Newer Therapies for Haemophilia

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Prophylaxis is the Standard of Care for People with Haemophilia

2014[1]:

The regular **Intravenous** infusion of **Missing Clotting Factor …** in people…..with the intent to **prevent bleeding** …….

6 years

2020[2] :

The regular **Administration** of a **Haemostatic Agent(s)** with the goal of **preventing bleeding** … **allowing them to lead Active Lives and achieve Quality of Life Comparable to Non-Haemophiliac individuals**

1: Blanchette VS , Key NS , Ljung LR , et al. Definitions in hemophilia: communication from the SSC of the ISTH . J Thromb Haemost. 2014 ; 12 (11): 1935 - 1939 . 2. Srivastava, A, Santagostino, E, Dougall, A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020: 26(Suppl 6): 1- 15

Evolution of Haemophilia Therapies

1950s-1960s

Blood, Plasma
Cryoprecipitate

1960s-1970s

Plasma-derived
clotting factor
concentrates
- On-demand
  therapy
- Wide spread viral
  contamination :
  Hepatitis, HIV

1980s-1990s

Recombinant
clotting factor
concentrates
- Improved
  pathogen safety
- Home prophylaxis
- Haemophilia
  Treatment
  Centres

**BURDEN of
treatment with
factor
concentrates**

2000s-2010s

Extended half-life
(EHL)
clotting factor
concentrates
- Fewer injections
- Improved
  QOL/adherence to
  prophylaxis

2010s and beyond

Novel Therapies
"Steady State"
- Non-factor
  replacement
  (NFT)
   - Antibodies
   - Re-
     balancing
     :siRNA
- Gene therapy

**BEYOND factor
concentrates**

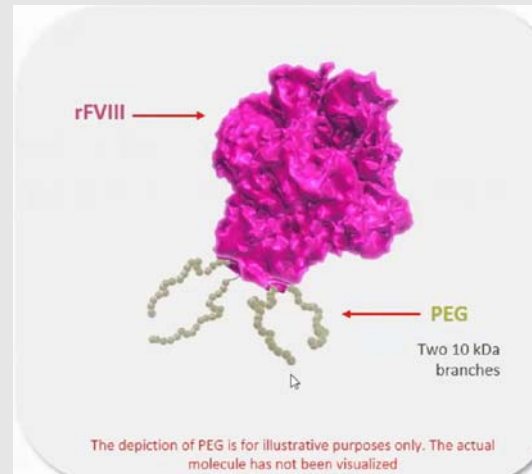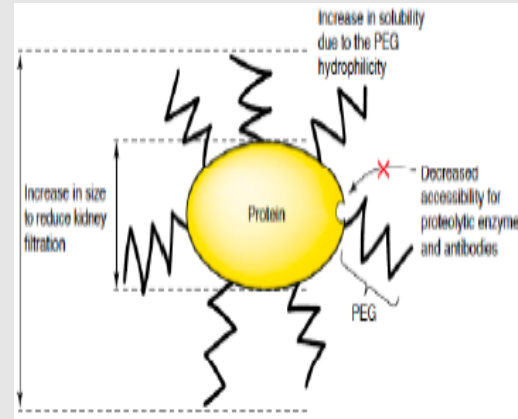# Technologies for half-life extension : current

PEGylation

PEG: polyethylene glycol
Aims of attaching PEG molecules to drugs:
- Improved drug solubility
- Extended circulating half life

Haemophilia A: Adynovate

Last Longer in The Body = Fewer Injections

Other drugs that use PEG to extend half-life : L-asparaginase, GCSF

1. Veronese and Pasut (2005) Drug Discovery Today, Vol 10, 21: 1451-1458. 2. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. 2007;7(9):715–725. 3. Chhabra ES, et al. *Blood.* 2020;135(17):1484-1496. 4. Konkle BA, et al. *N Engl J Med.* 2020;383(11):1018-1027.

Technologies for half-life extension :current

Fusion Proteins
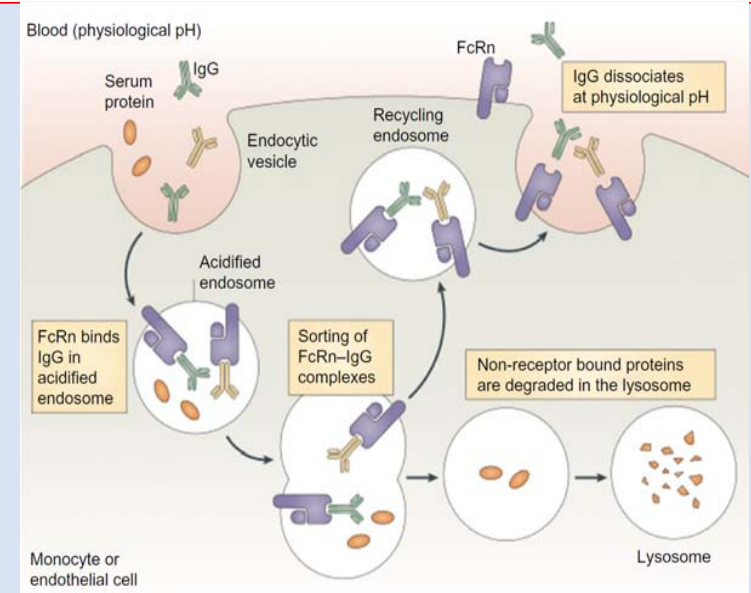
IgG$_1$. Fc receptor
- Important part of natural immune system recycling pathway
- Delays degradation of IgG; binding to the neonatal Fc receptor (FcRn)

    Haemophilia A: Elocate

    Haemophilia B: Alprolix

Albumin
- Half-life of approximately 20 days
- Drugs bound to albumin have a slower clearance by the kidneys
- Binding to neonatal Fc receptor

Other drugs that use IgG$_1$-Fc receptor : Romiplostim

Last Longer in The Body = Fewer Injections

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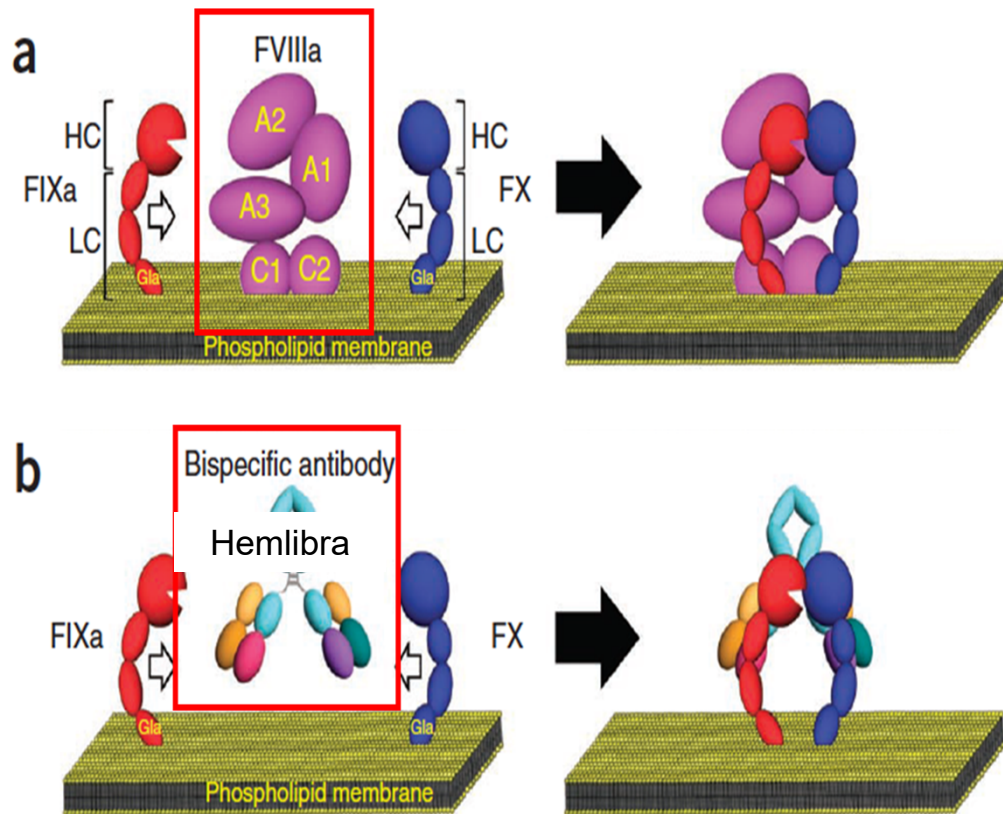# *Even Newer Technologies for half-life extension* *(Trial)*
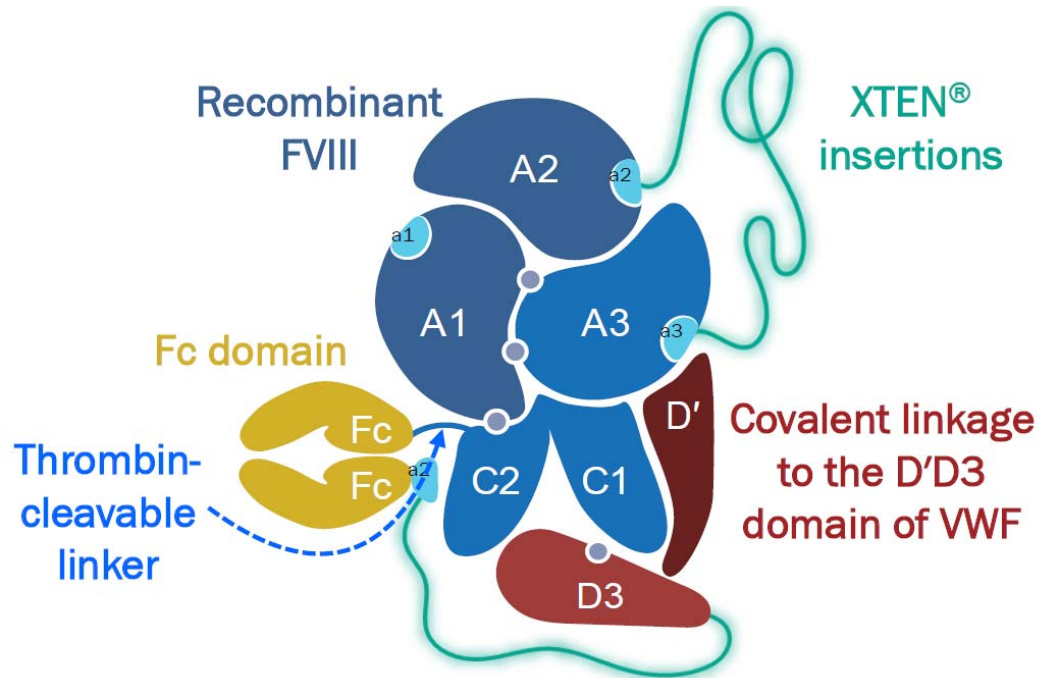
From Konkle BA, et al. *N Engl J Med.* 2020;383:1018-1027. Copyright © (2022) Massachusetts Medical Society. Reused with permission from Massachusetts Medical Society.

Recombinant FVIII

XTEN® insertions

A2

a2

a1

A1   A3

a3

Fc domain

Thrombin-cleavable linker

Fc

Fc

a2

C2   C1

D'   Covalent linkage to the D'D3 domain of VWF

D3

Sequential PK subgroup[a,b]

Week 1 (n=17)
Week 26 (n=17)

123.1%

68.0%

101.4%

59.1%

15.2%

12.8%

100%

40%

10%

1%
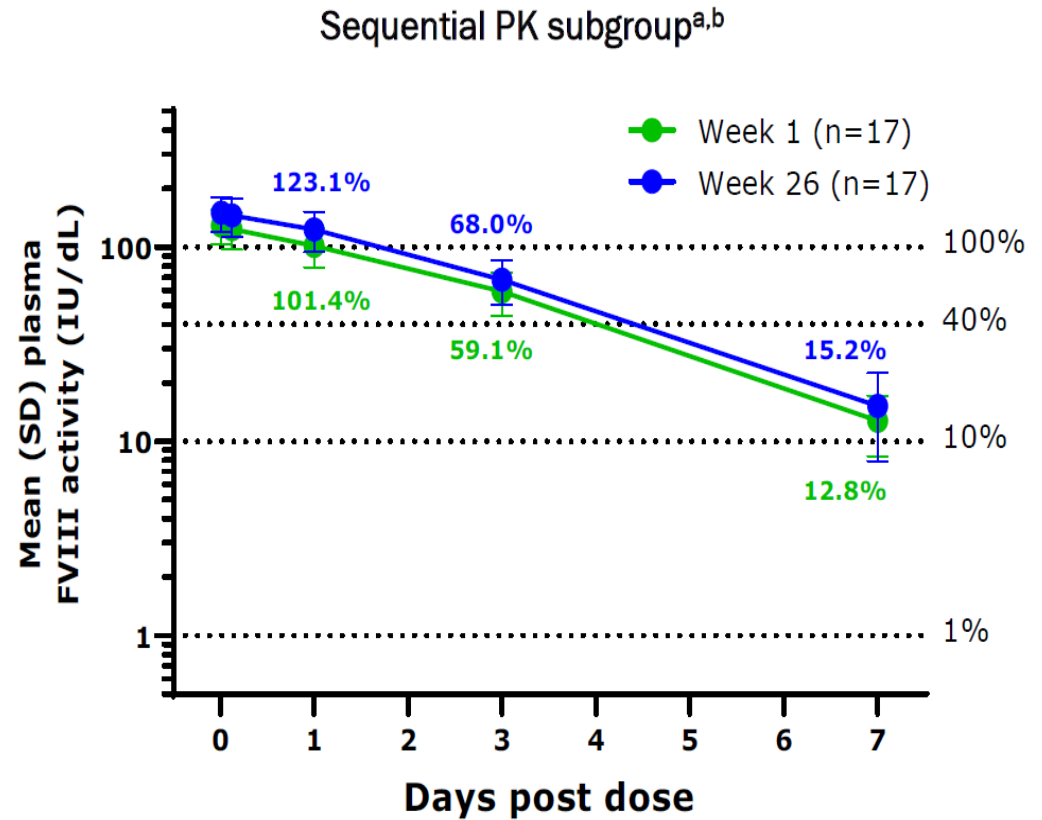
Non-Factor Replacement Therapies : Current

Monoclonal Antibodies

a

FVIIIa

HC
FIXa
LC

Gla

A2
A1
A3
C1 C2

Phospholipid membrane

HC
FX
LC

Gla

b

Bispecific antibody

Hemlibra

FIXa

Gla

FX

Phospholipid membrane

Kitazawa T *et al. 2012. Nature Medicine. 18(10): 1570-4.*

- **Restores the function of missing FVIII**
- **Haemophilia A patient WITH and Without inhibitors**
- **Steady state level**

Emicizumab Half-life = 4 Weeks*

Emicizumab concentration (µg/mL)[1]

60
50
40
30
20
10
0

HEMLIBRA QW (pooled HAVEN 1, 2, 3; n=274)
Emicizumab Q2W (HAVEN 3; n=49)
Emicizumab Q4W (HAVEN 4; n=41)

10 20 30 40 50 60 70 80 90

Time after starting emicizumab (weeks)

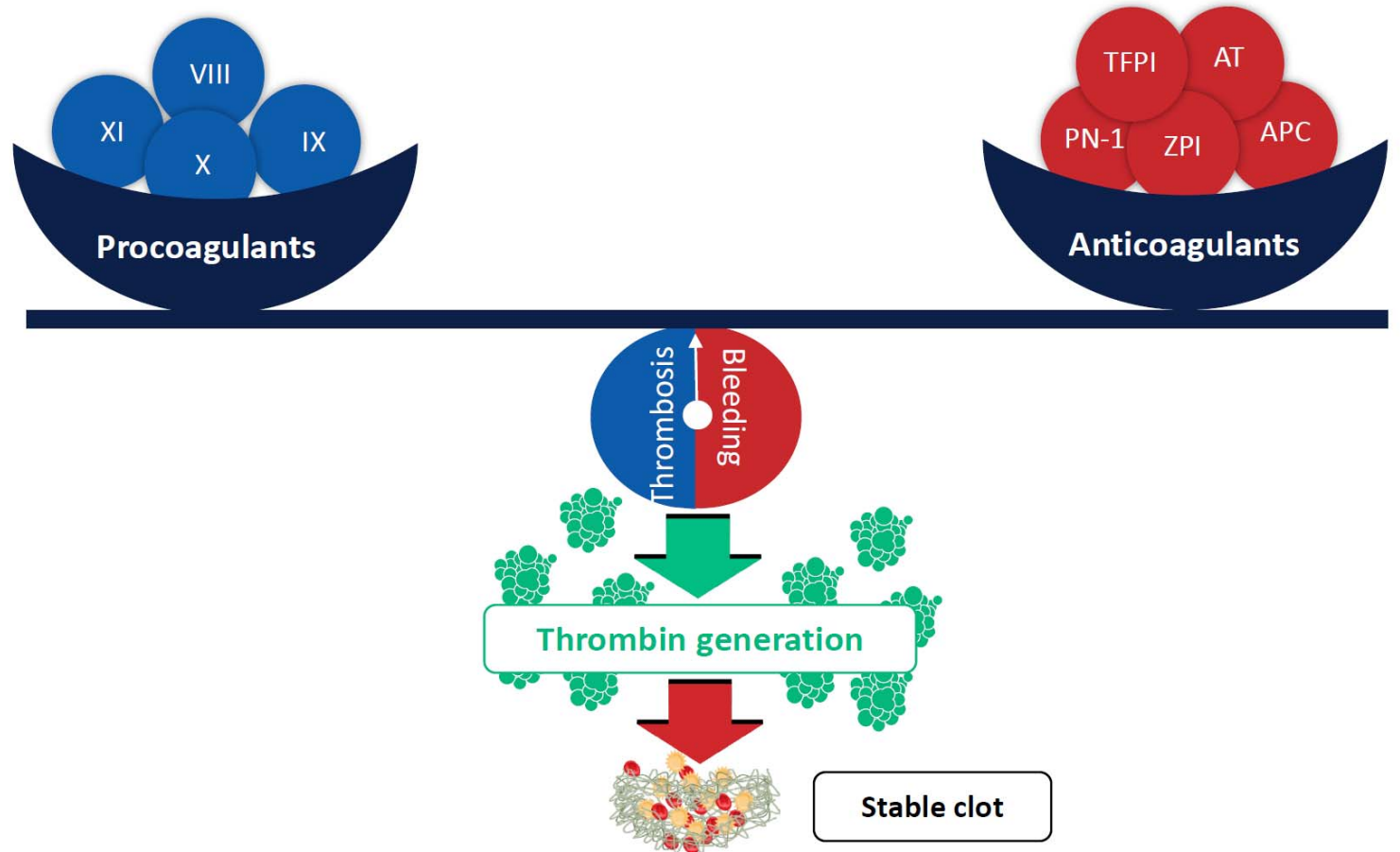- **Subcutaneous**

Front   Back

Non-Factor Replacement Therapies → Re-Balancing Therapies
(Trial)

Haemostasis depends on a **balanced coagulation** process that generates **thrombin sufficient** to enable stable clot formation[1,2]

In haemophilia, lack of factor VIII or IX results in **insufficient thrombin generation** and **inability to form stable blood clots**[1,2]

Novel non-factor therapies aim to **correct thrombin deficiency** by **lowering anticoagulant levels**; an **innovative approach** to treating haemophilia[2,3]

Procoagulants — XI, VIII, X, IX

Anticoagulants — TFPI, AT, PN-1, ZPI, APC

Thrombosis / Bleeding

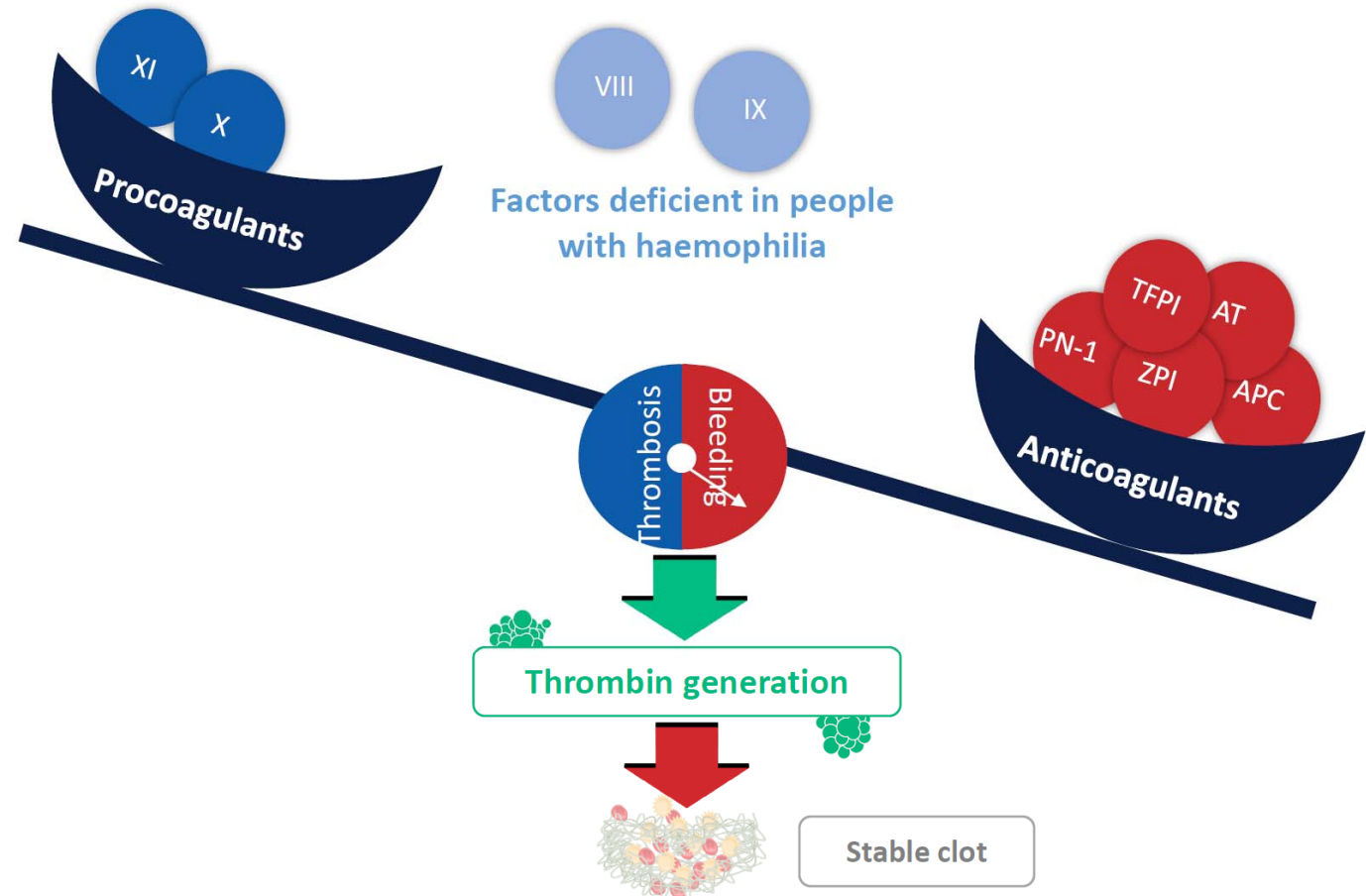**Thrombin generation**

Stable clot

APC, activated protein C; AT, antithrombin; PN-1, protease nexin-1; TFPI, tissue-factor protein inhibitor; ZPI, Z-dependent protease inhibitor.
1. Willyard, C. Nature. 2014;515;S168–9; 2. Negrier C, et al. Blood Rev. 2019;38:100582; 3. Nogami K and Shima M. Blood. 2019;133:399–406.
Figure adapted from Aymonnier K, et al. Thromb Haemost 2020

Non-Factor Replacement Therapies ➡ Re-Balancing Therapies
(Trial)

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Procoagulants

Factors deficient in people with haemophilia

Anticoagulants

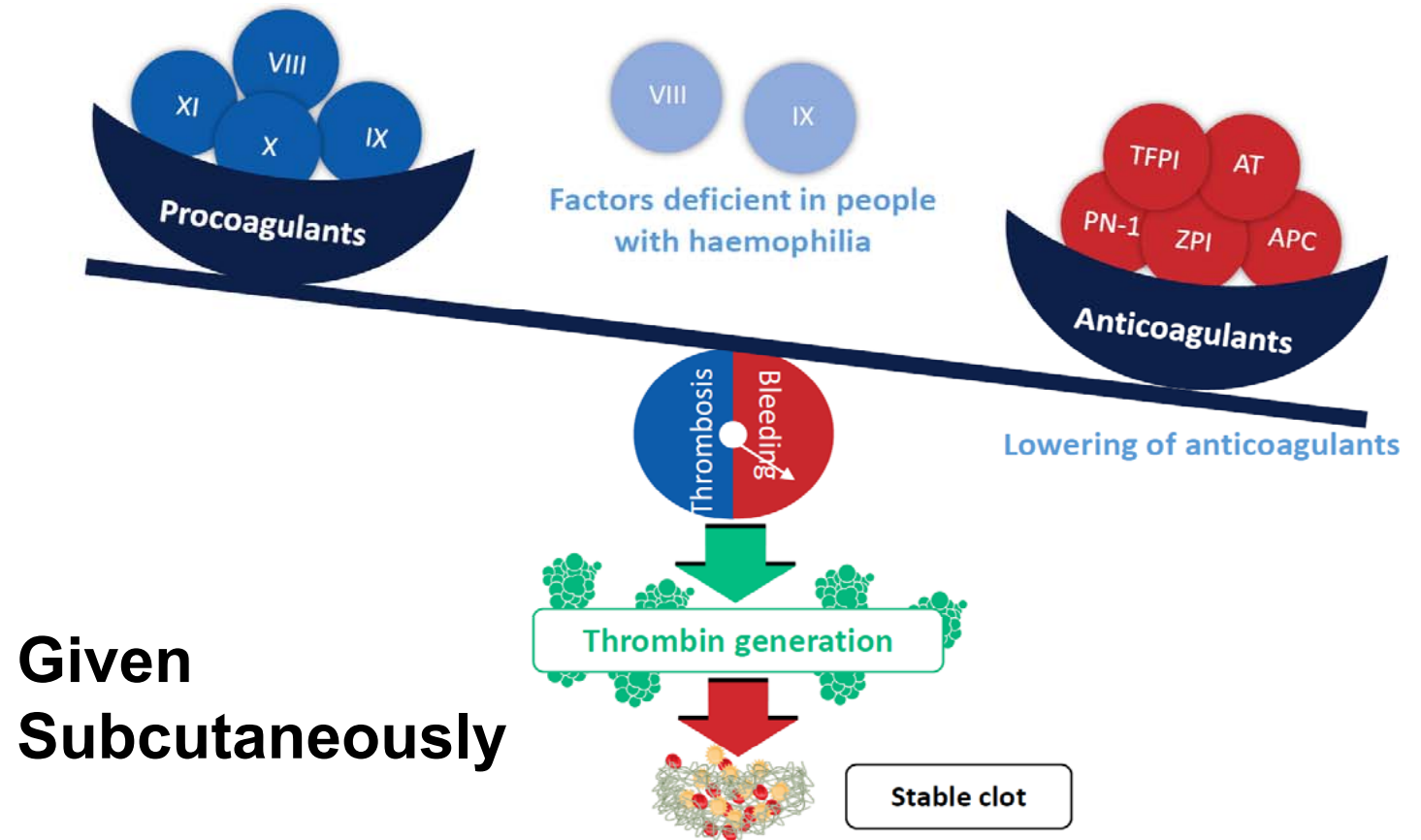Thrombosis / Bleeding

Thrombin generation

Stable clot

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Given Subcutaneously

Procoagulants

Factors deficient in people with haemophilia

Anticoagulants

Lowering of anticoagulants

Thrombosis / Bleeding

Thrombin generation

Stable clot

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New Comprehensive Care

Musculoskeletal Experts
- **Rheumatologist**
- **Orthopaedic surgeons**

Hospitals

Social Workers

Nurses

Doctors

Patient Support Organisation and Advocacy Groups

Physiotherapists

Laboratory Scientists

Patients and their families

Haemophilia Foundation

Psychologists

Chronic Pain Specialist

Research

General Practitioners

Telehealth

Geriatricians

Cardiologist

Psychologist

Dentists

HIV Specialists

Government Funders

Outreach to Rural areas

Liver Specialists