Novel Non-Factor Replacement Therapies in hereditary bleeding disorders: A focus on phase 3-4 products

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From Replacement to Re-Balancing

Bridging the gap between bleeding risk and thrombosis in hemophilia care

Session Roadmap

01

Background & Mechanisms

Limitations of factor replacement and mechanistic overview of FVIII mimetic vs re-balancing strategies

02

Key Agents & Clinical Data

Emicizumab, Mim-8, Marstacimab, Concizumab, Fitusiran, SerpinPC: efficacy and safety from headline trials

03

Practical Management

Dosing, labs, breakthrough bleed management, and thrombotic risk

04

Looking Ahead

Access, equity, and pipeline questions for the future

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Why Non-Factor Therapies?

Limitations of Factor Replacement

- High treatment burden: frequent IV infusions challenging in young children and adults with poor access
- Variable trough levels → breakthrough bleeds even on optimal prophylaxis
- Inhibitor development: ~25–30% of severe HA
- Bypassing agents inconvenient, expensive, not fully protective

What Non-Factor Approaches Solve

- Stable hemostatic protection with SC dosing (weekly to monthly)
- Bypass FVIII/FIX pathway → effective even with high-titer inhibitors
- Re-balance coagulation to "mild hemophilia or better" phenotype

★ Clinical pearl:
Many families experience non-factor prophylaxis as their first "near-normal life" period since diagnosis.

Mechanistic Framework: Two Big Families

FVIII Mimetic: Emicizumab, Mim8

Humanized bispecific antibody bringing FIXa and FX into proximity, functionally replacing missing FVIIIa cofactor activity. Promotes tenase complex function with predictable, sustained activity.

Re-Balancing Agents

Anti-TFPI (Marstacimab, Concizumab): block tissue factor pathway inhibitor → amplify thrombin generation

Anti-AT (Fitusiran): siRNA reduces antithrombin levels, shifting the balance toward thrombin generation

APC inhibitor (SerpinPC): an engineered inhibitor molecule designed to block the activity of Activated Protein C, maximizes endogenous thrombin burst potential

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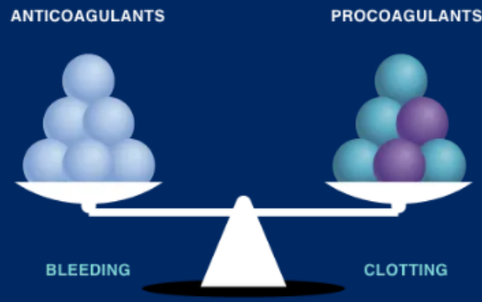
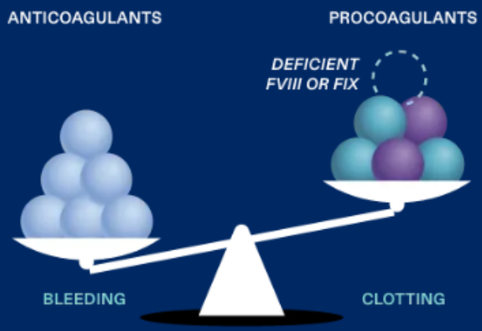
Rebalancing agents

How rebalancing may work to help restore hemostasis[1,3,9,10]

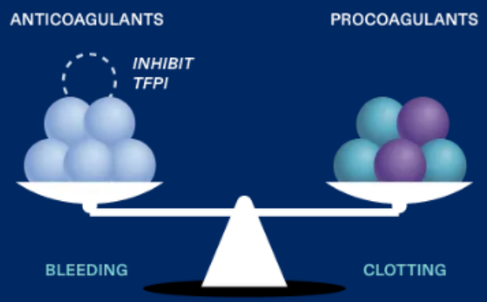
Normal **hemostatic balance** of the elements in the coagulation cascade



In hemophilia, loss of a procoagulant —factor VIII or factor IX—tips the balance in favor of bleeding



Hemostasis may be rebalanced in hemophilia by reducing the level of anticoagulants, like TFPI

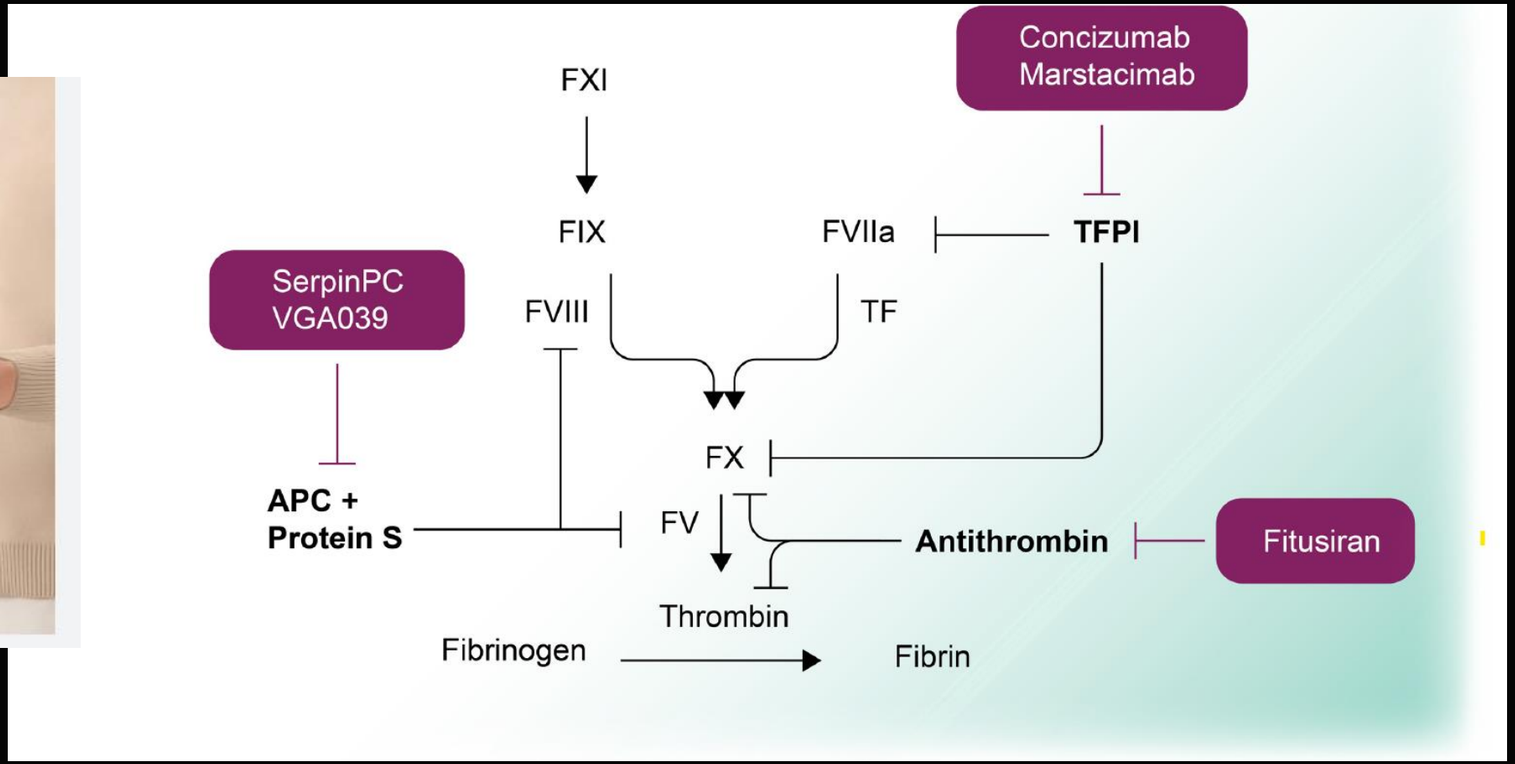


TFPI, APC, or AT | FVIII, FIX, FXI, FXII | TF, FVII

TFPI: tissue factor pathway inhibitor; APC: activated protein C; AT: antithrombin; FVIII: Factor VIII; FIX: Factor IX; FXI: Factor XI; FXII: Factor XII; TF: tissue factor; FVII: Factor VII.

The balance of hemostasis

Schematic overview of the position of action of various rebalancing agents within the coagulation cascade



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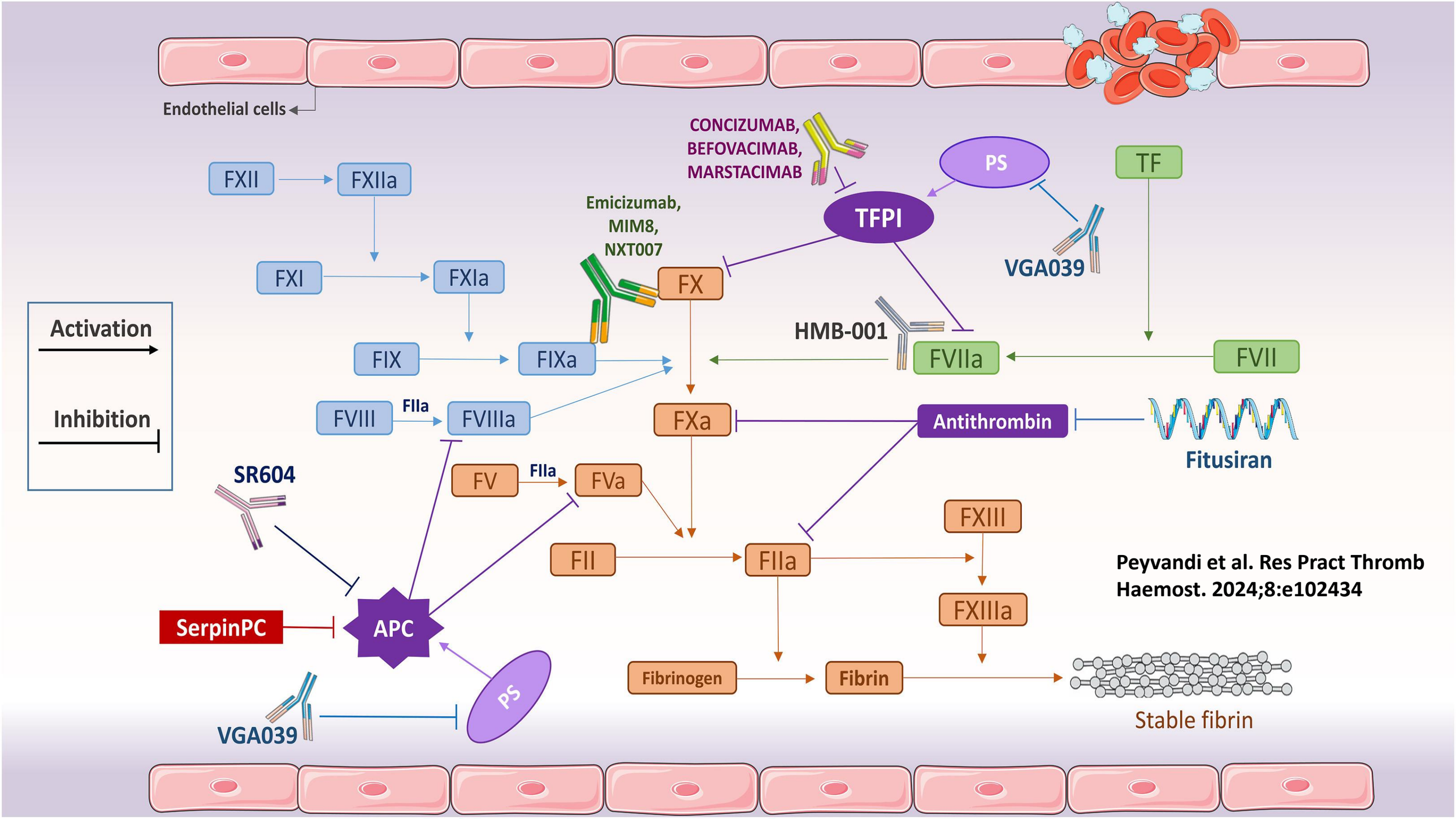


Peyvandi et al. Res Pract Thromb Haemost. 2024;8:e102434

Emicizumab (HEMLIBRA)

First-in-class FVIII mimetic that changed the standard for severe hemophilia A

Key Facts

- Humanized bispecific monoclonal antibody binding FIXa and FX
- First approved in 2017 for HA with inhibitors; now widely used across severe HA
- Subcutaneous, flexible dosing: Q1W, Q2W, or Q4W maintenance after loading
- Produces hemostatic state roughly equivalent to mild hemophilia or better

80–90%

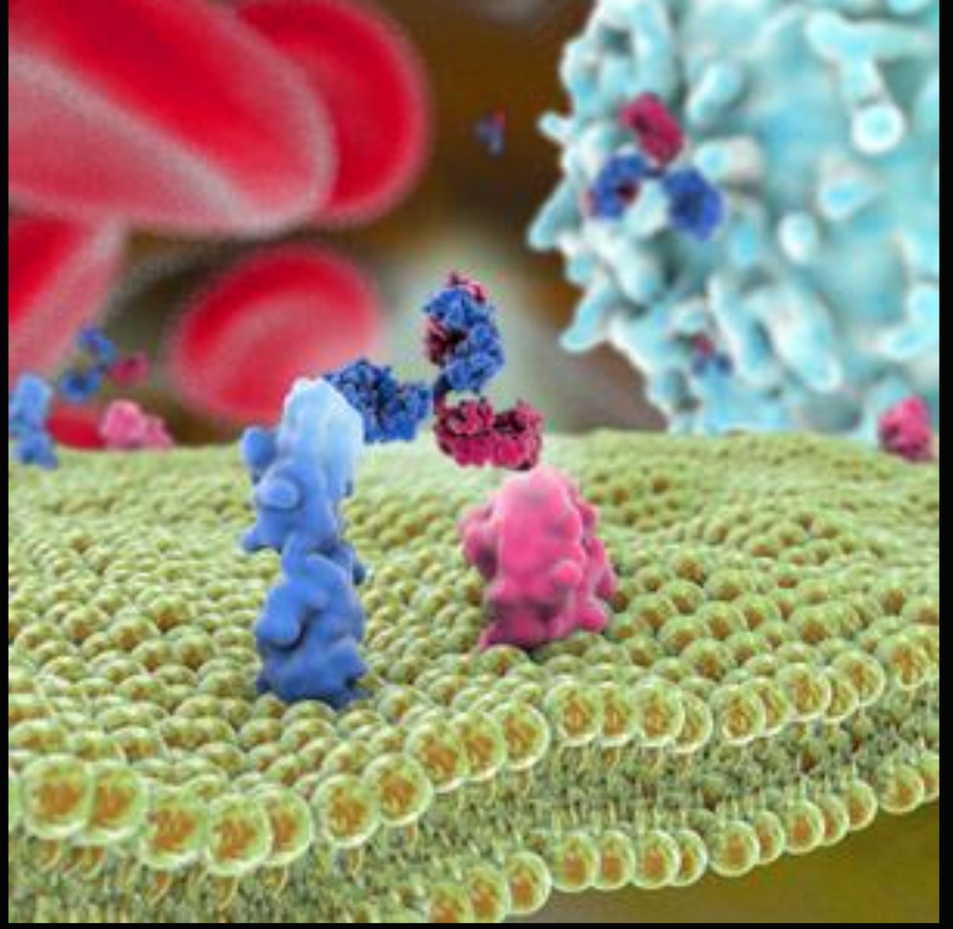
ABR Reduction

vs on-demand regimens in HAVEN studies

3

Dosing Options

Q1W, Q2W, or Q4W schedules



★ Clinical pearl:

Consider Emicizumab early in life for families struggling with IV access or adherence to FVIII prophylaxis.

Emicizumab: Safety and Critical Interactions

Overall Safety Profile

Most adverse events mild: injection-site reactions, headache, transient ALT/AST elevations. No clear increase in spontaneous thrombotic events when used alone at approved doses.

⚠ Red Flag: aPCC Interaction

Cases of thrombotic microangiopathy (TMA) and thrombosis with high-dose aPCC (≥100 U/kg/day for ≥24 hours). Combined supraphysiologic thrombin generation from Emicizumab + activated clotting factors in aPCC.

Avoid or strictly limit aPCC in patients on Emicizumab.

Preferred Bypass Agent

★ Clinical pearl:
Make rFVIIa your default bypassing agent for breakthrough bleeds in patients on Emicizumab.

Combination	Risk Level	Action
Emicizumab alone	Low	Routine monitoring
Emi + high-dose aPCC	High	AVOID
Emi + rFVIIa	Low	Preferred option

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Laboratory Interference & Breakthrough Bleeds

Lab Assay Interference

- **aPTT:** Markedly shortened despite severe HA → no longer reflects true FVIII activity

- **One-stage FVIII:** Artificially elevated; cannot be used to monitor FVIII

- **Chromogenic FVIII (bovine):** Preferred assay, largely insensitive to Emicizumab

Managing Breakthrough Bleeds

With inhibitors: Use rFVIIa as first-line; avoid high cumulative aPCC doses

Without inhibitors: Use FVIII concentrate for major bleeds or surgery; monitor with bovine chromogenic FVIII

Severe/life-threatening: rFVIIa (inhibitors) or FVIII bolus (no inhibitors); refer to the comprehensive hemophilia center

★ Clinical pearl:
For major surgery, specify "bovine-reagent chromogenic FVIII" on lab request and communicate with lab director.

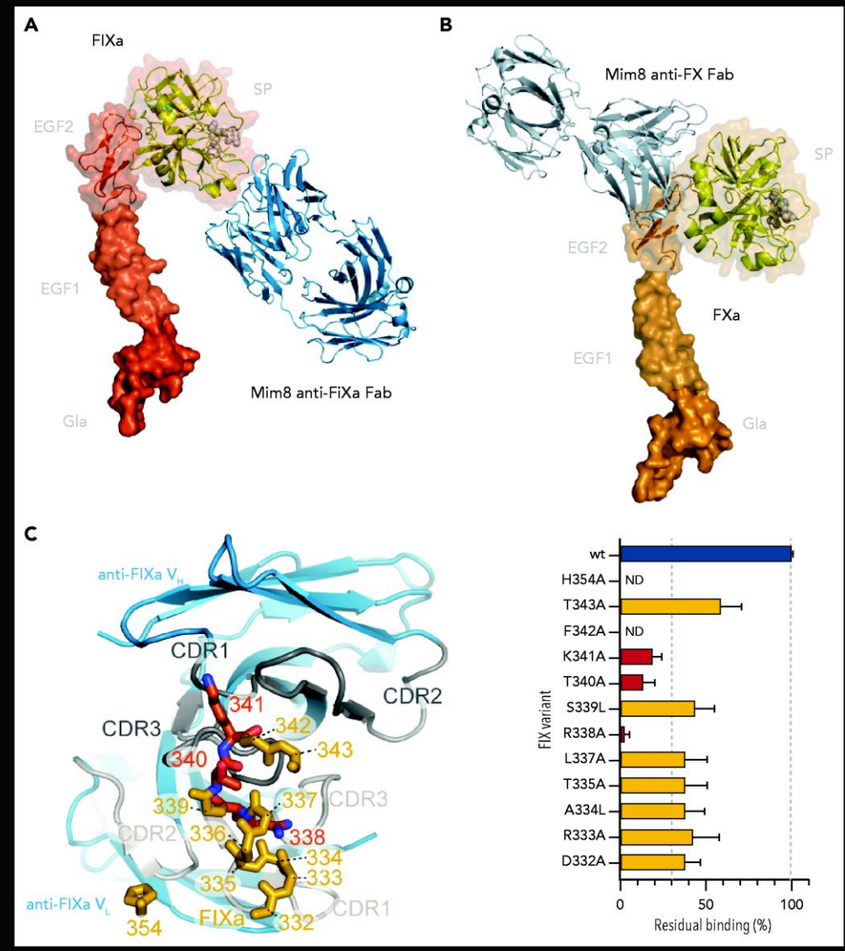
•More favorable **spatial orientation** of the catalytic complex

•Higher **catalytic efficiency** (per molecule) than emicizumab in thrombin-generation assays.

Mim8 Mechanism of Action: Advanced FVIIIa-Mimetic Bispecific Antibody

Bispecific Antibody

- Newer “tight” FVIII-mimetic with:
- Higher **affinity** for FIXa and FX
- More favorable **spatial orientation** of the catalytic complex
- Higher **catalytic efficiency** (per molecule) than emicizumab in thrombin-generation assays.



FRONTIER Clinical Program: Overview

1

Comprehensive Phase 3 Trials

Evaluating Mim8 in hemophilia A patients With and without inhibitors.

2

Flexible Dosing

Once weekly, biweekly, or monthly SC injections to suit individual patient needs.

3

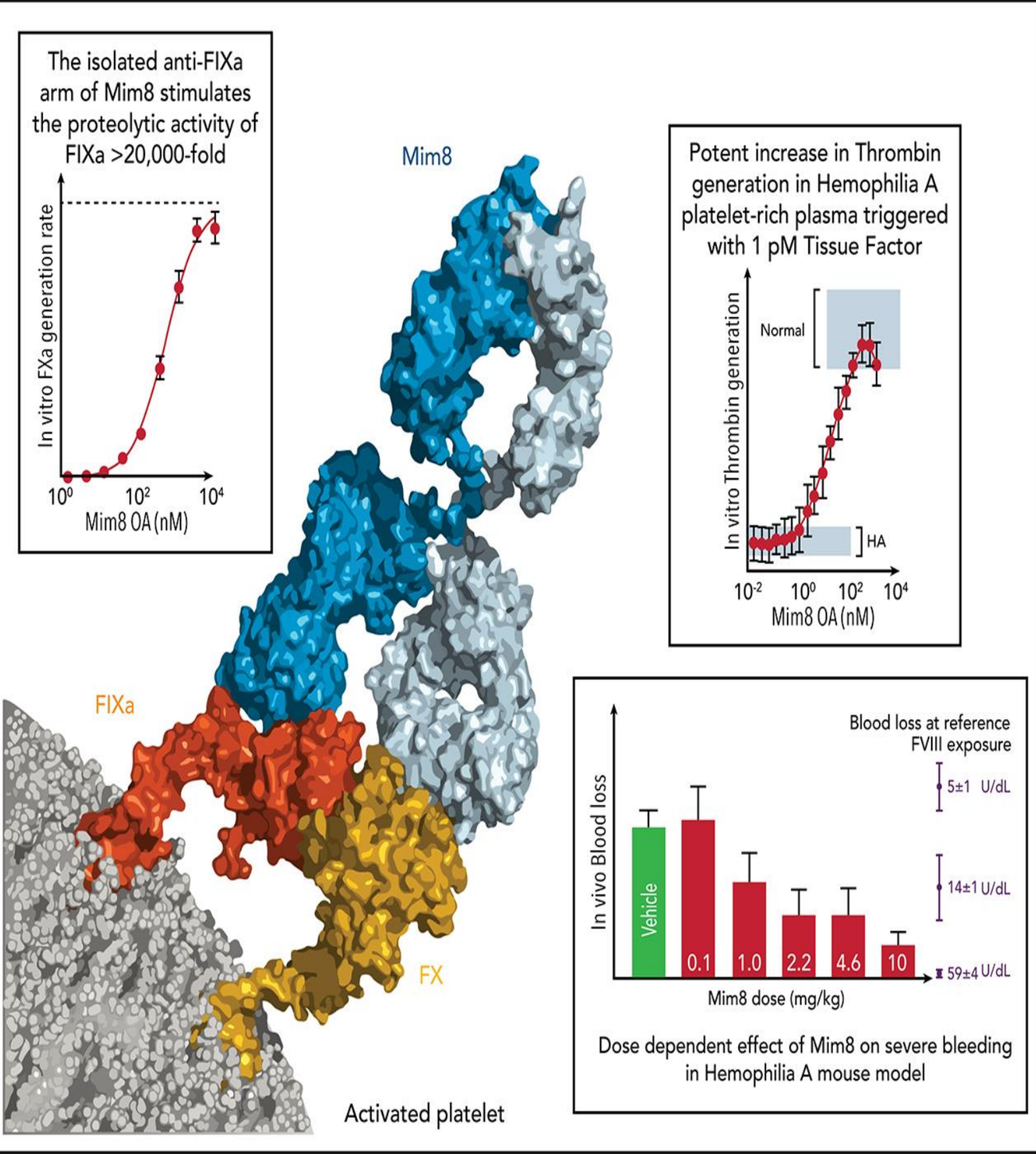
Diverse Patient Population

Includes pediatric and adult populations, both treatment-naïve and previously treated patients.

4

Key Endpoints

Focus on annualized bleeding rates (ABR), safety, pharmacokinetics, and patient-reported outcomes.



Efficacy Highlights from FRONTIER2 Phase 3 Trial

1

Robust Participant Count

254 participants evaluated, comparing Mim8 prophylaxis against on-demand or prior factor prophylaxis regimens

2

Significant ABR Reduction

Once-weekly Mim8 reduced the annualized bleeding rate (ABR) by 97%
Once-monthly achieved 99% reduction

3

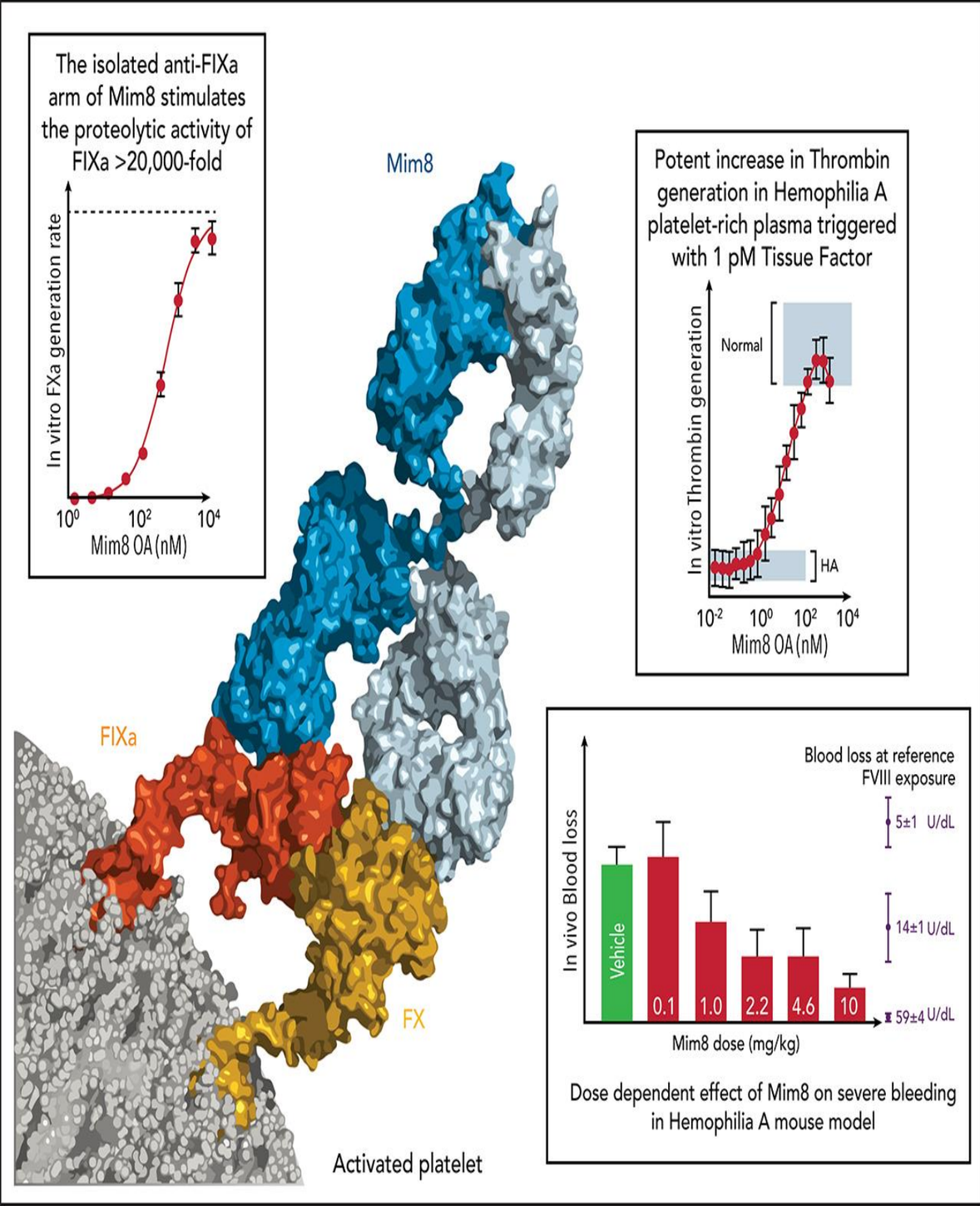
Zero Bleeds Achieved

86% (weekly) and 95% (monthly) of previously untreated patients experienced zero bleeds, demonstrating high efficacy.

4

Improved Quality of Life

Significant improvements in physical functioning and quality of life scores observed compared to on-demand therapy



Mim8 vs Emicizumab: Mechanism & Efficacy

Mechanism

Emicizumab: Bispecific IgG4 with moderate affinity and limited peak cofactor activity.

Mim8: Next-gen mimetic with optimized geometry and stronger FVIII-like activity.

Activity

Emicizumab: 5–15 IU/dL equivalent (ceiling effect).

Mim8: 20–40 IU/dL equivalent (robust thrombin generation).

Efficacy (ABR)

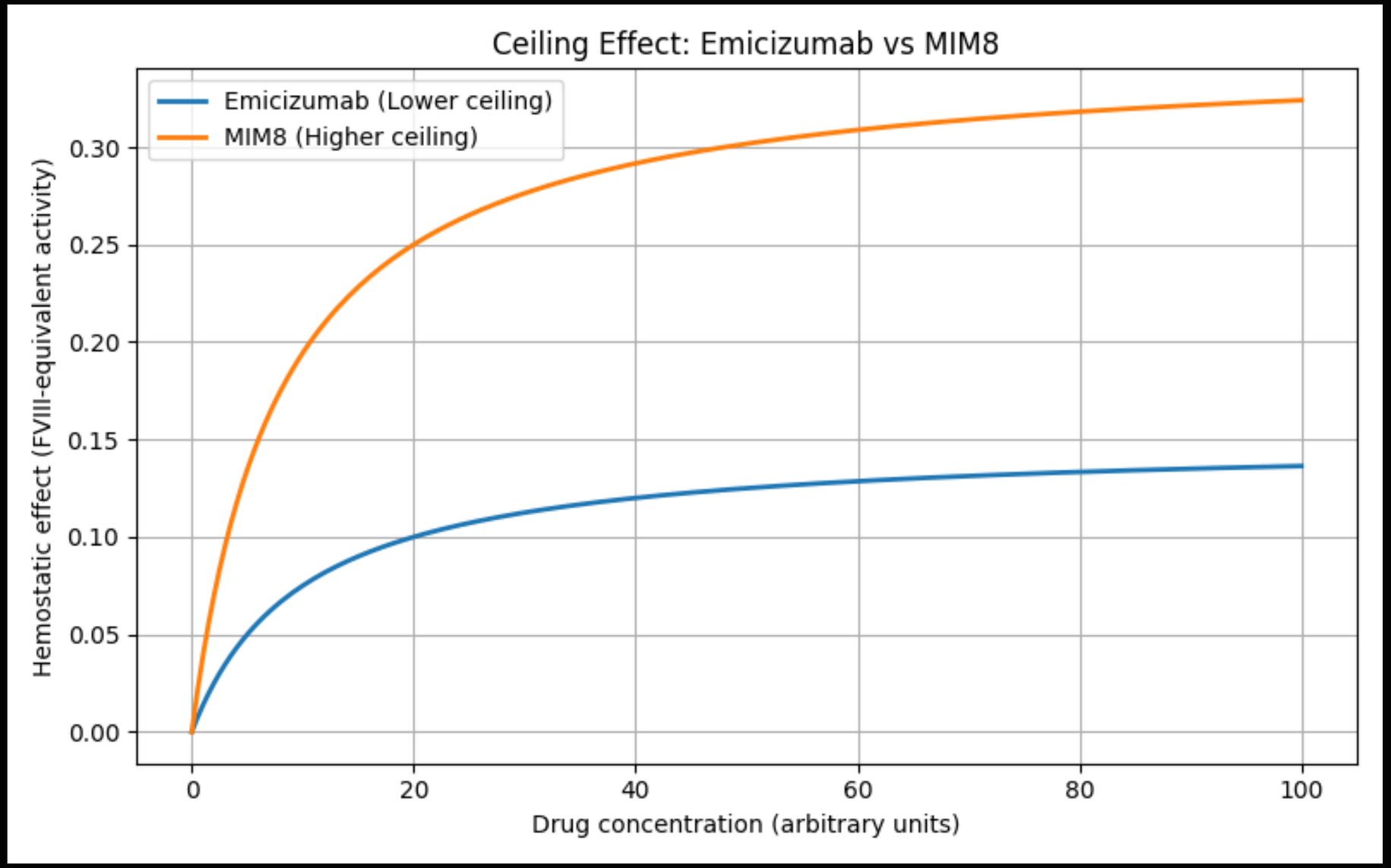
Emicizumab: ~1.5 ABR. Significant improvement over prophylaxis.

Mim8: 0.0–0.7 ABR. 85–90% bleed-free in FRONTIER trials.

Dosing

Emicizumab: Flexible weekly to monthly scheduling.

Mim8: Similar flexibility with often lower injection volumes.



“Pharmacodynamic ceiling: simulated dose–response curves for emicizumab vs MIM8.

MIM8 shows a steeper increase and a higher plateau in thrombin generation (FVIII-equivalent activity) compared with emicizumab, indicating a higher pharmacodynamic ceiling.”

Safety & Practical Considerations

Thrombosis Safety

Emicizumab: Excellent record; rare events only with high-dose aPCC.

Mim8: No thromboembolic events reported in Phase 3 data to date.

Reactions & Immunogenicity

Emicizumab: ~20% ISRs, ~5-6% ADA.

Mim8: ~15% ISRs, <2% ADA (none neutralizing so far).

Lab Interference

Both agents shorten aPTT and invalidate one-stage assays.
Bovine chromogenic assays are required for accurate monitoring.

Clinical Positioning

Emicizumab: The established standard of care.

Mim8: Next-gen challenger aiming for near-zero bleeds

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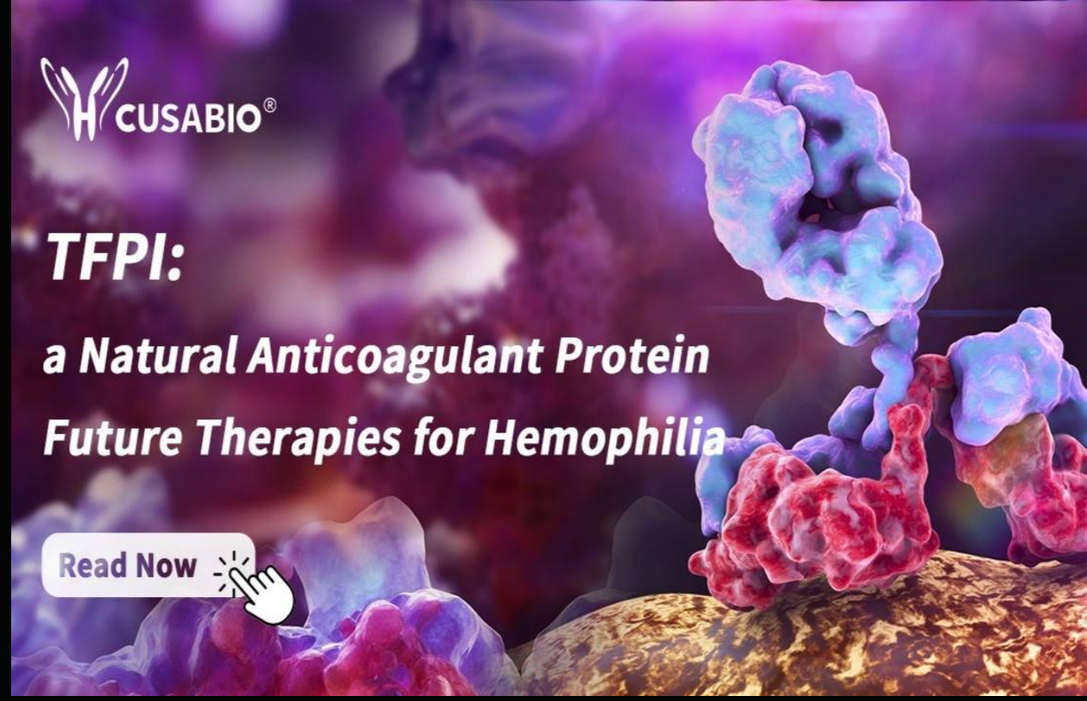
Anti-TFPI Agents

- Re-balancing Hemostasis via the Tissue Factor Pathway

- Marstacimab and Concizumab neutralize TFPI—a key physiological "brake" on the tissue factor pathway.

- By lifting this brake, they enhance thrombin generation to compensate for missing FVIII or FIX in hemophilia.



Why Target TFPI?

01

The Brake

TFPI inhibits TF-FVIIa and FXa, limiting thrombin generation

02

The Problem

In hemophilia, missing FVIII/FIX reduces clotting capacity

03

The Solution

Anti-TFPI antibodies neutralize TFPI to boost TF-driven thrombin

04

The Result

Partial compensation for deficient coagulation factors

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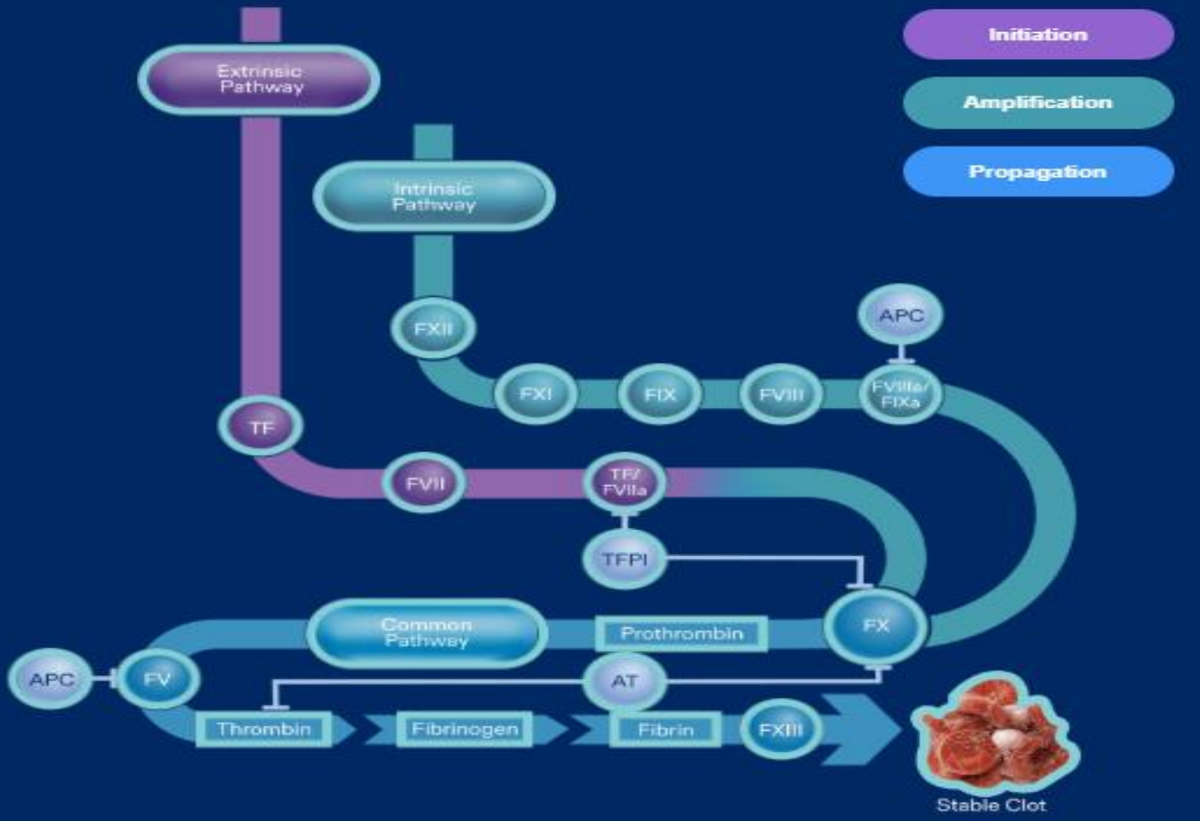
The Role of TFPI in the Extrinsic Pathway in the Coagulation Cascade[1,3-5,7-9,11,12]

Click on the image below and select each icon to learn about its function.



The coagulation cascade is an activation sequence that forms stable blood clots. It consists of the *extrinsic* and *intrinsic* pathways, both of which lead into the *common* pathway.[4,5]

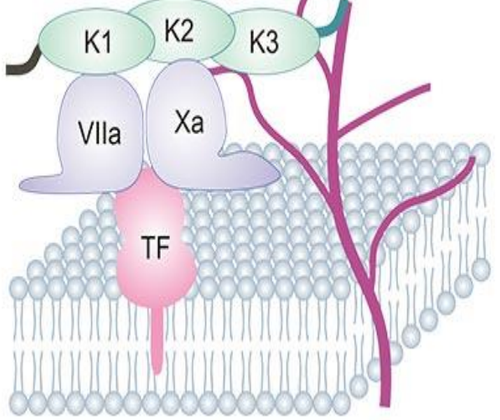
Activation of these pathways results in the production of **thrombin**, a component required for the subsequent production of **fibrin**. The formation of a fibrin mesh stabilizes the blood clot.[3,5,11]

TFPI is a key anticoagulant in hemostasis regulation because it inhibits procoagulant activity at an early stage of the clotting process. Because deficiencies in factor VIII or factor IX, both procoagulation elements, are the pathological basis for hemophilia A and B, limiting the action of an anticoagulant such as TFPI aims to "rebalance" the process.[3,4,7]

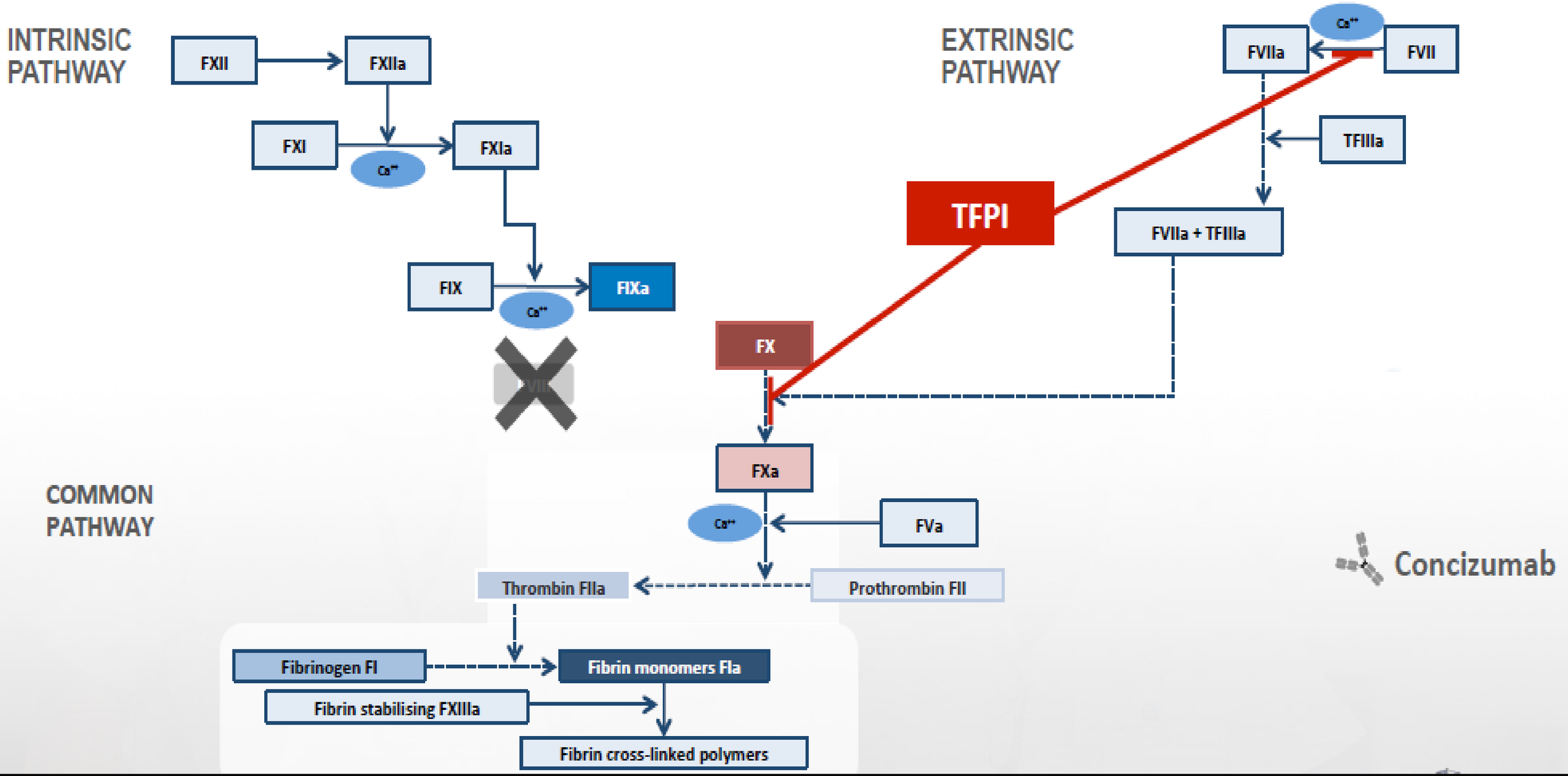
Concizumab (Alhemo®)

Mechanism & Approval

- High-affinity humanized IgG4 mAb directed against the Kunitz-2 domain of TFPI
- Designed to target and block Fxa selectively
- Approved in Canada, Australia, and Japan for **HA/HB with inhibitors (≥12 years)** in March 2023
- **Only for patients with inhibitors**
- ✕ Development for **non-inhibitor patients withdrawn (Oct 2024)**
- Daily SC injections may affect adherence vs weekly alternatives.



Concizumab targets TFPI



Efficacy

- Phase 3 data:
  - Significant reduction in annualized bleeding rate vs on-demand therapy
  - Failed to show non-inferiority vs factor prophylaxis in non-inhibitor population
- concizumab prophylaxis showed a positive long-term effect (56 weeks) on the target joints, their resolution, and joint bleeding

Safety Profile

- Development paused in 2020 due to 3 non-fatal thromboembolic events.
- Protocols revised with stricter monitoring and dose adjustments. Thrombotic risk remains a key consideration, especially with comorbidities.

Red flag:

In patients with multiple thrombosis risk factors (obesity, smoking, prior VTE), daily anti-TFPI warrants extra caution or alternative strategies.

Marstacimab (Hympavzi)

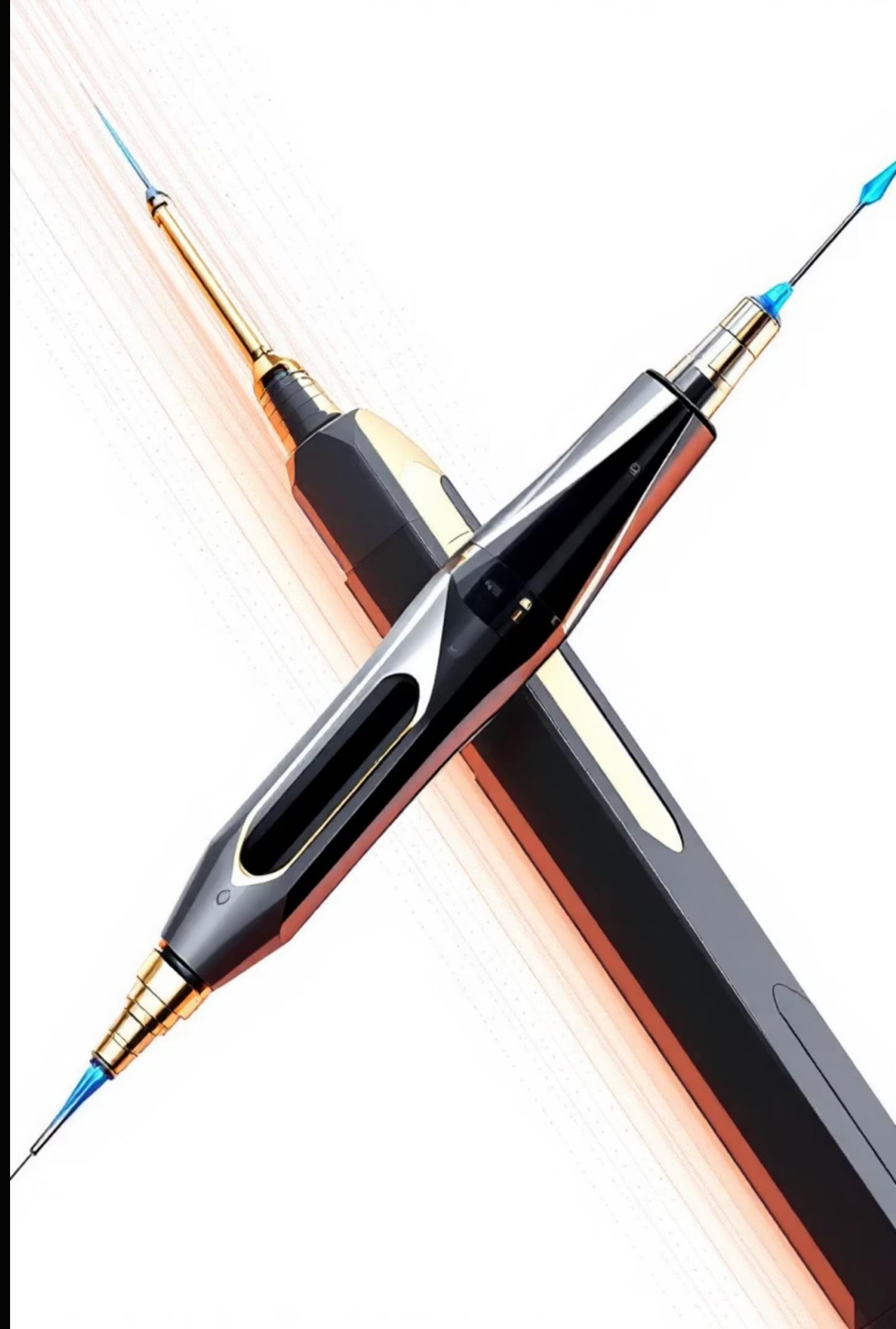
- A human IgG1 mAb that binds the Kunitz-2 domain of TFPI, preventing its interaction with FXa
- First non-factor SC option for hemophilia B without inhibitors

FDA Approval

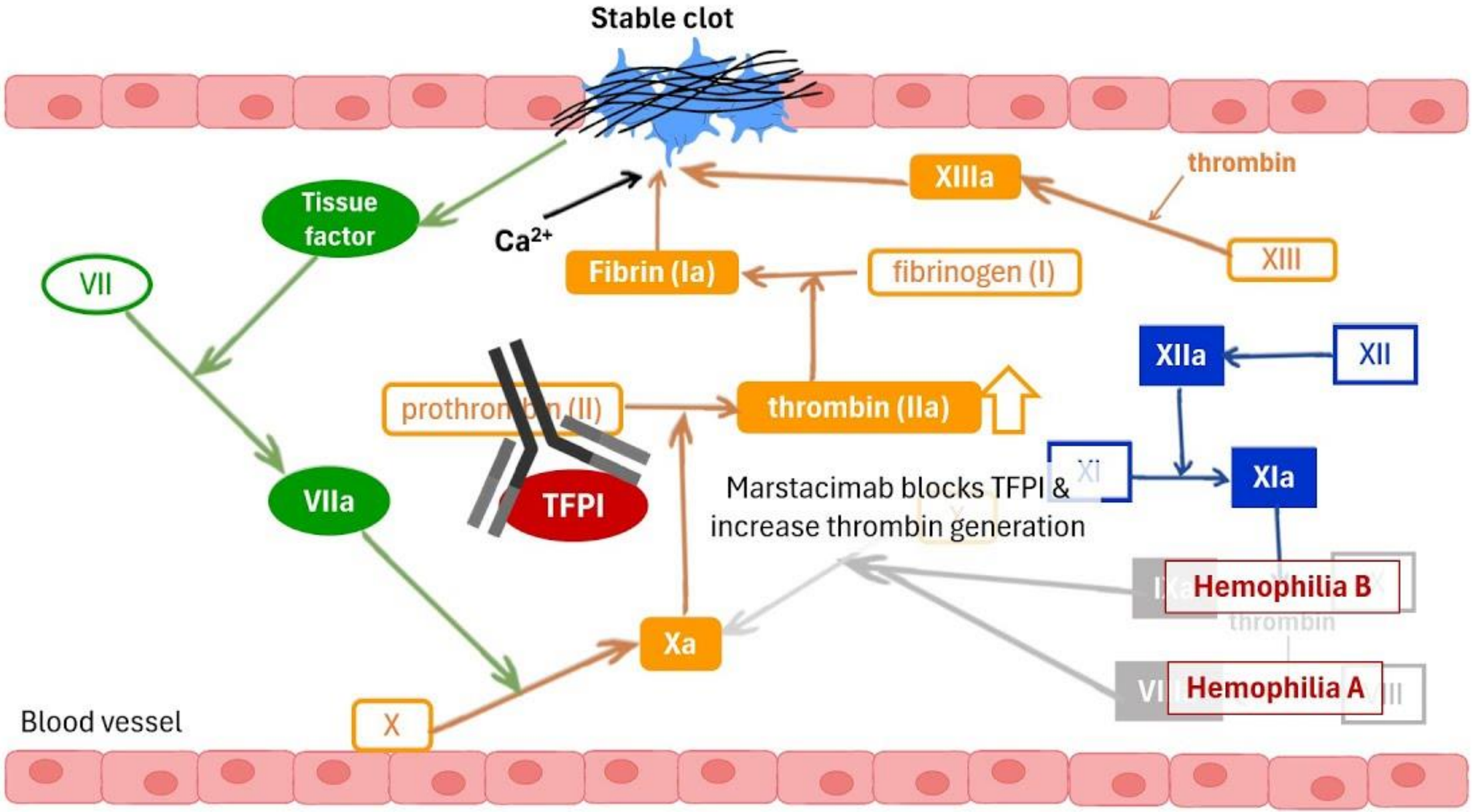
October 2024 for prophylaxis in HA or HB without inhibitors, age ≥12 years

Dosing

SC, once weekly, flat dosing regimen with no weight-based titration in adults



Marstacimab promotes blood clotting



BASIS Trial Results

93%

ABR Reduction

Reduction in annualized bleed rate vs on-demand treatment

1.39

Bleeds per Year

On Marstacimab prophylaxis in inhibitor patients

19.78

Historic Rate

Bleeds per year with on-demand bypassing agents

Clinical Pearl:

- Marstacimab offers convenient weekly SC dosing with meaningful bleed reduction, particularly attractive for HB with or without inhibitors.
- Efficacy is less potent than Emicizumab/Fitusiran/Concizumab.

Concizumab vs Marstacimab

Target

Both target TFPI but different epitope domains

Dosing

Concizumab: Daily SC
Marstacimab: Weekly SC

Population

Concizumab: HA/HB with inhibitors
Marstacimab: HA/HB with and without inhibitors (US label)

Key Concern

Concizumab has thrombosis signal requiring close surveillance

Both agents lift the TFPI "brake"; Concizumab's daily dosing and thrombotic history may influence agent choice where multiple options exist.

Fitusiran

Monthly siRNA Targeting Antithrombin

Mechanism

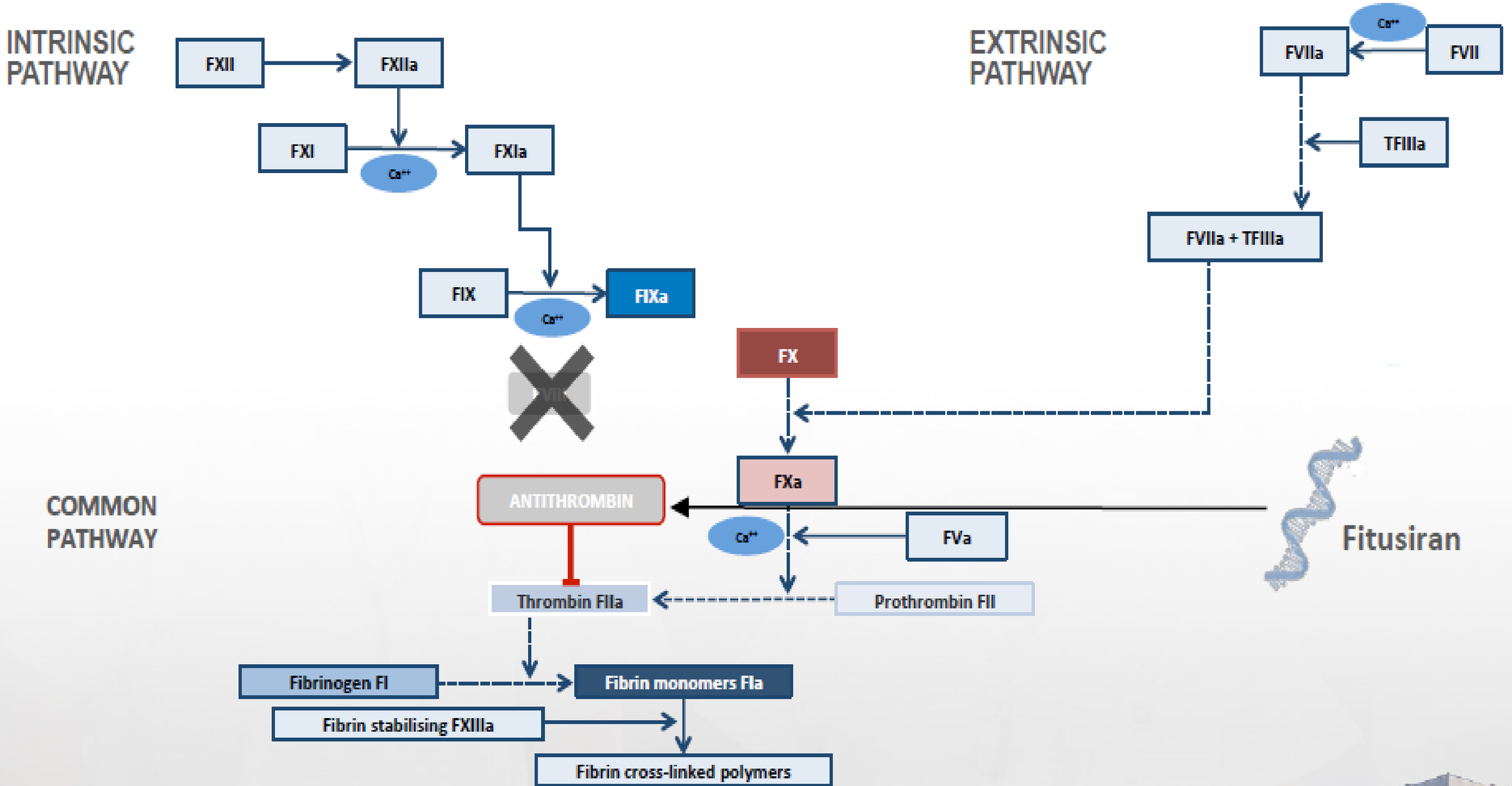
- GalNAc-conjugated siRNA reduces hepatic antithrombin production to 15-35% of normal.
- Removing this global thrombin inhibitor boosts generation regardless of FVIII/FIX levels.

Dosing & Monitoring

- Once-monthly SC after loading phase.
- Requires strict AT activity monitoring and dose adjustment if levels fall outside target window or thrombotic risk increases.

- **Mechanism:** siRNA → antithrombin (AT) knockdown
- **Indication:** Hemophilia A & B, **with or without inhibitors**
- **Age:** ≥12 years
- **Status:** ✓ **FDA approved – March 28, 2025**
- **Clinical Basis:** Phase 3 **ATLAS program**
- **Significance:**
  - First approved **AT-lowering therapy**
  - First rebalancing agent approved for **both inhibitor and non-inhibitor patients**

Fitusiran reduces antithrombin production



Fitusiran Safety Timeline

1 **2017**

Development halted after fatal CVST case. Risk-benefit reviewed.

2 **2018–2019**

Protocol changes: lower target AT, intensified monitoring impleme

3 **2020**

Program paused after additional thrombotic events. Further protocol refinement.

4 **2021**

Restarted with stricter safety measures.

2025

Received FDA approval

Red flag:

In any patient on Fitusiran with new neurological symptoms, chest pain, or limb swelling—treat as potential thrombosis until proven otherwise.

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Comparative overview of the phase III trials of the approved rebalancing agents

Comparative factor	Fitusiran	Concizumab	Marstacimab
Trial	ATLAS-OLE	explorer7 and 8	BASIS
Target	Antithrombin	TFPI K2	TFPI K2
Mechanism of action	siRNA	Monoclonal antibody	Monoclonal antibody
Number of patients	213	241	116
Frequency	Q2M (AT-DR)	daily	weekly
Dosing	50 mg Q2M (AT-DR)	0.2 mg/kg (1 mg/kg loading dose)	150 mg fixed dose (300 mg loading dose)
Mean ABR (95% CI)	6.4 (5.3-7.7)	explorer7: 1.7 (1.0-2.9) explorer8 HA: 2.7 (1.6-4.6) explorer8 HB: 3.1 (1.9-5.0)	5.08 (3.4-6.8)
Median ABR (IQR)	3.7 (0.0-7.5)	explorer7: 0.0 (0.0-3.3) explorer8 HA: 2.9 (0.0-5.2) explorer8 HB: 1.6 (0.0-4.8)	Not available
Thrombotic events	4	0 (3 prior to revised dosing)	1
Monitoring	Antithrombin levels	Concizumab, TFPI levels	No
Approval	HA/HB with or w/o inhibitors FDA	HA/HB with inhibitors FDA, EMA	HA/HB w/o inhibitors FDA, EMA
Anti-drug antibodies	1.8%	explorer7: 26% explorer8: 14% (HA) and 9% (HB)	20.5%
Adverse events	AST/ALT >3x ULN (3.5%) Cholecystitis, cholelithiasis (3.8%) Injection site reaction (5.6%)	Arthralgia (10%) Injection site reaction (7%) URTI (6%)	Injection site reaction (5.2%)
Co-treatment	FVIII 10 IU/kg, FIX 20 IU/kg aPCC 30 IU/kg, rFVIIa 45 μg/kg	FVIII 20 IU/kg, FIX 30 IU/kg aPCC 50 IU/kg, rFVII 90 μg/kg	Not available

https://doi.org/10.3324/haematol.2025.288245

Safety Comparison

Thrombosis Risk Across Non-Factor Agents

Agent	Thrombosis Risk	Key Mitigation
Emicizumab	Low (monotherapy)	Avoid high-dose aPCC; prefer rFVIIa for breakthrough bleeds
Marstacimab	Moderate	Weekly dosing; avoid stacking pro-coagulants unnecessarily
Concizumab	Moderate-Higher	Daily dosing; careful VTE assessment, dose adjustments if events occur
Fitusiran	Higher	Maintain AT in target range; hold dose if AT too low (< 15%) or new risk appears

Different mechanisms create distinct risk profiles. Always consult up-to-date prescribing information and build structured monitoring into clinic workflows.

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Dosing & Convenience

Emicizumab

SC, Q1W/Q2W/Q4W after loading. Weight-based dosing.

Marstacimab

SC, weekly. Flat dosing for adolescents/adults.

Concizumab

SC, daily. Weight-based, titratable dosing.

Fitusiran

SC, monthly after loading. Fixed/adjusted by AT levels.

Route and frequency strongly influence adherence and quality of life. The "lived experience" differs substantially between daily, weekly, and monthly regimens—especially in pediatrics.

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Practical Case Scenarios

3-Year-Old Severe HA

Poor IV access, no inhibitors. Parents exhausted by cannulation.

- Consider Emicizumab first-line SC prophylaxis
- Plan FVIII access for major trauma/surgery

Adolescent Severe HB

No inhibitors, active in sports, adherence struggles.

- Marstacimab: first non-factor SC weekly option
- Discuss realistic ABR expectations vs classic FIX

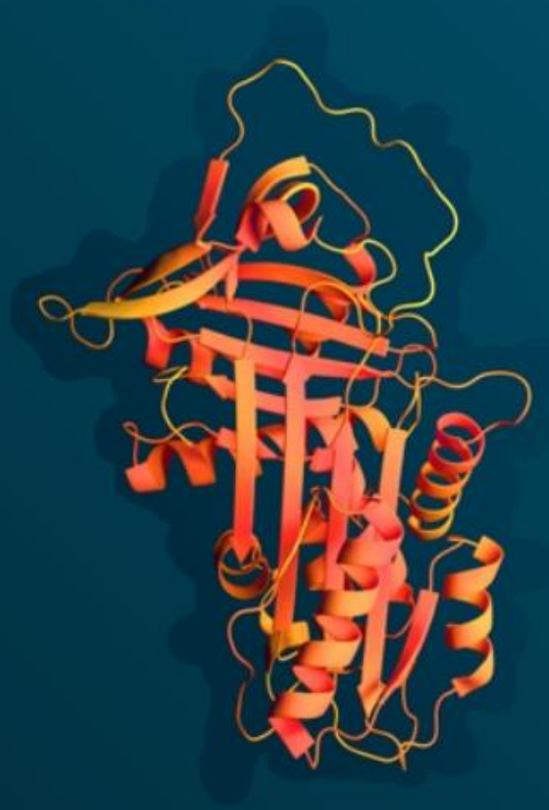
Adult HA with Inhibitors

On Emicizumab, obesity and smoking present.

- Avoid daily anti-TFPI or Fitusiran unless clear benefit
- Prioritize lifestyle modification, careful bypassing agent choice

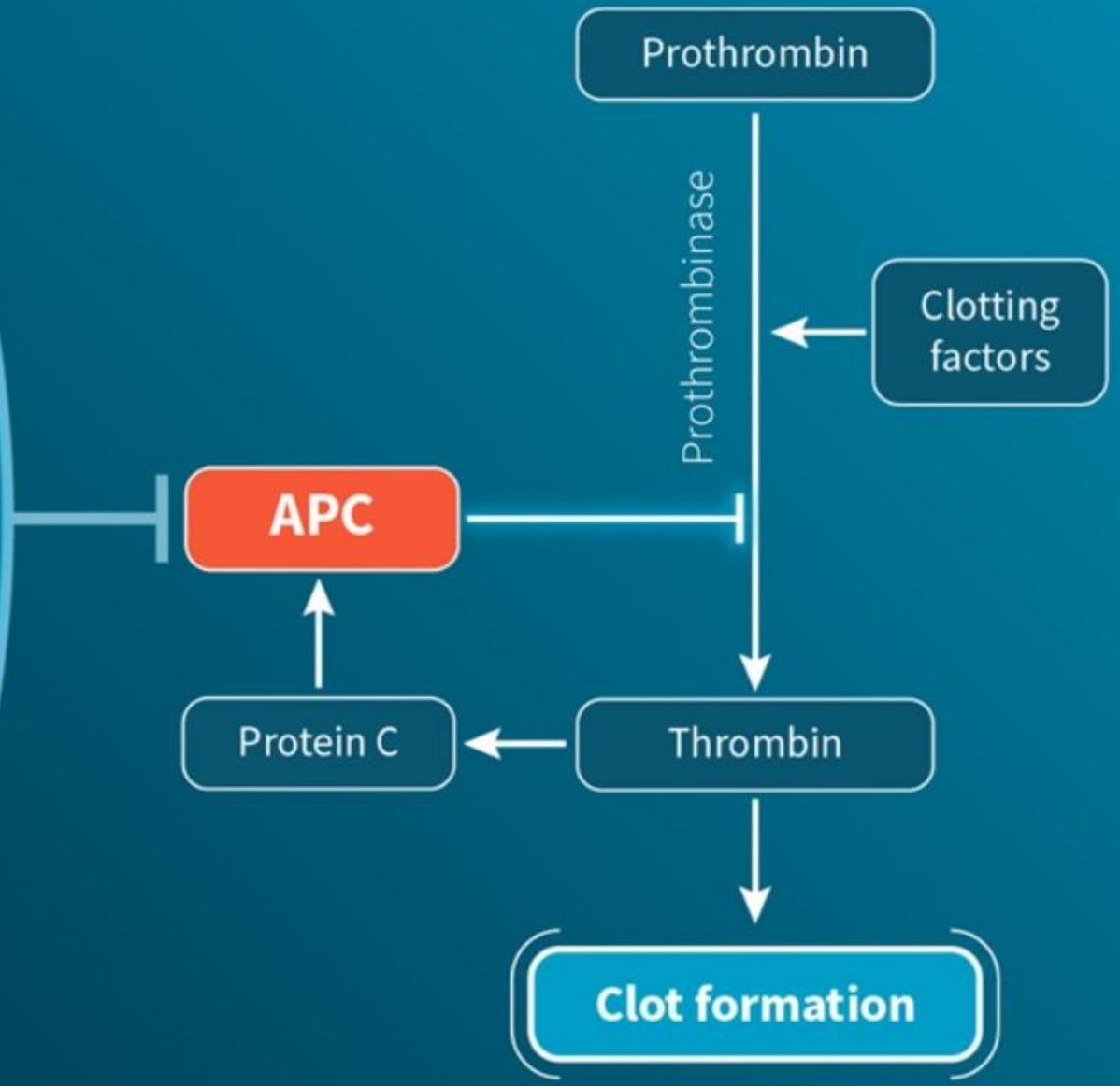
Clinical pearl:
Choice of agent isn't only about ABR—consider patient age, comorbidities, route, frequency, safety profile, and local access.

SerpinPC: Novel Approach Designed to Prevent and Reduce Bleeding



SerpinPC

Designed to reduce levels of circulating activated protein C (APC)



SerpinPC: How it Works

1

SerpinPC Inhibition

SerpinPC neutralizes APC.

2

Preserved FV/FVIII

Functionality of procoagulant cofactors FVa and FVIIIa is maintained.

3

Increased Thrombin Burst

Maximizes endogenous thrombin burst potential.

This mechanism is distinct from agents targeting Antithrombin or TFPI, offering a unique pathway modulation.

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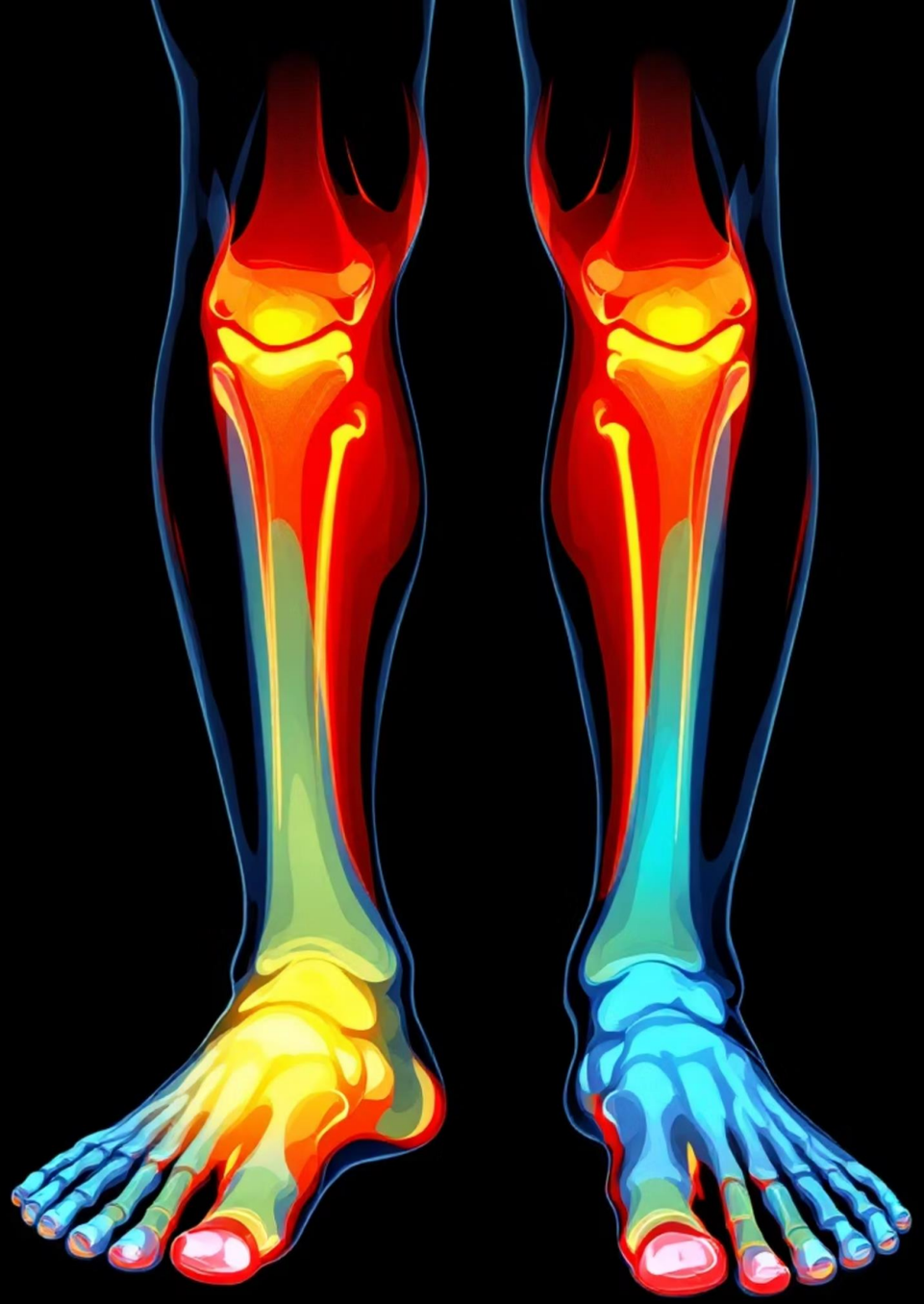


SerpinPC: VENUS Program (Phase 3)

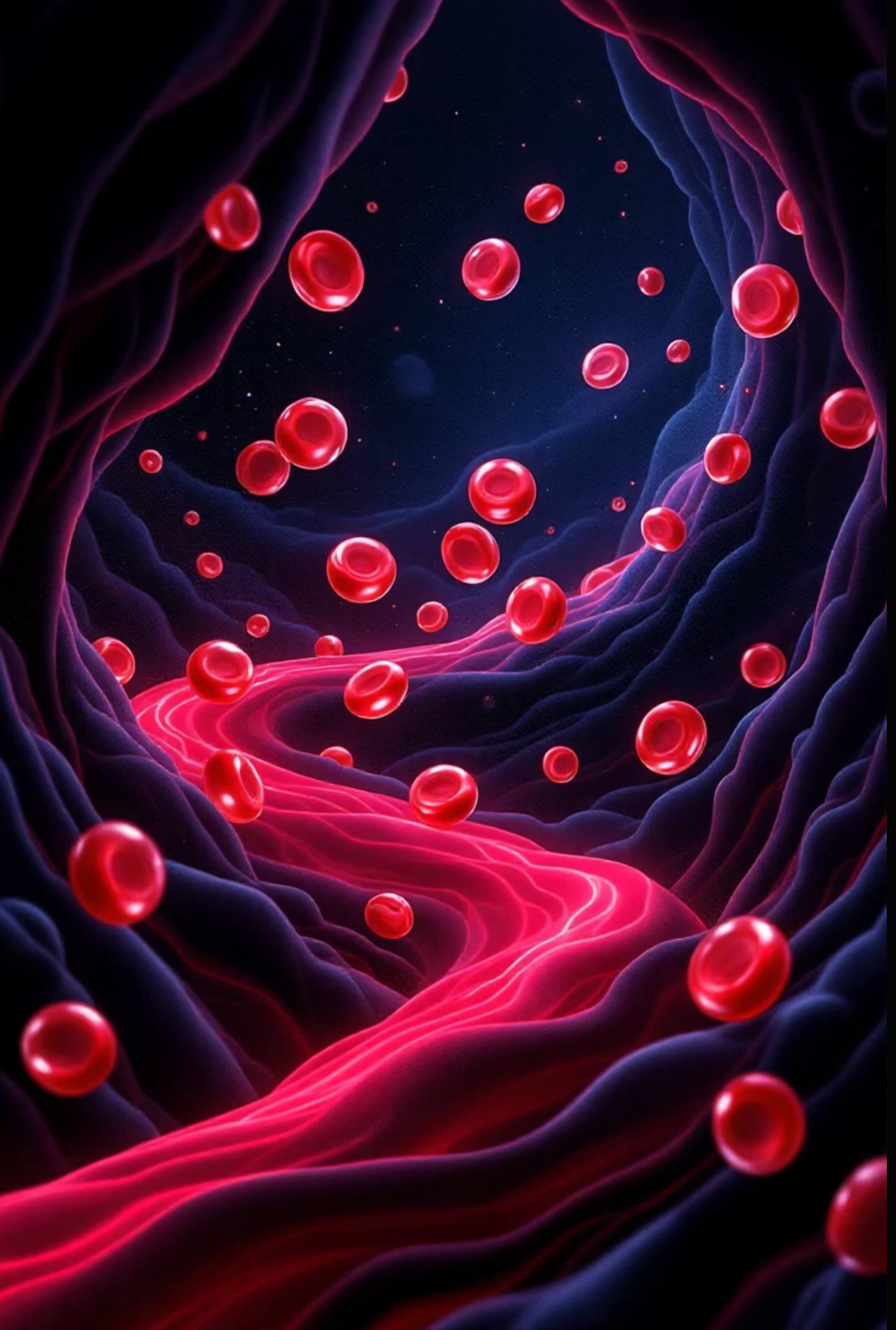
The VENUS program evaluated SerpinPC efficacy, often in patients with established inhibitor disease.

Sustained Prophylaxis

Long-acting nature provides sustained prophylaxis, reducing spontaneous bleeds.

Joint Protection

High proportion of subjects achieved ABR 0, indicating robust protection against chronic arthropathy.



SerpinPC: Safety Profile

Low Thrombosis Signal

APC inhibition strategy shows a low signal for clinically relevant thrombosis events, attributed to precision targeting.

Well-Tolerated

Generally well-tolerated with sustained subcutaneous dosing feasibility.

Despite proven efficacy and safety in phase 2 clinical trials, the development was discontinued by Centessa Pharmaceuticals.

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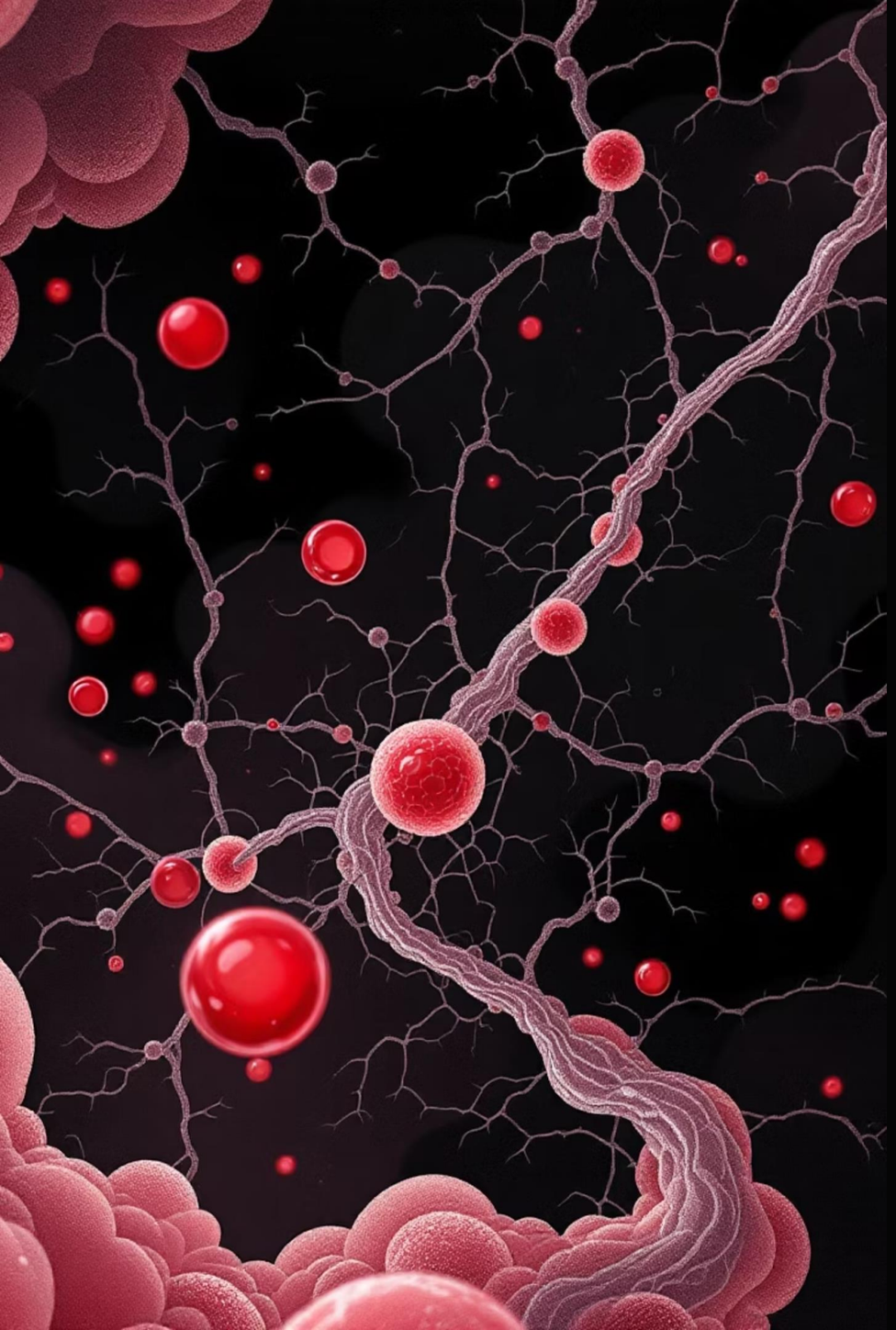
Table 2. Overview of the strengths and weaknesses of rebalancing agents.

Strengths	Risks or Limitations
Subcutaneous administration	Risk of thrombosis
Thrombin generation independent of FVIII/FIX	Not detectable or measurable with routine clotting factor assays; specialized assays required
Rapid onset of action	Inability to detect activity in acute settings (e.g., emergency department) with routine clotting assays
No cross-reactivity with FVIII/FIX inhibitors	Need for monitoring for some agents (e.g., AT/TFPI levels)
Use in patients with inhibitors	Requirement for individualized treatment regimens
Long half-life (allowing infrequent dosing) for some agents	Complex and unvalidated management of patients with inhibitors (modality of ITI and co-treatment with bypassing agents)
Potential to convert severe hemophilia A/B into a mild phenotype	Risk of anti-drug antibody development (detection and management modalities not standardized)
Availability of several therapeutic agents targeting different pathways	Complex mechanisms of action
Attractive option for patients with hemophilia B (with or without inhibitors)	Limited dosing flexibility; fixed treatment regimens
Potential normalization of blood coagulation (currently unknown)	Limited clinical data in women and girls with hemophilia A/B
Potential applicability in other rare bleeding disorders	Hemostatic efficacy: non-inferiority to current prophylaxis not demonstrated for some agents
Potential use in low-income countries (especially agents requiring minimal monitoring and infrequent dosing)	Competitive and evolving marketing environment; future adoption uncertain
Convenient storage conditions for some compounds	Complexity of shared decision-making

The strengths are shown on the left, and the risks or limitations on the right. FVIII: factor VIII; FIX: factor IX; AT: antithrombin; TFPI: tissue factor pathway inhibitor; ITI: immune tolerance induction.



Challenges in Hemophilia Rebalancing

Thrombotic Risk

Systemic procoagulant shift leads to uncontrolled thrombin generation.

Uncertain Hemostatic Equivalence

Lack of clear FVIII/FIX equivalence complicates surgery and acute bleeding management.

Laboratory Monitoring Limitations

Interference with routine assays necessitates specialized testing.

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Challenges in Hemophilia Rebalancing

1

Incomplete Efficacy

Bleeding is not fully eliminated; non-inferiority to current prophylaxis is not consistently demonstrated.

2

Complex Clinical Management

Perioperative and breakthrough bleeding strategies remain unvalidated.

3

Limited Long-Term & Pediatric Data

Ongoing uncertainty regarding durability, safety, and use in children.

4

Therapeutic Positioning Unclear

Competition with emicizumab, long-acting factors, and gene therapy.

Effective hemostatic rebalancing is delicate; benefits must be weighed against thrombotic risk and clinical uncertainty.

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Von Willebrand Disease: What is *New* in 2025?

- No Phase 3 or 4 **novel therapies** are currently available for VWD
- Rebalancing strategies (anti-TFPI, anti-AT)→ **not suitable for VWD** due to fundamental pathophysiologic differences
- Emerging research (early stage):
  - **siRNA** targeting pathogenic alleles in dominant Type 2 VWD
  - **VWF aptamers** interfering with VWF clearance
  - Bioengineered VWF molecules

Conclusion:

VWD management progress in 2024 is the **optimization of the existing therapies**, not the introduction of late-phase novel agents.

FVIII MIMETICS AND OTHER NON-REPLACEMENT THERAPIES IN DEVELOPMENT						
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Mode of administration**	**Developer / manufacturer**	**Development stage**
Bi-specific monoclonal antibody	Haemophilia A	Mim8	FVIII mimetic, bispecific monoclonal antibody binding to FIXa and FX	Subcutaneous	Novo Nordisk	Phase 3
Bi-specific monoclonal antibody	Haemophilia A	NXT007	FVIII mimetic, bispecific monoclonal antibody binding to FIXa and FX	Subcutaneous	Chugai	Phase 1/2
Bi-specific monoclonal antibody	Glanzmann Thrombasthenia	HMB-001	Bispecific antibody binding to FVIIa and TLT-1	Subcutaneous	Hemab	Phase 1/2
Aptamer	Haemophilia A, Type 2B VWD	Rondoroptivon pegol BT200	Pegylated aptamer binding to vWF	Subcutaneous	Medical University of Vienna	Phase 2

RE-BALANCING THERAPIES (NON-REPLACEMENT THERAPIES) IN DEVELOPMENT

Type of product	Indication / treatment of	Product name(s)	Mechanism of action	Mode of administration	Developer / manufacturer	Development stage
NRT Anti-TFPI	Haemophilia A or B w/ or w/o inhibitors	Concizumab	Anti-tissue factor pathway inhibitor (anti-TFPI)	Subcutaneous	Novo Nordisk	Phase 3 (approved for PHABwI in Canada, Australia, Japan and EU)
NRT Anti-TFPI	Haemophilia A or B w/ or w/o inhibitors	Marstacimab	Anti-tissue factor pathway inhibitor (anti-TFPI)	Subcutaneous	Pfizer	Approved by EMA
NRT siRNA	Haemophilia A or B w/ or w/o inhibitors	Fitusiran	Antithrombin Small interfering (si)RNA to down-regulate antithrombin	Subcutaneous	Sanofi	Phase 3
NRT Activated Protein C inhibitor	Haemophilia A or B w/ or w/o inhibitors	SerpinPC	Activated Protein C inhibitor	Subcutaneous	Apcintex	discontinued

Key Take-Home Messages

1 Paradigm Shift

We've moved from replacement (FVIII/FIX) to re-balancing (FVIII mimetic, anti-TFPI, anti-AT). Emicizumab has transformed severe HA prophylaxis and is now a reference standard.

2 Expanded Options

Marstacimab adds a weekly SC option for HA/HB without inhibitors, particularly valuable for HB. Concizumab and Fitusiran extend options but require respect for thrombotic risk profiles.

3 Safety Vigilance

Laboratory interference (Emicizumab) and safety interactions (aPCC, AT levels) must be understood by the whole team. Develop simple, written algorithms for ED and OR teams.

4 Practical Implementation

Review your center's protocols for lab testing, surgery, and management of breakthrough bleeding. Engage patients and families in shared decision-making, including realistic ABR expectations and safety monitoring.

Thanks for your attention