Schweizerische Hämophilie-Gesellschaft
Association Suisse des Hémophiles
Società Svizzera Emofilia

Journée Romande 2023

«Aspects cliniques et culturels de l'hémophilie»

DATE **SAMEDI, 10 JUIN 2023** | HEURE **9:30 – 16:00** | LIEU **HOTEL LA LONGERAIE, MORGES VD**

Non-replacement therapies : Le bienfait futur?

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Service et Laboratoire centrale d'Hématologie
CHUV, Lausanne

UNIL | Université de Lausanne
Faculté de biologie et de médecine

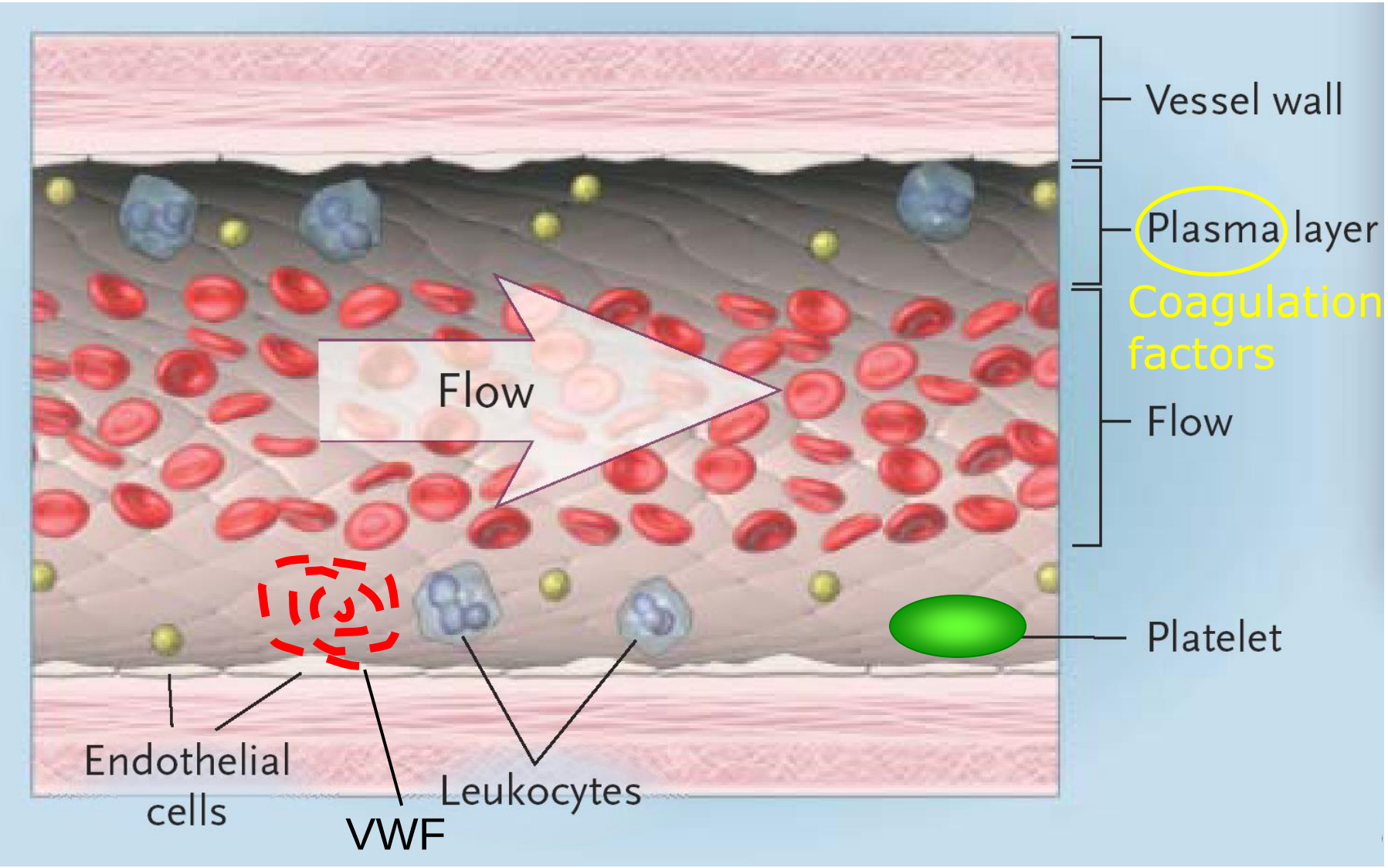
Merci!

Remerciements Sponsors consultation infirmière Hémophilie

- 2022

- 2023 (en cours)

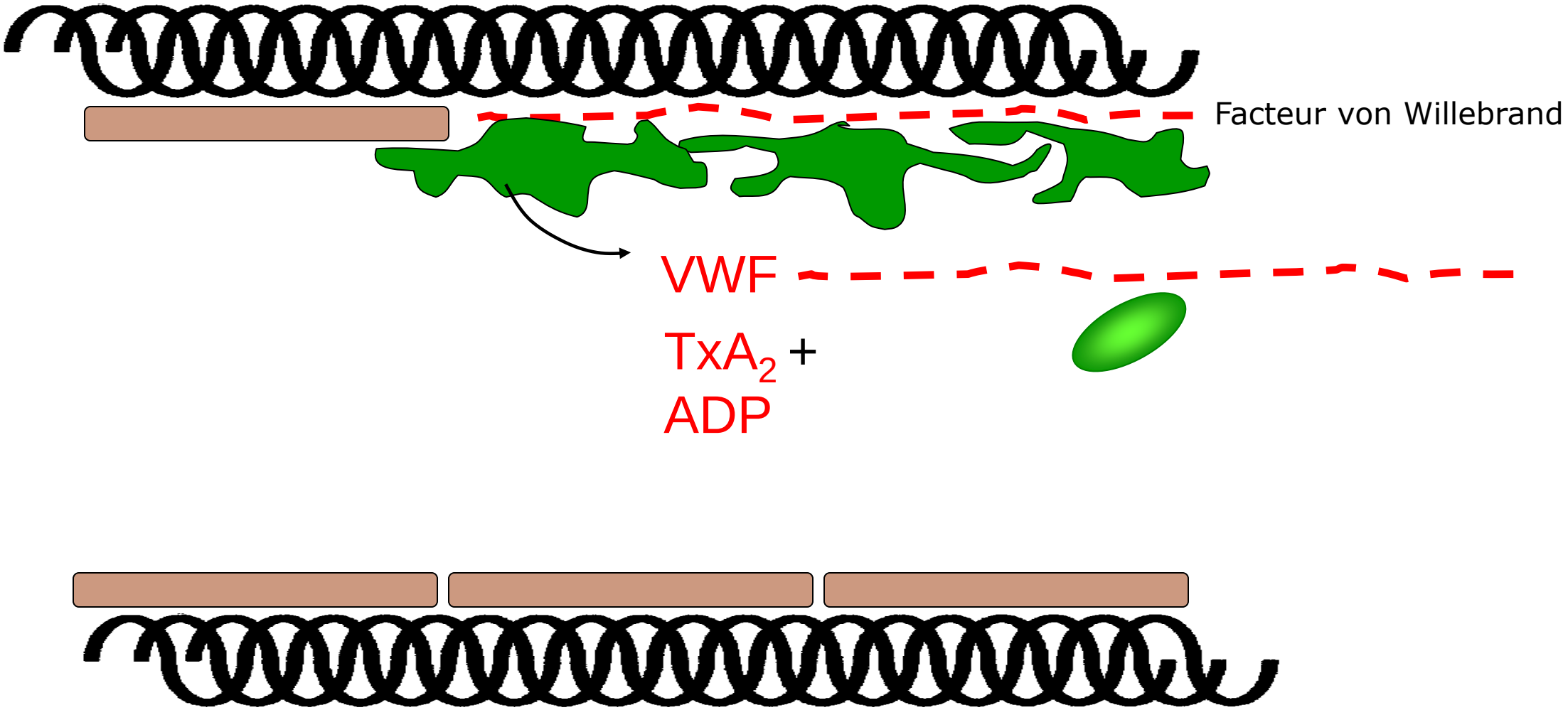
Hémostase



Legenda:
VWF, von Willebrand factor

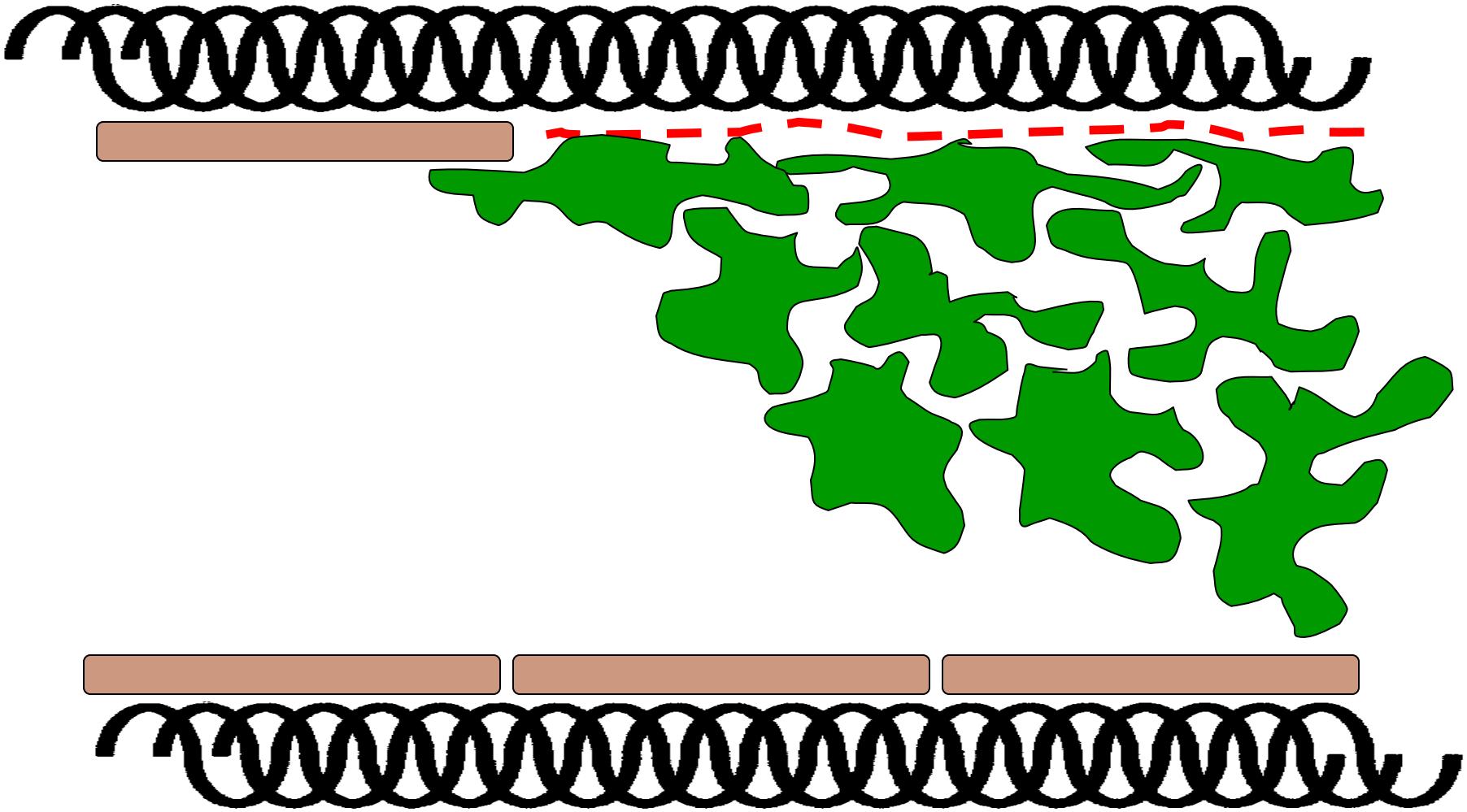
N Engl J Med 2004;350:99

Sécretions plaquettaires

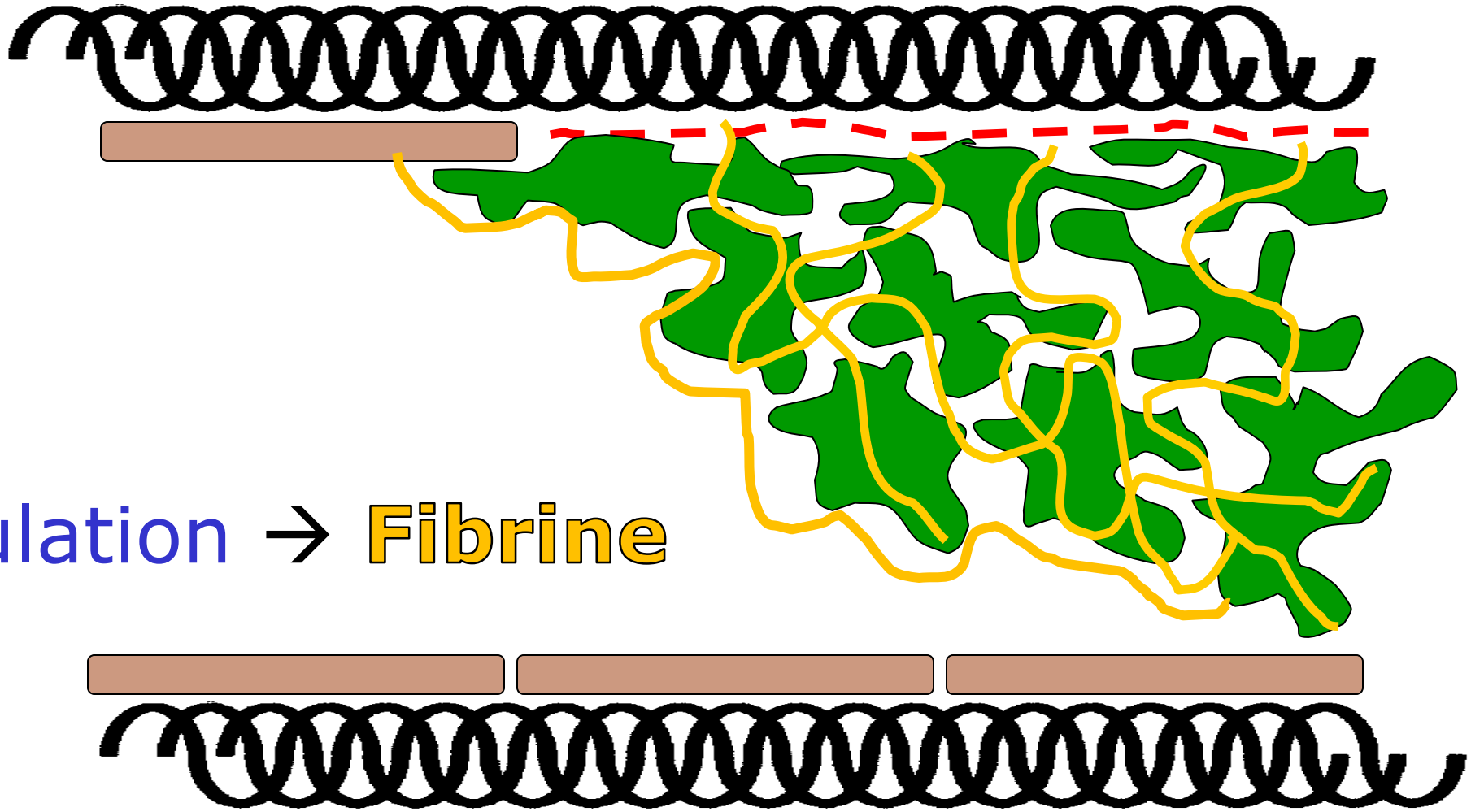


Legenda:
VWF, Facteur von Willebrand; TxA_2, thromboxane A2

Agrégation plaquettaire



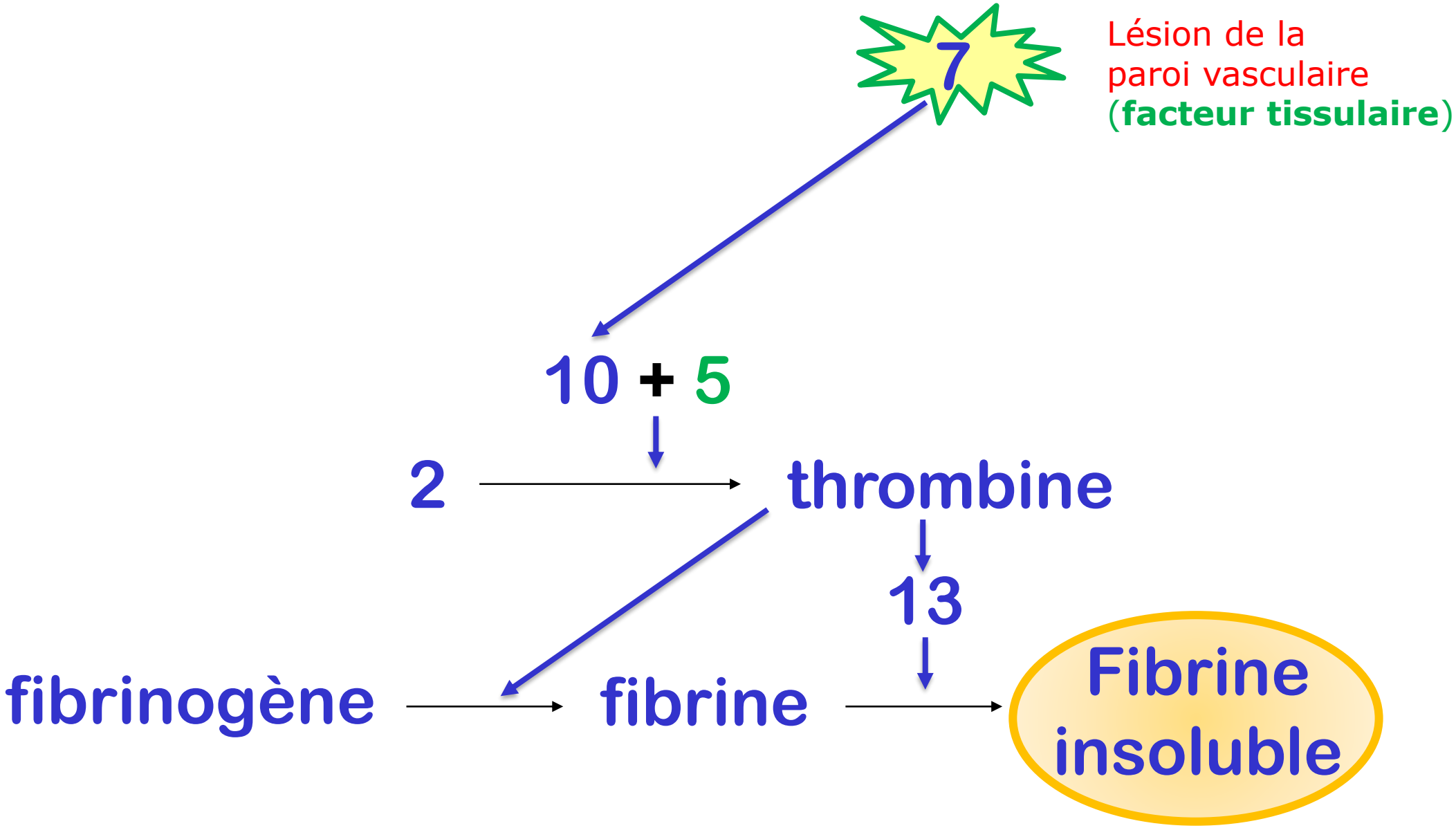
Stabilisation du caillot plaquettaire



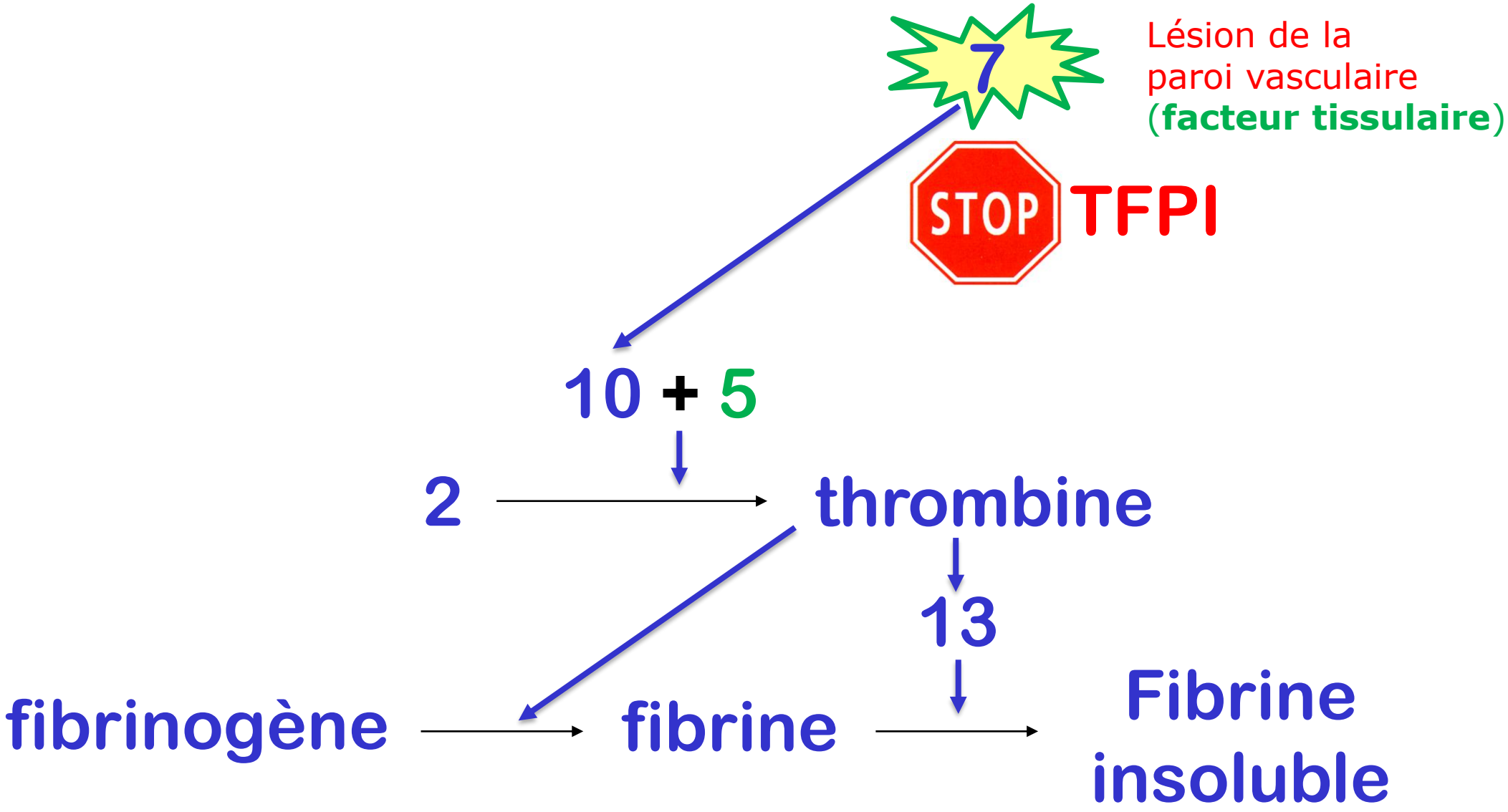
Coagulation → **Fibrine**

Legenda:
Orange, Fibrine

La coagulation *in vivo*

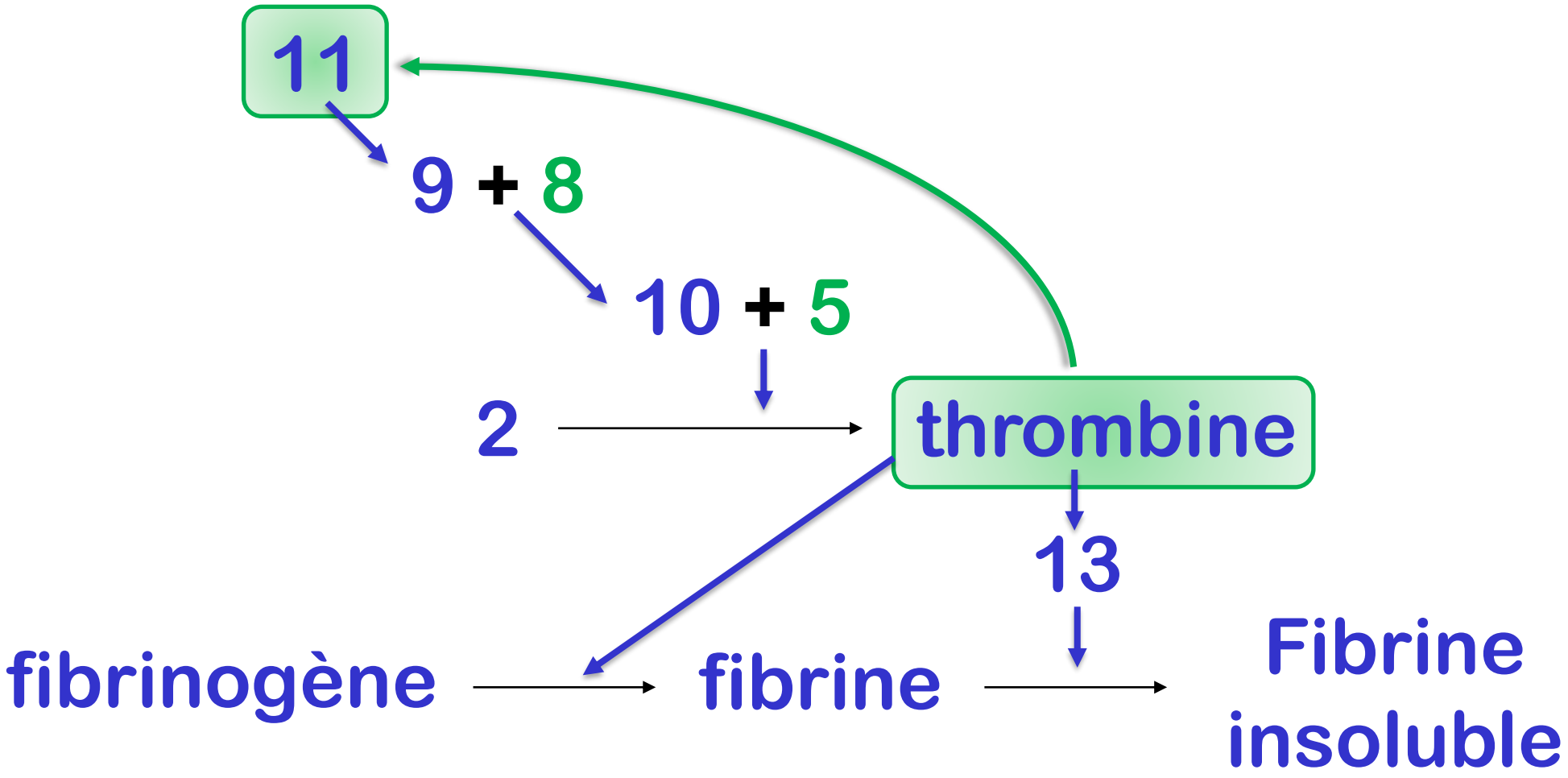


Inhibition de la *phase initiale* de la coagulation

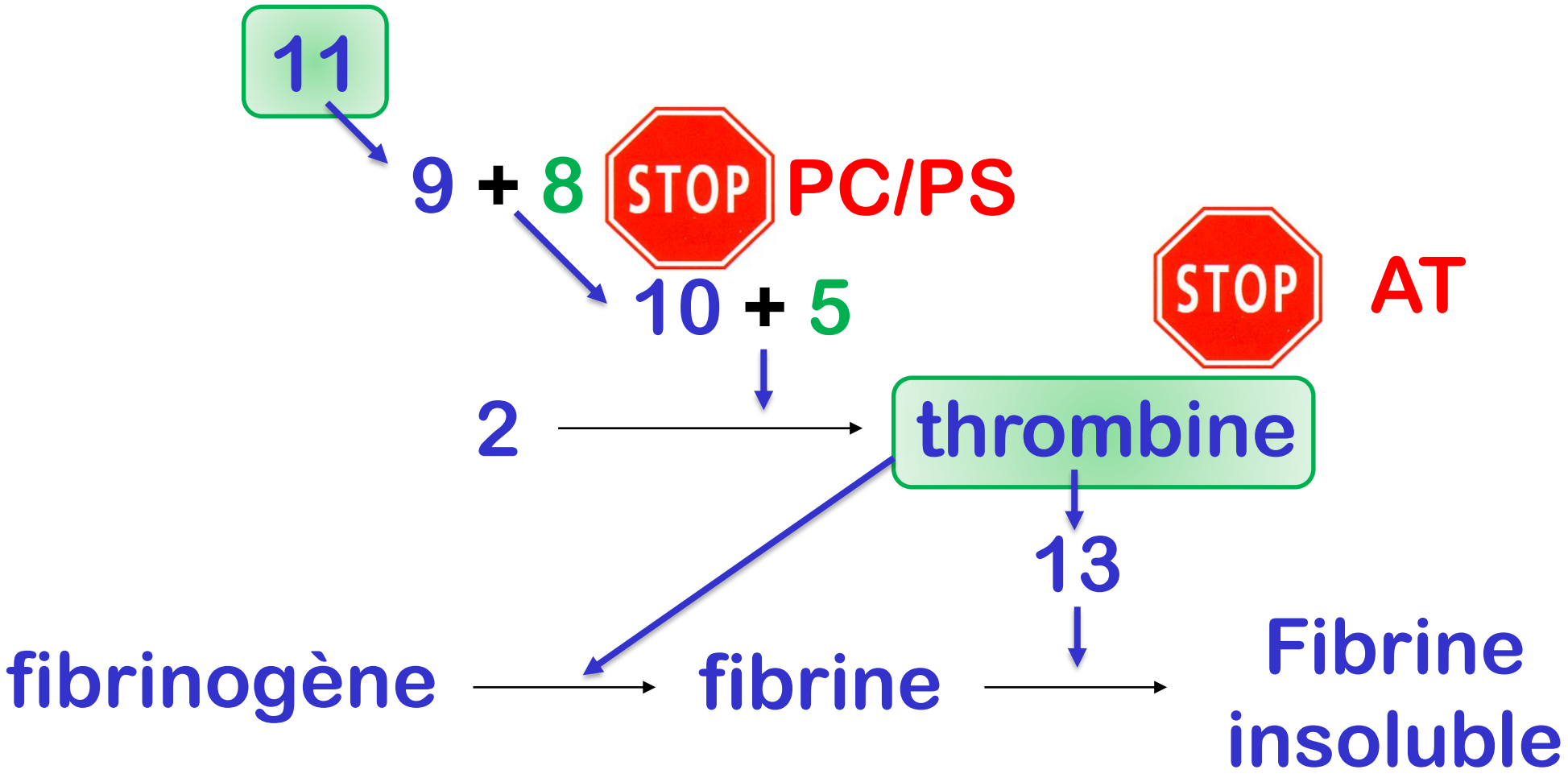


Legenda:
TFPI, tissue factor pathway inhibitor

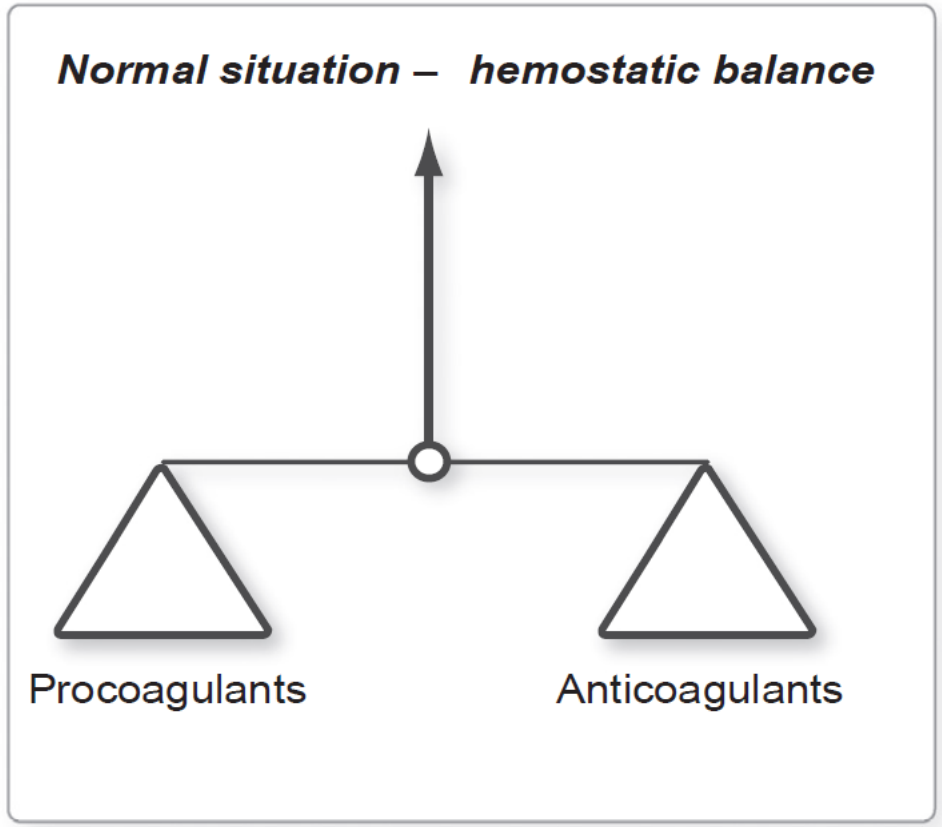
La *phase d'amplification* de la coagulation



Inhibition de la *phase d'amplification*

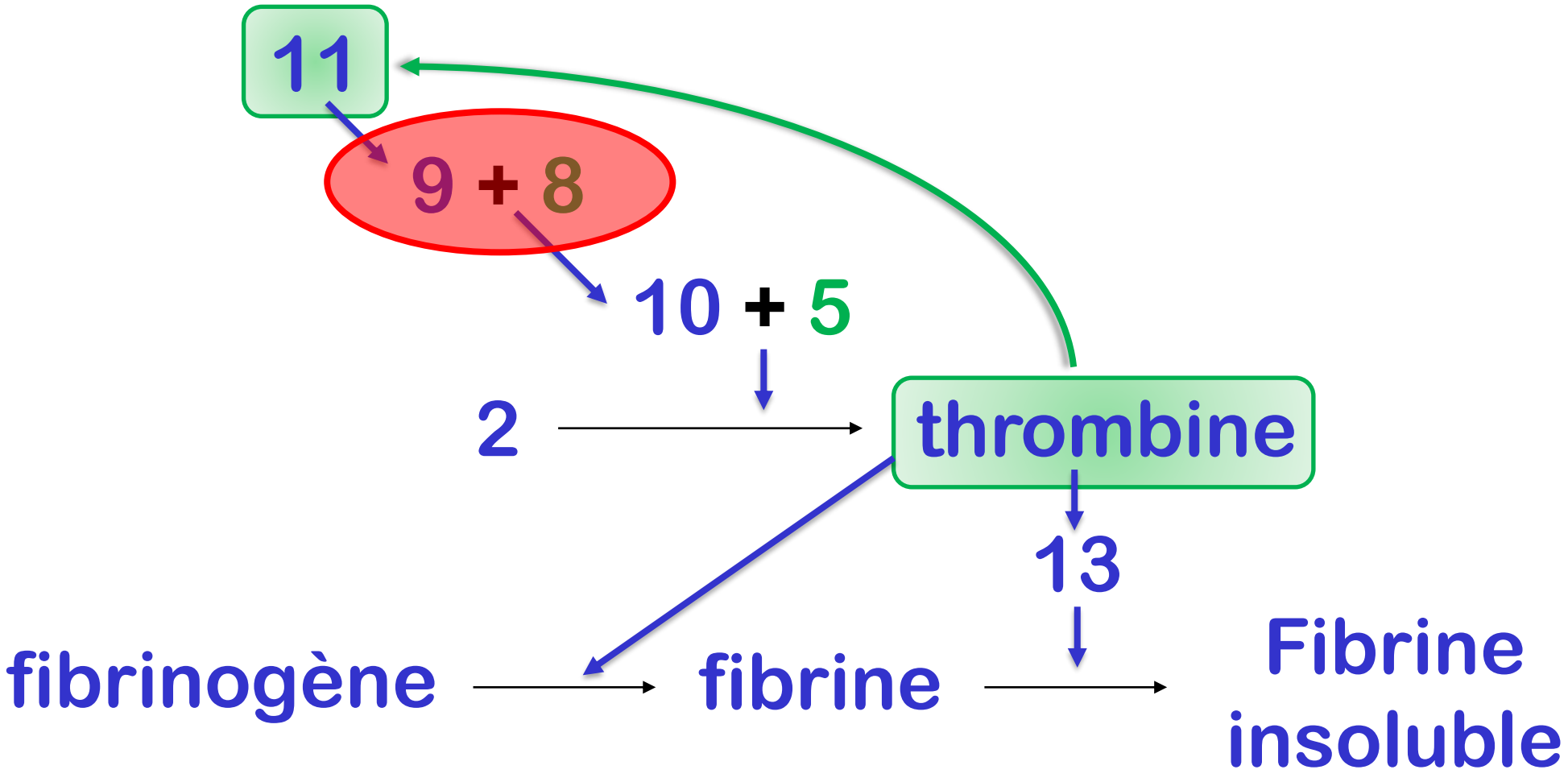


Coagulation normale = Balance

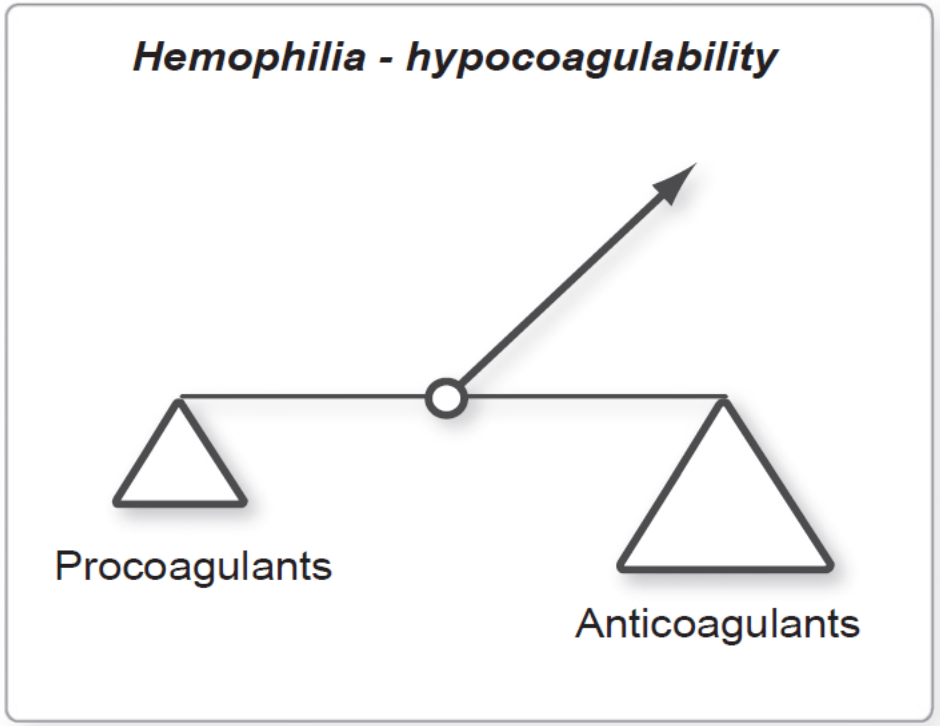


J Hepatol 2010;53:362

Hémophilie

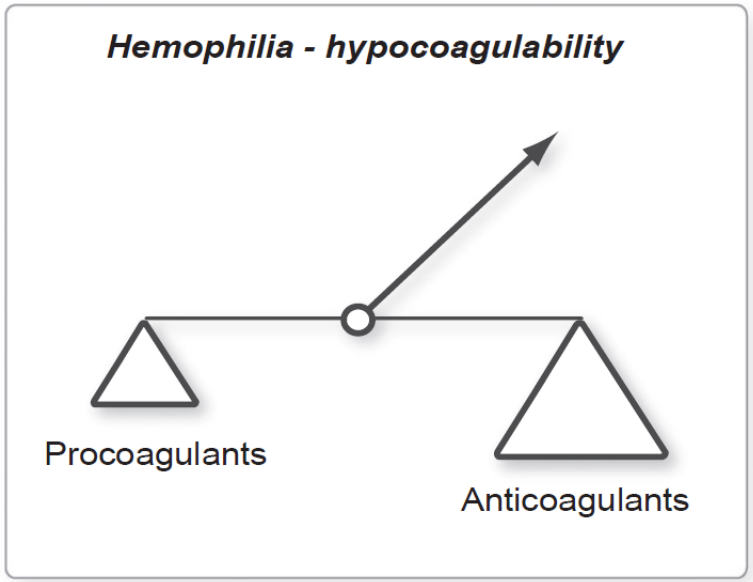

11
9 + 8
10 + 5
2
thrombine
13
fibrinogène
fibrine
Fibrine insoluble

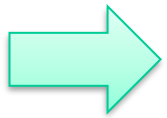
Hémophilie

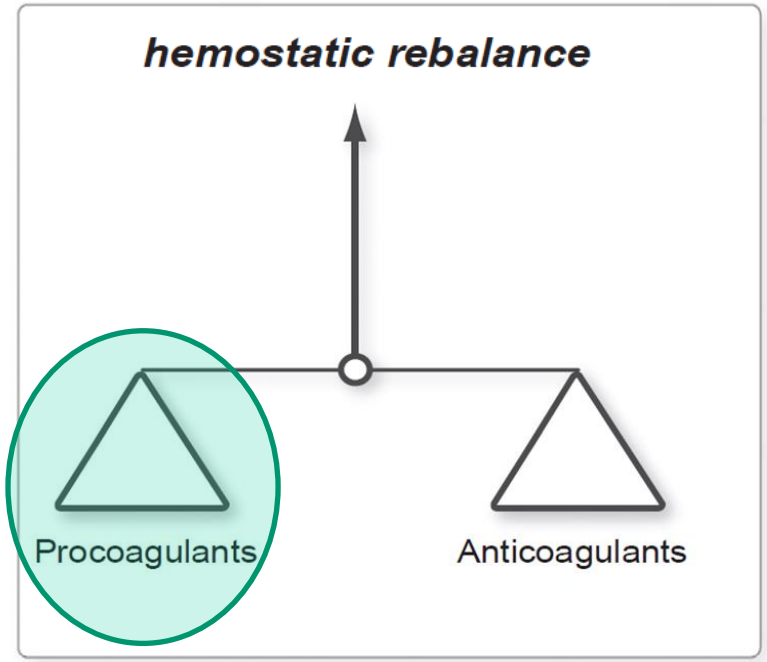


J Hepatol 2010;53:362

Traitement **1** : Remplacement du **facteur**





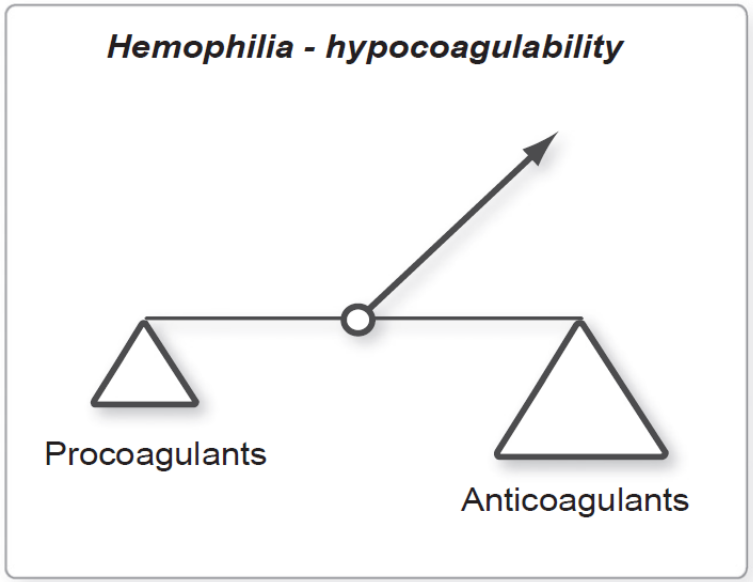


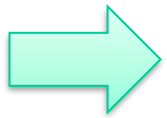
Coagulation factors:

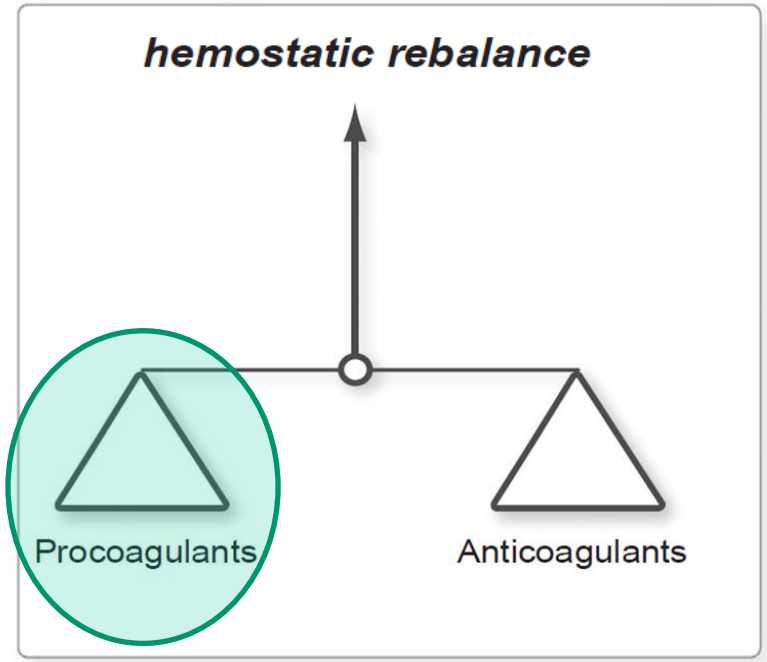
- **Plasma-derived**
- **Recombinant**
- **Extended half-life (EHL)**
- **Next: Super-EHL**

J Hepatol 2010;53:362

Traitement **2** : Remplacement de l'**activité**





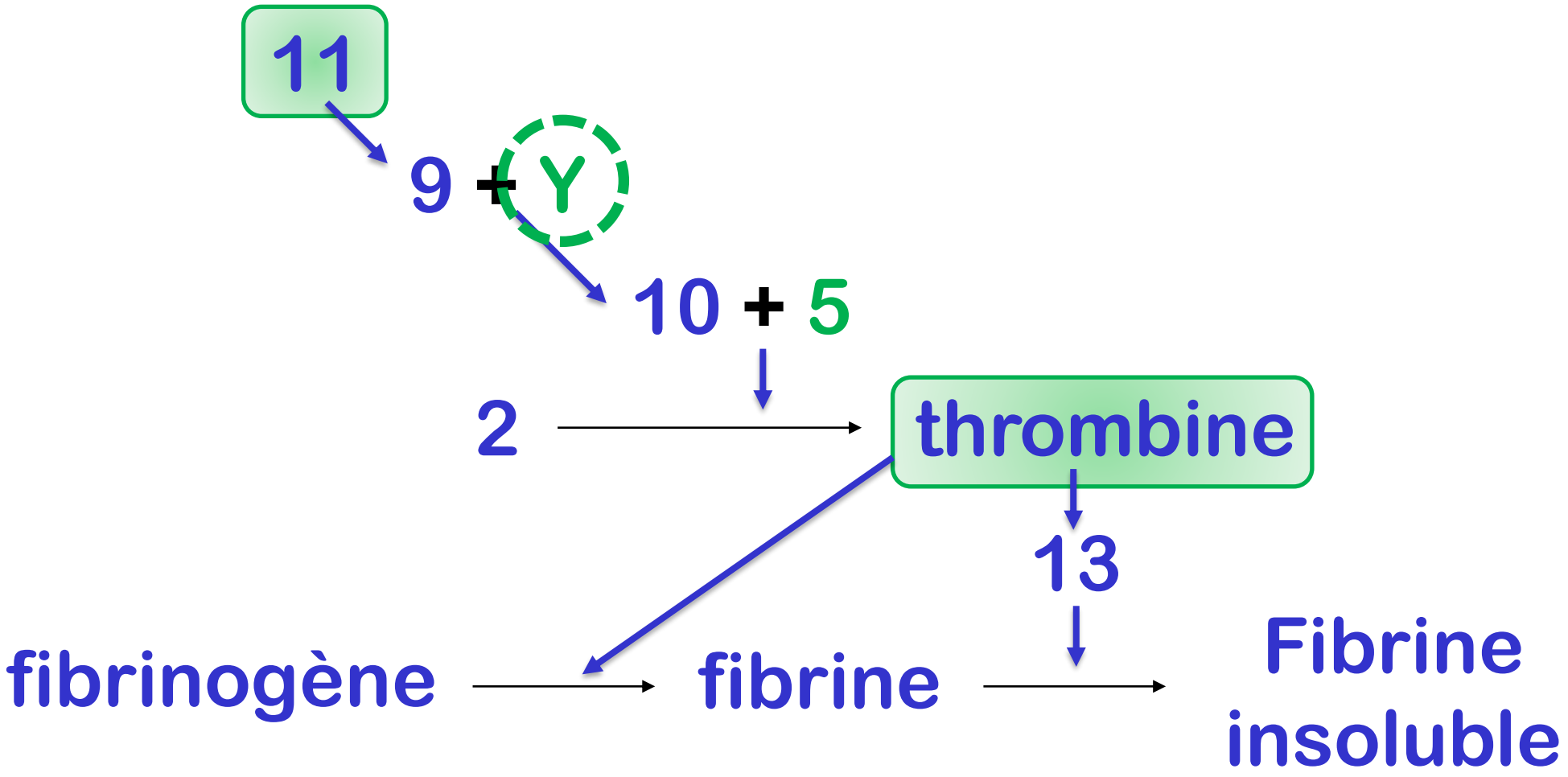


Non-factor treatment replacing FVIII activity:

- **Bispecific antibody**

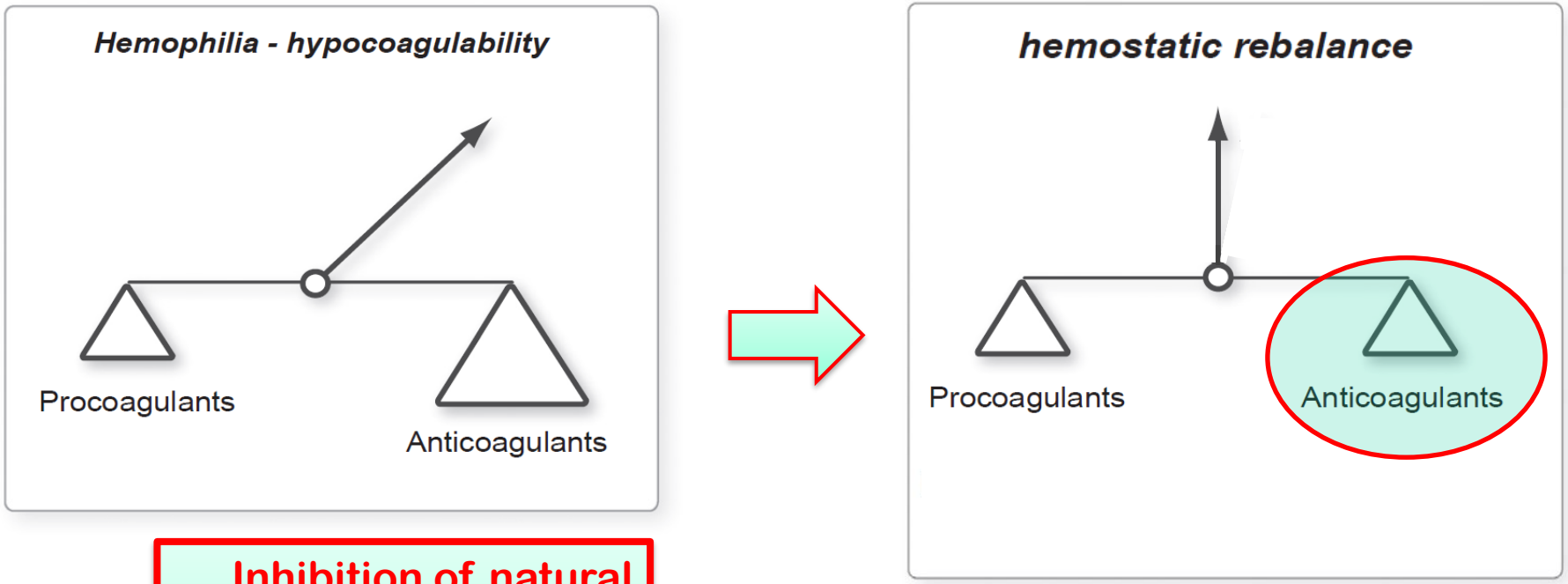
J Hepatol 2010;53:362

Traiter l'hémophilie avec un anticorps qui *remplace l'activité* du FVIII



Legenda
Y, emicizumab (Hemlibra ®)

Traitement 3 : Diminuer les inhibiteurs



Inhibition of natural anticoagulants:

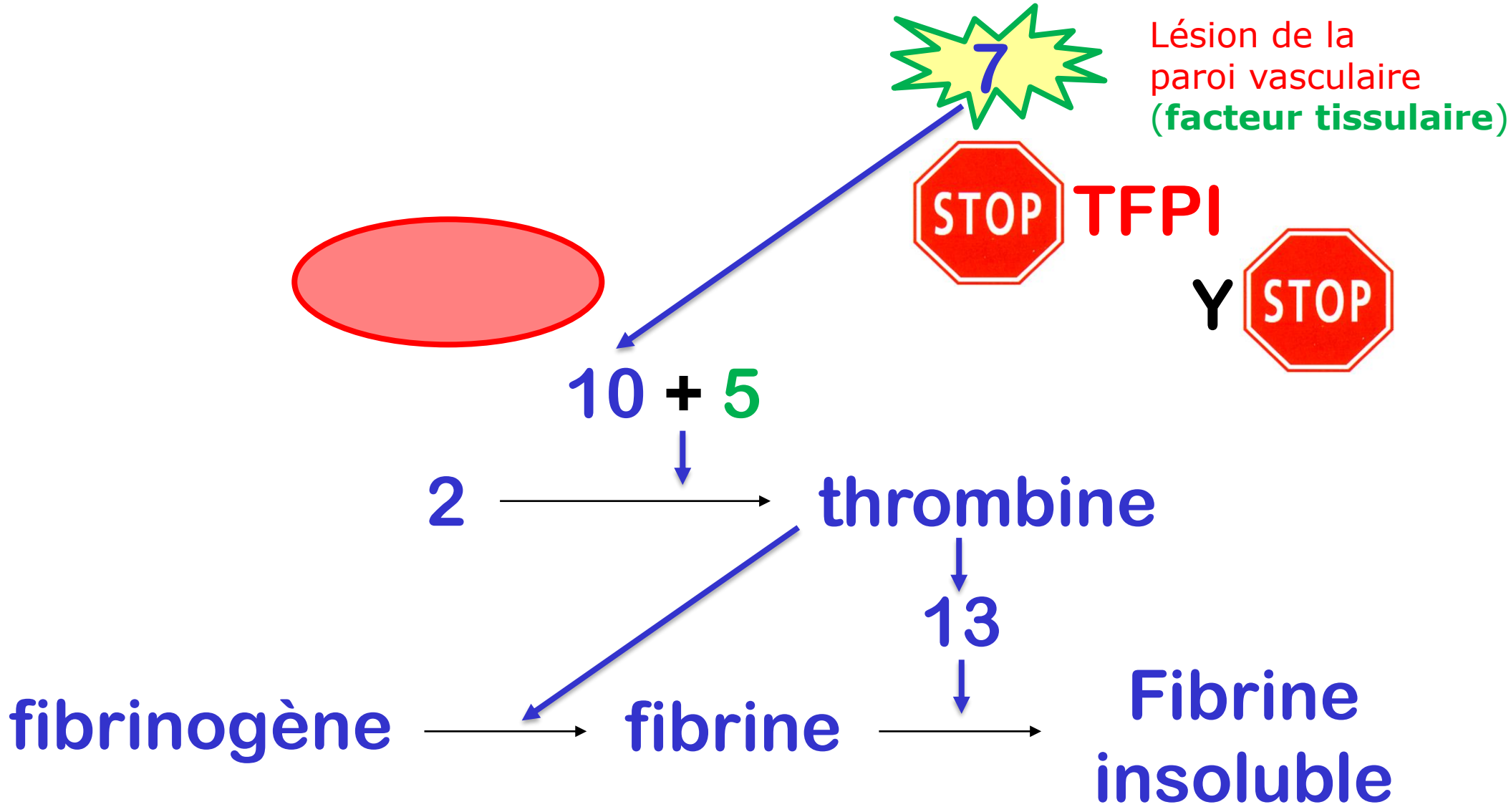
→ TFPI (antibodies)
→ AT (siRNA)
→ PC/S (serpin)

Legenda
AT, antithrombin; PC/S, protein C / S; TFPI, thrombin activatable fibrinolysis inhibitor

J Hepatol 2010;53:362

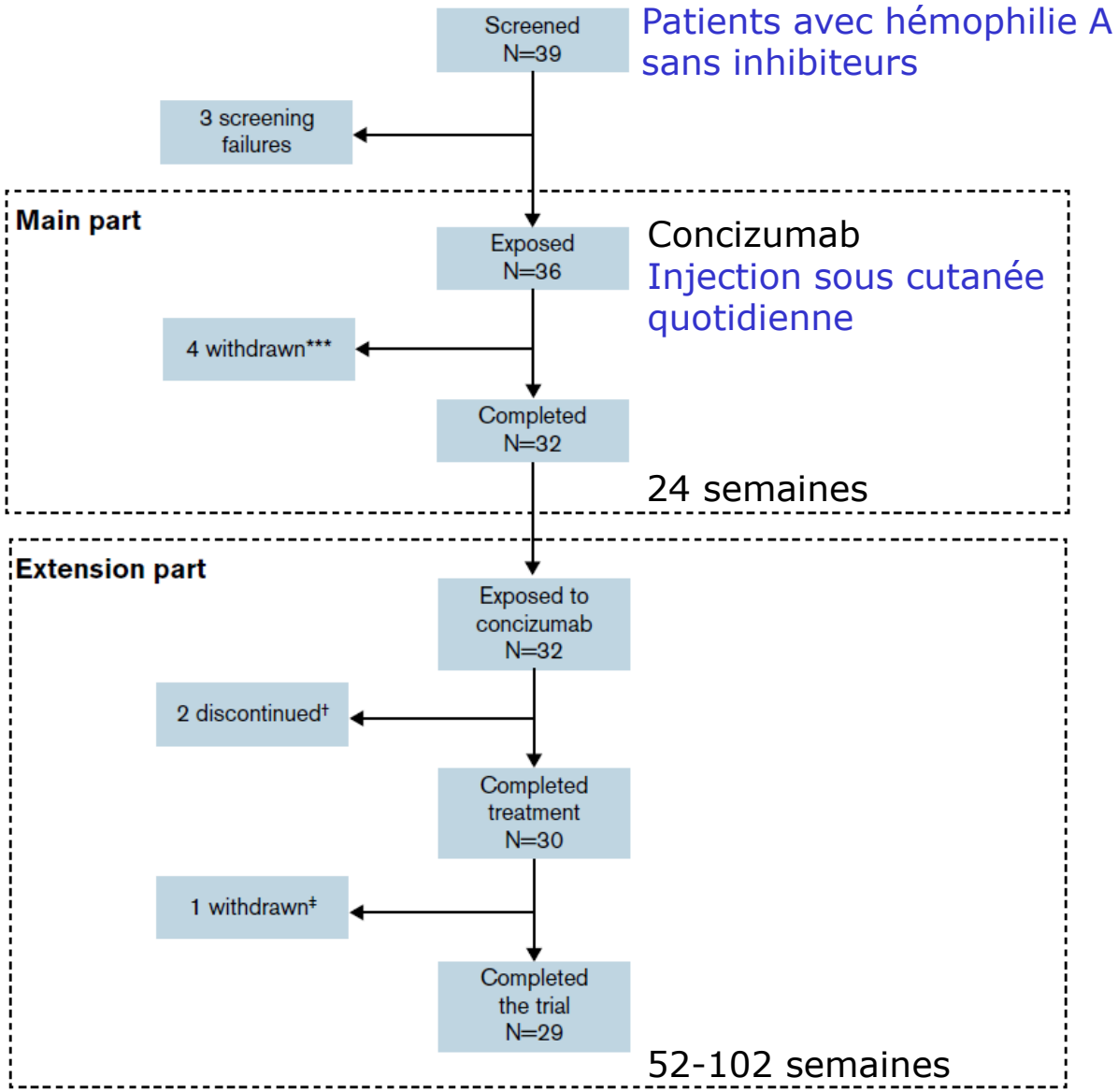
Concizumab : Inhibiteur du TFPI

Inhibition de l'inhibiteur de la *phase initiale*



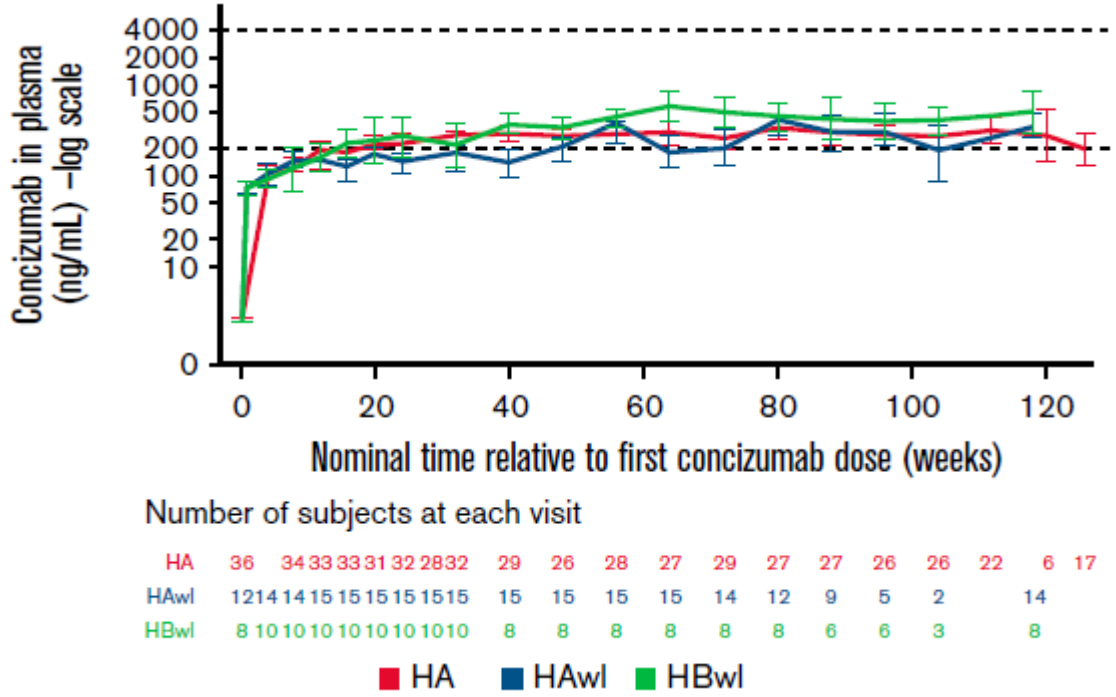
Legend:
TFPI, tissue factor pathway inhibitor

Concizumab : étude clinique *explorer 5*

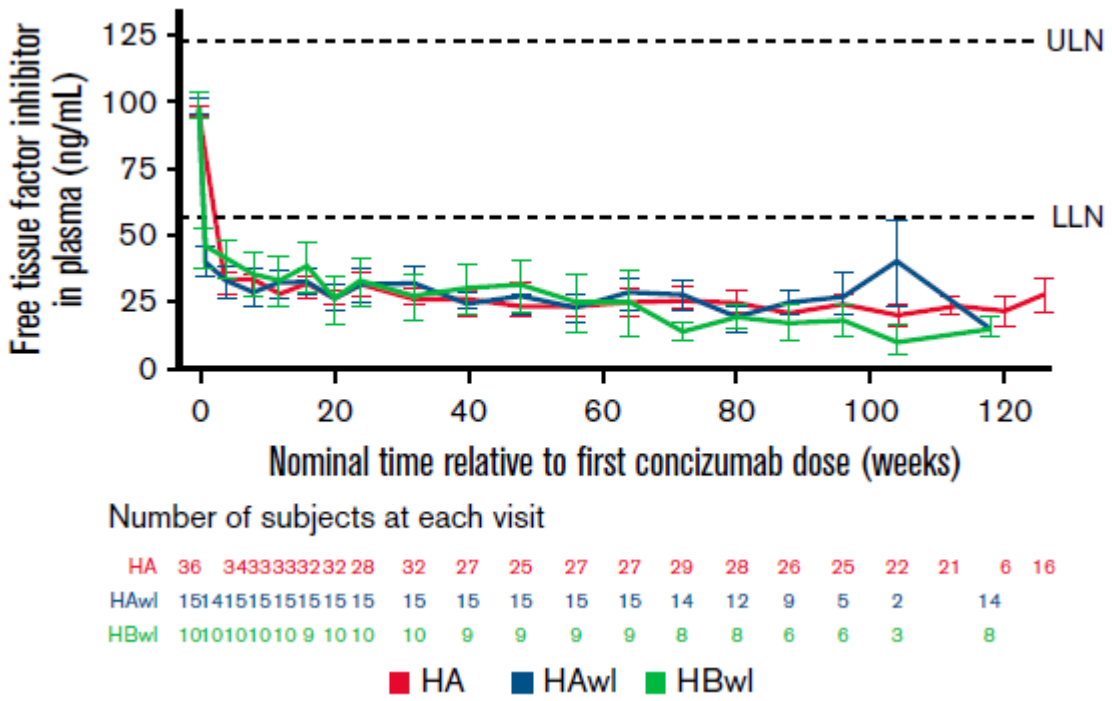


Blood Adv 2022;6:3422

Concizumab : étude clinique *explorer 5*



Concentration plasmatique du concizumab

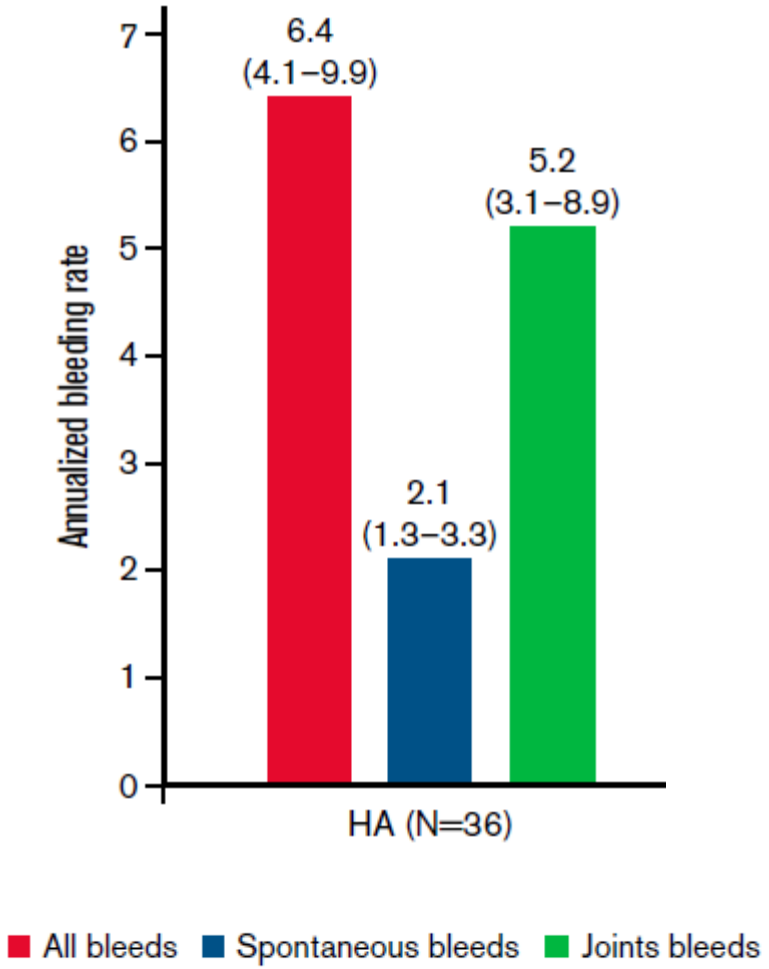


Concentration plasmatique du TFPI

Legenda
HA, hémophilie A; HB, hémophilie B; wI, avec inhibiteur

Blood Adv 2022;6:3422

Concizumab : étude clinique *explorer 5*



Hemophilia subtype	HA (n = 36)	
Cumulative concizumab exposure time, including follow-up, y	71.9	
	n (%)	E [R]
All AEs	33 (91.7)	298 [4.1]
Serious AEs	5 (13.9)	5 [0.1]
Severe	4 (11.1)	4 [0.1]
Fatal	0	
AEs leading to withdrawal	0	
AESI (thromboembolic events)	0	
Most frequent AEs		
Injection site reactions*	14 (38.9)	25 [0.3]
Nasopharyngitis	12 (33.3)	22 [0.3]
D-dimer level increased	9 (25.0)	12 [0.2]
Headache	8 (22.2)	12 [0.2]

Legenda:
n, nombre de patients
E, nombre d'évènements
AE, adverse events (évènements indésirables)
AESI, AE of special intestest (… d'intérêt particulier)

Études de phase 3 en cours (*explorer 7 et 8*)

Blood Adv 2022;6:3422

Concizumab en Suisse

swissmedic

Schweizerisches Heilmittelinstitut
Institut suisse des produits thérapeutiques
Istituto svizzero per gli agenti terapeutici
Swiss Agency for Therapeutic Products

Demandes reçues concernant des médicaments à usage humain

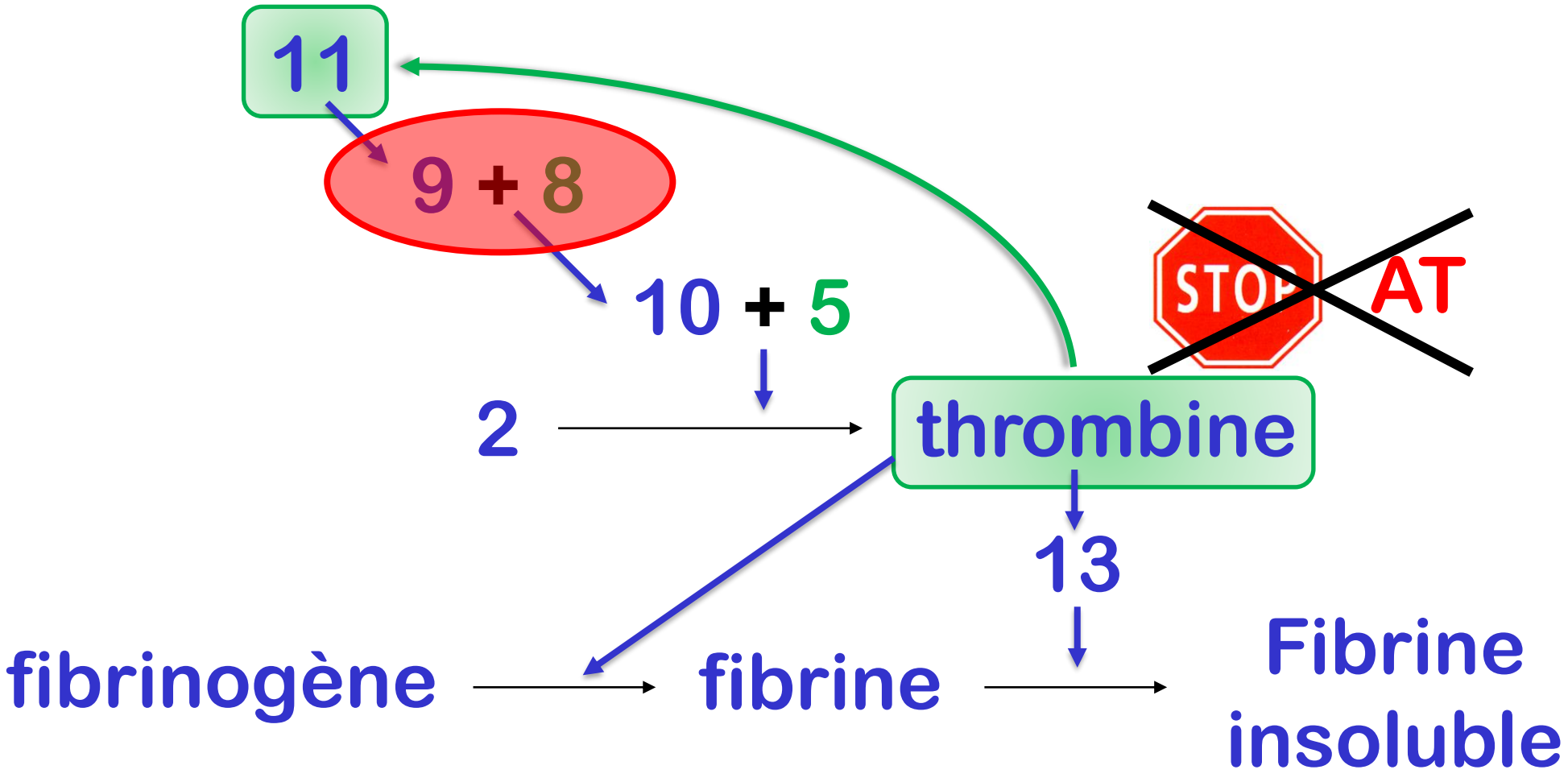
XLSX, 483 kB, 31.05.2023

Datum Eingar	Gesuchstellerin Requérant	Gesuchstyp Type de demande	Wirkstoff(e) Principe(s) actif(s)	Anz. A	Anwendungsgebiet Champ d'applicati
22.09.2022	Novo Nordisk Pharma AG 8302 Kloten	Neuanmeldung eines Arzneimittels mit neuem Wirkstoff	concizumab	1	Haemophilia A with Inhibitors
22.09.2022	Novo Nordisk Pharma AG 8302 Kloten	Neuanmeldung eines Arzneimittels mit neuem Wirkstoff	concizumab	1	Haemophilia B with Inhibitors

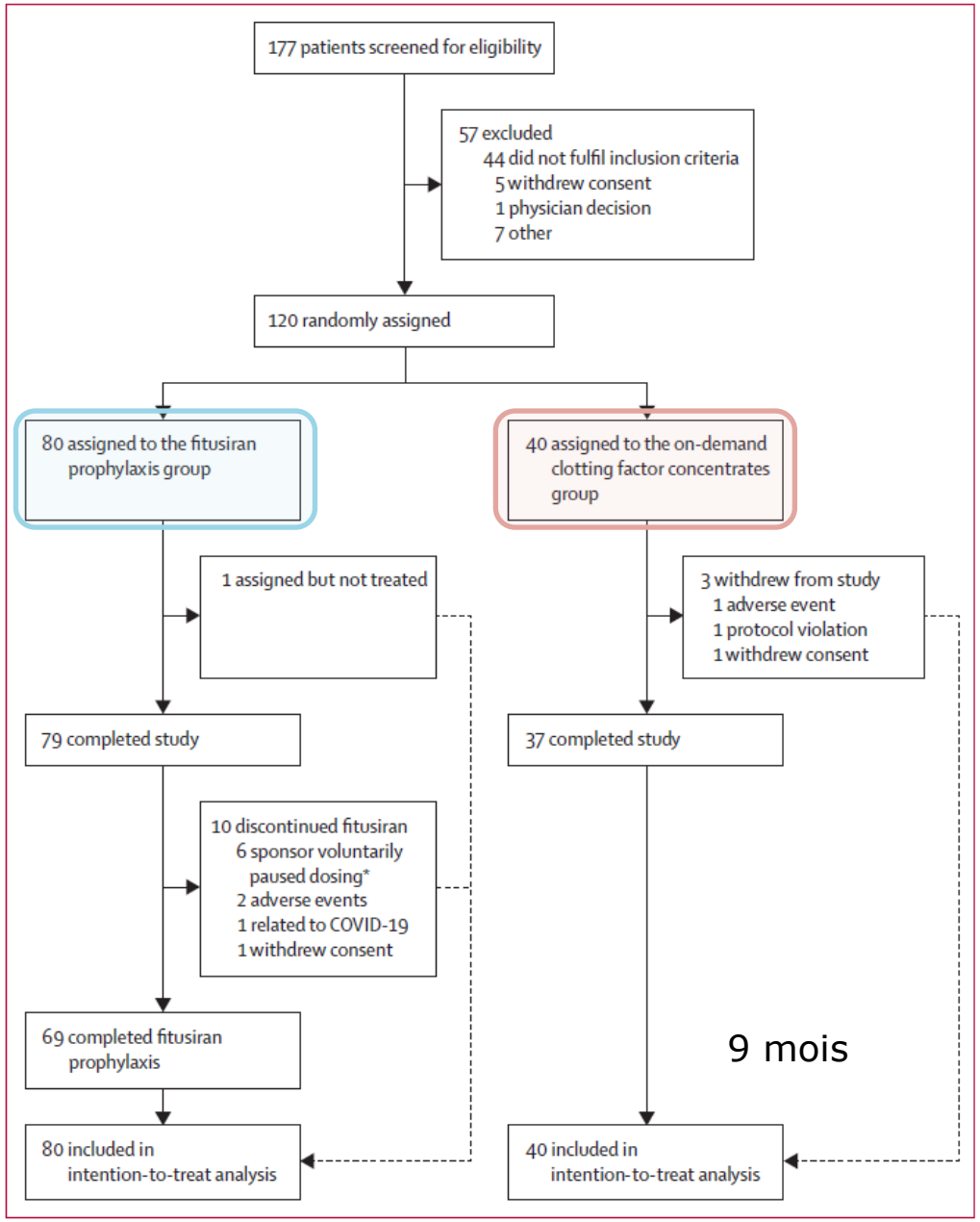
www.swissmedicinfo.ch

Fitusiran : Inhibiteur de l’antithrombine

Inhibition de l'inhibiteur de la thrombine

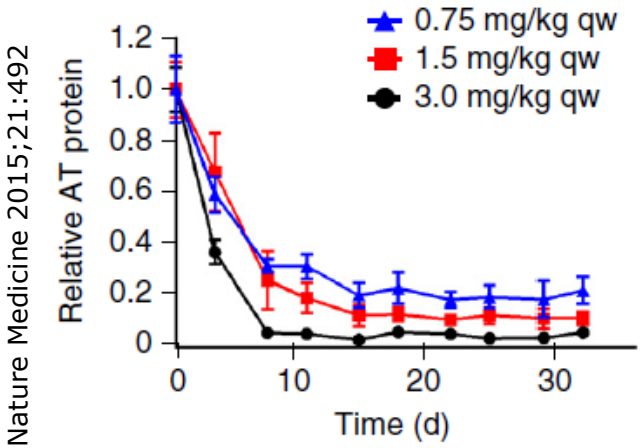


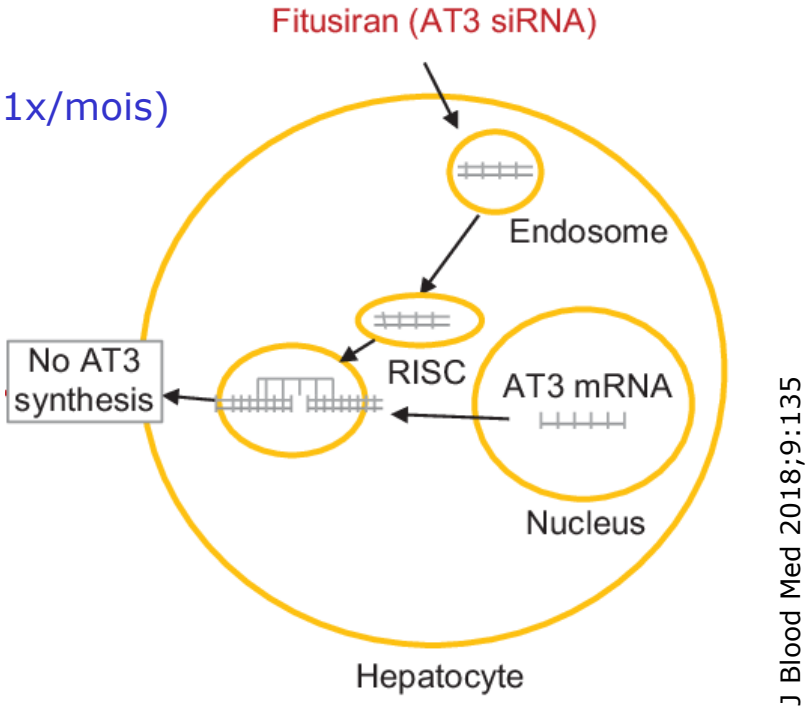
Fitusiran



Patients avec hémophilie A ou B
sans inhibiteurs

Fitusiran,
un siRNA
administré par voie sous-cutanée (1x/mois)
cible l'antithrombine

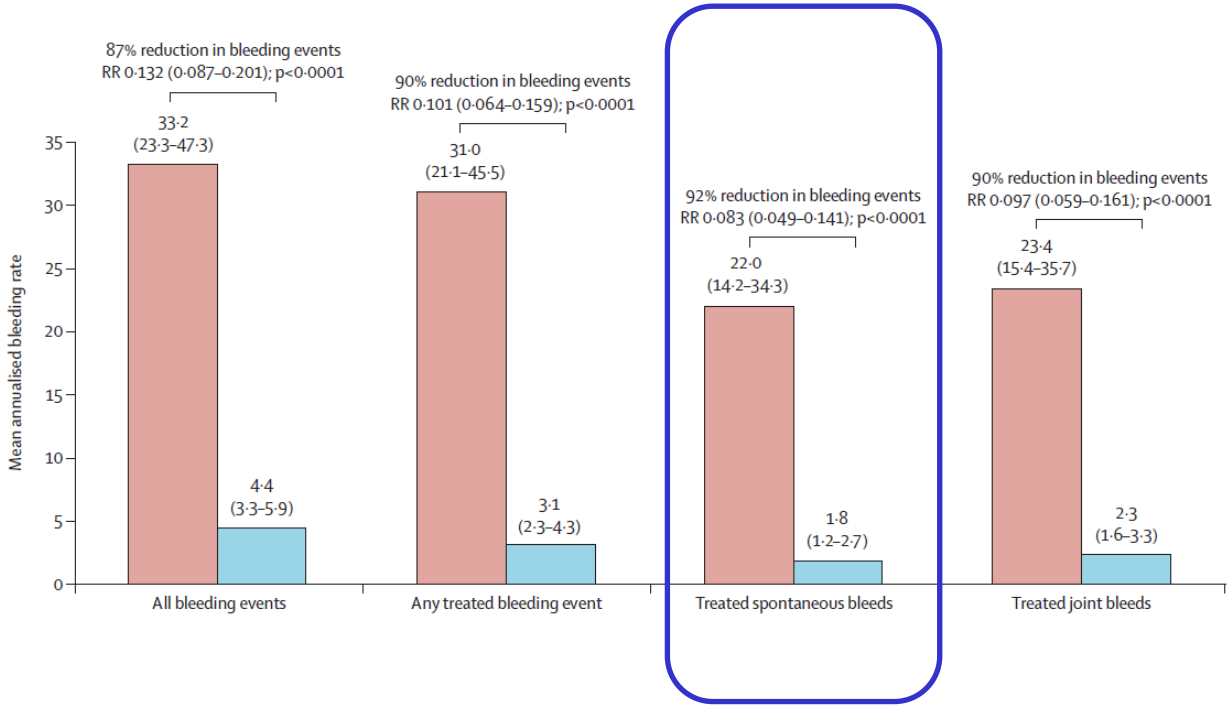




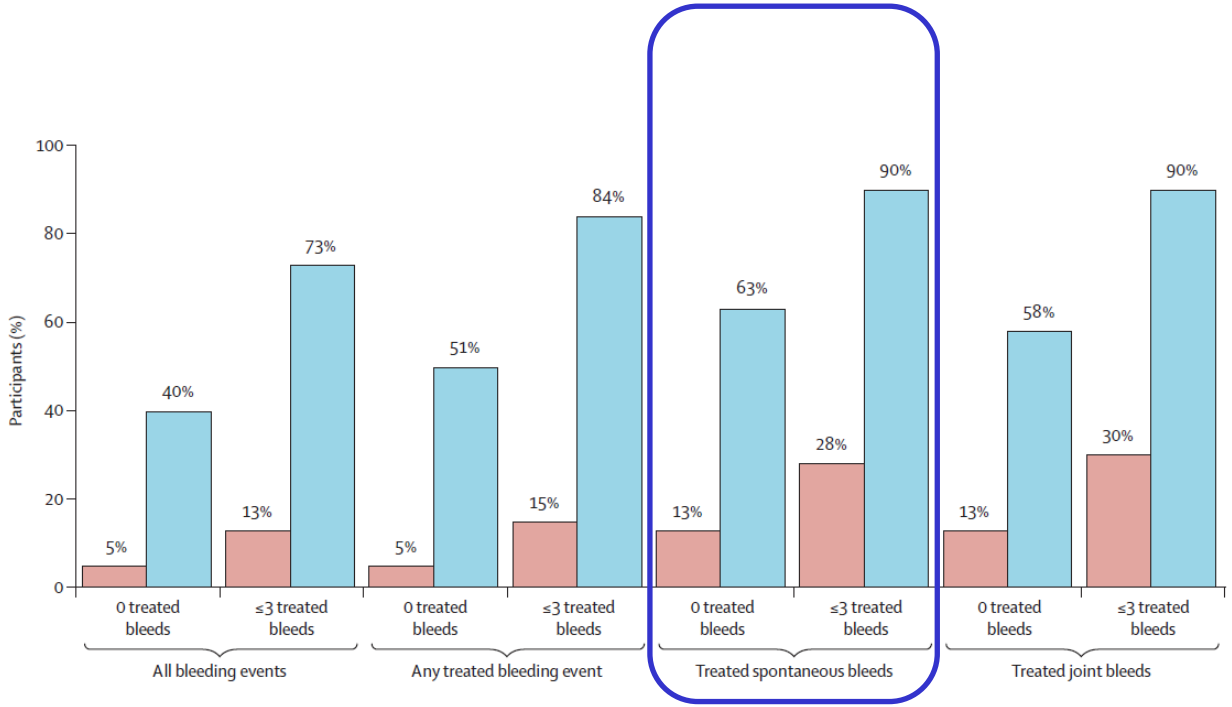
Legenda:
siRNA, silencing RNA
RISC, RNA silencing complex

Lancet Haematol 2023;10:e322

Fitusiran



Taux de saignement annualisé moyen



Pourcentage de participants (0 | ≤3 saignements)

On-demand clotting factor concentrates (n=40)
Fitusiran 80 mg prophylaxis (n=79)

Lancet Haematol 2023;10:e322

Fitusiran

	On-demand clotting factor concentrates group (n=40)	Fitusiran prophlyaxis group (n=79)
Any TEAE	18 (45%)	62 (79%)
Most common TEAEs in fitusiran group (≥5% of participants)		
Increased ALT concentration	1 (3%)	18 (23%)
Upper respiratory tract infection	0	9 (11%)
Nasopharyngitis	3 (8%)	7 (9%)
Abdominal pain	1 (3%)	6 (8%)
Increased AST concentration	2 (5%)	6 (8%)
Cough	0	6 (8%)
Arthralgia	1 (3%)	5 (6%)
Asthma	0	5 (6%)
Gastritis	1 (3%)	5 (6%)
Headache	0	5 (6%)
Upper abdominal pain	0	4 (5%)
Increased blood bilirubin concentration	0	4 (5%)

Pas de

- thrombo-embolies suspectées ou confirmées,
- réactions sévères ou graves au point d'injection
- réactions systémiques associées à l'injection

ont été rapportées.

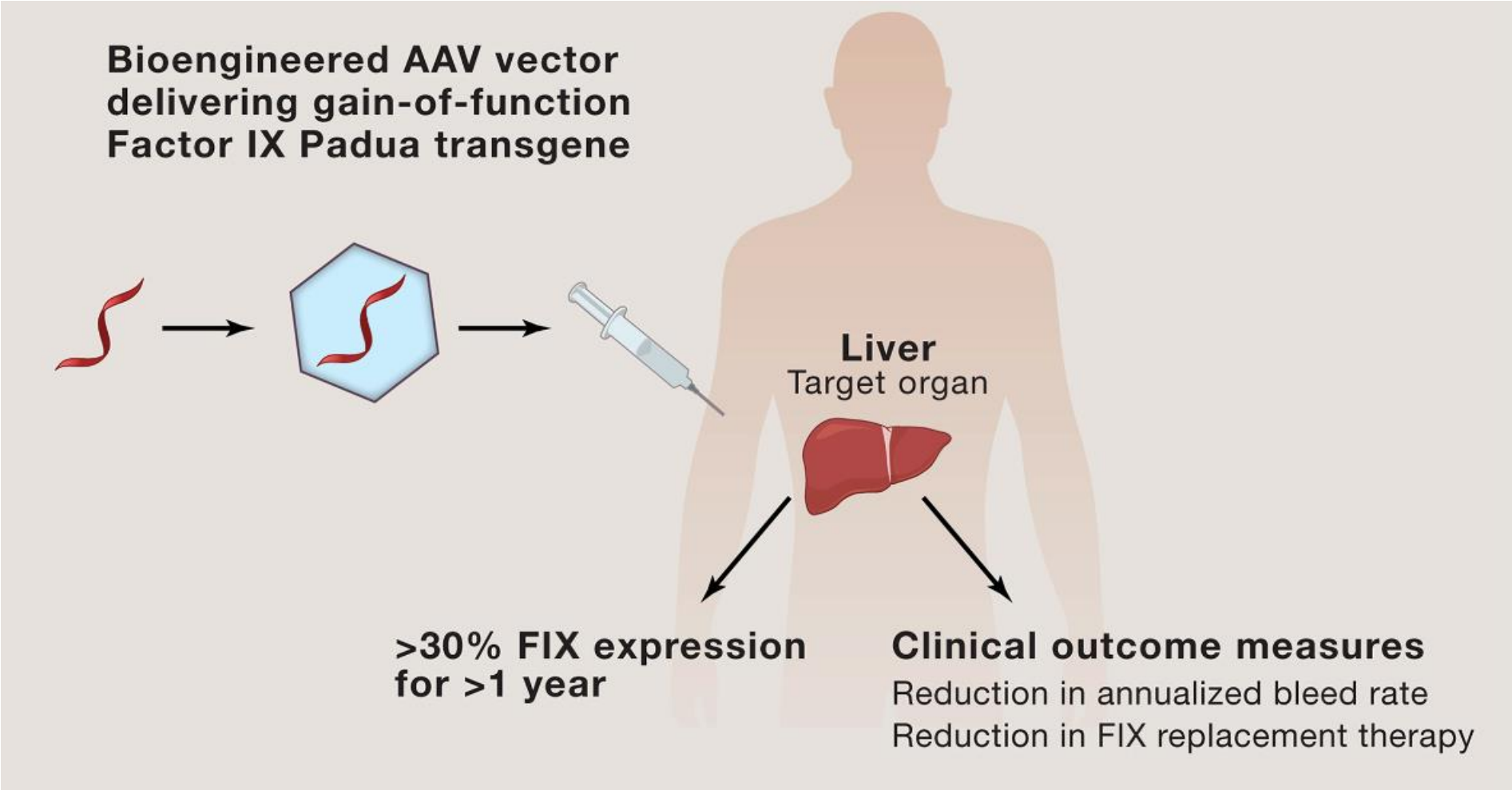
Lancet Haematol 2023;10:e322

Fitusiran en Suisse

www.swissmedicinfo.ch

Traitement **4 : Thérapie génique**

Thérapie génique : Facteur IX



Legenda
AAV, adeno-associated virus

Cell 2017;171:1478

Thérapie génique : Facteur IX

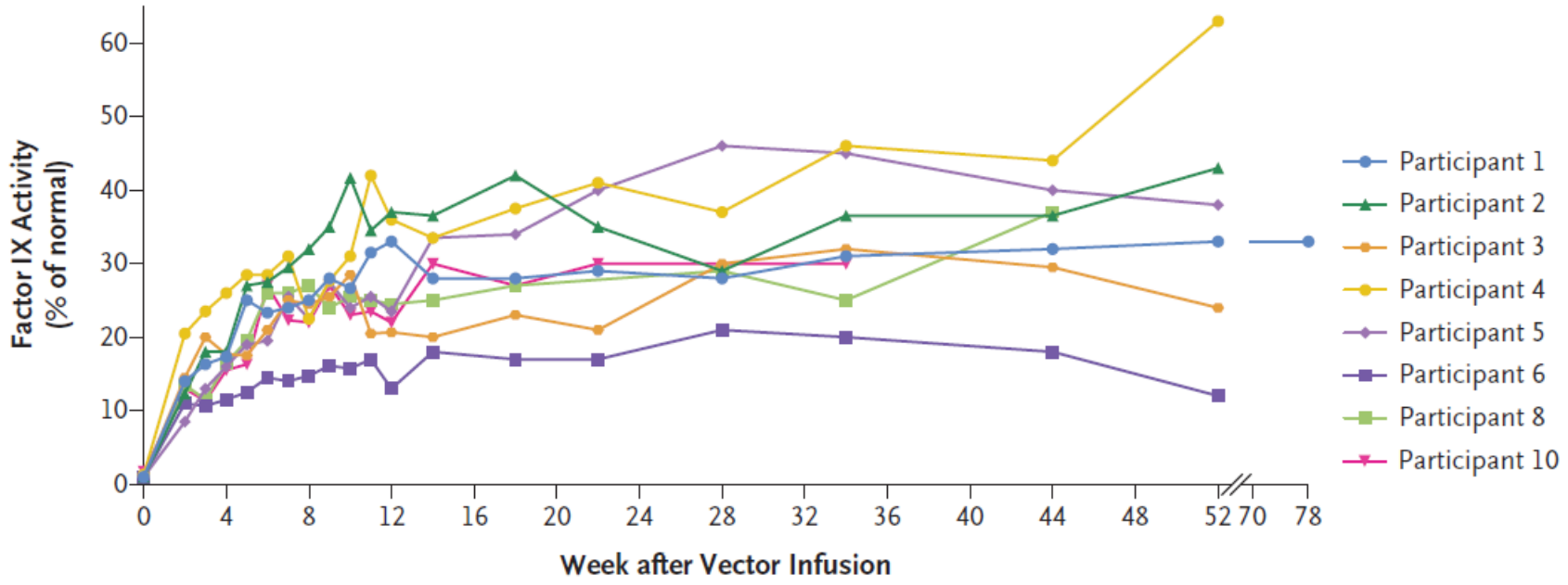


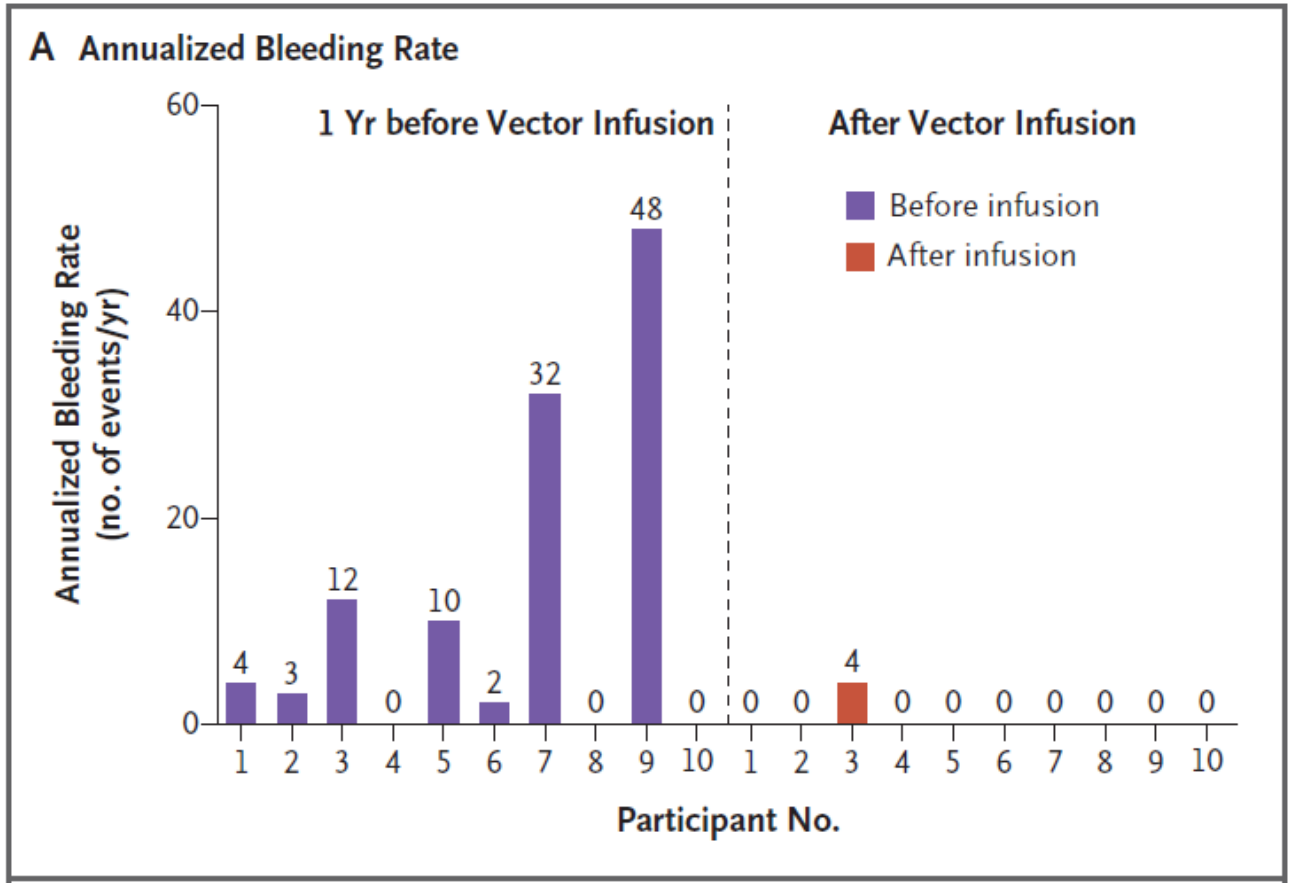
Figure 1. Factor IX Activity after One Peripheral Infusion of SPK-9001 in the Eight Participants Who Did Not Have an Adeno-Associated Viral Capsid-Directed Immune Response.

The vector SPK-9001 was administered at a dose of 5×10^{11} vector genomes per kilogram of body weight.

Activité du facteur IX

N Engl J Med 2017;377:2215

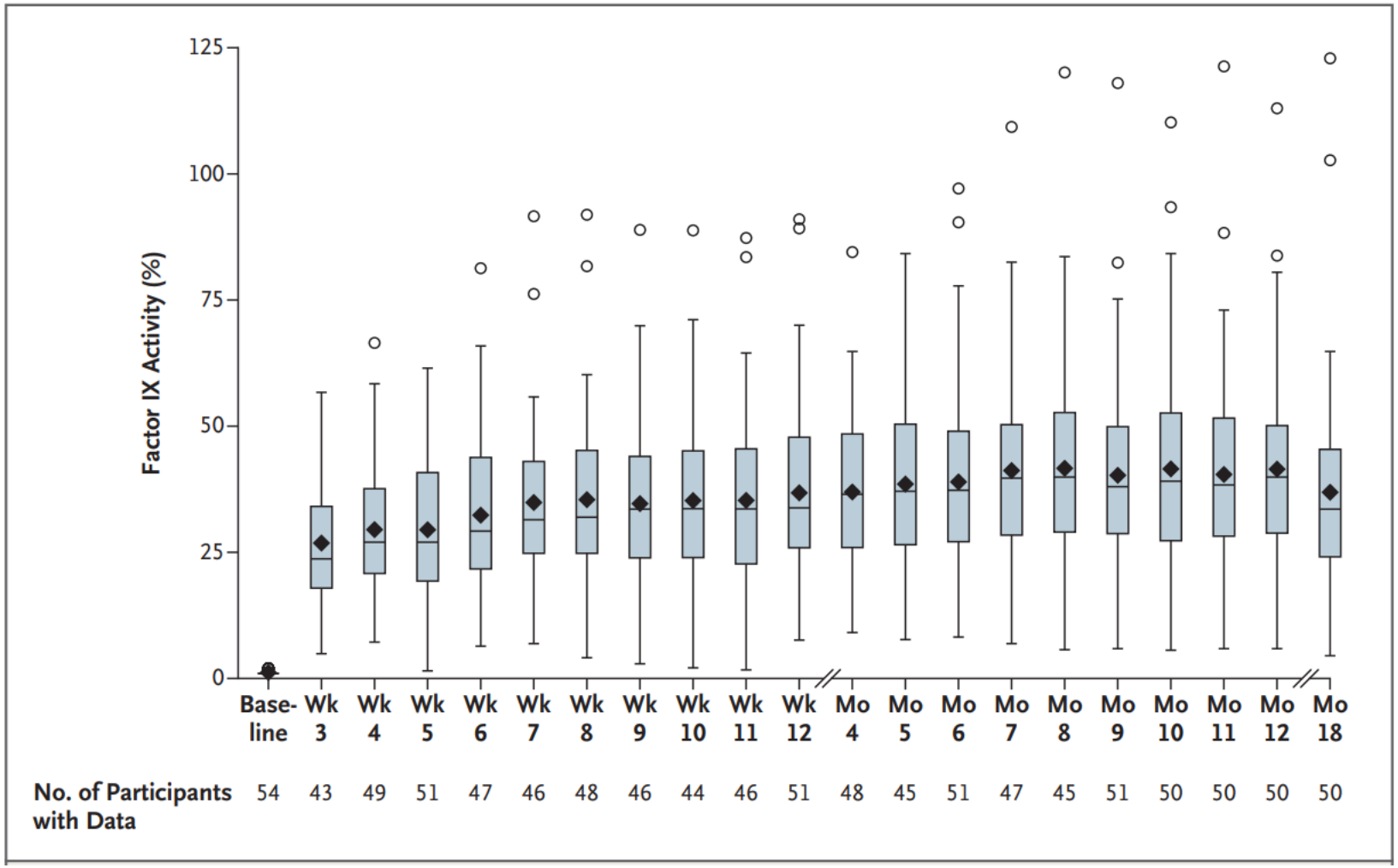
Thérapie génique : Facteur IX



Taux de saignement annualisé moyen

N Engl J Med 2017;377:2215

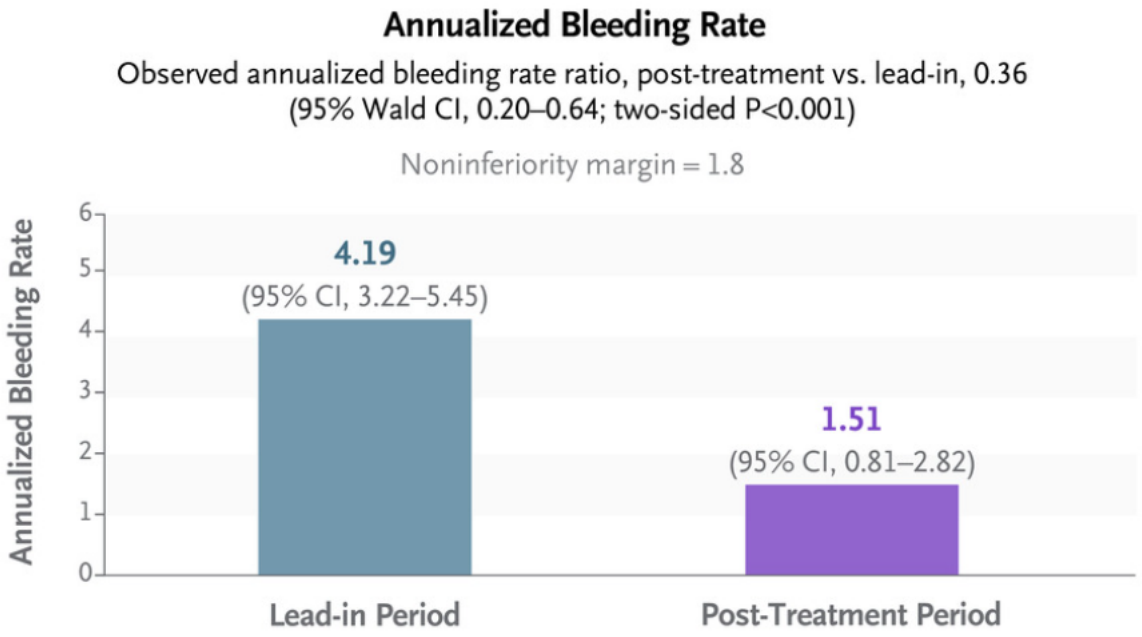
HOPE-B



Activité du facteur IX

N Engl J Med 2023;388:706

HOPE-B



Taux de saignement annualisé moyen

N Engl J Med 2023;388:706

HOPE-B

Table 4. Adverse Events from Any Cause That Occurred or Worsened in at Least 10% of the Participants and Drug-Related Adverse Events in the Post-treatment Period (Safety Population).

Type of Event*	Adverse Events from Any Cause (N=54)		Treatment-Related Adverse Events (N=54)†	
	no. of participants (%)	*no. of events*	*no. of participants (%)*	*no. of events*
Any adverse event	54 (100)	465	37 (69)	92
Arthralgia	18 (33)	31	3 (6)	3
Headache	16 (30)	31	8 (15)	9
Nasopharyngitis	15 (28)	20	1 (2)	1
Fatigue	14 (26)	16	4 (7)	4
Alanine aminotransferase increased	11 (20)	12	9 (17)	10
Blood creatine kinase increased	8 (15)	10	4 (7)	6
Back pain	7 (13)	10	1 (2)	1
Influenza-like illness	7 (13)	11	7 (13)	8
Aspartate aminotransferase increased	7 (13)	8	5 (9)	6
Oropharyngeal pain	7 (13)	7	0	0
Pain in extremity	6 (11)	7	0	0
Diarrhea	6 (11)	6	2 (4)	2
Nausea	6 (11)	6	4 (7)	4
Cough	6 (11)	6	0	0

N Engl J Med 2023;388:706

Thérapie génique de l'hémophilie en Suisse

swissmedic

Schweizerisches Heilmittelinstitut
Institut suisse des produits thérapeutiques
Istituto svizzero per gli agenti terapeutici
Swiss Agency for Therapeutic Products

Demandes reçues concernant des médicaments à usage humain

XLSX, 483 kB, 31.05.2023

Datum Eingar	Gesuchstellerin Requérant	Gesuchstyp Type de demande	Wirkstoff(e) Principe(s) actif(s)	Anz. A	Anwendungsgebiet Champ d'applicati
17.03.2023	CSL Behring AG Wankdorfstrasse 10, 3014 Bern	Neuanmeldung eines Arzneimittels mit neuem Wirkstoff	Etranacogen dezaparvovec	1	Behandlung der Hämophilie B

www.swissmedicinfo.ch

Synthèse

Traiter l'hémophilie sans les facteurs

- Substituer l'activité (facteur VIII)
  - ✓ Emicizumab
- Diminuer les inhibiteurs
  - Concizumab swissmedic
  - Fitusiran
- Corriger le défaut génétique
  - Prometteur swissmedic