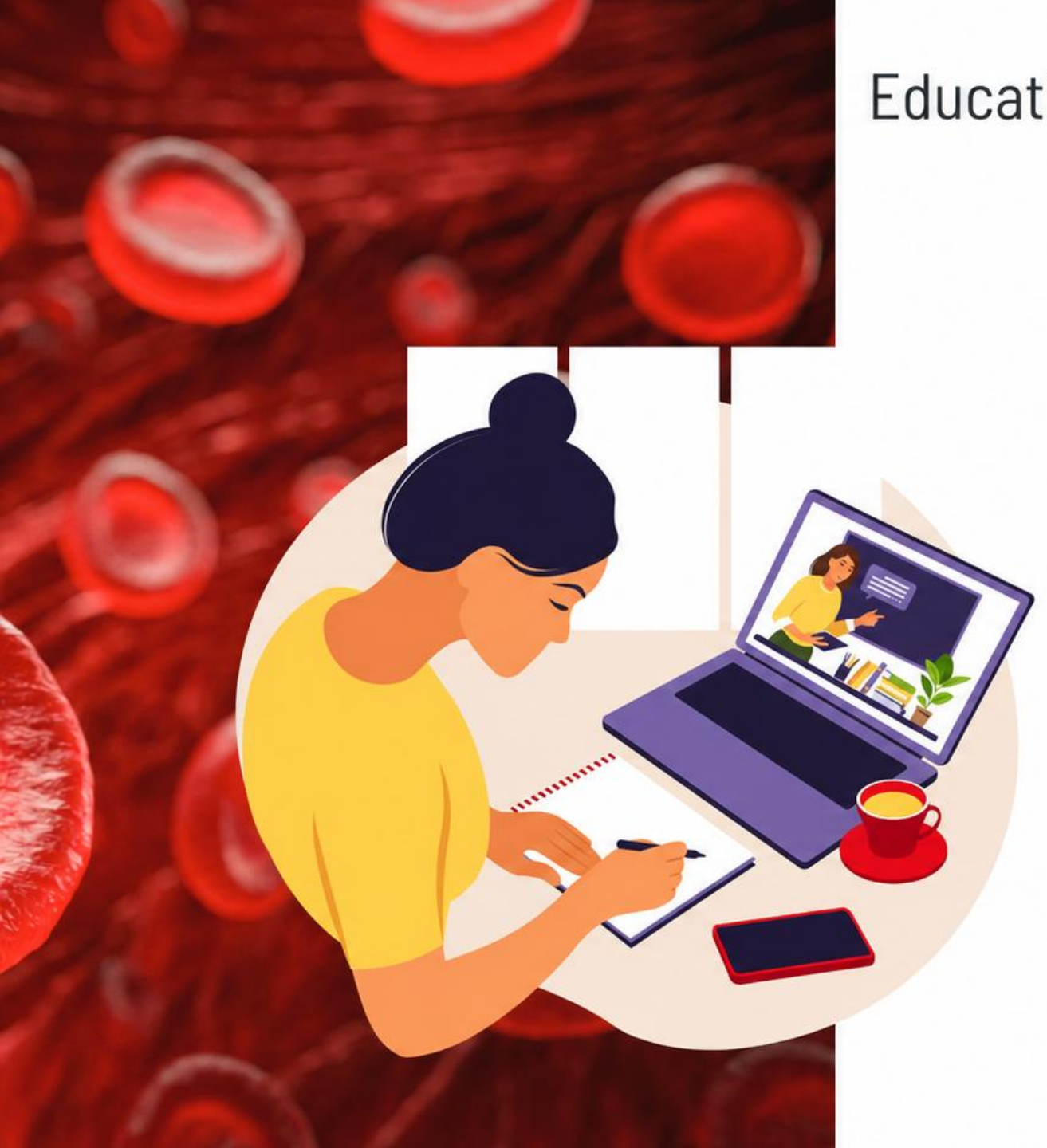


Educational Courses

BHS

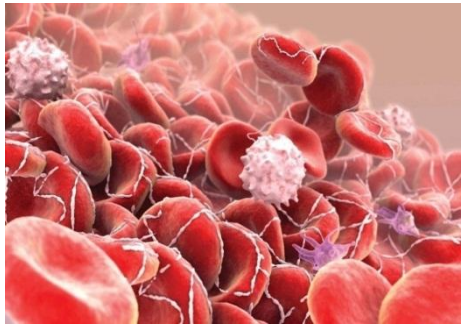
Blood coagulation: General Introduction and overview

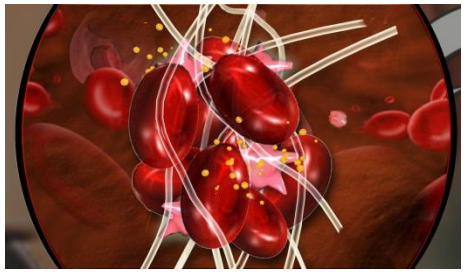
Cédric Hermans (UCLouvain)

Blood coagulation revisited

General Introduction and overview

Cedric HERMANS, MD, FRCP, PhD







UCLouvain

INSTITUT DES MALADIES RARES
Cliniques universitaires SAINT-LUC | UCL Bruxelles

EuroBloodNet

Cliniques universitaires SAINT-LUC UCL BRUXELLES

More than ever the blood coagulation cascade is fascinating

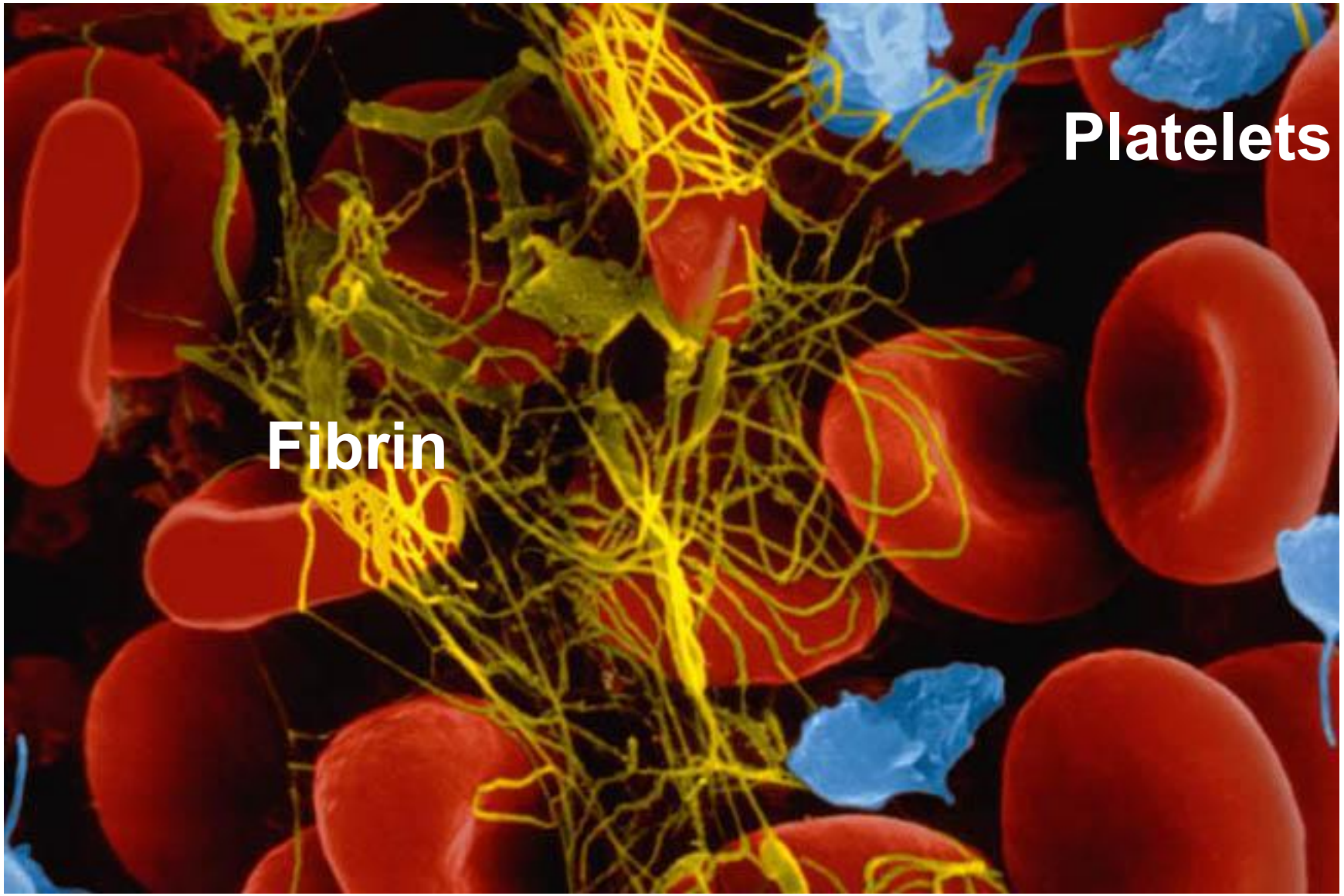
Let us discover more during this course….



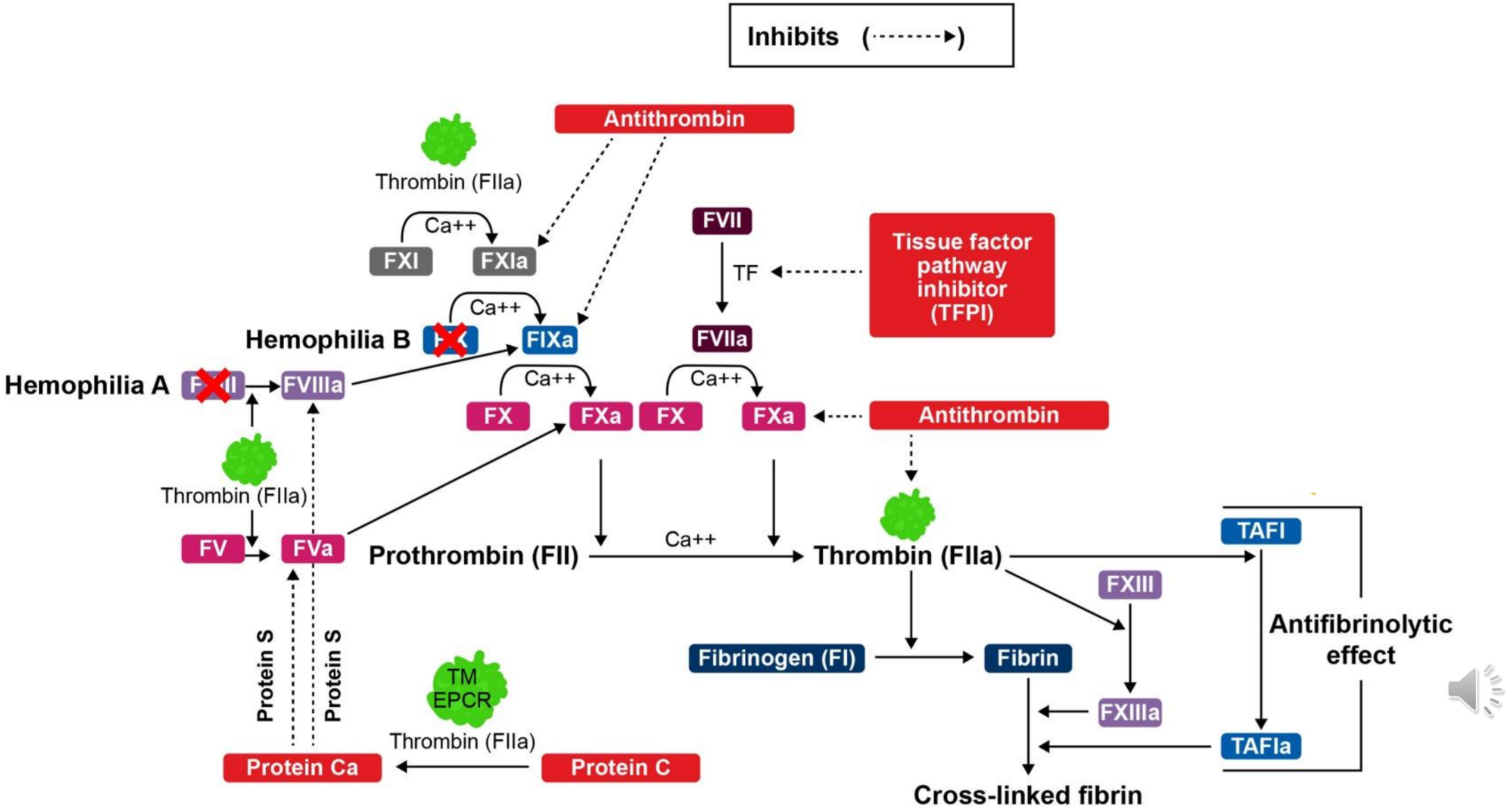
Why is it important to understand the blood clotting process in 2024 ?

- Physiology of clot/thrombus formation
- Interpretation of routine clotting tests
- Understanding of bleeding and thrombotic diseases
- Mode of action of old, new and future anticoagulants
- Principles of replacement therapy
- Understanding new therapies of diseases such as haemophilia (rebalancing of blood coagulation, Ab mimicking FVIII, gene therapy)

THROMBUS FORMATION



The complexity of blood coagulation



Young-G / RPTH May 2023 https://doi.org/10.1016/j.rpth.2023.100179

Blood Coagulation

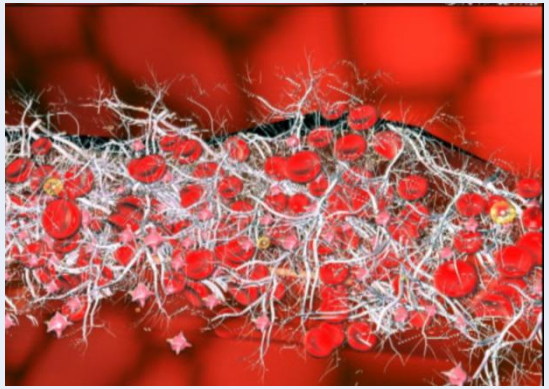
Simplified...



Clot formation:
A 3-step process[1,2]

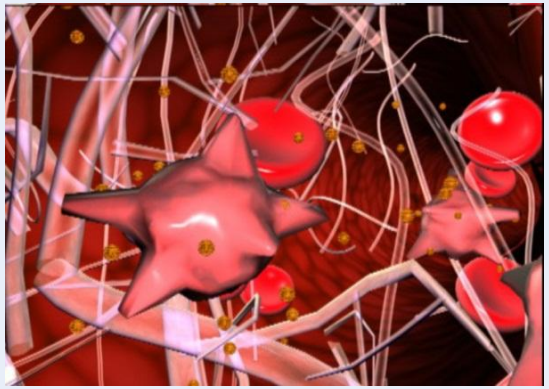
1. Platelet plug

Primary haemostasis



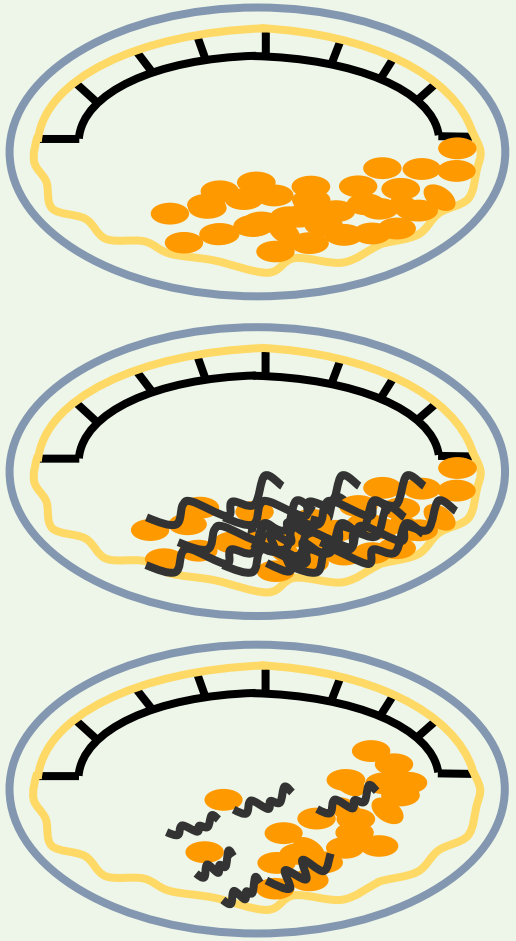
2. Fibrin formation

Coagulation cascade



3. Destruction

Fibrinolysis



Partners

Platelets (Nb / Function)
vWF
Collagen

FVII-TF
FX-II-I
FV-VIII
FXI
FXIII
Thrombomodulin

Plasminogen
Alpha2-AP
tP-A / PAI-1

Figures created from Sang Y, et al. & Versteeg HH, et al.

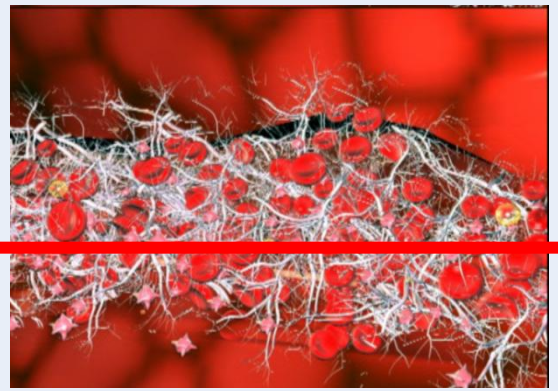
TF: Tissue factor; vWF: von Willebrand factor.

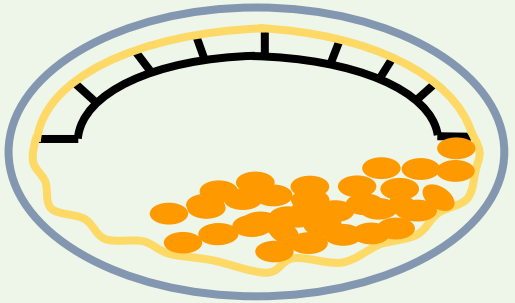
1. Sang Y, Roest M, de Laat B, et al. Interplay between platelets and coagulation. Blood Rev. 2021;46:100733. doi:10.1016/j.blre.2020.100733. 2. Versteeg HH, Heemskerk JW, Levi M, et al. New fundamentals in hemostasis. Physiol Rev. 2013;93(1):327–358. doi:10.1152/physrev.00016.2011.

Clot formation:
A 3-step process[1,2]

Partners

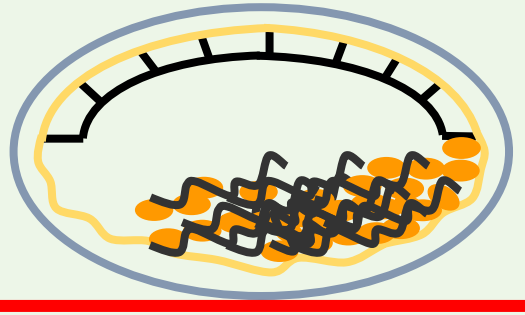
1. Platelet plug
Primary haemostasis





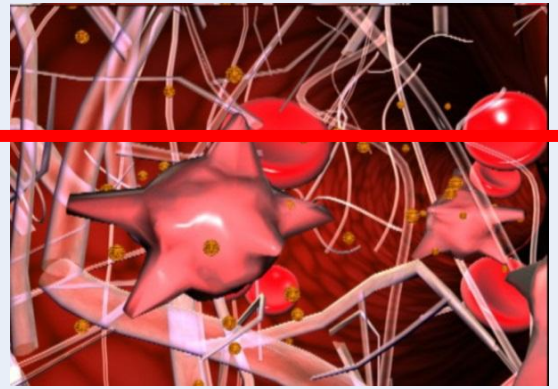
Platelets (Nb / Function)
vWF
Collagen

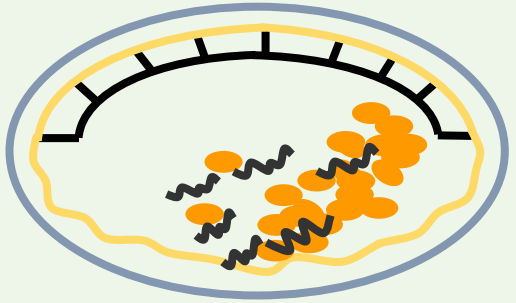
2. Fibrin formation
Coagulation cascade



FVII-TF
FX-II-I
FV-VIII
FXI
FXIII
Thrombomodulin

3. Destruction
Fibrinolysis





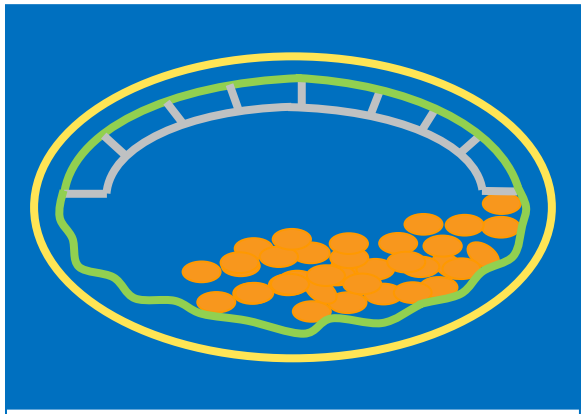
Plasminogen
Alpha2-AP
tP-A / PAI-1

Figures created from Sang Y, et al. & Versteeg HH, et al.

TF: Tissue factor; vWF: von Willebrand factor.

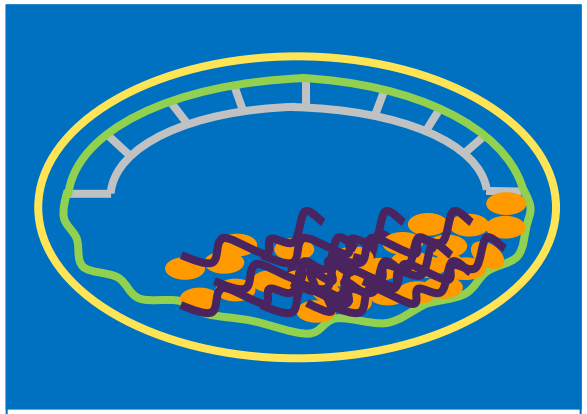
1. Sang Y, Roest M, de Laat B, et al. Interplay between platelets and coagulation. Blood Rev. 2021;46:100733. doi:10.1016/j.blre.2020.100733. 2. Versteeg HH, Heemskerk JW, Levi M, et al. New fundamentals in hemostasis. Physiol Rev. 2013;93(1):327–358. doi:10.1152/physrev.00016.2011.

Blood clotting: a three steps process



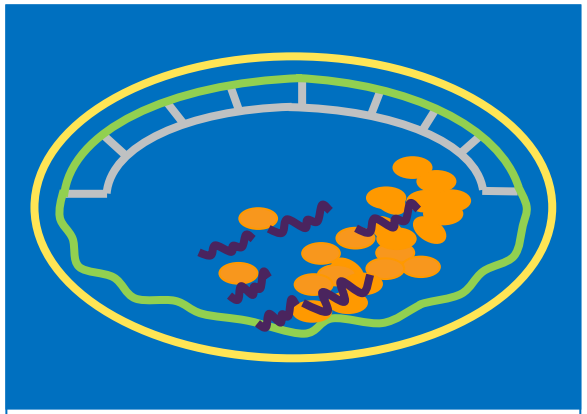
1. Platelets plug

Primary Haemostasis



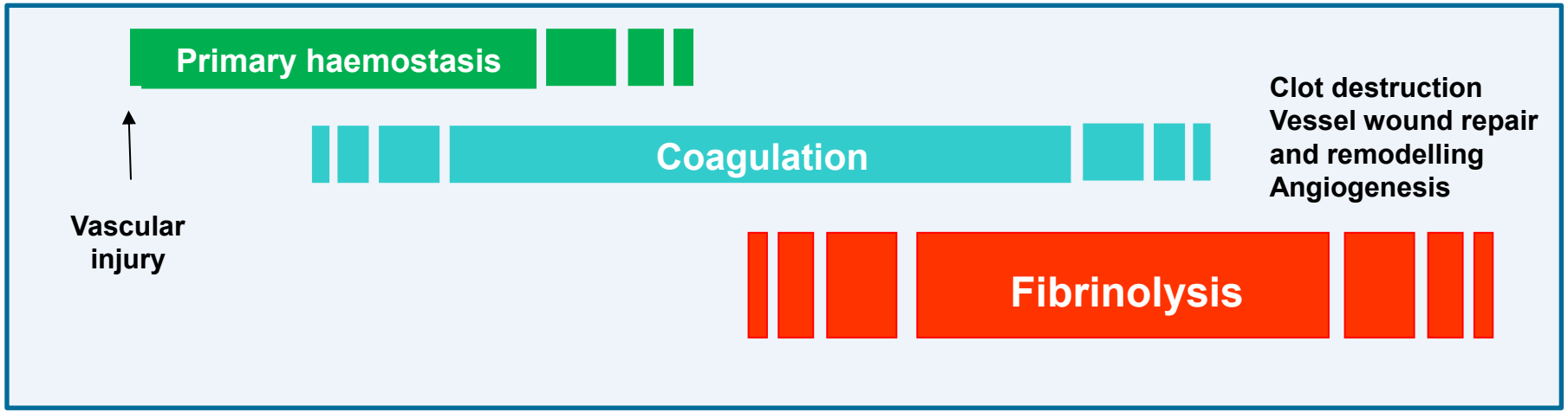
2. Fibrin formation

Coagulation cascade



3. Clot destruction

Fibrinolysis

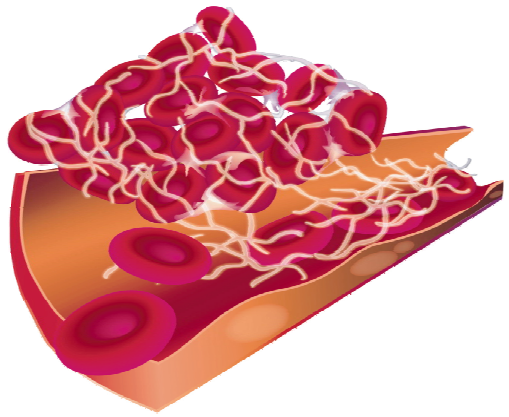


Coagulation cascade

Thrombin (FIIa)

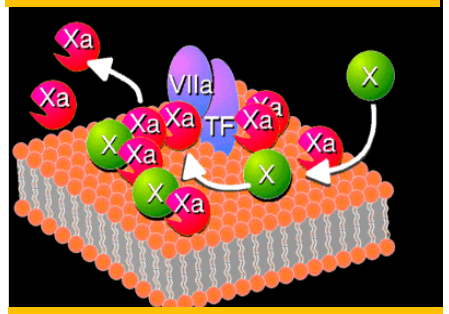
Fibrinogen
(Factor I)

Fibrin



Classical theory of the coagulation cascade

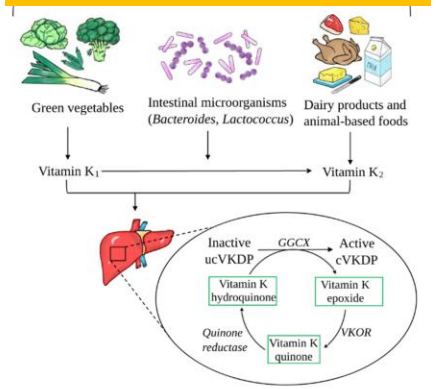
Phospholipids



Liver



Vitamin K



Intrinsic pathway

Contact Phase
FXII

FXI

FIX + FVIII

Extrinsic pathway

Tissue Factor + FVIIa

Common pathway

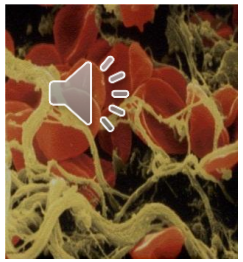
FX

FV

Thrombin

Fibrinogen → **Fibrin**

Blood clot

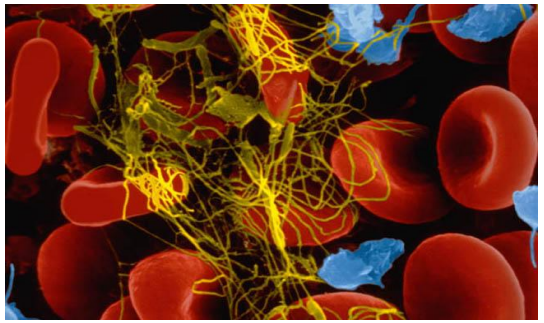


Thrombus formation
Platelet activation and fibrin formation

Primary Haemostasis

↓

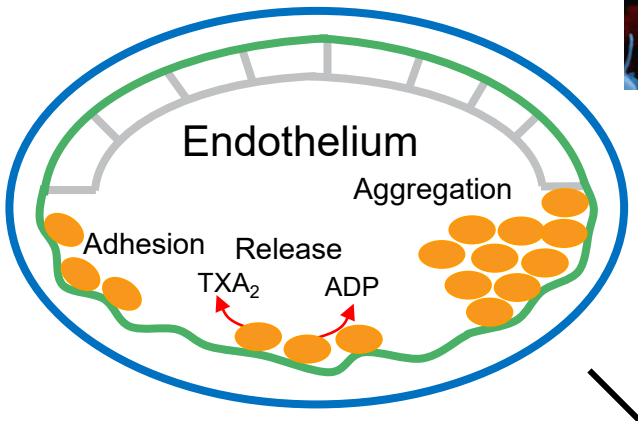
Platelets aggregates

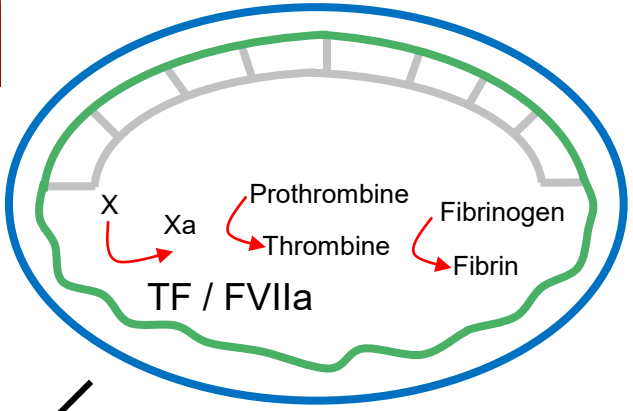


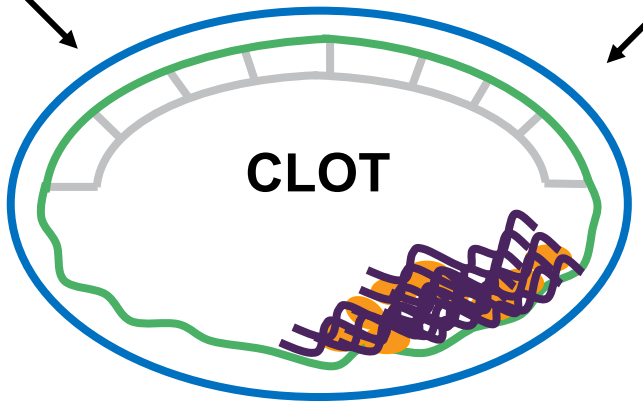
Blood coagulation

↓

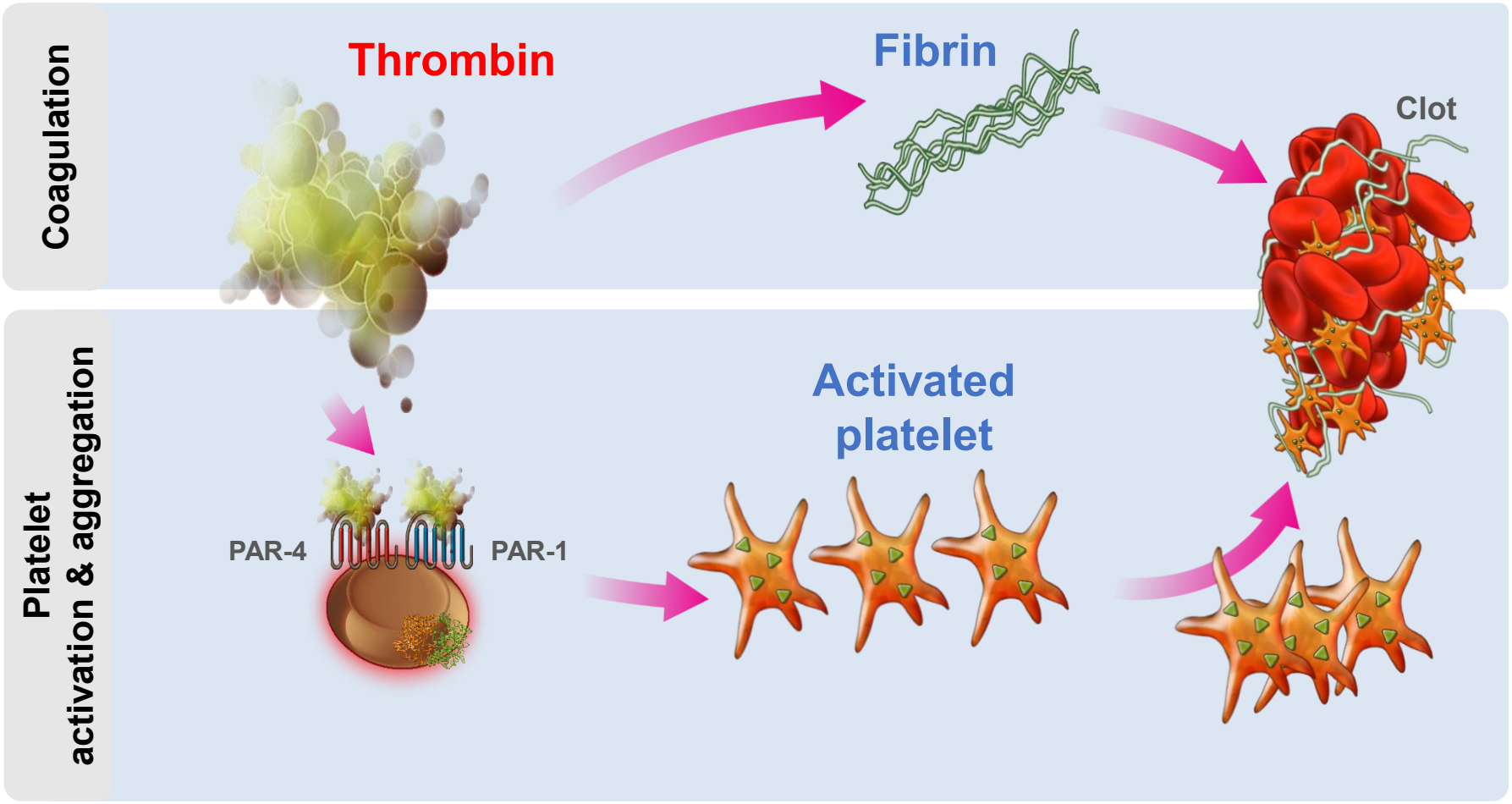
Fibrin network







Role of thrombin : Fibrin formation + Platelet activation

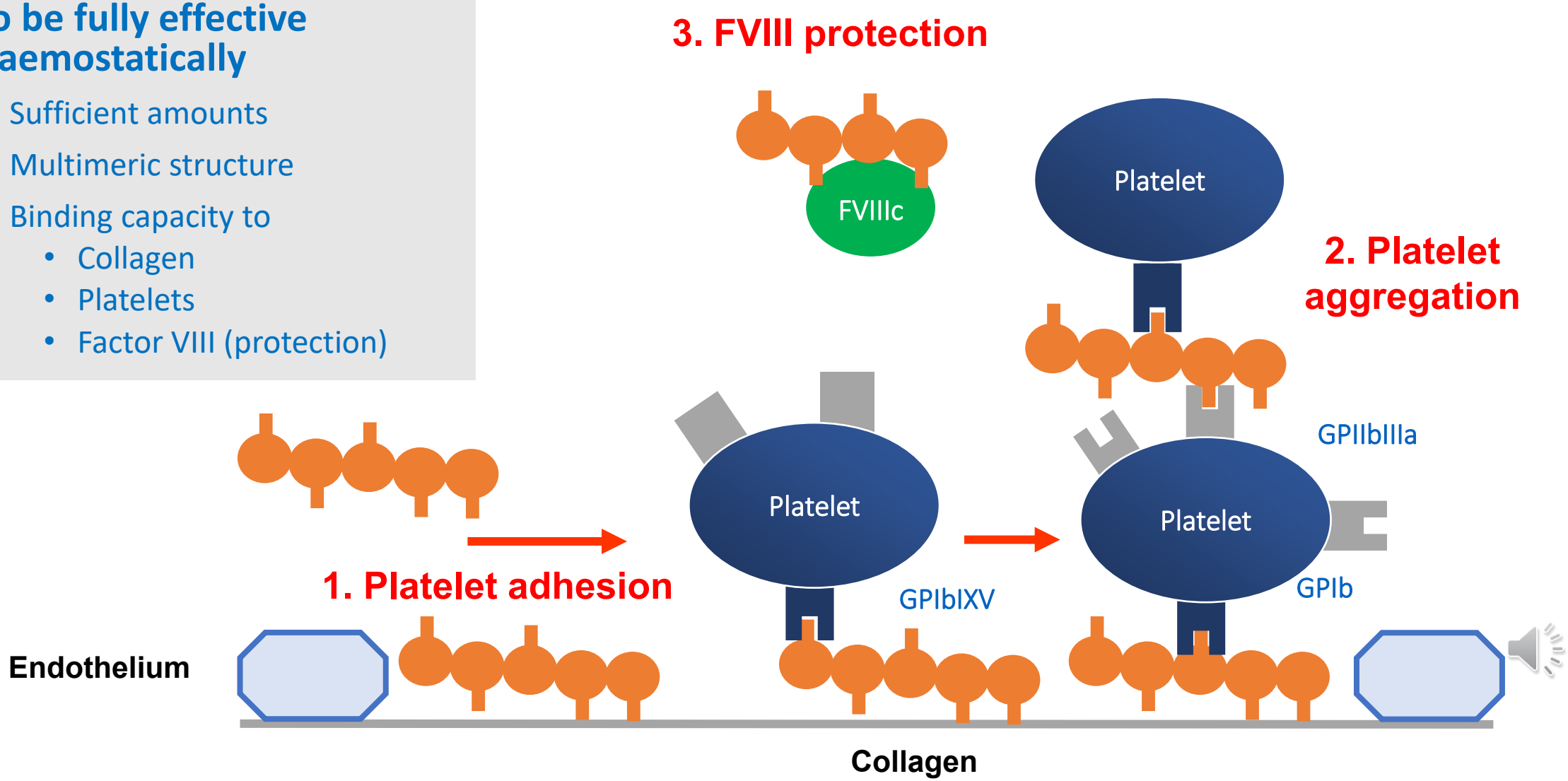


1. Adapted from Angiolillo DJ *et al. Eur Heart J* 2010;31:17–28; 2. Adapted from Mitchell JRA. *BMJ* 1981;282:590–594

The major roles of VWF in blood clotting

Required properties of VWF to be fully effective haemostatically

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



Major functions of VWF

Primary haemostasis by mediating platelet adhesion and aggregation

(dependent on multimeric structure and affinity of binding sites)

Contribution to coagulation by protection of endogenous FVIII

Anti-Angiogenic properties

(High-Molecular Weight Multimers)

Ultra-large multimers more efficient to inhibit neoangiogenesis

Consequences of VWF defects

Defective primary haemostasis

Mucosal bleeding (epistaxis, menorrhagia, GI bleeding)

FVIII deficency

(Type I, 2N, 3)

Soft tissue, joint and postoperative bleeding

Enhanced angiogenesis

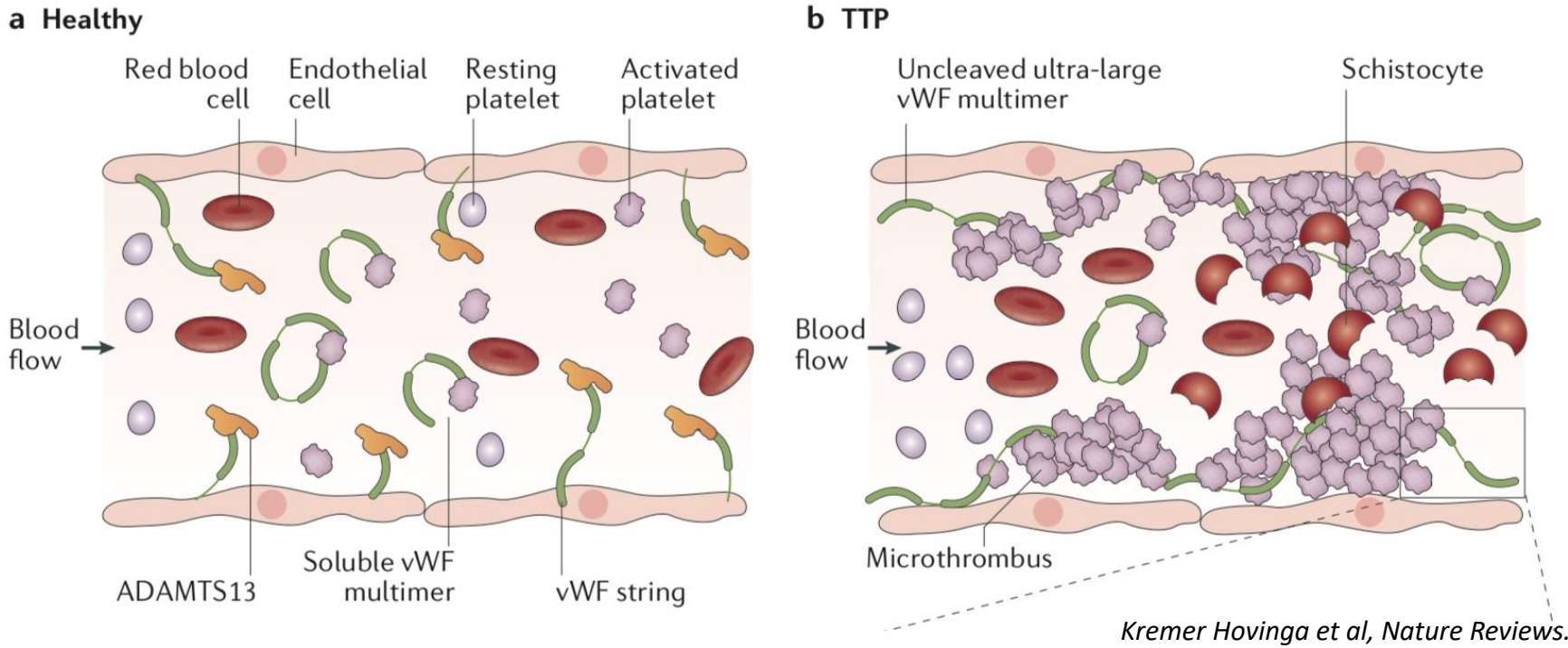
Angiodysplasia



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

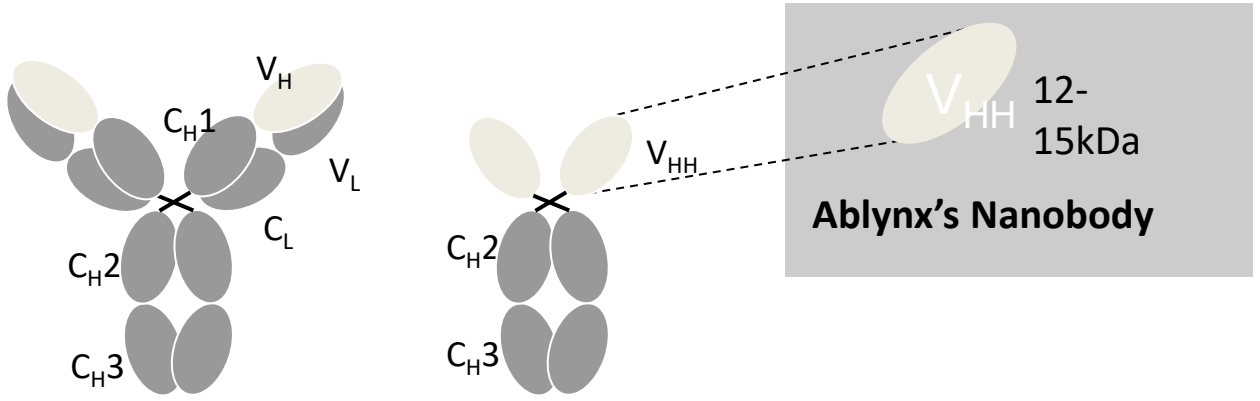
Acquired Thrombotic Thrombocytopenic Purpura (aTTP)

- **Very rare condition: incidence 1.5 to 6 per million people per year**
- **Impaired ADAMTS13 activity leads to accumulation of constitutionally active ultra-large vWF multimers**



Kremer Hovinga et al, Nature Reviews. 2017

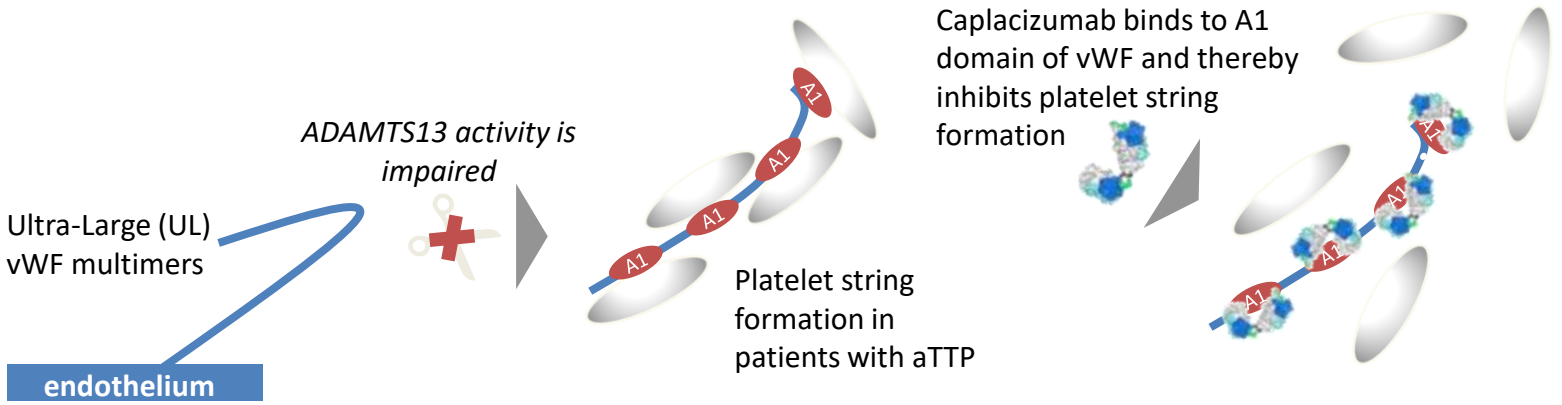
Caplacizumab in aTTP



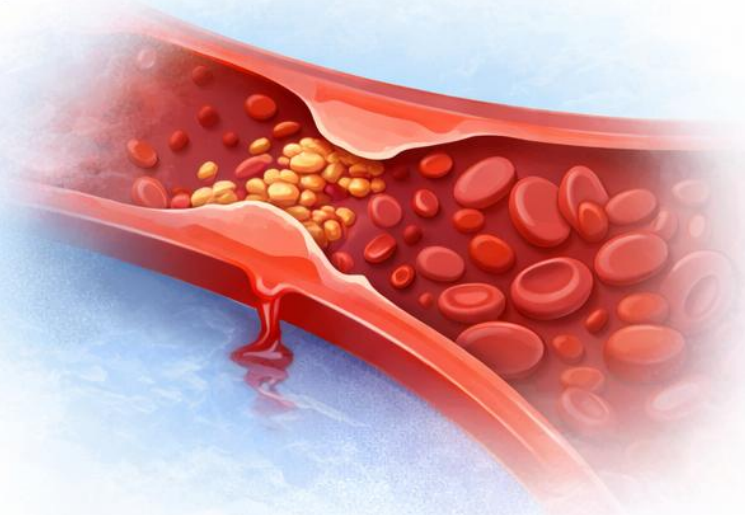
Conventional antibodies

Heavy chain only antibodies

Caplacizumab is bivalent nanobody that inhibits ULvWF mediated platelet aggregation by blocking the interaction between the A1 domain of VWF and the platelet receptor GPIb-IX-V.



« GOOD » CLOT

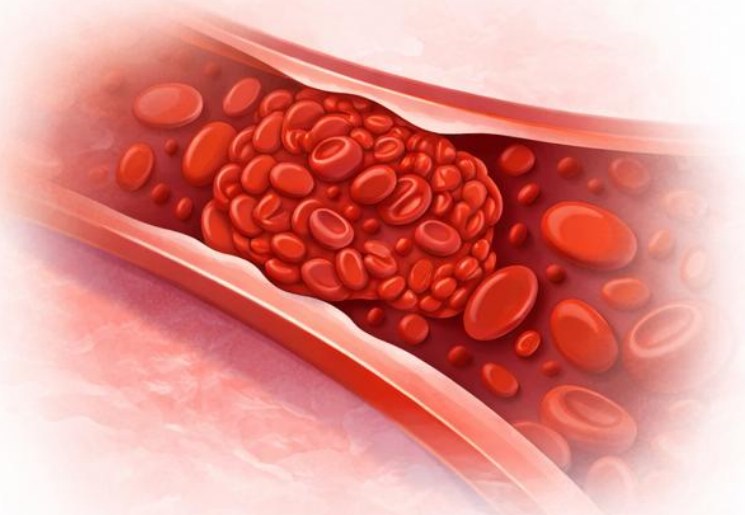


Haemostasis

Stop bleeds

This is what patients with inherited bleeding disease expect from their treatment

« BAD » CLOT

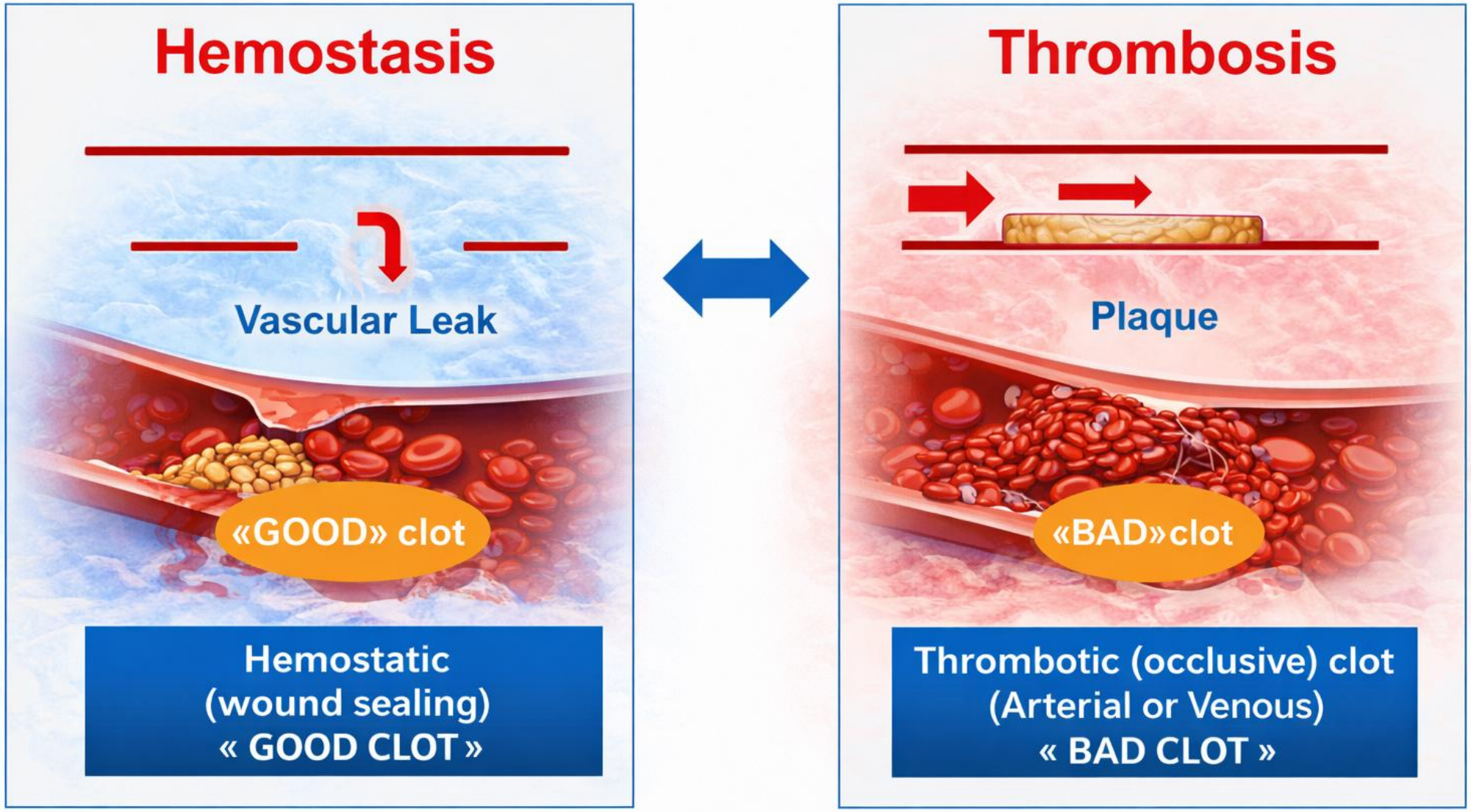


Thrombosis

Occlusion

Is this what patients with inherited bleeding disease should fear from their treatment ?

Haemostatic versus Occlusive Blood CLOT



The spectrum of inherited bleeding diseases

Hemophilia A/B

Von Willebrand Disease
Low VWF

Factor VII deficiency
Factor X deficiency
Factor XI deficiency

Fibrinogen (Fg) deficiency

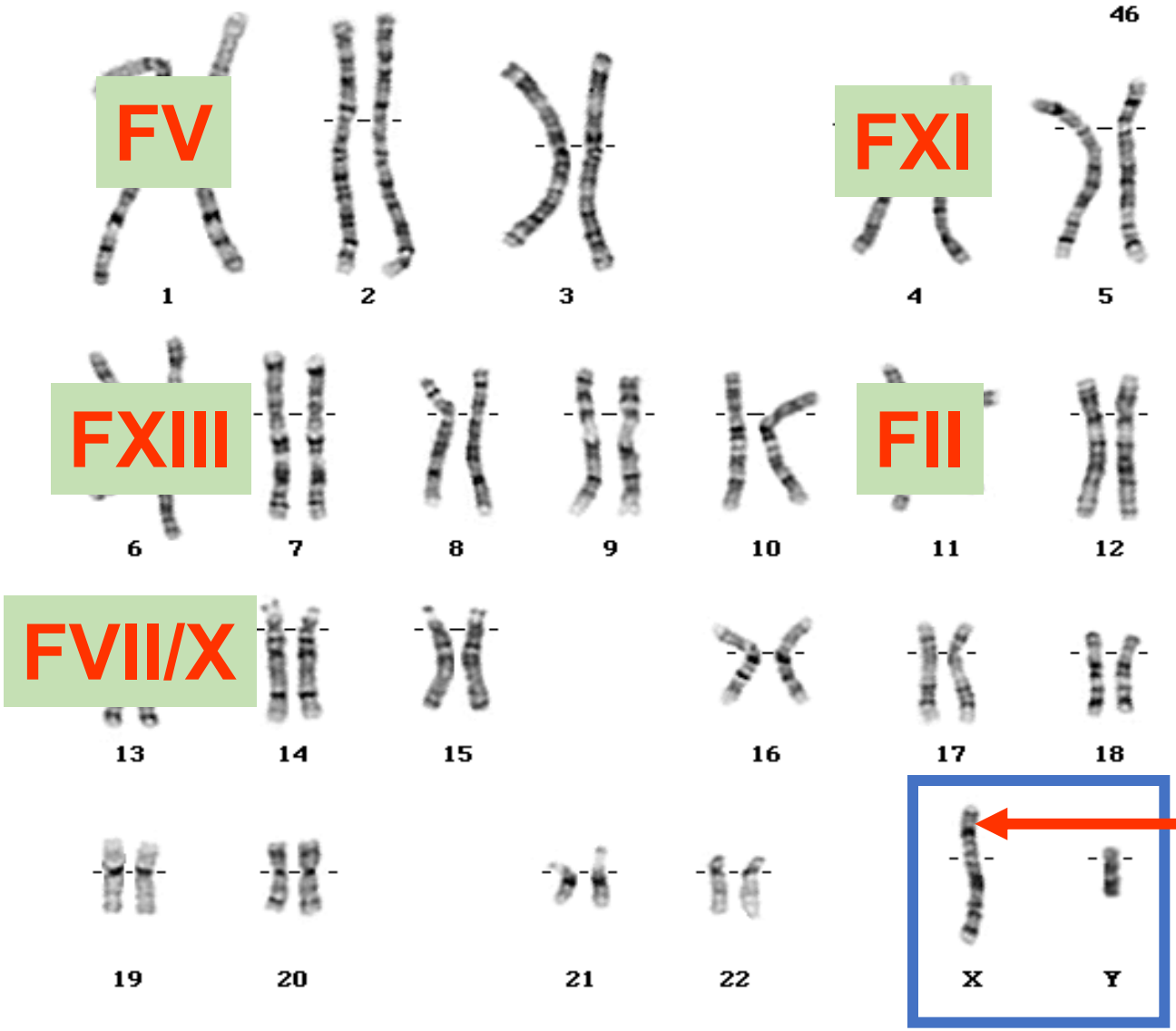
Factor V deficiency

Factor XIII deficiency

Platelet dysfunction

Collagen vascular diseases

Osler Rendu Disease



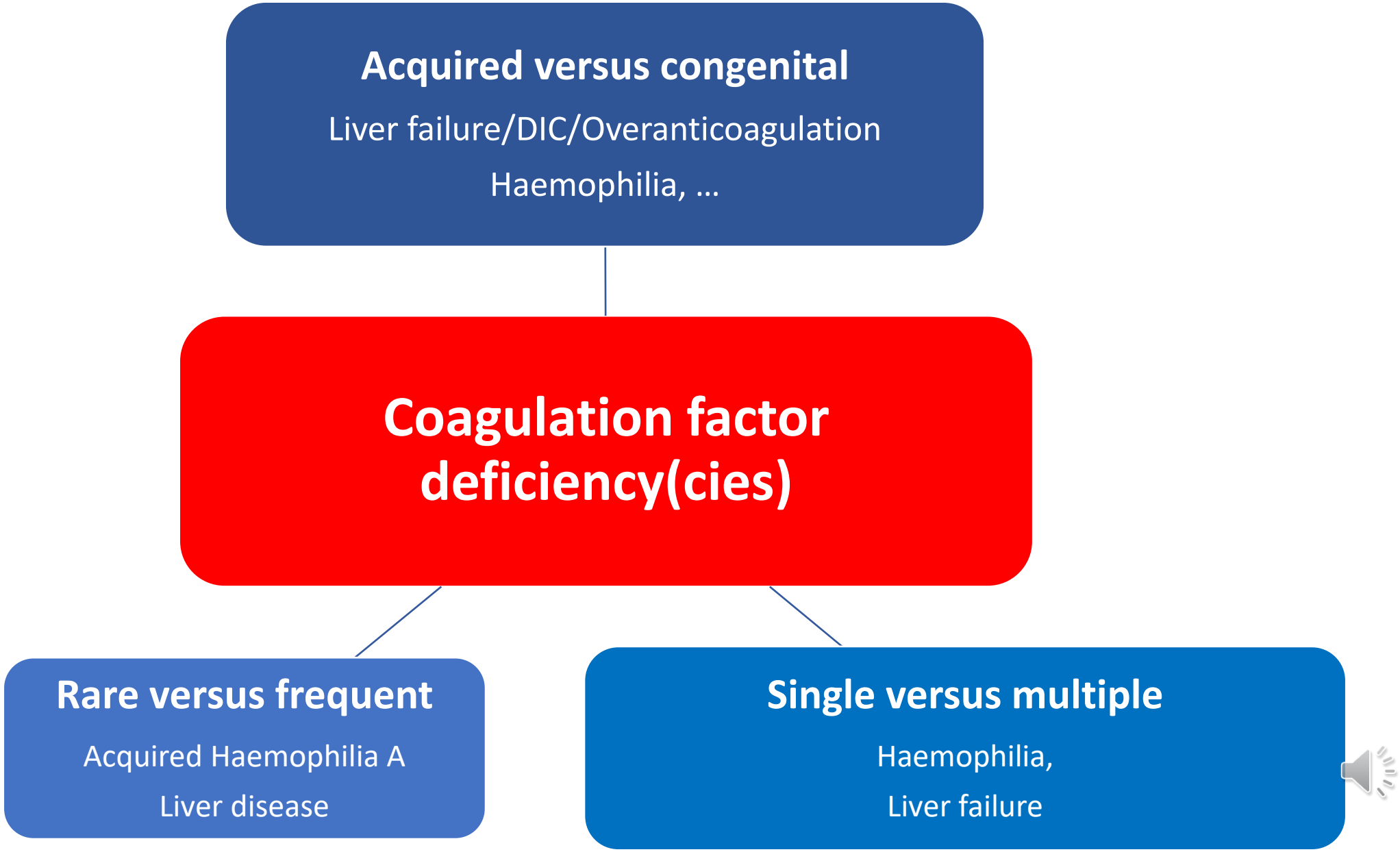
Genetic transmission of other clotting factors :
- Not X-Linked
- Autosomal recessive
- Very rare (consanguinity)

Haemophilia A and B

FVIII - FIX

X-linked

X Y


Acquired versus congenital
Liver failure/DIC/Overanticoagulation
Haemophilia, …
Coagulation factor deficiency(cies)
Rare versus frequent
Acquired Haemophilia A
Liver disease
Single versus multiple
Haemophilia,
Liver failure

Classical theory of the coagulation cascade

Intrinsic pathway

Contact Phase
FXII

FXI

FIX + FVIII

Extrinsic pathway

Tissue Factor
+ FVIIa

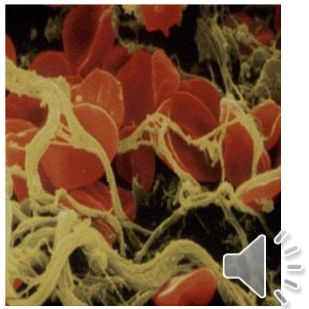
Common pathway

FX

FV

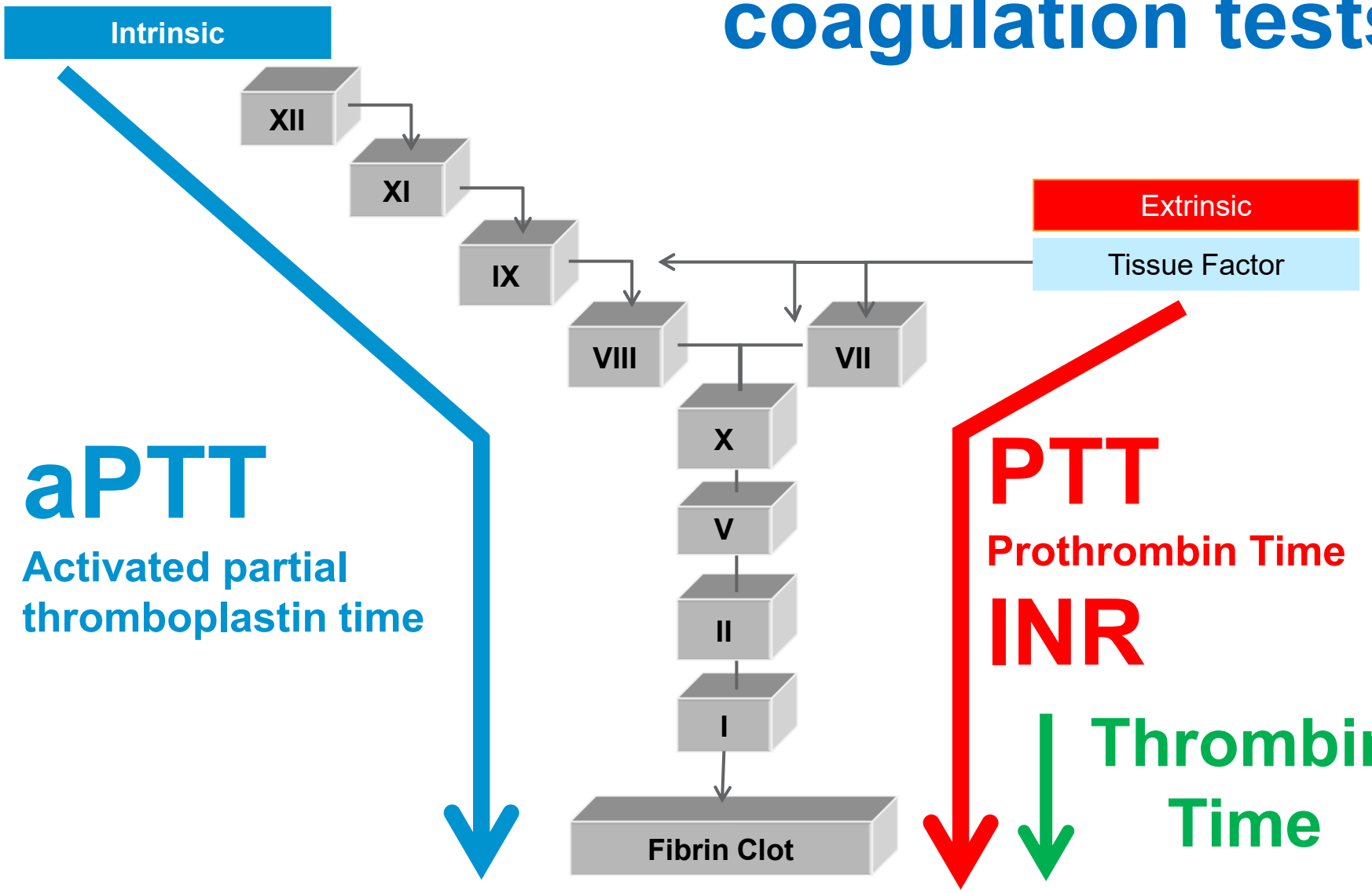
Thrombin

Fibrinogen → Fibrin

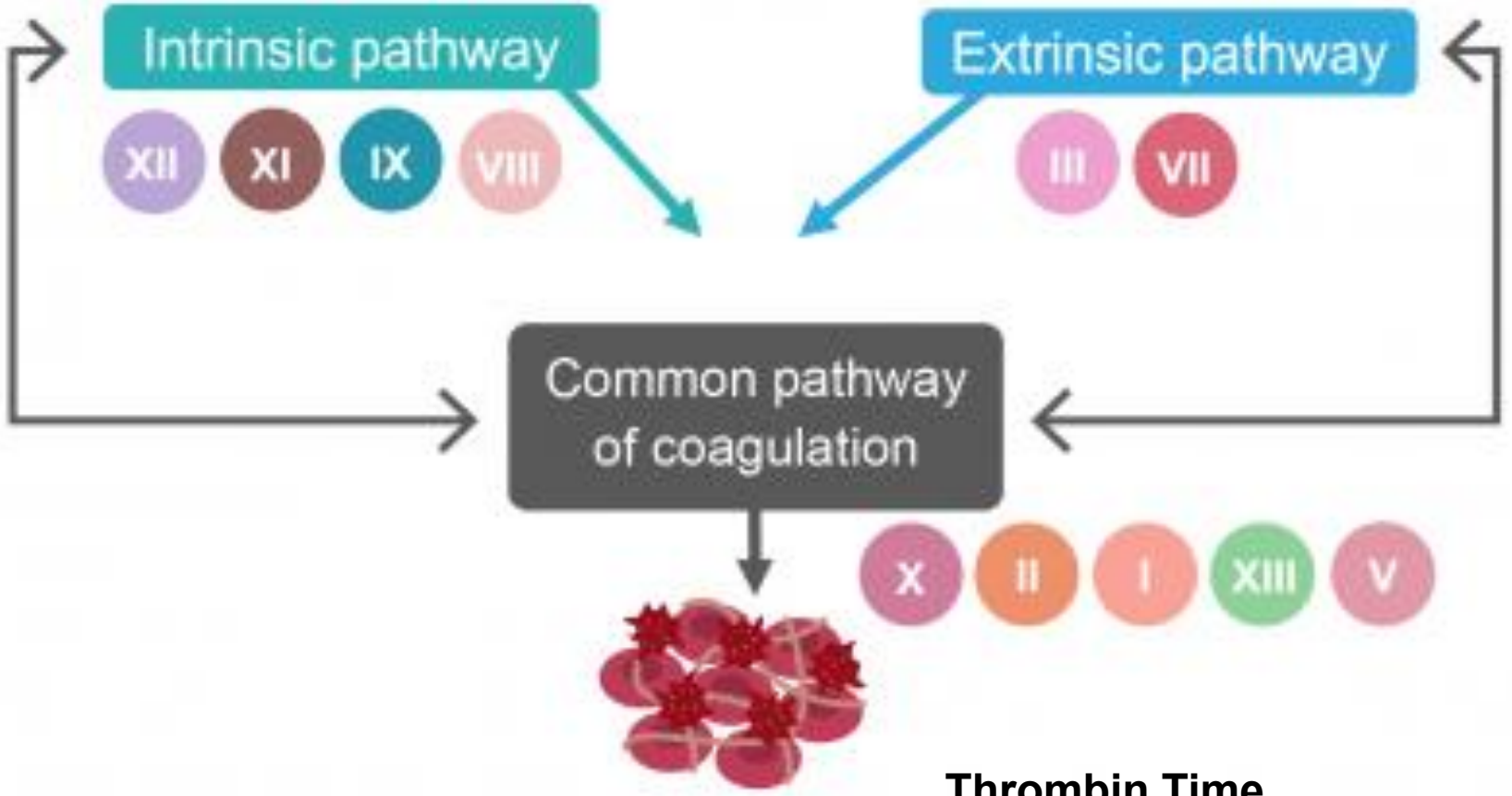


Blood clot

Interpretation of routine coagulation tests



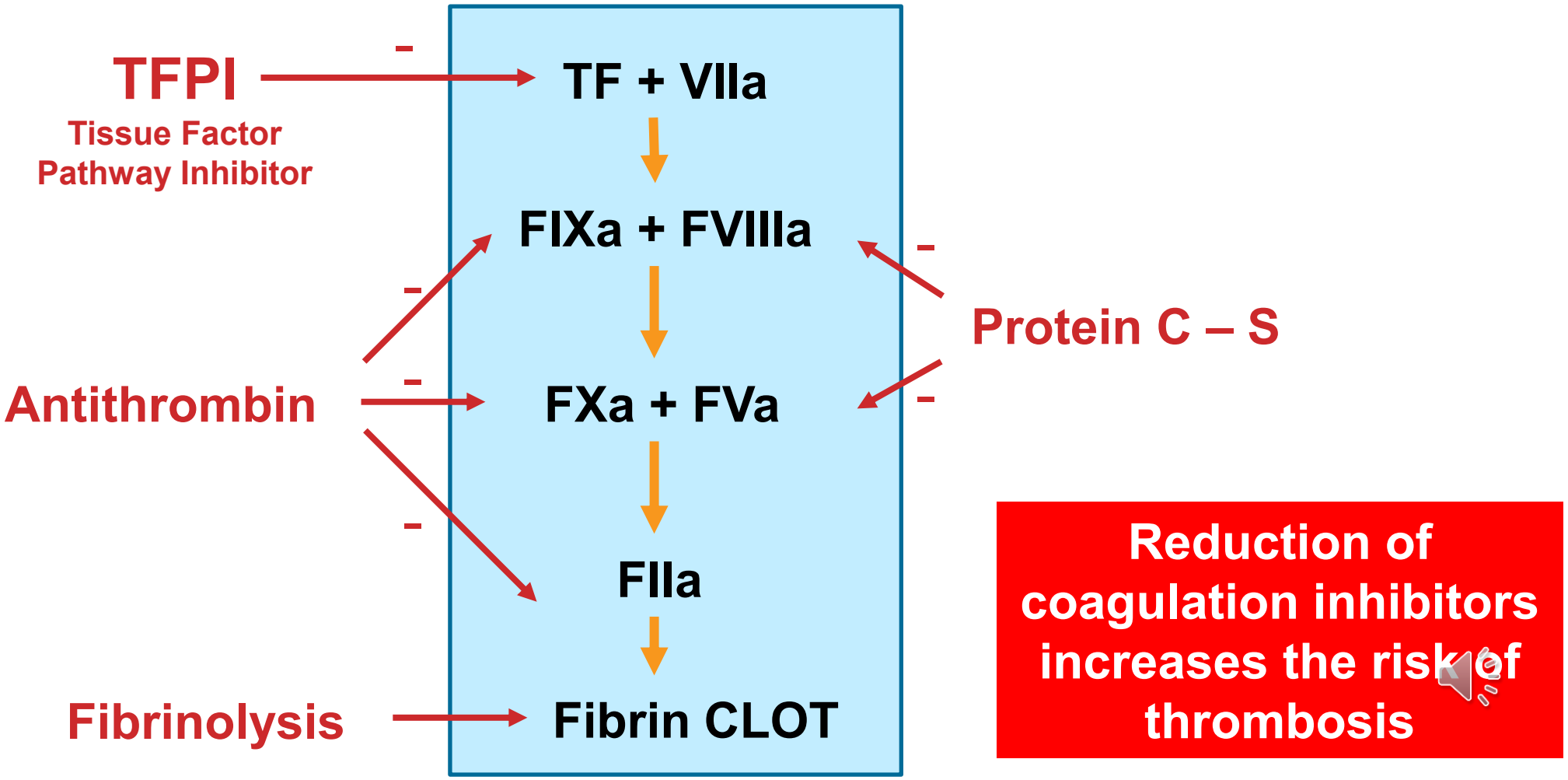
TCA
APTT



Prothrombin
Time

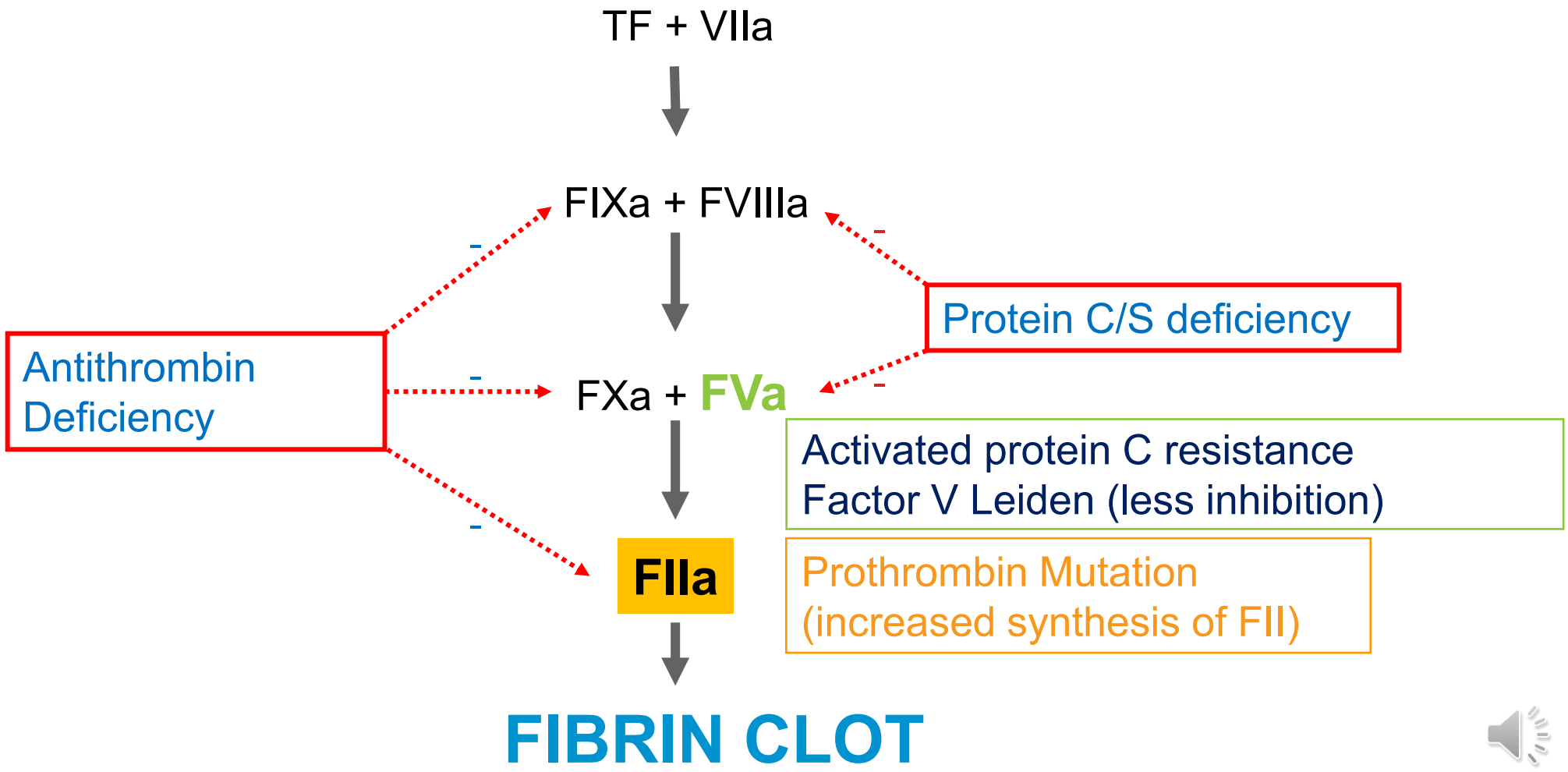
Thrombin Time
Conversion of Fg into Fibrin

Physiological inhibitors of blood coagulation



Reduction of coagulation inhibitors increases the risk of thrombosis

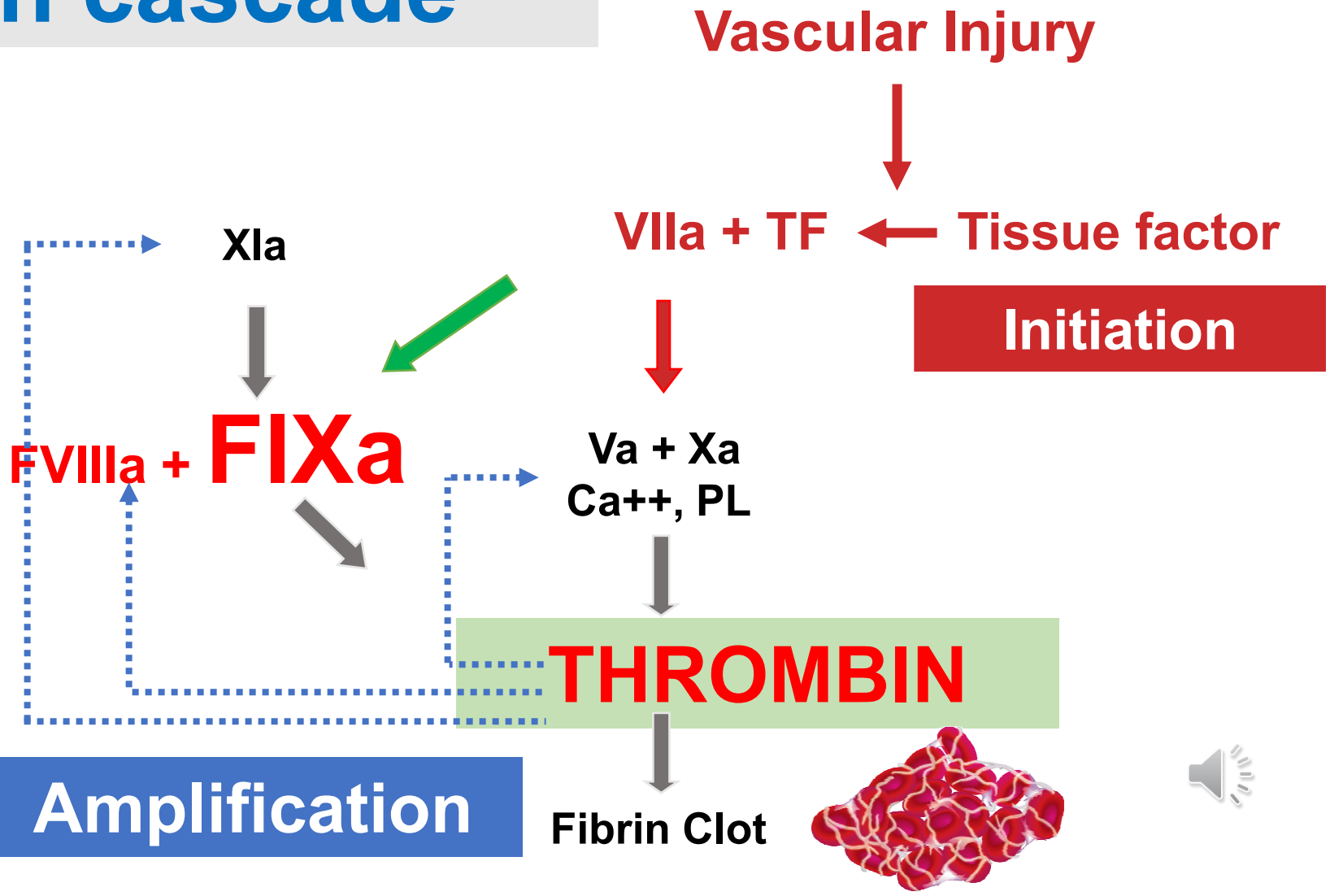
Hereditary thrombophilia



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

BLOOD COAGULATION DISORDERS

Thrombin production / generation

LOW THROMBIN → **BLEEDING**

- Haemophilia
- Other clotting factors deficiencies
- Excessive anticoagulation

HIGH THROMBIN → **THROMBOSIS**

- Hypercoagulability
- Thrombophilia

Thrombin is not routinely measured by blood tests

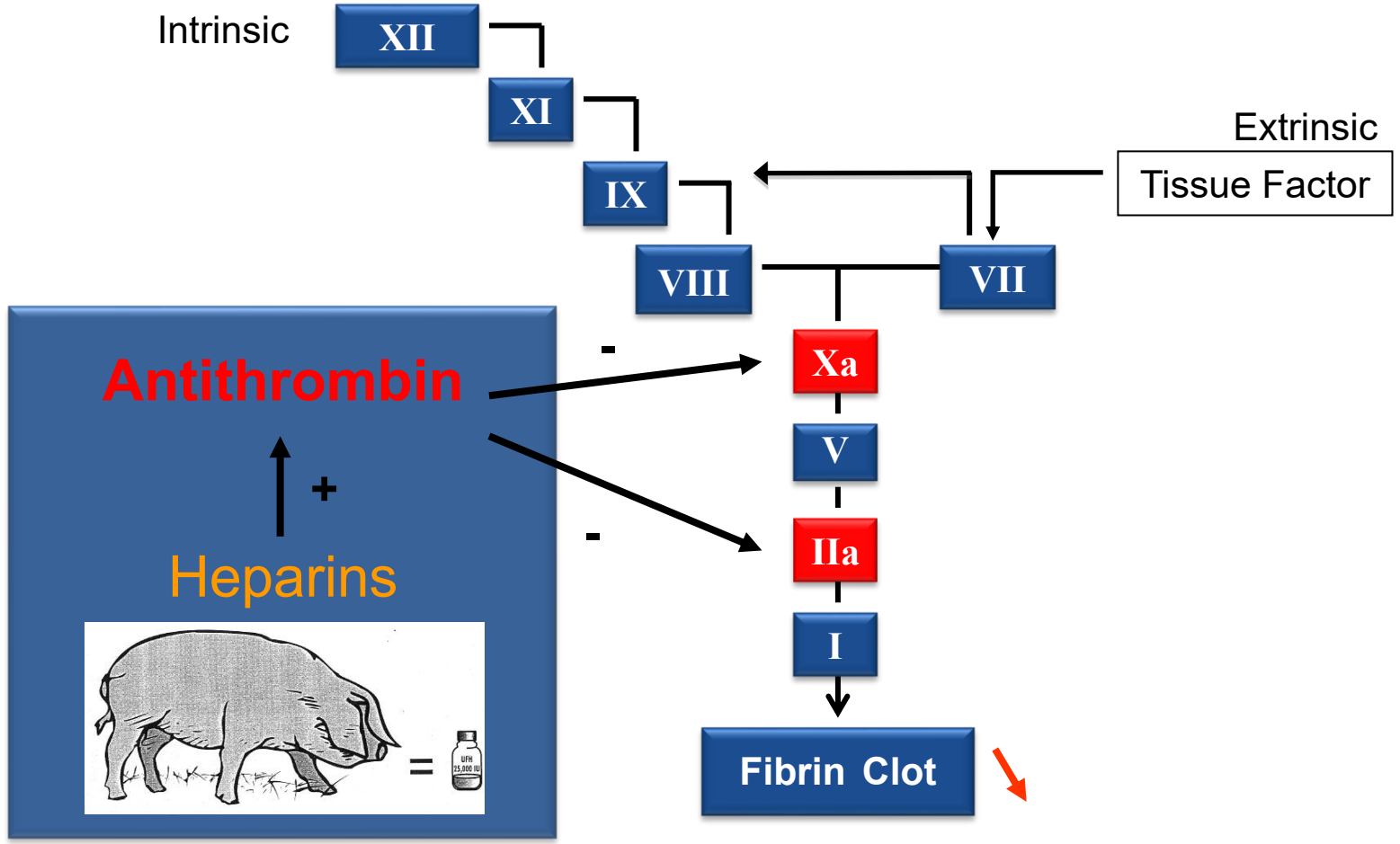
Inhibiting blood coagulation: Anticoagulant agents



INDIRECT AND DIRECT ANTICOAGULANTS : MULTIPLE- VERSUS SINGLE-FACTOR INHIBITION

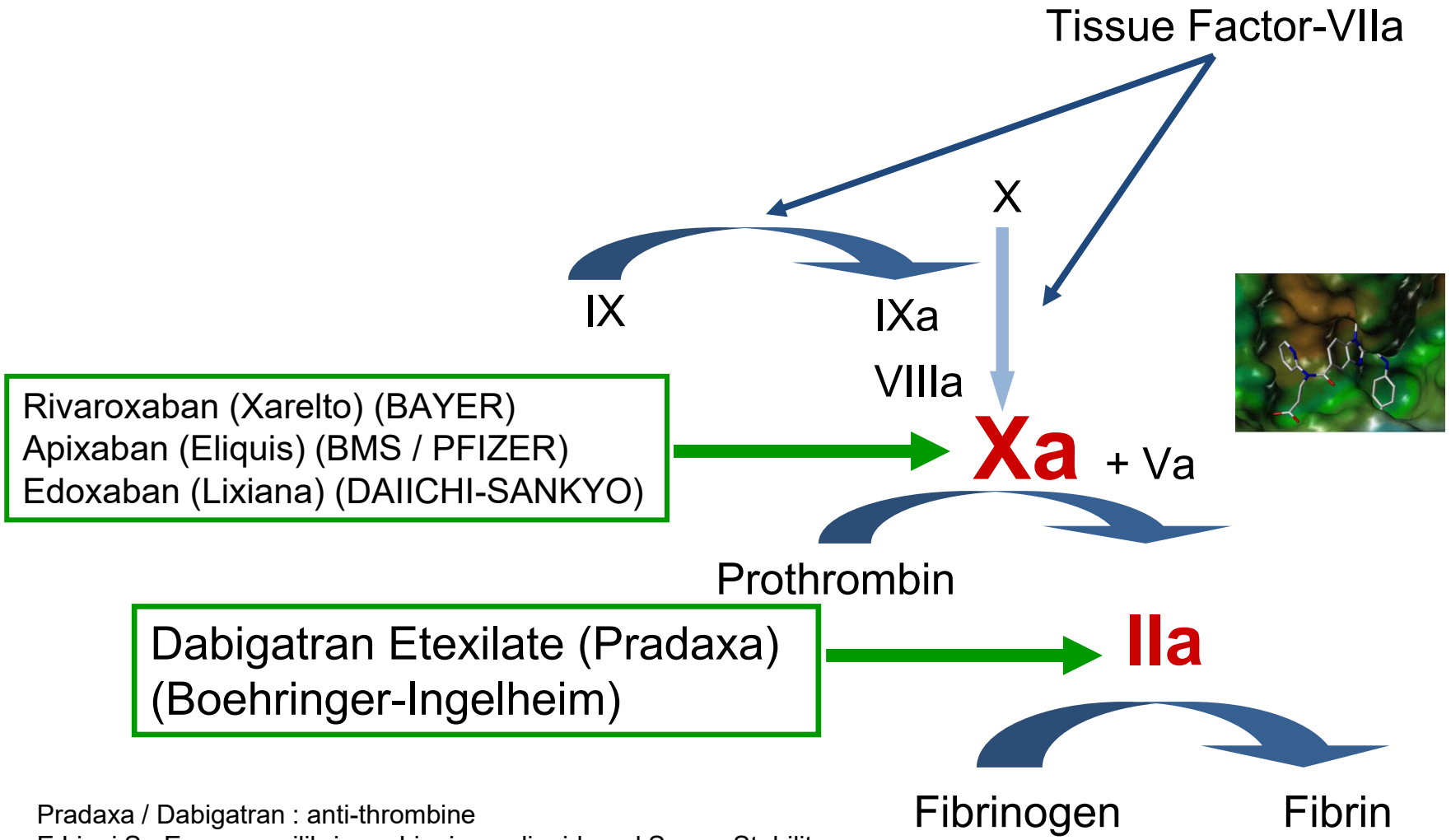
	Vitamin K Antagonists	Heparins	Anti-Xa Anti-IIa
Mode of action	Interference with vit K recycling	Potentiation of antithrombin	Direct inhibition of FXa or FIIa
Targets	FII, FVII, FIX, FX Reduced synthesis	Indirect inhibition of FXa and FIIa	Selective inhibition of FXa or FIIa
Indication	Universal anticoagulants including mechanical Cardiac Valve	Universal anticoagulants Acute phase of PE	Prevention and treatment of VTE (DVT/PE) Prevention of stroke in AF

HEPARINS
MODE OF ACTION



Direct Oral AntiCoagulants (DOACs)

Direct and targeted inhibition of clotting Factors Xa or IIa

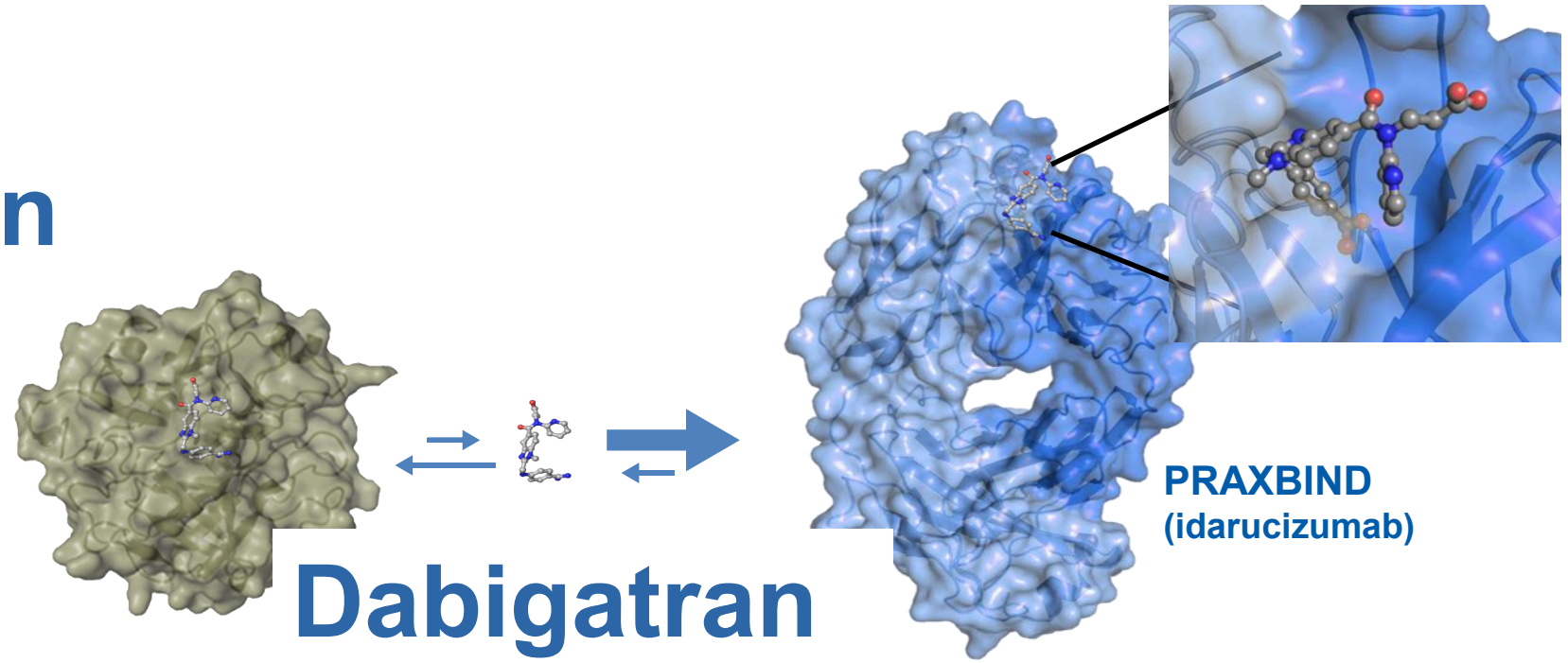


Pradaxa / Dabigatran : anti-thrombine
E Liqui S : E pour equilibrium - Liqui pour liquid and S pour Stability
Xarelto : Xa, RELiable, Treatment, Oral

Reversing inhibition of the coagulation cascade by neutralizing antibodies

Idarucizumab (Praxbind) Mode of action

Thrombin



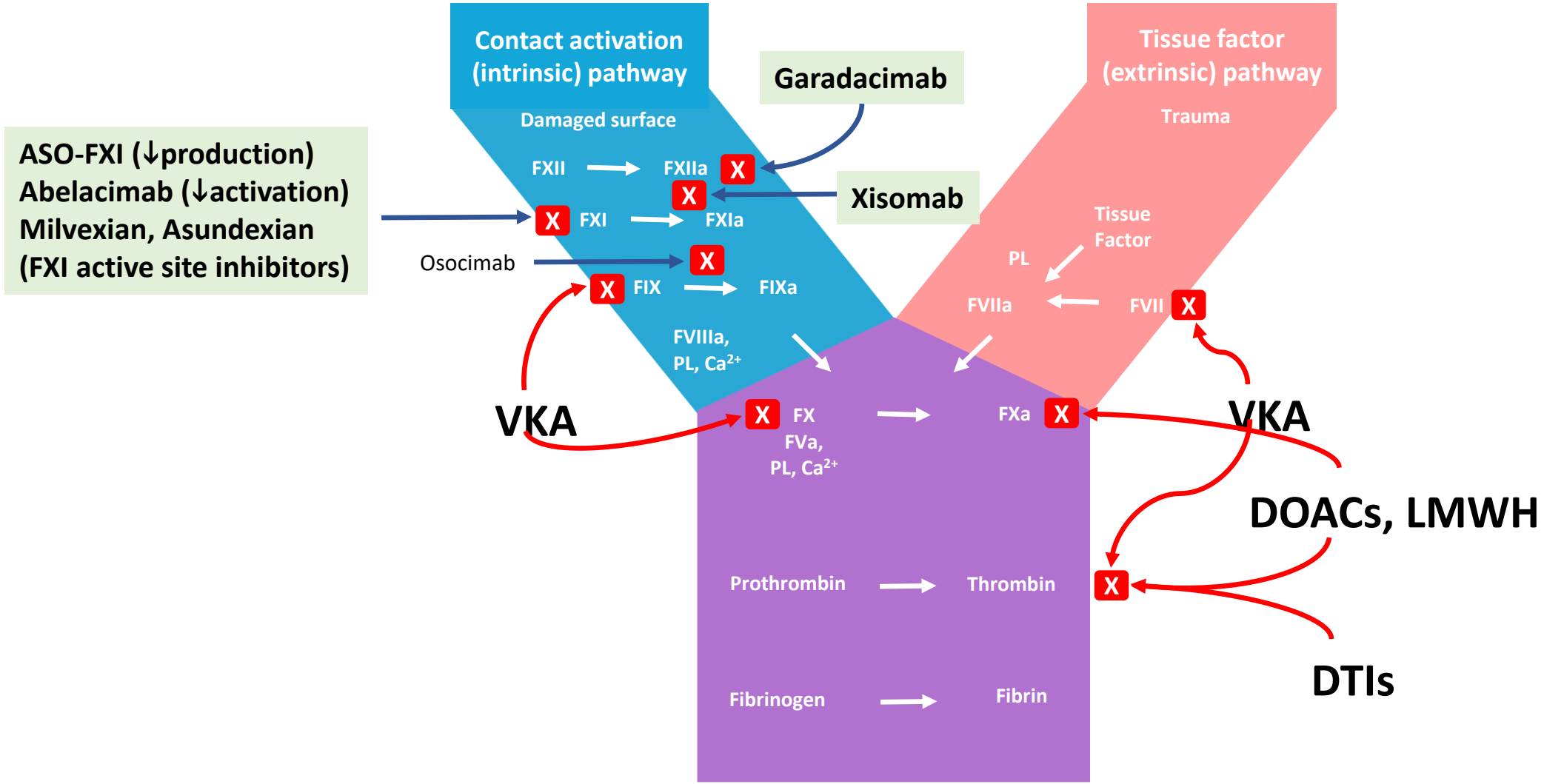
Dabigatran

Praxbind : Monoclonal antibody with a high affinity for Pradaxa / Dabigatran

Schiele F et al. Blood 2013

FXI and FXII as targets for new anticoagulants




ASO-FXI (↓production)
Abelacimab (↓activation)
Milvexian, Asundexian
(FXI active site inhibitors)
Contact activation (intrinsic) pathway
Damaged surface
Garadacimab
Xisomab
FXII
FXIIa
FXI
FXIa
Osocimab
FIX
FIXa
FVIIIa, PL, Ca2+
Tissue factor (extrinsic) pathway
Trauma
Tissue Factor
PL
FVIIa
FVII
VKA
FX
FVa, PL, Ca2+
FXa
VKA
DOACs, LMWH
Prothrombin
Thrombin
DTIs
Fibrinogen
Fibrin

FXI and FXII as targets for new anticoagulants ?

- FXII (and FXI) are mainly involved in the formation of bad clots
- Inhibiting FXII (and FXI) would preserve the haemostatic potential
- Less risk of bleeding complication

ATVB Named Lecture Review

2017 Scientific Sessions Sol Sherry Distinguished Lecture in Thrombosis

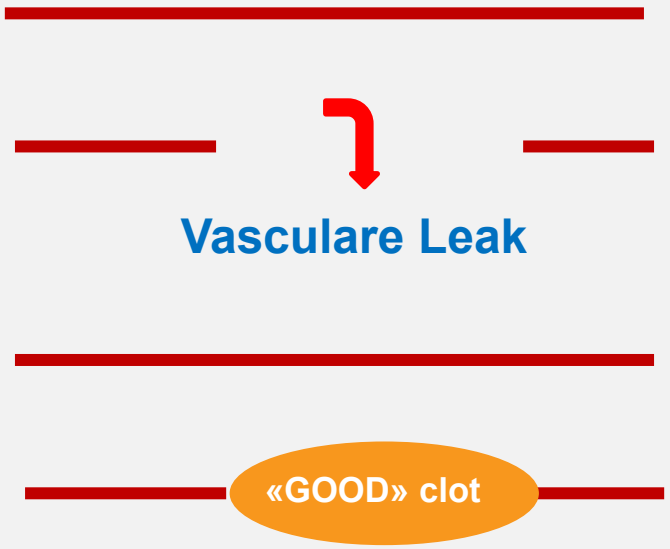
Factor XI as a Target for New Anticoagulants

Jeffrey I. Weitz, James C. Fredenburgh

Abstract—The goal of anticoagulant therapy is to attenuate thrombosis without compromising hemostasis. Although the direct oral anticoagulants are associated with less intracranial hemorrhage than vitamin K antagonists, bleeding remains their major side effect. Factor XI has emerged as a promising target for anticoagulants that may be safer than those currently available. The focus on factor XI stems from epidemiological evidence of its role in thrombosis, the observation of attenuated thrombosis in factor XI–deficient mice, identification of novel activators, and the fact that factor XI deficiency is associated with only a mild bleeding diathesis. Proof-of-concept comes from the demonstration that compared with enoxaparin, factor XI knockdown reduces venous thromboembolism without increasing bleeding after elective knee arthroplasty. This article rationalizes the selection of factor XI as a target for new anticoagulants, reviews the agents under development, and outlines a potential path forward for their development. (*Arterioscler Thromb Vasc Biol*. 2018;38:00-00. DOI: 10.1161/ATVBAHA.117.309664.)

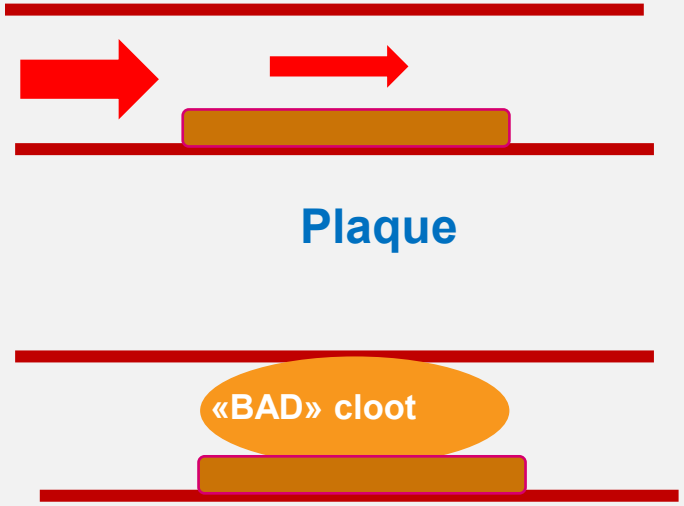
American Heart Association.

Hemostasis



Hemostatic
(wound sealing)
« GOOD CLOT »

Thrombosis



Thrombotic (occlusive) clot
(Arterial or Venous)
« BAD CAILLOT »

STOP with anti-Xa

OK with anti-XIa

STOP with anti-Xa

STOP with anti-XIa

Anti-FXIa : Decoupling hemostasis and thrombosis

The coagulation cascade and replacement therapy : Substitution of the missing factor(s)



The concept of replacement therapy

- Many diseases are associated with clotting factor(s) deficiency (acquired or congenital)

- Treatment options are multiple :
  - Fresh Frozen Plasma (FFP
  - Factor concentrate (plasma-derived or recombinant, inactive or active form)
  - Complex of clotting factor concentrates

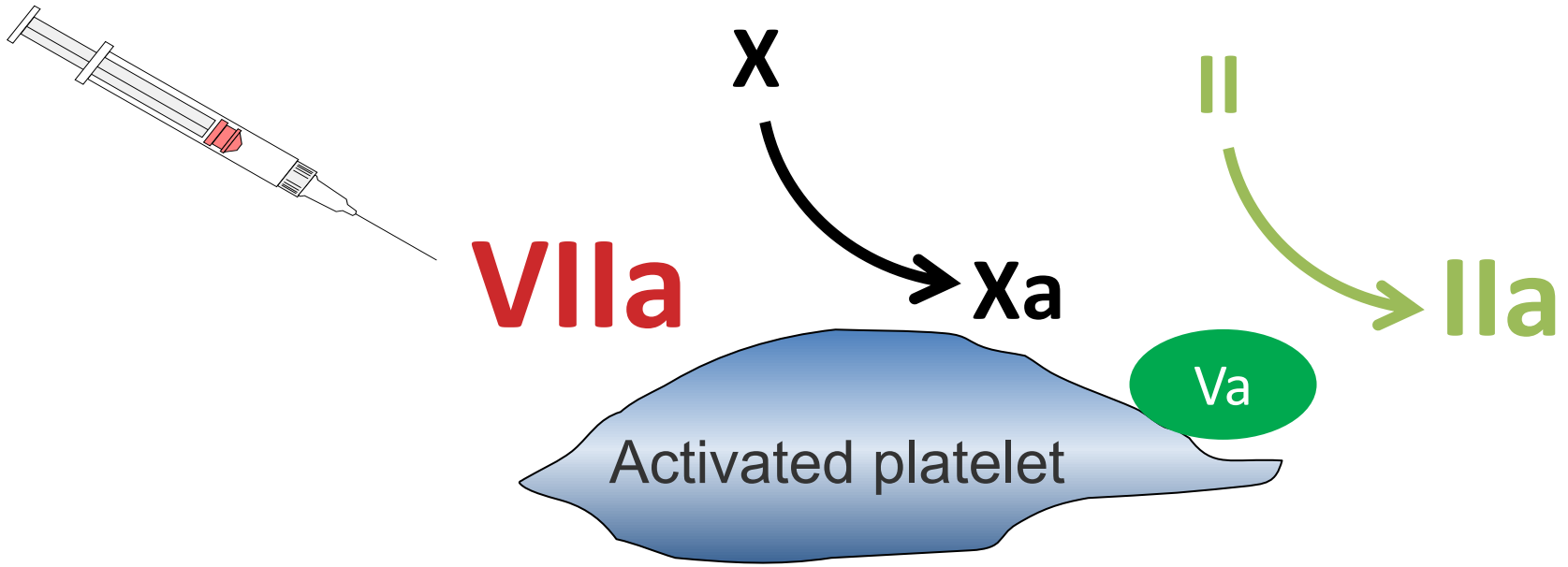


Treatment of bleeding disorders

Defect	Treatment options
Primary haemostasis	Platelet concentrates DDAVP (Minirin) FVIII-vWF/ Pure VWF concentrates Antifibrinolytics
Coagulation cascade Thrombin generation Fibrin formation	Fresh frozen plasma (FFP) FVIII, FIX, (FXI) FVII, (FI : Fibrinogen) rFVIIa (Novoseven) PCC (II, VII, IX et X) aPCC
Fibrinolysis	Tranexamic acid (Exacyl) Aprotinin (Trasylol)



Recombinant Activated Factor VII (rFVIIa) (Novo Seven): a potent hemostatic agent

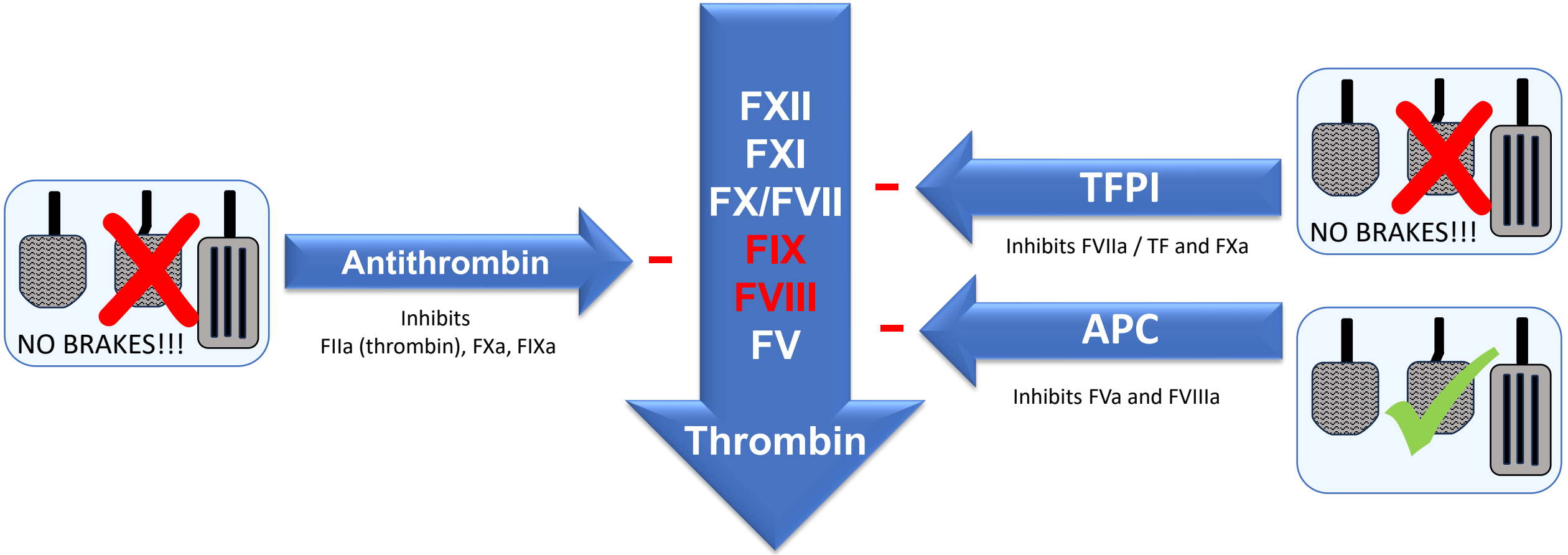


Generation of FXa at the platelet surface following administration of recombinant active FVII (rFVIIa)



Rebalancing the coagulation cascade in haemophilia

The coagulation cascade is strictly controlled by physiological inhibitors



Antithrombin, TFPI and APC inhibit the coagulation cascade

APC: Activated protein C; TFPI: Tissue factor pathway inhibitor.
Figure developed by speaker.
Lee CA, et al. Textbook of Hemophilia, Third edition. Jon Wiley & Sons, 2014.

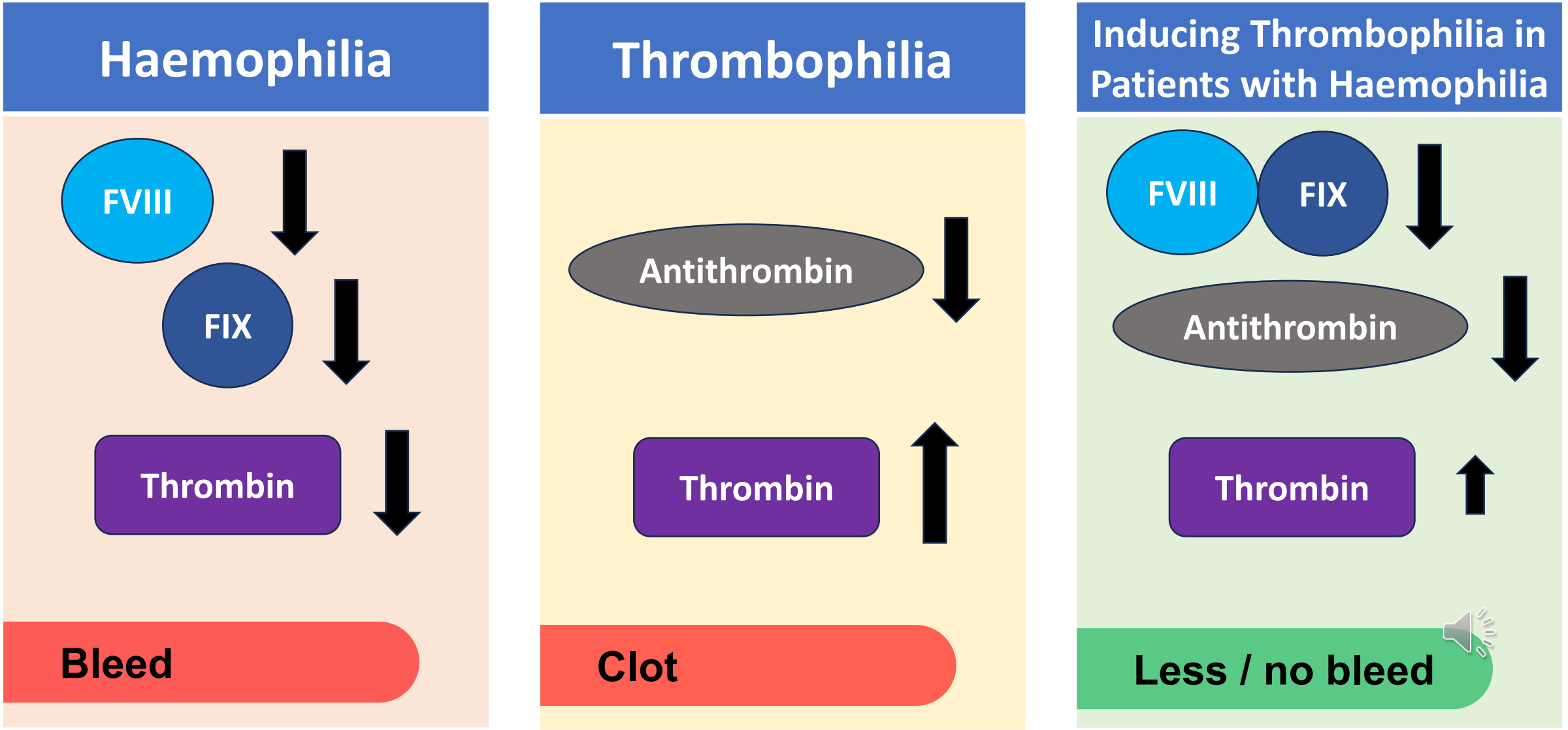
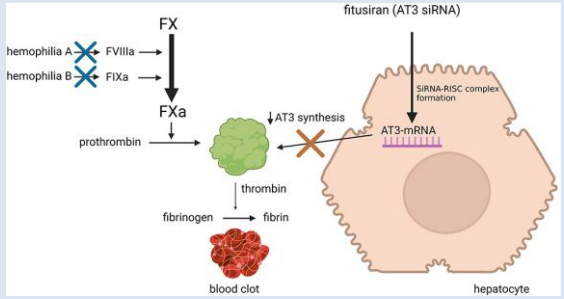


Figure developed by speaker.
Hermans C. *Hemasphere* 2023;7(6):e918.

Rebalancing agents and thrombosis

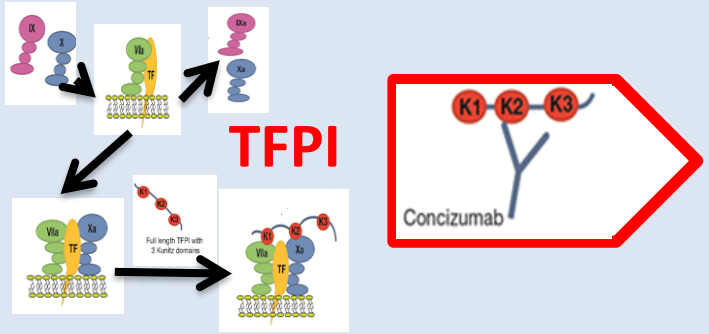
FITUSIRAN



Reduced production of antithrombin by the liver

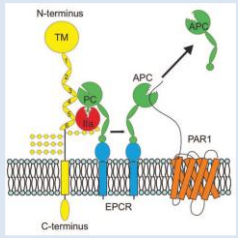
https://doi.org/10.2147/JBM.S390521

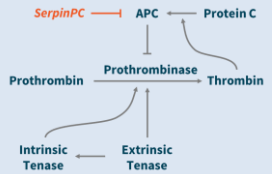
TFPI-INHIBITORS



Inhibition of TFPI in the blood

SERPIN-PC





Inhibition of APC in the blood

Cases of thrombosis

Precipitating factors :

Low AT : 10-20 % or < 10 %

Concomitant FVIII or FVIIa

Comorbidities

New target : 15-35 % AT

Concizumab

Thrombotic events

Dose reduction

Marstacimab

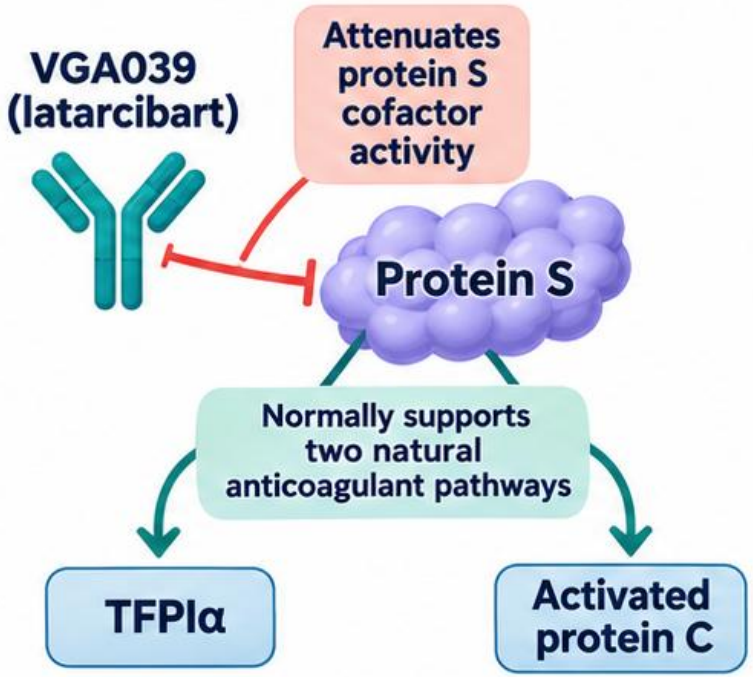
Thrombotic events

Zero thrombosis in phase 1/2

VGA039 (latarcibart)

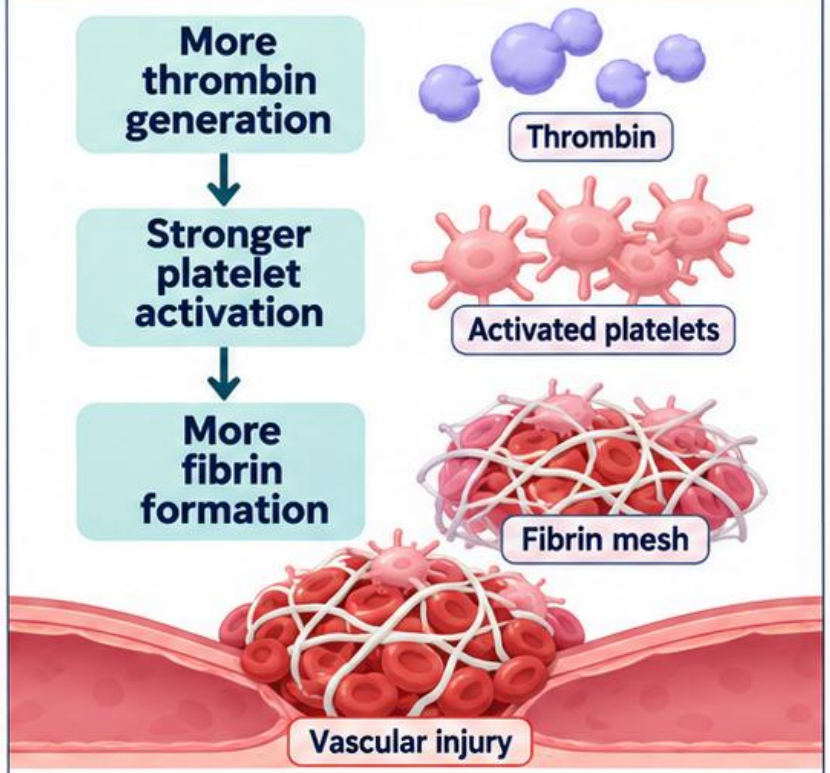
Enhancing haemostasis by targeting protein S

1 HOW IT WORKS



Reduces two natural brakes on coagulation

2 WHAT IT DOES



Does not replace VWF or FVIII

3 WHO COULD BENEFIT



People with von Willebrand disease

Across VWD types • Under clinical evaluation

Other bleeding disorders: exploratory potential

Less anticoagulant restraint → more thrombin → stronger haemostasis

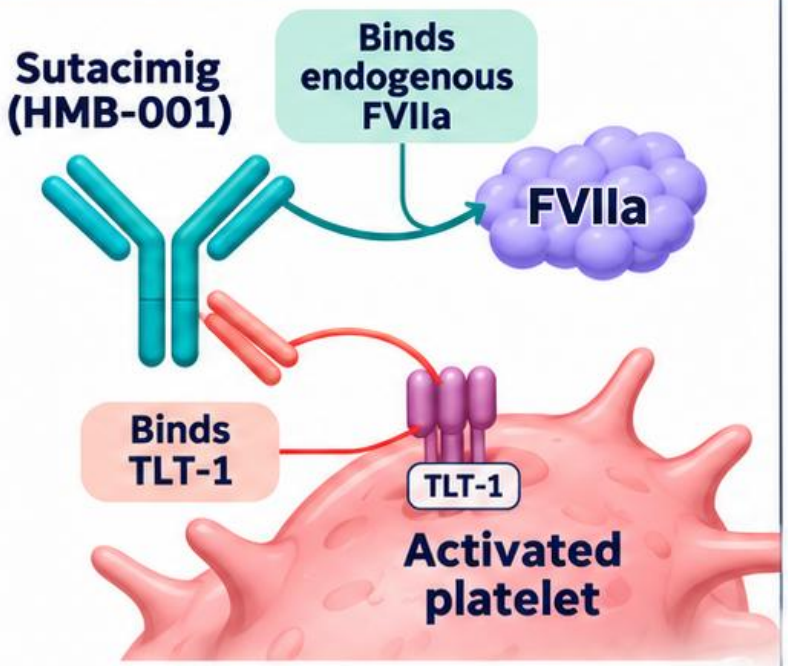
Investigational therapy • Phase 3 in VWD • Monthly subcutaneous dosing under study • Efficacy and thrombotic safety require confirmation

Sources: VIVID-6 (NCT07115004); Incyte Medical Information • November 2026

Sutacimig (HMB-001)

Concentrating endogenous FVIIa at activated platelets

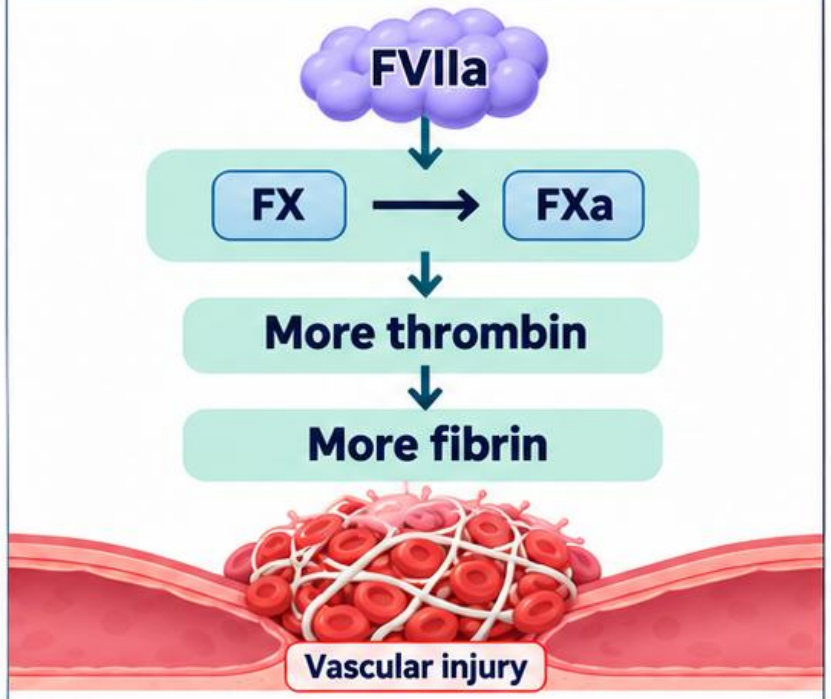
1 HOW IT WORKS



Stabilizes FVIIa and increases its circulating availability

Recruits FVIIa to activated platelets

2 WHAT IT DOES



Reinforces clot formation at the injury site

Does not correct the αIIbβ3 defect in Glanzmann thrombasthenia

3 WHO COULD BENEFIT



Glanzmann thrombasthenia

Clinical prophylaxis data

Congenital factor VII deficiency

Early clinical investigation

Potential benefit depends on available, functional endogenous FVII(a)

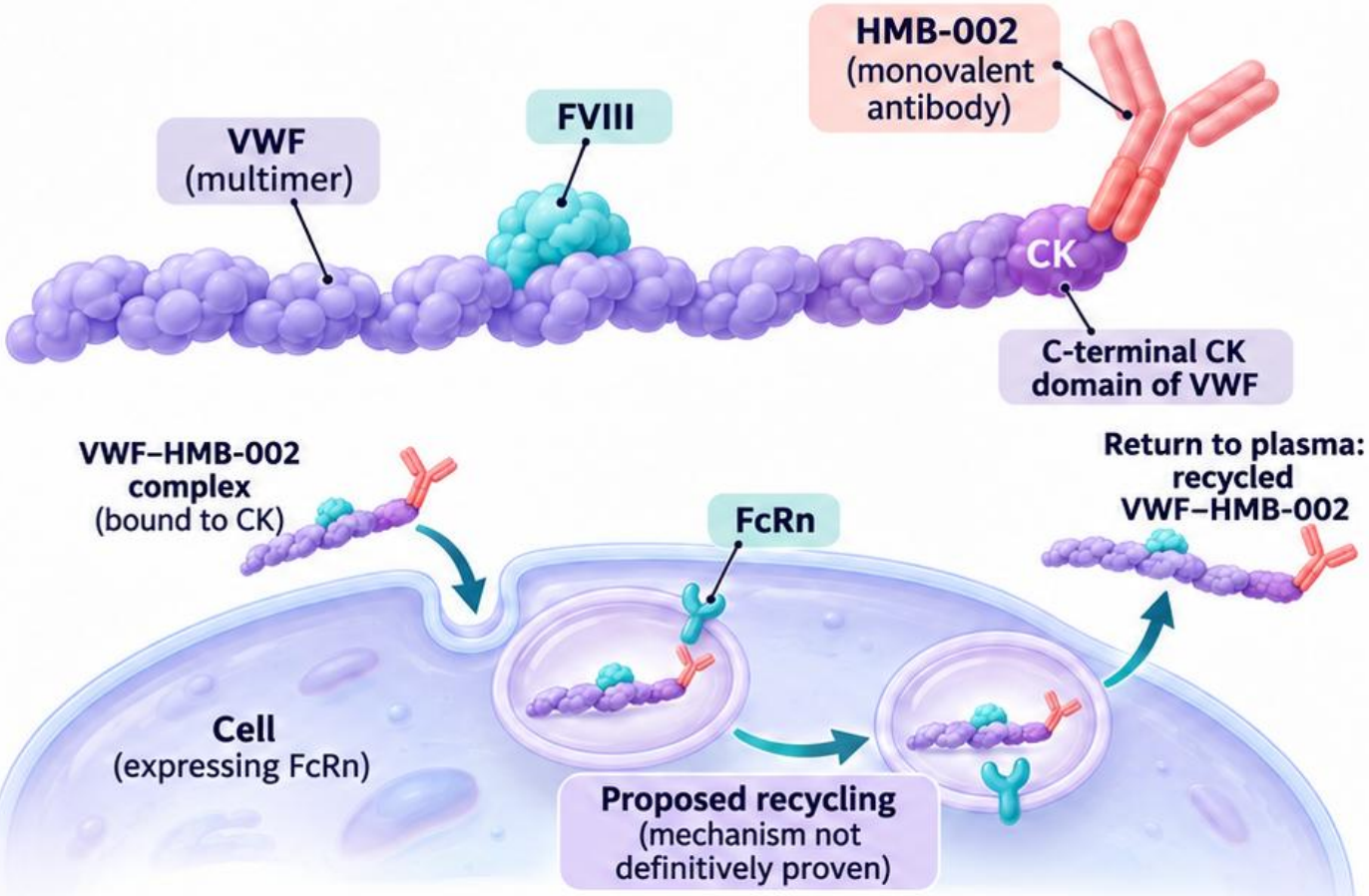
Stabilize FVIIa → target activated platelets → enhance local haemostasis

Investigational subcutaneous therapy • Thromboembolic events reported; dose and safety remain under evaluation

Sources: Hemab clinical updates, August–November 2026; NCT06211634; NCT07347249

HMB-002: prolonging VWF circulation

An antibody designed to increase circulating VWF and FVIII



Subcutaneous prophylaxis under investigation

Phase 1/2 — VELORA Pioneer

1 HOW DOES IT WORK?

- Binds to the C-terminal CK domain of VWF.
- Designed to slow clearance through a proposed FcRn recycling mechanism.

2 WHAT DOES IT DO?

- ↑ Circulating VWF
- ↑ FVIII, carried and protected by VWF
- VWF functions preserved in preclinical studies.

3 WHO COULD BENEFIT?

- Potential mainly in type 1 von Willebrand disease with residual VWF.
- Does not directly correct qualitative VWF defects.
- Type 3: no endogenous VWF to prolong.

TAKE-HOME MESSAGE: retain available VWF for longer to support haemostasis.

Investigational treatment: clinical benefit and safety remain to be confirmed.

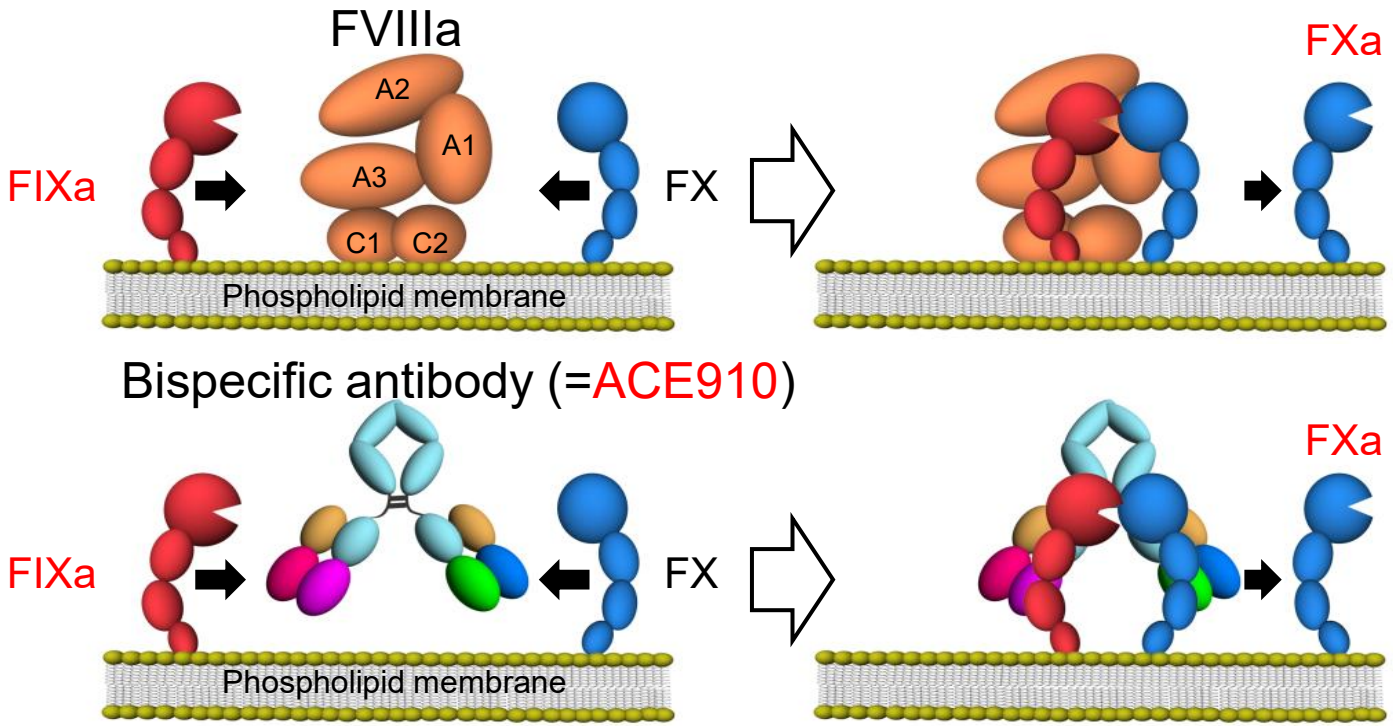
Sources: Häger et al., Blood Advances, 2026; VELORA Pioneer data, ISTH 2026.



Mimicking missing FVIII with a bispecific antibody

A revolutionary subcut treatment for patients with severe/moderate Hemophilia A

EMICIZUMAB / HEMLIBRA : MODE OF ACTION



Emicizumab is not FVIII but a so-called bispecific antibody that mimics the action of FVIII in coagulation.

FVIII

Intravenous administration
Short half-life
Neutralized by inhibitor

Emicizumab

Sub-cutaneous administration
Long half-life
Not affected by inhibitor

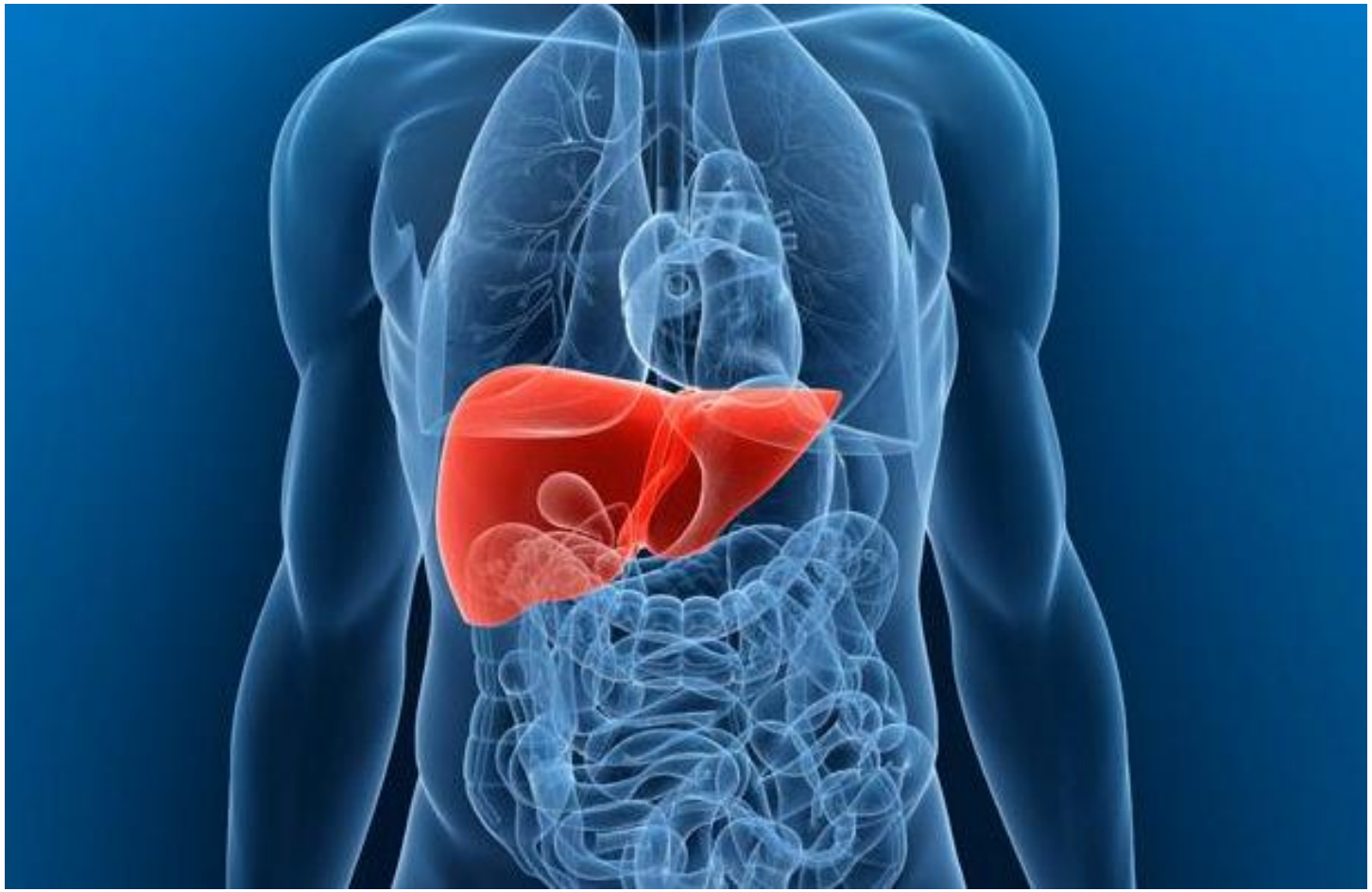
Kitazawa T, et al *Nat Med* 2012;18:1570.



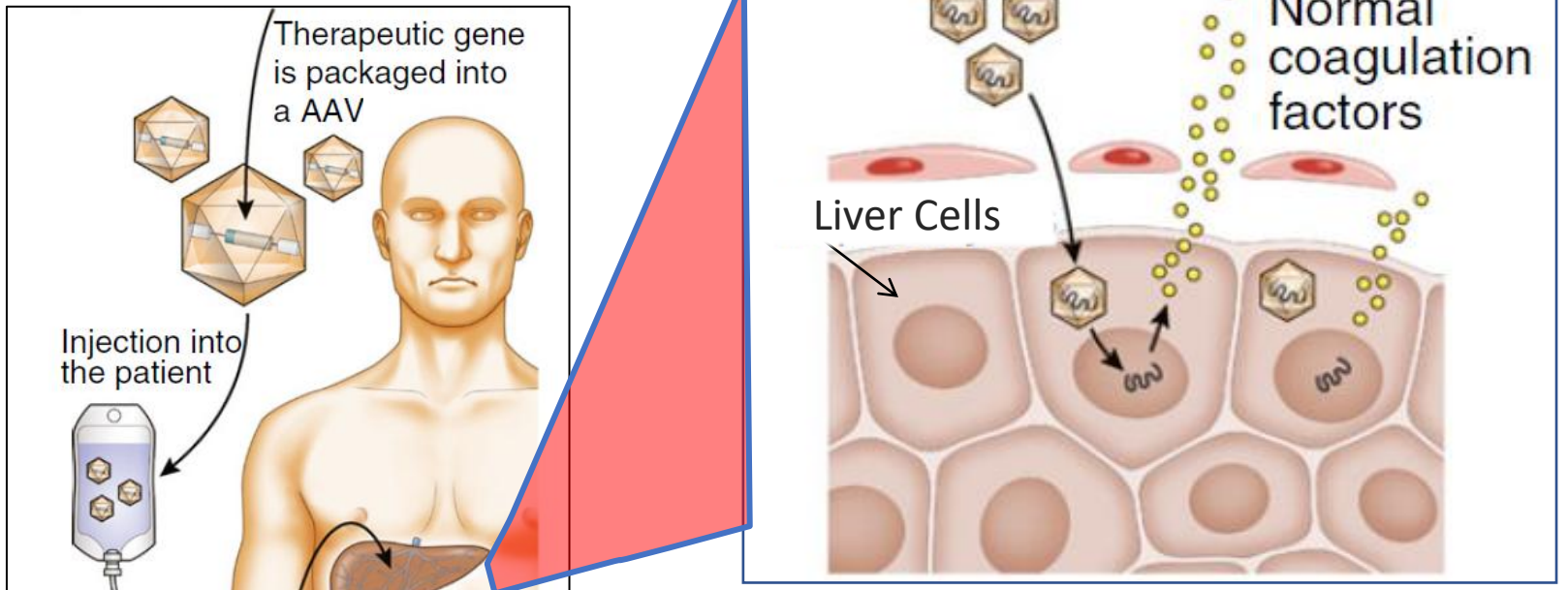
Correcting congenital clotting factor deficiency by gene therapy



HEMOPHILIA : LIVER-DIRECTED GENE THERAPY



Gene Therapy for Hemophilia



A working FIX or FVIII gene is packaged into a specially made carrier called AAV.

- In liver cells, FIX/FVIII gene taken to the nucleus
- The transferred gene does not change the existing genetic code in chromosomes
- Liver cells make functional FIX/FVIII

1. Ohmori et al. *J Thromb and Haemost*. 2015;13(S1):S133–S142. Figure adapted.

The largest haemophilia gene therapy clinical trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 17, 2022 VOL. 386 NO. 11

Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A

M.C. Ozelo, J. Mahlangu, K.J. Pasi, A. Giermasz, A.D. Leavitt, M. Laffan, E. Symington, D.V. Quon, J.-D. Wang, K. Peerlinck, S.W. Pipe, B. Madan, N.S. Key, G.F. Pierce, B. O'Mahony, R. Kaczmarek, J. Henshaw, A. Lawal, K. Jayaram, M. Huang, X. Yang, W.Y. Wong, and B. Kim, for the GENEr8-1 Trial Group*

NEW!

March 2022

The NEW ENGLAND JOURNAL of MEDICINE

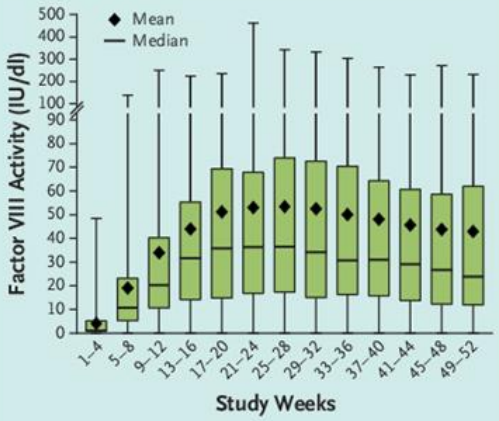
Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A

PHASE 3, OPEN-LABEL, SINGLE-GROUP STUDY

134 Adult men with severe hemophilia A (factor VIII activity ≤1 IU/dl)

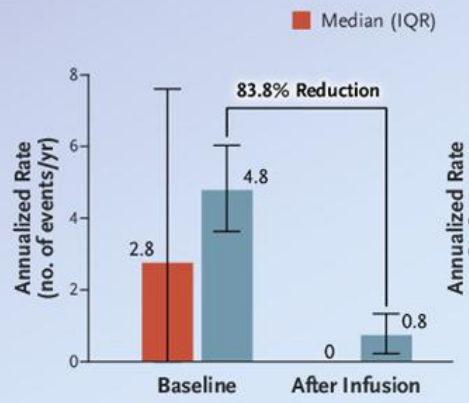
Change in Factor VIII Activity

Mean increase, 41.9 IU/dl (95% CI, 34.1 to 49.7); P<0.001



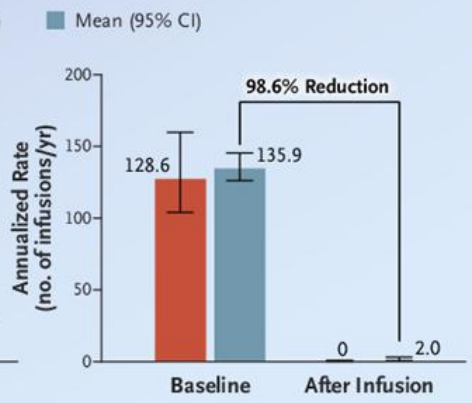
Treated Bleeding Episodes

Mean change, −4.1



Factor VIII Infusions

Mean change, −133.9



Valoctocogene roxaparvovec significantly increased factor VIII activity and reduced bleeding and factor VIII use; 16.4% of patients had serious adverse events.

M.C. Ozelo et al. 10.1056/NEJMoa2113708

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TREATMENT LANDSCAPE OF HAEMOPHILIA

REPLACEMENT AND NON-REPLACEMENT THERAPIES

Standard half-life FVIII/FIX

FVIII

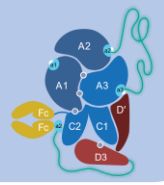
FIX

Extended half-life FVIII/FIX

EHL FVIII

EHL FIX

rFVIIIFc-VWF-XTEN*



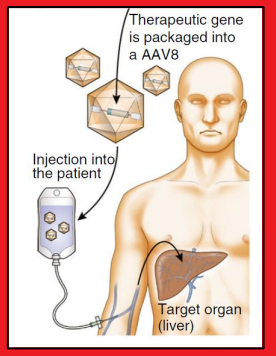
Bispecific antibody

FVIIIa mimetic

Non-factor therapies that rebalance hemostasis

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

Gene therapy (AAV-based)



Replacement therapy

Intravenous

Non-replacement therapy

Subcutaneous

Endogenous production

Unique IV Infusion

Some non-factor therapies for hemophilia are currently under development and are not yet approved by regulatory agencies.

Laffan M. Br J Haematol 2016;172:23–31.

Suggested readings

Blood coagulation dissected

Transfus Apher Sci 2018 Aug;57(4):449-457.

Edward L G Pryzdial et al.

A Molecular Revolution in the Treatment of Hemophilia

Mol Ther. 2020 Apr 8;28(4):997-1015.

Butterfield JSS et al.

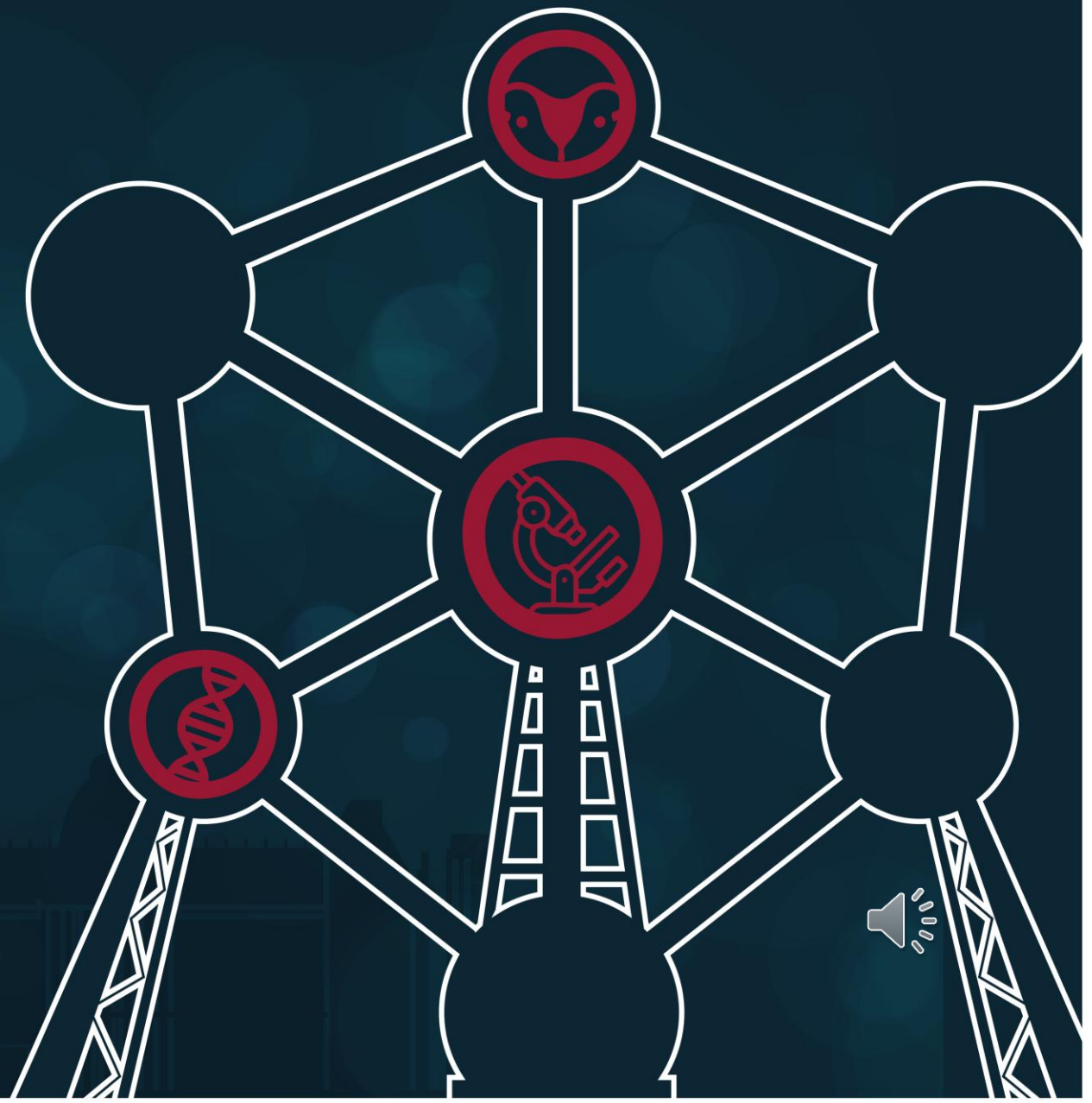
Emicizumab: A Review in Haemophilia A

Drugs. 2019 Oct;79(15):1697-1707. Blair HA.

EAHAD
European Association for Haemophilia and Allied Disorders
2027

20th ANNUAL CONGRESS OF THE EUROPEAN ASSOCIATION FOR HAEMOPHILIA AND ALLIED DISORDERS

20 YEARS OF UNITING EXPERTISE, ADVANCING CARE



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THANK YOU

for your attention

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