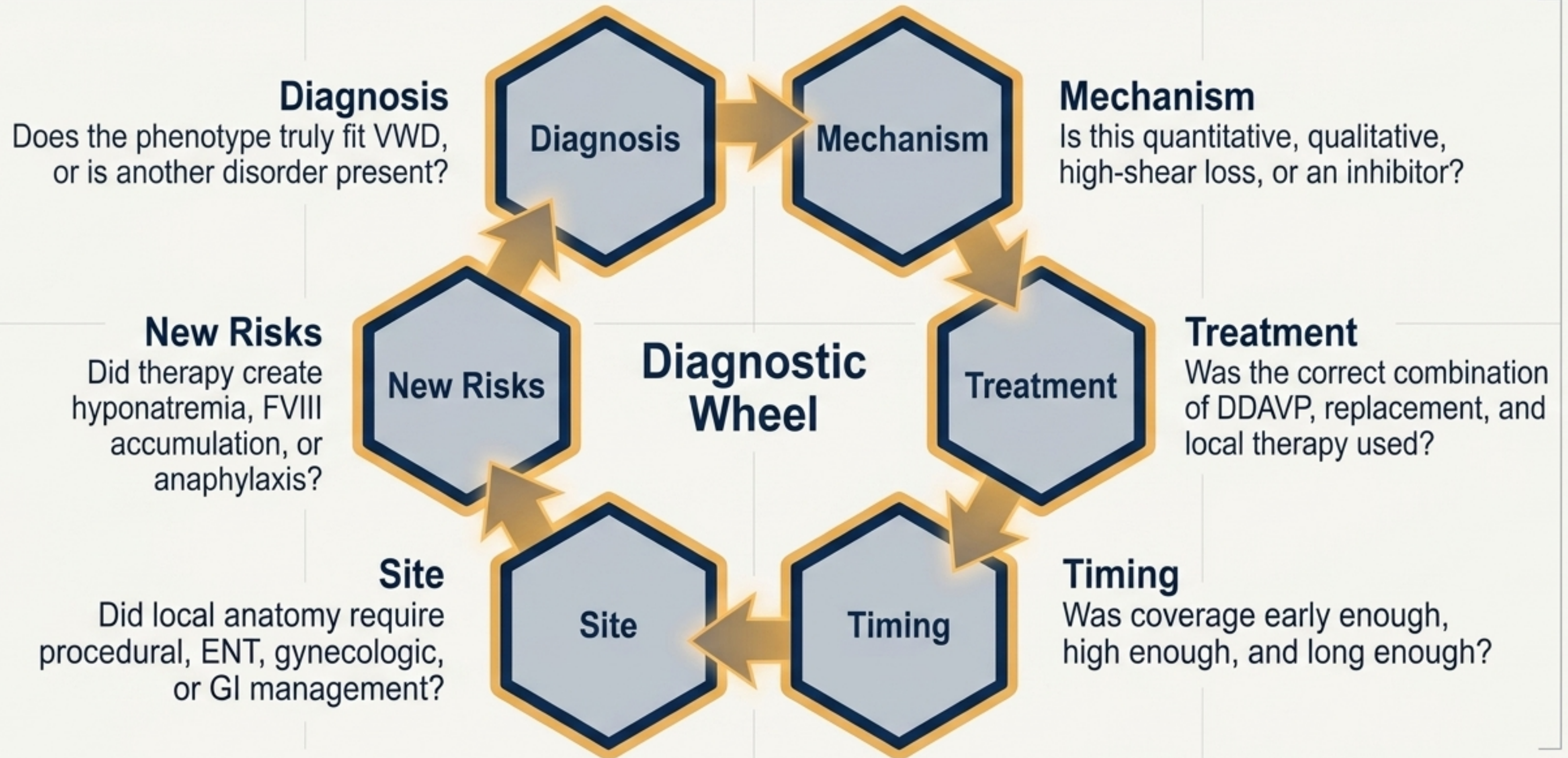
# The anatomy of treatment failure in VWD

## 4-Quadrant Failure Matrix

|                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <div data-bbox="169 414 203 480">1</div> <div data-bbox="249 484 719 964"></div> <div data-bbox="833 476 1386 570"><b>Dose / Timing</b></div> <div data-bbox="833 596 1536 990"><p>Not enough VWF/FVIII, poor durability, or coverage that ended before the bleeding risk ended.</p></div> | <div data-bbox="1692 414 1725 480">2</div> <div data-bbox="1772 514 2242 964"></div> <div data-bbox="2332 476 2802 570"><b>Mechanism</b></div> <div data-bbox="2332 596 3078 990"><p>Product mismatched to VWD subtype, acquired high-shear VWF loss, or development of anti-VWF alloantibodies.</p></div> |
| <div data-bbox="169 1118 203 1183">3</div> <div data-bbox="269 1193 703 1662"></div> <div data-bbox="833 1174 999 1268"><b>Site</b></div> <div data-bbox="833 1294 1502 1688"><p>Uncontrolled mucosal fibrinolysis, untreated surgical source, or persistent angiodysplasia.</p></div>   | <div data-bbox="1692 1118 1725 1183">4</div> <div data-bbox="1802 1230 2219 1643"></div> <div data-bbox="2332 1174 2745 1268"><b>Diagnosis</b></div> <div data-bbox="2332 1294 3002 1688"><p>Concomitant bleeding disorder, medication interference, or a non-VWD primary explanation.</p></div>         |

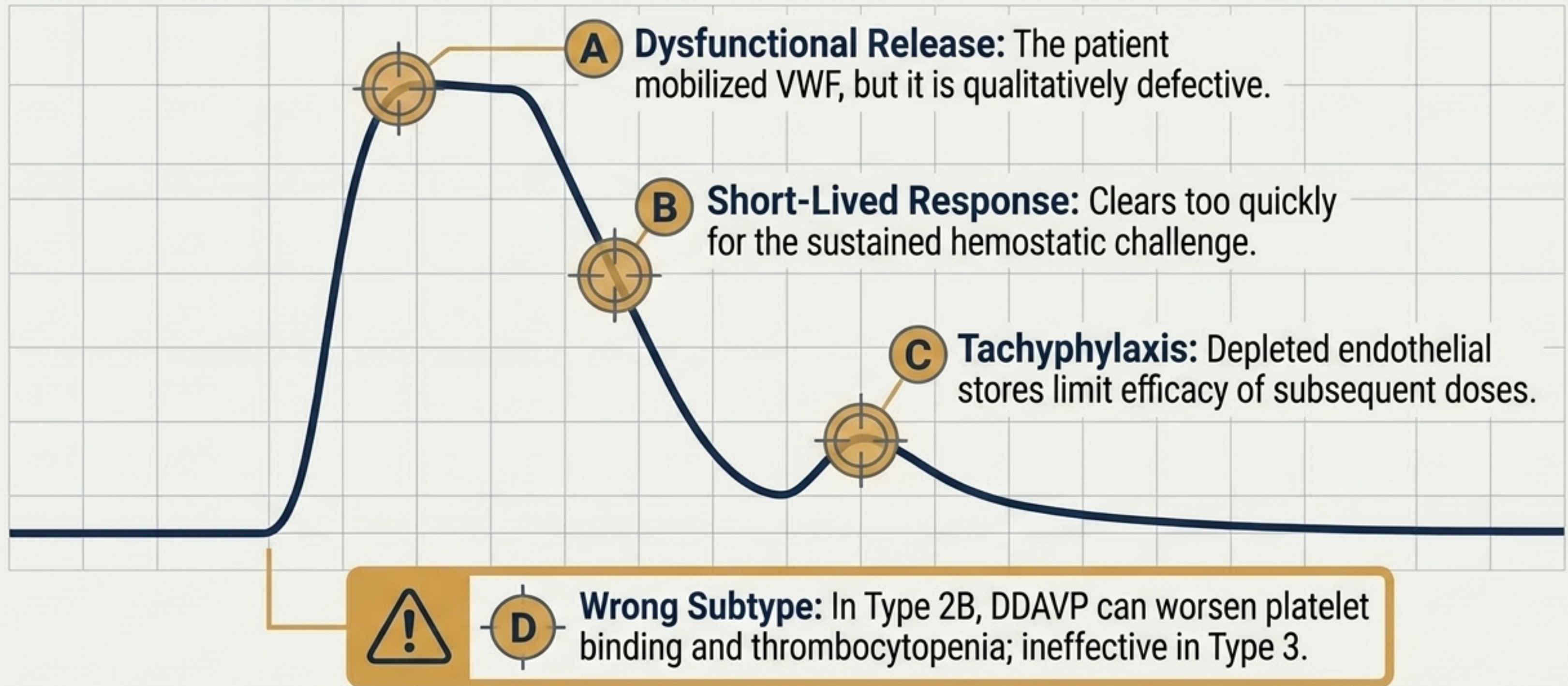


# The six diagnostic questions for persistent bleeding





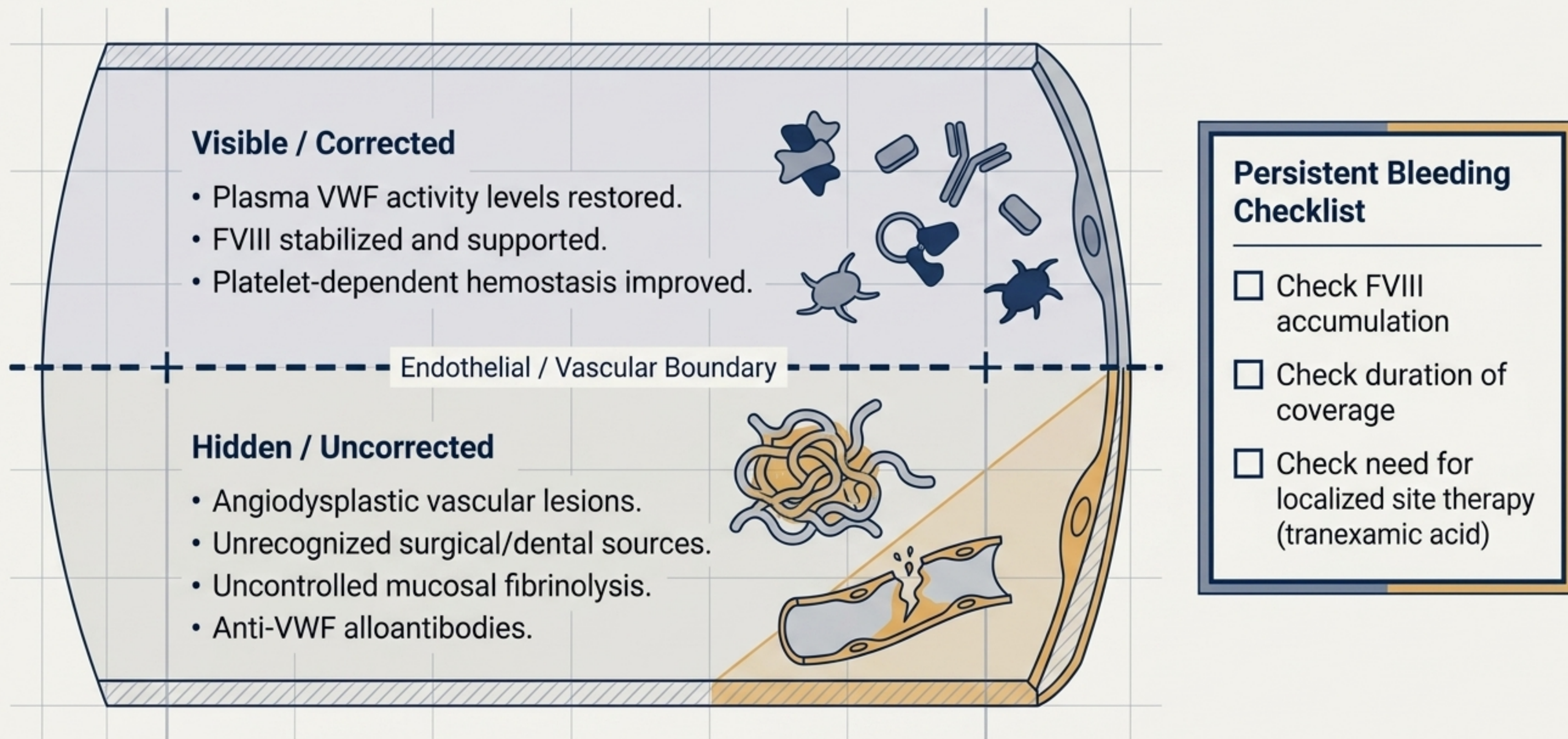
# Desmopressin creates a response curve, not a permanent fix



A good one-hour rise does not guarantee durable protection.



# Replacement therapy corrects the plasma, not the anatomy





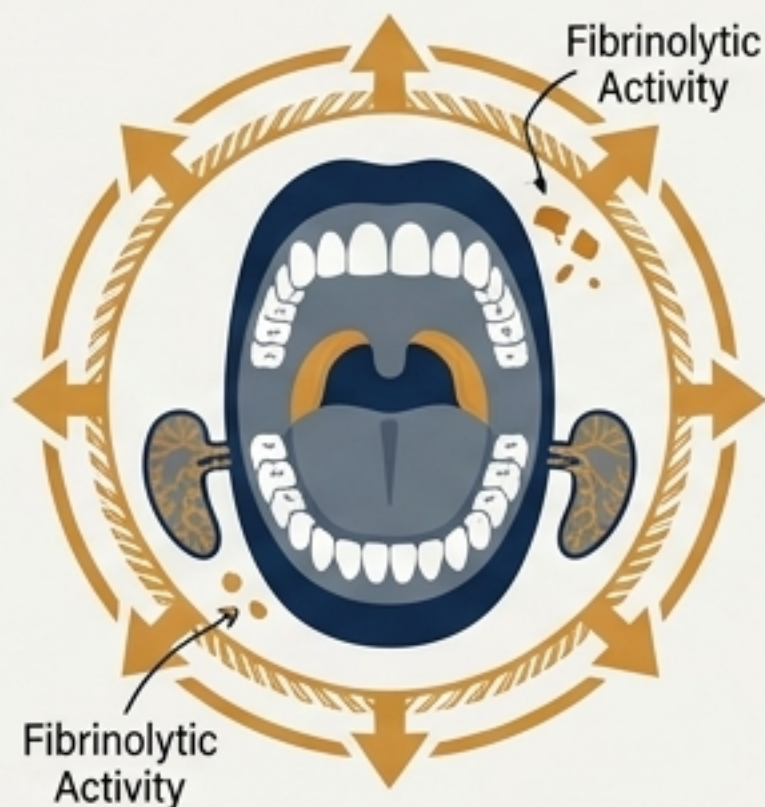
# A clot can be biochemically possible but mechanically unsuccessful

## Nose



Exposed, mobile, and easily re-injured.

## Mouth



Wet, mechanically active, and highly fibrinolytic.

## Uterus



Cyclically remodeling; postpartum state involves simultaneous healing and hemostatic decline

## GI Tract

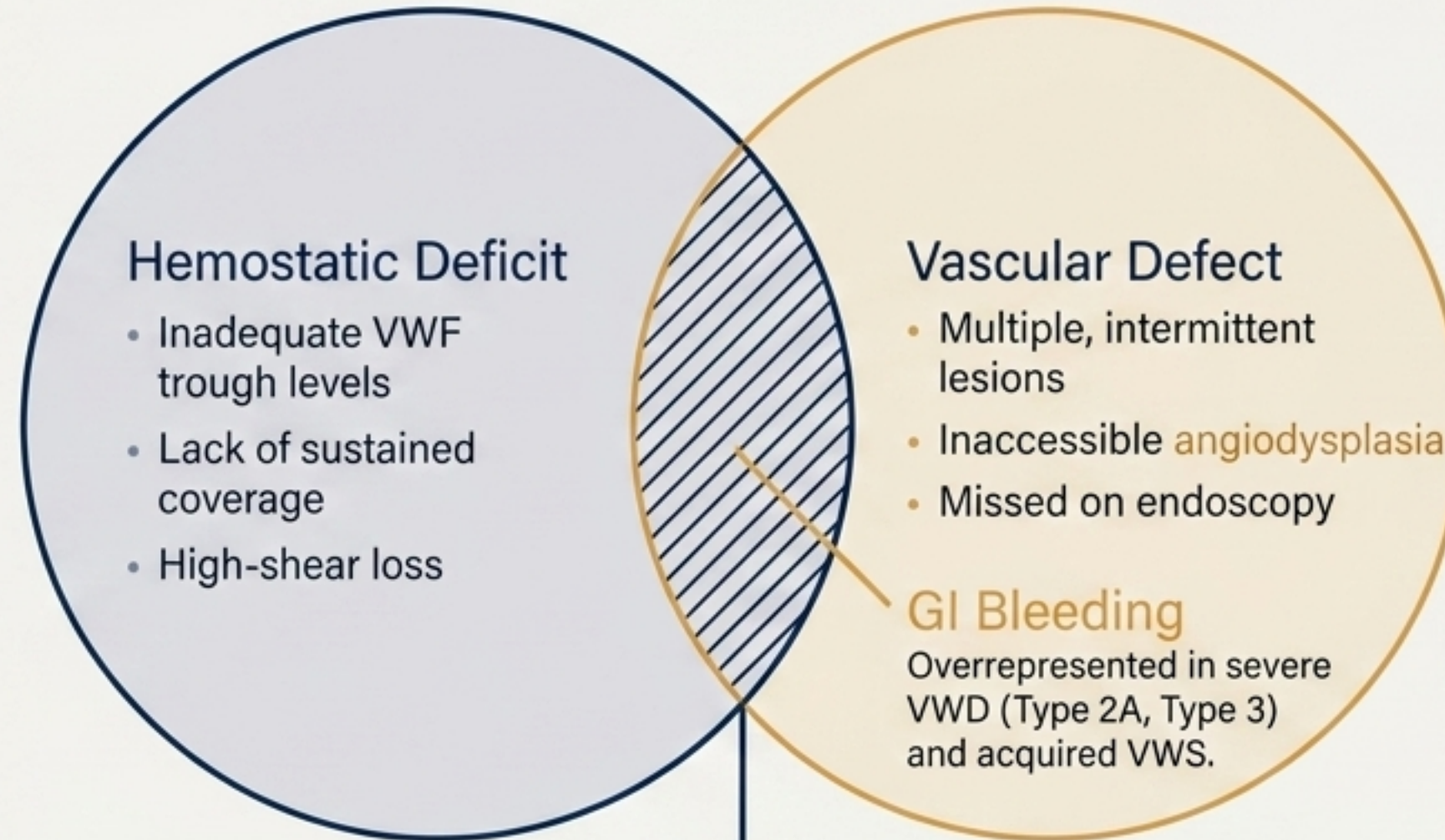


Houses fragile vascular malformations (angiodysplasia).

VWF replacement is insufficient alone. Survival requires site-specific defense: antifibrinolytics, cautery, packing, or hormonal therapy.



# Gastrointestinal bleeding exists at the intersection of hemostasis and angiogenesis

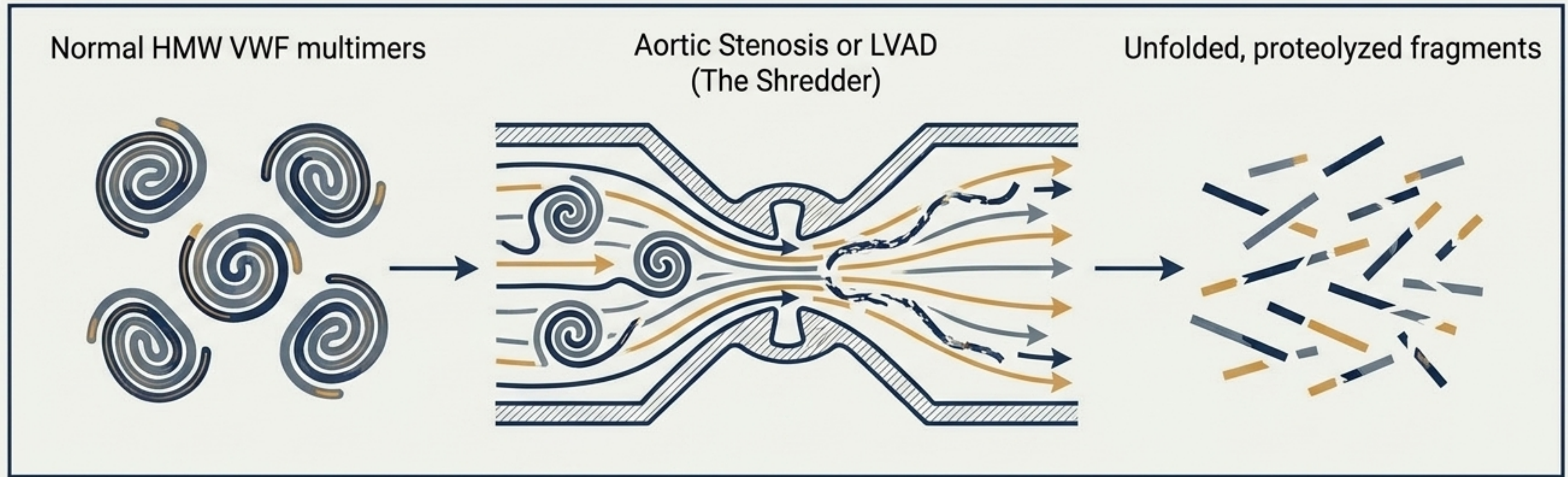


## Actionable Insight

The “failed treatment” may actually be a successful hemostatic correction applied to an ongoing vascular lesion. Requires localization (endoscopy/enteroscopy) and highly specialized salvage approaches (antiangiogenics), not just dose escalation.



# Acquired VWF Loss: When the circulation actively destroys the therapy



## The Mechanism

High shear stress across stenotic valves or mechanical support devices forces VWF to unfold, promoting rapid proteolysis and loss of the most effective HMW multimers.

## Clinical Impact (Heyde Syndrome)

Acquired Type 2A-like defect, driving severe mucosal/GI bleeding.

## Definitive Treatment

If the mechanical lesion persists, replacement is temporary. Definitive hemostatic treatment is cardiovascular intervention (valve replacement).



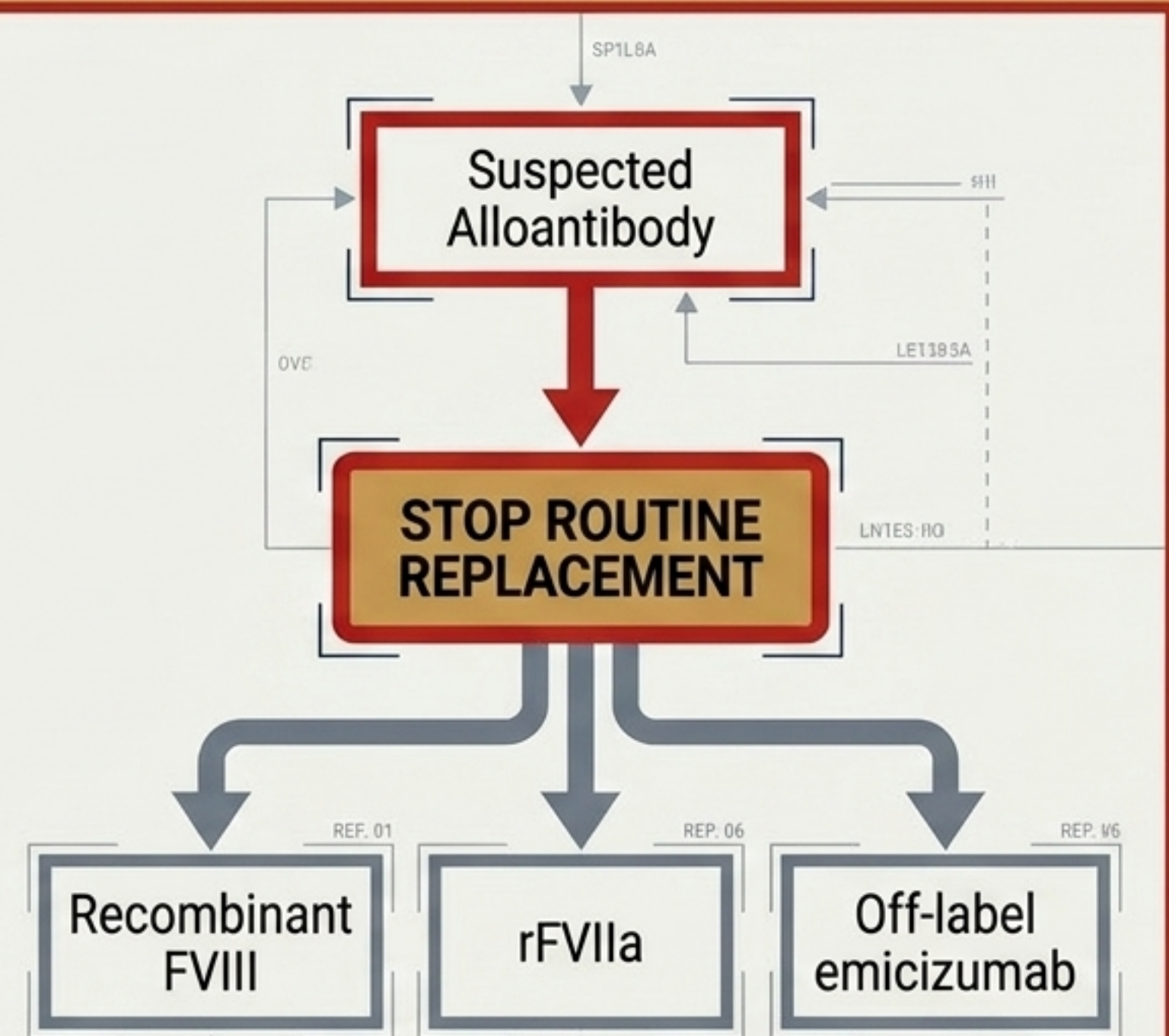
# The Alloantibody Threat: When 'more replacement' becomes dangerous



**The Threat:** Rare anti-VWF alloantibodies cause complete loss of response to VWF concentrates and trigger life-threatening anaphylaxis.

**The Profile:** Occurs primarily in Type 3 VWD (patients with large deletions or severe null genotypes).

**Clinical Triggers:** Poor post-infusion recovery, unexpectedly short VWF survival, or infusion reactions.





# The complications of success: Managing FVIII and cardiovascular risk

## FVIII Accumulation



- Repeated VWF/FVIII concentrate dosing drives FVIII dangerously high.
- Creates severe thrombotic risk during surgery, cancer, or immobility.
- **Goal:** Proportional hemostasis, not maximal hemostasis.



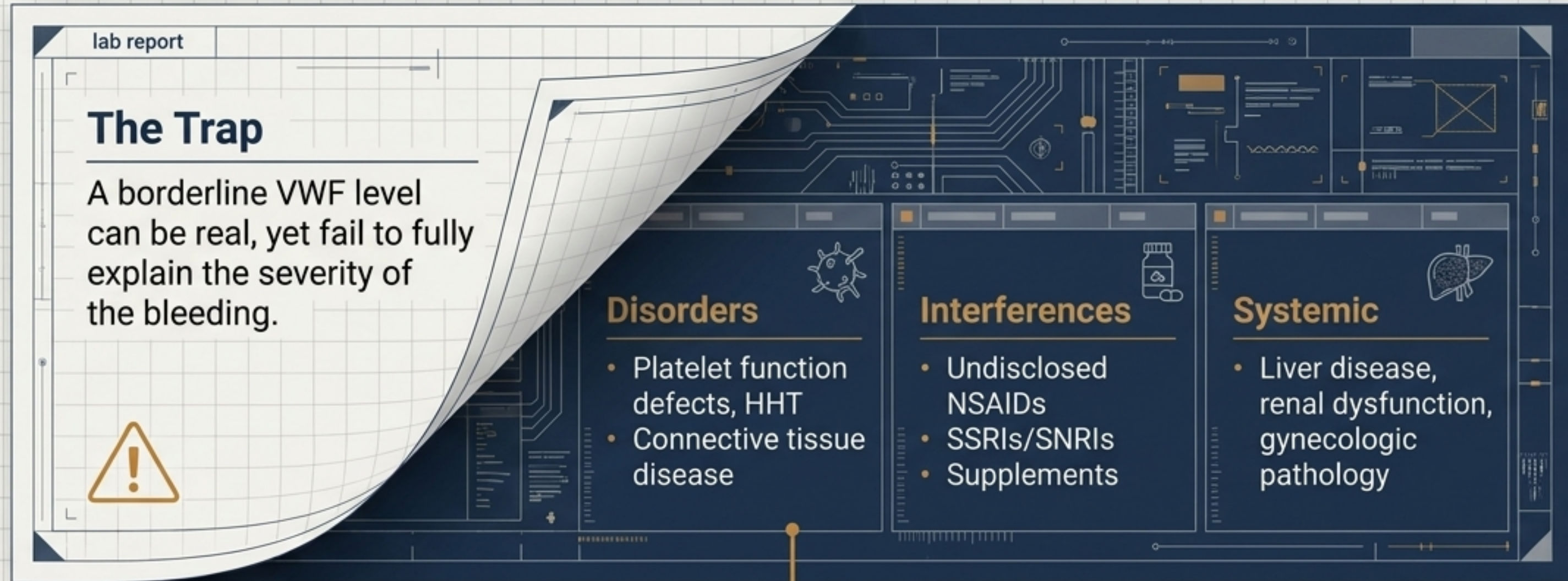
## Antithrombotic Needs



- VWD does not erase baseline thrombotic risk (Afib, mechanical valves, strokes).
- **Goal:** Build a hemostatic plan that permits appropriate cardiovascular care (antiplatelets/anticoagulants); do not simply withhold thrombosis therapy.



# Incomplete diagnosis: When the phenotype is worse than the lab predicts

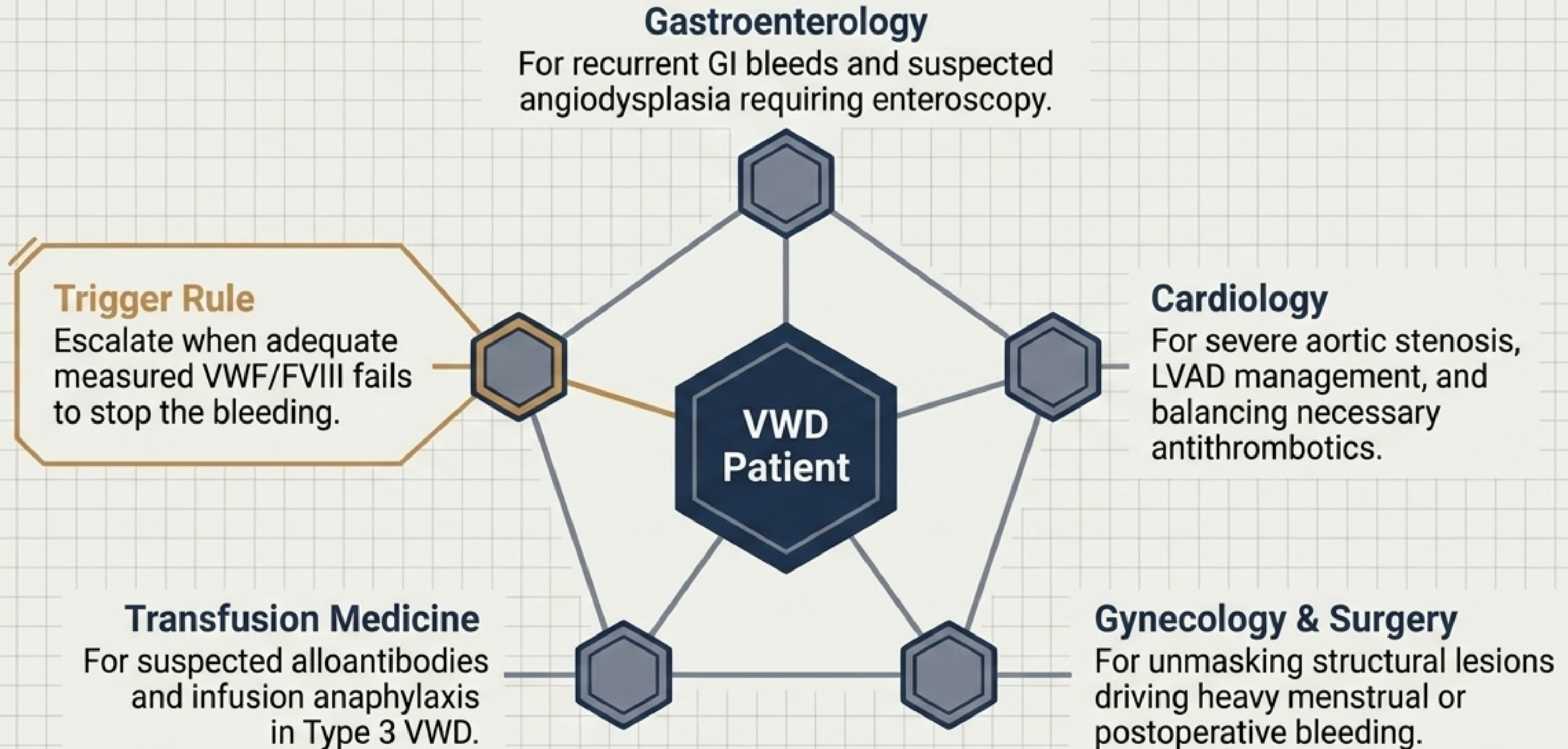


## Takeaway

When therapy fails to match the expected outcome, reopen localization. VWF therapy cannot out-compete untreated local lesions.



# Treatment failure is a multidisciplinary problem



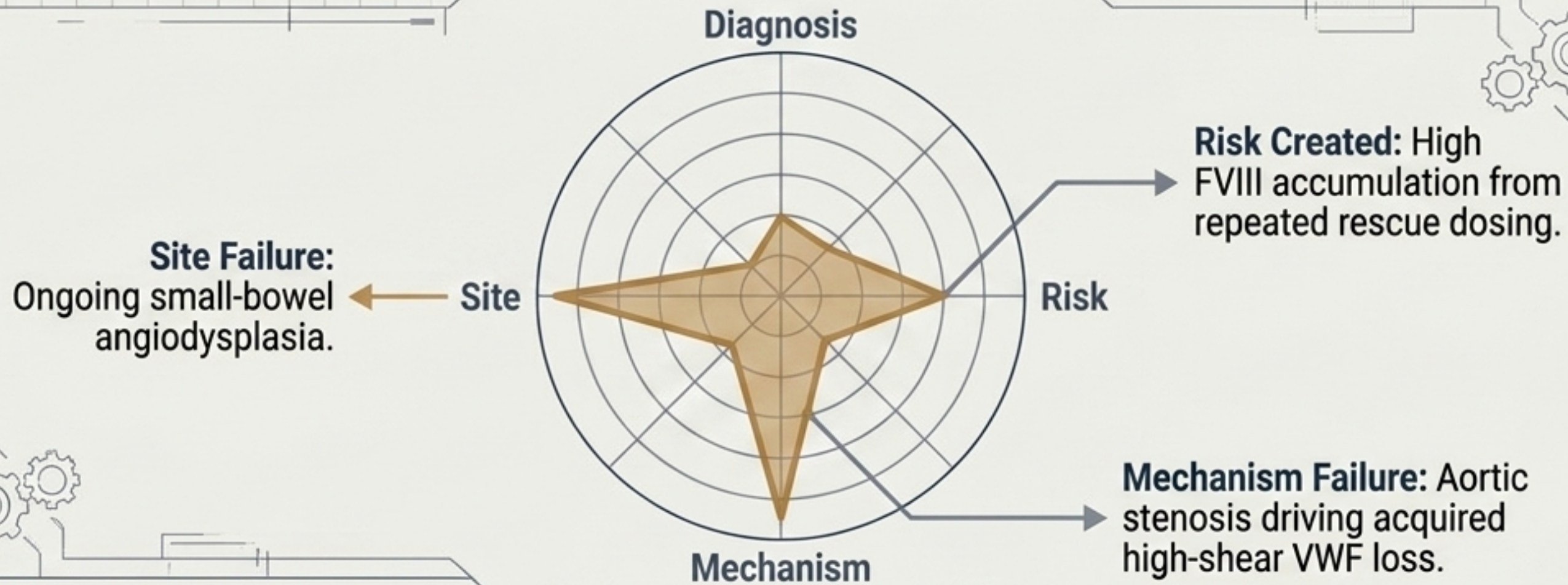


# Clinical Synthesis: Decoding the 72-Year-Old Patient

Patient Dashboard

**Patient Profile:** 72yo, Type 2A VWD, recurrent melena (suspected angiodysplasia), moderate-severe aortic stenosis.

**The Paradox:** Good post-infusion VWF rise, but episodic treatment fails to prevent recurrence.



**The Solution:** Redefine success. Shift focus from post-infusion lab levels to lesion control, cardiology intervention, and improved iron status.



# Persistent bleeding is not a failure of will, dose, or compliance. It is a signal.

When treatment fails in VWD, do not begin with more.

**Begin with localization.**