Hemophilia Clinical Research Highlights: ISTH 2025

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Continuing Education Information

In support of improving patient care, this activity has been planned and implemented by American Academy of CME, Inc. and CheckRare CE. American Academy of CME, Inc. is Jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Learning Objective: Describe the latest research about hemophilia A and B presented at ISTH 2025 and its clinical relevance in real-world settings.

Planner/Faculty Educator Dr. Pipe discloses the following relevant financial relationships with ineligible companies:

- Consultant: Bayer, BioMarin, CSL Behring, Hema Biologics, Inovio, LFB, Metagenomi, Novo Nordisk, Pfizer, Poseida Therapeutics, Roche/Genentech, Sanofi, Takeda, Spark Therapeutics
- Scientific Advisory Committee: GeneVentiv, Equilibra Bioscience
- Grant/Research Support: Siemens, YewSaving

Planners and reviewers for this activity have no relevant financial relationships with any ineligible companies.

All relevant financial relationships listed have been mitigated. This activity will discuss off-label uses and investigational agents.

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What is Hemophilia?

A rare bleeding disorder that slows the blood clotting process.

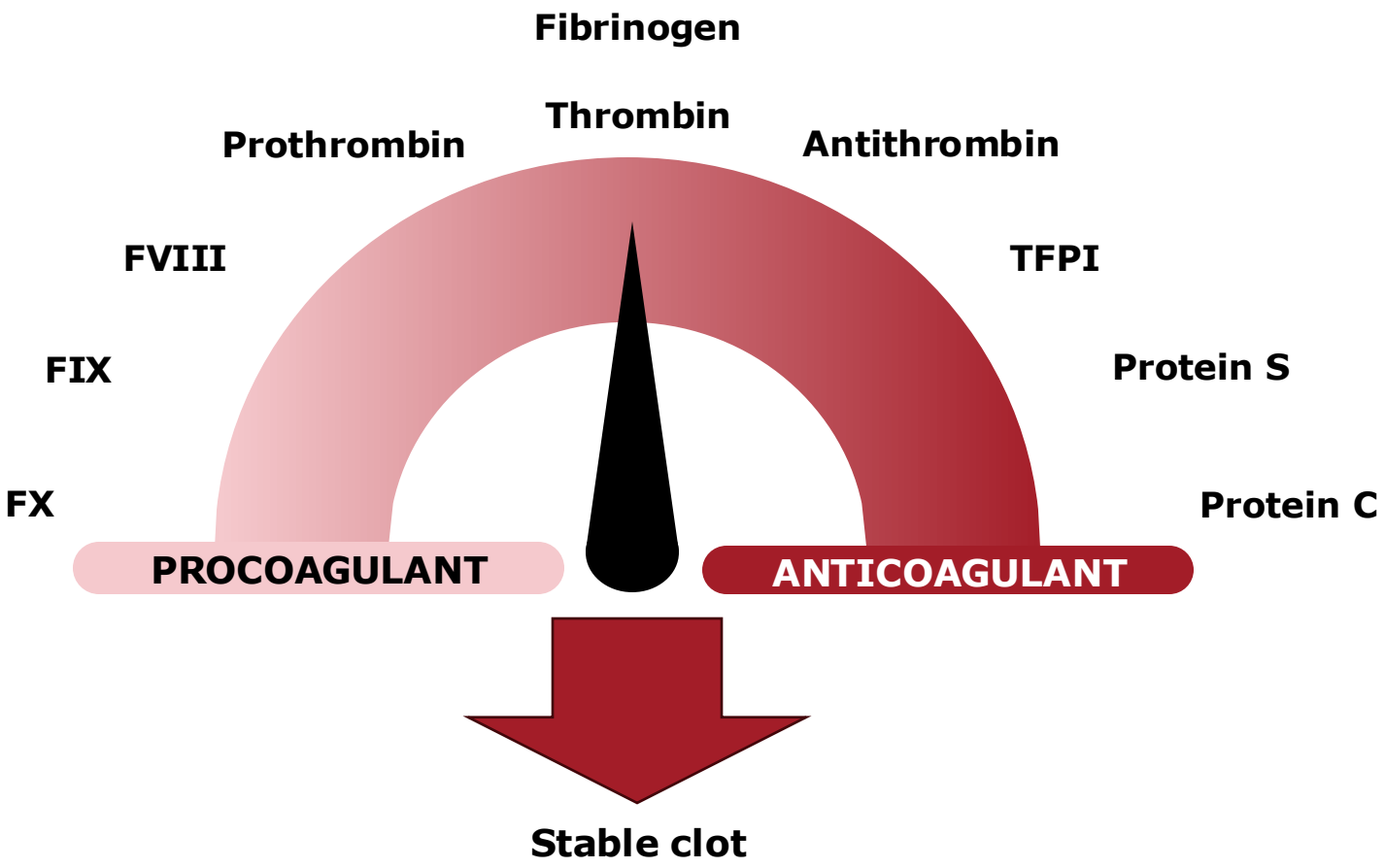
- Individuals may experience prolonged bleeding after injury or surgery.
- In severe cases, heavy bleeding can occur after minor trauma or without any injury.
- Serious complications may result from bleeding into joints, muscles, the brain, or other internal organs.
- Standard of care is regular prophylactic therapy to prevent bleeding.[1]

The two major types are:

- **Hemophilia A:** caused by a deficiency of clotting factor VIII
- **Hemophilia B:** caused by a deficiency of clotting factor IX

1. Rezende SM et al. J Thromb Haemost. 2024; 22: 2629.

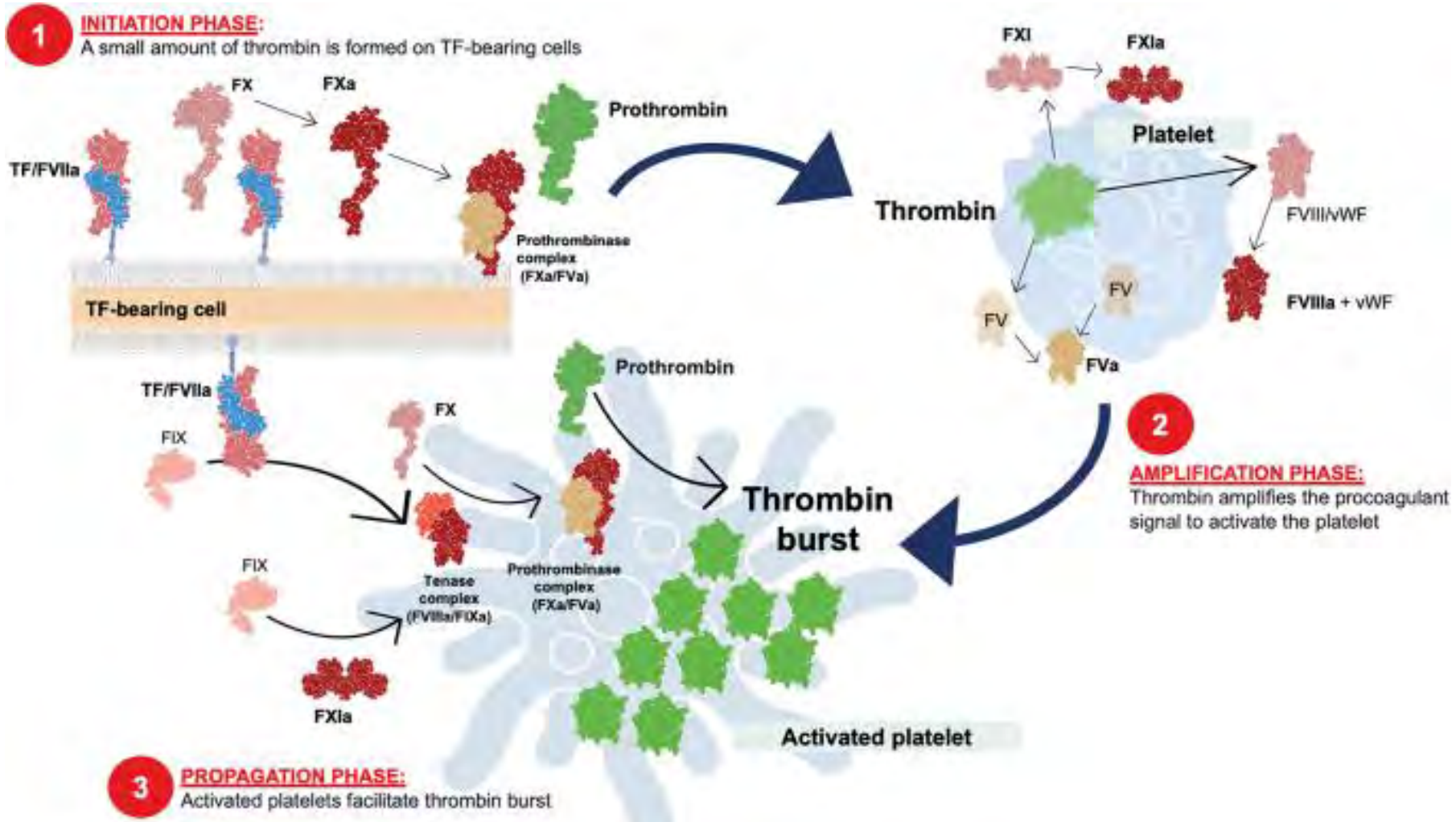
Hemostasis depends on a balanced coagulation system of procoagulants and anticoagulants



Disruption of the **balance** between procoagulants and anticoagulants leads to **insufficient thrombin generation**, resulting in **uncontrolled bleeding**

F, factor; TFPI, tissue factor pathway inhibitor.
Negrier C, et al. Blood Rev 2019;38:100582.

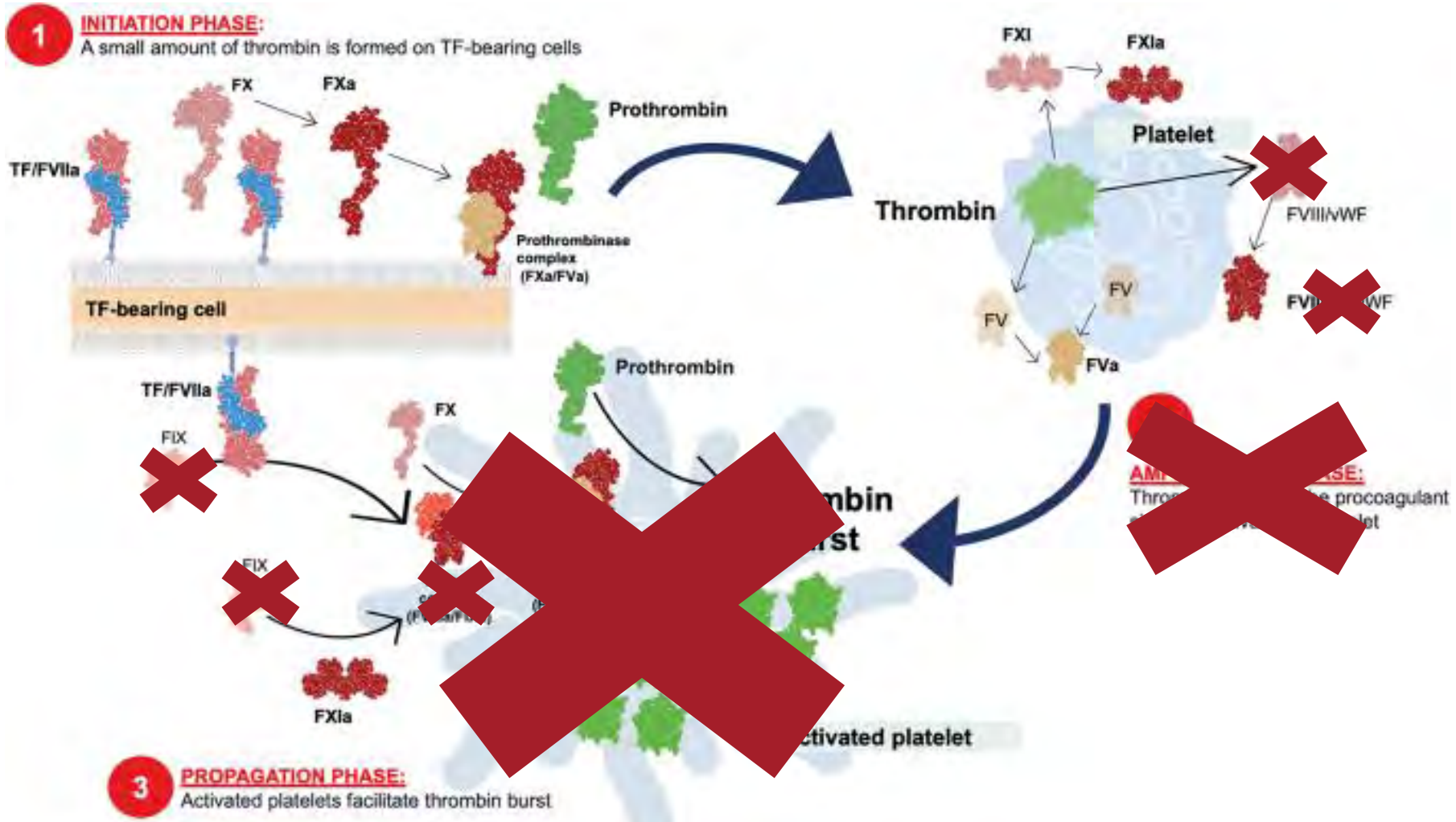
Thrombin is the key enzyme in interconnected, overlapping cellular and proteolytic events that maintain hemostasis



a, activated; F, fa

Figure from Sidonio RF Jr, et al. Res Pract Thromb Haemost. 2022;7(1):100018

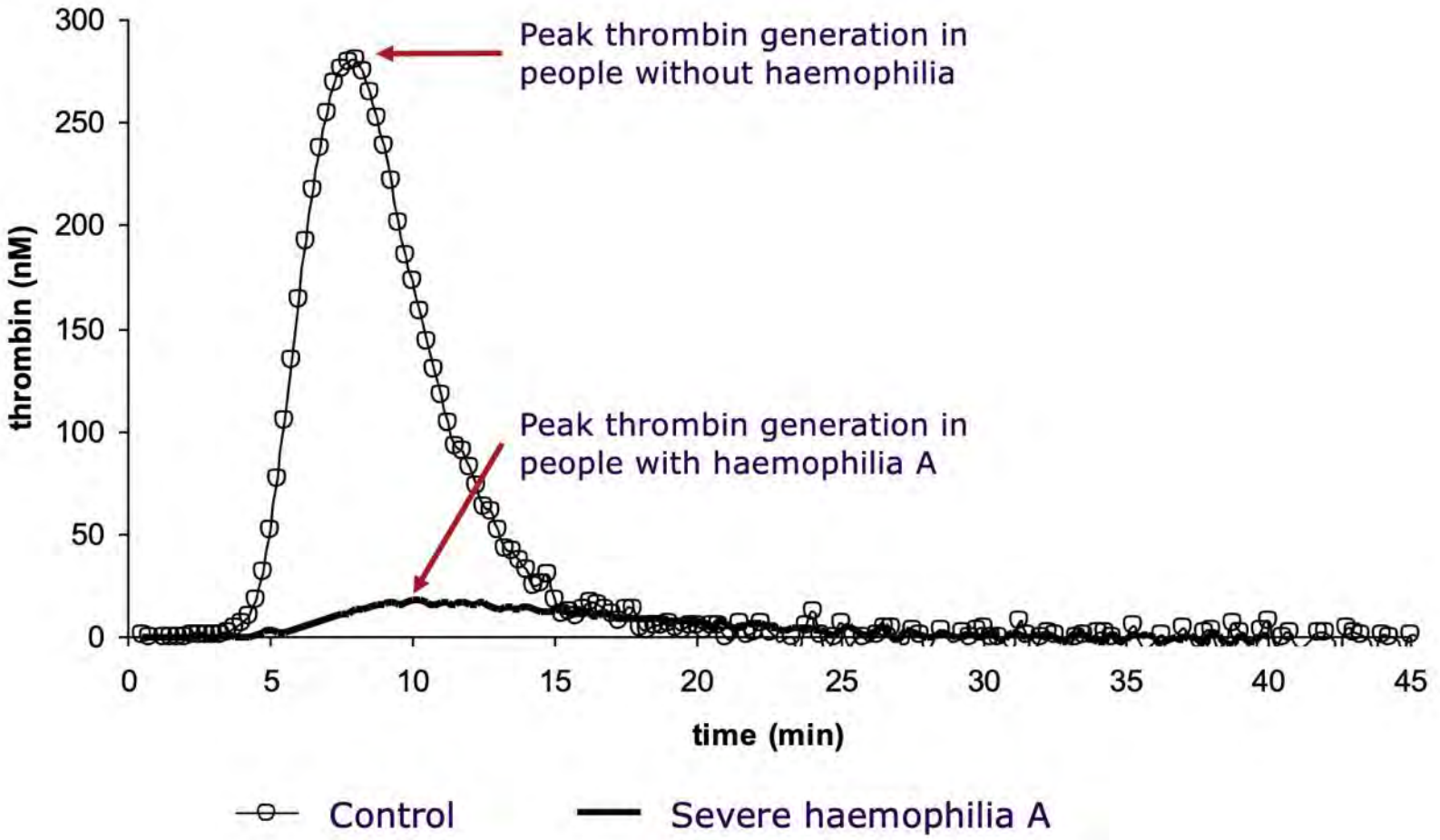
In people with haemophilia, deficiency of FVIII or FIX disrupts hemostasis and results in the inability to form stable clots



a, activated; F, fa

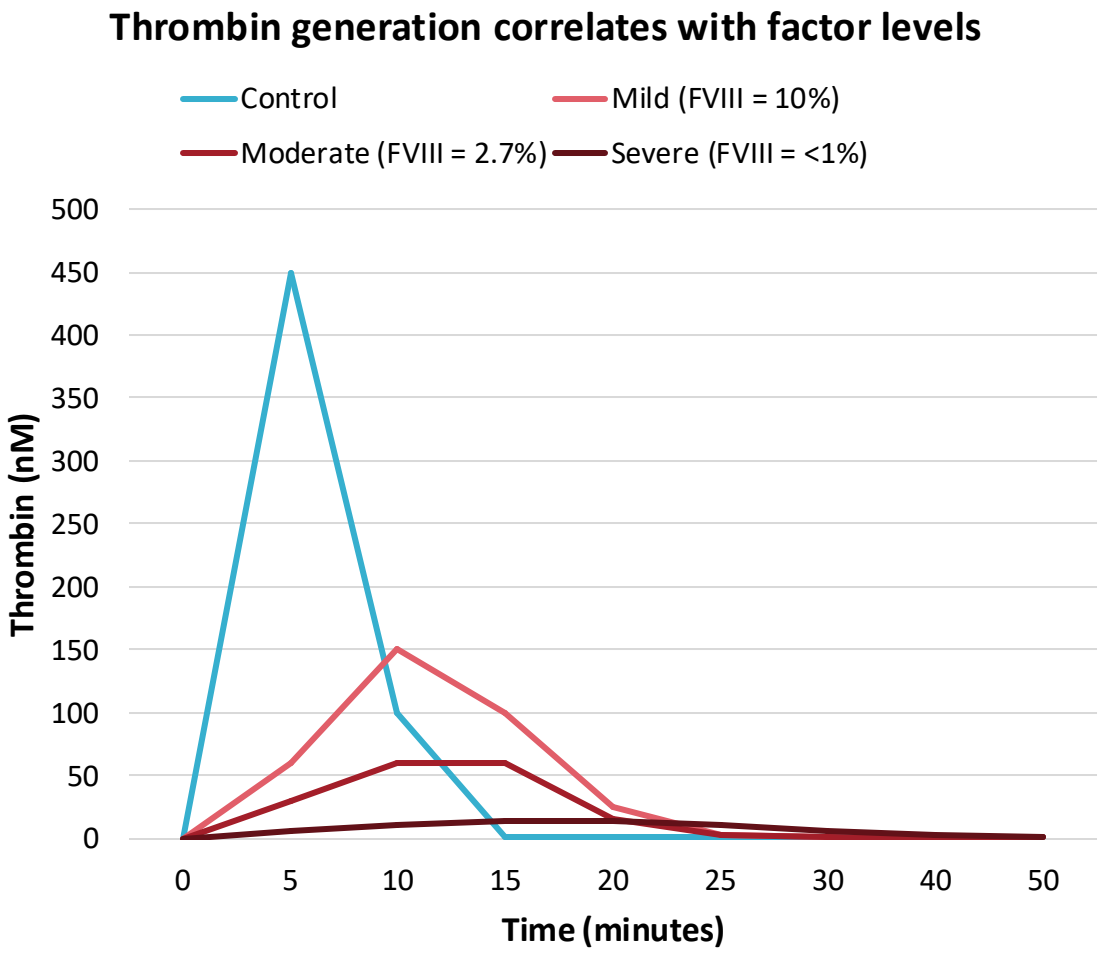
Figure from Sidonio RF Jr, et al. Res Pract Thromb Haemost. 2022;7(1):100018

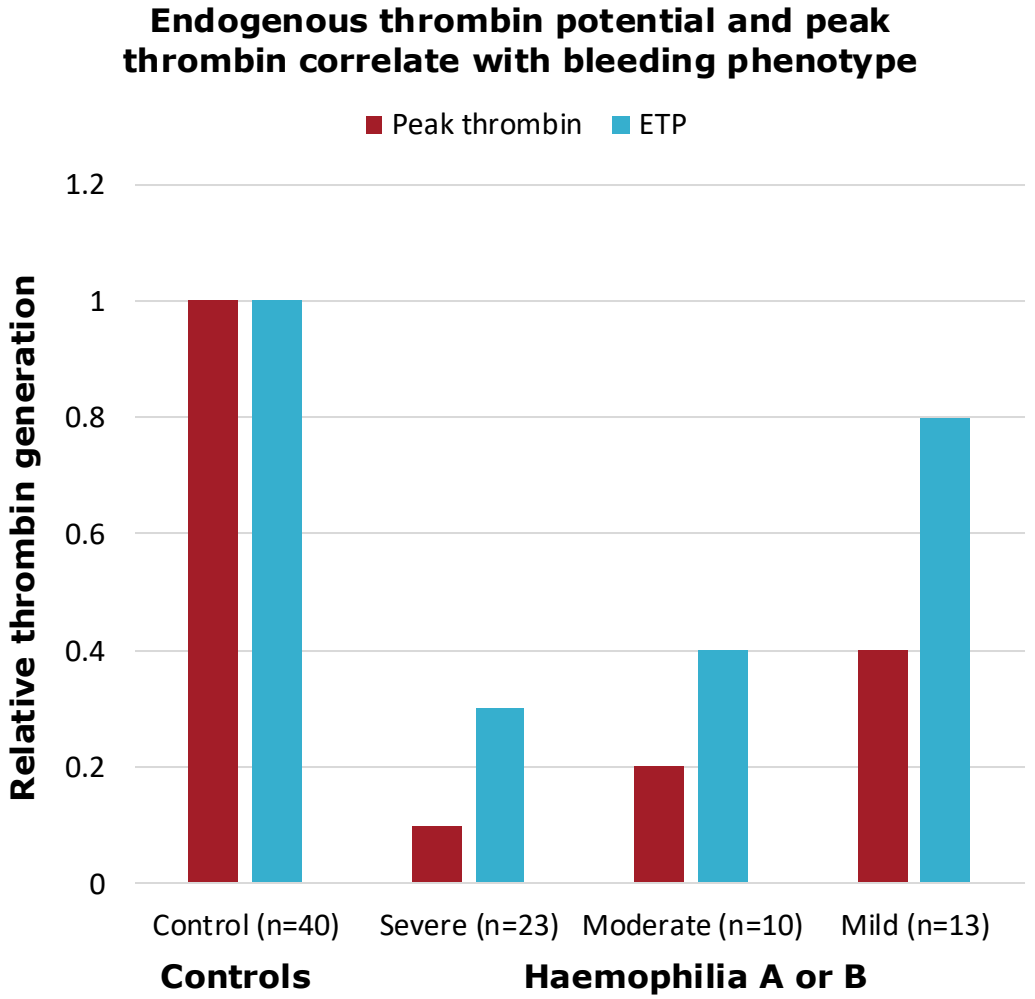
Hemophilia is a disorder characterised by impaired thrombin generation



1. Figure from: Young G, et al. Blood 2013;121:1944–50

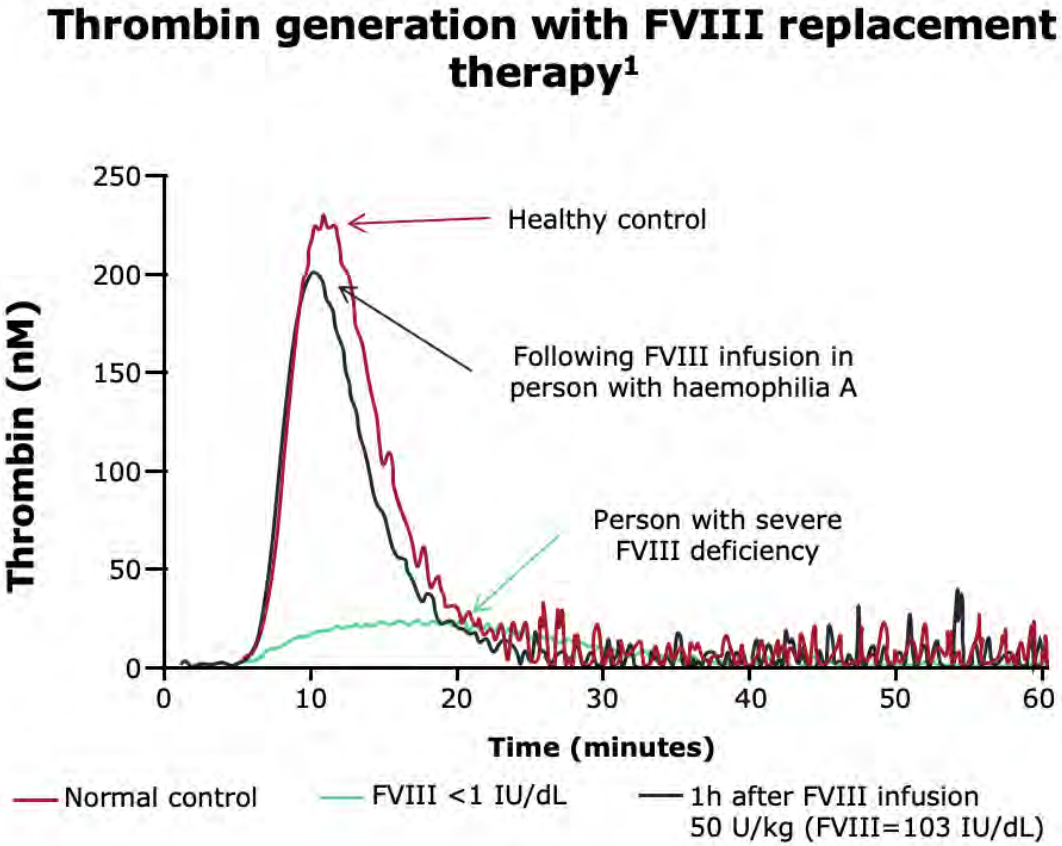
Thrombin generation correlates with factor levels and bleeding risk in people with hemophilia

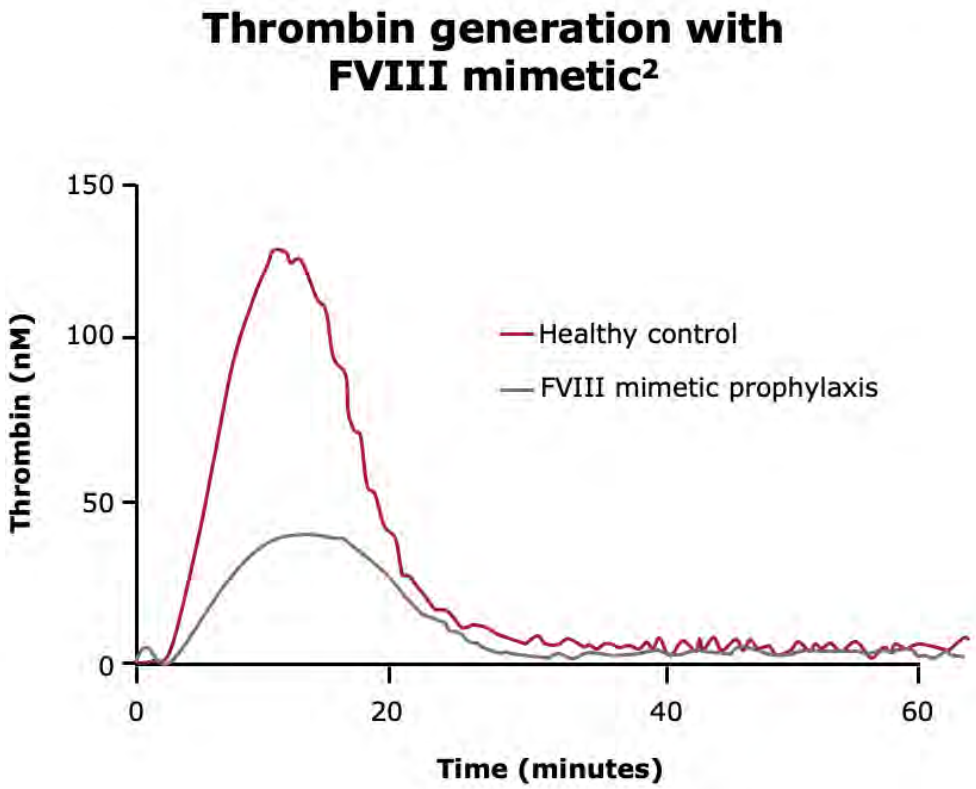




ETP, endogenous thrombin potential; F, factor; TF, tissue factor.
Figures adapted Dargaud Y, et al. Thromb Haemost 2005;93:475–80.

Replacing or mimicking the action of procoagulants can increase thrombin generation in people with hemophilia





1. Young G, et al. Blood 2013;121:1944–50; 2. Dargaud Y, et al. Haematologica 2018;103:e181–83.

Factor Replacement Therapy

Benefits

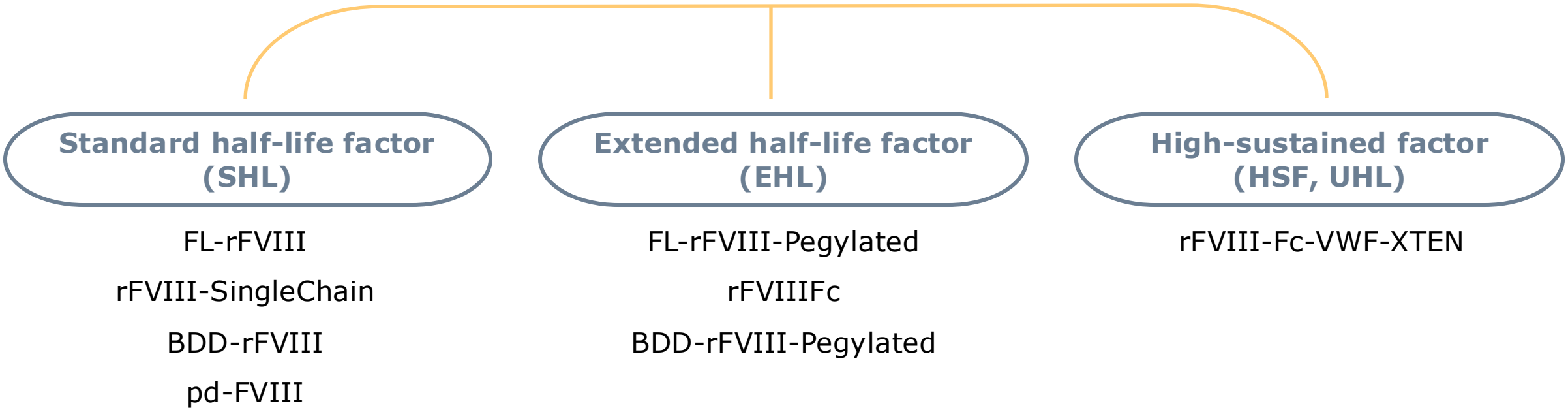
- “Replaces what's missing”
- Retains natural regulation
- Wide therapeutic window
- Experience of efficacy in almost any clinical scenario
- Availability of laboratory monitoring

Risks

- Peaks and troughs do not mimic normal physiology
  - Consequences of non-adherence
  - Has not abrogated adverse joint outcomes
- Therapeutic burden/cost
- Adverse events
  - Inhibitors, thromboembolism

Based in clinical practice – presenter experience

FACTOR VIII REPLACEMENT THERAPY



Abbreviations: FL: full length; rFVIII: recombinant FVIII; BDD: B-Domain deleted; pd-FVIII: plasma derived factor VIII; rFVIIIFc: recombinant FVIII Fc fusion protein; rFVIII-Fc-VWF-XTEN: recombinant coagulation factor VIII Fc-von Willebrand factor-XTEN fusion protein; UHL: ultra-long half-life

Future Treatments Should Aim to Address Unmet Needs for People with Hemophilia

Unmet needs	Expectations for future treatments
Breakthrough bleeds and joint deterioration[1–4]	Zero bleeds, particularly joint bleeds[5]
Treatment burden[6]	Easier and less frequent administration
Development of inhibitors[7]	Available for PwH both with and without inhibitors
Quality of life[1]	Enable PwH to live active lives (similar to non-hemophilic individuals)[5]
Access to treatment[6]	Accessible to all PwH

PwH, people with hemophilia.

1. O'Hara S, et al. Hemophilia 2020;27:113–19; 2. Wilkins RA, et al. BMJ Open 2022;12:e052358; 3. Berntorp E, et al. Hemophilia 2017;23:105–14; 4. Warren B, et al. Blood Adv 2020;4:2451–9; 5. Srivastava A, et al. Hemophilia 2020;26(S6):1–158; 6. Mannucci PM, Haematologica 2020;105:545–53; 7. Odalapo A, et al. Orphanet J Rare Dis 2018;13:198.

Nonfactor Therapies Have Changed the Hemophilia Treatment Landscape

Nonfactor Therapies	Aim to correct hemostatic defect(s) **without replacing** the missing protein (FVIII or FIX)

Abbreviations: FVIII, clotting factor VIII; FIX, clotting factor IX.
Young G. *Hemasphere.* 2023;7:e911.

Non-factor Therapies

(e.g., emicizumab)

Benefits

- "substitution therapy" for hemophilia A
  - "FVIII avoidance"
- Demonstrated superior bleed protection to FVIII prophylaxis
- Positive effect on HRQoL
- Unparalleled health equity advance for persons with hemophilia A with inhibitors

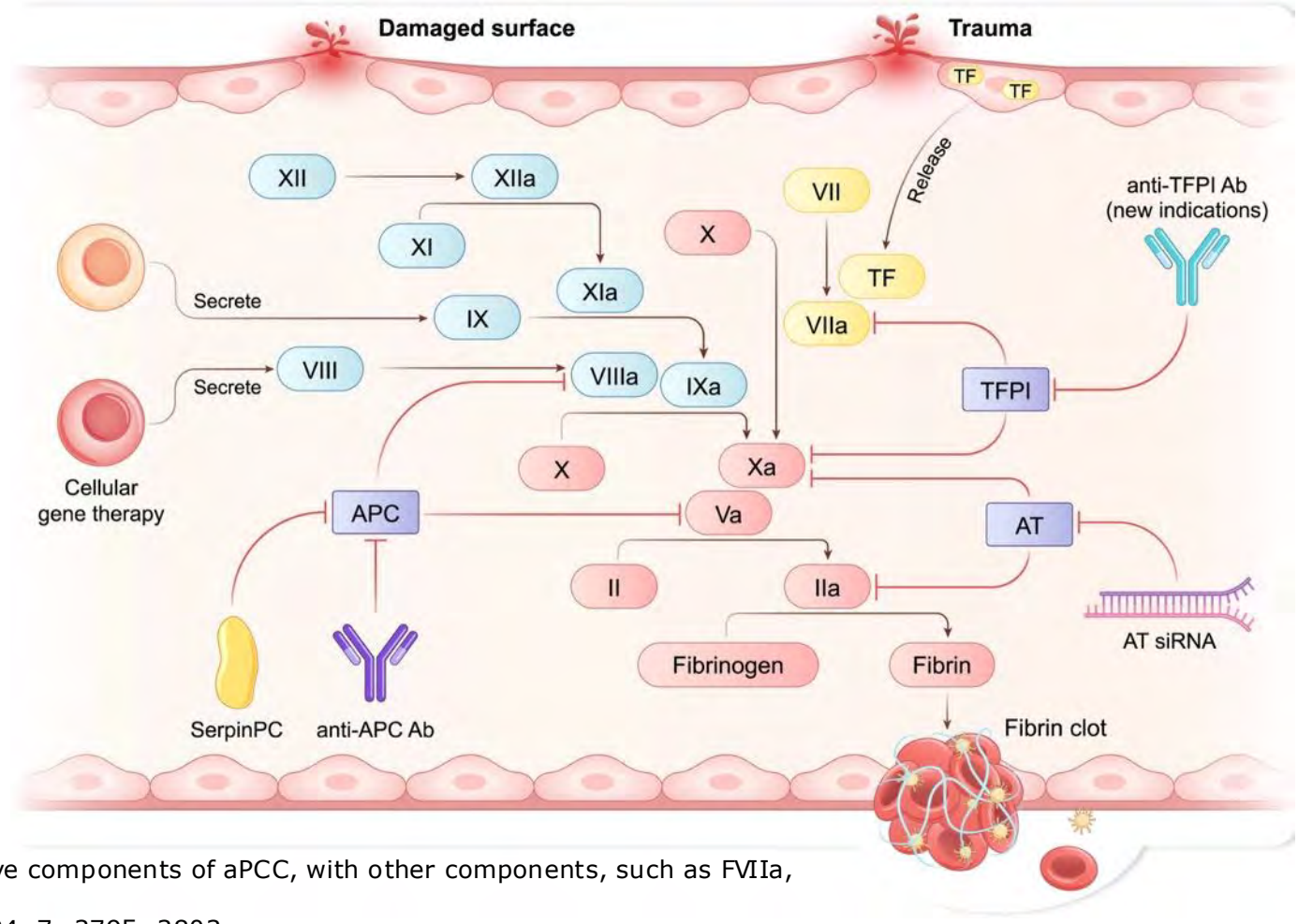
Risks

- Does not treat acute bleeding events
- "ceiling effect" for efficacy
  - Does not provide sufficient hemostasis for all traumatic injuries or surgical interventions
- Reduces therapeutic burden but not cost
- Loss of some natural coagulation regulation
- Adverse events
  - TMA, thromboembolism
  - Need for risk mitigation

Muniz et al. Exp Rev Hematol (2023) Jul-Dec;16(12):1087-1097; Callaghan et al. Blood (2021) 137(16):2231-2242; Garcia et al. RPTH (2023) Oct 20;7(8):102238; Batsuli et al. Am J Hematol (2023) Oct;98(10):E285-E287

Sufficient thrombin generation is the goal of emerging rebalancing treatments

Emerging rebalancing agents **increase thrombin generation** by reducing **anticoagulant** levels[1]



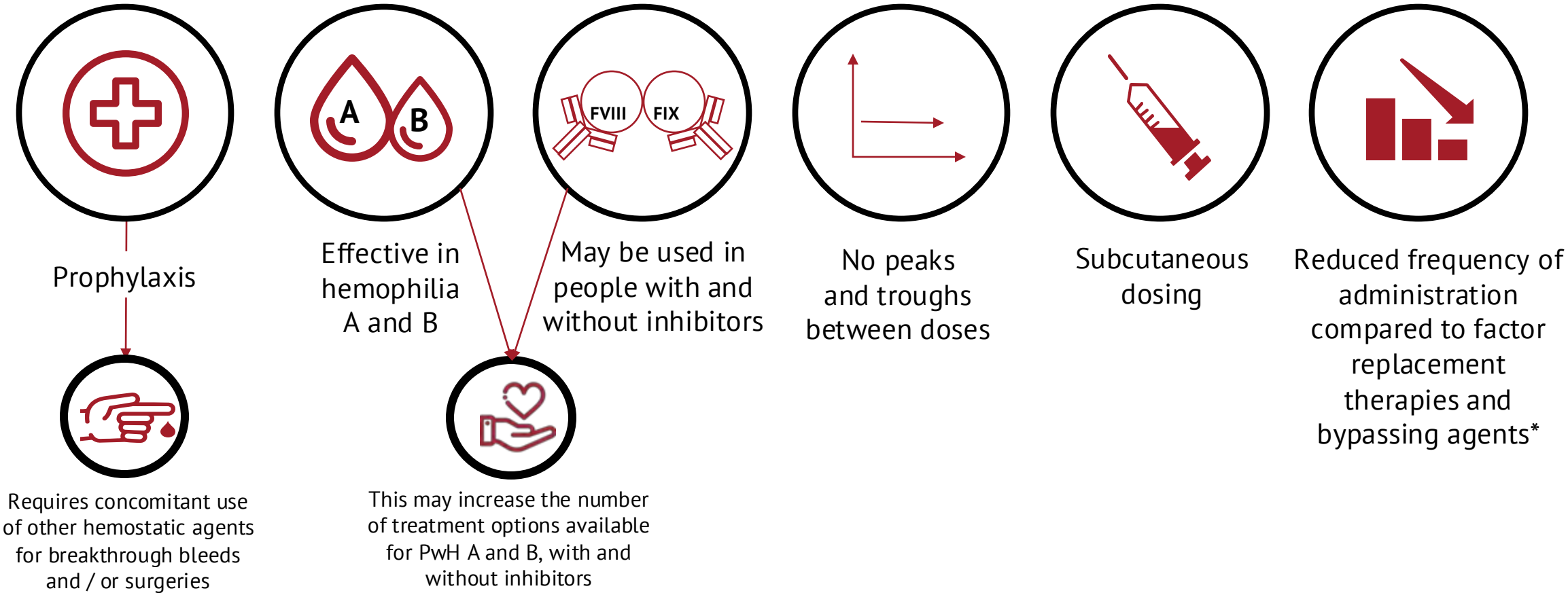
*Prothrombin (Factor II) and FXa are purported to be the primary active components of aPCC, with other components, such as FVIIa, playing a complementary role in its haemostatic effect.

Figure adapted from Wichaiyo S, et al. ACS Pharmacol. Transl. Sci. 2024, 7: 3795−3803.

a, activated; APC, activated protein C; aPCC, activated prothrombin complex concentrate; BPA, bypassing agent; EPCR, endothelial protein C receptor; F, factor; PAR, proteinase-activated receptor; r, recombinant;

TF, tissue factor; TFPI, tissue factor pathway inhibitor. 1. Weyand A and Pipe S. Blood 2019;133:389–98; 2. Clinical trials.gov. NCT06349473. Available at: https://clinicaltrials.gov/study/NCT06349473 (Last accessed December 2024).

Summary: Emerging Non-factor Therapies Share Key Similarities That May Improve the Management of People with Hemophilia



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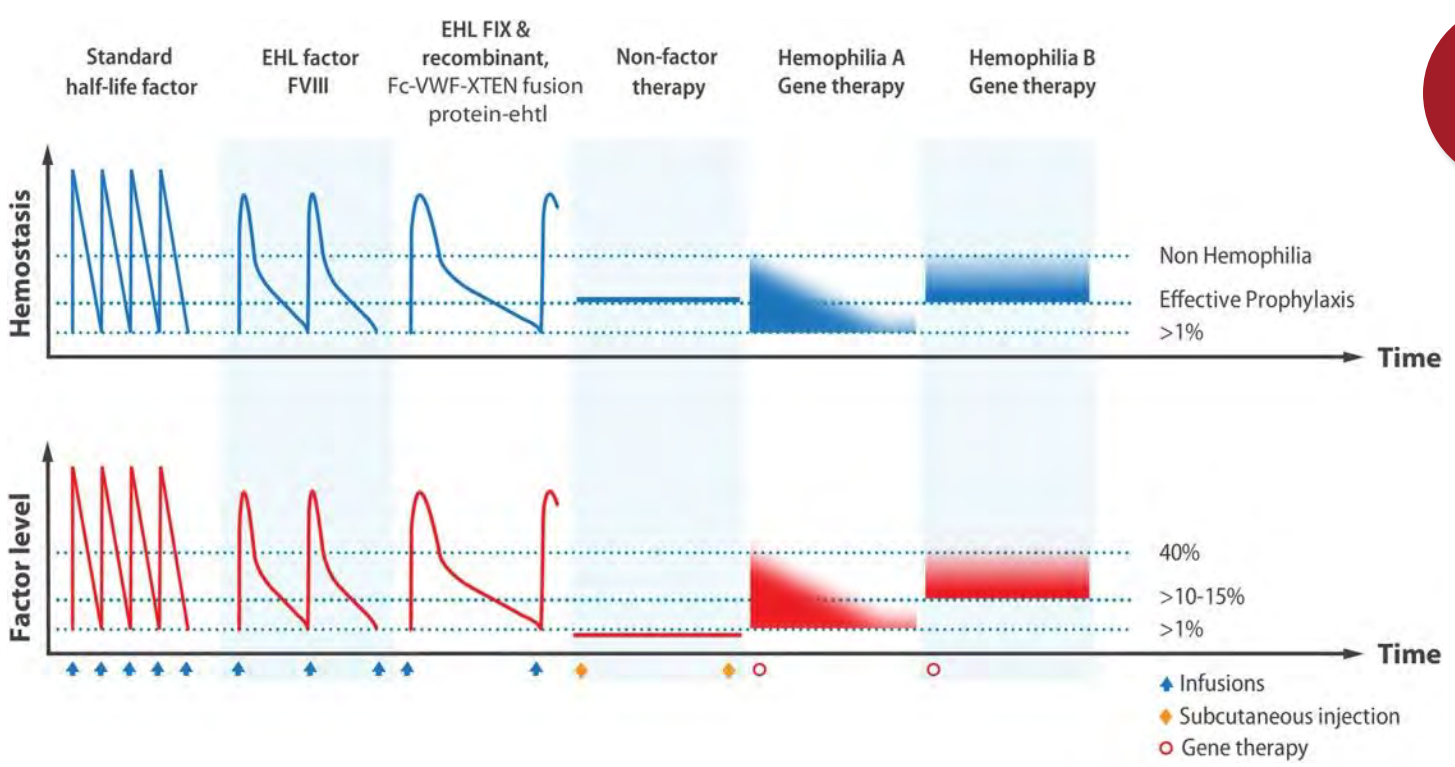
Young G. *Hemasphere.* 2023;7:e911.

The Potential of Gene Therapy

Single treatment with gene therapy may lead to **long-term correction of deficient clotting factors**

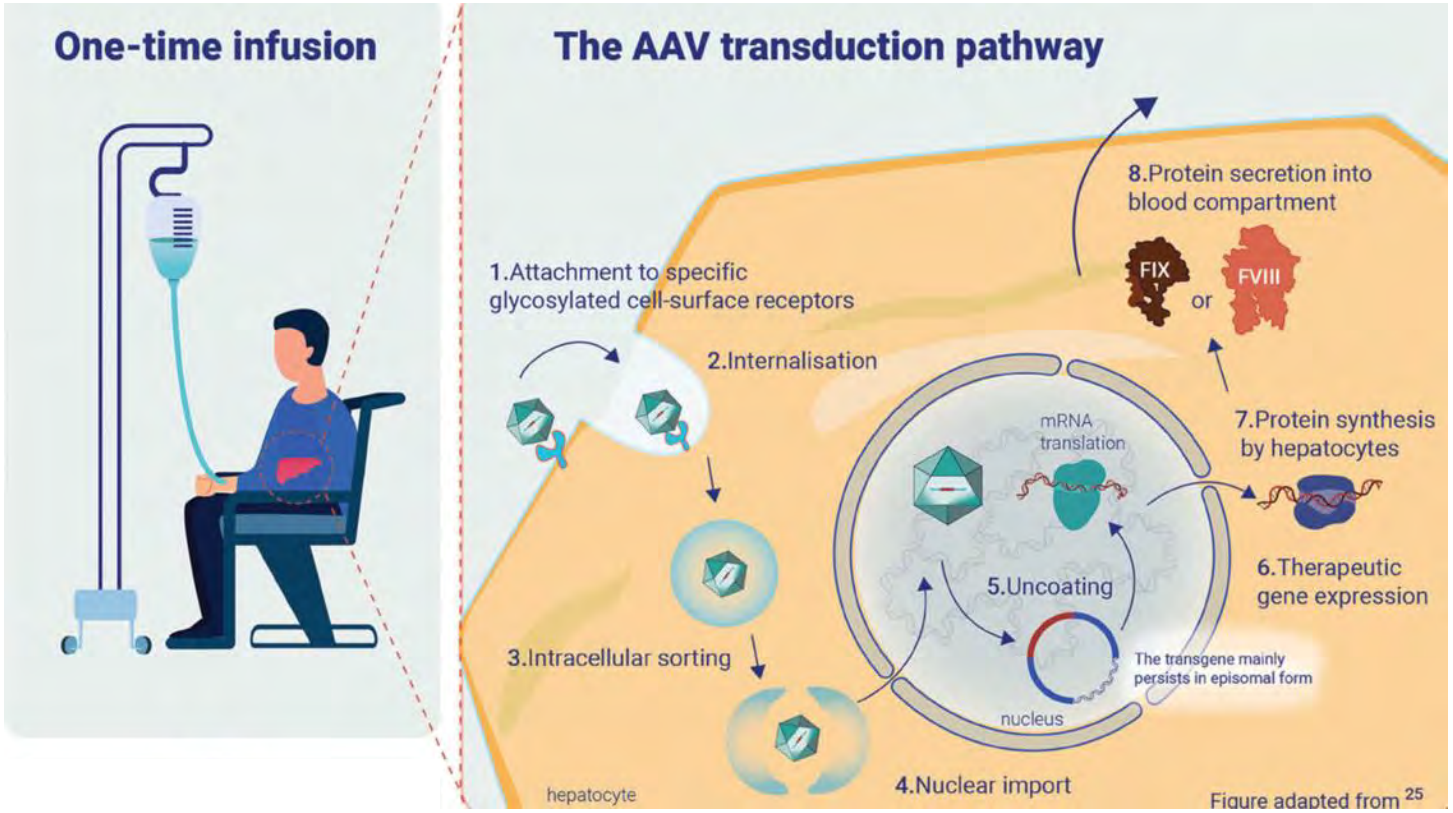


Attaining hemostasis in non-hemophilic range

Currently only achievable with successful **gene therapy**

Figure from: Pierce G et al. J Thromb Haemost 2023;22:1263-89; Figure from: Valentino LA et al. Res Pract Thromb Haemost 2025;9:102696

In vivo AAV-based liver-directed gene transfer



Direct administration of **AAV vector** delivering **therapeutic *F9* gene** into hepatocytes

The transgene mainly persists in episomal form

Marketed: **etranacogene dezaparvovec**

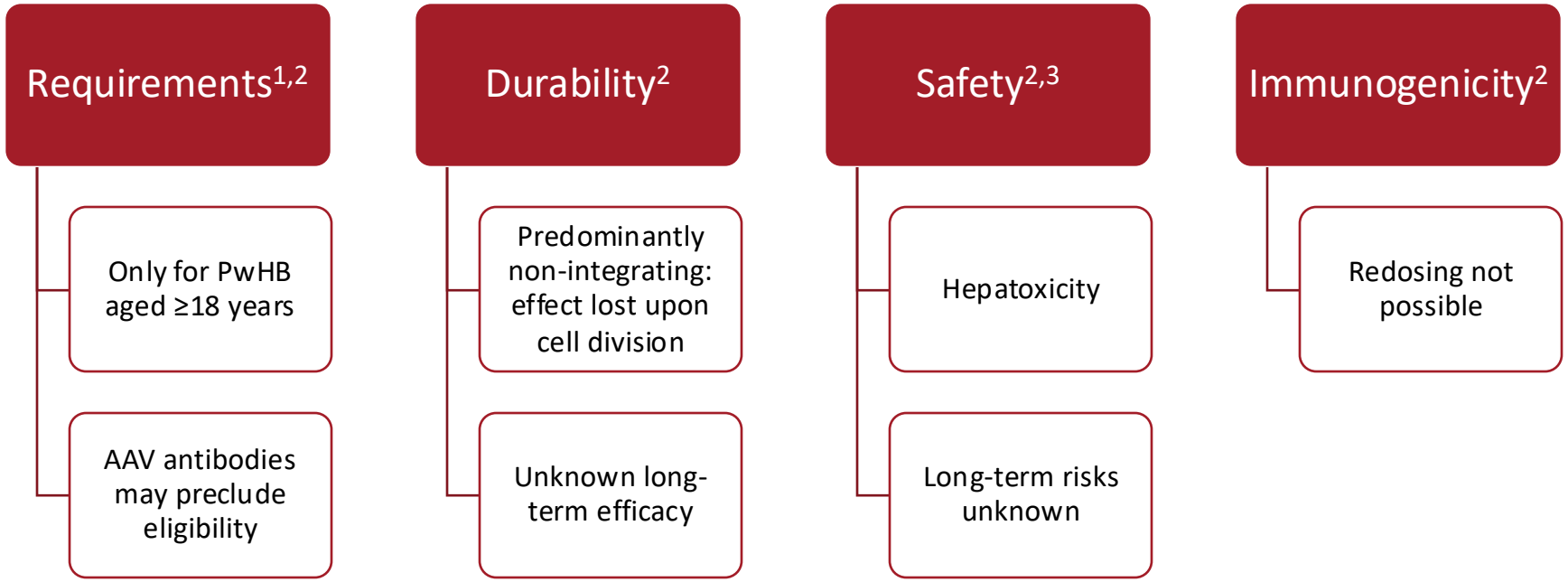
*Development and commercialization of fidanacogene elaparvovec was recently discontinued
F9: factor 9; mRNA: messenger RNA
Valentino LA et al. Res Pract Thromb Haemost 2025;9:102696; Figure from: Ay C et al. Haemophilia 2024;30:5-15

Beneficial clinical outcomes observed with AAV gene transfer

- Durable FIX activity at therapeutic levels
- Reduced bleeding rates compared with prior replacement therapy
- Reduced factor concentration usage
- Acceptable safety profiles

Valentino LA et al. Res Pract Thromb Haemost 2025;9:102696; Cuker A et al. N Engl J Med 2024;391:1108-18; Coppens M et al Lancet Haematol 2024;11:e265-75

Challenges with gene transfer therapy



Gene therapy administered early in life could address some challenges[2]

- Reduced likelihood of immunity against AAV
- No progression to chronic joint damage

1. Valentino LA et al. Res Pract Thromb Haemost 2025;9:102696; 2. Thornburg CD et al. Mol Ther 2025; doi:10.1016/j.ymthe.2025.04.023;
3. Mancuso ME et al. Lancet 2021;397:630-40

Clinical Pearls

Efanesoctocog Alfa for Treating Bleeds in Children

- Evaluated efficacy of efanesoctocog alfa (50 IU/kg) for on-demand treatment of bleeding episodes (BEs) in children with severe hemophilia A.
- Ongoing phase 3 extension study (XTEND-ed) enrolling children <12 years previously treated in XTEND-Kids
- A single injection resolved nearly 89% of bleeds; most bleeds rated as excellent/good response with a low overall ABR.

Measure	Result
Mean Treatment Duration	68.6 weeks (SD 16.5)
Treated Bleeding Episodes (BEs)	61 total
Most Common BE Locations	Joints (44.3%), Skin/Mucosa (27.9%)
Mean Model-Based ABR	0.67
BEs Resolved with Single Injection	88.5%
BEs Requiring ≥2 Injections	7 bleeds
Median Dose for BE Resolution	53.4 IU/kg (Q1: 51.0, Q3: 56.8)
Response Rated Excellent/Good	95.6% of BEs
Treatment-Related AEs	2 (injection reaction, headache); no serious AEs

Malec L et al. Treatment of Bleeding Episodes with Efanesoctocog Alfa in Children: XTEND-ed Second Interim Analysis. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Perioperative Hemostatic Control with Efanesoctocog Alfa in XTEND-ed

- Reported outcomes of major surgeries in pts with severe hemophilia A receiving efanesoctocog alfa during XTEND-ed extension study.
- Pts received 50 IU/kg preoperatively, with 30–50 IU/kg as needed every 2–3 days postoperatively; thromboembolic prophylaxis permitted.
- Efanesoctocog alfa provided excellent/good hemostatic control in 93–100% of cases with low product use and minimal complications.

	Orthopedic Surgeries (n=30; 28 pts)	Non-Orthopedic Surgeries (n=10, 10 pts)
Pre-op Dose Required	28/30 (93.3%)	10/10 (100%)
Median Total Dose to Maintain Hemostasis	50.0 IU/kg	51.7 IU/kg
Median # Injections (Day -1 to 14)	5.0	3.0
Median Blood Loss	140 mL (range: 0–1000)	Not reported
Transfusions Required	2 pts	Not reported
Time to Resume Prophylaxis	15 days	9 days
Hemostatic Response	Excellent/Good in 93.3%	Excellent/Good in 100%
Tolerability	Well tolerated	Well tolerated

Khoo L et al. Major Surgical Outcomes with Efanesoctocog Alfa: 4 Years' Experience in the XTEND Clinical Program. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21-25, 2025; Washington, D.C.

Prospective Evaluation of Perioperative Hemostasis Protocol in Patients on Emicizumab

- Evaluated efficacy and safety of a standardized perioperative protocol using rFVIII or rFVIIa in pts on emicizumab undergoing elective major surgery.
- Investigator-initiated, prospective study in pts aged 2–60 with/without inhibitors on emicizumab ≥4 weeks
- Perioperative hemostasis effective in most procedures; breakthrough bleeds mostly minor and occurred after stopping replacement therapy. No thrombotic complications observed.

Measure	Result
Total Pts / Surgeries	39 pts / 40 surgeries
Pts with Inhibitors	15 pts
Surgery Types	75% orthopedic; 15% abdomino-pelvic; others varied
Standard-Risk Procedures (n=37)	
Surgical Hemostasis Efficacy	Excellent: 91.9%, Good: 5.4%, Fair: 2.7%
Wound Healing Hemostasis	Excellent: 97.3%, Good: 2.7%
Breakthrough Bleeds (BTBs)	12 events in 9 procedures (post-op, mostly during rehab)
High-Risk Procedures (n=3)	
Surgical Hemostasis Efficacy	Fair: 67%, Poor: 33%
Wound Healing Hemostasis	Good: 67%, Moderate: 33%
Mortality	1 pt (with inhibitor, sepsis post-op, day +23)
Safety Outcomes	
Thromboembolism / TMA	0 events
Use of Thromboprophylaxis	None

Abraham A et al. Prospective evaluation of a defined replacement protocol for peri-operative hemostasis in patients with severe hemophilia A with and without inhibitors on emicizumab prophylaxis undergoing elective major surgeries–final results. (EmiSurg Study). Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Thrombosis Rates in Inherited Bleeding Disorders – EUHASS 2008–2023

- Analyzed thrombotic events associated with factor concentrates and bispecific antibodies in inherited bleeding disorders using EUHASS data from 2008–2023.
- Participating European centers prospectively reported AEs and product exposures; 204 thrombotic events occurred within 30 days of product use.
- Rates of thrombosis varied by product class; rebalancing agents require continued monitoring against these established baselines.

Product/Class	Events / Exposure (PY)	Rate (per 1000 PY)
Plasma FVIII/VWF	56 / 41,718	1.34
Standard rFVIII	62 / 84,498	0.73
EHL rFVIII	7 / 17,808	0.40
Advate	19 / 33,036	0.58
FEIBA	10 / 3,621	2.76
NovoSeven	17 / 6,954	2.45
Emicizumab	7 / 7,516	0.93

Total Events Analyzed	204 thrombotic events (≤30 days post-treatment)
Most Common Events in HA	37 MIs, 26 VTEs, 16 strokes
Total PY Exposure	209,058 PY (2008–2023)

Makris M et al. Thrombotic rates in bleeding disorder individuals treated with concentrate or bispecific antibody. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Safety of Switch from Emicizumab to Mim8 Prophylaxis

- Assessed safety of switching to Mim8 prophylaxis in pts with hemophilia A (with/without inhibitors) previously treated with emicizumab.
- Open-label, 26-week phase 3b trial; N=61
- Mim8 was well tolerated after direct switch; no thromboembolic events or neutralizing antibodies were observed.

Measure	Result
Total Mim8 Exposure	30.8 PY
Total TEAEs	107 events in 43 pts (70.5%)
TEAE Rate	3.5 per PY
Serious TEAEs	4 (6.6%), none related to Mim8
TEAEs Possibly/Probably Related to Mim8	24 events in 18 pts (29.5%)
Injection Site Reactions	15 events in 12 pts (19.7%)
Thromboembolic Events	0
Hypersensitivity or Discontinuation Events	0
Neutralizing Antibodies	None detected
Steady-State Mim8 Achieved	By Week 16
Emicizumab Elimination Complete	By Week 26

Oldenburg J et al. FRONTIER5 direct switch study: Safety of initiating Mim8 prophylaxis without washout of emicizumab. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

ABR Outcomes in the Phase 3 explorer8 Trial of Concizumab Prophylaxis

- Compared ABR in pts receiving concizumab prophylaxis vs on-demand treatment, stratified by baseline target joint status.
- Prospective, multicenter, OLE with daily subcutaneous concizumab dosing
- Concizumab significantly reduced ABR versus on-demand, with sustained efficacy over 56 weeks regardless of presence of target joints.

	With target joints at baseline		Without target joints at baseline	
	On-demand (arm 1)	CZM PPX (arm 2)	On-demand (arm 1)	CZM PPX (arm 2)
n	17	37	4	5
Estimated mean ABR	14.9	3.4	26.9	0.4
ABR ratio	0.23		0.01	
% reduction	77% reduction		99% reduction	
P-value	<0.001		<0.001	
Zero treated spontaneous and traumatic bleeding episodes, n (%)	1 (5.9%)	13 (35.1%)	0	3 (60.0%)
Zero treated spontaneous and traumatic target joint bleeding episodes, n (%)	2 (11.8%)	17 (45.9%)	N/A	N/A

Wheeler A et al. Annualized bleeding rates in hemophilia A/B and target joints: Concizumab explorer8 study. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

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	32-week cut-off	56-week cut-off	32-week cut-off	56-week cut-off
	With target joints (n=67)		Without target joints (n=77)	
All treated and untreated spontaneous and traumatic bleeding episodes				
Median ABR	3.5	3.6	3.0	2.4
Mean	7.3	6.8	6.3	5.8
Treated spontaneous and traumatic bleeding episodes				
Median ABR	2.9	2.9	1.6	1.0
Mean	6.4	6.1	4.7	4.4
Treated spontaneous and traumatic joint bleeding episodes				
Median ABR	1.8	2.8	0.0	0.5
Mean	5.2	4.9	2.4	2.2
Treated spontaneous and traumatic target joint bleeding episodes				
Median ABR	1.3	0.9	N/A	N/A
Mean	3.4	3.2	N/A	N/A

Wheeler A et al. Annualized bleeding rates in hemophilia A/B and target joints: Concizumab explorer8 study. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Long-term efficacy of marstacimab

- Evaluated long-term efficacy of marstacimab in pts with severe hemophilia A or B without inhibitors following the BASIS trial.
- OLE; pts continued marstacimab (150 or 300 mg weekly).
- Marstacimab shows sustained reduction in bleeding over ~30 months, supporting long-term use.

ABR for treated bleeds

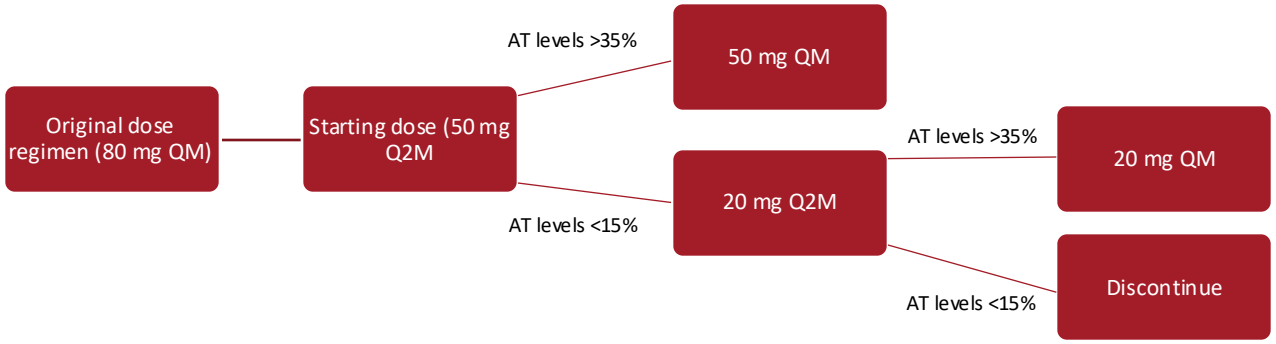
	BASIS			OLE		
	OD (n=33)	RP (n=83)	Overall (n=116)	OD (n=32)	RP (n=75)	Overall (n=107)
Mean estimate	3.18	5.08	4.52	3.34	2.79	2.94
Median	2.02	2.02	2.02	1.56	0.94	0.96

ABR for total bleeds

	BASIS			OLE		
	OD (n=33)	RP (n=83)	Overall (n=116)	OD (n=32)	RP (n=75)	Overall (n=107)
Mean estimate	7.39	5.97	6.39	4.49	3.16	3.57
Median	5.03	2.89	3.03	3.23	0.96	1.58

Matino D et al. Long-Term Efficacy of Marstacimab in Participants With Severe Hemophilia A or B Without Inhibitors. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Population PK-PD Modeling of Fitusiran AT-Targeted Dosing Regimen in Hemophilia A/B



	50 mg Q2M	50 mg QM	20 mg Q2M	20 mg QM
Peak modeled mean intra-individual variability in AT activity (%)	24.3	23.1	26.2	20.1
Trough modeled mean intra-individual variability in AT activity (%)	19.4	23.0	19.4	18.1
Predicted distribution of participants achieving AT 15–35%	578	236	242	17
Observed distribution of participants achieving AT 15–35%	115	45	84	6
Predicted time to steady state (weeks)	19.9	22.7	19.9	22.7
Observed time to steady state, median (weeks)	19.6	22.5	19.6	22.5

- Characterized PK-PD of fitusiran in hemophilia A/B using clinical data and a PopK-PD model targeting antithrombin levels between 15–35%.
- OLE using individualized antithrombin-based dosing (20/50 mg) guided by PopK-PD simulation
- Antithrombin levels were effectively maintained in target range with 0–1 dose adjustments in most pts, confirming model accuracy and treatment consistency.

Pipe S et al. Pharmacodynamics and pharmacokinetics of fitusiran antithrombin-based dose regimen (AT-DR): clinical and population modeling data. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Predictive Modeling of AT Levels and Bleeding Risk During Fitusiran Prophylaxis

Measure	Result (N=254)
Total Observation Time	552.9 PYs
Median AT Levels: AT-DR vs ODR	23.2% vs 11.5%
ABR at 10% AT Level	0.73
ABR at 15% AT Level	2.31
ABR at 35% AT Level	4.58
Relationship Between AT & ABR	Monotonic increase in ABR with rising AT levels

- Investigated relationship between AT levels and ABR during fitusiran treatment in hemophilia A/B.
- Predictive modeling used data from phase 2 and 3 studies (ATLAS trials), comparing original dosing vs individualized AT-based regimens.
- Lower AT levels were associated with lower ABRs, supporting individualized dosing within the 15–35% AT range for optimized efficacy.

Young G et al. Association of antithrombin levels with efficacy of fitusiran prophylaxis in people with hemophilia A or B with and without inhibitors: a predictive modeling approach. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

4-Year Outcomes of Etranacogene Dezaparvovec

Median ABR	Lead-in	Year 1 (Reduction from lead-in)	Year 2 (Reduction)	Year 3 (Reduction)	Year 4 (Reduction)
All bleeds	4.00	1.10 (73%); p<0.0001	0.90 (78%); p<0.0001	0.82 (79%); p<0.0001	0.40 (90%); p<0.0001
Treated bleeds	3.44	0.57 (83%); p<0.0001	0.51 (85%); p<0.0001	0.56 (84%); p<0.0001	0.19 (94%); p<0.0001
Spontaneous bleeds	1.38	0.24 (83%); p<0.0001	0.20 (85%); p<0.0001	0.43 (68%); p=0.0063	0.08 (94%); p<0.0001
Joint bleeds	2.20	0.34 (84%); p<0.0001	0.29 (87%); p<0.0001	0.32 (85%); p<0.0001	0.09 (96%); p<0.0001
Traumatic bleeds	2.17	0.65 (71%); p<0.0001	0.55 (75%); p<0.0001	0.30 (86%); p<0.0001	0.29 (86%); p<0.0001

- Evaluated long-term efficacy and safety of a single-dose gene therapy (etranacogene dezaparvovec) in adults with hemophilia B.
- Single-arm, 4-year follow-up study in 54 males; 52 expressed FIX-Padua post-infusion and discontinued regular prophylaxis.
- Gene therapy achieved sustained FIX expression, 90% ABR reduction, near-complete elimination of FIX prophylaxis, and remained well tolerated.

Pipe S et al. Etranacogene dezaparvovec in haemophilia B: a 48-month post hoc responder analysis of HOPE-B. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Long-Term Efficacy and Safety of Fidanacogene Elaparvovec – 6-Year Follow-Up

- Analyzed long-term outcomes in pts with hemophilia B who received single-dose fidanacogene elaparvovec in phase 1/2a trial + 5-year follow-up.
- Follow-up enrolled 14/15 original participants; FIX activity and safety data were collected through year 6 post-infusion.
- FIX expression was maintained in the mild hemophilia range; treated bleeds remained low; no participants resumed FIX prophylaxis.

FIX activity levels

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	**Years 1–6**
Mean	23.4	24.7	22.9	22.3	22.6	26.1	**22.9**
Median	20.8	19.5	19.8	16.1	16.9	22.4	**19.5**
Participants, n	14	14	14	13	13	11	**14**

ABR levels

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	**Years 1–6**
Mean	0.4	0.9	0.4	0.1	0.2	0.3	**0.4**
Median	0	0	0	0	0	0	**0**
Participants, n	14	14	14	14	13	12	**14**

Samelson-Jones B et al. Six-year outcomes following fidanacogene elaparvovec in adults with hemophilia B. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

5-Year Musculoskeletal Outcomes of Valoctocogene Roxaparvovec

- Assessed long-term musculoskeletal health of pts with severe hemophilia A after valoctocogene roxaparvovec.
- Prospective 5-year study using assessments (HJHS, FISH, HAL, HEAD-US) and annual biomarker evaluations for inflammation, cartilage, and bone metabolism.
- Musculoskeletal health remained stable at year 5; biomarkers indicated reduced inflammation and signs of joint and bone remodeling.

Biomarker	Function	Baseline	Year 5	p-value
IL17a, pg/mL	Inflammation	40	10.3	**0.003**
IL1β, pg/mL	Inflammation	40.9	8	**0.0005**
IL6, pg/mL	Inflammation	61.1	35.5	**0.03**
TNFα, pg/mL	Inflammation	16.5	9.3	0.21
LOX1, pg/mL	Extracellular matrix repair	19.6	7.1	**0.002**
MMP1, pg/mL	Extracellular matrix degradation	37.3	30	0.79
MMP13, pg/mL	Extracellular matrix degradation	188.0	29.9	**0.0005**
RANKL, pg/mL	Bone resorption	3.7	7.8	0.123
SOST, pg/mL	Bone remodeling	205.4	1325	**0.0005**
OC, ng/mL	Bone formation	2.9	15.1	**0.002**
OPG, pg/mL	Bone remodeling	68.5	19.6	**0.0005**
Calcitonina, pg/mL	Osteoclast inhibition	23.3	97.5	**0.003**
MIP1α, pg/mL	Cell migration	1.1	1.1	0.38
P-selectin, pg/mL	Cell migration	10819	35031	**0.0005**
E-selectin, pg/mL	Cell migration	7638	19480	**0.0005**
VEGF-A, pg/mL	Neoangiogenesis	31.4	43.2	**0.027**
Thrombospondin 5, ng/mL	Neoangiogenesis	109	514.8	**0.005**
HIF1a, pg/mL	Neoangiogenesis	5	22.5	**0.002**

Yamaguti-Hayakawa GG et al. Steady Musculoskeletal Health After Gene Therapy in Severe Hemophilia A: 5-Year Results. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Clinical Pearls

- **Efanesoctocog Alfa**
  - During major surgery, provides **reliable perioperative hemostasis** with **low product consumption** and minimal transfusion needs.
  - Offers **effective, single-injection bleed resolution in children** with severe hemophilia A, maintaining a low ABR and high response rates over time.
- **Emicizumab**
  - When combined with **short-term rFVIII or rFVIIa**, allows for **effective perioperative hemostasis** in major surgeries.
  - Breakthrough bleeds were rare, with **no thrombotic complications** observed.
- **EUHASS Safety Surveillance (Various Products)**
  - Provides baseline **thrombosis rates for FVIII products and bypassing agents**, e.g.:
    - Standard rFVIII: 0.73/1000 PY
    - EHL rFVIII: 0.40/1000 PY
    - Emicizumab: 0.93/1000 PY
    - FEIBA and NovoSeven: ~2.4–2.8/1000 PY
  - Serves as a **reference for evaluating thrombotic risk** of newer rebalancing agents like fitusiran and TFPI inhibitors (concizumab/martacimab)

Clinical Pearls

- **Mim8 (Denecimig)**
  - Can be **safely initiated immediately after emicizumab** without a washout or loading dose, offering a flexible transition for pts on prophylaxis.
- **Concizumab**
  - Once-daily subcutaneous prophylaxis significantly reduces ABR compared to on-demand treatment, **regardless of baseline target joint status**, making it broadly applicable across pt subgroups.
- **Marstacimab**
  - Provides **sustained long-term bleeding control** in hemophilia A and B without inhibitors, with a favorable safety profile even after extended follow-up.
- **Fitusiran**
  - **AT-based dose regimen (AT-DR)** maintains steady-state AT levels in the target 15–35% range with minimal dose adjustments.
  - **Lower AT levels are strongly associated with reduced ABR**, supporting **personalized prophylaxis** based on AT monitoring.

Clinical Pearls

- **Etranacogene Dezaparvovec (Gene Therapy for Hemophilia B)**
  - Offers **durable FIX-Padua expression** with **90% ABR reduction** sustained over 4 years, with **reduced prophylaxis needs** and **no new safety concerns**.
- **Fidanacogene Elaparvovec (Gene Therapy for Hemophilia B)**
  - Maintains **mild-range FIX levels for up to 6 years** with minimal bleeding, no resumed prophylaxis, and no treatment-related serious adverse events.
- **Valoctocogene Roxaparvovec (Gene Therapy for Hemophilia A)**
  - Maintains **maintains stable musculoskeletal health** and **improves inflammatory biomarkers** over 5 years, **supporting long-term joint protection** in severe hemophilia A.