V. Final CH

# Treatment and Access for All Bleeding Disorders

*EHC Leadership Conference*

**Professor Cedric HERMANS, MD, PhD, FRCP (Lon, Edin)**

**Division of Haematology**

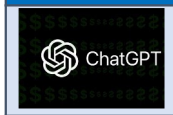
**Cliniques universitaires Saint-Luc - Brussels**

M-ES-00009150

Desirable treatment(s) and standards of care for all bleeding disorders within the next 5 years

What treatment and care should be available to patients and why ?

# Disclosures – Cedric Hermans

| | |
|---|---|
| **Shareholder** | No relevant conflicts of interest to disclose |
| **Grant / Research Support** | Pfizer, Bayer, Shire |
| **Consultant** | Pfizer, Bayer, Sanofi, CAF-DCF, CSL Behring, LFB, Novo Nordisk, Octapharma, Roche, Takeda, Sobi, Biomarin, FreeLine |
| **Employee** | No relevant conflicts of interest to disclose |
| **Paid Instructor** | No relevant conflicts of interest to disclose |
| **Speaker Bureau** | Pfizer, Bayer, Sanofi, CAF-DCF, CSL Behring, Kedrion, LFB, Novo Nordisk, Octapharma, Roche, Takeda, Sobi |
| **Other** | Editor-in-Chief Haemophilia Journal, Medical Member Board WFH |
|  | Not used |
| **Carbon Foot-Print** | Public transports |

# Inherited bleeding diseases

| | | |
|---|---|---|
| Hemophilia A/B | Von Willebrand Disease<br>Low VWF | Factor VII<br>Factor X deficiency<br>Factor XI deficiency |
| Fibrinogen (Fg) deficiency | Factor V deficiency | Factor XIII deficiency |
| Platelet dysfunction | Collagen vascular diseases | Osler Rendu Disease |

Severity, bleeding phenotype, inhibitor (if applicable), treatment options, …

# Treatment options for inherited bleeding diseases

## Clotting factor deficiency (FI to FXIII + VWF)

- Replacement (IV)
  - Concentrates (not all)
  - Fresh Frozen Plasma
- Mimicking agent (FVIII) (SC)
- Rebalancing agent (SC)
- Endogenous production (FVIII and FIX) (Gene Therapy)

## Platelet dysfunction

- Replacement by platelets transfusion
- Non-specific haemostatic agents
  - Tranexamic
  - DDAVP
- Bypassing agents (rFVIIa)

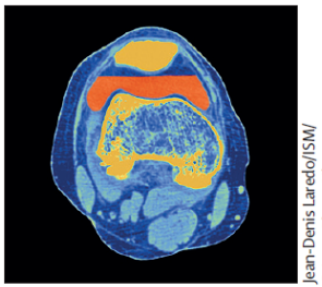
## Vascular diseases (Osler Rendu)

- Red Cells Transfusions
- Iron
- Anti-Angiogenic agents..

# Hemophilia

# Haemophilia—unparalleled progress but inadequate access

Haemophilia is an inherited bleeding disease estimated to affect 818 928 people worldwide in 2021. The condition can be life-threatening if an external bleed cannot be controlled or when there is an internal bleed to a vital organ. Internal bleeding around joints is the most common complication for patients, which can result in best treatment option. Longer term results are needed to shed light into the main caveats, including vector expression over time, impossibility of re-infusion, and the risk of hepatotoxicity and genotoxicity. Additionally, some patients are ineligible for these therapies because they have pre-existing anti-AVV antibodies, and trials are

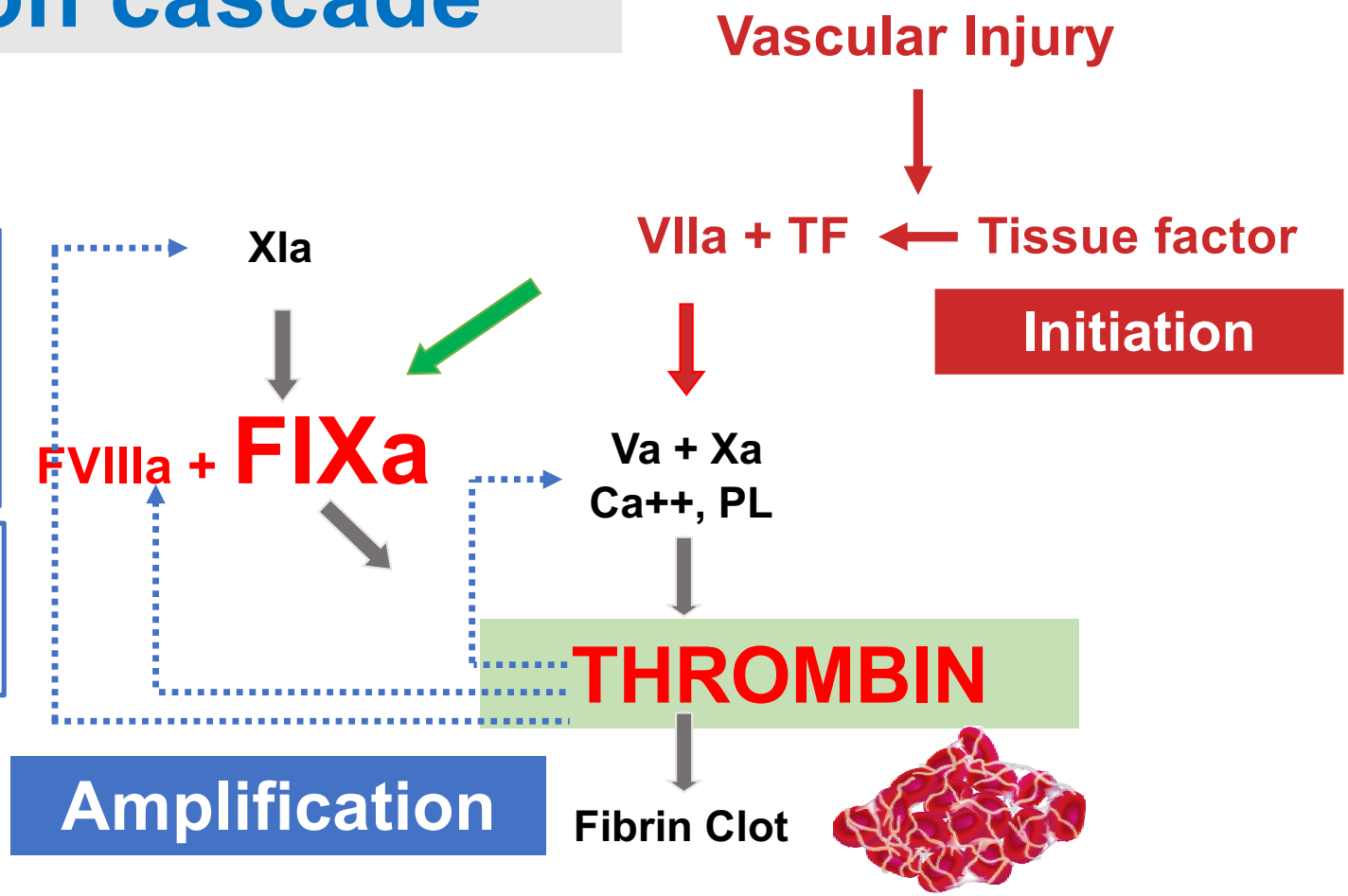


Jean-Denis Laredo/ISM/
Science Photo Library

# Revised model of the coagulation cascade

*The amplification loop is critical for thrombin generation in tissues with limited expression of tissue factor (joints and muscles…)*

*FVIII and FIX play a critical role in amplifying the generation of thrombin and in clot formation*



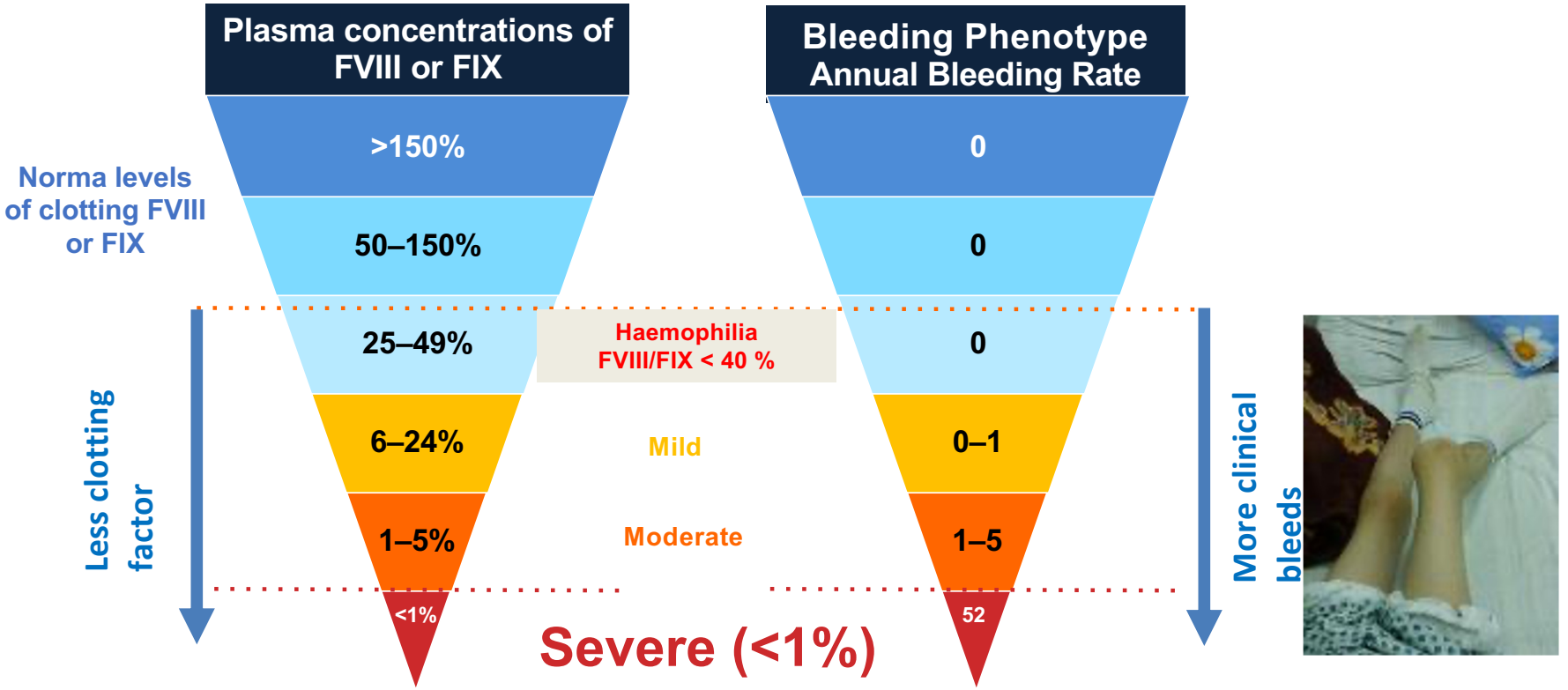

Ca: Calcium; PL: Phospholipid; TF: Tissue factor

Gailani and Broze. Science 1991

Illustrated by speaker

# Hemophilia A (FVIII) and B (FIX)

## The plasma levels of clotting FVIII or FIX determine the severity of these bleeding diseases

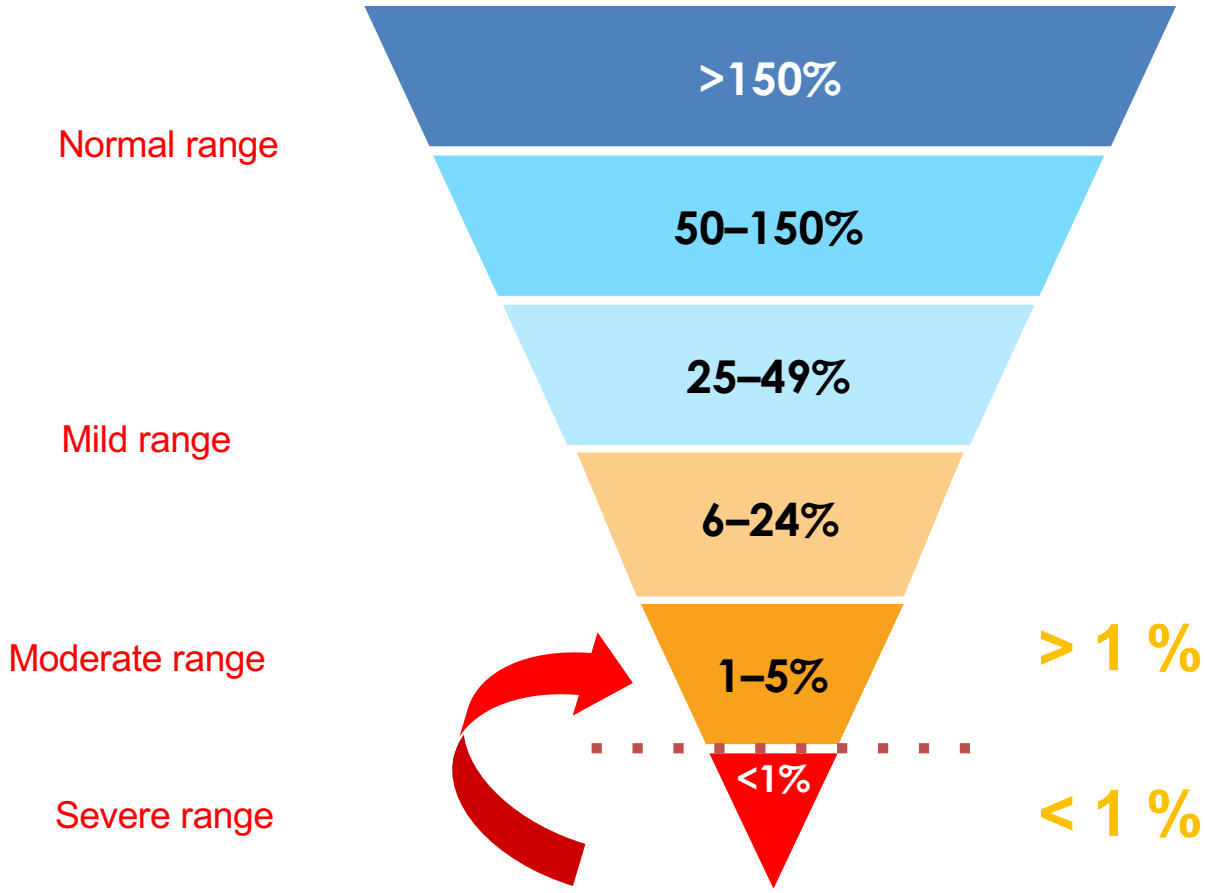





**Untreated patients with severe HA or HB (FVIII/IX < 1 %) bleed in their joints/muscles up to 50x/year**

McDaniel, National Hemophilia Foundation, 2013:1–9.

# « Past » Ambition of Prophylactic Treatment of Haemophilia




**During decades, prophylaxis has been a priority for patients with severe HA/HB**

**The objective has been to convert severe H into moderate H**

**This objective is achievable by SHL and EHL-FVIII/FIX**

McDaniel, Treatment of Hemophilia A and B, National Hemophilia Foundation, 2013:1–9.

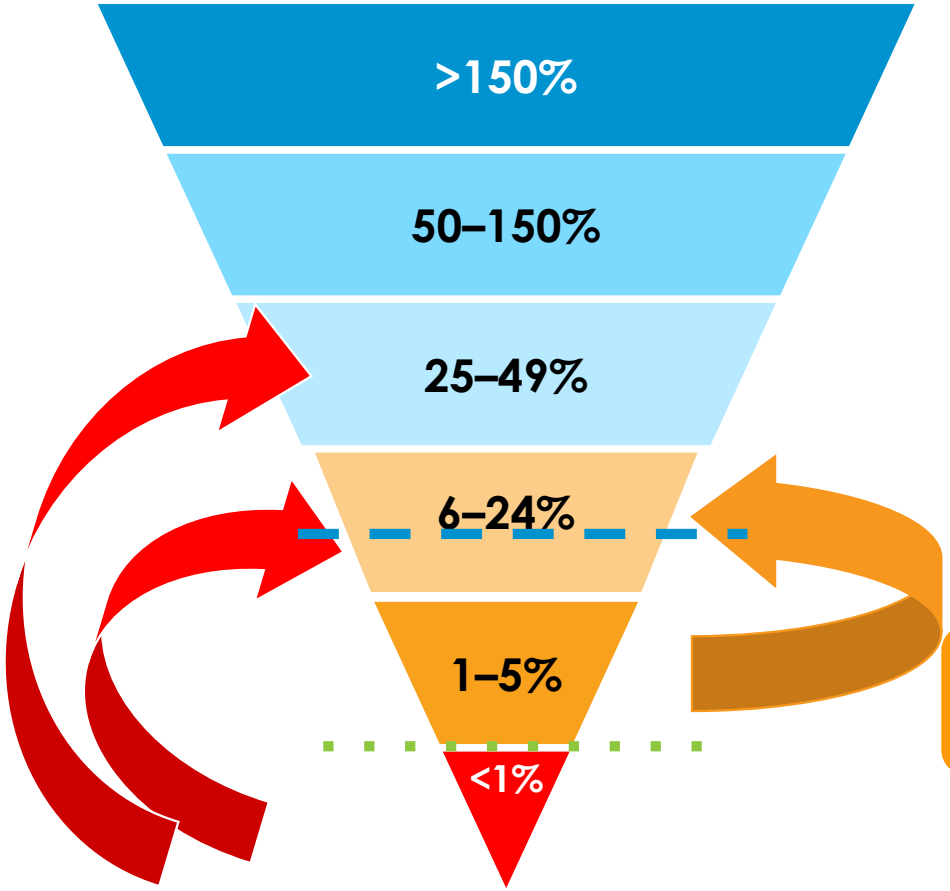
# WFH Guidelines for the Management of Hemophilia, 3rd edition

**Chapter 6: Prophylaxis – Standard of Care <u>everywhere</u>**

## Recommendation 6.1.1:

- For patients with hemophilia A or B with a severe phenotype (may include patients with moderate hemophilia), **the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent BLEEDS AT ALL TIME**

# Current ambition of prophylactic treatment of Haemophilia

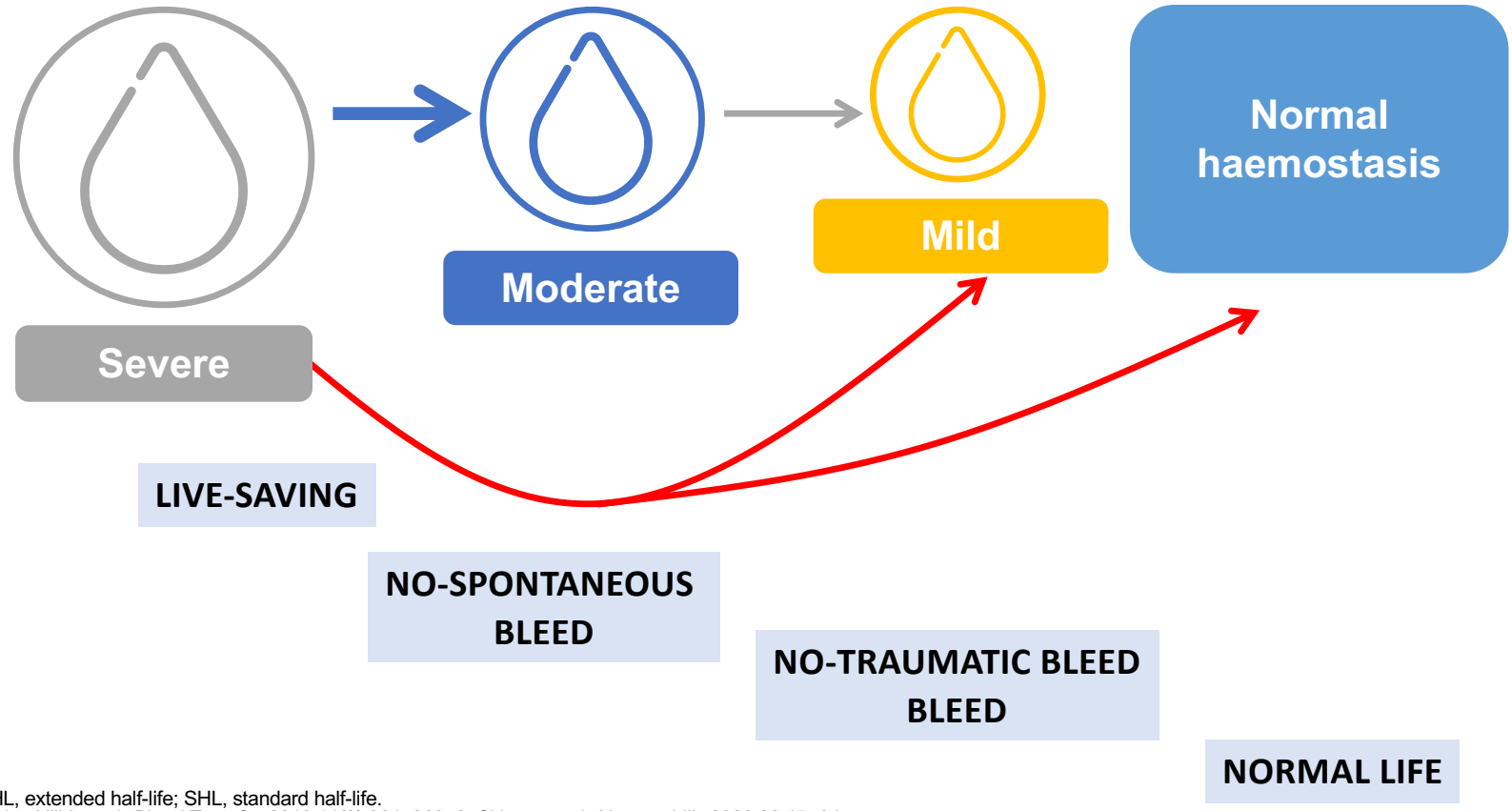



Prophylaxis is recommended for all patients with a severe bleeding phenytype including patients with moderate HA/HB

Conversion into the mild range or even normalisation of factor levels are now achievable with different treatment options

McDaniel, Treatment of Hemophilia A and B, National Hemophilia Foundation, 2013:1–9.

# The evolving goals of hemophilia therapies
# From saving life to normalizing life

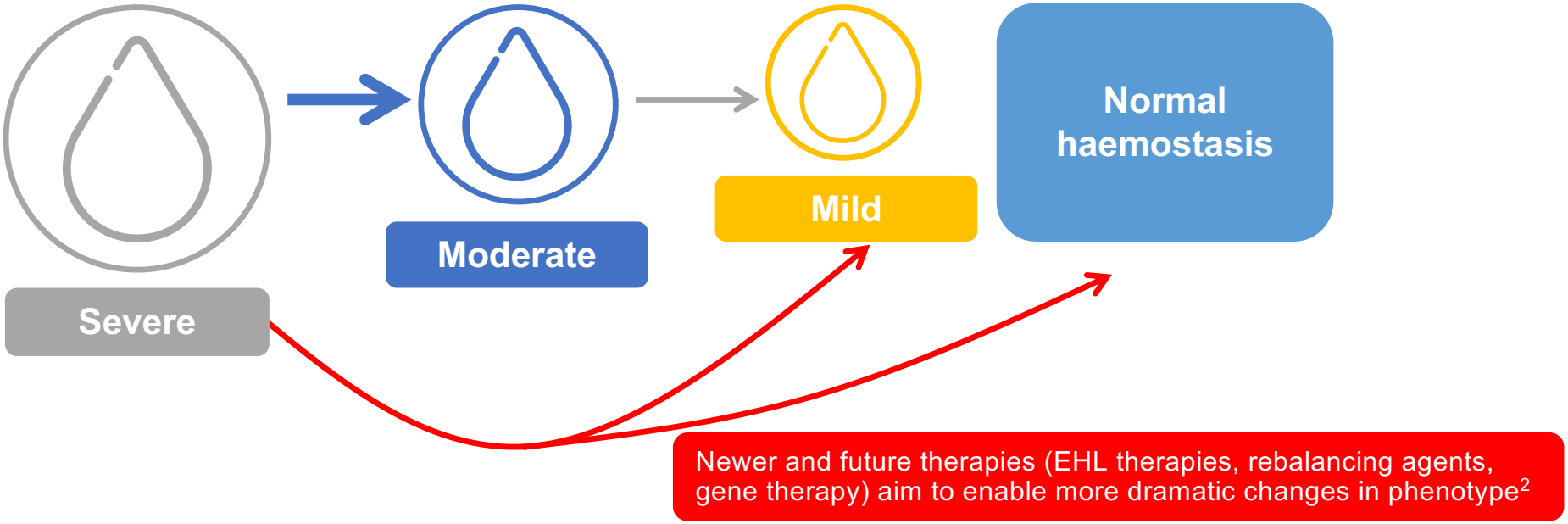



EHL, extended half-life; SHL, standard half-life.
1. den Uijl I, et al. *Blood Transfus* 2013;11(3):364−369. 2. Skinner et al. *Haemophilia* 2020;26:17−24.

# The goals of hemophilia therapies :

## Reducing or ideally abolishing the severity of bleeding phenotype[1,2]

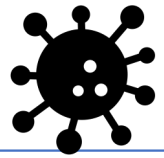
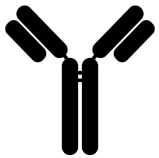
With standard half-life (SHL) **prophylaxis**, hemophilia severity can be reduced one degree (from severe to moderate)[1]




EHL, extended half-life; SHL, standard half-life.

1. den Uijl I, et al. *Blood Transfus* 2013;11(3):364−369. 2. Skinner et al. *Haemophilia* 2020;26:17−24.

# Current ambitions in Hemophilia therapy

| Goals | | In clinical practice |
|---|---|---|
| Zero joint bleeds |  | Achievable with personalized primary or secondary prophylaxis with replacement or non-replacement therapies |
| **Zero joint microbleeds** | | **Achievable today?** |
| Zero infection |  | Achievable with current plasma-derived or recombinant concentrates<br>Eradication of HCV now possible in most patients |
| Zero inhibitors |  | Currently impossible to avoid inhibitor formation in many patients<br>Currently impossible to eradicate inhibitors in many patients<br>Currently possible to avoid most bleeds in patients with INH |

HCV: Hepatitis C virus.
Speaker's own clinical opinion.

# A New Era of Expected Freedoms for Patients with Hemophilia

| TYPE OF FREEDOMS |
| --- |
| Bleed-free |
| Arthropathy-free |
| Pain-free |
| Burden-free |
| Mind-free |

Received: 26 May 2021 | Accepted: 16 June 2021
DOI: 10.1002/rth2.12567

FORUM

## Living with a "hemophilia-free mind" – The new ambition of hemophilia care?

Evelien Krumb MD | Cedric Hermans MD, FCRP (Lon, Edin), PhD

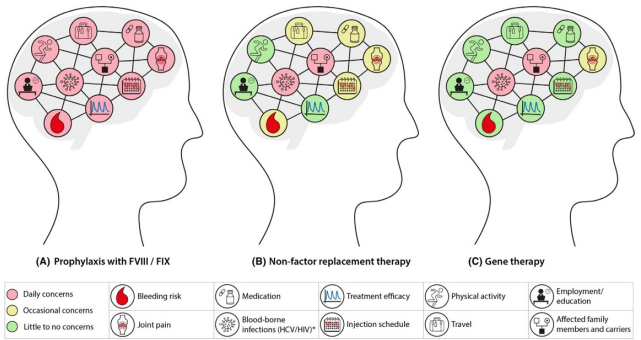



FIGURE 1 Concerns of people with moderate or severe hemophilia according to different treatment modalities. FVIII, coagulation factor VIII; FIX, coagulation factor IX. * In patients born before 1990

Krumb E and Hermans C. Res Pract Thromb Haemost 2021;5:e12567

# Treatment of haemophilia
# New ambitions

**Prevention of bleeds for all patients with a severe bleeding phenotype**

**Zero spontaneous joint bleed**
**« Bleed Free »**

**« Bleeding disease free Mind »**

**Bleed / Burden / Haemophilia « Brain » FREE**

# Current challenges

Many patients candidates for prophylaxis are NOT on prophyalxis

Few patients have ZERO joint bleeds

Access to treatment is highly heterogenous

# Treatment modalities of Hemophilia and impact on bleeds

| HA | HB |
| --- | --- |
| Severity<br>< 1 %<br>1-5 %<br>5-40 % | |
| Bleeding phenotype | |

**No treatment**
**Minimal treatment**

**Replacement therapy**

SHL-FVIII-FIX

EHL-FVIII
UL-FVIII
EHL-FIX

**Non-Replacement therapy**

FVIII bispecific Ab
Re-balancing agents
Gene therapy

**Bleeds with no treatment**

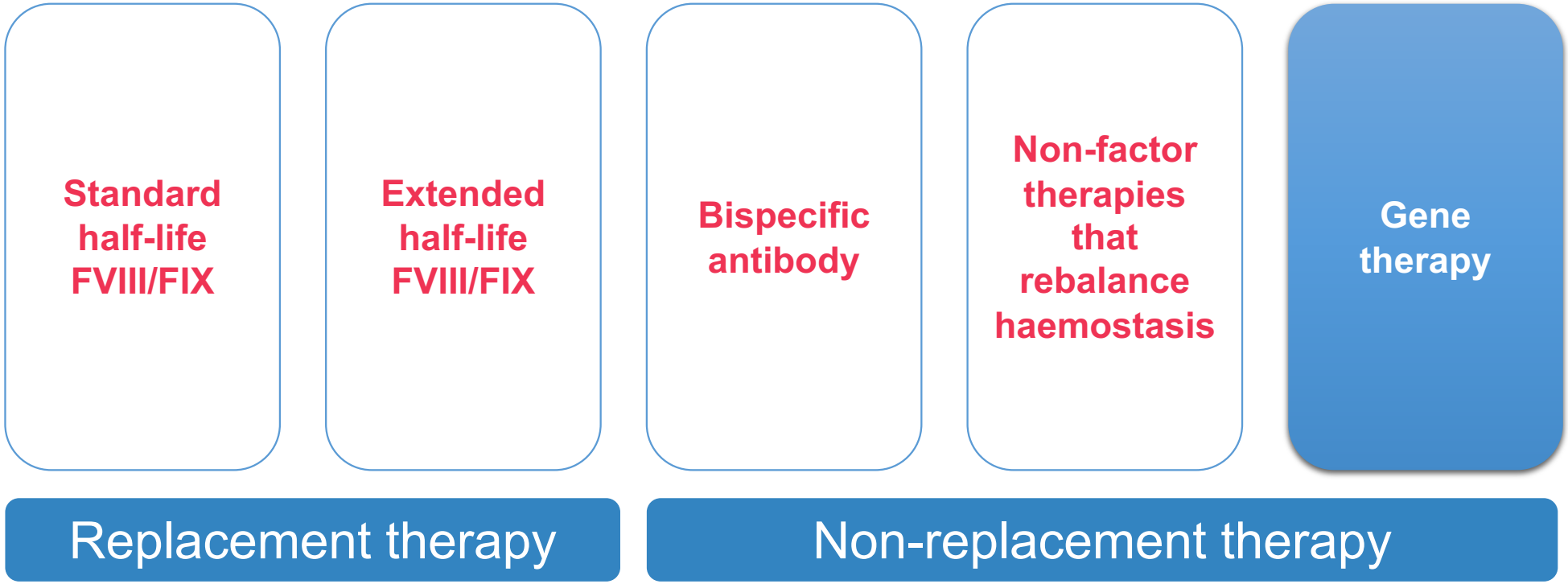
Life-threatening bleeds
High mortality
Recurrent spontaneous joint/muscle bleeds

**Bleeds under treatment**

**CLINICAL BLEEDS**
Joint – Muscle
Provoked > spontaneous
(ABR – AJBR – ASJBR)

**SUBCLINICAL BLEEDS**

# New and future treatment options for haemophilia




TFPI, tissue factor pathway inhibitor

# Haemophilia : basic principles of treatment

| | |
|---|---|
| **HA&HB (severe bleeding phenotype)** | Prophylaxis with any product available, even plasma derived.<br>There is no room/indication for episodic treatment.<br>Low-dose prophylaxis is better than on-demand |
| **HA with inhibitor** | Prophylaxis with emicizumab |
| **HB with inhibitor** | rFVIIa (ideally prophylactically)<br>Prophylaxis with rebalancing agents (not yet available) |

# The different treatment options

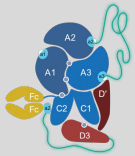
SHL rFVIII

SHL rFIX

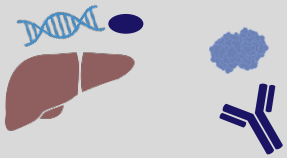
EHL FIX

EHL FVIII

rFVIIIFc-
VWF-
XTEN*

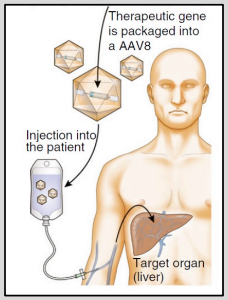



Antithrombin (siRNA)
Anti-TFPI (mAb)
Protein C-serpin



FVIIIa mimetic

Gene therapy




All patients with HA/HB and a severe bleeding phenotype should have access to one of these treatment options and be treated prophylactically without interruption

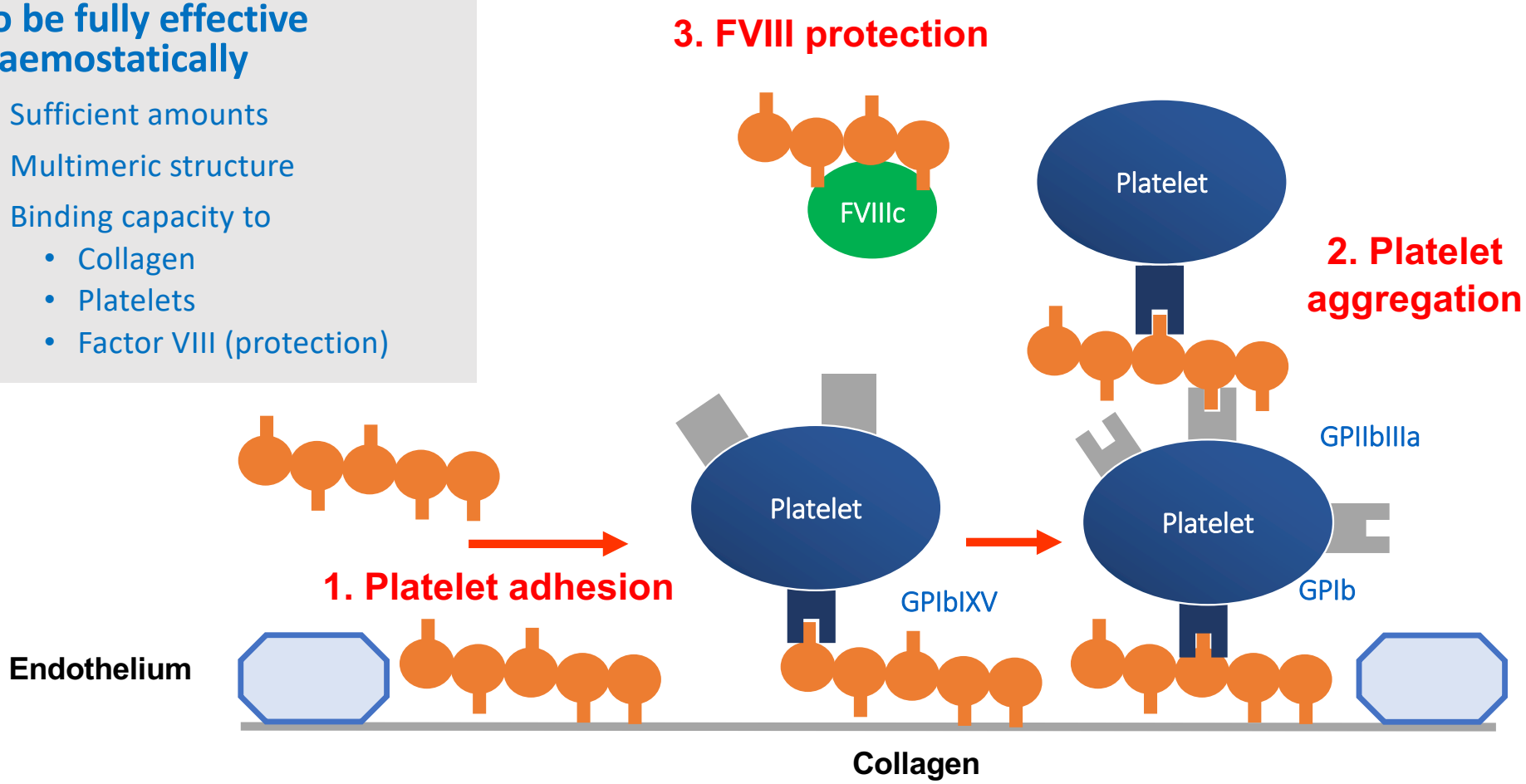
All patients with HA/HB not candidates for prophylaxis should have access to appropriate on-demand treatment in case of trauma, invasive procedure…

# Von Willebrand disease

# The multiple functions of VWF

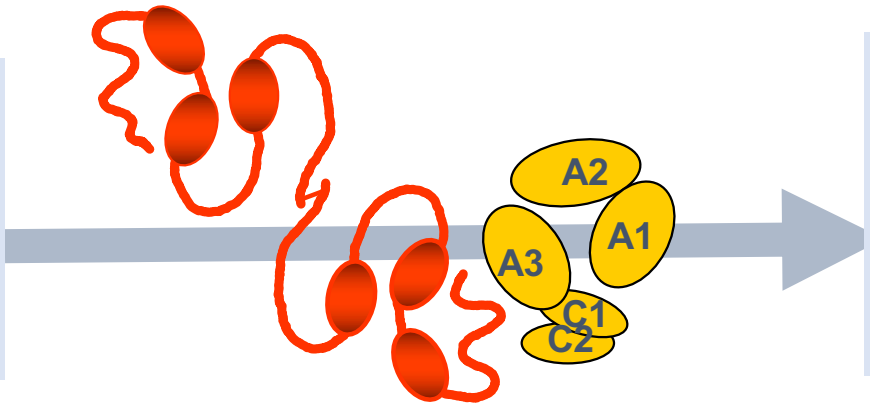
**Required properties of VWF to be fully effective haemostatically**

- Sufficient amounts
- Multimeric structure
- Binding capacity to
  - Collagen
  - Platelets
  - Factor VIII (protection)



# Pathophysiology of VWD

**Primary quantitative or qualitative defect of VWF**




**Secondary quantitative deficiency of FVIIIc not efficiently protected**

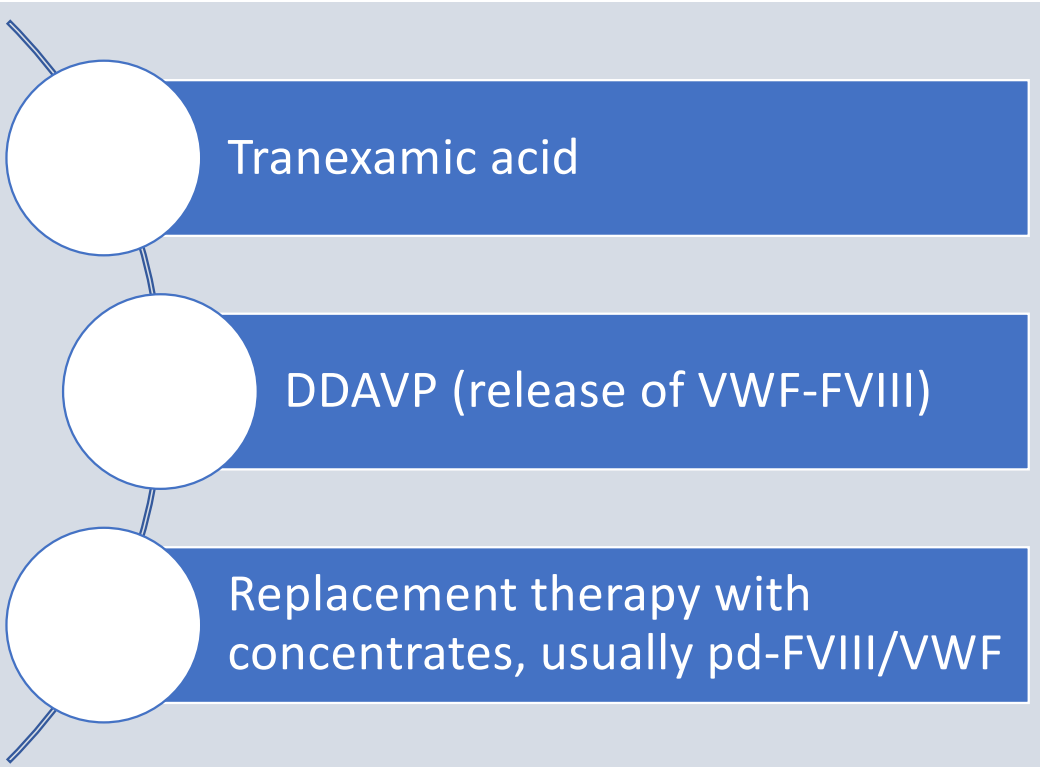
**FVIII deficiency in patients with VWD results from an ineffective protection by VWF**

**Mucosal and cutaneous bleeding symptoms (VWF defect)**

**Joint and muscle bleeds**
**Post-op bleeds**
**(FVIII deficiency)**

# Management of VWD

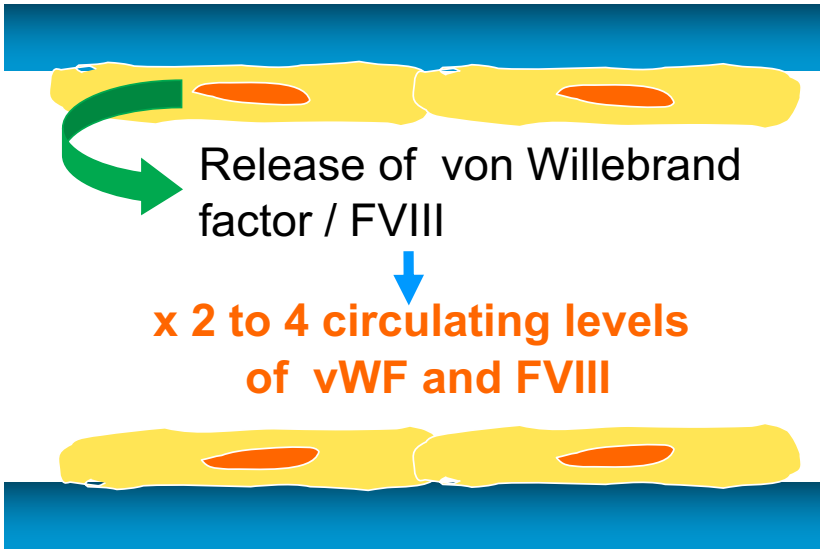
- The care burden of VWD is lower than that of hemophilia (1/10 of patients need replacement therapy)
- Replacement therapy is more complex because of the variability of the different types of VWD and of the dual factor deficiency
- The development of neutralizing anti-VWF alloantibodies is very rare in VWD
- Cure by gene therapy is much less advanced than for the hemophilias




Mannucci-P 2019 Dec 6;2019(1):590-595. doi: 10.1182/hematology.2019000368

# DESMOPRESSIN (DDAVP) – MINIRIN

DDAVP: 1-deamino-8-arginin vasopressin,




Intravenous 0.3µg/kg

Nasal Spray Octostim

- Synthetic analogue of vasopressin
- Induces a release of endothelial FVIII
- Dosage: 0.2 - 0.3 µg/kg iv (subcutaneous)
- Intra-nasal spray (Octostim®)
- Response and tolerance should be evaluated!
- For mild (sometimes moderate) haemophilia A
- Not effective in haemophilia B
- Side-effects: flush, fluid retention
- Contra-indicated in elderly patients or with hypertension

Response to DDAVP should be tested in every VWD patient

# Von Willebrand disease : general principles of treatment

| | |
|---|---|
| VWD Type 1 (2) | DDAVP (easy and cheap) (also for mild Hemophilia A)<br>Tranexamic acid |
| VWD Type 2 | (FVIII)-VWF concentrates<br>It is important not to overload with FVIII (risk of thrombosis) |
| Severe type 2<br>VWD Type 3 | (FVIII)-VWF concentrates<br>Prophylaxis is optimal and the desirable treatment<br>It is important to start prophylaxis before joint damage |

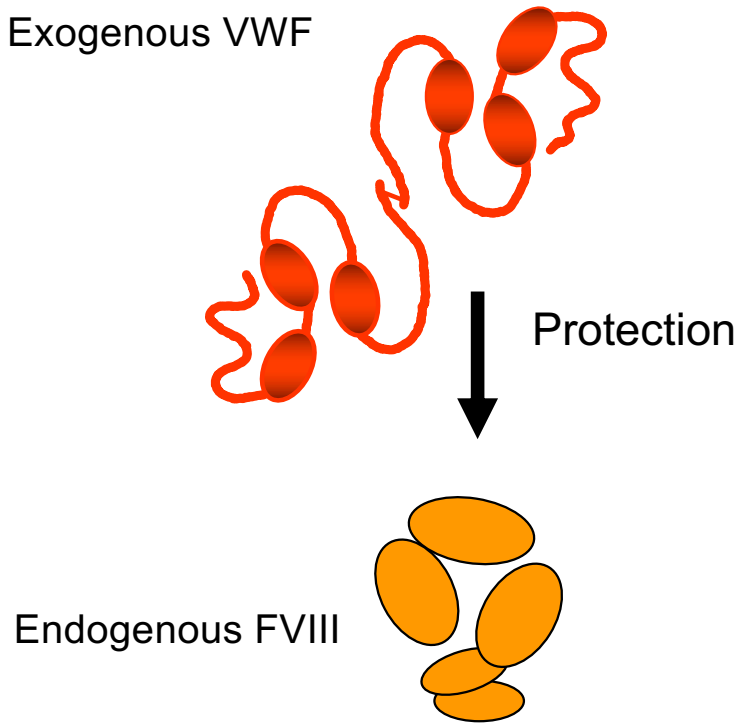
# The dual challenge of replacement therapy of VWD

- **Correct and maintain VWF:Activity in the normal range**
  - Depends on the quality of infused VWF multimers and their degradation post-infusion in smaller subunits

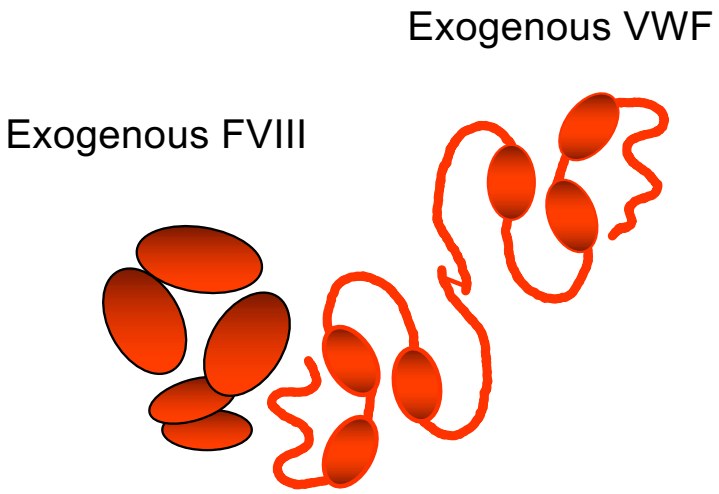
- **Correct FVIII deficiency (if present) without accumulation of FVIII (< 150-200 %)**
  - Exogenous FVIII infused adds to the endogenous FVIII normally synthesized in VWD and stabilized by VWF replacement

# Treatment of VWD

## Monotherapy (Pure exogenous VWF)




## Dual therapy (Exogenous FVIII-VWF)



# Replacement therapy options for patients with VWD

- Haemate-P (2400U VWF – 1000U FVIII – 20 ml)
- Wilate (1000U VWF – 1000U FVIII – 10 ml)
- Wilfactin (1000U VWF – 10 ml)

# Matching VWD patients'needs with treatment characteristics

| | | VWF concentrate content | | |
|---|---|---|---|---|
| **VWD patient's blood** | | **FVIII** | **VWF:Ag** | **VWF:Ac** |
| **FVIII** | Normal FVIII | NOT NEEDED<br>Will increase circulating FVIII | Will protect endogenous FVIII and increase circulating FVIII | |
| | Low FVIII | NEEDED | Will protect endogenous FVIII | |
| **VWF:Ag** | Normal VWF:Ag | | Will increase circulating VWF:Ag | |
| | Low VWF:Ag | | NEEDED | |
| **VWF:AC** | Low VWF:Ac in all patients | | | Always needed<br>Will correct endogenous VWF:Ac depending on quality of VWF multimers |

Accepted: 31 January 2018
DOI: 10.1111/hae.13451

ORIGINAL ARTICLE

WILEY Haemophilia

# Analysis of current perioperative management with Haemate® P/Humate P® in von Willebrand disease: Identifying the need for personalized treatment

H. C. A. M. Hazendonk[1] | J. M. Heijdra[1] | N. C. B. de Jager[2] | H. C. Veerman[1] | J. Boender[3] | I. van Moort[1] | R. A. A. Mathôt[2] | K. Meijer[4] | B. A. P. Laros-van Gorkom[5] | J. Eikenboom[6] | K. Fijnvandraat[7] | F. W. G. Leebeek[3] | M. H. Cnossen[1] | for the "OPTI-CLOT" and "WIN" study group*

"Although perioperative replacement therapy in patients with VWD is successful with few bleeding complications, it can be optimized as patients are currently overtreated with accumulation of FVIII as a consequence"

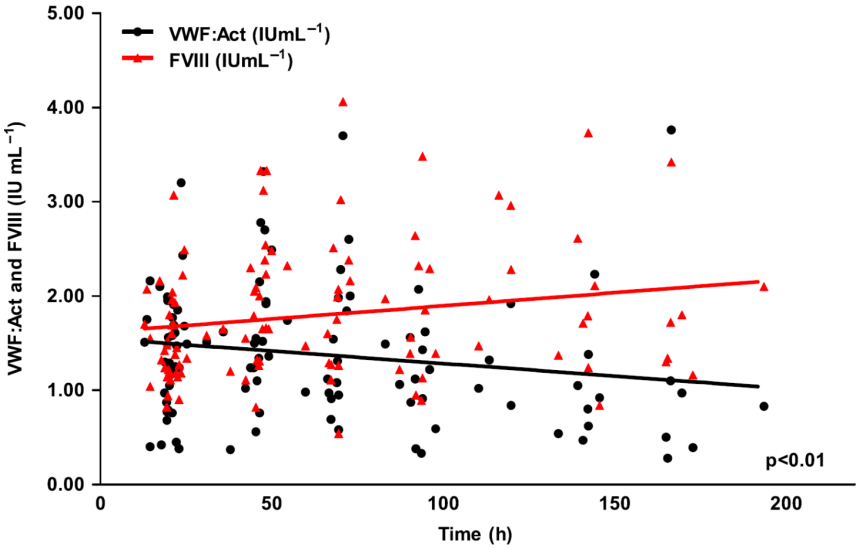



**FIGURE 3** Accumulation of FVIII after repetitive dosing of VWF/FVIII concentrate. Accumulation of FVIII was present after repetitive dosing of VWF/FVIII concentrates, resulting in increased FVIII in comparison with VWF:Act ($P < .01$) ($F = 6.90$ DFn = 1, DFd = 209); Haemate® P

# Treatment of secondary FVIII deficiency in patients with severe VWD by Emicizumab

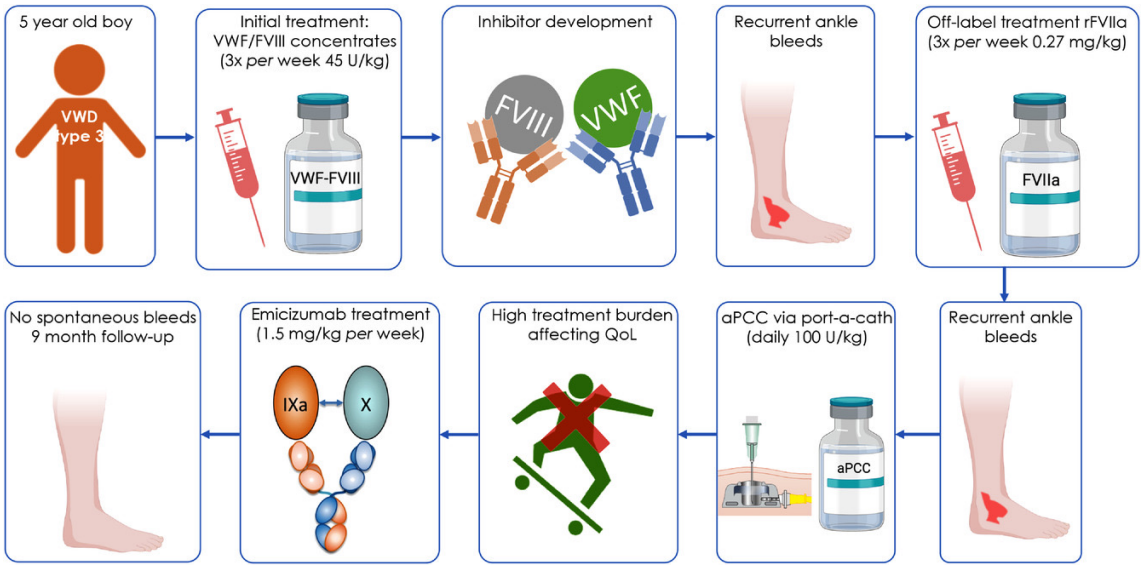
Received: 7 January 2022 | Revised: 7 February 2022 | Accepted: 7 February 2022
DOI: 10.1111/hae.14518

Haemophilia WILEY

SUPPLEMENT ARTICLE

**Towards novel treatment options in von Willebrand disease**

Peter J. Lenting | Claire Kizlik-Manson | Caterina Casari




Emicizumab for von Willebrand disease (VWD)-type 3.

Early case report by Weyand et al. on the off-label use of emicizumab in a young boy with VWD-type 3 and inhibitors against both factor VIII (FVIII) and von Willebrand factor (VWF).

**Haemophilia, Volume: 28, Issue: S4, Pages: 5-10, First published: 06 May 2022, DOI: (10.1111/hae.14518)**

# APTAMERS

Aptamers are small single stranded DNA or RNA molecules that bind to a specific target.

As such, they reflect the working mechanism of an antibody.

The difference between them is that aptamers are composed of nucleic acids (oligonucleotides) and antibodies of amino acids (proteins).

Aptamers are more stable than antibodies, have longer shelf lives, are more specific with higher affinity, have an animal free production line, and are easier to produce.

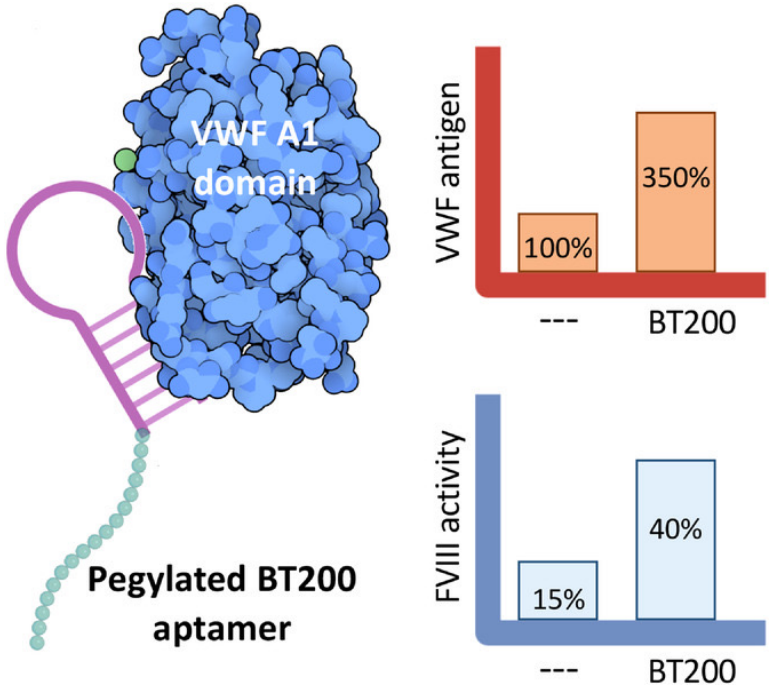
# Aptamer binding to VWF for patients with VWD and Haemophilia A

BT200 is a pegylated aptamer that binds to the VWF A1 domain.

Aptamer BT200 increases endogenous factor VIII (FVIII) and von Willebrand factor (VWF) levels.

This aptamer has been shown to reduce clearance of the VWF/FVIII complex, resulting in a transient increase in plasma levels of both proteins.

Its use in normal volunteers is associated with VWF levels being increased 3–4 fold, while its use in mild/moderate hemophilia A patient increase FVIII levels 2–3 fold




blood
American Society of Hematology
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Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

von Willebrand Factor-binding aptamer rondoraptivon pegol as treatment for severe and non-severe hemophilia A

Tracking no: BLD-2022-016571R2

Haemophilia, Volume: 28, Issue: S4, Pages: 5-10, First published: 06 May 2022, DOI: (10.1111/hae.14518)

# Bypassing Agents
## (FVIII-FIX)

# CURRENT AND NEW TREATMENT OPTIONS FOR INH PATIENTS

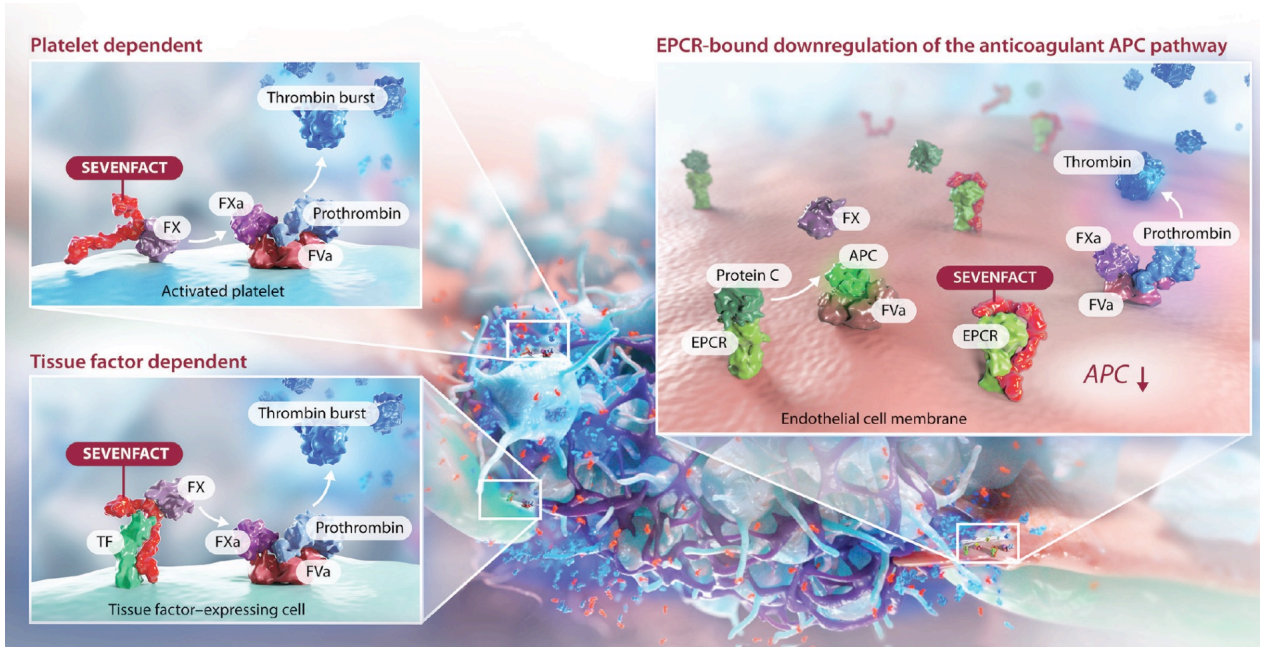
| OVERDRIVE EXISTING PATHWAYS | MIMETICS | REBALANCE THROUGH LOSS OF INHIBITION |
|---|---|---|
| • rFVIIa<br>  • Extrinsic and common pathway<br>• aPCC<br>  • Extrinsic and common pathway | • FVIII mimetics<br>  • Emicizumab<br>  • MIM8 | • Inhibition of TFPI<br>  • Concizumab<br>  • Other anti-TFPI antibodies<br>• Decreased synthesis of anti-thrombin<br>  • Fitusiran |

# BYPASSING Agents
# For INH patients

- Recombinant FVIIa

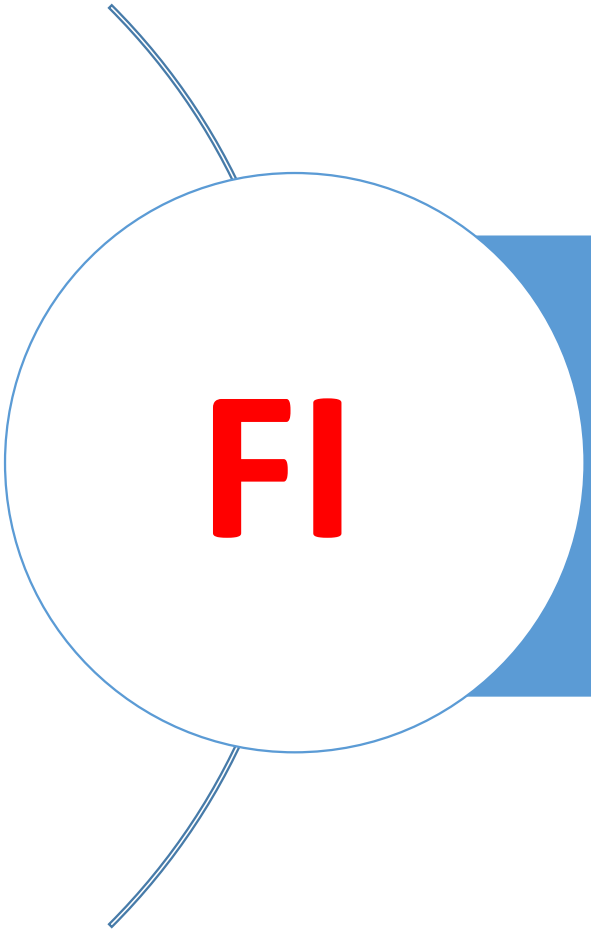
- FEIBA
- FIIa, FVIIa, FIXa, FXa

SevenFACT®
Coagulation Factor VIIa (Recombinant)-jncw




Eptacog beta (SevenFact; LFB Biotechnologies, Hema Biologics) is a new rFVIIa product produced via expression in the milk of transgenic rabbits.
Better ability to scale up production and better protein yields.
Eptacog beta is currently approved by the U.S. Food and Drug Administration (FDA) for the on-demand control of bleeding episodes in patients with hemophilia aged 12 to 75 with inhibitors.

# Other clotting factor deficiencies




Fg concentrate is available, as well as cryoprecipitate which contains a lot of FI.

For severe bleeding phenotype treatment prophylaxis is standard

For mild phenotype, it is not needed.

# FVII

Three products are available currently - one plasma derived and 2 recombinant (activated FVII, Sevenfact and Novo7).

Prophylaxis is recommended for severe bleeding phenotype.

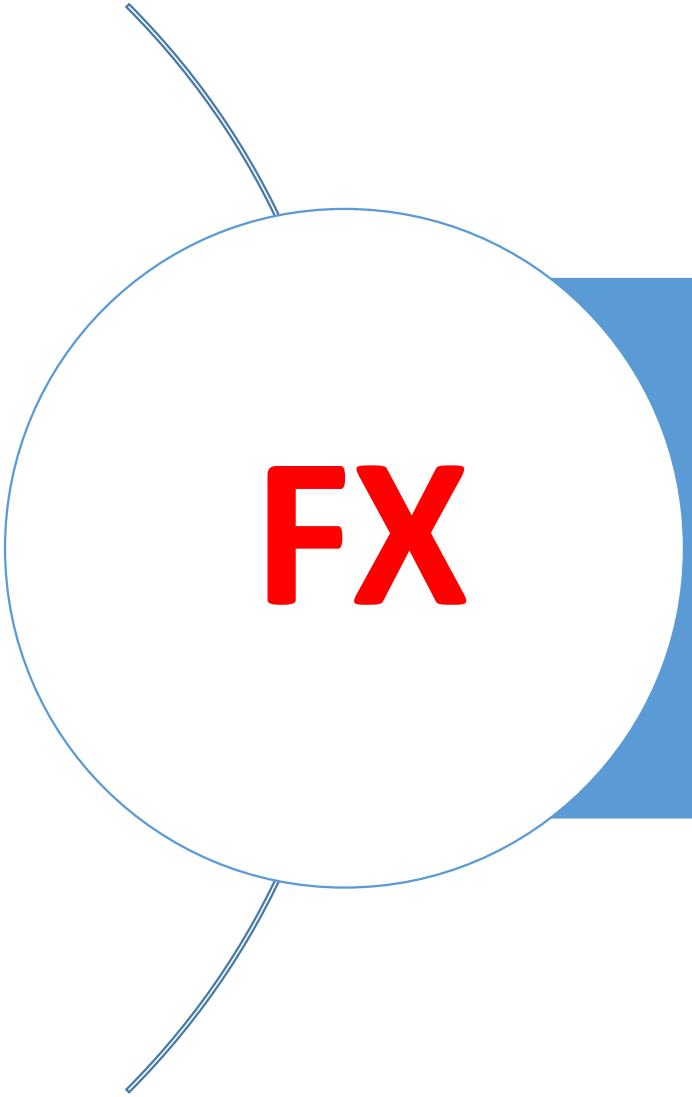
# FXI

Factor XI concentrate exists, but it is not licensed everywhere.

Use of the concentrate is rare and presents a risk of thrombosis.

Fresh frozen plasma can be used for surgery and tranexamic acid for smaller treatments.

No indication for prophylaxis.




Purified plasma-derived factor X is available, but not widely accessible.

PCC (many products available) can be used in treatment of factor X,
PCC is usually readily available as is used for other medical issues.

Prophylaxis is not standard for factor X deficiency as it is very rare.

# FXIII

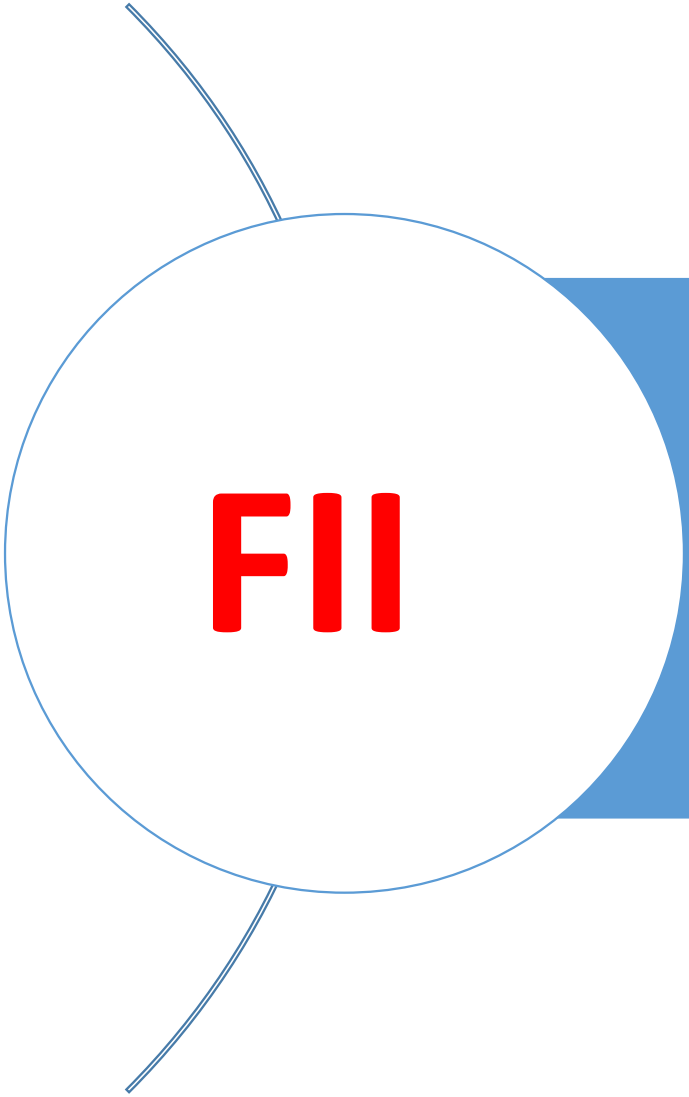
Very rare disorder. Severe bleeding phenotype is related to high risk of intracranial haemorrhage.

Plasma derived and recombinant products are available, and ideally both should be accessible to patients.

T1/2 is long, therefore prophylaxis is manageable, with 1x month injection.

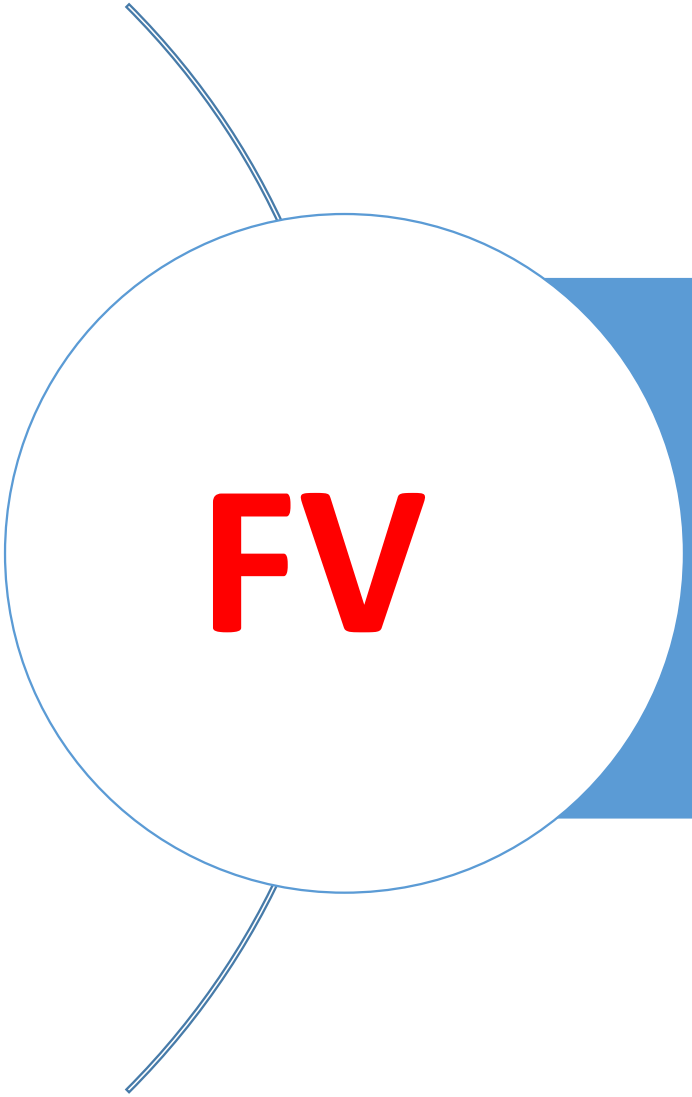
Access to the factor concentrate is uncommon as the disorder is very rare.

1 x monthly prophylaxis should be the standard of treatment without taking into account the bleeding phenotype




Very very rare bleeding disorder. Severe prothrombin deficiency is not compatible with life.

PCC is used to treat FII deficiency.




Remains an orphan disease and can be very problematic.

The only treatment option for factor V deficient patients is fresh frozen plasma weekly prophylaxis (10-20ml/kg)

# Treatment options for clotting factors deficiencies

| | Plasma | PD-concentrate | Rec-SHL | Rec-EHL | Rec-Ultra LONG | Mimicking Agent | Rebalancing Agent | Nanobody | Aptamer | Gene therapy | Sub-cutaneous treatment options |
|---|---|---|---|---|---|---|---|---|---|---|---|
| FI | | | | | | | | | | | No |
| FII | | FII-VII-IX-X | | | | | | | | | No |
| FV | | | | | | In theory | | | | | No |
| FVII | | FVII<br>FII-VII-IX-X | | Marzeptacog alfa | | | | | | | Yes |
| FVIII | | | | | | Emicizumab | | FVIII-nanobody fusion protein | BT200 (VWF-A1) | | Yes |
| FIX | | | | | | | | | | | Yes |
| FX | | FIX/X<br>FX<br>FII-VII-IX-X | | | | | | | | | No |
| FXI | | | | | | | | | | | No |
| FXIII | | | | | | | | | | | No |
| VWF | | | Vonvendi | | | | | | | | No |
| VWF low FVIII | | | Vonvendi | | Correction of low FVIII | Correction of low FVIII | | | | | No except emicizumab |
| 2B | | | Vonvendi | | | | | | ARC1779 (A1)<br>BT200 (A1) | | No |

# Treatment options for inherited bleeding diseases

## Clotting factor deficiency (FI to FXIII + VWF)

- Replacement (IV)
  - Concentrates (not all)
  - Fresh Frozen Plasma
- Mimicking agent (FVIII) (SC)
- Rebalancing agent (SC)
- Endogenous production (FVIII and FIX) (Gene Therapy)

## Platelet dysfunction

- Replacement by platelets transfusion
- Non-specific haemostatic agents
  - Tranexamic
  - DDAVP
- Bypassing agents (rFVIIa)

## Vascular diseases (Osler Rendu)

- Red Cells Transfusions
- Iron
- Anti-Angiogenic agents..

# Platelet disorders

The most common, are **Glanzmann Thrombasthenia** and **Bernard-Soulier syndromes**. GT is quite severe.

Standard treatment is prophylaxis with Novo7 (used as a bypassing agent), but not all the patients respond.

Platelet transfusions are used with caution due to the risk of allo-immunisation.

# Laboratory expertise

- Clotting factor assays (chromogenic)
- Reliable assays of all clotting factors
- VWF:Activity assays
- Inhibitor detection
- Thrombin generation assay
- Genetic testing and Next Generation Sequencing (NGS) (genetic confirmation, family screening)
- AT and TFPI assays (for rebalancing agents)
- AAVs neutralizing Abs (gene therapy)

# MULTIDISCIPLINARY CARE

## Haemophilia and other RBDs related comorbidities

Haemophilia and other rare bleeding diseases

→

« Classical » comorbidities

Arthropathy
Functional disability
Pain
HCV infection
HIV infection

Expertises required

Physiotherapist
Orthopaedic surgeon
Rheumatologist
Liver specialist
Infectious disease specialist
Dentist
Chronic pain specialist

# MULTIDISCIPLINARY CARE

## Haemophilia and other RBDs not-directly related comorbidities

Haemophilia and other rare bleeding diseases

+

Non directly related comorbidities

- Hypertension
- Atrial fibrillation
- Cancer
- Obesity
- Diabetes
- Liver steatosis
- Osteoporosis
- Depression
- Any internal disease

Expertises required

- Cardiologist
- Oncologist
- Endocrinologist
- Rheumatologist
- Liver specialists
- Psychologist
- Internist

# Comorbidities have an increasing impact on treatment options in patients with RBDs

| Comorbidities | → | Impact(s) on haemophilia treatment |
|---|---|---|
| Liver disease | → | Not eligible for gene therapy |
| History of thrombosis<br>Risk(s) factor(s) for thrombosis | → | Great caution with some treatments possibly associated with a risk of thrombosis |
| Past history of inhibitor | → | Not eligible for gene therapy |
| Depression | → | Difficulties to adopt new treatment strategies |

**NEED FOR AN EXPERT MULTIDISCIPLINARY TEAM**

# Conclusions

- Multiple (innovative) treatment options, at least for hemophilia and VWD, have been validated
- For many rare congenital bleeding diseases, the treatment options remain limited
- More than ever, the **treatment ambitions** are very heterogenous (from minimal correction to normalization)
- **Prophylaxis should be the standard of care for male and female patients with a severe bleeding phenotype**
- Treatment options for rare platelet disorders, very rare clotting factor defects and vascular diseases are clearly needed.

# Thank you for your attention

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