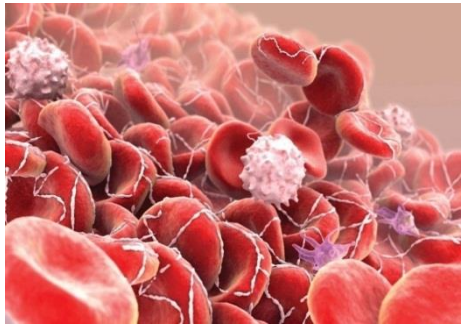
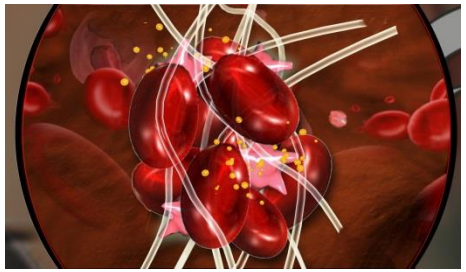
FORTE-U

Forum pour la Recherche Thrombo-Embolique aux Urgences





Tests biologiques de la coagulation : Indications et interprétation en salle d'urgences

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Review

Emergency medicine misconceptions: Utility of routine coagulation panels in the emergency department setting

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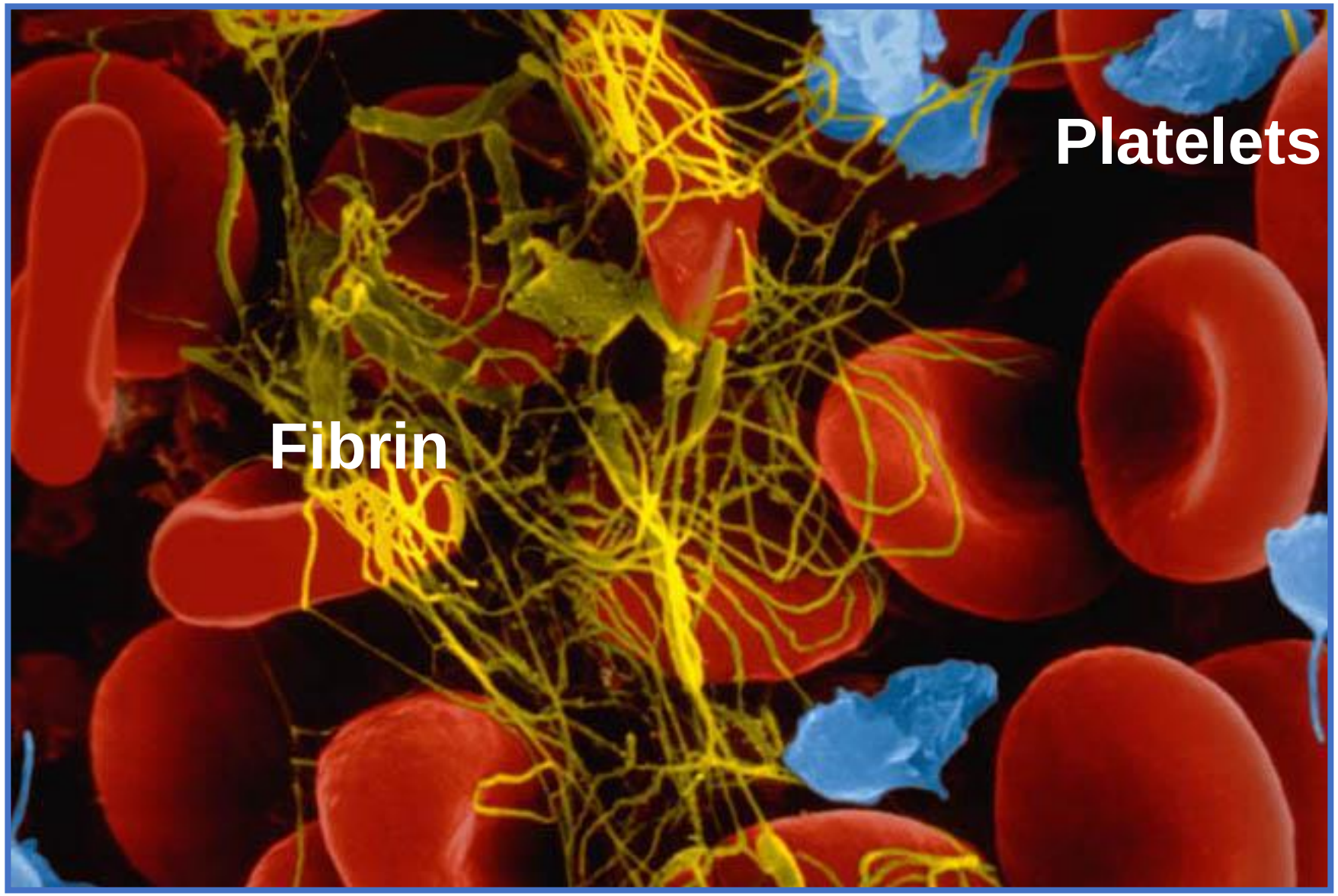
Is it useful to request APTT/PT/TT in patients admitted in the Emergency ?
Which patients should be tested ? Not tested ?

Thrombus / Blood Clot

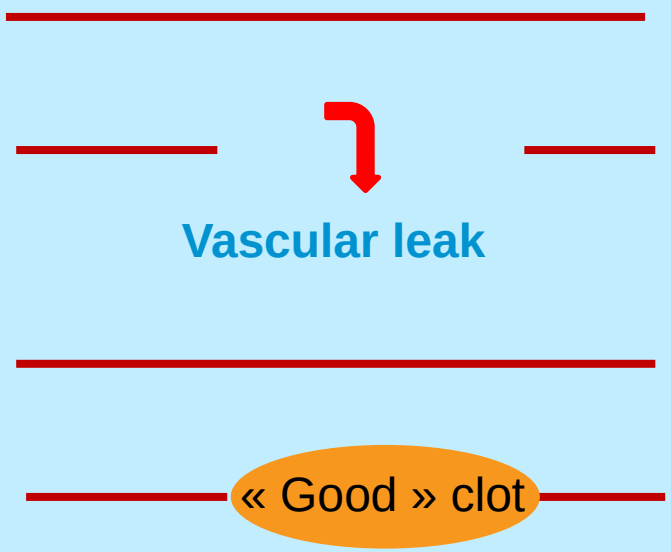


« GOOD » CLOT

« BAD » CLOT

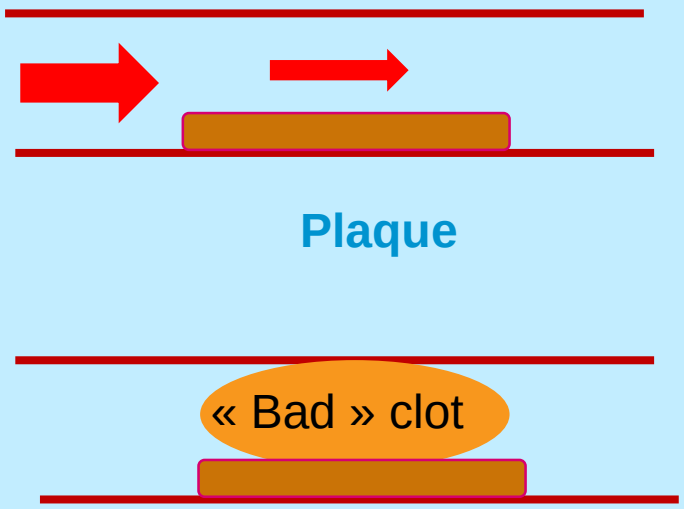
Haemostatic versus occlusive clot

Haemostasis



Haemostatic (Wound Sealing) clot
« GOOD CLOT »

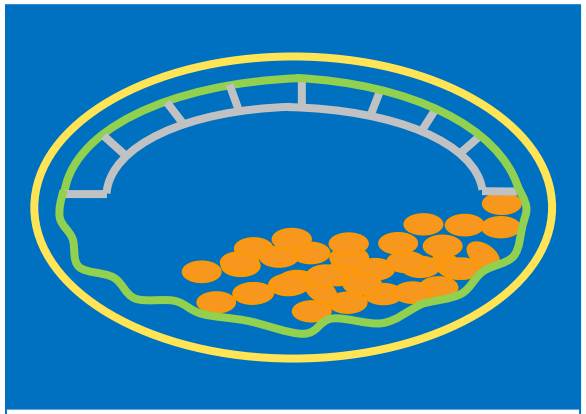
Thrombosis



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

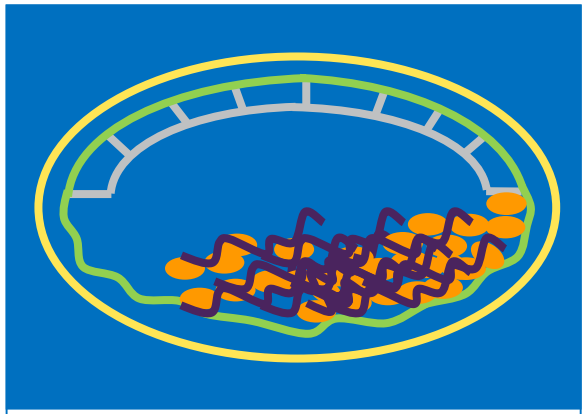
Blood coagulation dissected

Coagulation : a three steps process



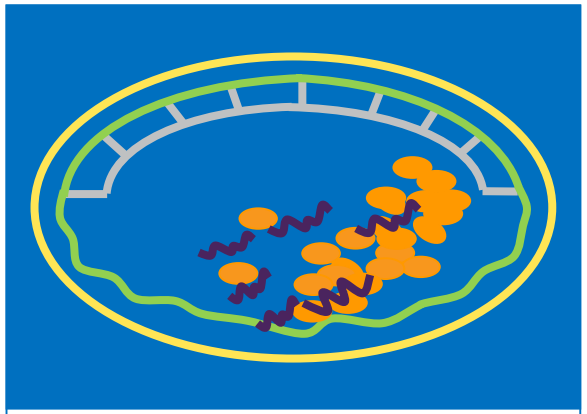
1. Platelets plug

Primary Haemostasis



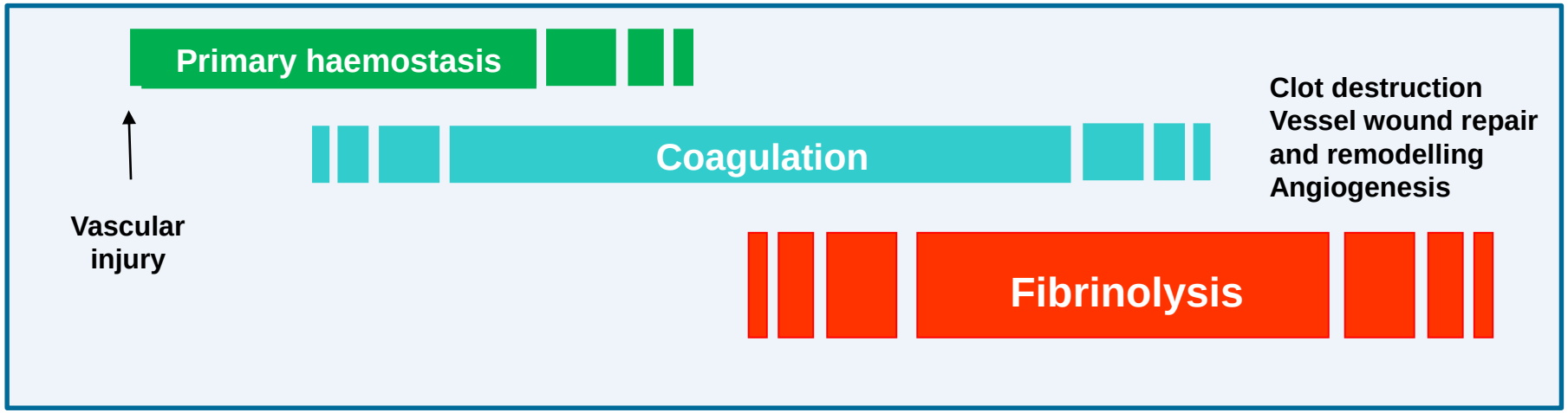
2. Fibrin formation

Coagulation cascade



3. Clot destruction/dissipation

Fibrinolysis

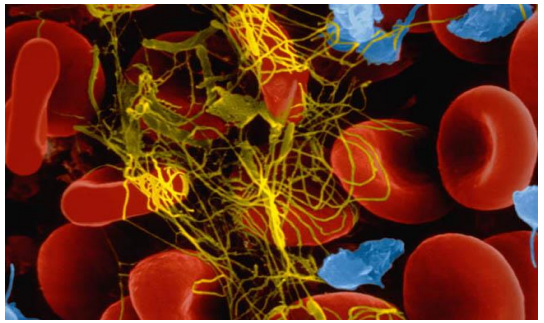


Thrombus formation
Platelet activation and fibrin formation

Primary Haemostasis

↓

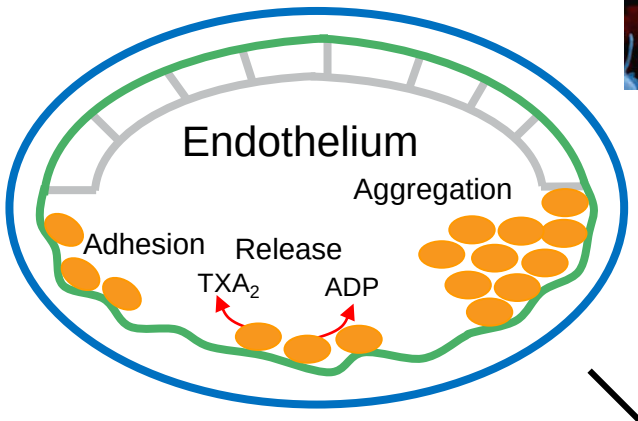
Platelets aggregates

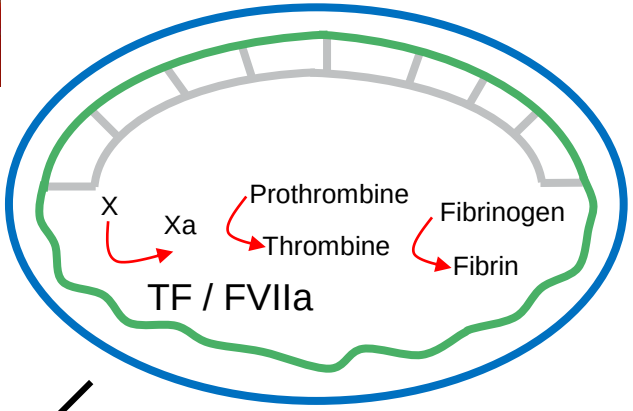


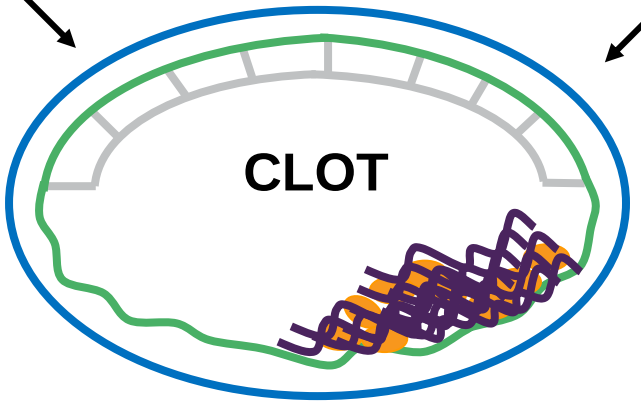
Blood coagulation

↓

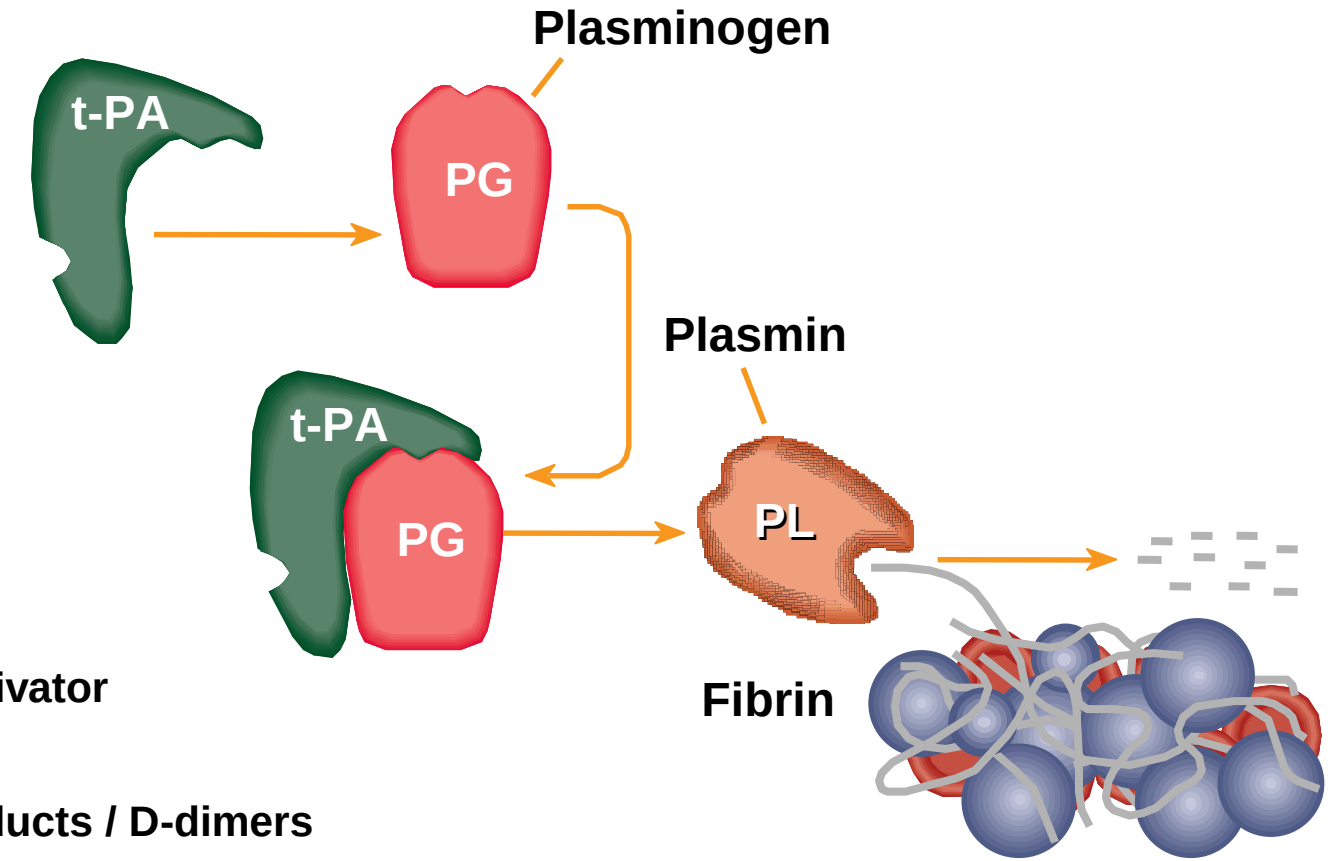
Fibrin network







Fibrinolysis



D-dimers

T-PA = Tissue Plasminogen activator

PG = plasminogen

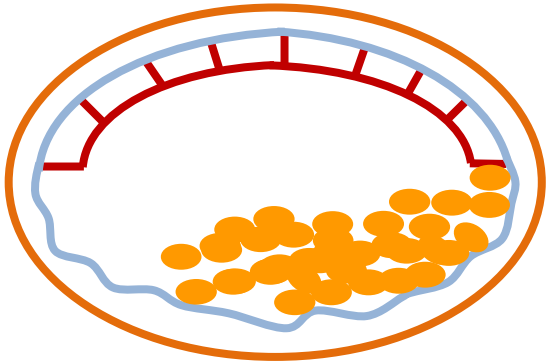
FDPs = Fibrin Degradation Products / D-dimers

D-Dimer : a marker of clot formation + destruction

Haemostasis-thrombosis players

Primary Haemostasis	Blood vessels Platelets von Willebrand factor
Coagulation Thrombin Generation Fibrin formation	FVII, FX, FIX, FII (Vit K dependent) FV and FVIII (co-factors) FXI FI (Fibrinogen) FXIII (cross-linking)
Fibrinolysis	T-PA, Plasminogen, …

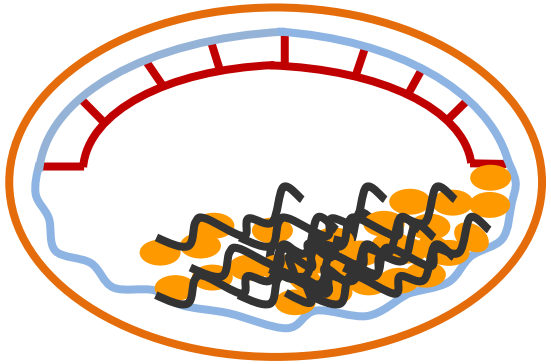
ANTITHROMBOTIC TREATMENTS



Anti-platelet agents

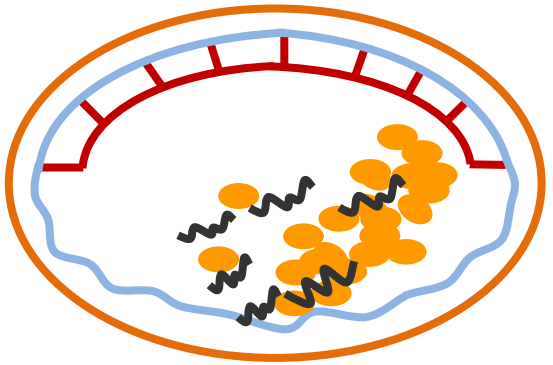
Aspirin
Clopidogrel

Prasugrel (Efient)
Ticagrelor (Brilique)



Anticoagulant agents

Heparins
VKA
New or Direct oral Anticoagulants (NAOCs/DOACs)



Fibrinolytic agents

HAEMOSTATIC THERAPIES

Primary Haemostasis

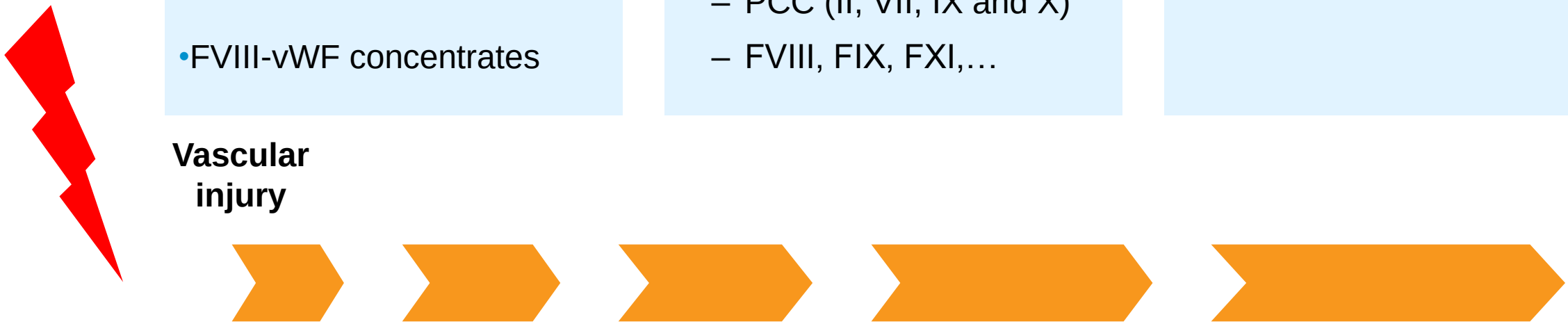
- Platelet concentrates
- Antifibrinolytics (EXACYL)
- DDAVP (Minirin)
- FVIII-vWF concentrates

Secondary Haemostasis

- Fresh frozen plasma (FFP)
- Clotting factor concentrates
  - Fibrinogen (FI)
  - rFVIIa (Novo Seven)
  - PCC (II, VII, IX and X)
  - FVIII, FIX, FXI,…

Fibrinolysis

- Tranexamic acid (Exacyl)



Classical theory of blood coagulation

Classical theory of the coagulation cascade

Intrinsic pathway

Contact Phase
FXII

FXI

FIX + FVIII

Extrinsic pathway

Tissue Factor
+ FVIIa

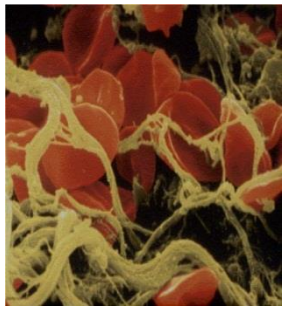
Common pathway

FX

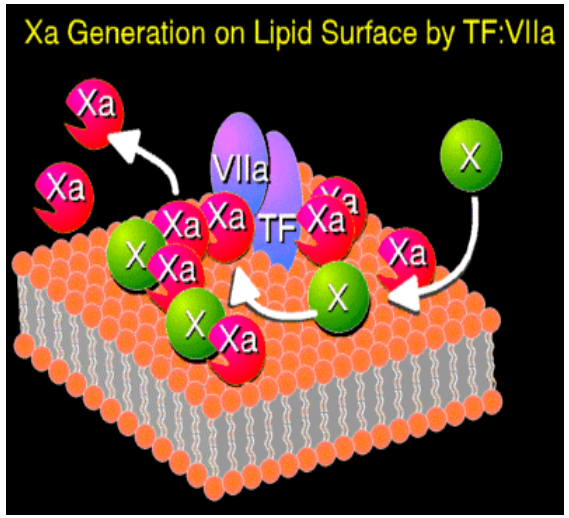
FV

Thrombin

Fibrinogen → Fibrin



Blood clot



Coagulation cascade

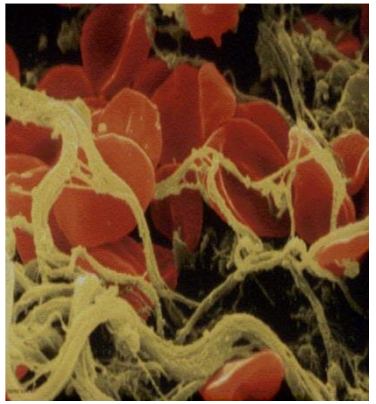
(FXII, XI, VII, X, IX, VIII, V, II)

↓

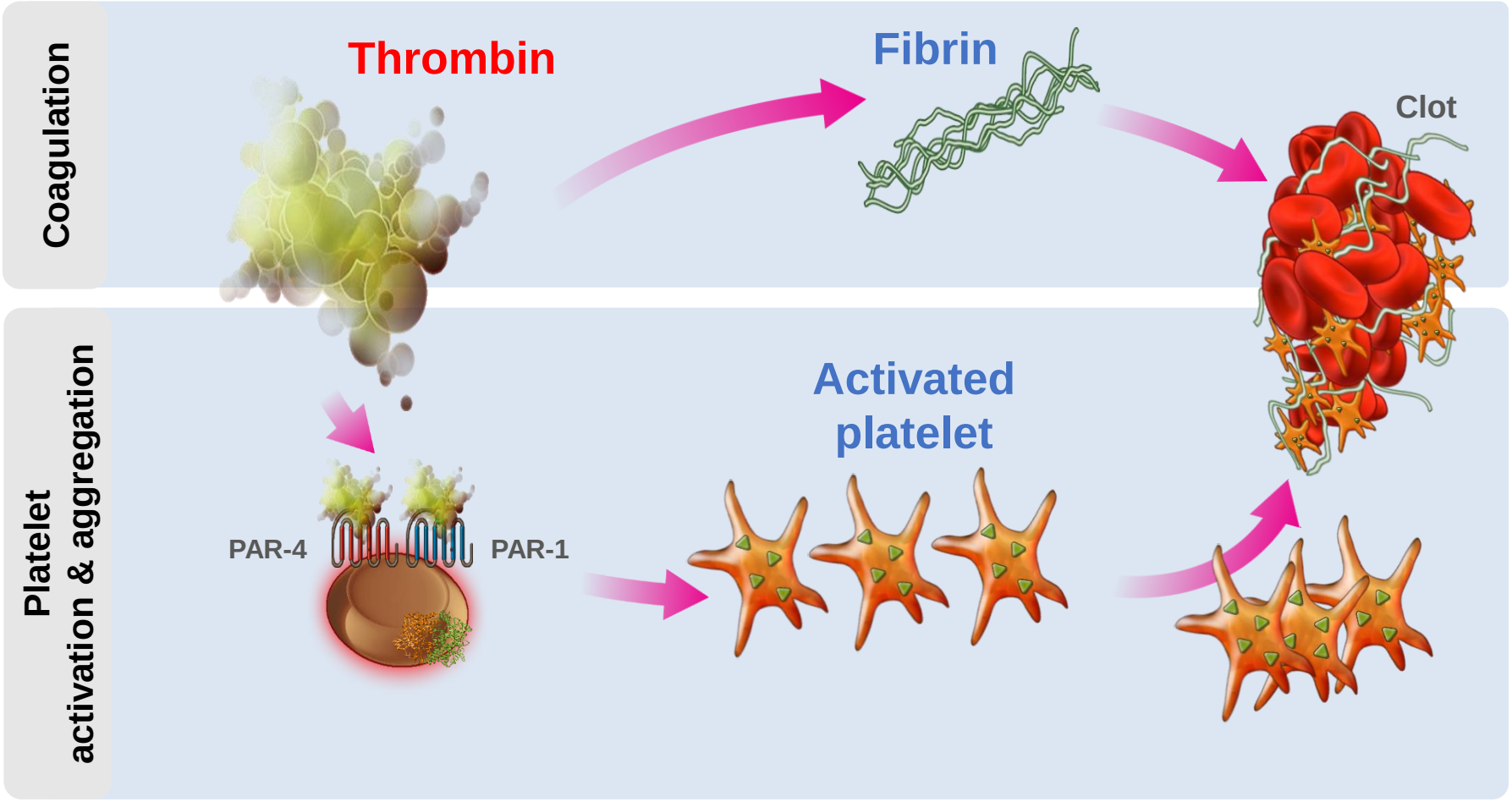
Thrombin (FIIa)

↓

Fibrinogen (FI) → Fibrin

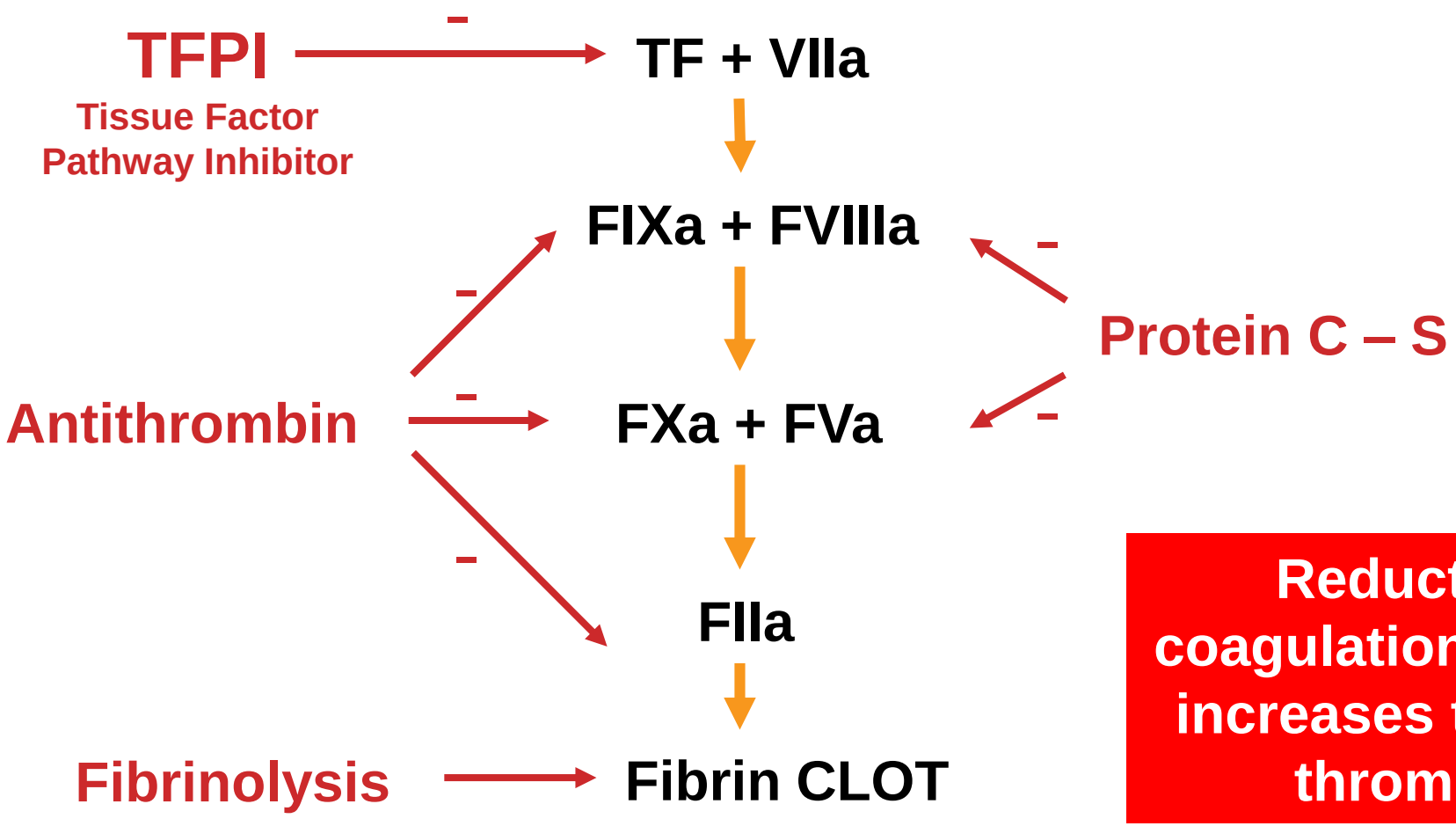


Role of thrombin : Fibrin formation and platelet activation



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

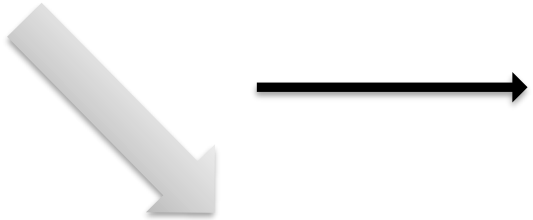
Keeping coagulation under control : Physiological inhibitors



Reduction of coagulation inhibitors increases the risk of thrombosis

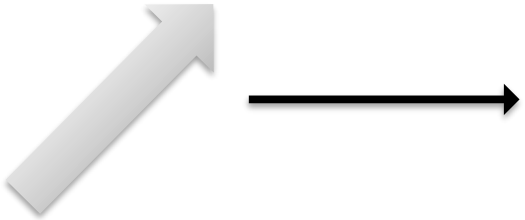
Coagulation diseases

Altered thrombin generation (FIIa)



Bleeding

- Hemophilia
- Acquired clotting factor(s) deficiency
- Overdosing of Anticoagulant



Thrombosis

- Hypercoagulability
- Thrombophilia

BLOOD TESTS OF HAEMOSTASIS

Primary Haemostasis

Platelet count/number

Platelet function

(Bleeding time
PFA-100 - Platelet aggregation tests)

Coagulation Cascade

Prothrombin Time (INR)

APTT

Thrombin Time

Fibrinogen

Point of care

- INR (point-of care)
- ACT (activated clotting time)
- RoTEM

Fibrinolysis

Euglobulin lysis time

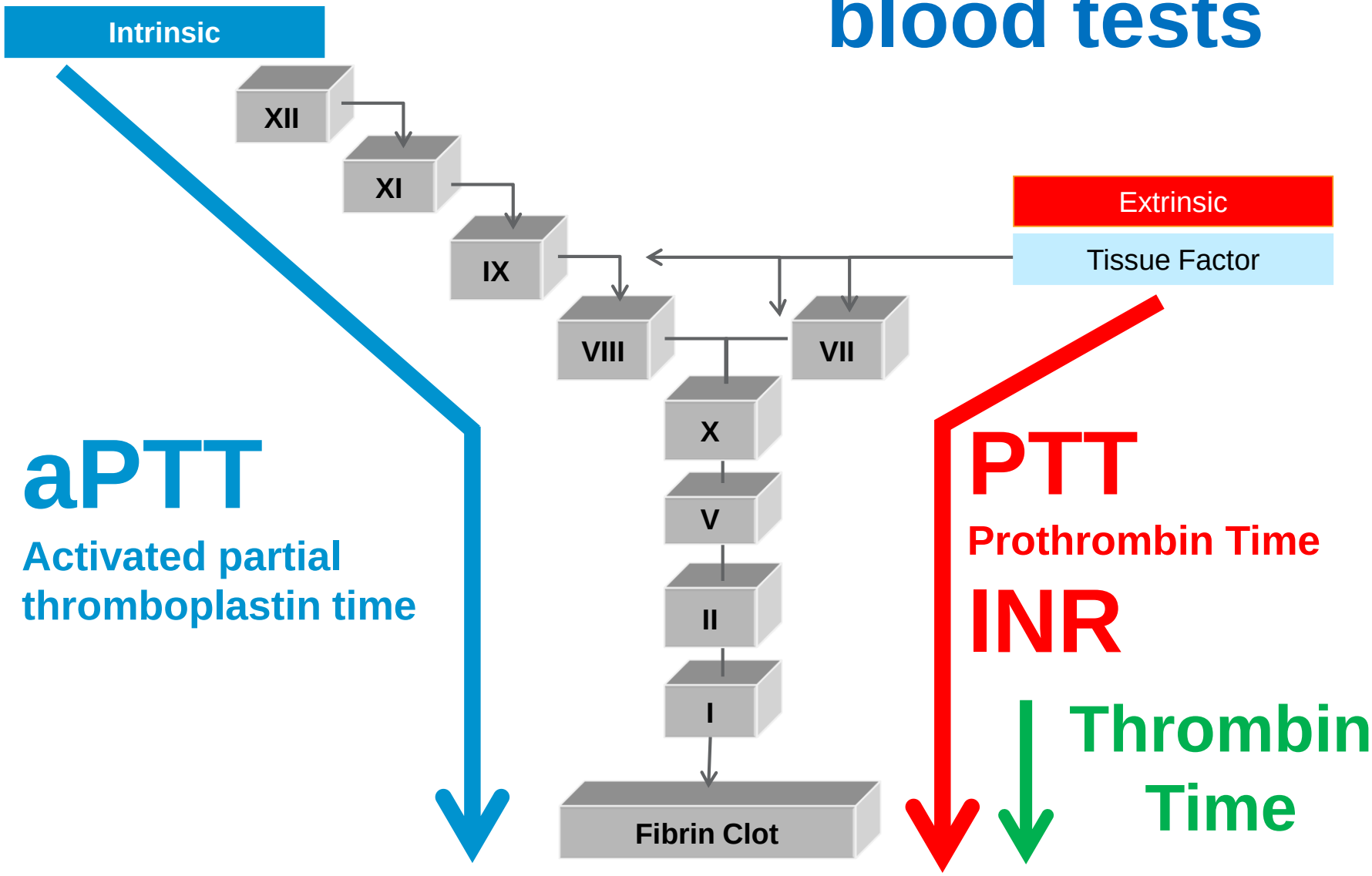
D-dimers

RoTEM

Routine tests

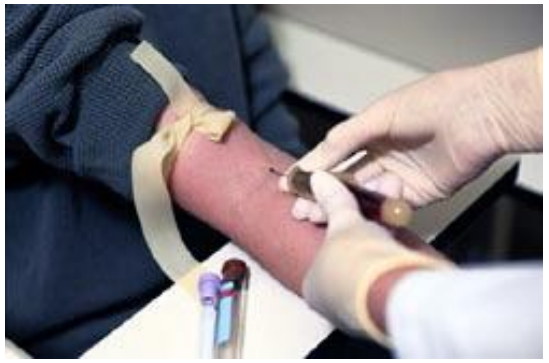
- Platelet count
- APTT
- Prothrombine Time (INR)
- Thrombin Time
- Fibrinogen
- D-Dimers

Routine coagulation blood tests



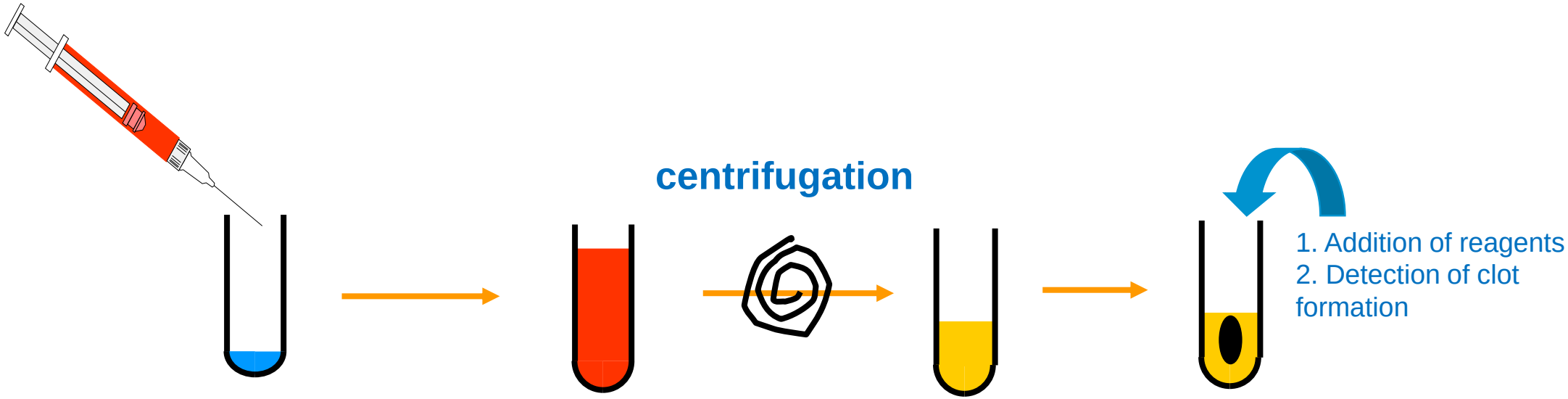
Measurement of APTT and PT in the lab : TIME is needed

- Decision
- Blood sampling (1 min)
- Transfer to the lab (x min to …)
- Lab registration (1 min to ....)
- Centrifugation (10 min to 15 min)
- Test (3 min to 5 min)
- Results by phone, fax... (1 min to ...)



- **TOTAL: >20 min to ..... x hours !!!**

Blood sampling and plasma preparation: Critical steps



Citrate tube
(Reversible
calcium chelation and
anticoagulation)

Sampling of anticoagulated
whole blood
(9 vol blood /
1 vol citratre)

Platetet
poor plasma
(PPP)

Addition of reagents
in order to activate either
FXII (Intrin) or FVII (Extrins)
with calcium
and phospholipids

Clotting screen : basic rules

Always request all tests (personal view)

APTT + PT + Thrombin Time + Fg level

Appropriate sampling method

(Citrate tube and correctly filled (9 vol/ 1 vol))

Exclure interference :

- Patients on anticoagulant / Contamination by heparin / High Htc

The multiple factors influencing hemostasis but not reflected in blood tests

- Hypovolemia
- Hypothermia
- Acidosis
- Hematocrit
- Hypocalcemia

LIMITATIONS OF SCREENING CLOTTING TESTS

1. Only reflect the activity of most clotting factors (not primary haemostasis and fibrinolysis)

2. Prolonged when clotting factor(s) are deficient (mainly used for diagnosis of bleeding tendency, bleeding diseases, bleeding complications)

3. May be spuriously normal

- In case of mild clotting factor deficiency
- Elevation of some clotting factors (like FVIII) can compensate deficiency.ies of other clotting factors

LIMITATIONS OF SCREENING CLOTTING TESTS

4. APTT/PT/TT are measured in an artificial environment

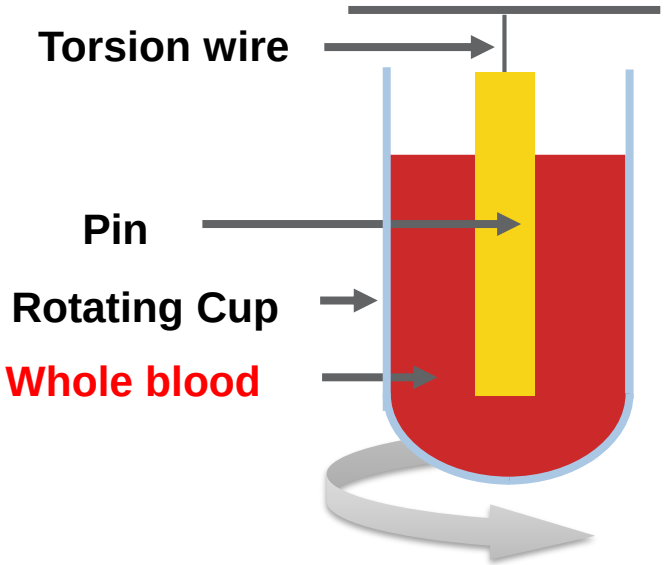
    1. The tests are performed on platetet poor plasma without blood cells

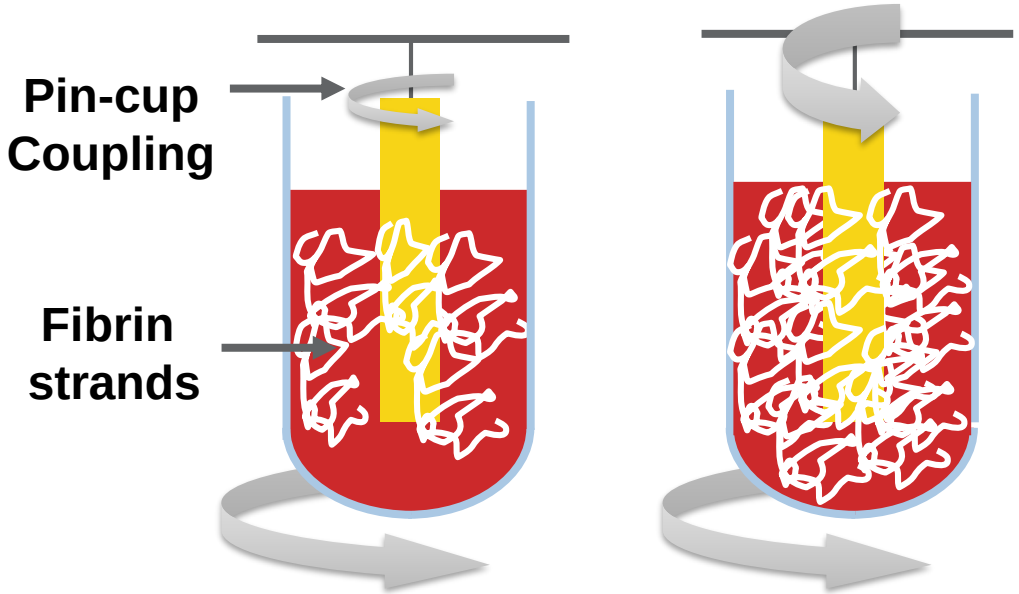
    2. Static test (different from high shear in microvessels)

    3. No vessels – endothelial cells involved

    4. The influence of hypovolemia, hypothermia, … is not reflected

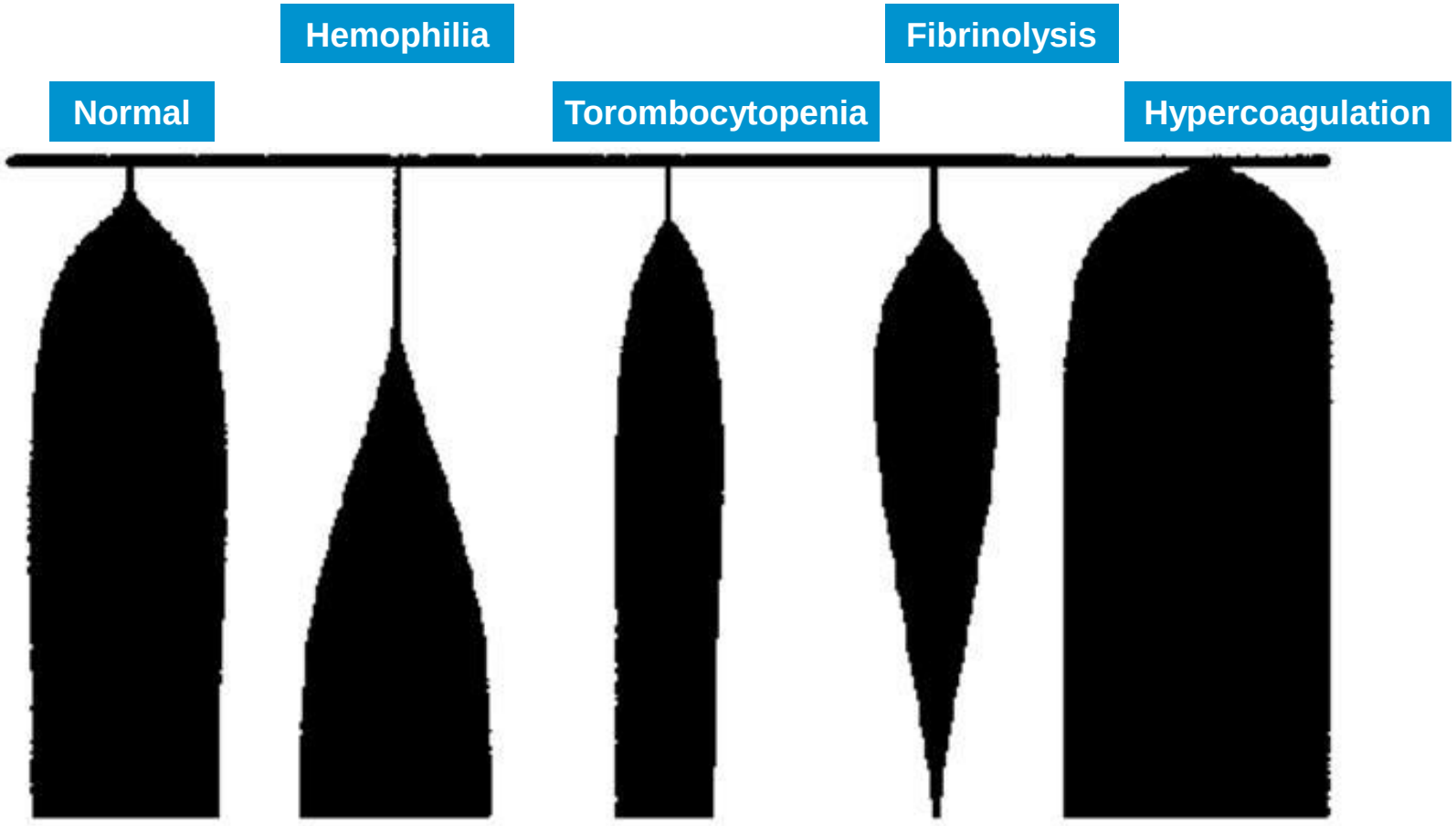
Thromboelastography (TEG) : an alternative to classical tests





TEG recording

TEG tracings



Cedric Hermans – UCL.

Clinical case 1 : 65-yr-old male with liver cirrhosis

Test	Results
APTT	Prolonged
PT	Prolonged
TT	Prolonged
Fg	Reduced
DD	Increased
Platelets	Reduced

In patients with liver cirrhosis, screening tests over-evaluate the risk of bleeding

The impact of high VWF, decrease of physiological inhibitors (AT, proteins C and S) can mitigiate the risk of bleeding and even be responsible for thrombosis

Clotting tests in patients with cirrhosis should be interpreted with great caution

Most patients with liver cirrhosis do not need transfusion (FFP – platelets)

Clinical case 2 : 65 year-old male with post-op bleeding

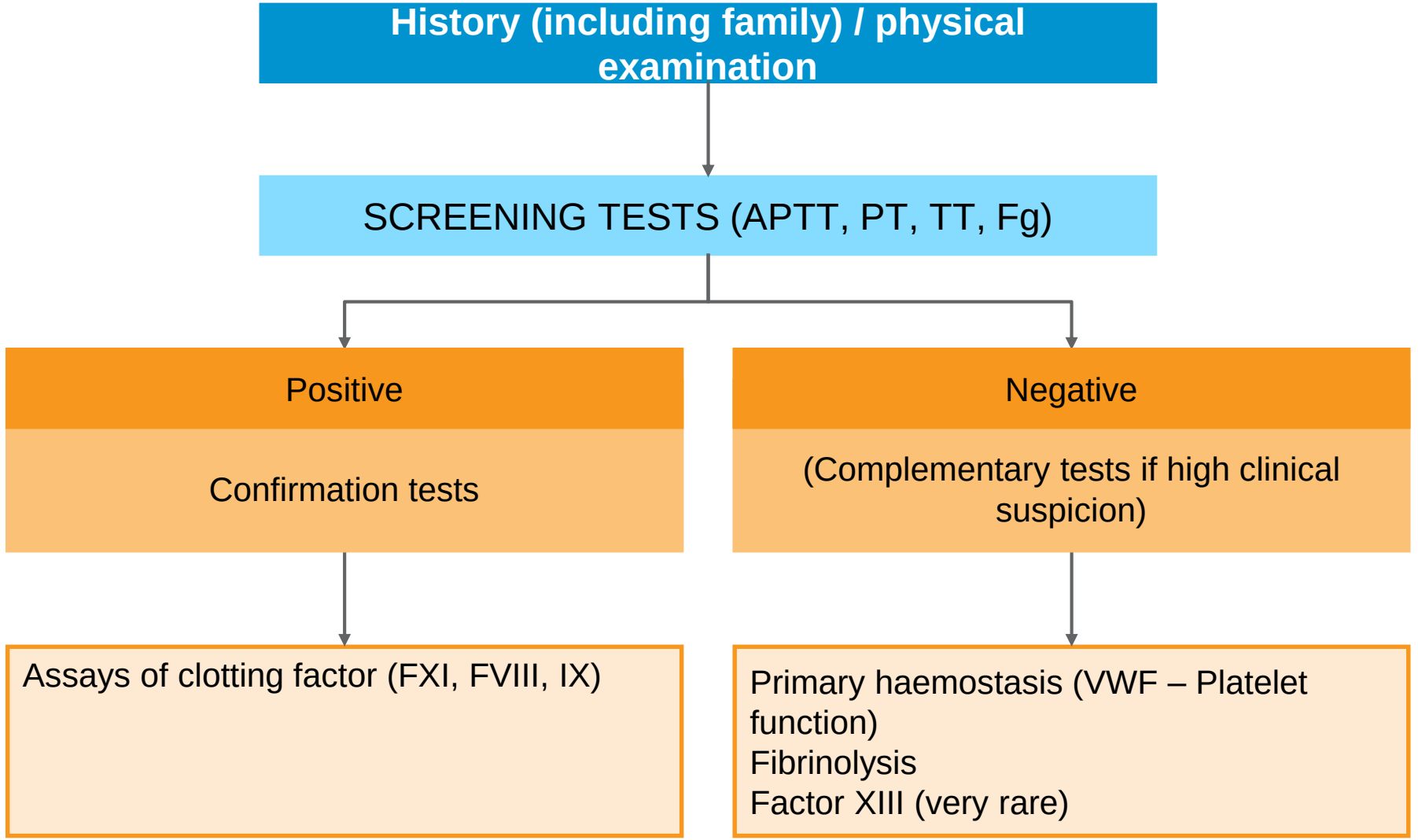
Test	Results
APTT	Normal
PT	Normal
TT	Normal
Fg	Normal
DD	Increased
Platelets	Normal

Routine clotting tests do not rule out coagulation disorders

Primary haemostasis, vessel diseases, mild clotting factor deficiencies, fibrinolytic diseases are not excluded by a normal APTT and PT

In spite of normal routine screening tests (APTT, PT), patients can have a severe bleeding disease

EVALUATION OF THE BLEEDING TENDENCY BEFORE INVASIVE PROCEDURES



Clinical case 3 : 65 year-old male with diffuse haematomas

Test	Results
APTT	Prolonged ++
PT	Normal
TT	Normal
Fg	Normal
DD	Increased
Platelets	Normal

Markledly prolonged APTT should raise suspicion of (acquired) hemophilia A

Mixing studies with normal plasma should be performed

Anti-phospholipid antibodies (Lupus anticoagulant) should be excluded

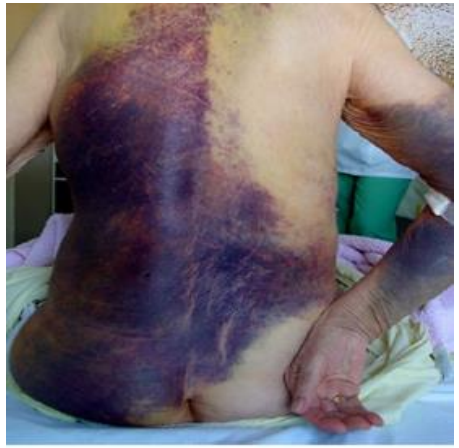
Heparin contamination very unlikely (normal Thormbin Time)

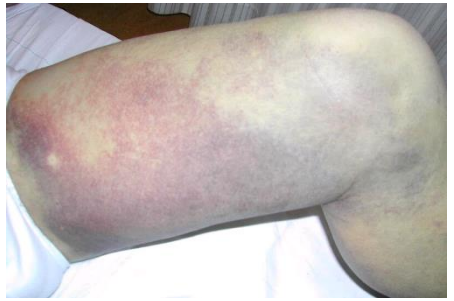
Diagnosis of Acquired Haemophilia A (AHA) should not be missed in a bleeding patient with a markedly prolonged APTT

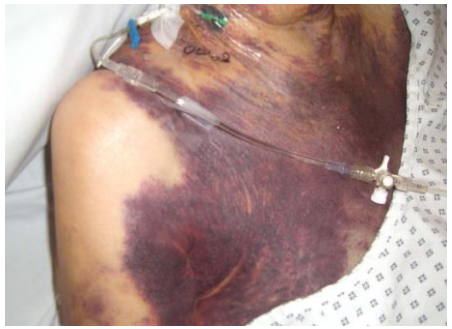
What is Acquired Haemophilia?

- Rare and serious bleeding disorder
- Mostly older people (>65 yrs), males and females
- Deficiency in coagulation factor VIII due to auto-antibodies
- Spontaneous bleeds: subcutaneous, deep tissue, mucous membrane and soft tissue.
- Even treated, high mortality rate (7.9 to 33%) if gastrointestinal, intracranial and retroperitoneal bleeds occur.

- **Treatment objectives:**
  - Stop bleeding fast and effectively with bypassing agents
  - Suppress antibodies (immunosuppression)



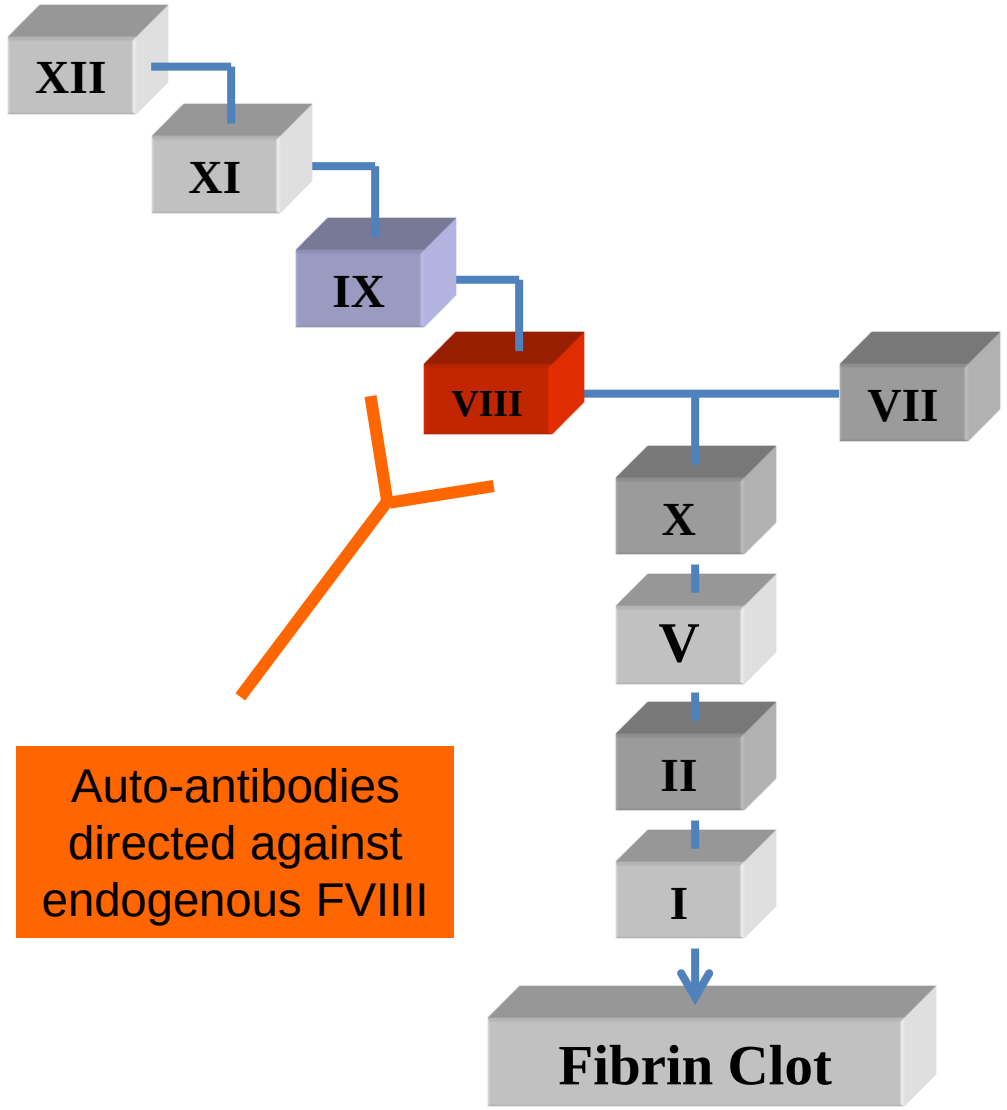




Acquired Haemophilia A :
Inhibition of endogenous clotting FVIII by auto-antibodies

AHA is an autoimmune disease caused by the spontaneous production of neutralizing immunoglobulin G (IgG) autoantibodies (inhibitors) targeting endogenous FVIII.

Recent research suggests that the breakdown of immune tolerance is caused by a combination of genetic and environmental factors.



Clinical case 4 : 34 year-old female with bleeding post wisdom teeth extraction

Test	Results
APTT	Prolonged
PT	Normal
TT	Normal
Fg	Normal
DD	Normal
Platelets	Normal

Mixing studies with normal plasma are needed
Correction of the APTT with normal plasma suggests FXII, FXI, FIX, FVIII deficiency

Clotting factors should be measured

This patient was found to have FVIII deficiency (secondary to VWF deficiency)

Clotting factor deficiency (FXI, IX, VIII) should be suspected in all patients with bleeding + prolonged APTT

Clinical case 5 : 34 year-old female admitted with a fourth unexplained miscarriage

Test	Results
APTT	Prolonged
PT	Normal
TT	Normal
Fg	Normal
DD	Normal
Platelets	Low

Mixing studies with normal plasma did not show APTT correction

The absence of correction should raise suspicion for anti-phospholipid antibodies.

The Rosner Index should be calculated

This lady was found to have anti-PL syndrome

Anti-phospholipid antibodies/syndrome should be suspected in patients with prolonged APTT not correcting after mixing with normal plasma

INDICE DE ROSNER

- L'indice de Rosner (IR) permet de mettre en évidence la présence d'un anticoagulant circulant (ACC) dans le sang, qui peut être associé à un syndrome des antiphospholipides.
- Cet indice se calcule à l'aide des temps de céphaline activée ou TCA :
- TCA du patient - TCA témoin – TCA mélange
- IR = (TCA mélange - TCA témoin) / TCA patient.
- L'IR s'exprime en pourcentage.

R	Interprétation
inférieur à 12 %	Pas d'ACC
entre 12 % et 15 %	Douteux, à recontrôler
supérieur à 15 %	Présence d'ACC

Clinical case 6 : 83 year-old male on Pradaxa admitted with a new stroke

Test	Results
APTT	Prolonged +
PT	Normal
TT	Prolonged +++
Fg	Normal
DD	Normal
Platelets	Normal

Pradaxa is a direct oral anticoagulant targeting thrombin

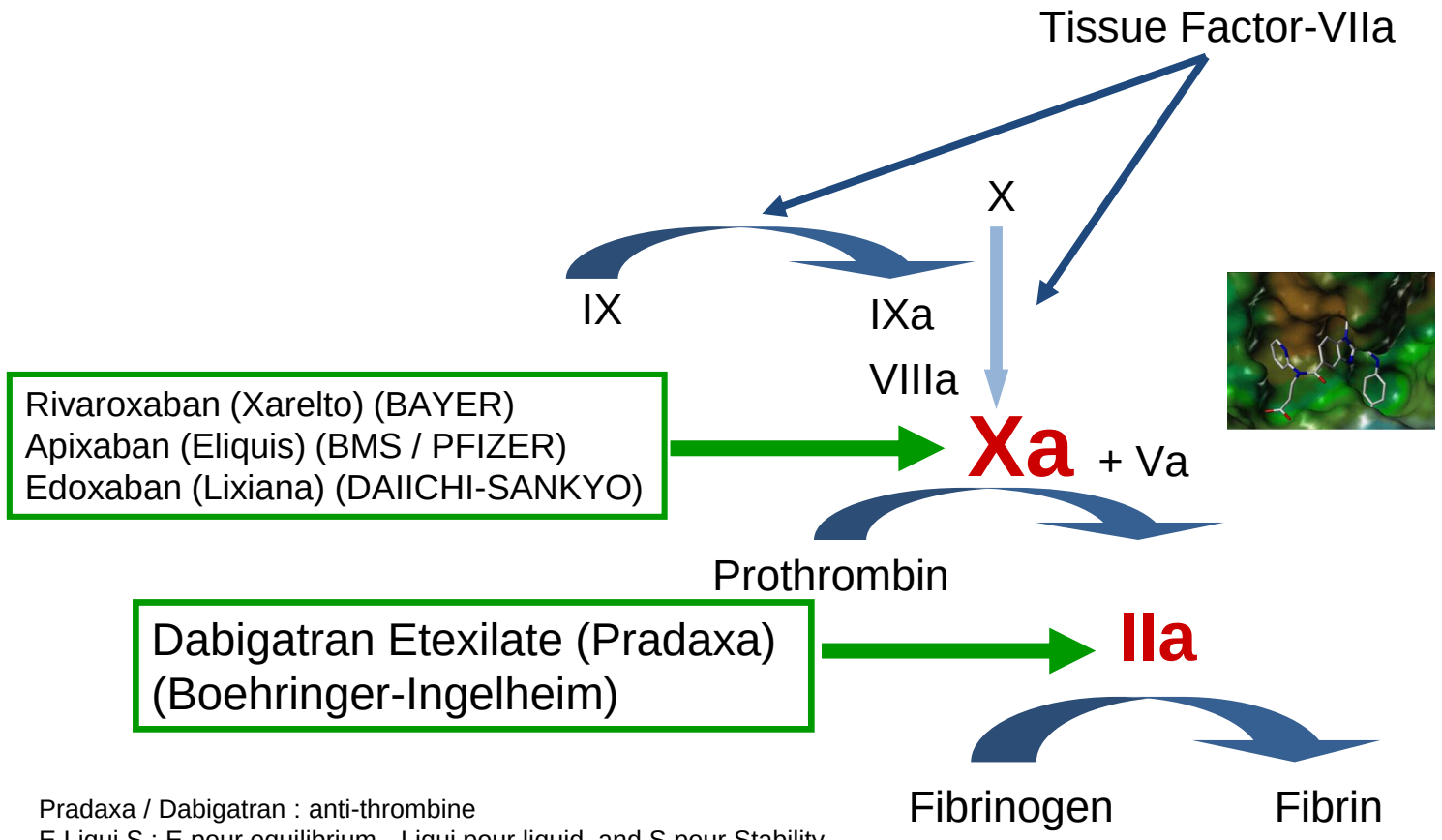
A markeldy prolonged TT in a patient on Pradaxa means that the drug is present (recent intake – slow clearance)

Reversal with Praxbind could be considered before thrombolysis / thrombectomy

The thrombin time is very useful parameter to detect anticoagulation induced by Pradaxa

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

Influence of DOACs on blood coagulation tests

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban*
aPTT	✓	✗	✗	✗ †
TT, dTT	✓	✗	✗	✗
ECT	✓	✗	✗	✗
Anti-FXa assays	✗	✓ ‡	✓ §	✓ ‡
PT	✗	✓ ǀ	✗	✗ †
INR	✗	✗	✗	✗

Time of last NOAC dose should always be considered when interpreting test results.
Green = quantitative; orange = qualitative only; red = not applicable
*No EMA approval yet; †Prolonged, but not useful in monitoring the anticoagulant effect; ‡No data on threshold values for bleeding or thrombosis; §No data yet; ǀInfluenced by rivaroxaban in a dose-dependent way with a close correlation to plasma concentrations only if neoplastin is used. aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; FXa, Factor Xa; INR, international normalized ratio; PT, prothrombin time; TT, thrombin time; Adapted from references 1–5; **1.** Heidbuchel H et al. Europace 2013;15:625–51; **2.** Pradaxa®: EU SPC, 2015; **3.** Eliquis®: EU SPC, 2014; **4.** Xarelto®: SPC, 2014; **5.** Savaysa™ US PI, 2015

Monitoring biologique des AODs

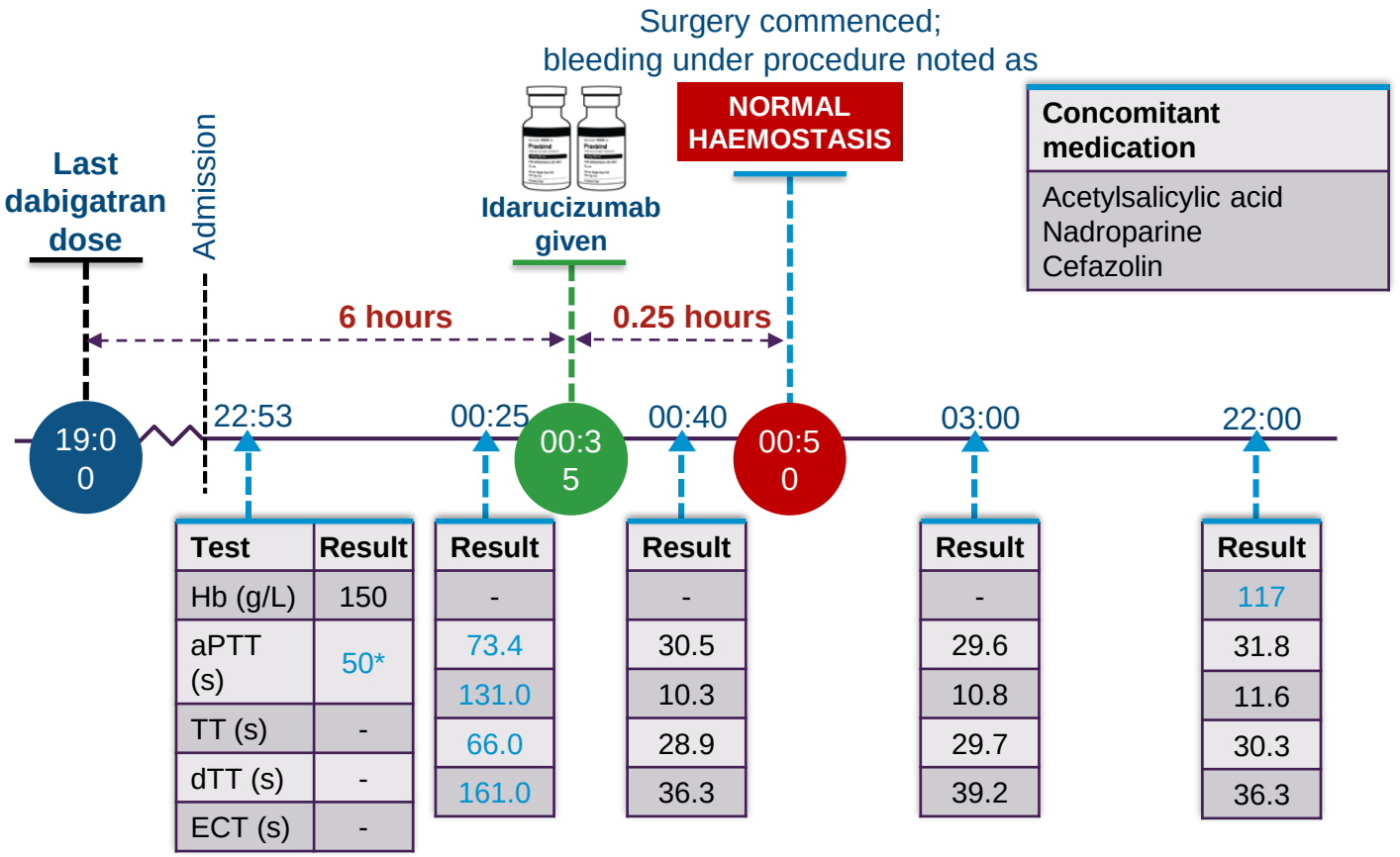
Monitoring Apixaban		
	C max (ng/mL)	Anti-Xa max (UI/mL)
Prévention des ETEV : chirurgie programmée pour prothèse totale de hanche ou genou		
2,5 mg x 2/j	41-146	0,67-2,4
Prévention AVC et embolie systémique		
2,5 mg x 2/j	69-221	1,0-3,3
5 mg x 2/j	91-321	1,4-4,8
Traitement de la TVP, de l'EP et prévention de la récidive de TVP et EP		
2,5 mg x 2/j	30-153	0,46-2,5
5 mg x 2/j	59-302	0,91-5,2
10 mg x 2/j	111-572	1,8-10,8

Monitoring Xarelto		
	Cmax (ng/mL)	Anti-Xa max
10 mg x 1/jour	91,4-194,4	Non précisé
20 mg x 1/jour	159,6-359,8	Non précisé

Monitoring Pradaxa	
	Cmax (1-3h) (ng/mL)
220 mg x 1/jour	62-447
150 mg x 2/jour	64-443

Dabigatran (=Pradaxa) = anti-IIa
Cmax (1-3h) après la prise doit être < 400 mg/dL
Antidote =Praxbind. Se référer à la BDS DSQ 105 pour prise en charge et délivrance.

Clinical illustration of the use of Pradaxa



- Hb, haemoglobin

Clinical case 7 : 75 year-old male admitted with suspicion of COVID-19

Test	Results
APTT	Normal
PT	Prolonged +
TT	Normal
Fg	Increased
DD	Increased ++++
Platelets	Slight decrease

COVID-19 coagulopathy

Feature	COVID coagulopathy	DIC
• Pulmonary involvement • Bleeding • Thrombosis • Thrombocytopenia • PT/APTT prolongation • Anemia and hemolysis • Fibrinogen • D-Dimer	• ++++ • Uncommon • ++ • + • Mild, common • Unusual • Increased • ++++	• ++ • Prominent • + • +++ • Marked, very common • Common • Decreased • ++

Coagulation laboratory characteristics of COVID-19 infection

	Survivors	Non-survivors
Platelet count <150x10⁹/L	30-70%	45-80%
Platelet count <100x10⁹/L	0-1%	3-5%
Prothrombin time > 3 sec. prolonged	0-5%	15-25%
Fibrinogen < 1.0 g/L	0%	5-10%
Fibrinogen > 4.0 g/L	80-100%	80-100%
D-dimer > 1 mg/L (2x ULN)	15-25%	80-90%
D-dimer > 3 mg/L (6x ULN)	1-5%	50-70%
Antithrombin < 80%	0%	0-2%

The laboratory characteristics of (severe) COVID-19 infection are:[1-3]

a mildly to moderately reduced platelet count in the most severe patients ↓

a mild prolongation of the prothrombin time in a minority of patients ↑

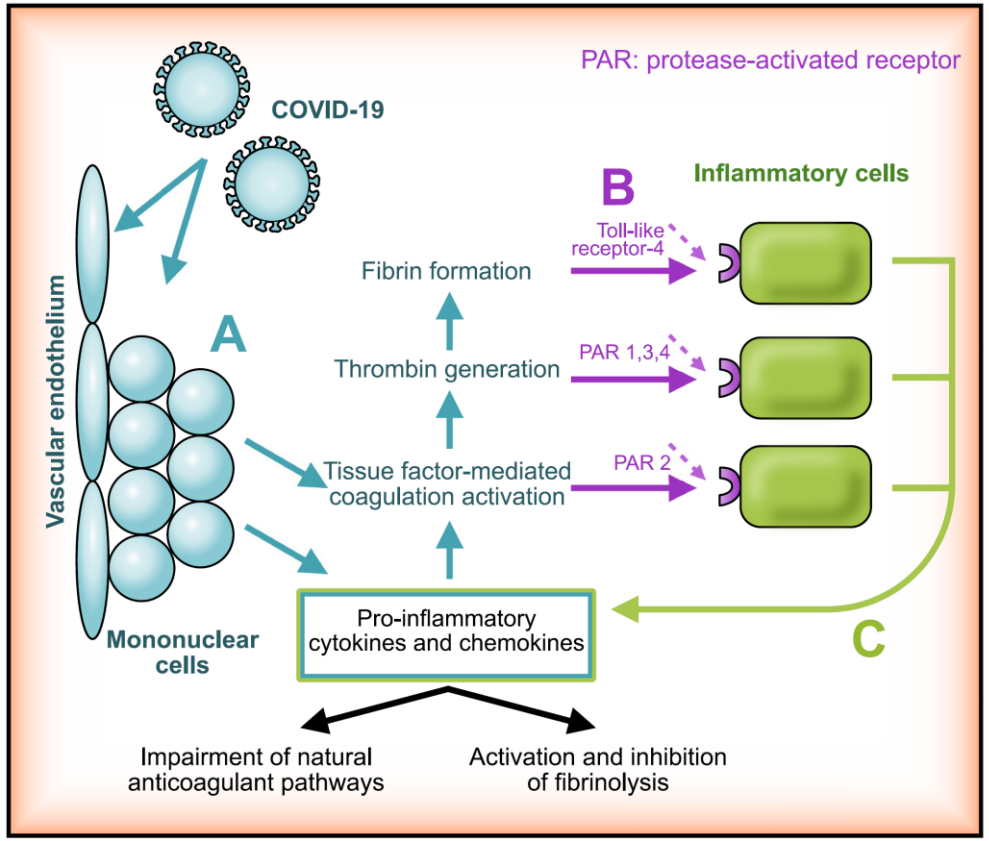
high fibrinogen levels in virtually all patients ↑

(with very low levels in severely ill patients briefly before death)

(very) elevated D-dimer levels, in particular in non-survivors ↑

normal antithrombin levels =

Like many other infections, there is significant cross-talk between inflammation and coagulation



A Severe COVID-19 generates an increase in pro-inflammatory cytokines and activates endothelial cells, neutrophils, mononuclear cells, and platelets leading to tissue factor-mediated activation of coagulation.[2,9]

B Coagulation proteases bind to specific receptors that mediate further pro-inflammatory responses.[10]

C The inflammatory response to COVID-19 results in activation of coagulation that itself may modulate further inflammatory activity.

Clinical case 8 : 37 year-old male presenting with abdominal pain and hematuria – diffuse hematomas

Test	Results
APTT	Prolonged
PT	Prolonged ++++
TT	Normal
Fg	Normal
DD	Increased
Platelets	Normal

Major elevation of the Prothrombin Time
INR : 8
No intake of VKA
No evidence of vitamin K deficiency
FV : normal
FII, FVII and FX : < 10 %

Initial suspicion of sepsis

VIT K1 : 10-30 mg/day

Repeated history : intake of phytocannabinoids

Cannabinoids are molecules frequently used by drug addicts. These molecules can be of "natural' (phyto-cannabinoids) or synthetic (synthetic cannabinoids or SC) origin. Formulations containing cannabinoids (especially SC) are sometimes contaminated with anti-vitamin K anticoagulant rodenticides.

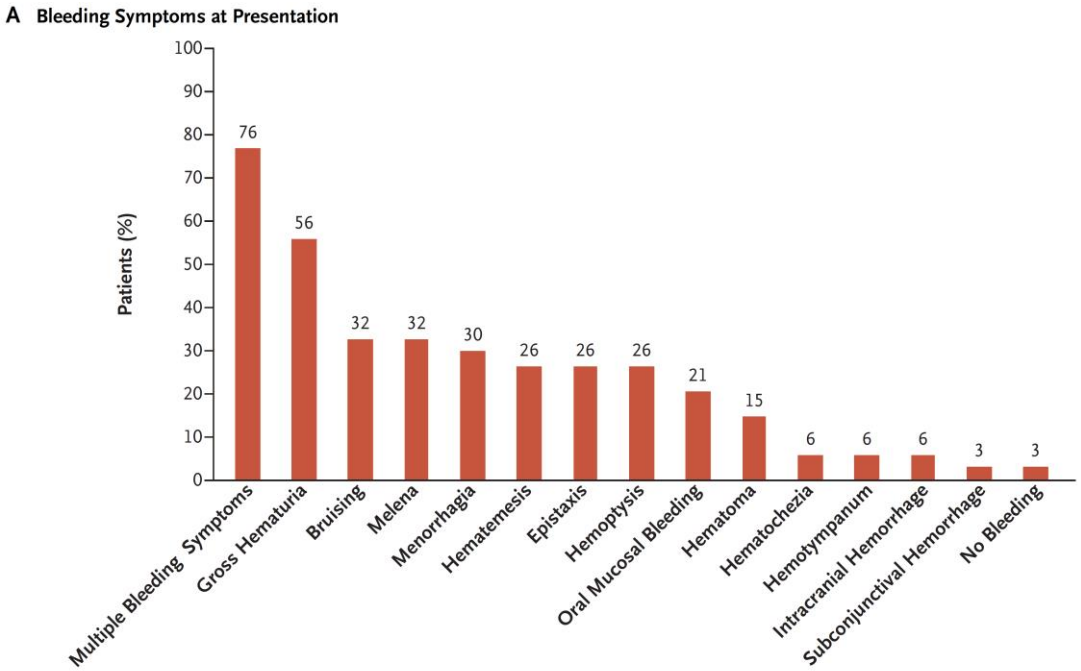
ORIGINAL ARTICLE

An Outbreak of Synthetic Cannabinoid–Associated Coagulopathy in Illinois

Amar H. Kelkar, M.D., Nichole A. Smith, M.D., Annia Martial, M.D., Harsha Moole, M.D., Michael D. Tarantino, M.D., and Jonathan C. Roberts, M.D.

Table 1. Institutional Diagnostic Criteria for Synthetic Cannabinoid–Associated Coagulopathy.*

Major criteria
Presence of vitamin K–dependent factor coagulopathy (defined as a prothrombin time of ≥14.8 seconds and an international normalized ratio of ≥1.3)
Recent exposure to synthetic cannabinoids (within the past 30 days)
Minor criteria
Active bleeding symptoms
Exposure to contaminated synthetic cannabinoids obtained from a person with known superwarfarin poisoning
Positivity for superwarfarin on anticoagulant poisoning panel
Confounding factor
Prescribed use of anticoagulants†



Clinical case 9 : 55 year-old male presenting with severe spontaneous bleeding after a bite in africa

Test	Results
APTT	Prolonged
PT	Prolonged
TT	Prolonged ++++
Fg	Not measurable
DD	Increased +
Platelets	Normal

Diffuse bleeding

FFP and Fg concentrate did not result in clinical or bioogical improvement

Improvement after Polyspecific antivenom that was well tolerated

Fibrinogenolysis - Defibrination

Defibrination/fibrinogenolysis is a rare entity
The fibrinolytic pathway is activated independently of coagulation activation
Pathologic degradation of fibrinogen by plasmin. Hypofibringenemia without marked thrombocytopenia and DD elevation (different from DIC). Treatment : Tranexamic /FFP/Fg

Test	Indication
PT/INR	- Warfarin therapy and concern for bleeding - Liver disease/failure - Vitamin K deficiency
PTT/aPTT	- Hemophilia - Severe von Willebrand disease with bleeding
Both PT/INR and PTT/aPTT	- Bleeding of unknown etiology - History suggestive of bleeding - Suspected or known coagulopathy (on anticoagulation and bleeding) - Administration of thrombolytics - Presence of severe, systemic illness (sepsis, disseminated intravascular coagulation, liver malfunction/-disease, preeclampsia, malnutrition)

Routine coagulation tests in A&E setting

When should APTT, PT, TT and Fg be measured ?

- Suspicion or proven personal / family beeding tendency
- Before invasive procedures if abnormal bleeding is suspected
- In patients on or candidates for anticoagulation
- In patients with COVID-19 infection
- In all patients with severe conditions / systematically ill
- In cases of suspicion of physical abuse

Thank you for your attention

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