Congenital haemophilia

Quentin Van Thillo

UZ Leuven

14.11.2026





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

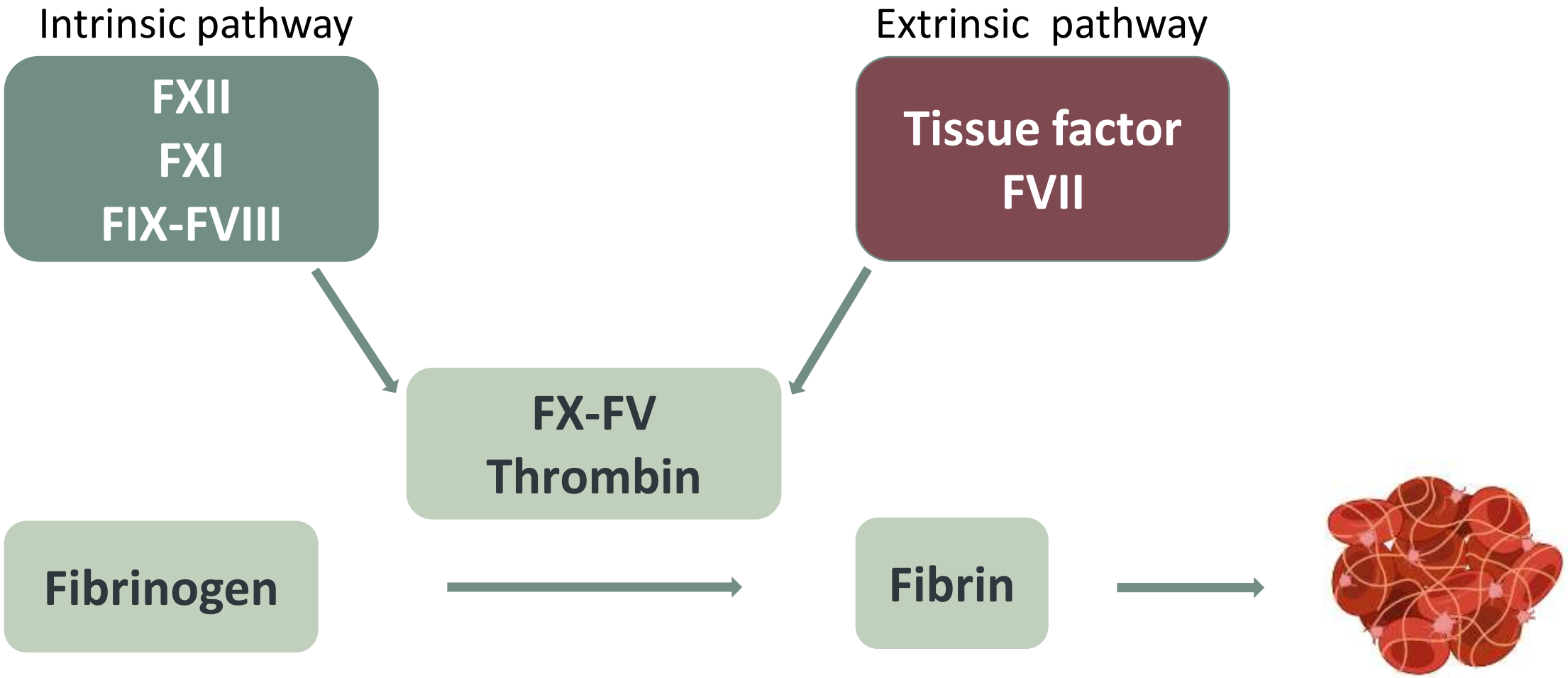


Chronic pain

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



FVIII (HA) or FIX (HB) deficiency reduces clot formation



diagnosis

treatment

what about women?

diagnosis

treatment

what about women?

The diagnosis is most often made in childhood





Joint bleeds are a hallmark

prolonged bleeding

spontaneous, post-trauma, post-surgery

bleeds in joints and muscles

intracranial haemorrhage

A good clinical biologist is needed

prolonged aPTT

correction with mixing study

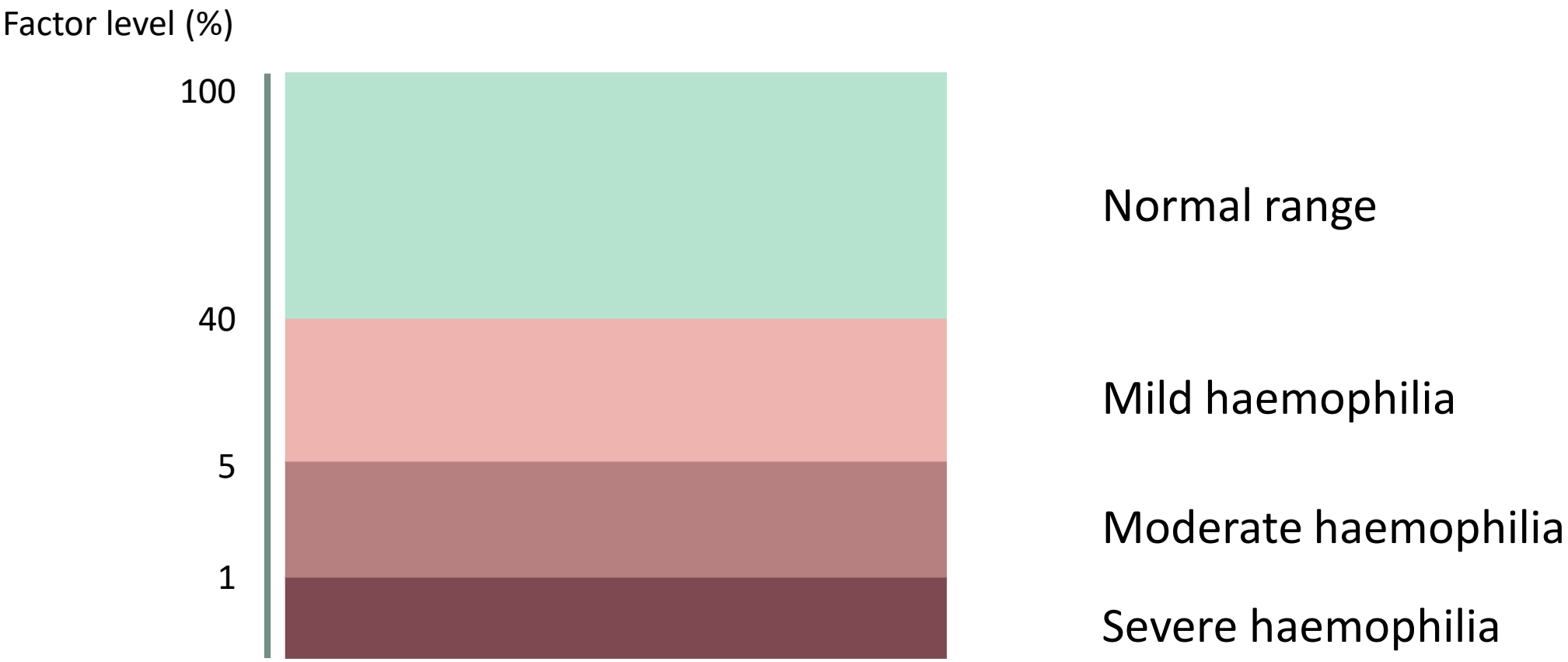
measurement of FVIII/FIX

genetic confirmation

Consider alternate diagnoses

type 3 VWD:	low FVIII, but preserved FVIII production mimics moderate HA
type 2N VWD:	reduced binding of VWF to FVIII mimics mild HA (genetic confirmation)
acquired HA:	no prior history, no correction in mixing study

The severity of haemophilia depends on the factor level



Do not miss mild cases

aPTT can be normal in mild haemophilia

FVIII is an acute phase protein: stress, pregnancy

diagnosis in adults is possible:
no prior surgery, bleeding on DOAC

also women can have haemophilia

Patients need a multidisciplinary evaluation

physio and ortho: haemophilic arthropathy

psychologist: isolation, childhood trauma

specialist nurse, social assistant

dentist

Past treatments resulted in comorbidities and patients face new comorbidities

plasma-derived factor concentrates in the 1980s

→ HCV

→ HIV

difficult balance in case of cardiovascular events

diagnosis

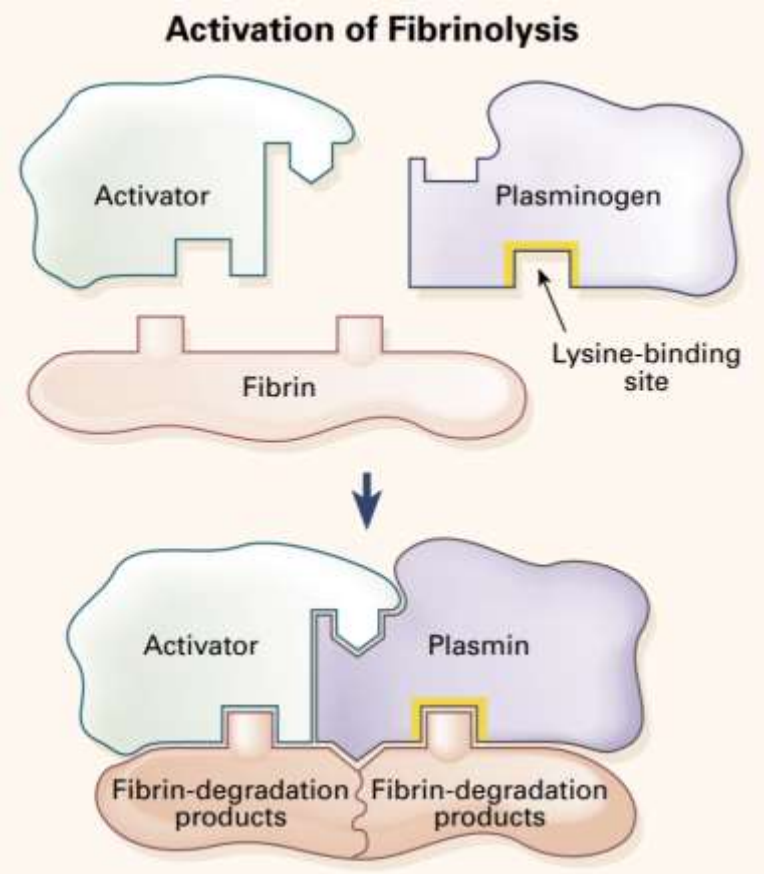
treatment

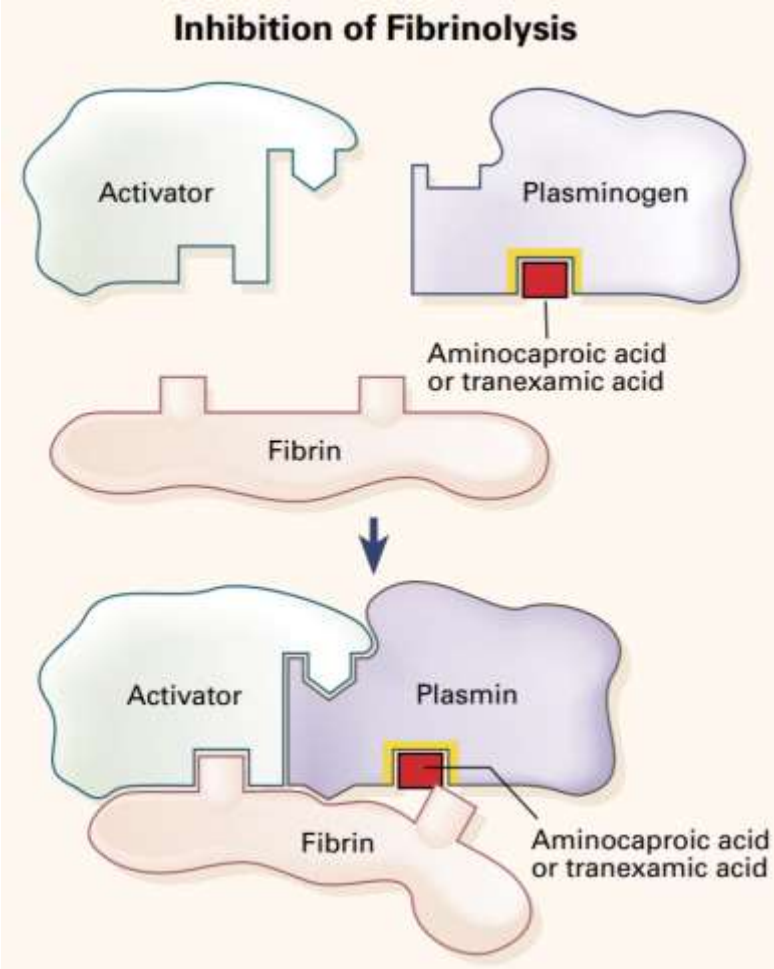
acute treatment

prophylaxis

what about women?

Tranexamic acid is the first-line option in minor mucosal bleeds





Mannucci NEJM 1998

Tranexamic acid is the first-line option in minor mucosal bleeds

efficient in mucocutaneous bleeding

cheap, different formulations

1000 mg 3-4 times a day

not in urinary tract bleeding!

Mannucci NEJM 1998

DDAVP can be used in mild haemophilia A

DDAVP (1-deamino-8-D-arginine vasopressin)
or Minirin or desmopressin

iv 0.3 µg/kg, max 20 µg (nasal spray not available anymore)

releases endothelial VWF and FVIII (2-4x)

DDAVP can be used in mild haemophilia A

test dose needed: 0h – 30/60 min – 4h

AE: flushing, fluid retention, hypoNa (fluid restriction for 24h)

NOT in elderly patients or < 2y
heart failure, uncontrolled hypertension

CAVE tachyphylaxis

DDAVP is also effective in VWD

Table 5. Practical considerations for desmopressin trial/challenge and administration

Domain	Description
Route	Desmopressin trials may be performed with either IV or intranasal desmopressin, but intranasal desmopressin trials may not be successful because of issues with administration and/or absorption. Subcutaneous administration has also been used.
Dose	IV desmopressin is given as 0.3 μg/kg, with a maximum dose of 20 μg. The desmopressin nasal spray (150 μg per spray) is given as 1 spray for individuals weighing <50 kg and 2 sprays for individuals weighing ≥50 kg.
Timing of laboratory testing	VWF antigen, VWF activity, and FVIII activity levels should be determined immediately before administration of desmopressin, ~30-60 min after administration of desmopressin, and ~4 h postadministration, because in type 1C VWD, there is a rapid decrease in VWF levels.
Responsiveness	There are multiple definitions of desmopressin responsiveness.[128-130] The panel considered that an increase of at least 2 times the baseline VWF level and the ability to achieve both VWF and FVIII levels of >0.50 IU/mL were required to consider the patient responsive to desmopressin. Desmopressin responsiveness does not guarantee, however, that the level achieved is adequate to prevent bleeding in all procedures (eg, higher levels may be indicated based on type of procedure).
Precautions	Because of the risk of hyponatremia, desmopressin should not be given on >3 concurrent days and is generally not administered to children age <2 y. In addition, tachyphylaxis occurs after repeated infusions. Caution is advised when desmopressin is used in patients with active cardiovascular disease. Additionally, desmopressin trials should be avoided in pregnancy.

ASH guidelines VWD – James Blood 2021

Give factor immediately in case of a severe bleed

do not wait for exams (e.g. CT brain)

contact a haemophilia treatment centre

NO intramuscular injections, avoid NSAIDs

Give factor immediately in case of a severe bleed

Target	FVIII 80-100%
	FIX 60-80%
Recovery	1 IU/kg increases FVIII with +/- 2%
	1 IU/kg increases FIX with +/- 1%
CAVE	FVIII increases with age
	check for inhibitors

Inhibitors are/were a major issue in haemophilia

neutralising alloantibodies against FVIII or FIX, Bethesda assay

FVIII: +/- 20-30%

FIX: +/- 3-5% (very rare)
risk of anaphylaxis and proteinuria

NovoSeven iv (short t1/2, expensive), FEIBA, high dose FVIII

need for immune tolerance induction

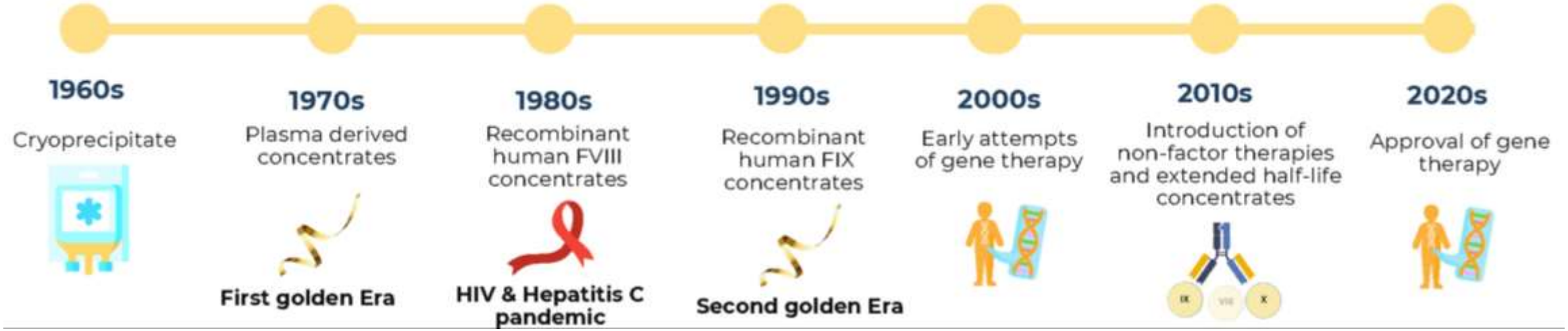
diagnosis

treatment

prophylaxis:
factor concentrates

what about women?

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



Español et al. RPTH 2024

Regular prophylaxis to maintain levels > 1% protects the joints

ORIGINAL ARTICLE

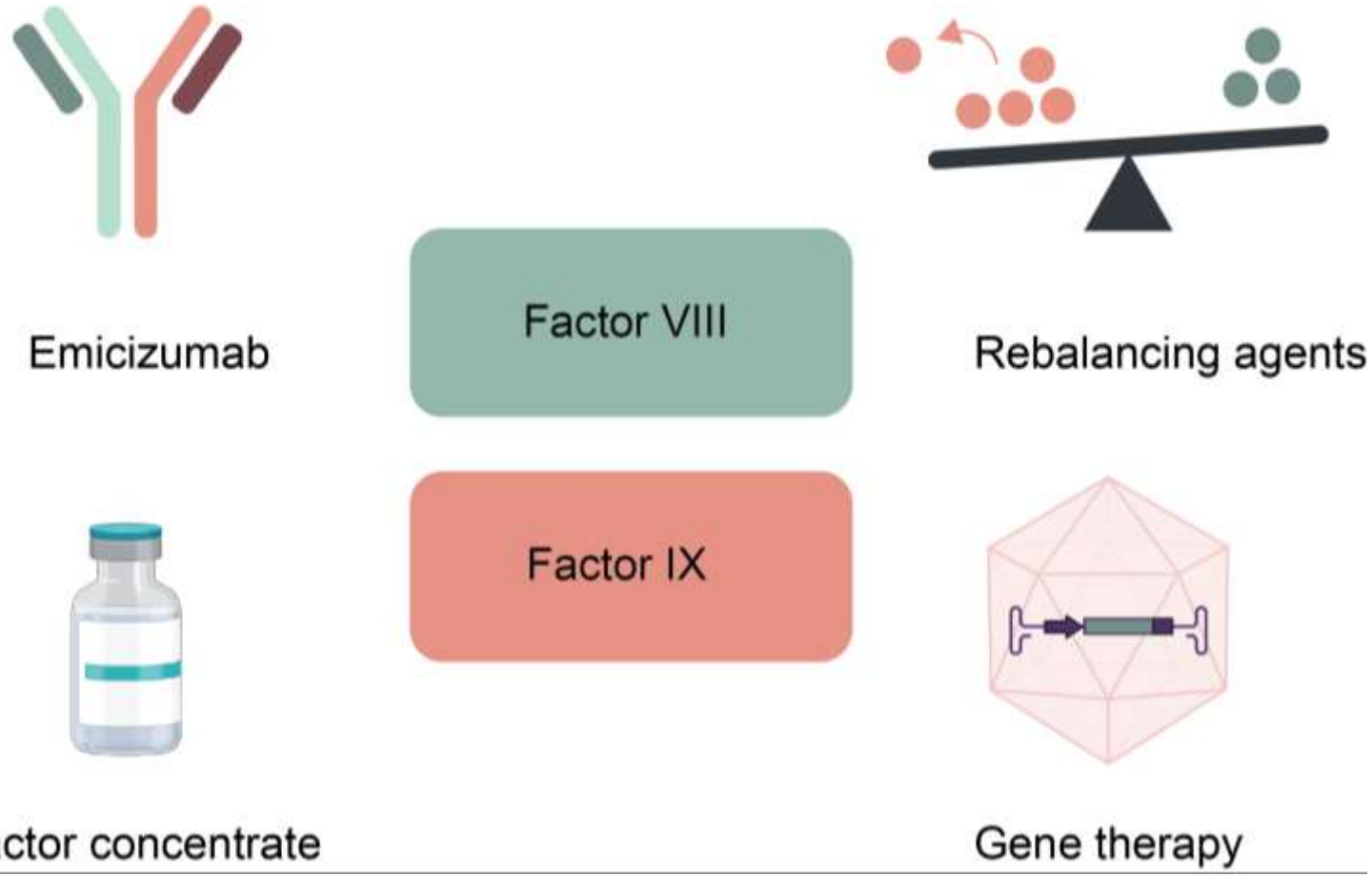
Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia

Authors: Marilyn J. Manco-Johnson, M.D., Thomas C. Abshire, M.D., Amy D. Shapiro, M.D., Brenda Riske, M.S., M.B.A., M.P.A., Michele R. Hacker, Sc.D., Ray Kilcoyne, M.D., J. David Ingram, M.D., +21 , and Bruce L. Evatt, M.D. Author Info & Affiliations

Published August 9, 2007 | N Engl J Med 2007;357:535-544 | DOI: 10.1056/NEJMoa067659 | VOL. 357 NO. 6

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Different treatment classes are available



Most therapies either supplement the missing factor or mimic its activity



Factor concentrate

Factor VIII

Factor IX

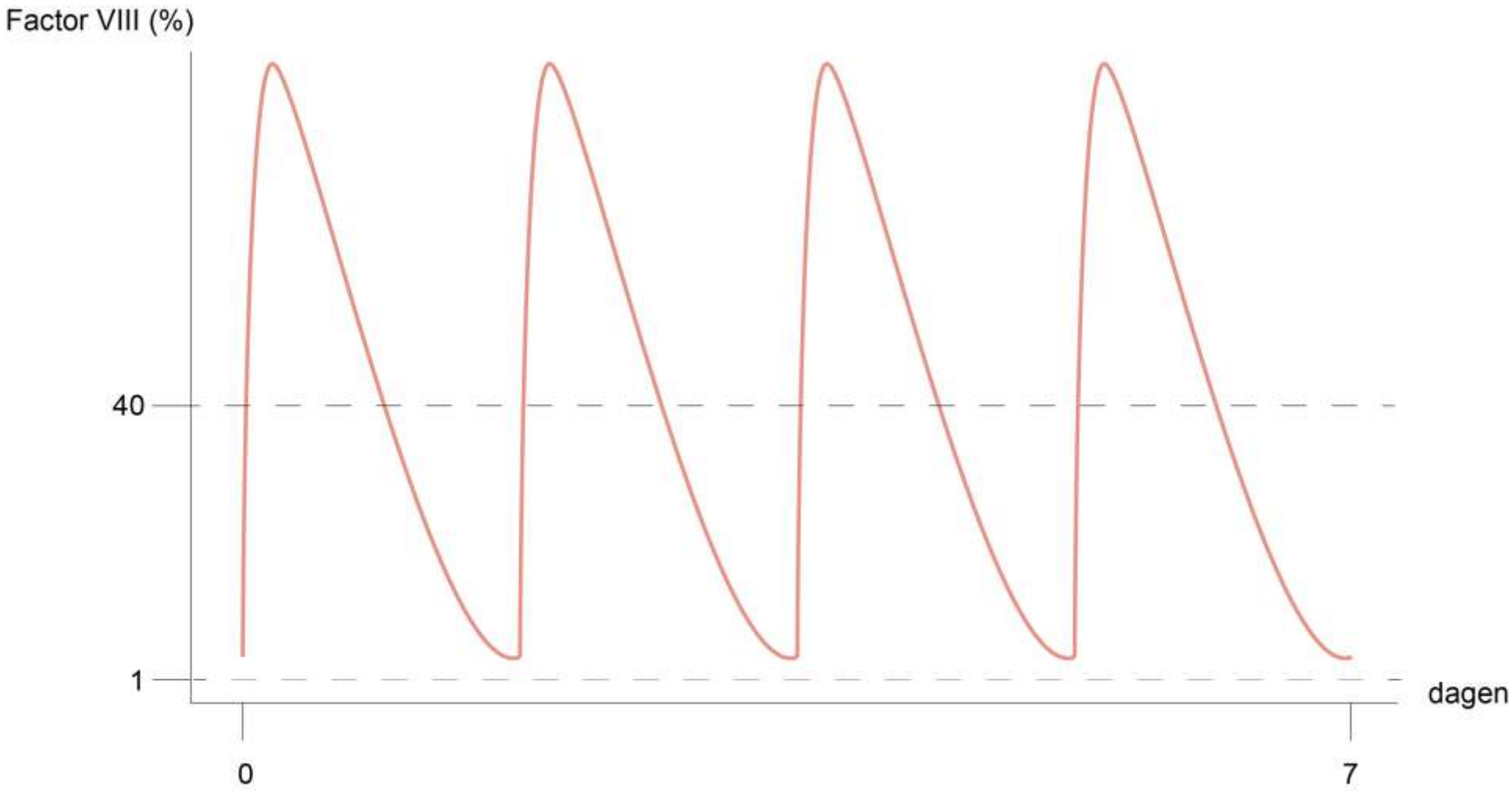


Emicizumab
(Hemlibra)

Children learn to self-infuse at a young age



Factor infusion results in peaks and troughs



Factor infusion is limited by its half-life

standard half-life concentrates

t1/2 FVIII: 12h; FIX: 18h e.g. Nuwiq, Benefix

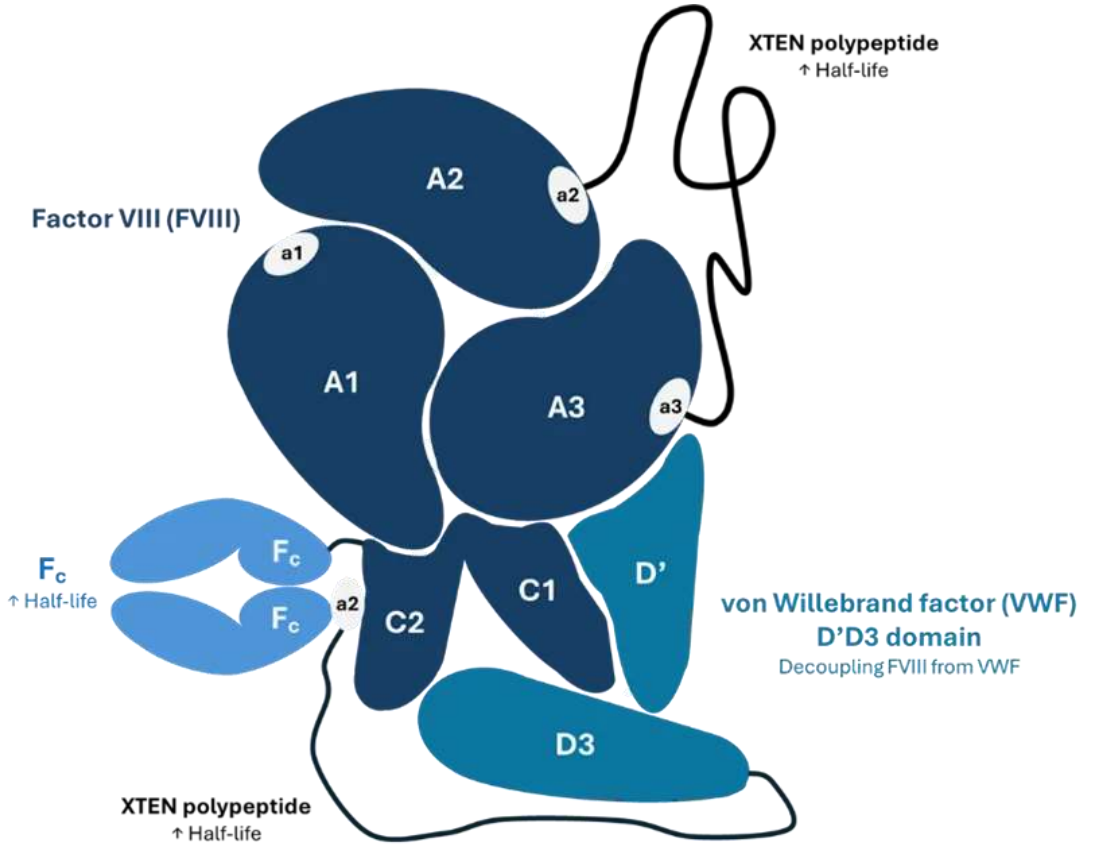
extended half-life concentrates

Fc fusion: Alprolix, Elocta

albumin fusion: Idelvion (not for FVIII)

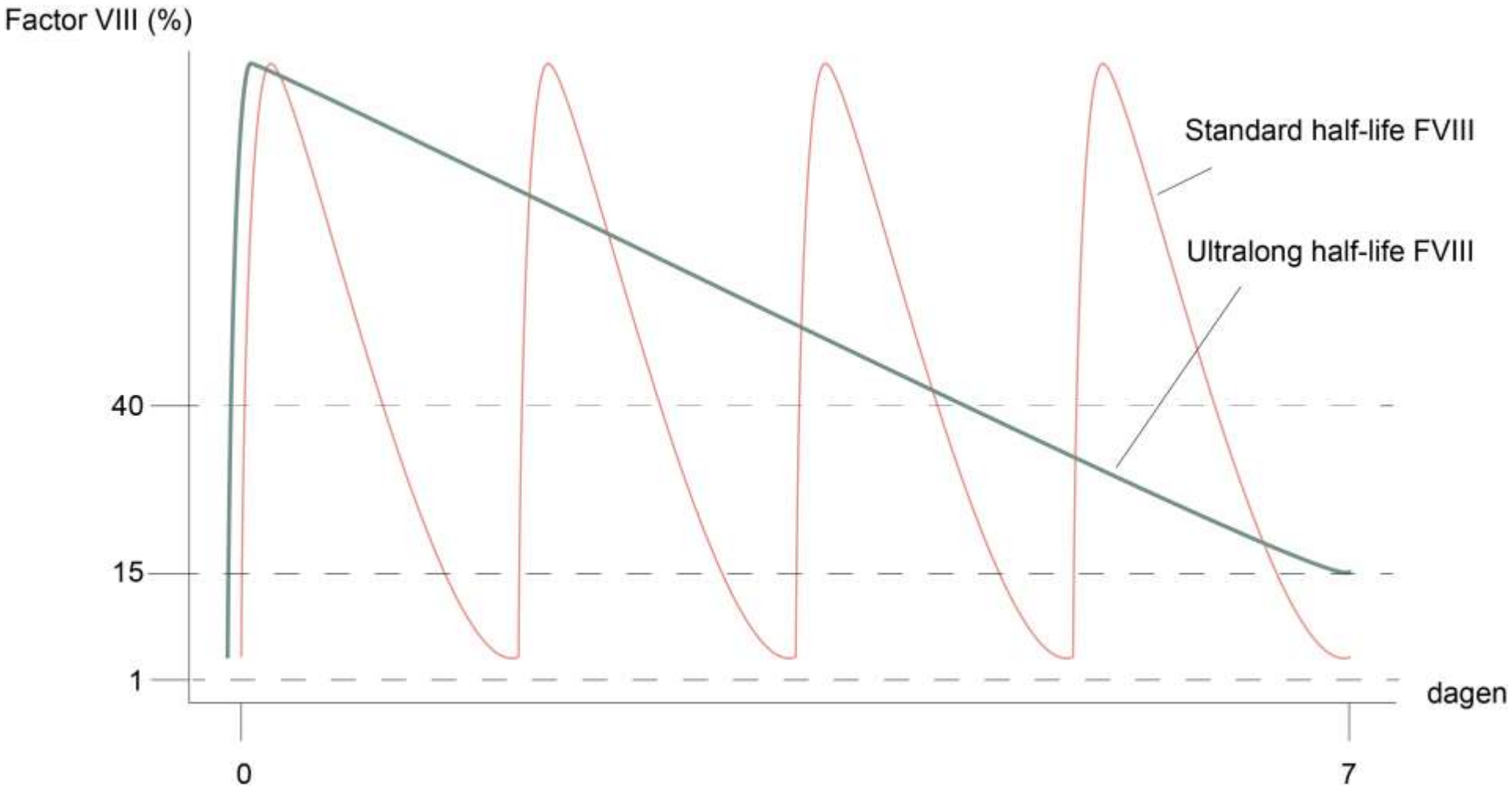
pegylation: Refixia, Adynovate

Efanesoctocog alfa (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

Factor infusion is very burdensome for patients



Factor concentrate

Intravenous

Not in case of inhibitors

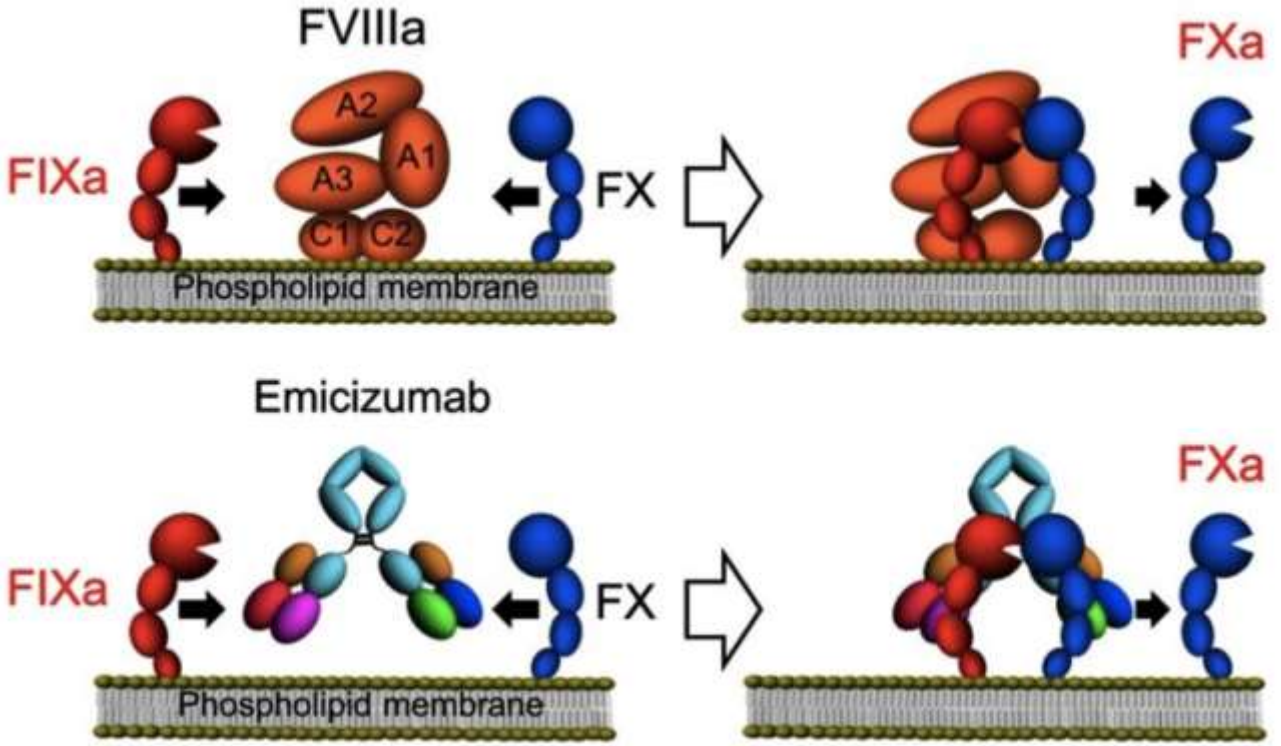
diagnosis

treatment

prophylaxis:
FVIII mimetics

what about women?

Emi mimics the function of FVIII



Yada and Nogami, J Blood Med 2019

Emi mimics the function of FVIII



Emicizumab

Few bleeds

Subcutaneous

Also for inhibitor patients

Young RPTH 2024

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



Emicizumab

Only for haemophilia A

Insufficient protection for some activities

Young RPTH 2024

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



Emicizumab

Only for haemophilia A

Insufficient protection for some activities

No FEIBA because of potential TMA

Young RPTH 2024

Standard coagulation assays cannot be used



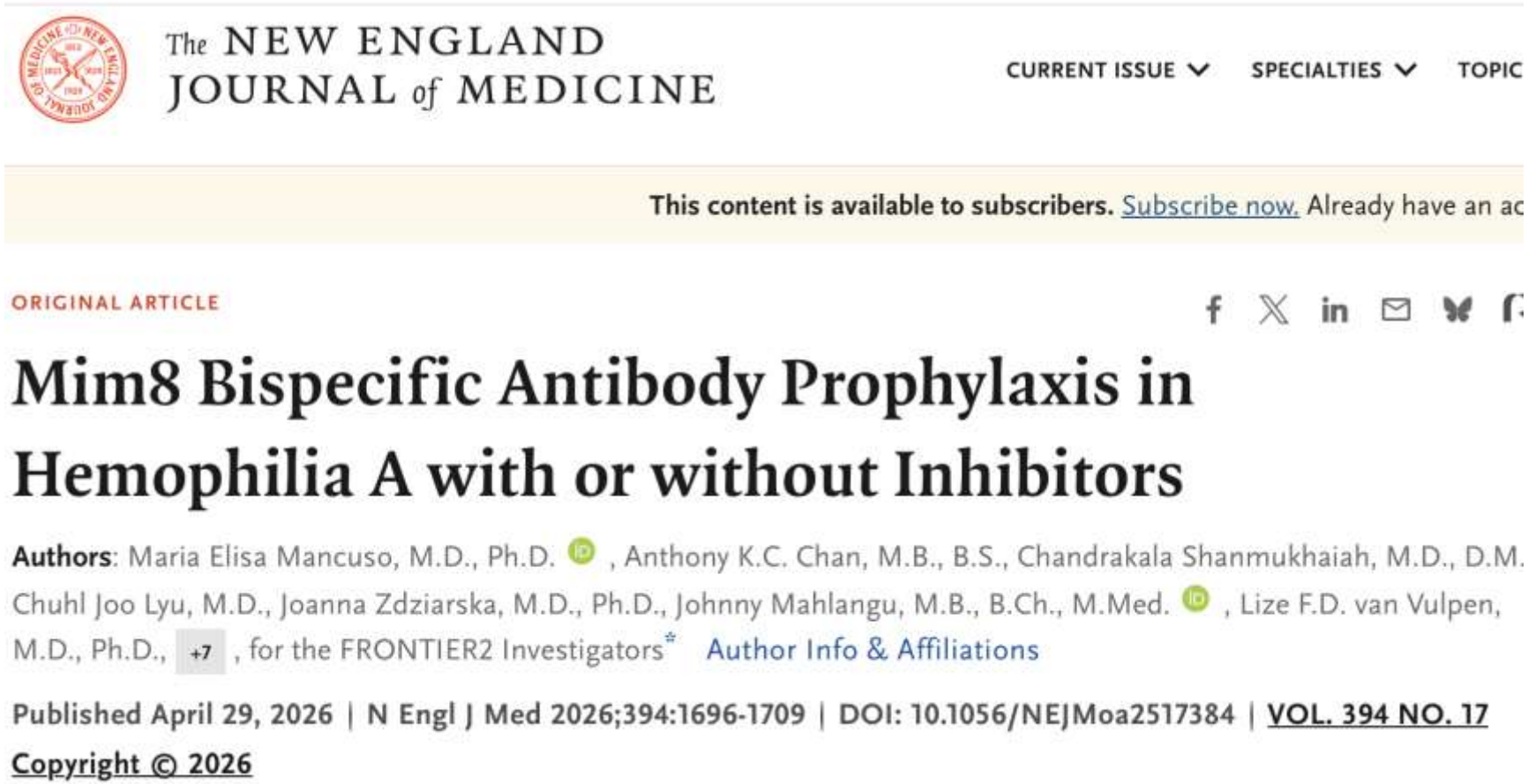
Emicizumab

Shortened aPTT, but only around 15% FVIII-like activity

Chromogenic assay (bovine) > one-stage assay

Young RPTH 2024

New mimetics are coming: mim8 and NXT-007



The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPIC

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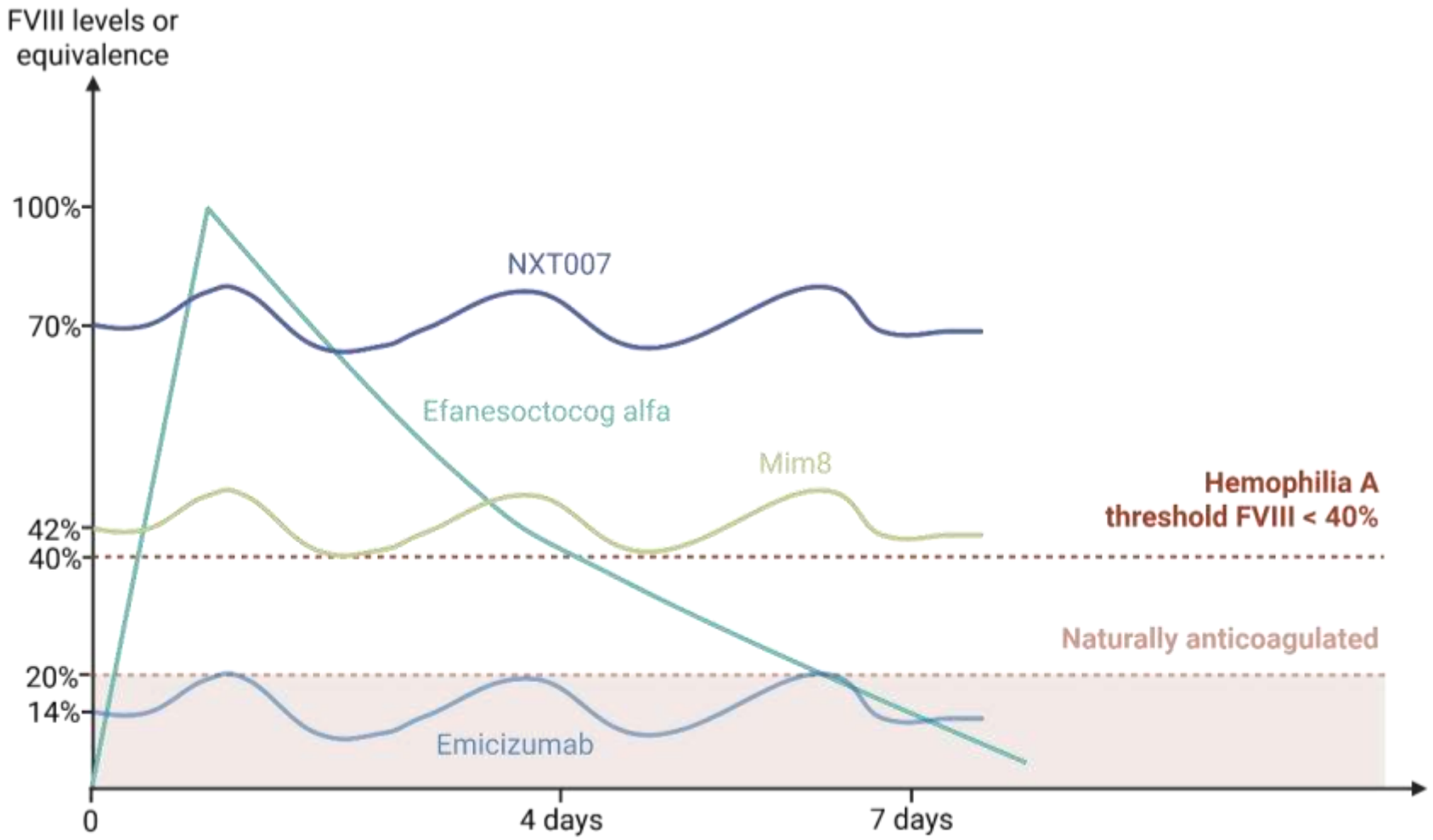
Mim8 Bispecific Antibody Prophylaxis in Hemophilia A with or without Inhibitors

Authors: Maria Elisa Mancuso, M.D., Ph.D., Anthony K.C. Chan, M.B., B.S., Chandrakala Shanmukhaiah, M.D., D.M. Chuhl Joo Lyu, M.D., Joanna Zdziarska, M.D., Ph.D., Johnny Mahlangu, M.B., B.Ch., M.Med., Lize F.D. van Vulpen, M.D., Ph.D., +7, for the FRONTIER2 Investigators* Author Info & Affiliations

Published April 29, 2026 | N Engl J Med 2026;394:1696-1709 | DOI: 10.1056/NEJMoa2517384 | VOL. 394 NO. 17

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Normalisation of haemostasis is within reach



Erard RPTH 2026 under review

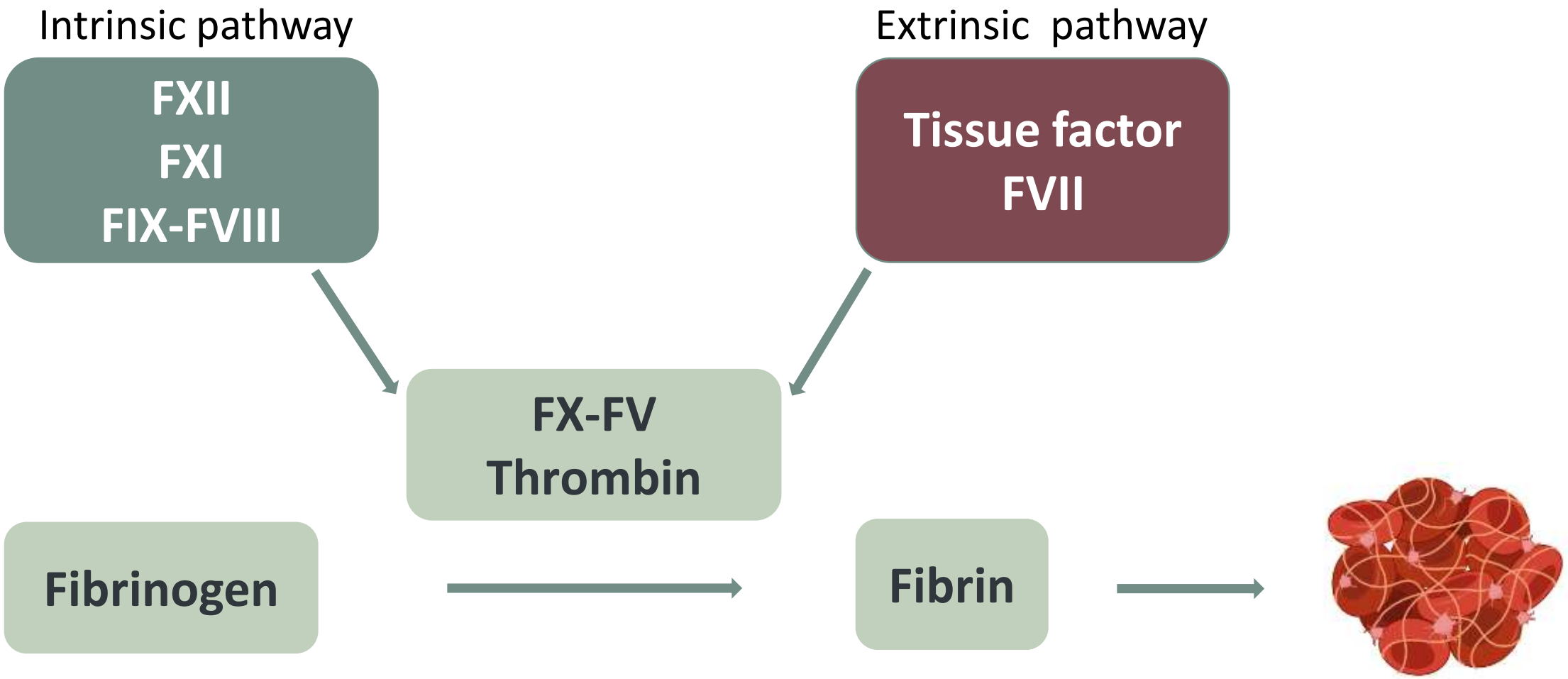
diagnosis

treatment

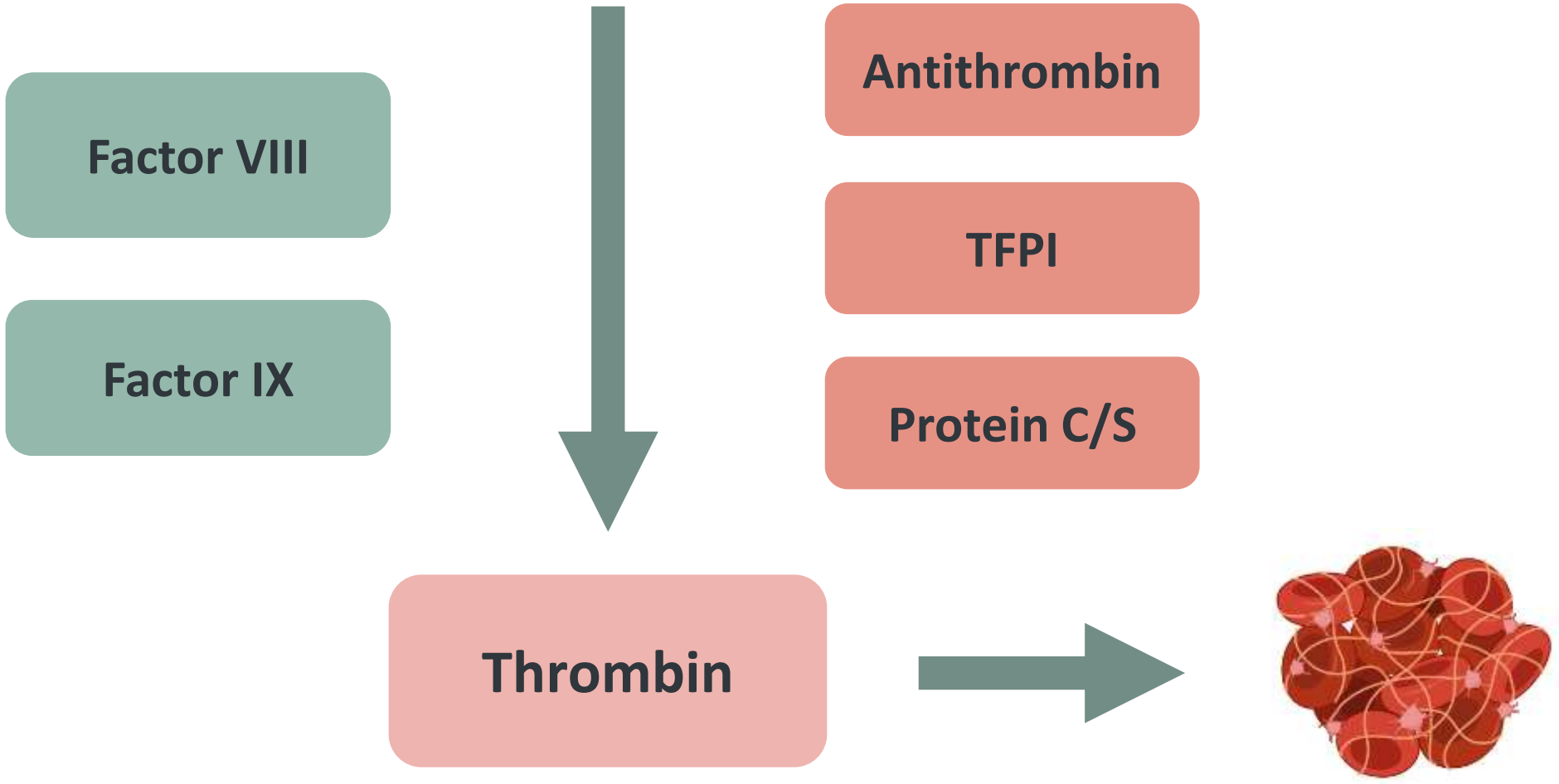
prophylaxis:
rebalancing agents

what about women?

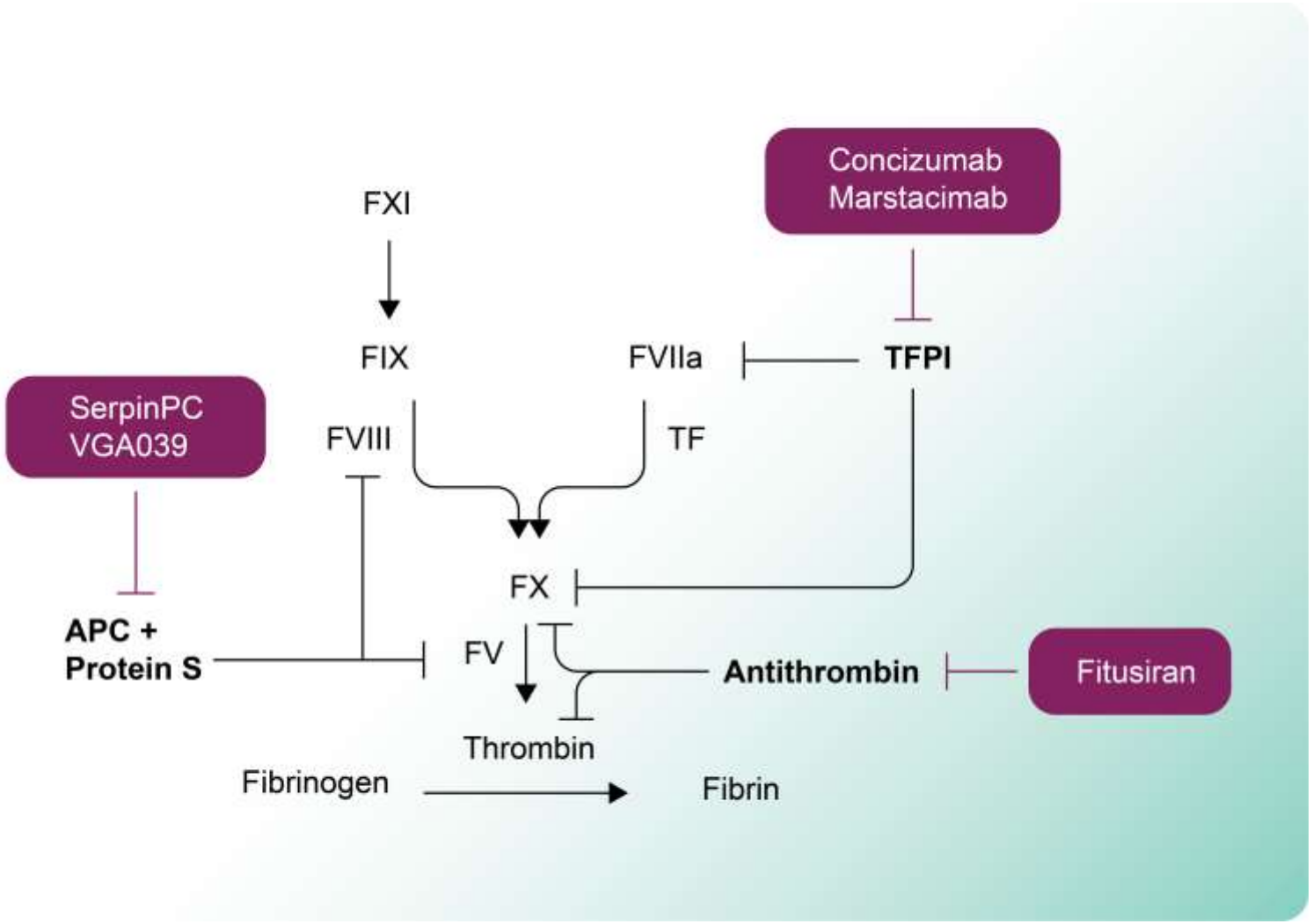
FVIII or FIX deficiency reduces clot formation



Thrombin is the key player in coagulation



Rebalancing agents target the natural anticoagulants



Van Thillo and Hermans Haematologica 2025



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CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE

Phase 3 Trial of Concizumab in Hemophilia with Inhibitors

Authors: Tadashi Matsushita, M.D., Ph.D. , Amy Shapiro, M.D., Aby Abraham, M.D., Giancarlo Castaman, M.D., Katarina Cepo, M.D., Roseline d'Oiron, M.D., + Investigators* Author Info & Affiliations

Published August 30, 2023 | N Engl J Med 2023;389:783-794 | DOI: 10.1056/N

THE LANCET Haematology

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ARTICLES · Volume 10, Issue 5, E322-E332, May 2023 Download Full Issue

Fitusiran prophylaxis in people with severe haemophilia A or haemophilia B without inhibitors (ATLAS-A/B): a multicentre, open-label, randomised, phase 3 trial

Prof Alok Srivastava, MD [a,b] · Prof Savita Rangarajan, MD [c,d] · Prof Kaan Kavakli, MD [e] · Robert Klamroth, MD [f] · Prof Gili Kenet, MD [g] · Liane Khoo, MD PhD [h] · et al. Show more



blood

ISSUES FIRST EDITION ABSTRACTS COLLECTIONS AUTH



CLINICAL TRIALS AND OBSERVATIONS | OCTOBER 2, 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 S. Acharya, Johnny Mahlangu, Victor Jiménez-Yuste, Nirmalkumar Choraria, Renchi Yang, Chi-kong Li, Murtadha Al-Khabori, Yasser Wali, Javier Morales Adrián, Young-Shil Park, O. Bülent Zülfikar, John Teeter on behalf of the BASIS Investigators

Risk for clots!

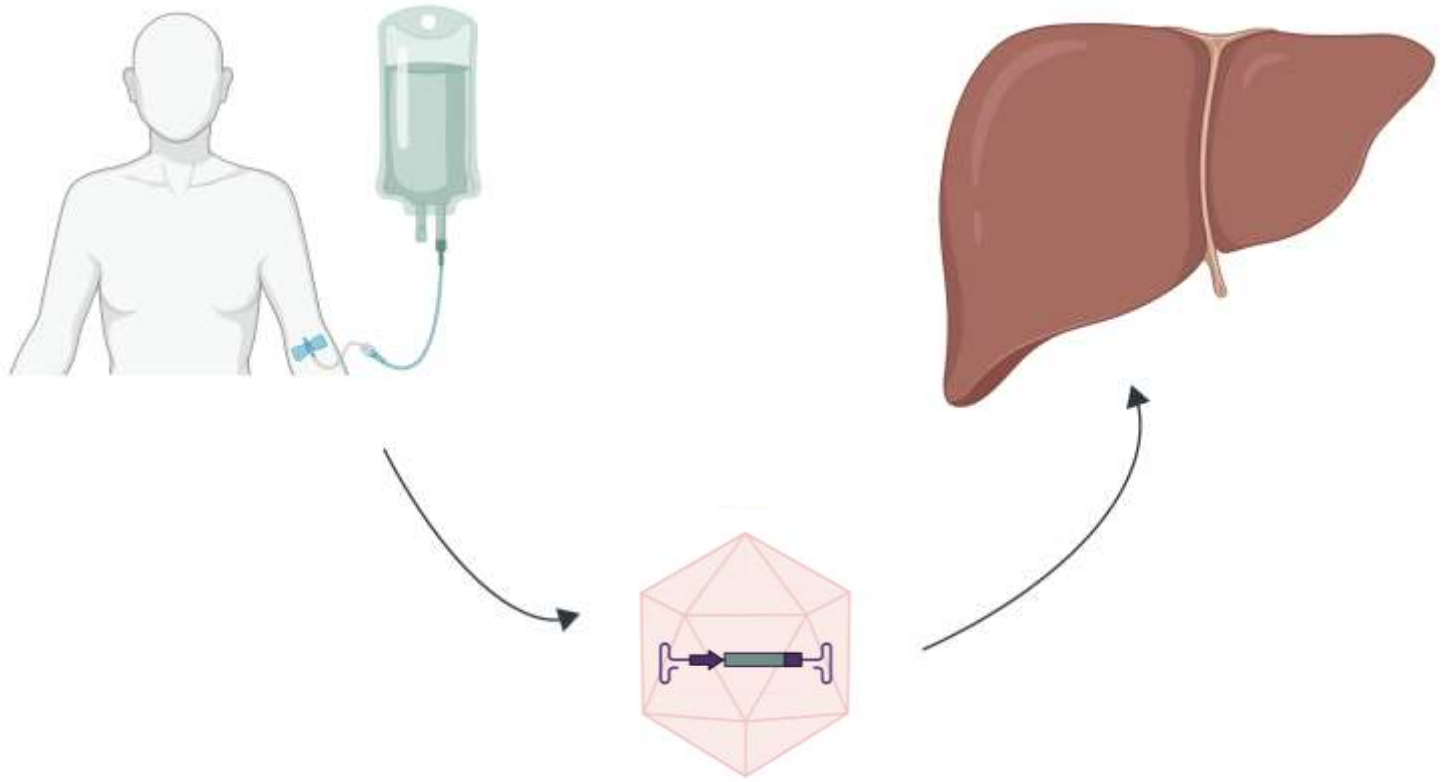
diagnosis

treatment

prophylaxis:
gene therapy

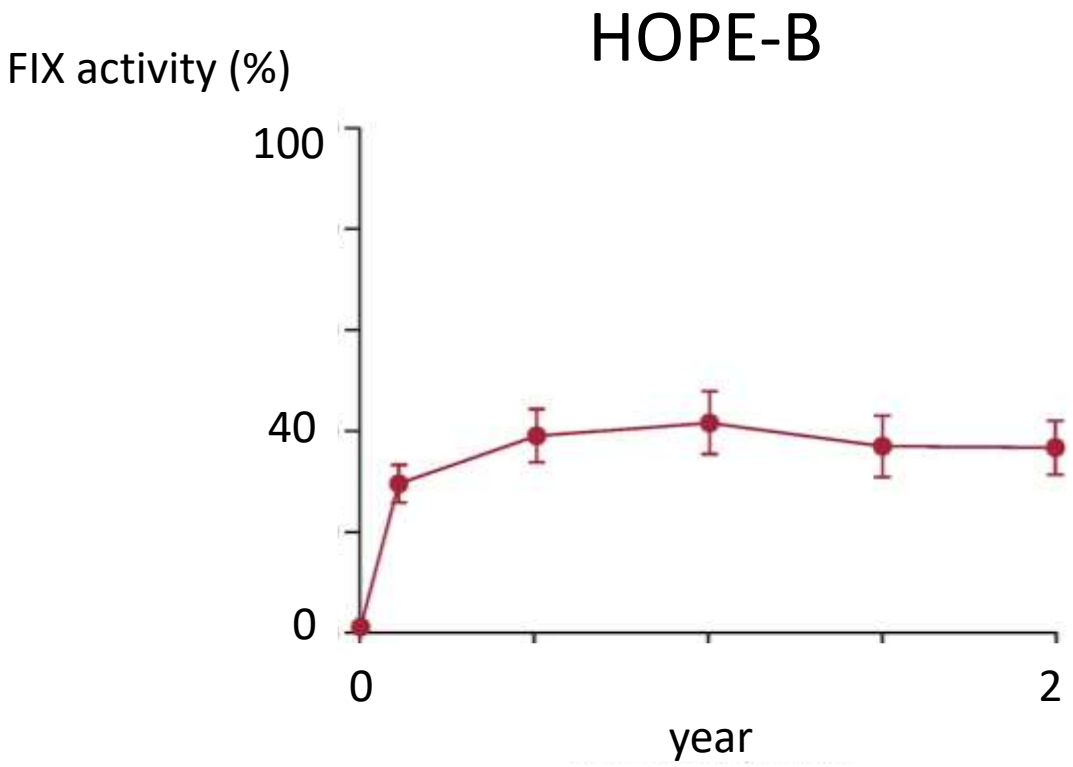
what about women?

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



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

Gene therapy has a durable effect in HB



Coppens et al. Lancet Haematol 2024

Reimbursement of Hemgenix in Belgium is anticipated



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ORIGINAL ARTICLE

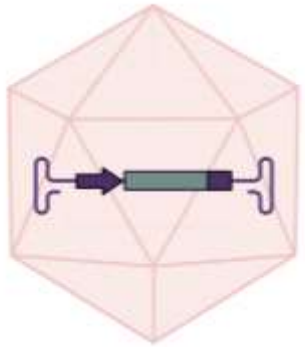
Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B

Authors: Steven W. Pipe, M.D., Frank W.G. Leebeek, M.D., Ph.D., Michael Recht, M.D., Ph.D., Nigel S. Key, M.B., Ch.B., Giancarlo Castaman, M.D., Wolfgang Miesbach, M.D., Susan Lattimore, R.N., +30, and Paul E. Monahan, M.D. Author Info & Affiliations

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



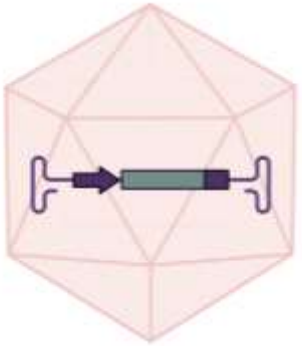
Gene therapy

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 haemophilia A?

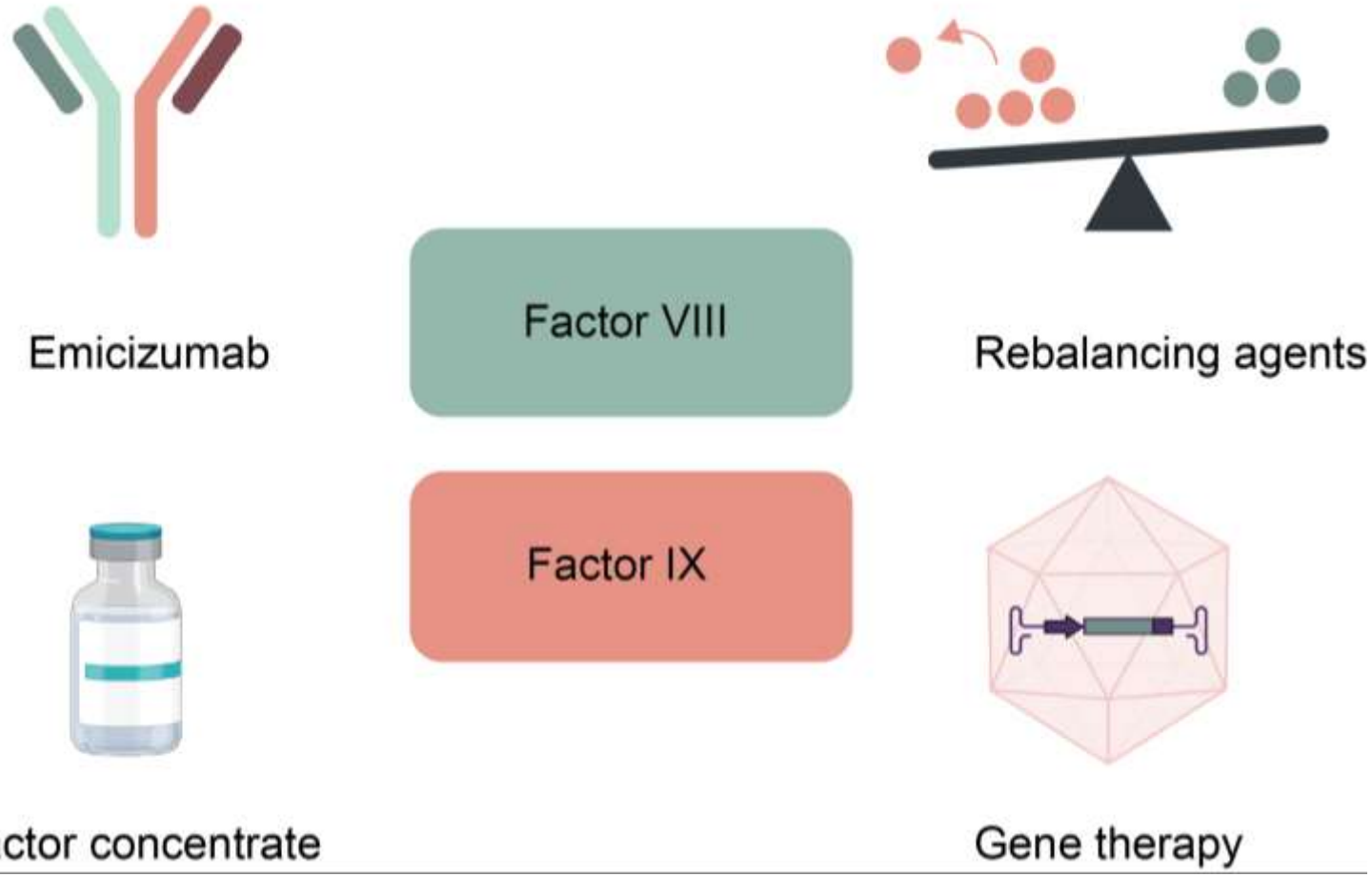
Frequent need for steroids

Not in case of inhibitors

Only in adults

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

Many good options will be available in the near future

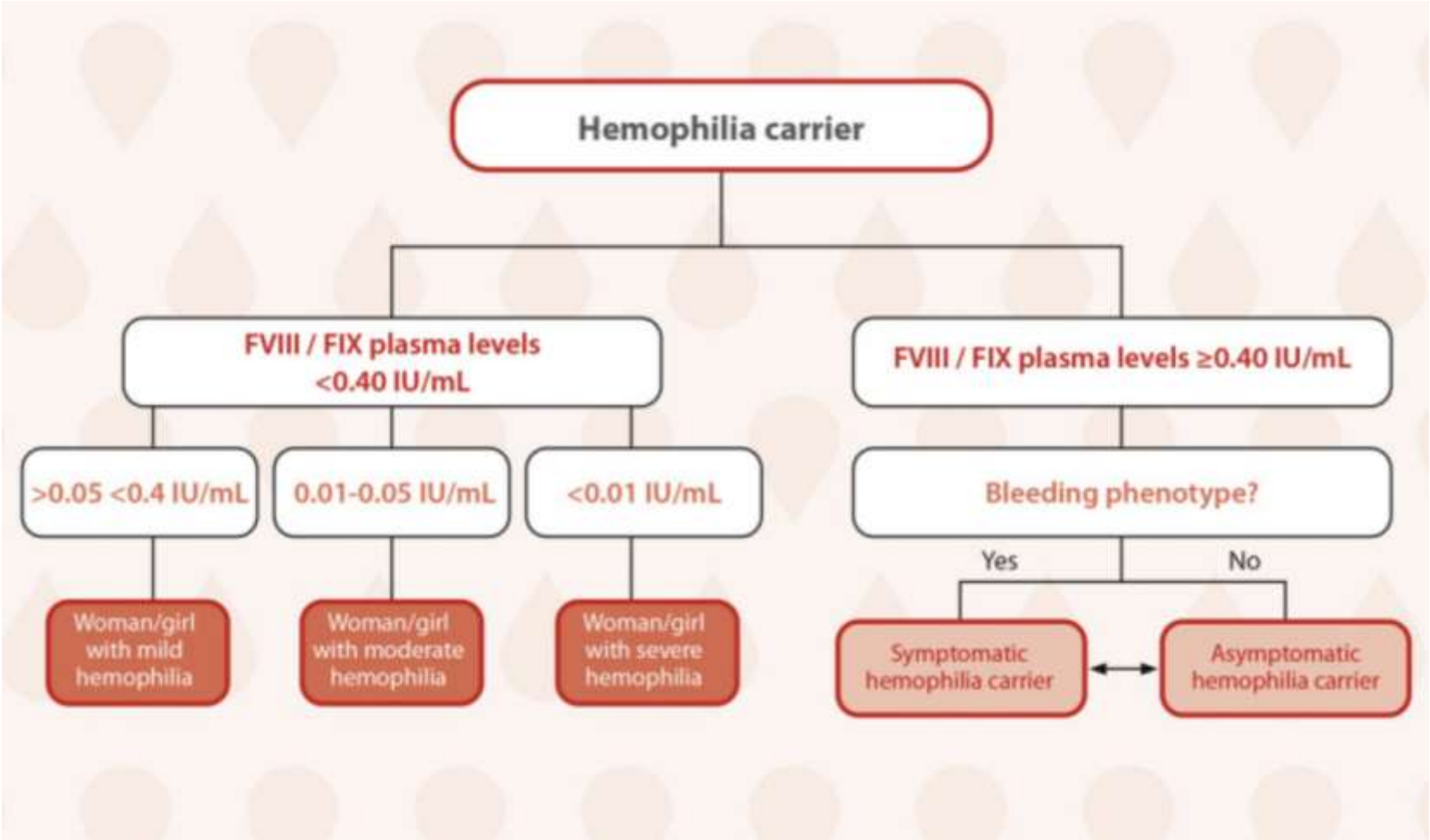


diagnosis

treatment

what about women?

1 out of 3 women has values < 40%



van Galen JTH 2021

1 out of 3 women has values < 40%

heavy menstrual bleeding

pregnancy-related complications:

measure FVIII/FIX in 3rd trim

CAVE epidural anaesthesia

many women remain undiagnosed!

genetic counseling before pregnancy (option for PGT)

Check carrier status in all female relatives

normal FVIII does not exclude carriership

genetic confirmation is needed

Case 1

male patient with 15% FVIII, 75 years, no inhibitor
history of hep C, total hip prosthesis, recent prostatectomy

falls on the head, headache
brought to ER by PIT

What do you do?

Case 1

urgent administration of FVIII before CT scan

weight 70 kg, desired FVIII level 100%

(100 – 15%)x70kg/2 = 2975 => 3000 IU FVIII

measure peak level after 15-30 min, inform your clinical biologist

plan subsequent doses depending on the half-life of the product

CT: subarachnoidal haemorrhage, occipital fracture

Case 2

18y old male from Syria
history of mucocutaneous bleeding and bleeding after tooth extr
no family history

aPTT prolonged
FVIII 2.2%

Diagnosis?

Case 2

VWF:Ag < 0.5%

VWF:GPIb < 0.3%

=> type 3 von Willebrand

consider prophylaxis with VWF/FVIII concentrate

Case 3

23y old female

consults for heavy menstrual bleeding

no prior surgery, regular epistaxis

father has moderate haemophilia A

aPTT prolonged; FVIII 19%, normal VWF: mild haemophilia

Treatment?

Case 3

1/ trial with Exacyl 1g 3-4 daily during periods

2/ plan DDAVP trial
use DDAVP in case of insufficient response to Exacyl and good response of FVIII in the DDAVP trial

3/ correct iron deficiency if present

Case 4

42y old male with 12% FVIII (85 kg)

knee trauma while playing football

self-administers 2000 IU EHL FVIII on day 1 and 2
without much effect

comes to the ER on day 5 for continued pain, minimal swelling

What do you do?

Case 4

ultrasound of the knee on the ER

→ haemarthrosis

administer 4000 IU of FVIII, ice, compression

plan subsequent doses with check after 3-4 days

Case 5

68y old male with moderate haemophilia B (1.4% FIX)

prophylaxis with rFIX-albumin 3500 IU q2w

prior to prophy multiple bleeds, chronic Hep C

consultation for TIA

known afib, MRI negative

what to do? nothing, DOAC (reduced), LAA closure

Case 5

we opted for no anticoagulation

< 20% natural antico (comparable to INR 2-3)

“small” event

carotid ultrasound showed atherosclerosis

→ focus on CV risk factors

diagnosis	also in adult patients
treatment	treating a bleed is urgent
what about women?	do not forget about women




sky
PINARELLO

quentin.vanthillo@uzleuven.be

Bloedings- en Vaatziekten

References

Chowdary. Haemophilia. *Lancet* 2025

Hermans and Lambert. How I Identify and Diagnose Carriers of Hemophilia and Women and Girls with Hemophilia. *Blood* 2026

Srivastava WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia* 2020