Behandeling van hemofilie

Quentin Van Thillo

Les Klinische Biologie

04.11.2025

Prince Albert

Queen Victoria

Friedrich III.

Victoria jun.

Ludwig v. Hessen

Alice v. Engl.

Leopold v. Albany

Helene v. Waldeck

Beatrice v. Engl.

Heinrich v. Battenberg

Heinr. v. Pr.

Irene v. H.

Friedrich v. Hessen

Alix v. H.-D.

Nikolaus II.

Alice v. E.

Alexander v. T.-A.

Moritz

Leopold v. Battenberg

Victoria

Alfons XIII. v. Spanien

Waldemar v. Preußen

Heinrich v. Preuße

Alexej v. Russland

Rupprecht

Alfonso v. Spanien

Jaime de Borbón

Beatrix Isabel

Maria Christina

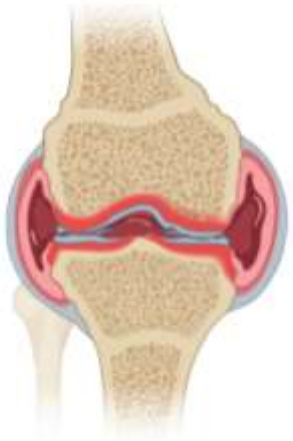
Gonzalo v. Borbón u. Battenberg

Juan de Borbón

María de las Mercedes

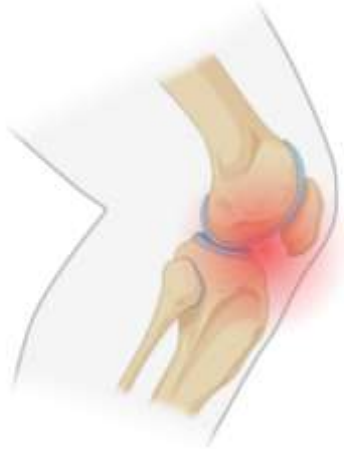
Juan Carlos

Haemophilia is chronic, debilitating disease



Haemarthrosis

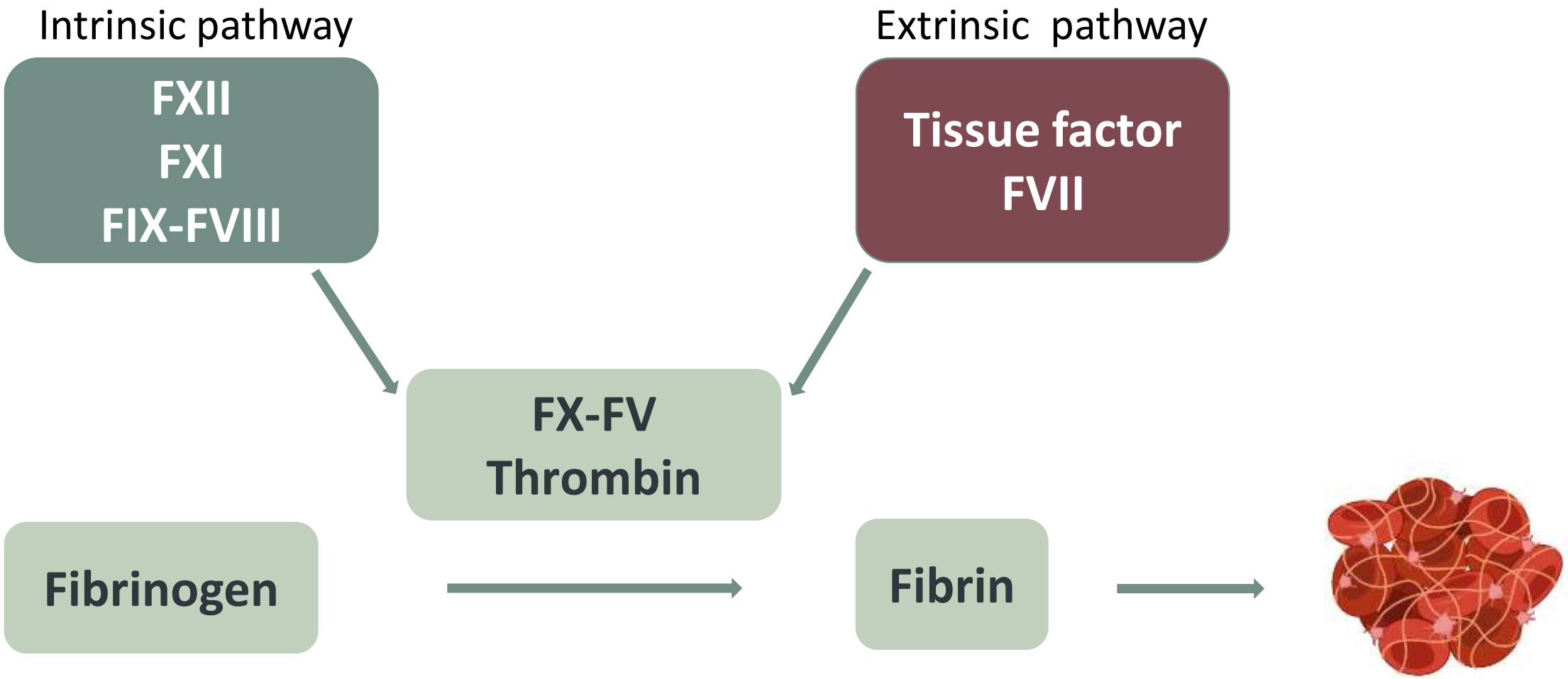
Severe bleeding



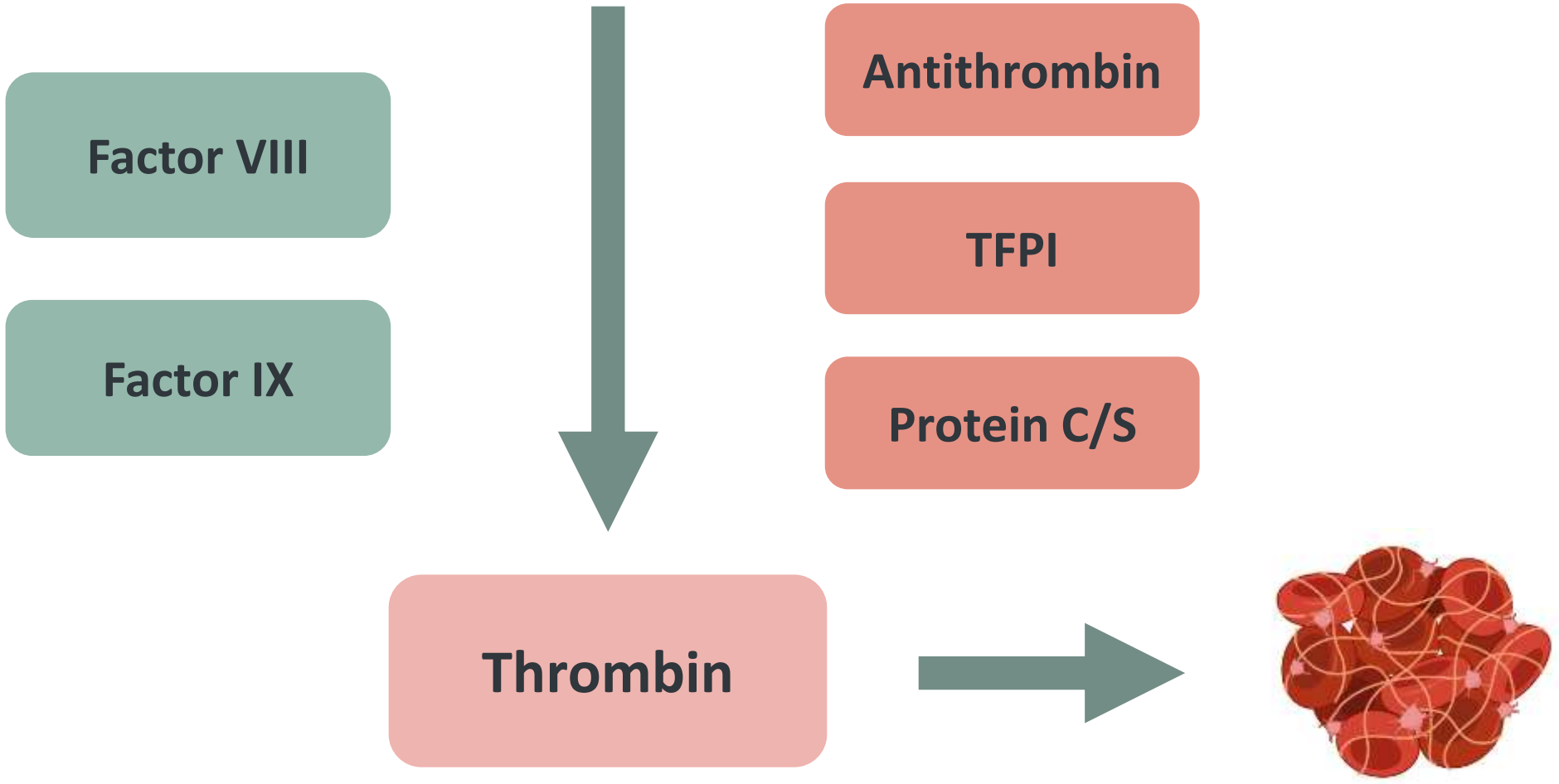
Chronic pain

Images on this slide and on the coming slides were taken from Biorender

FVIII or FIX deficiency reduces clot formation

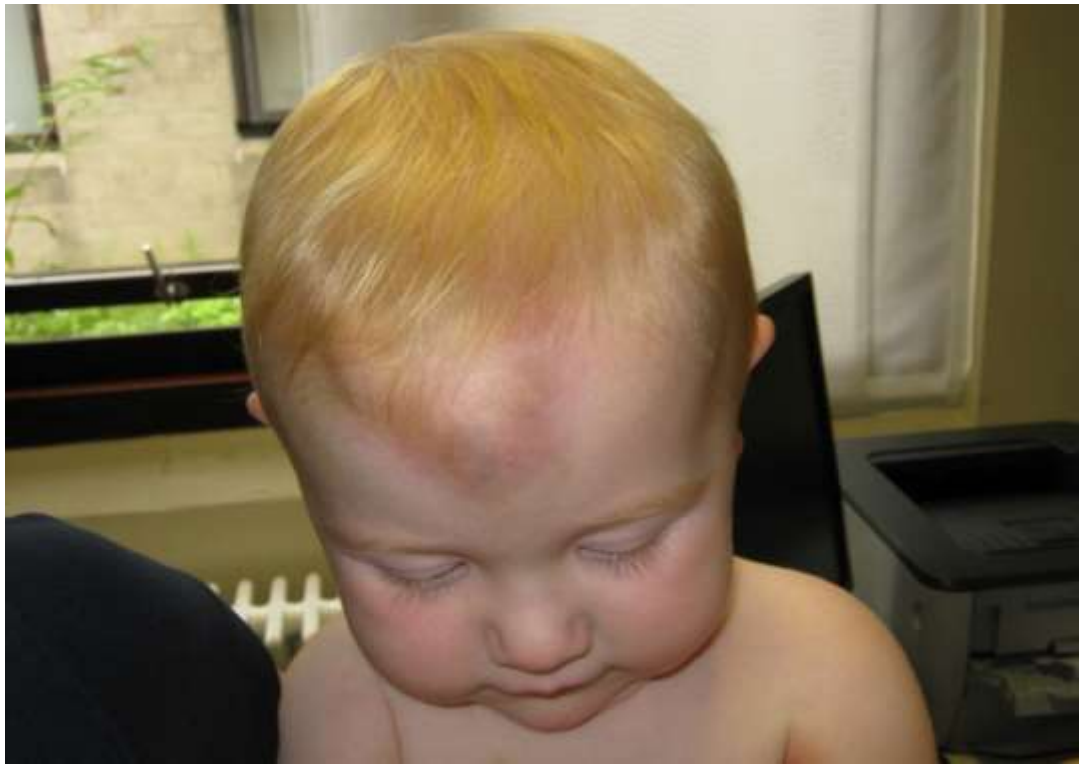


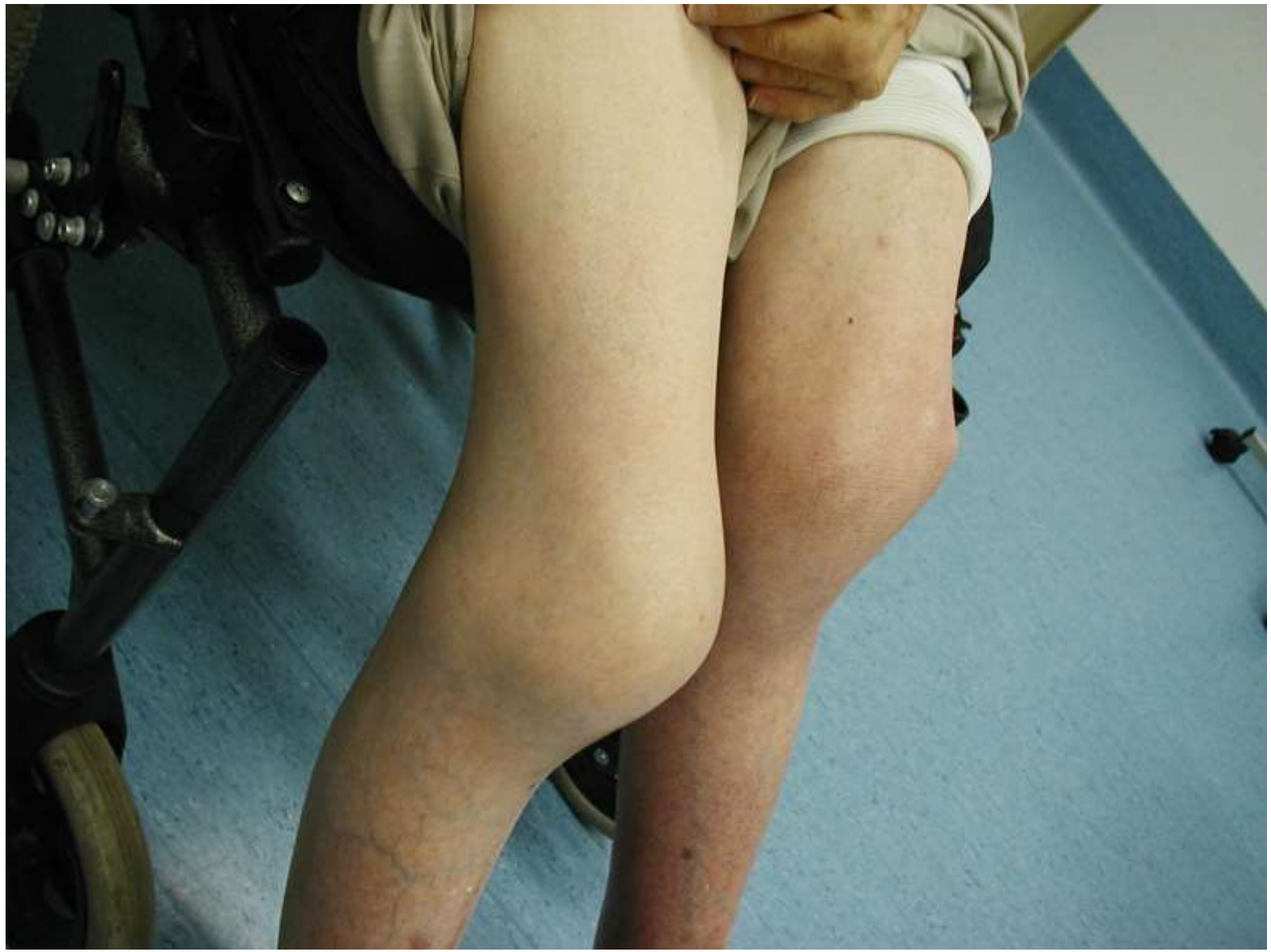
Thrombin is the key player in coagulation



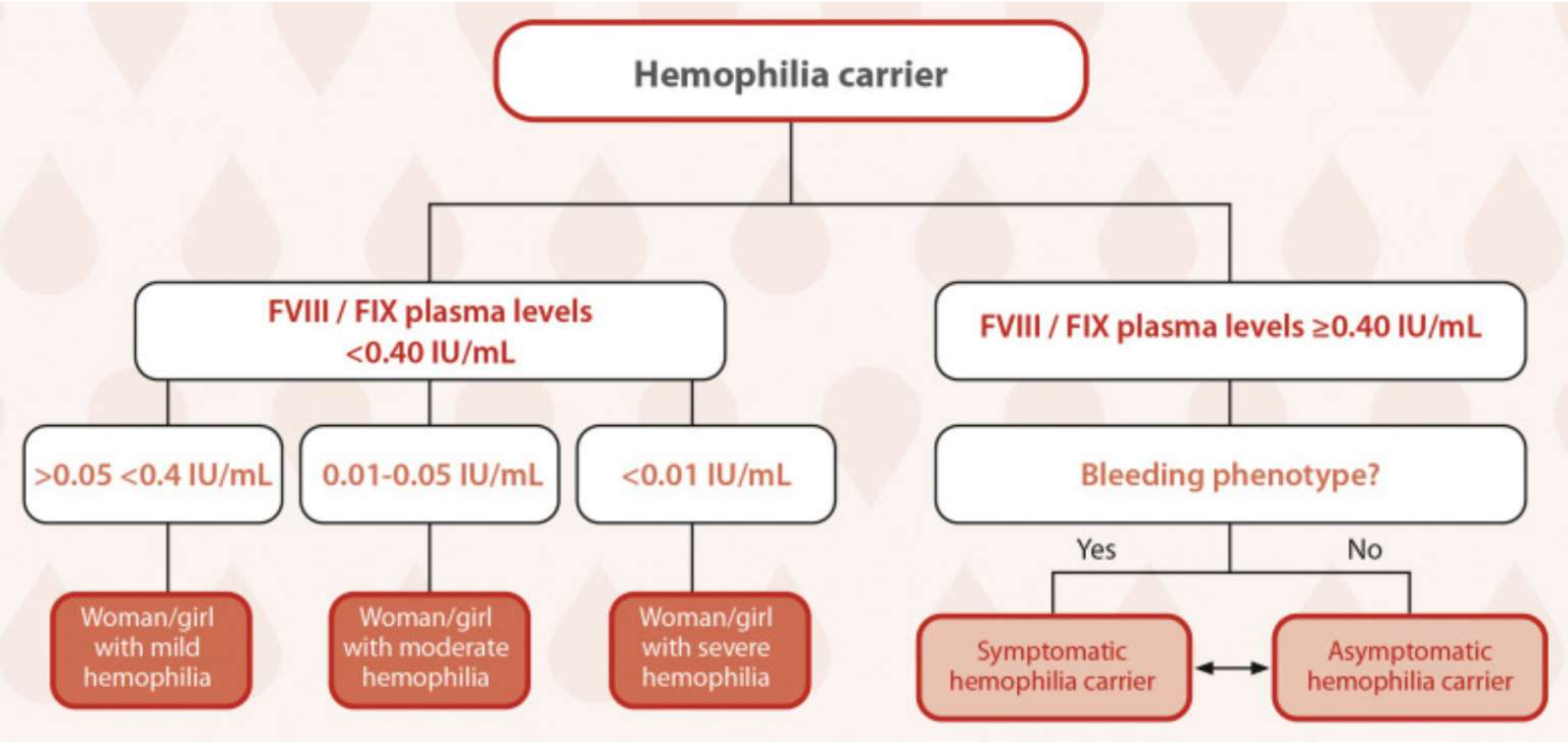
The severity of haemophilia depends on the factor level

Haemophilia is typically diagnosed in the first year of life





Women are also affected by haemophilia



Van Galen et al. JTH 2021

Haemophilia is not always congenital

75-year old man, history of Afib (apixaban 2x 2.5 mg)

gastro-intestinal bleed and shock – duodenitis

Haemophilia is not always congenital

75-year old man, history of Afib (apixaban 2x 2.5 mg)

gastro-intestinal bleed and shock – duodenitis

secondary NSTEMI → clopidogrel

The patient continues to bleed

haematuria after self-removal urinary catheter

→ stop clopidogrel and apixaban, switch to prophylactic LMWH

The patient continues to bleed

haematuria after self-removal urinary catheter

→ stop clopidogrel and apixaban, switch to prophylactic LMWH

bleeding after removal arterial line

haematoma after fall

bruises +++

What about the coagulation?

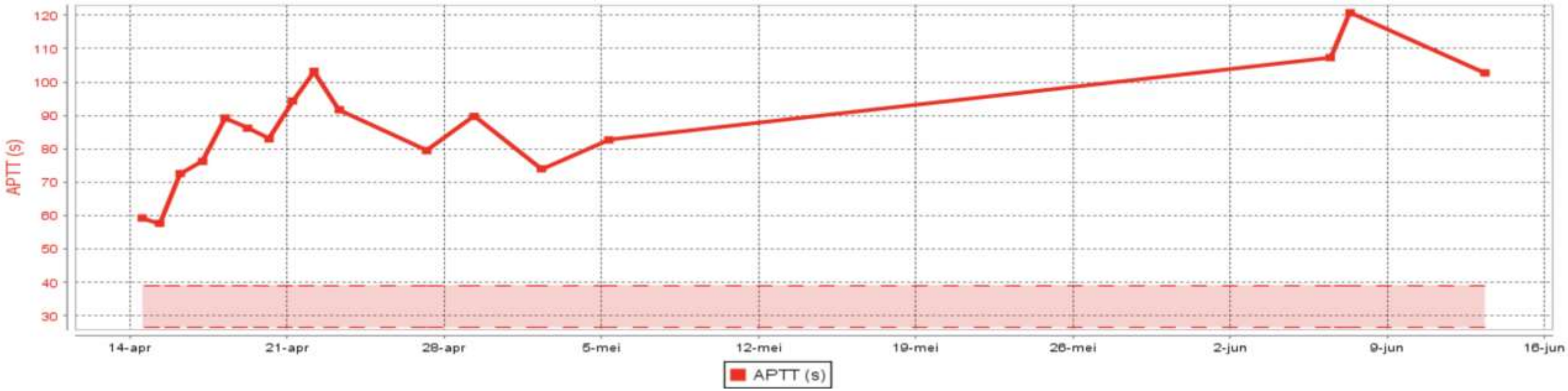
06-06-2025 10:43 - bloed

Protrombinetijd (PT)	15.8	s	11.7 - 15.3
Protrombinetijd (PT)	76	%	70 - 150
Protrombinetijd (PT)	1.20	INR	

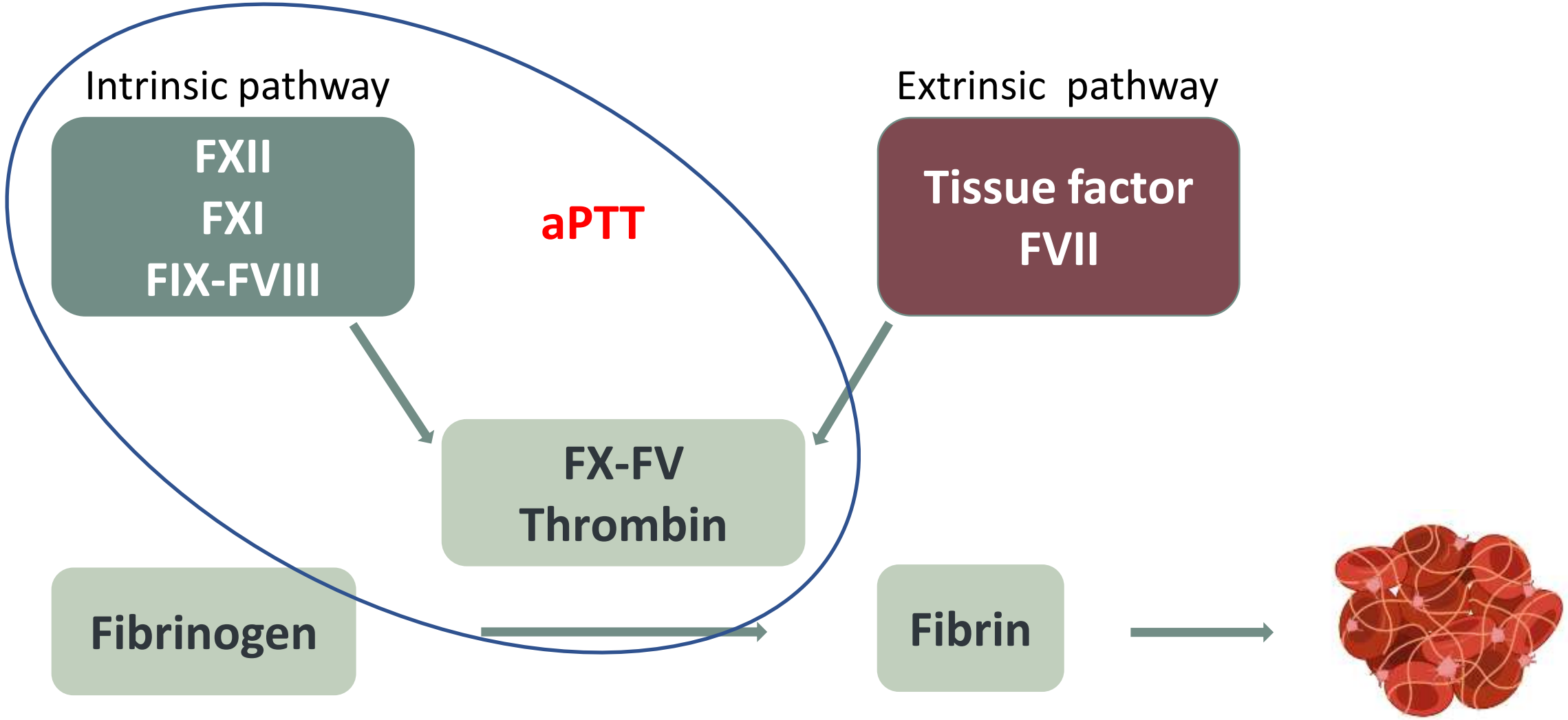
↳ Resultaat voor patiënten behandeld met vitamine-K-antagonisten: therapeutische antistolling bij INR = 2 - 3.
Enkel bij mechanische hartkleppen en bij sommige patiënten met het antifosfolipidensyndroom wordt intenser geanticoaguleerd: INR = 2,5 - 3,5.

APTT	107.3	s	26.6 - 39.2

aPTT has already been prolonged for 2 months!



The aPTT evaluates the intrinsic pathway



07-06-2025 08:00 - bloed

APTT	120.7	s	26.6 - 39.2
Resultaat werd telefonisch doorgegeven op 07-06-2025 10:08 op tel. nr. 013354263 (dokterskamer hospitalisatie 2220)			
Trombinetijd	18.1	s	18.0 - 26.0
Factor VIII coagulans	0.6	%	50.0 - 150.0
Factor VIII coagulans inhib. screening	Aanwezig		
Factor VIII coagulans inhibitor	46.0	BU	≤ 0.3
Factor IX coagulans	71.8	%	70.0 - 130.0
Factor XI	62.8	%	70.0 - 130.0
Factor XII	52.9	%	70.0 - 130.0
Lupus anticoagulans	De analyse laat niet toe om de aanwezigheid van een licht lupus anticoagulans uit te sluiten. De		

07-06-2025 08:00 - bloed

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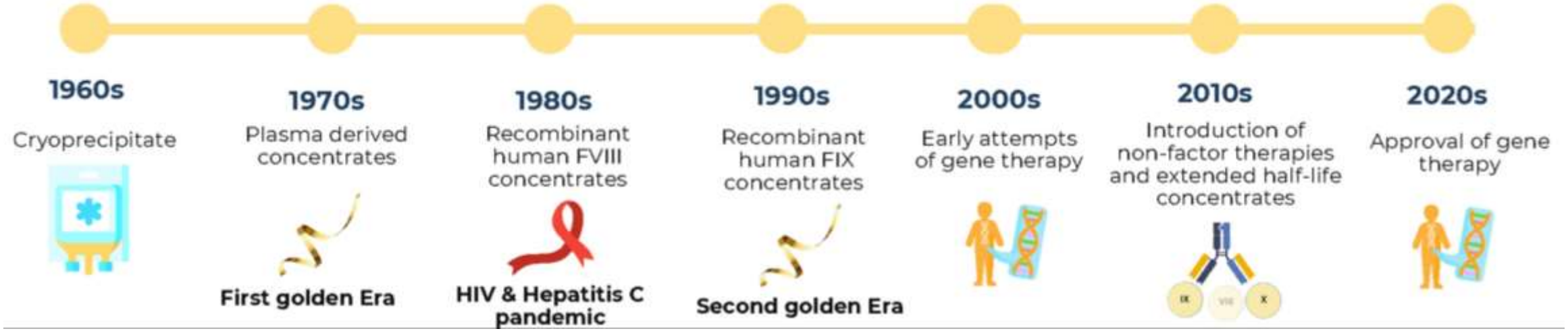
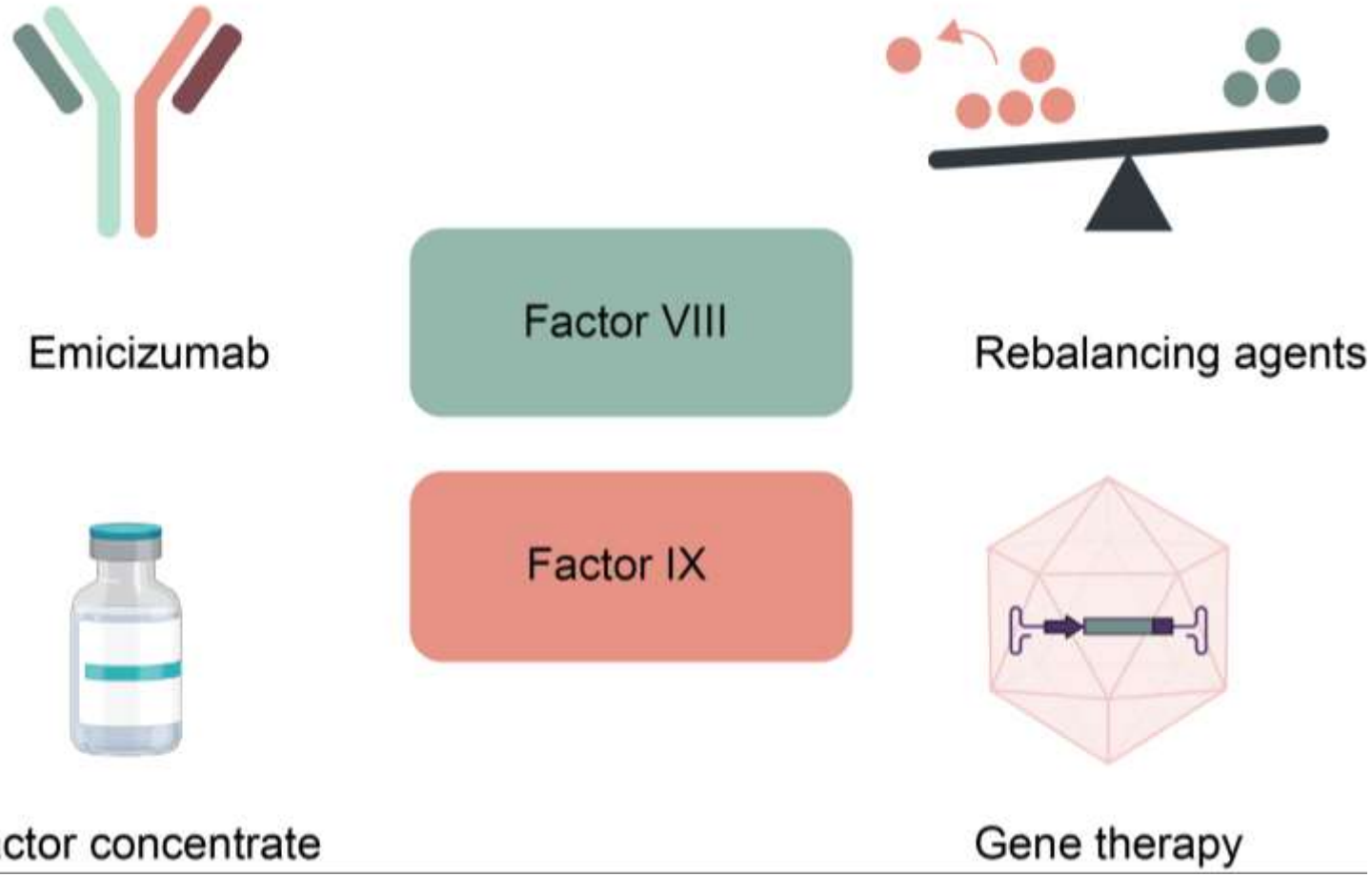
Acquired haemophilia A

A 60-year old patient has seen many changes to his treatment



Español et al. RPTH 2024

Many good options will be available in the near future



current treatments

upcoming treatments

rebalancing agents

current treatments

factor concentrate

emicizumab

upcoming treatments

rebalancing agents

Current therapies either supplement the missing factor or mimic its activity

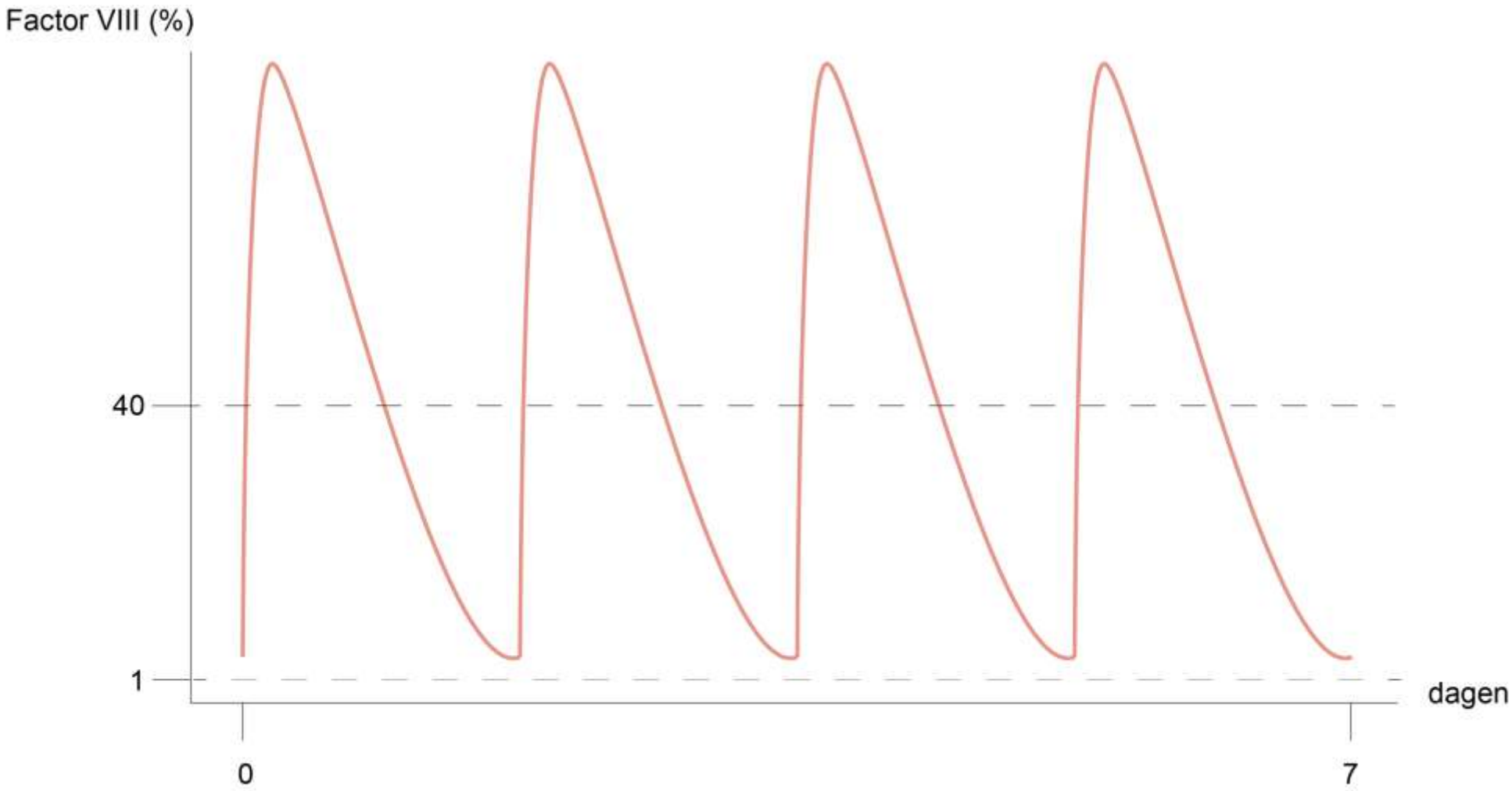
Factor concentrate

Factor VIII

Factor IX

Emicizumab
(Hemlibra)

Factor infusion results in peaks and troughs

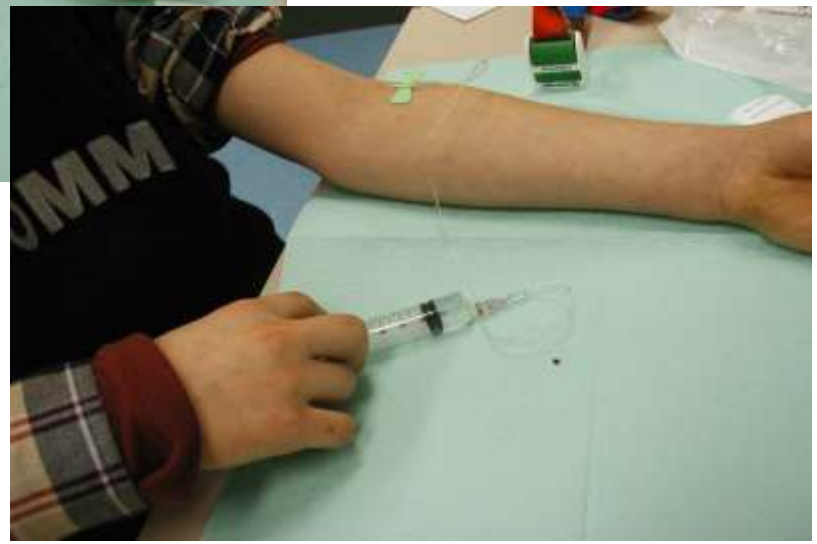


Factor infusion is very burdensome for patients

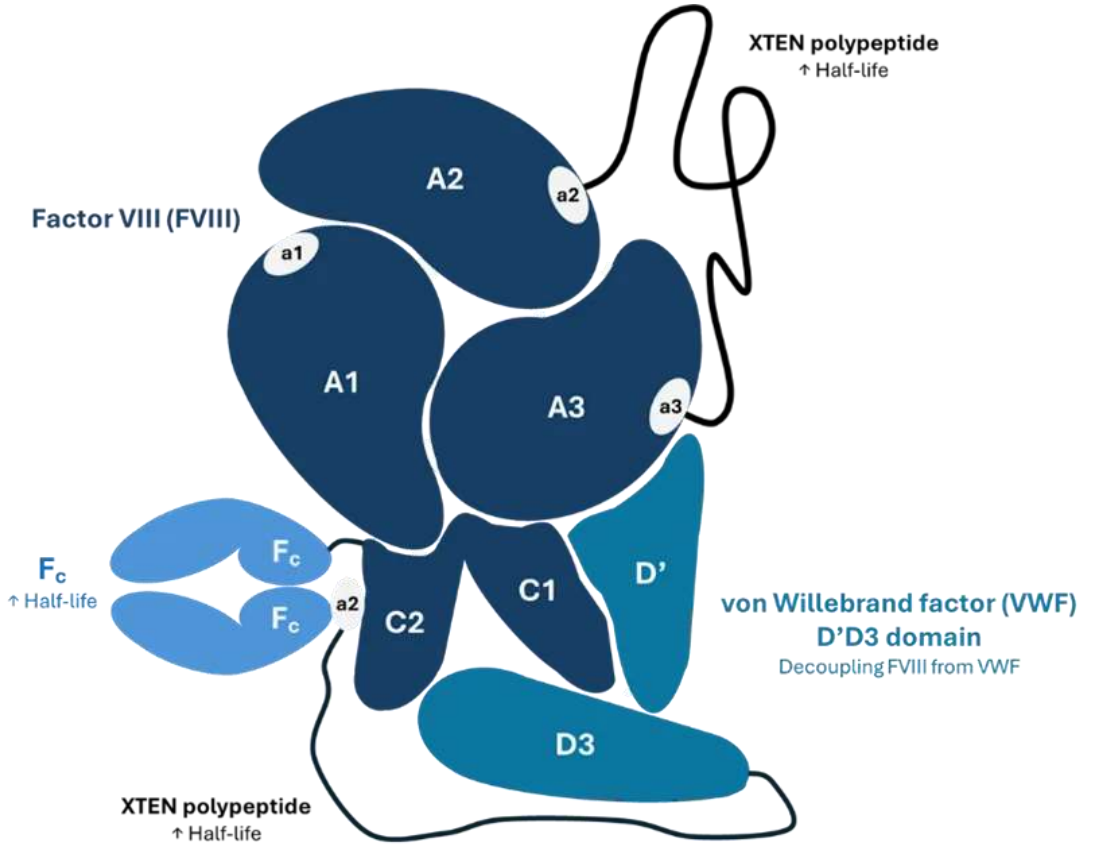
Factor concentrate

Intravenous

Not in case of inhibitors

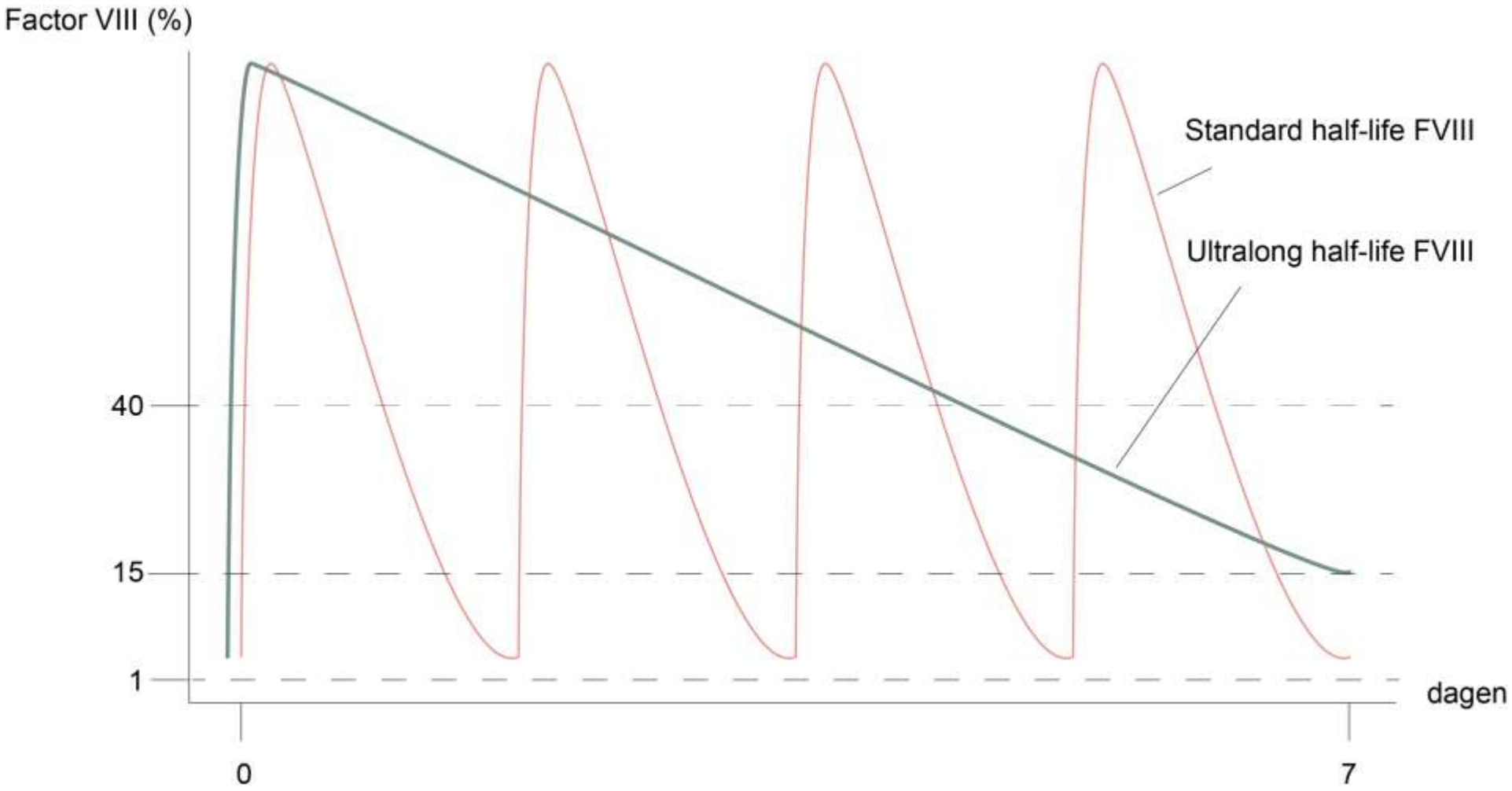


Efanosoctocog alpha (efa) overcomes the VWF-imposed half-life ceiling



Konkle Exp Rev Hemat 2023

Efa has an ultralong half-life



Adapted from von Drygalski et al. NEJM 2024

current treatments

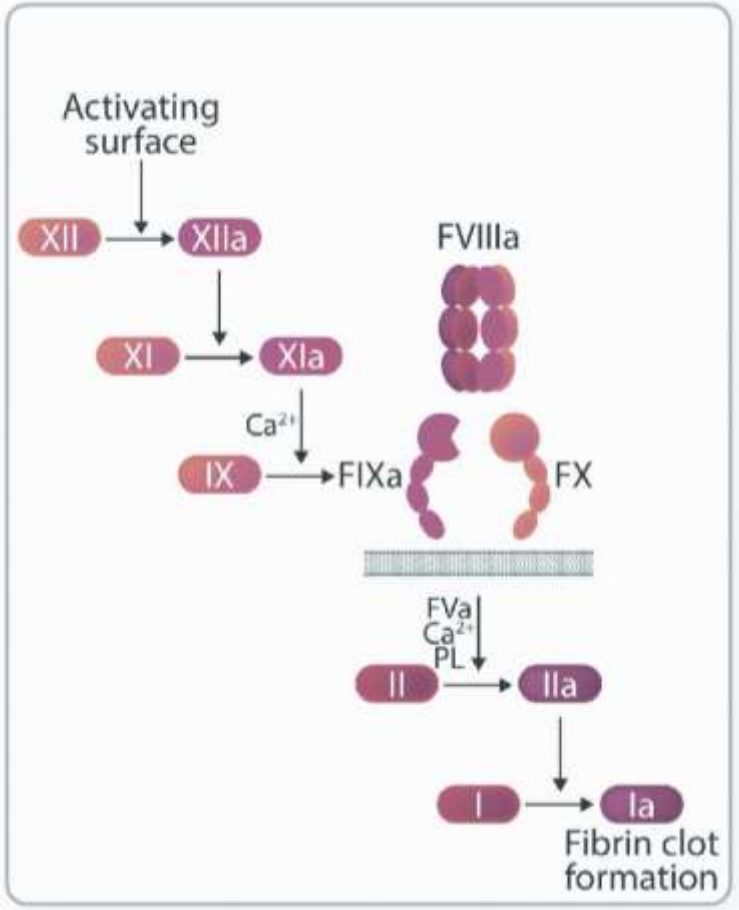
factor concentrate

emicizumab

upcoming treatments

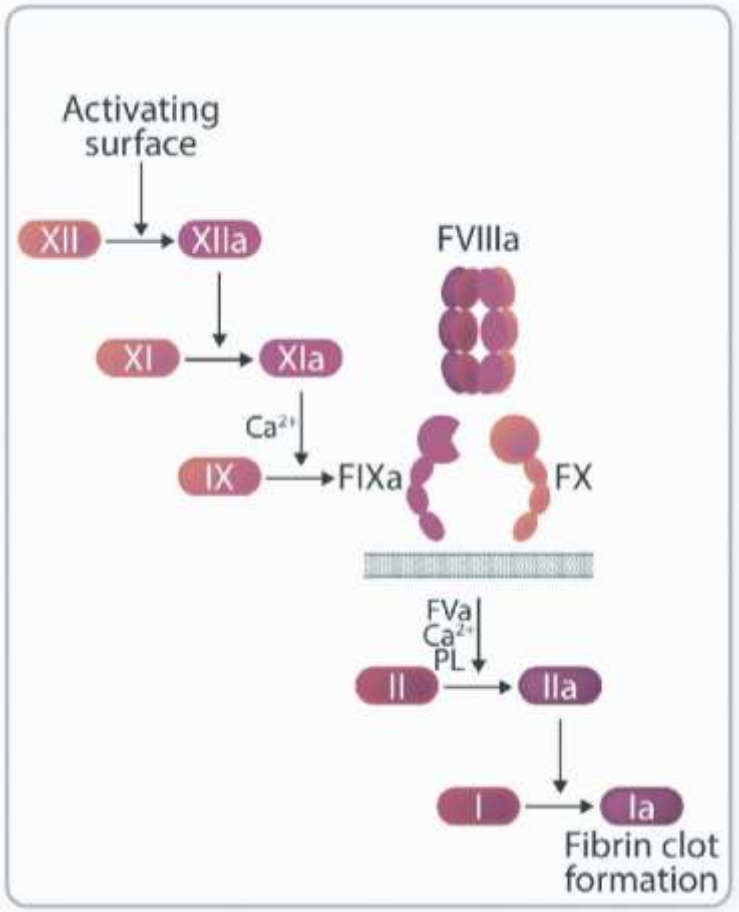
rebalancing agents

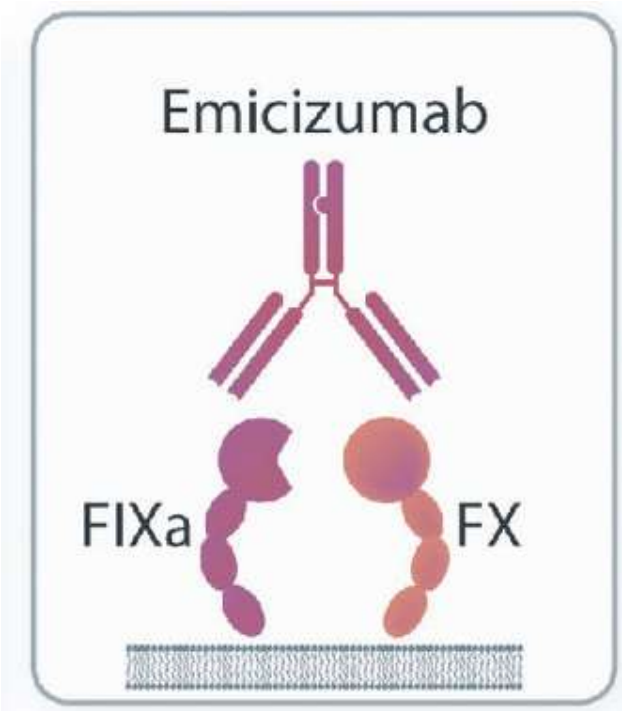
Emi mimics the function of FVIII



Andrade et al. Haematologica, 2024

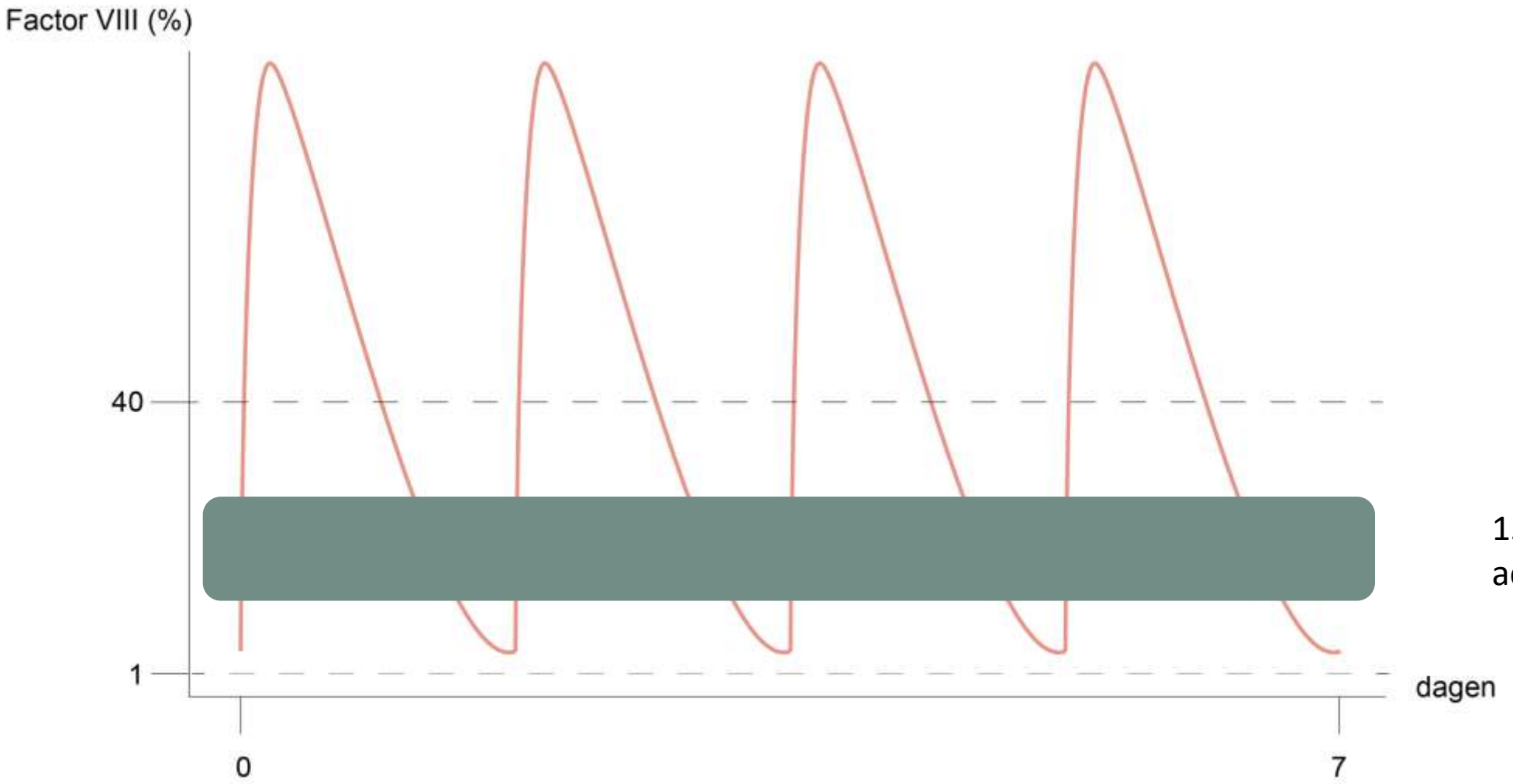
Emi mimics the function of FVIII





Andrade et al. Haematologica, 2024

Emi results in a constant FVIII-like activity



15-20% FVIII-like activity

Emi provides excellent protection

Emicizumab

Few bleeds

Subcutaneous

Young RPTH 2024

But emi does not protect against traumatic and surgery-related bleeds

Emicizumab

Only for hemophilia A

Insufficient protection for some activities

Young RPTH 2024

Emi is the backbone of the management of acquired haemophilia

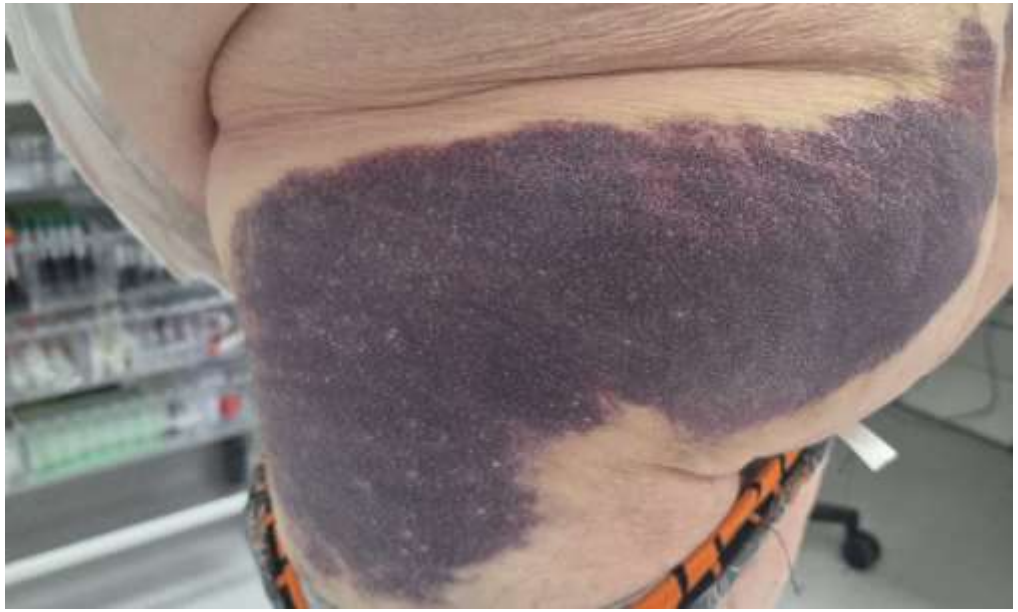
quick step-up dosing of emicizumab

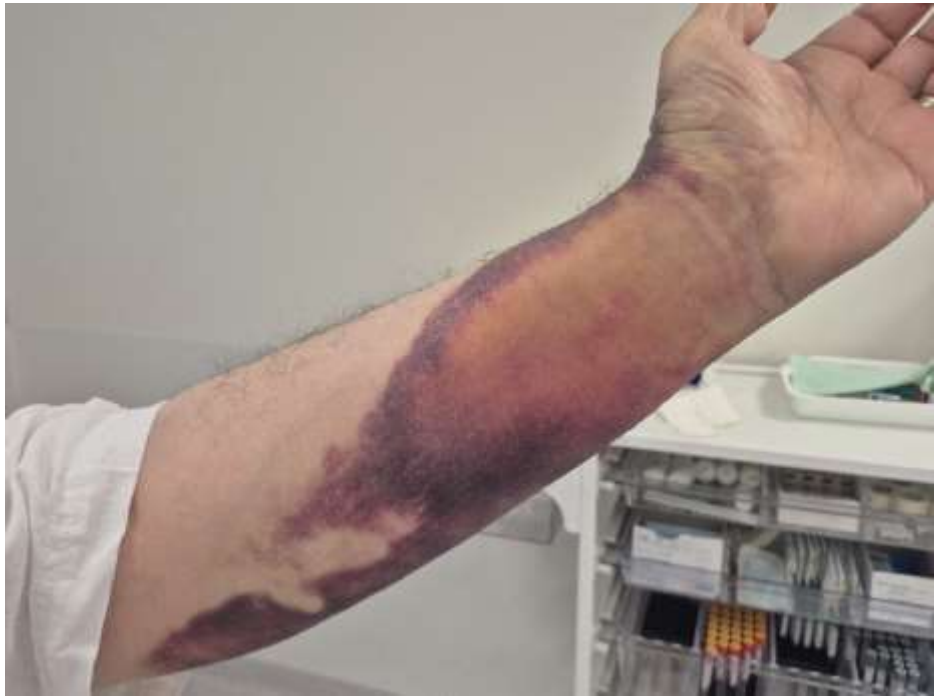
rFVIIa in case of acute bleeds

only start immunosuppression after initial stabilisation

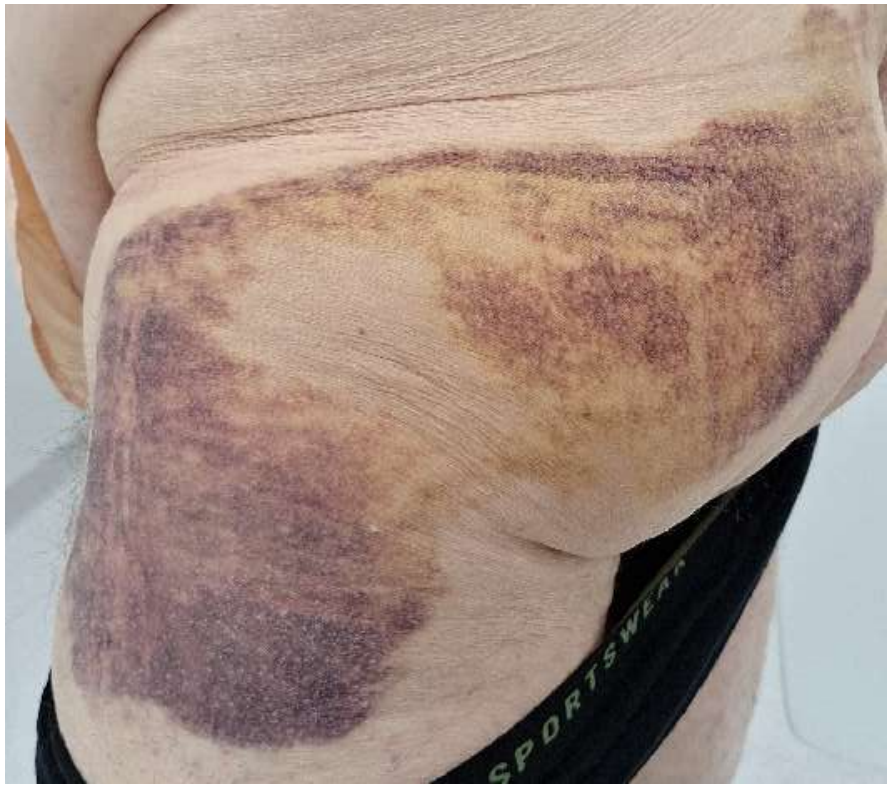
Tiede et al. Lancet Haematol 2023

Emi is the backbone of the management of acquired haemophilia





After 1 week of emicizumab



current treatments

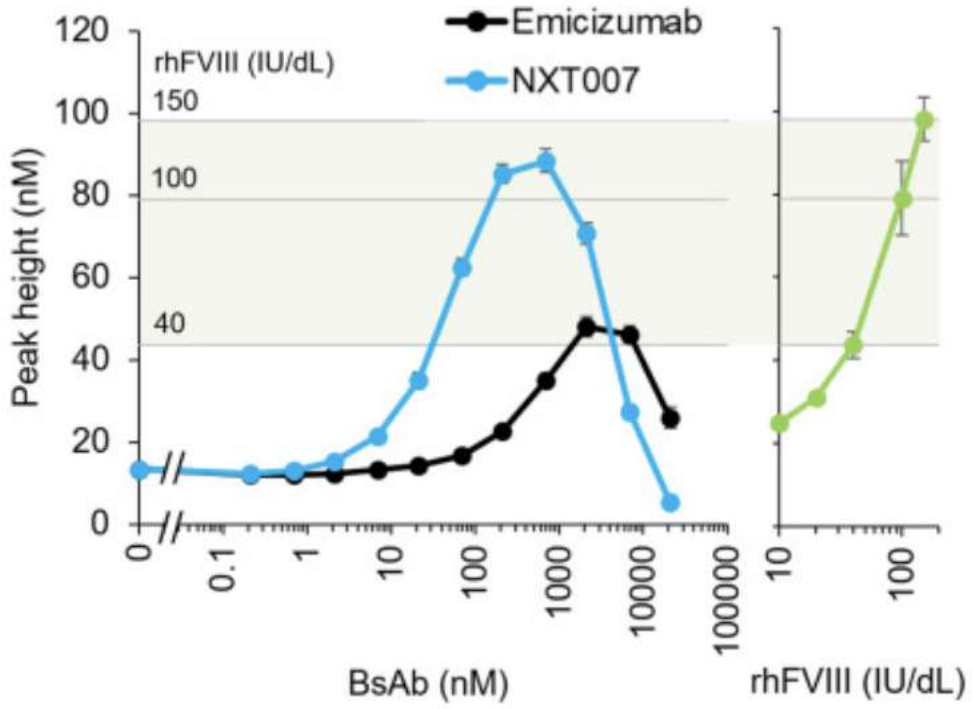
upcoming treatments

2nd generation mimetics

gene therapy

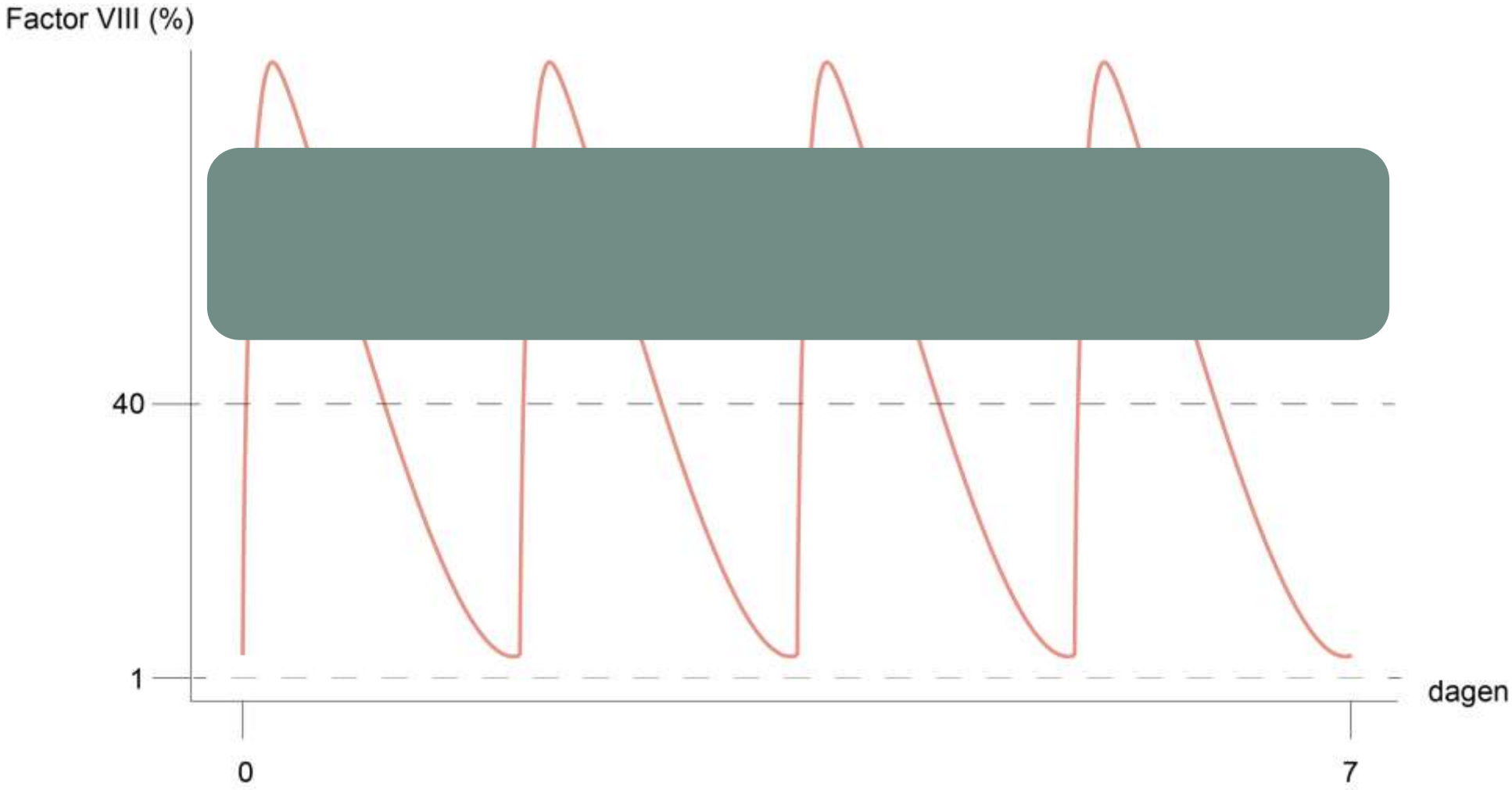
rebalancing agents

NXT007 induces a high peak of thrombin in FVIII-deficient plasma



Teranishi-Ikawa et al. JTH 2024

NXT007 and mim8 will result in a non-hemophilia range of FVIII activity



Inno8 is an ultrapotent oral FVIII mimetic

nanobody technology

daily oral treatment

in vitro +/- 100x more powerful than emi

5x more powerful than mim8

Lund et al. Oral ISTH 2024

current treatments

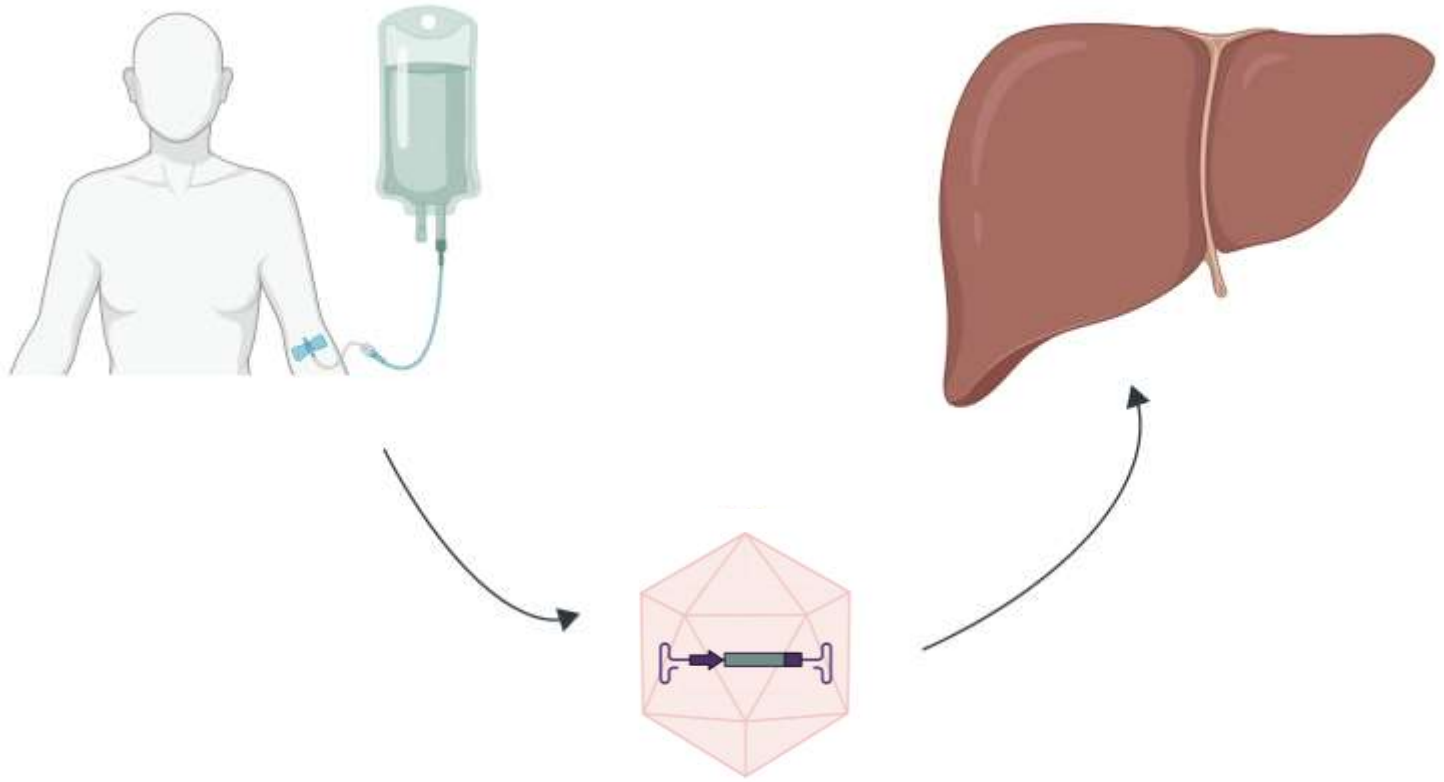
upcoming treatments

2nd generation mimetics

gene therapy

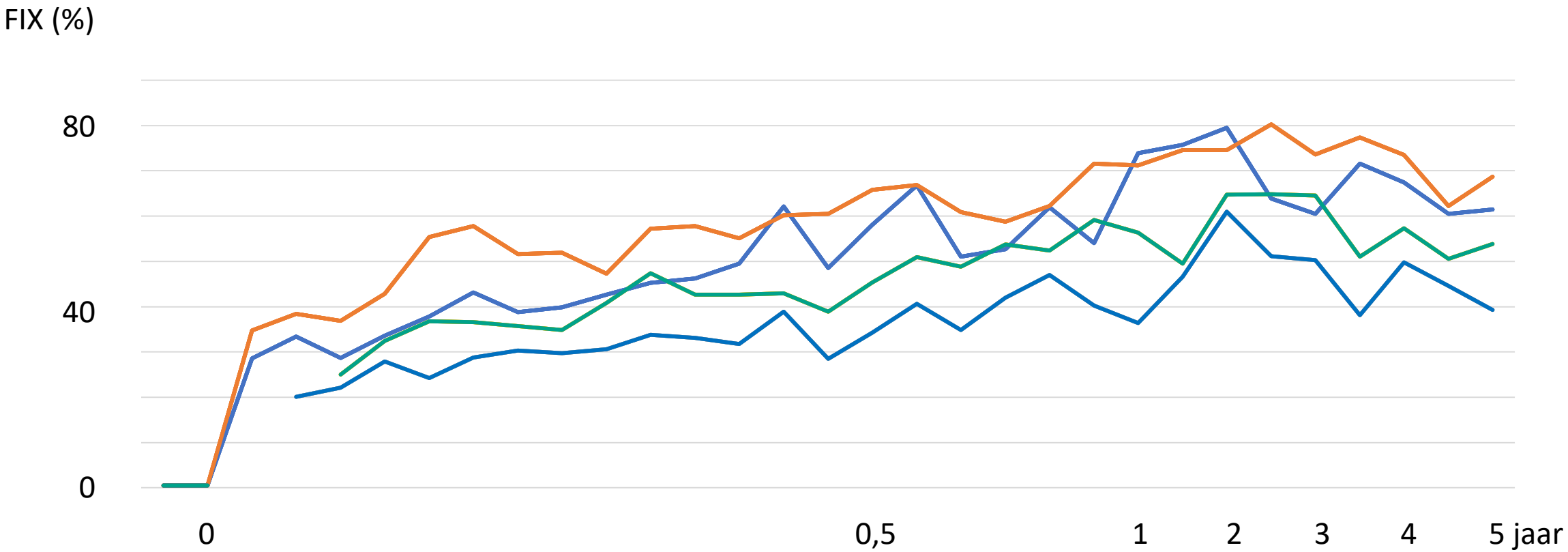
rebalancing agents

Using an AAV vector, the gene product is directed towards the hepatocytes

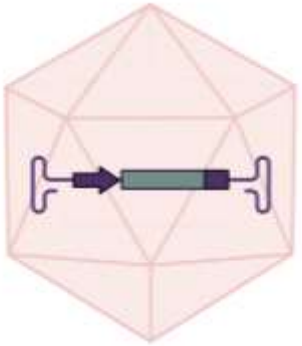


Pipe et al. NEJM 2023
Castaman et al. Exp Rev Hem 2023

In Leuven 4 people with haemophilia B were successfully treated with gene therapy



Gene therapy aims to replace the missing factor in a permanent way



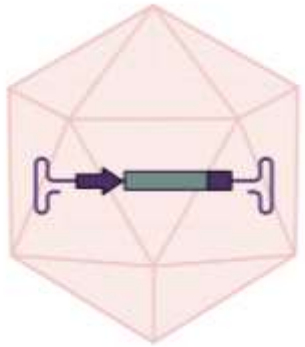
Gene therapy

One infusion

Majority remains free from prophylaxis

Ozelo et al. NEJM 2022; Coppens et al. Lancet Haematol 2024; Cuker et al. NEJM 2024

Gene therapy aims to replace the missing factor in a permanent way



Gene therapy

Durability in hemophilia A?

Frequent need for steroids

Not in case of inhibitors

Only in adults

Ozelo et al. NEJM 2022; Coppens et al. Lancet Haematol 2024; Cuker et al. NEJM 2024

Partly porcine ET3 FVIII induces stable activity after transplantation with CD34+ cells

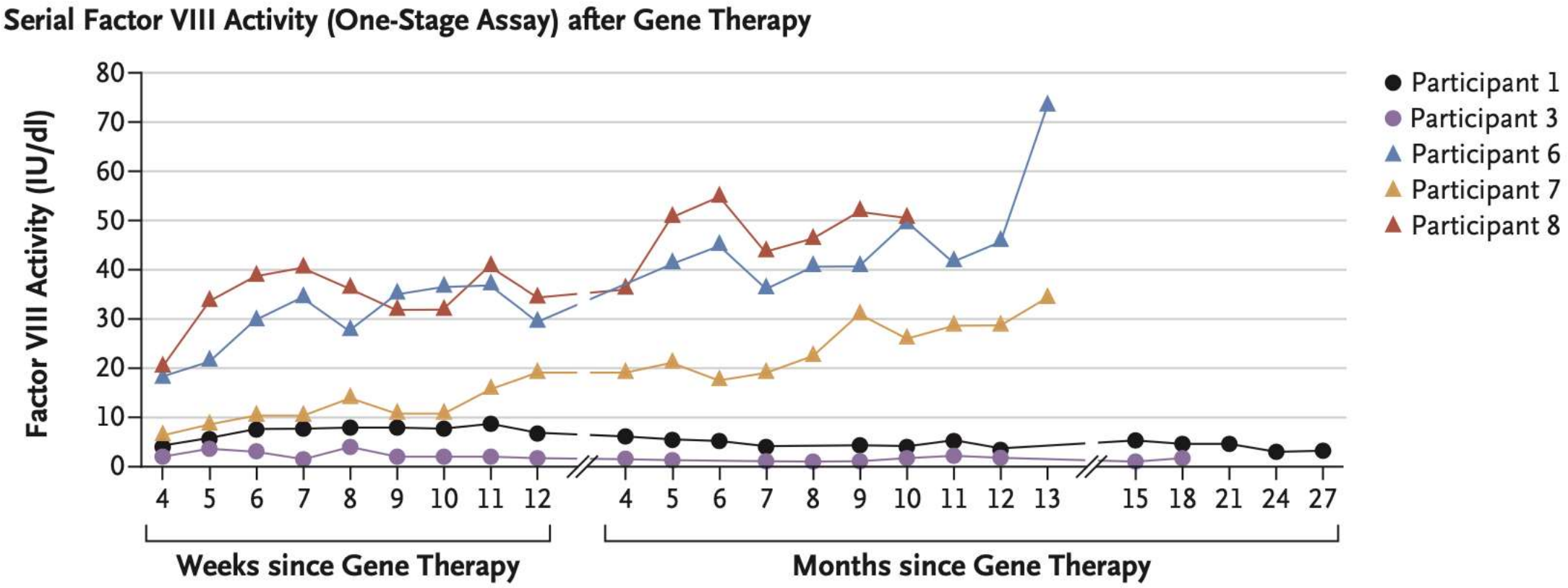
5 patients undergoing autologous stem cell transplantation

CD68-LV-ET3 (partly porcine)

requires myeloablative conditioning

Srivastava et al. NEJM 2025

Partly porcine ET3 FVIII induces stable activity after transplantation with CD34+ cells



Srivastava et al. NEJM 2025

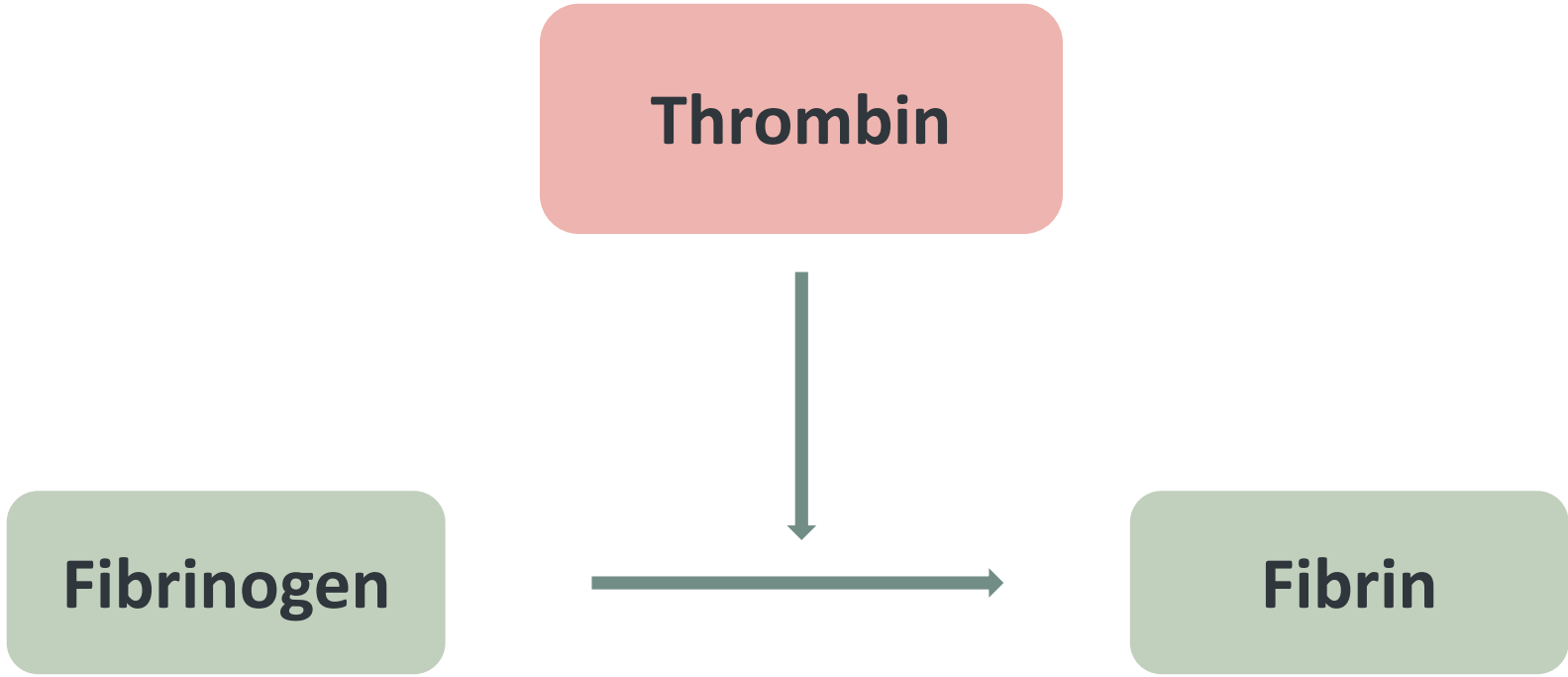
current treatments

upcoming treatments

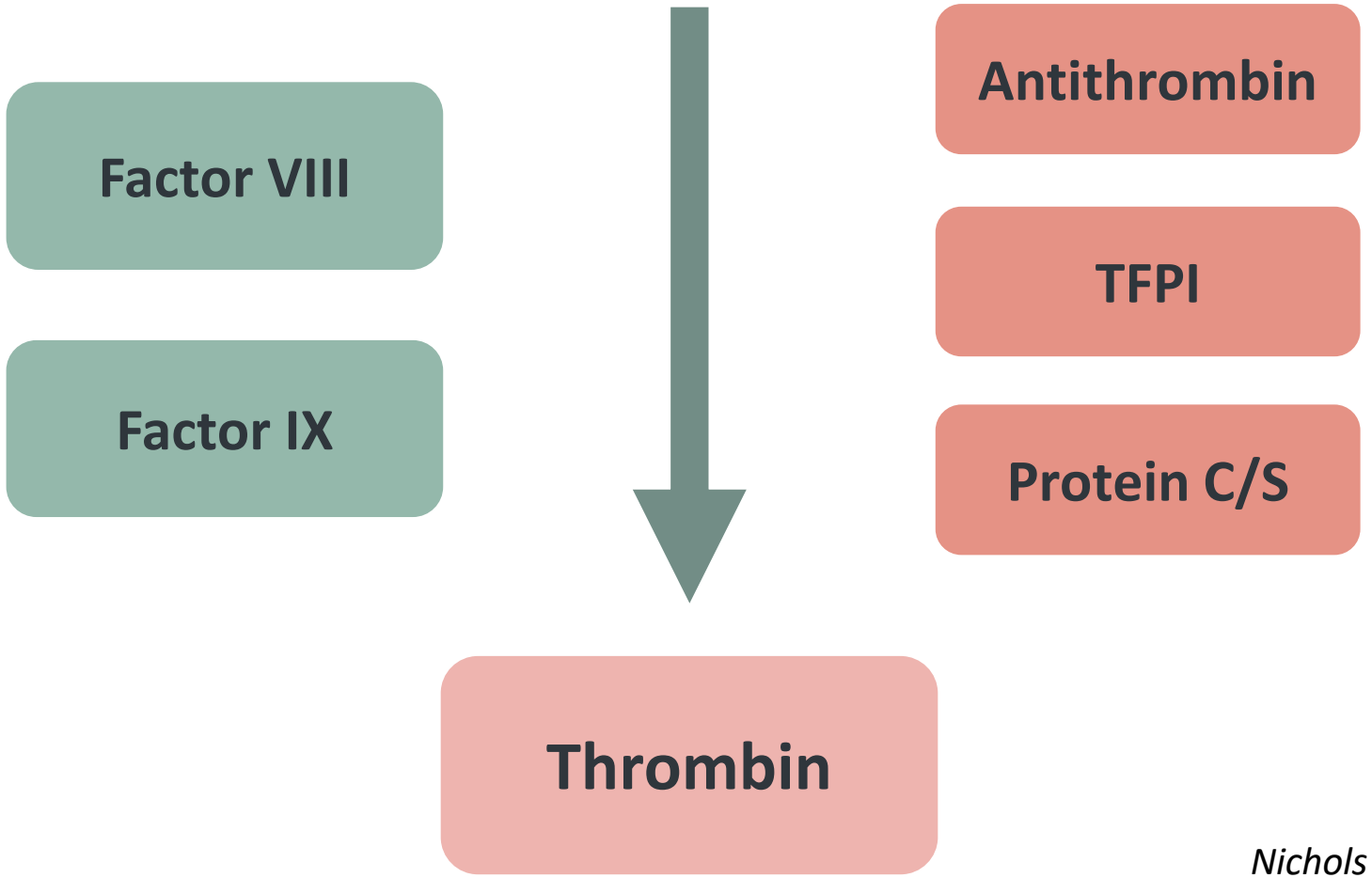
- ultralong FVIII
- 2nd generation mimetics
- gene therapy

rebalancing agents

Haemophilia is a disease of thrombin generation

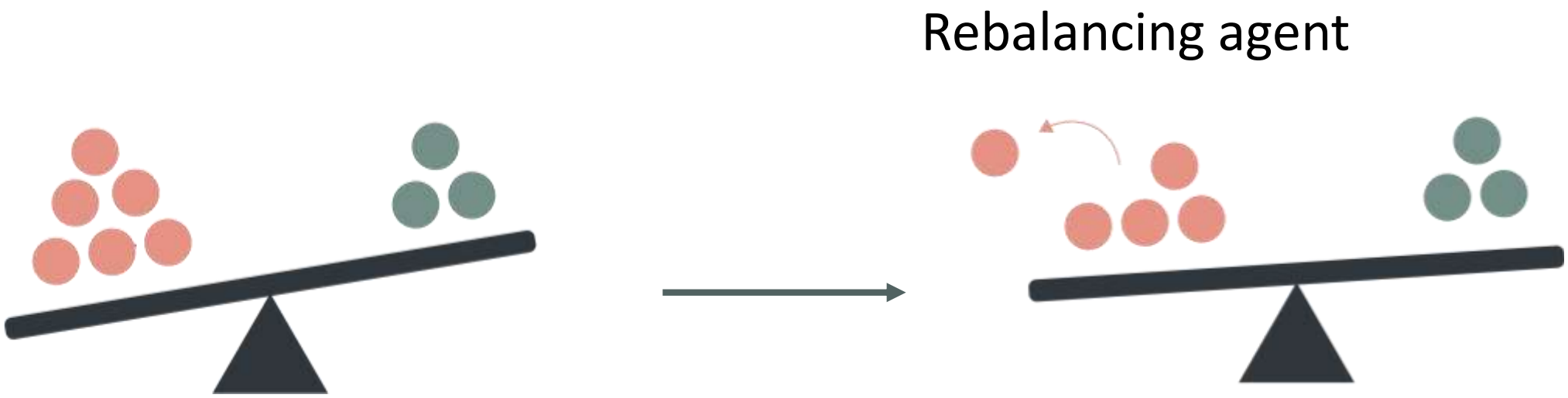


Thrombophilia can attenuate the bleeding phenotype in haemophilia



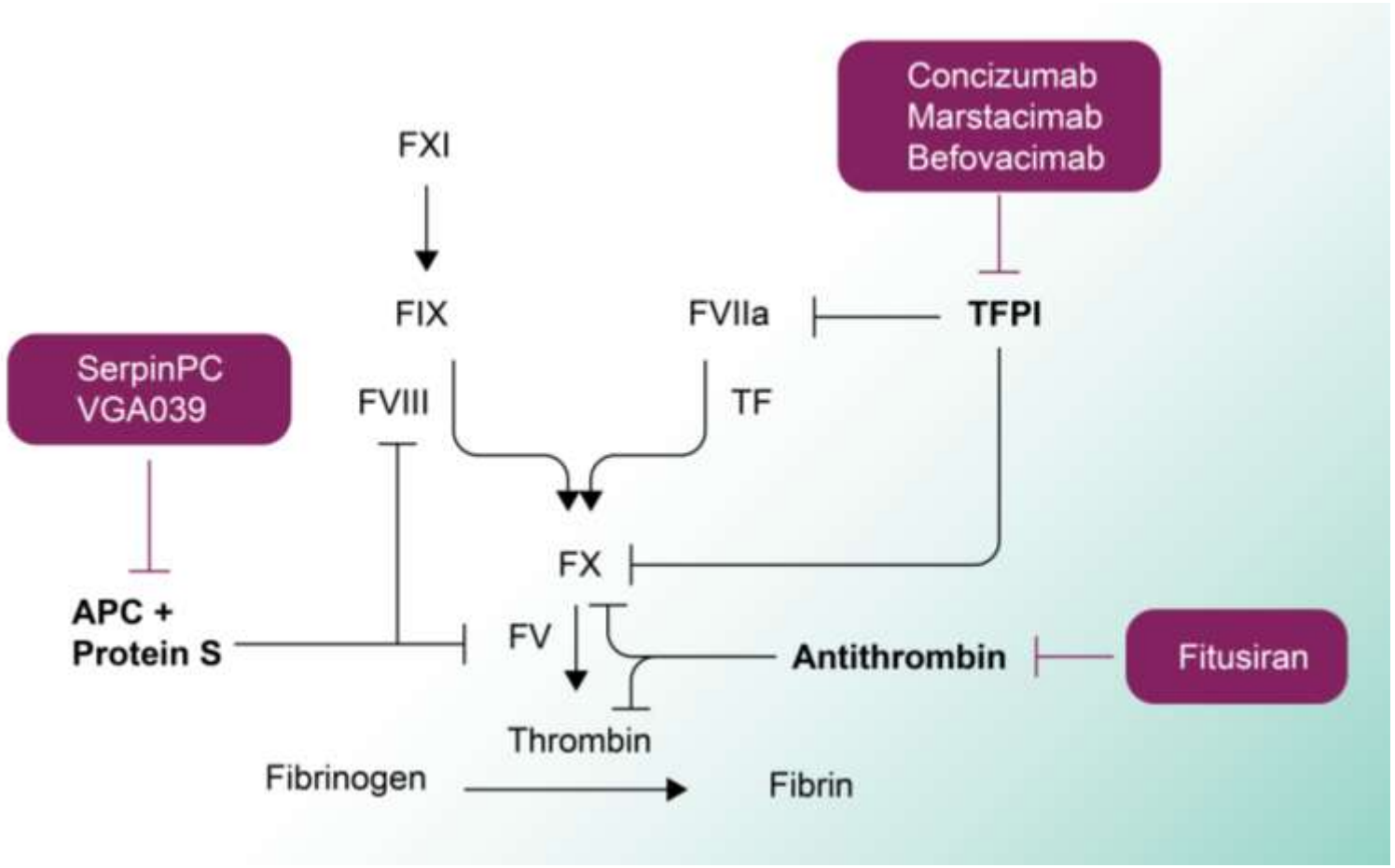
Nichols et al. Blood 1996
van Dijk et al. Thromb Haemost 2004
Franchini et al. Semin Thromb Hemost 2009

Haemostasis can be rebalanced in haemophilia



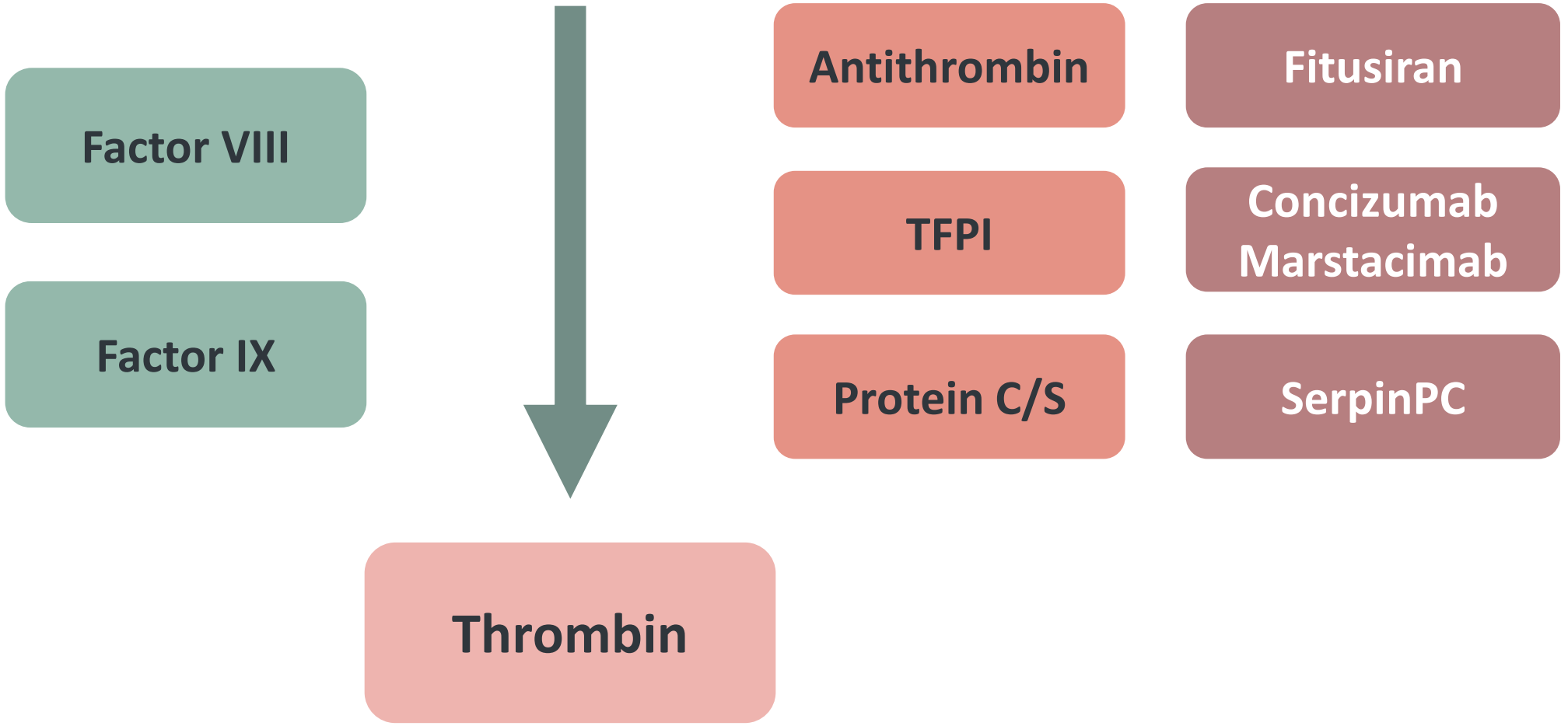
Haemophilia

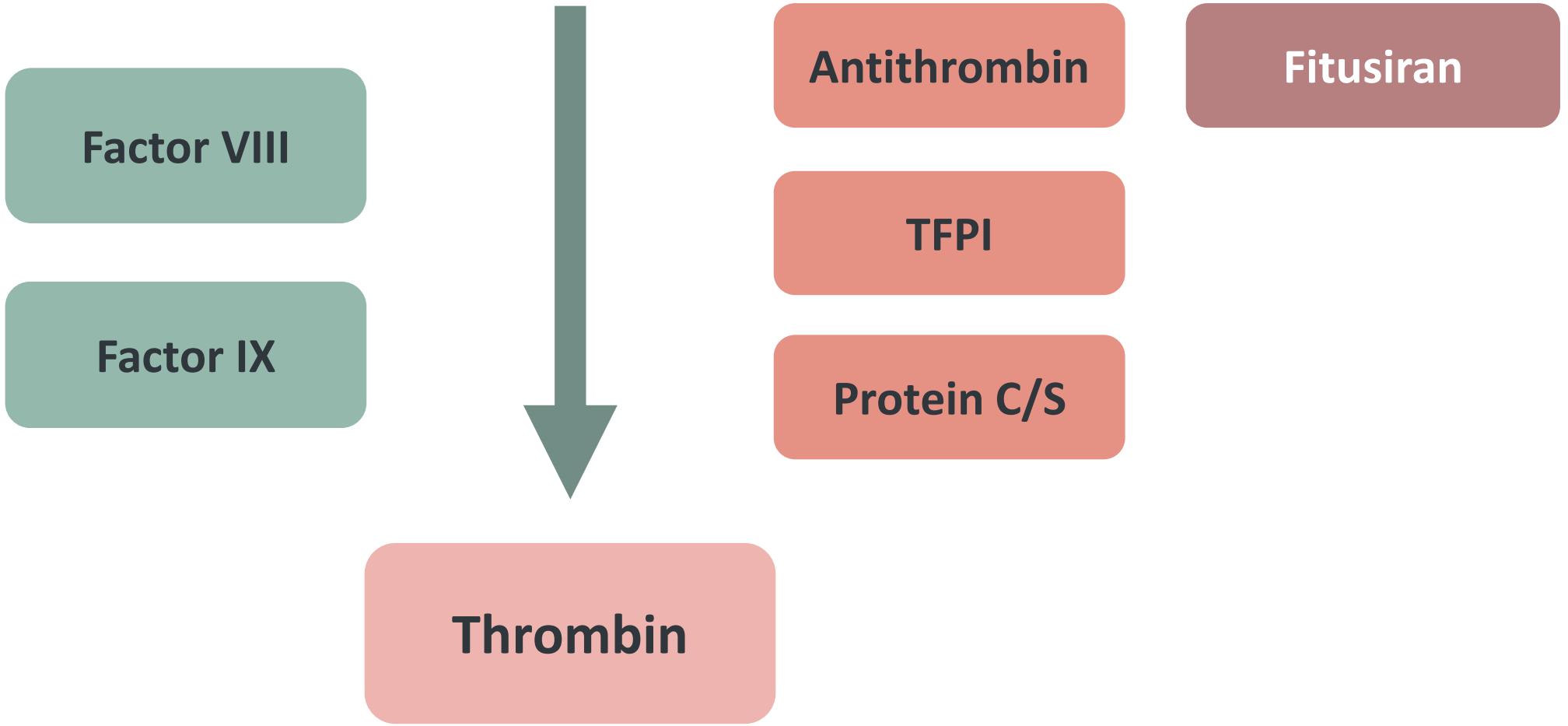
Rebalancing provides new options for treatment



Van Thillo and Hermans, Haematologica 2025

Haemostasis can be rebalanced in haemophilia



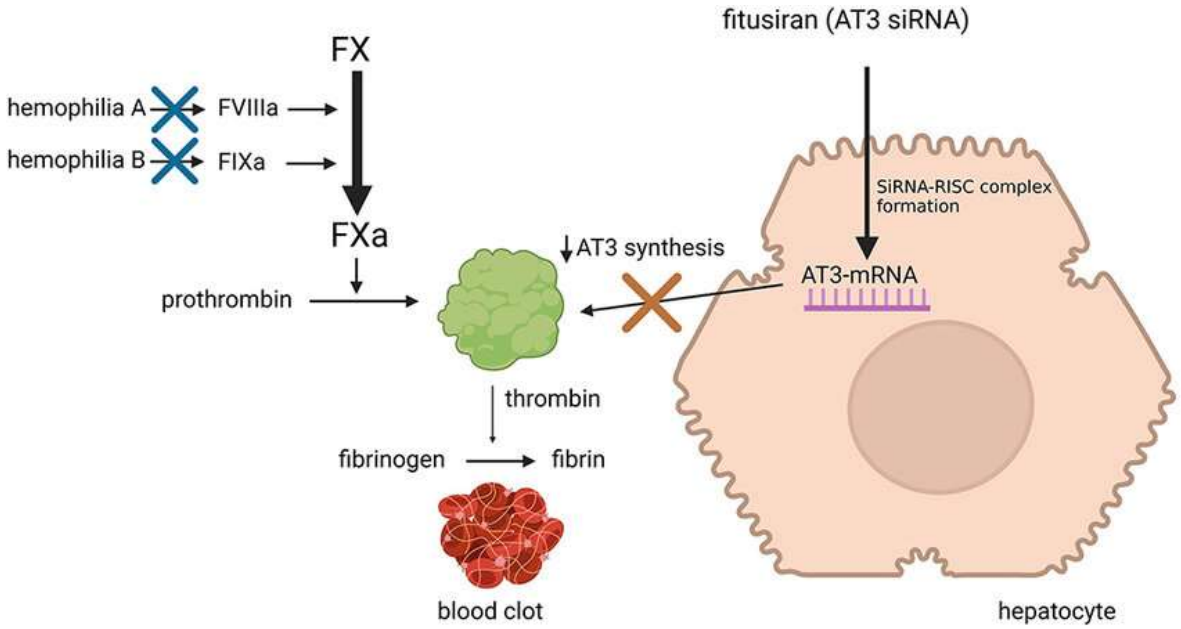

Factor VIII
Factor IX
Antithrombin
TFPI
Protein C/S
Fitusiran
Thrombin

Fitusiran downregulates antithrombin

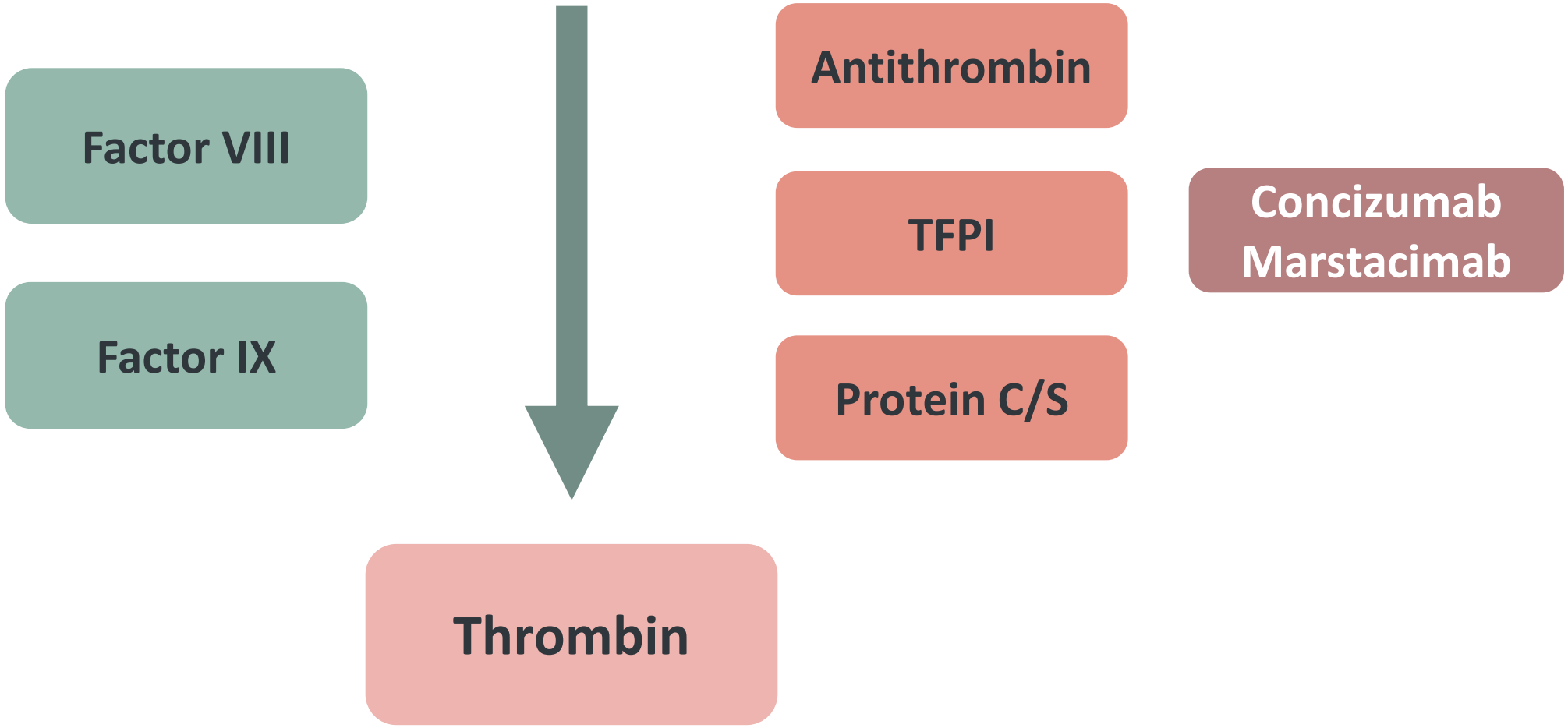
siRNA against antithrombin

directed at hepatocytes (N-acetylgalactosamine)

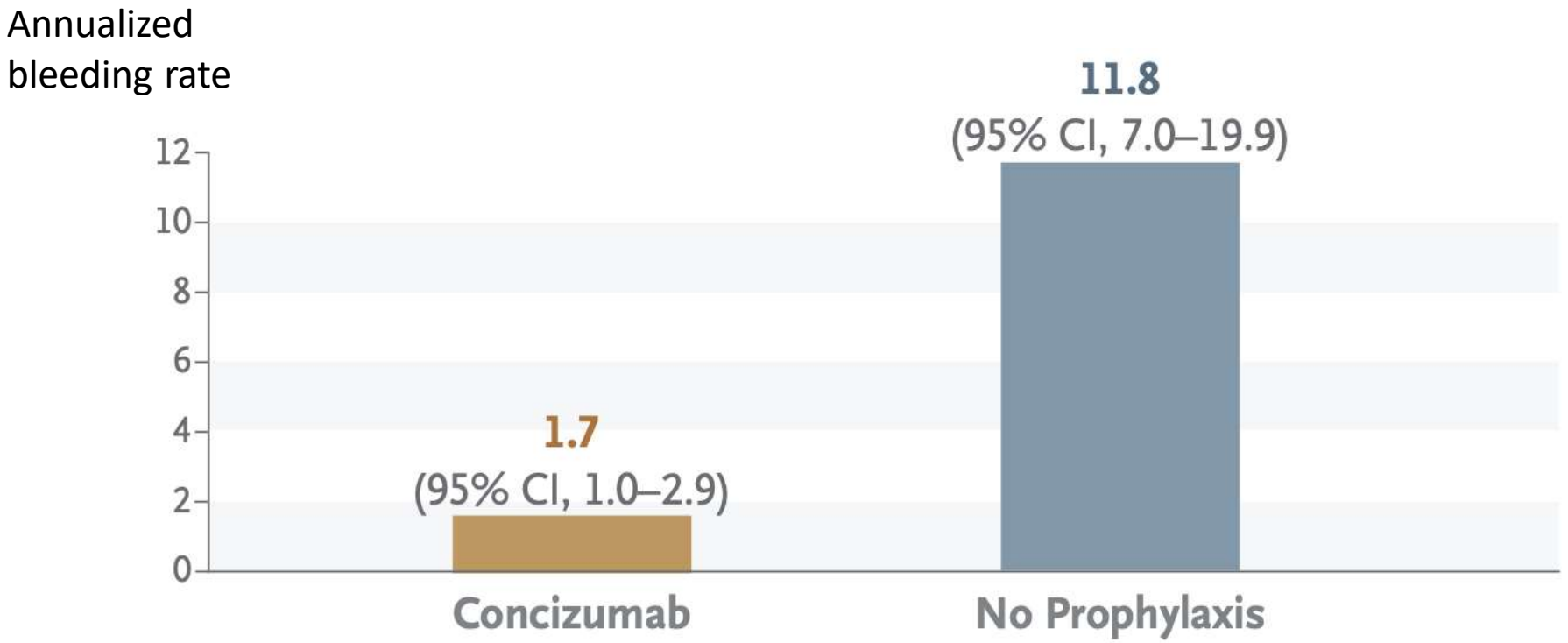
AT levels 15-35 ~
FVIII activity of 20-40%



Seghal et al. Nat Med 2015
Kaddi et al. Blood 2022
Boyce and Rangarajan J Blood Med 2023


Factor VIII
Factor IX
Thrombin
Antithrombin
TFPI
Protein C/S
Concizumab
Marstacimab

Concizumab reduces bleeding in patients with and without inhibitors



Matsushita et al. NEJM 2023
Chowdary et al. Lancet Haemat 2024

Marstacimab is approved for patients without inhibitors

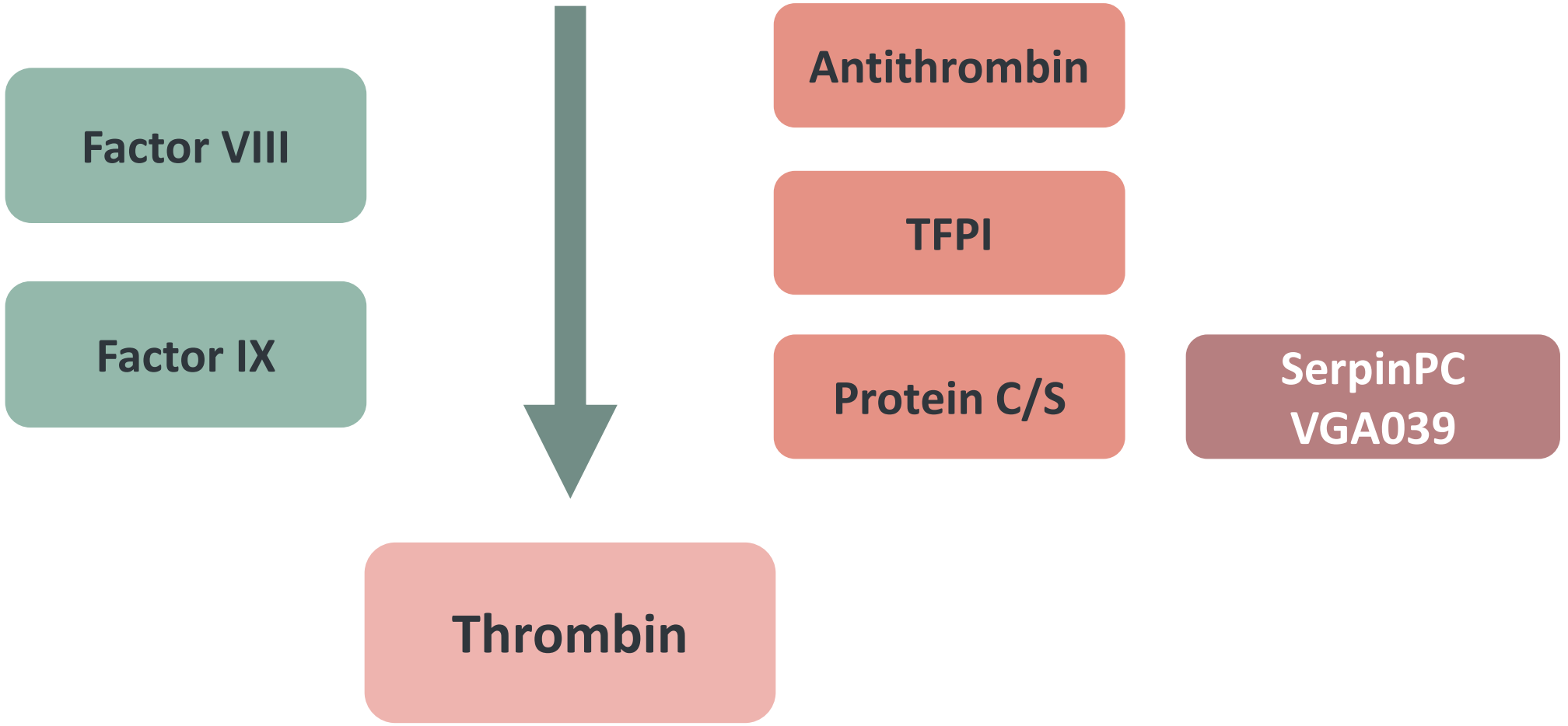
RESEARCH ARTICLE | JULY 3, 2025

Marstacimab Prophylaxis in Hemophilia A/B Without Inhibitors: Results from the Phase 3 BASIS Trial

Clinical Trials & Observations

Davide Matino, Andrew Palladino, Carrie Turich Taylor, Eunhee Hwang, Sangeeta Raje, Satyaprakash Nayak, Regina McDonald, Suchitra Acharya, Johnny Mahlangu, Victor Jiménez-Yuste, Nirmalkumar G Choraria, Dr., Renchi Yang, Chi-kong Li, Murtadha Al-Khabori, Yasser Ahmed Mohamed Soliman Wali, Javier De Jesus Morales-Adrian, Young-Shil Park, Osman Bülent Zülfikar, John Teeter

Matino et al. Blood 2025


Factor VIII
Factor IX
Antithrombin
TFPI
Protein C/S
SerpinPC
VGA039
Thrombin

SerpinPC inhibits activated protein C

Centessa discontinues development of SerpinPC for hemophilia

Treatment was found to be safe, well tolerated in Phase 2 PRESent-2 study

by *Andrea Lobo, PhD* | November 15, 2024

Hemophilia News Today

VGA039

monoclonal Ab against protein S

increases thrombin generation
in vWD, FVII-, FVIII-, FIX-, FXI-, and FXIII-deficient plasma

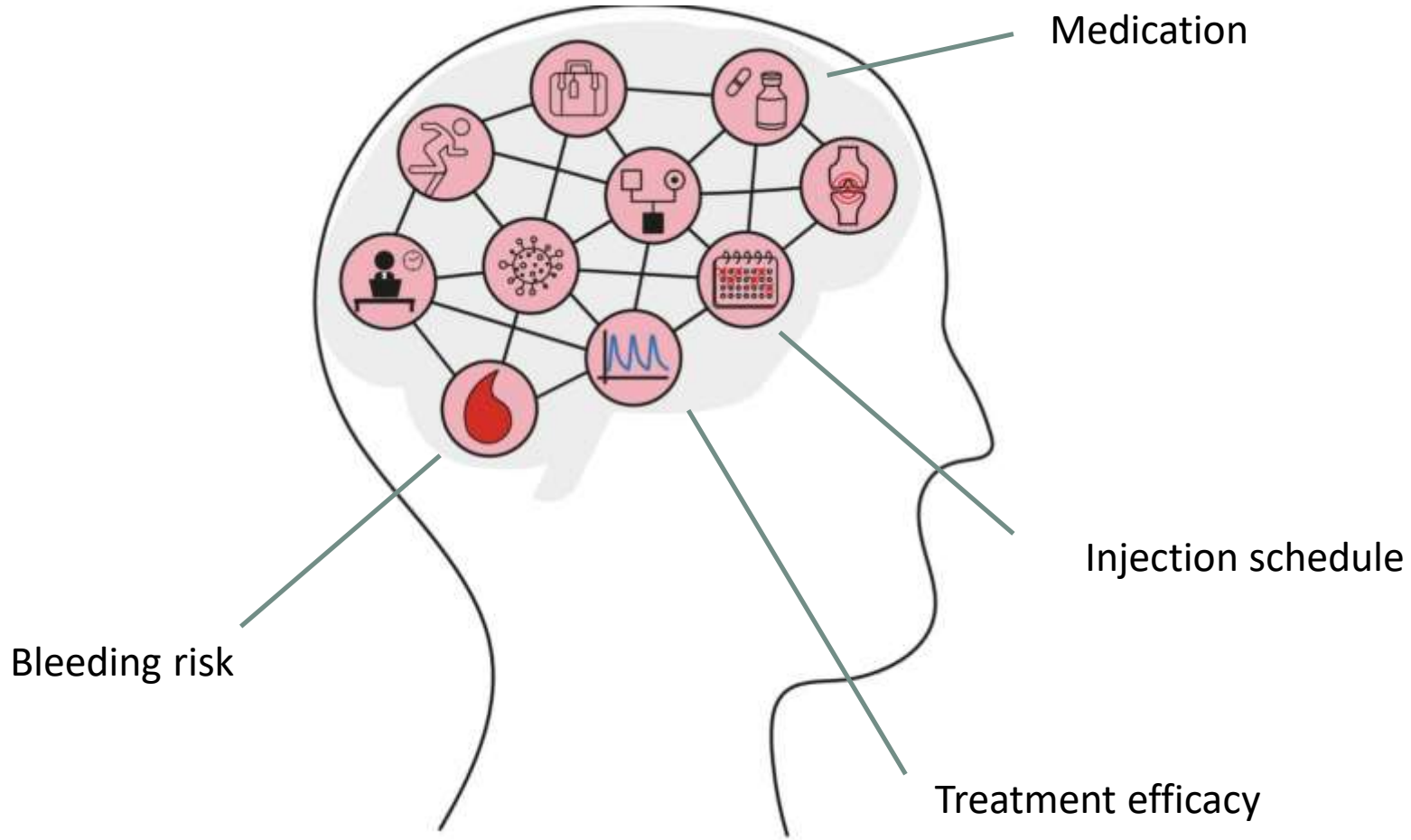
phase 1 trial running (NCT05776069)

Leong et al. Blood 2022

Several questions remain unanswered

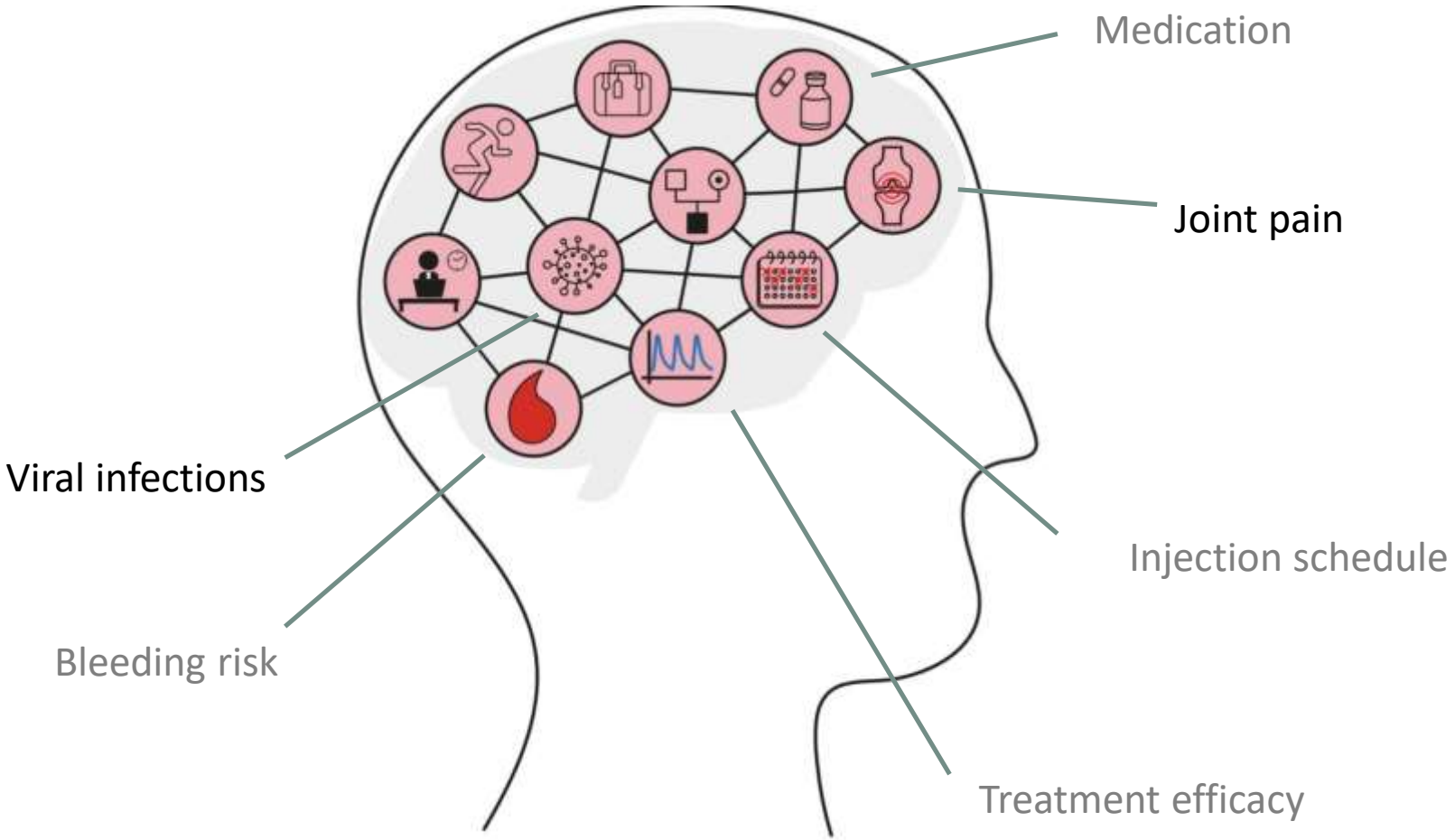
Thrombotic risk	Sport	No intensification
Surgery? Trauma?	Effect of inhibitors	Response prediction
Hemostatic effect	Non-hemostatic functions	No easy monitoring

Patients are not only concerned about their factor level



Krumb and Hermans, RPTH 2021

Patients are not only concerned about their factor level



Krumb and Hermans, RPTH 2021

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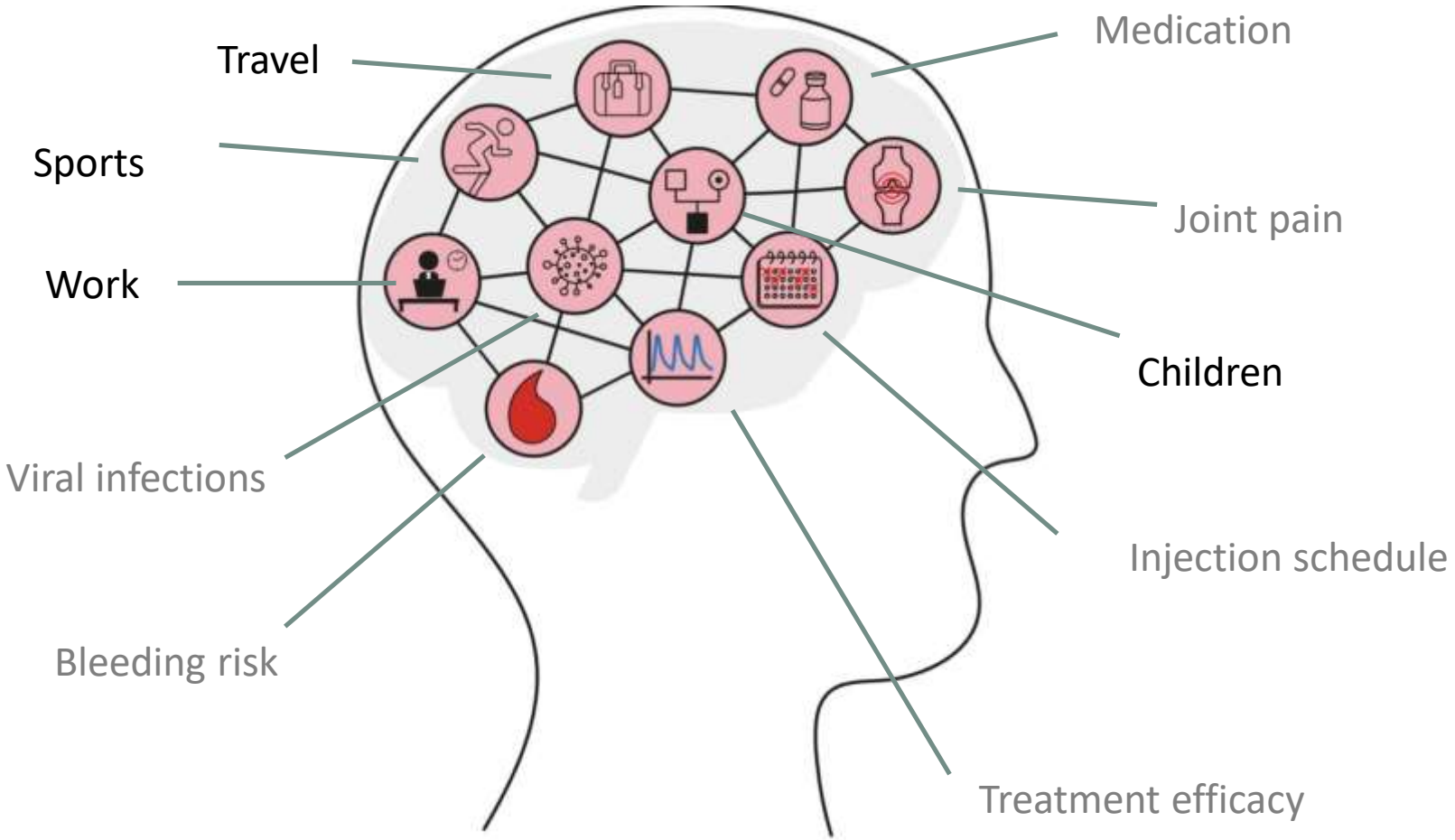


Krumb and Hermans, RPTH 2021

Treatments in the future should be tailored to and discussed with the patient

The choice of treatment depends on age, activity, comorbidities, patient preference

The choice of treatment depends on age, activity, comorbidities, patient preference

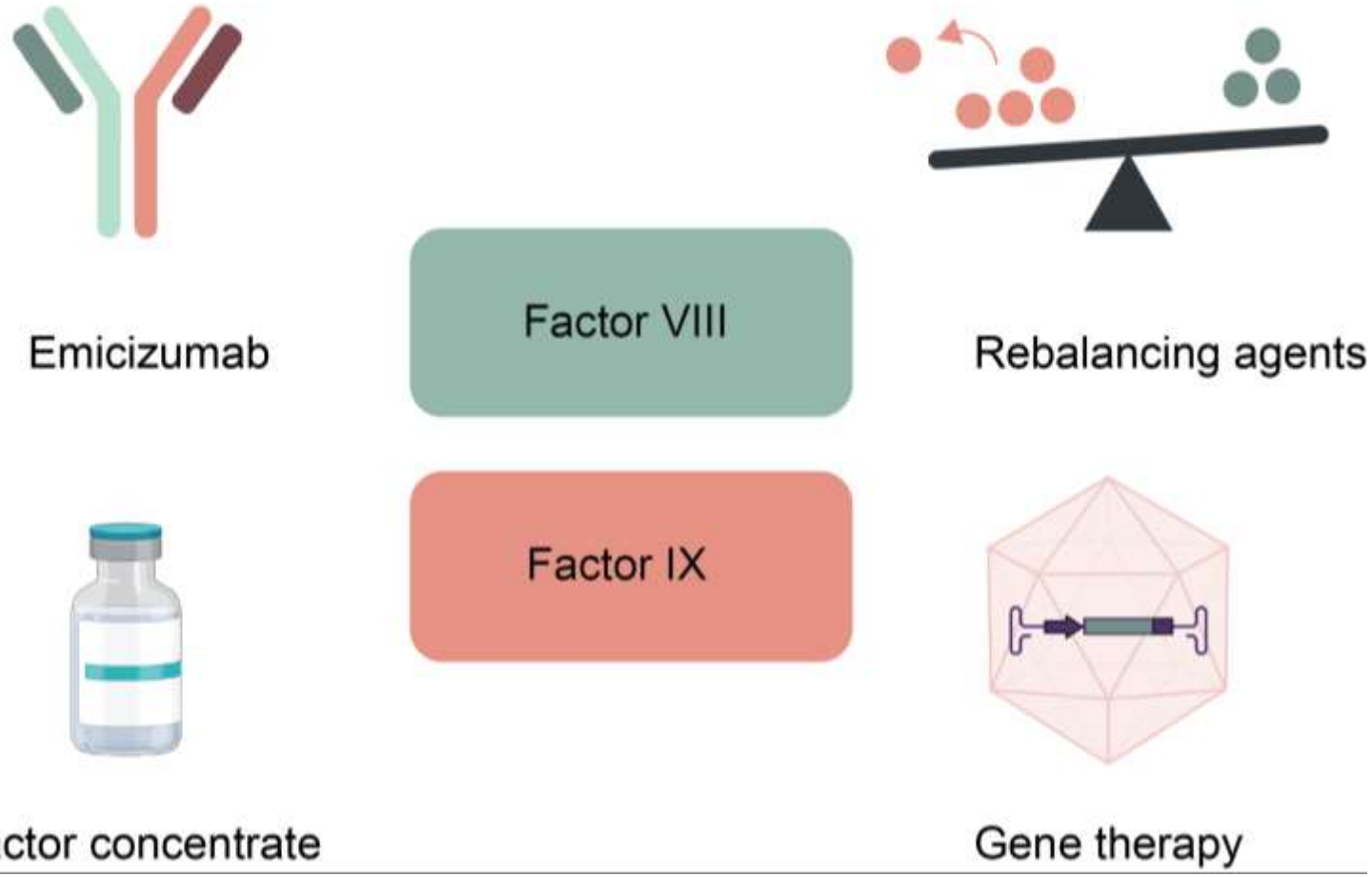
Cardiovascular comorbidities!

current treatments

upcoming treatments

rebalancing agents

Many good options will be available in the near future

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