The coagulation cascade

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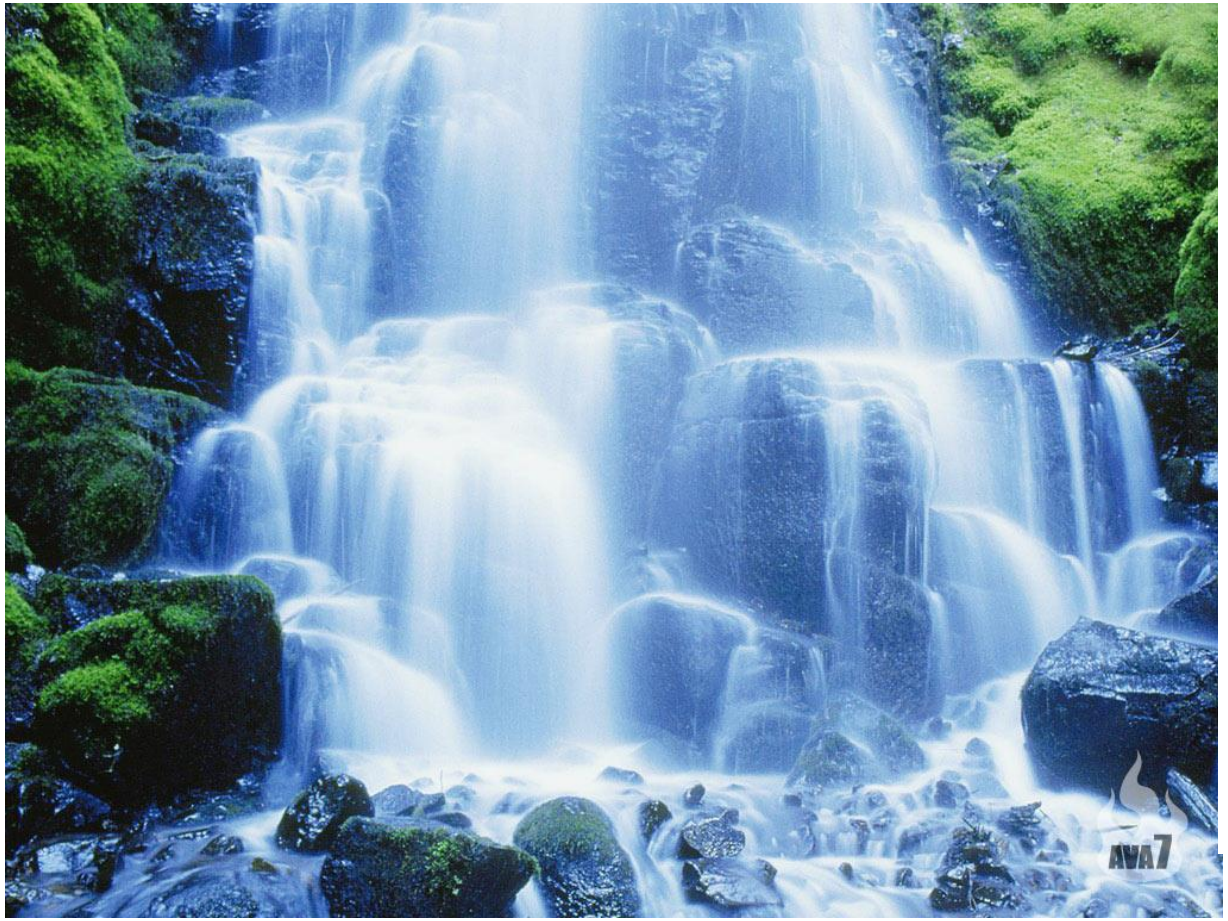
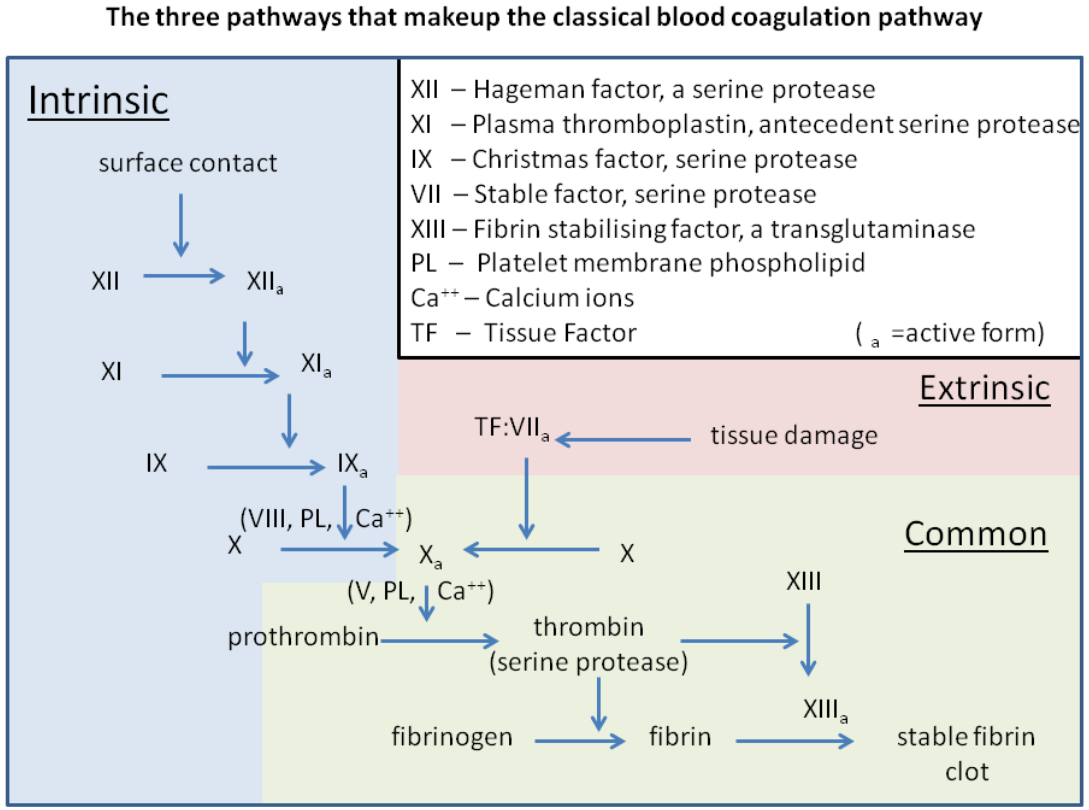
Cascade…….




The three pathways that makeup the classical blood coagulation pathway
Intrinsic
surface contact
XII
XIIa
XI
XIa
IX
IXa
(VIII, PL, Ca++)
X
Xa
(V, PL, Ca++)
prothrombin
thrombin
(serine protease)
fibrinogen
fibrin
XIII
XIIIa
stable fibrin clot
XII – Hageman factor, a serine protease
XI – Plasma thromboplastin, antecedent serine protease
IX – Christmas factor, serine protease
VII – Stable factor, serine protease
XIII – Fibrin stabilising factor, a transglutaminase
PL – Platelet membrane phospholipid
Ca++ – Calcium ions
TF – Tissue Factor
(a =active form)
Extrinsic
TF:VIIa
tissue damage
Common
X

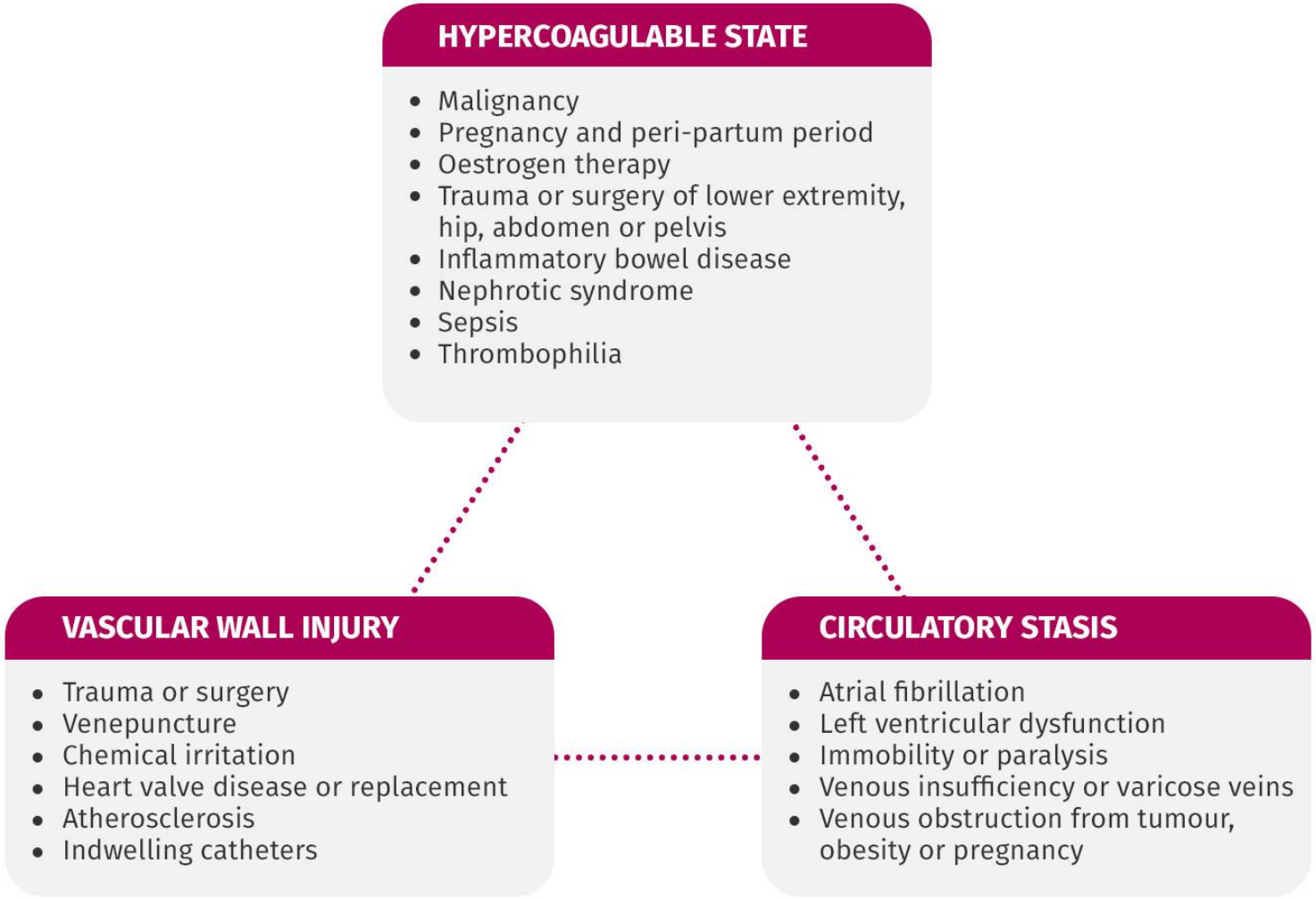
Controlled, localised reaction

Useful Concept

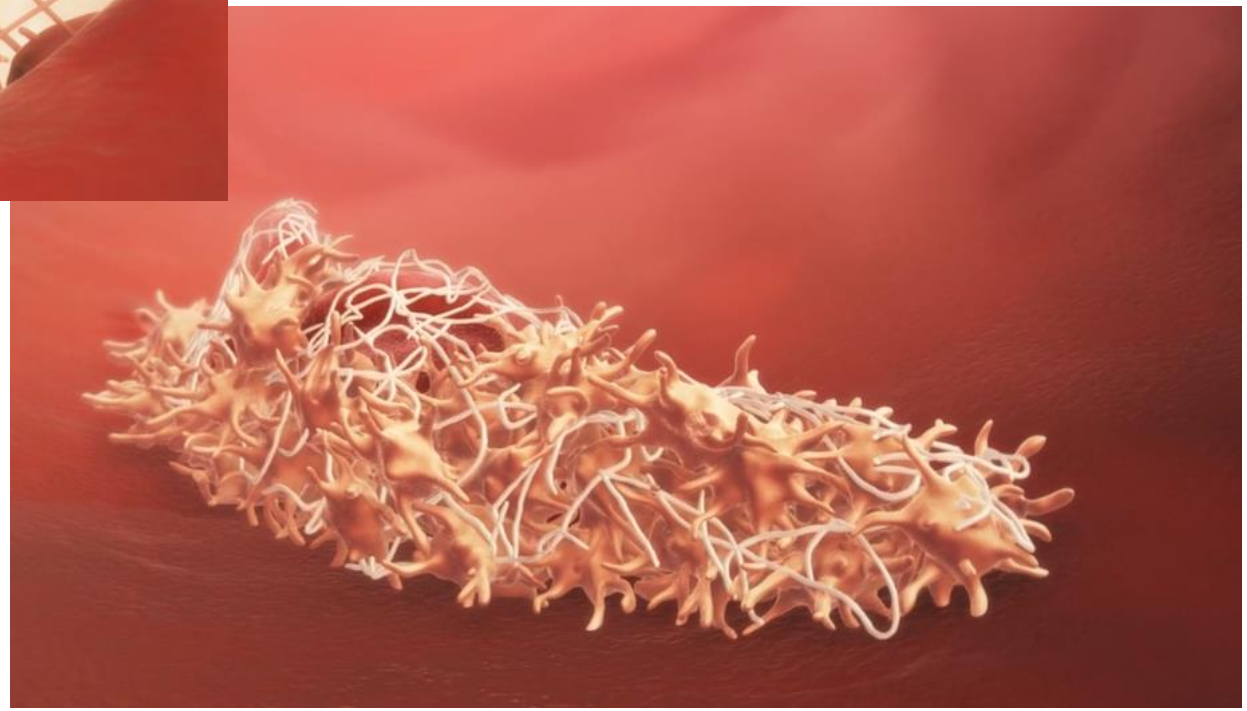
- Aims:
- Coagulation cascade:
  - screening tests
  - limitations
  - Inherited disorders of the coagulation cascade
  - Acquired haemophillic disorders
    - Pharmaceutical:
      - DOACS
      - VKAs
      - Heparins
  - Hypercoagulability

- Alternative measures of coagulation: ‘global assays’

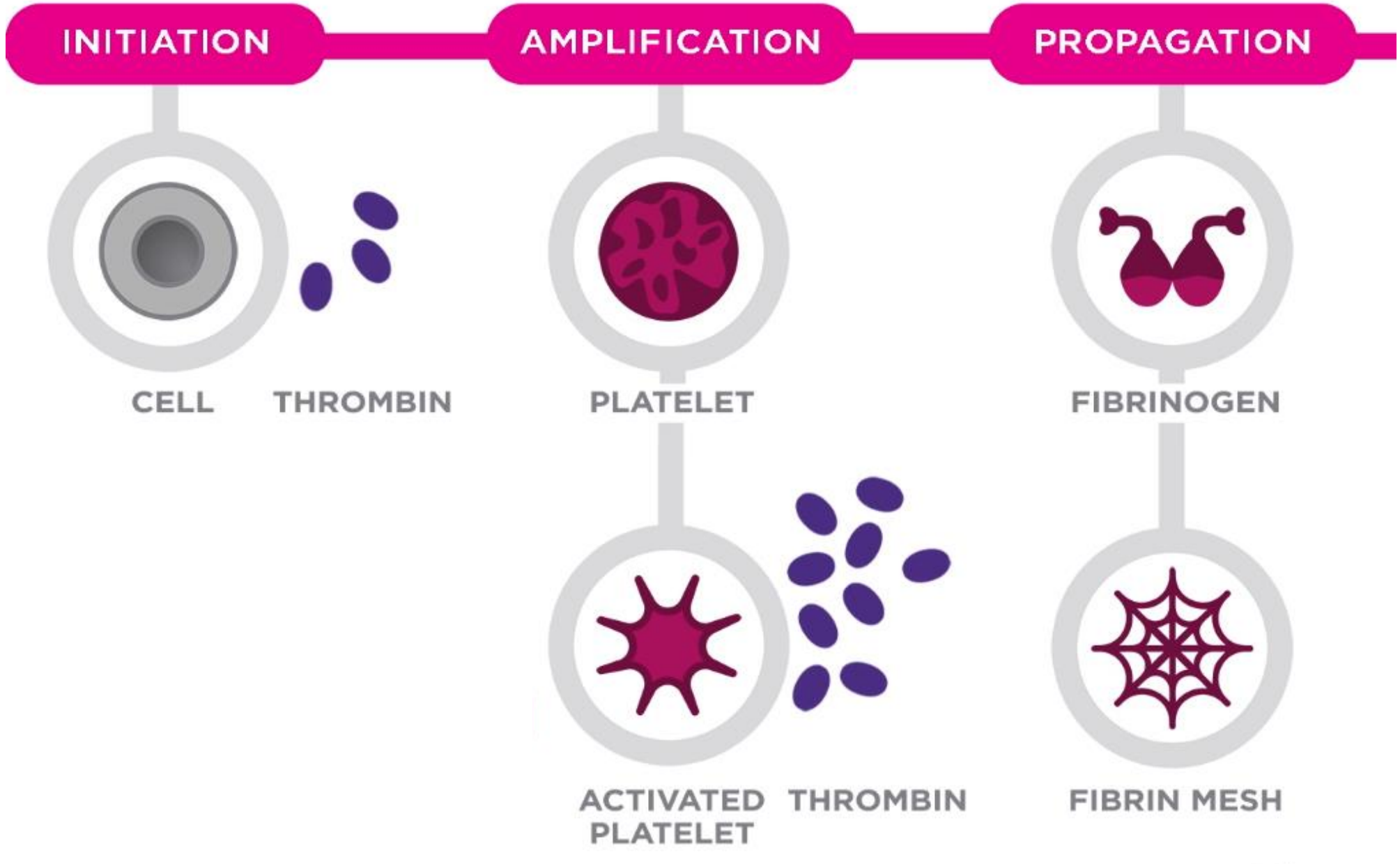
Virchow's Triad



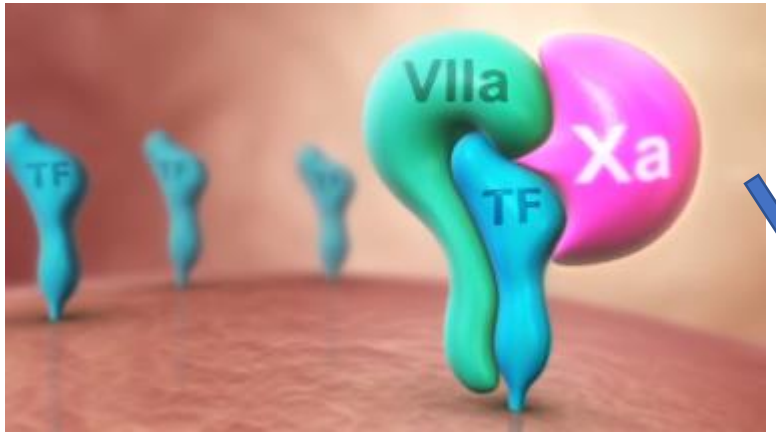
Cellular component: primary haemostasis



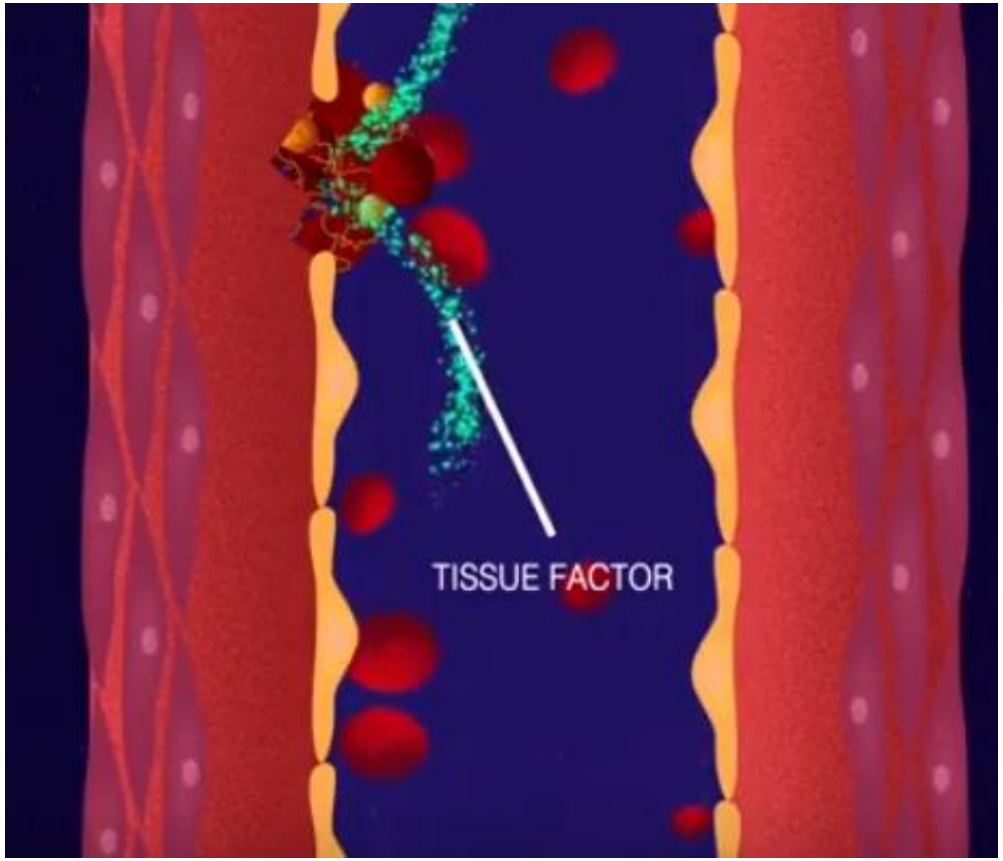
Courtesy: CAST pharma, Bayer


INITIATION
AMPLIFICATION
PROPAGATION
CELL
THROMBIN
PLATELET
FIBRINOGEN
ACTIVATED PLATELET
THROMBIN
FIBRIN MESH

Extrinsic pathway (TF pathway)

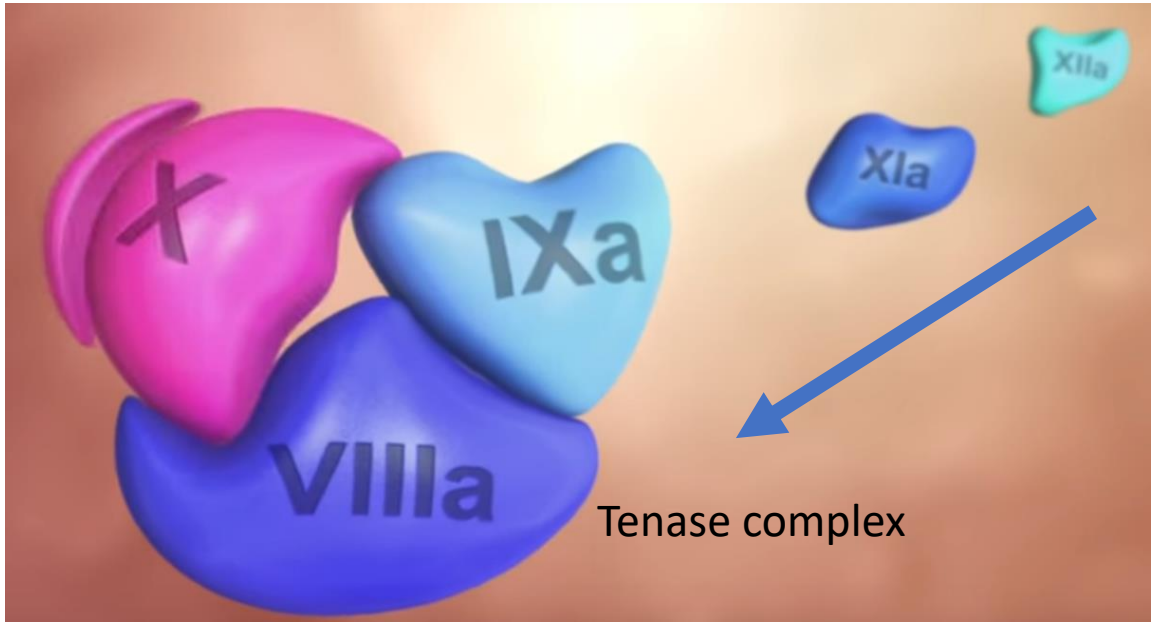


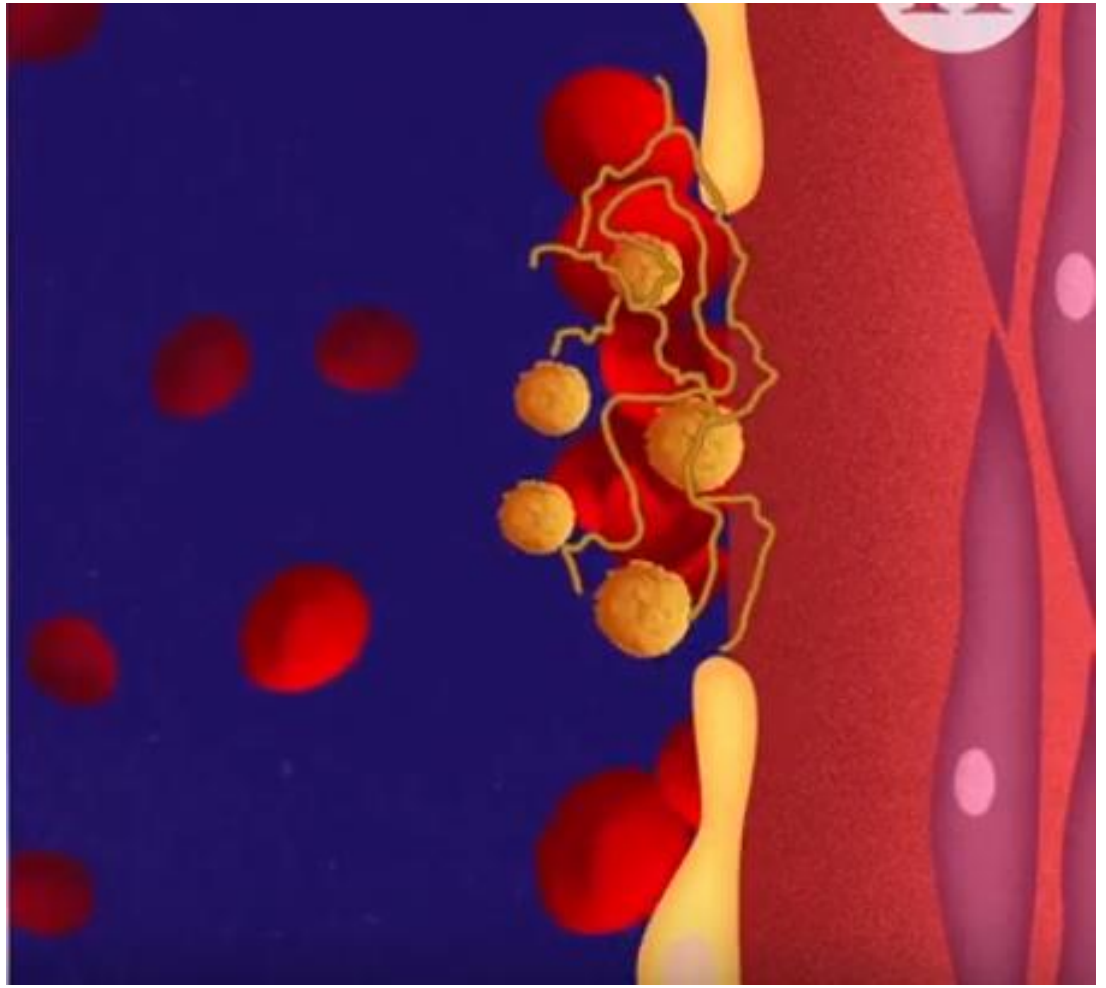
Prothrombinase complex



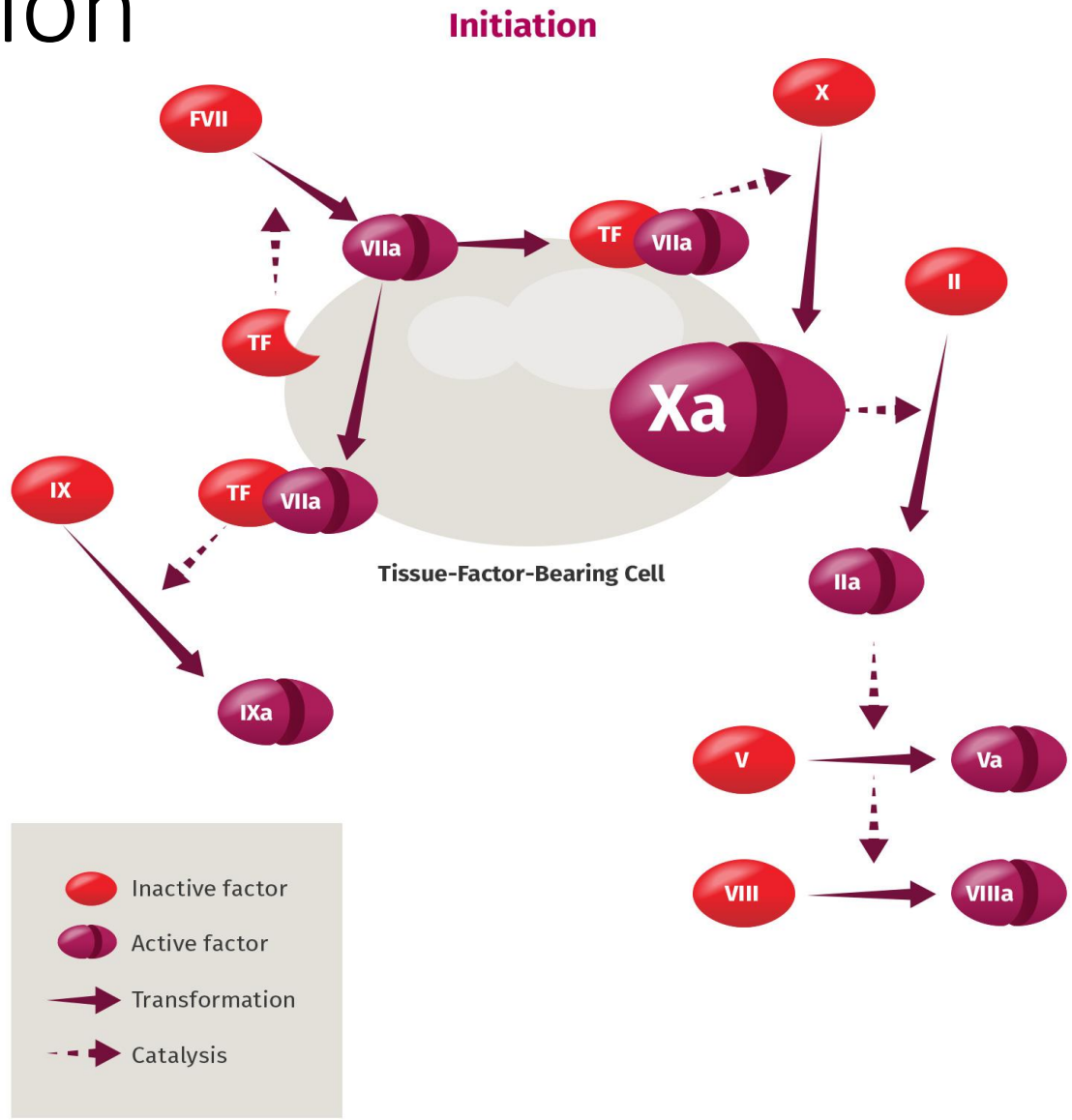
Intrinsic pathway (contact pathway)

- Amplification step
- Activated by thrombin (II) catalyzing activation of Factors 5, 7,8, 11,13

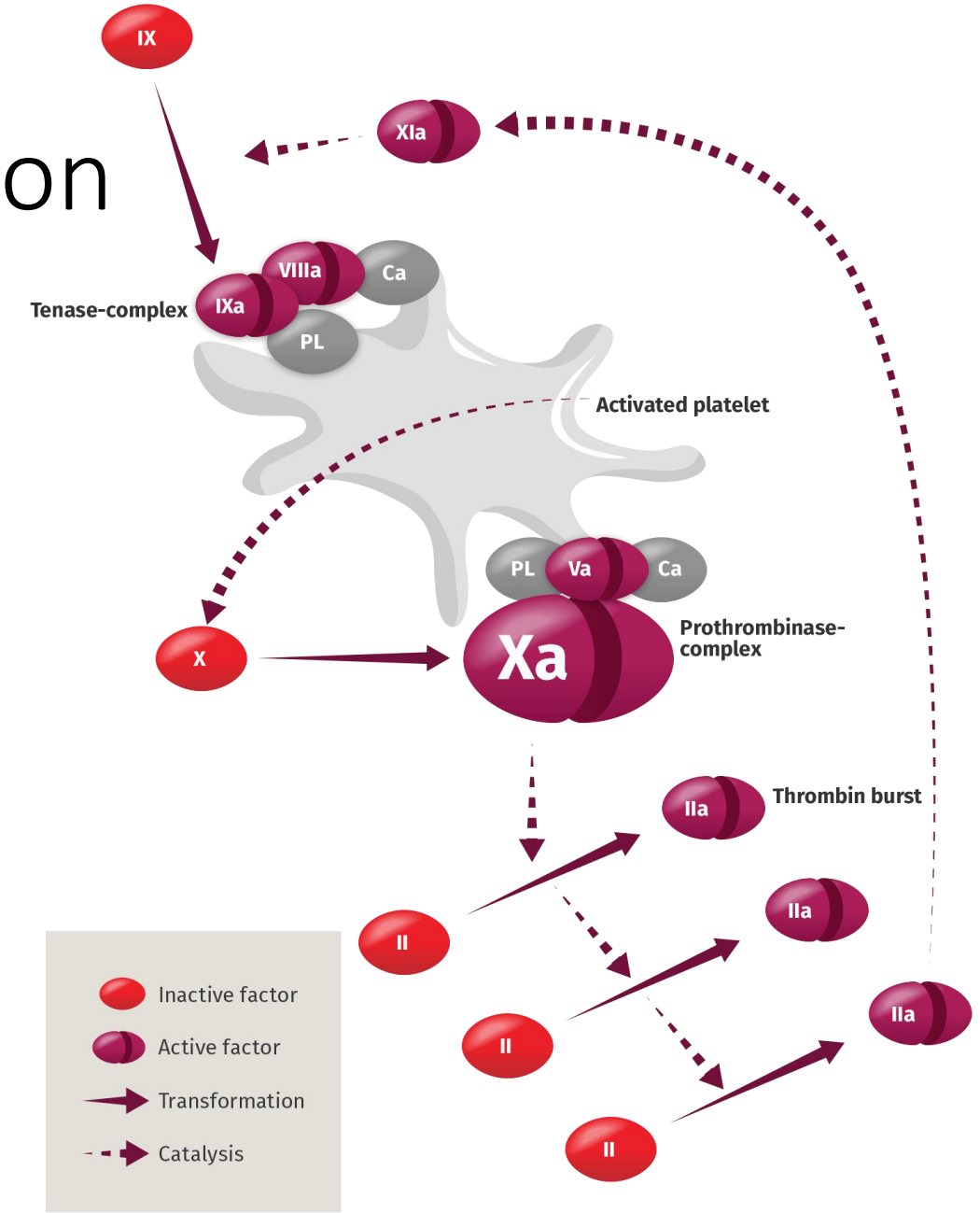




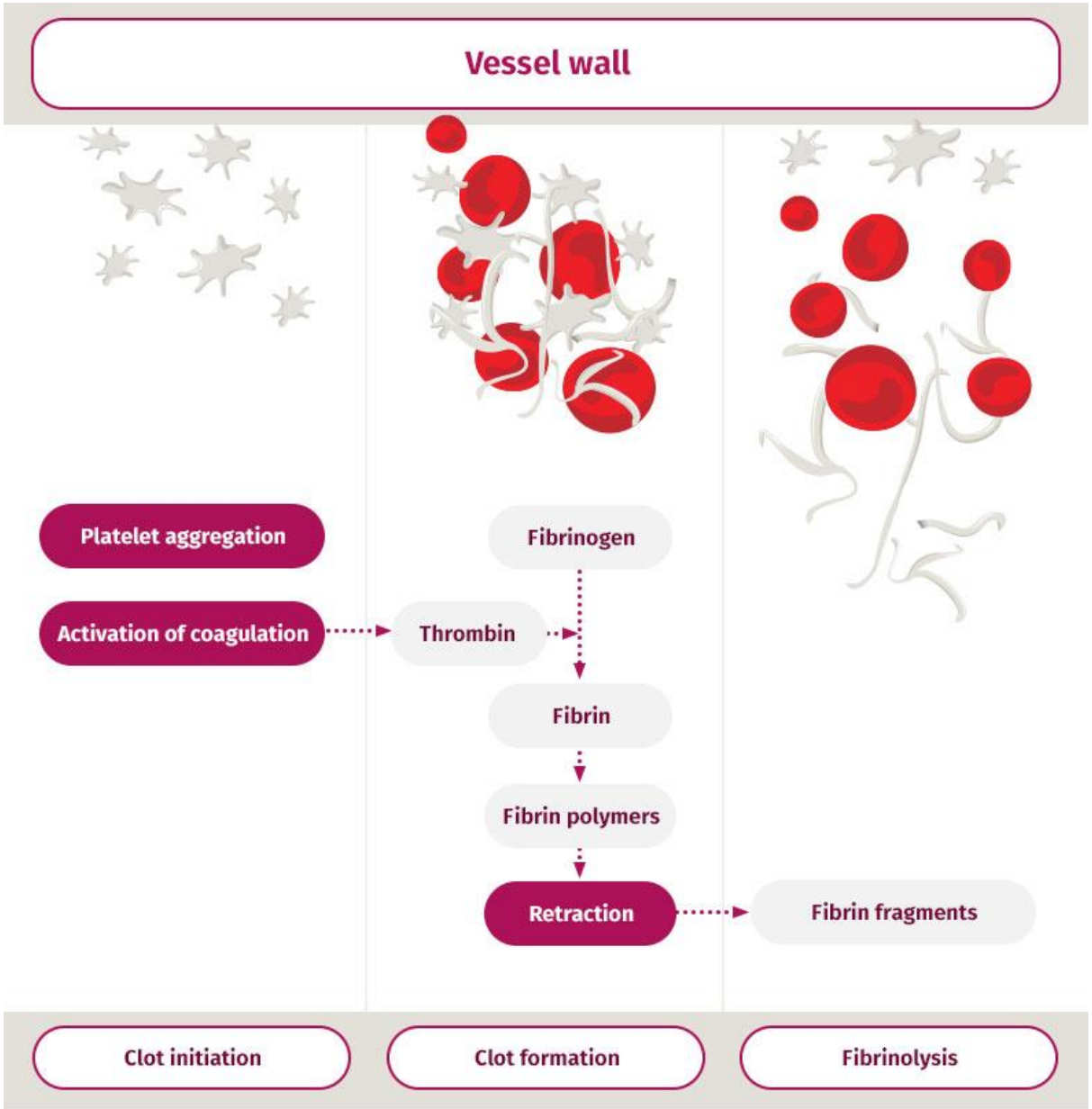
Cell-based model- initiation



Clot propagation



Summary: overview:



Why do people bleed?

- Almost always a defect of procoagulant effect
  - Includes
    - adhesive functions of platelet-VWF
    - stabilising effect of FXIII
- Very rarely excess anticoagulant effect
  - except for anticoagulant drugs (eg warfarin, NOACs)
- Very rarely excess fibrinolytic effect
  - except therapeutic (tPA)
- In hospital, most bleeding disorders are acquired
  - major haemorrhage, trauma, DIC, liver disease

Why do people bleed?
Defects of procoagulant function

- Too little protein (quantitative)
  - Usually inherited — specific assays
  - Excess consumption — global pattern
  - Liver failure — global pattern
  - Drugs — specific assays
- Defective function (qualitative)
  - Usually inherited — specific assays
- Inhibited function
  - Antibody present — specific assays
  - Drugs

Tests of haemostasis

- Screening tests
  - Clotting screen
    - Prothrombin time (PT)
    - Activated partial thromboplastin time (APTT)
  - Fibrinogen
  - Full blood count (platelets)

- Specific factor assays (eg Factor VIII)
- Platelet function (PFA-100, platelet aggregation)
- Global tests: ROTEM, TEG, thrombin generation

Why are coagulation screens done?

- Detect a bleeding tendency
- Detect a cause for bleeding
- Detect a systemic disease
- Detect a thrombotic disorder
- ‘Reassurance’

In fact they are reliable for none of these things:

- Unphysiological
- Limited sensitivity & specificity
- Test a very limited portion of haemostasis
- ie practical but unreliable

Bleeding disorders not detected by routine clotting tests

- Mild factor deficiencies
- Platelet disorders
- von Willebrand disease
- Factor XIII deficiency (cross linking)
- Excessive fibrinolysis
- Vessel wall disorders
- Metabolic disorders (e.g. uraemia)
- (Thrombotic disorders)
- DOACs

Screening assays:

- **Prothrombin Time (PT)**
- **Activated Partial Thromboplastin Time (APTT)**
- Can be misleading
  - normal results even in individuals with bleeding disorders
  - laboratory tests are *in vitro* tests and may not necessarily reflect the underlying haemostatic mechanism
- most important screening test in haemostasis is
  - the patient's personal bleeding history
  - their use of anti-thrombotic drugs including anti-platelet agents
  - family history suggestive of an inherited bleeding diathesis

  Ordering a screening test before taking a thorough history and examining the patient is inappropriate
- Thrombin time, Fibrinogen
- Always check platelet count if concerned

Pre-operative coagulation tests

- BCSH guideline 2008
  - Positive predictive value of abnormal tests 0.03-0.23
  - No significant increase in bleeding associated with abnormal tests
- Routine pre-op screening not recommended
- Patients should have a bleeding history taken
  - previous surgery and trauma
  - family history
  - anti-thrombotic medication

ISTH BAT score:

- Useful to predict probability inherited bleeding disorders
- Not useful to predict future risk of bleeding

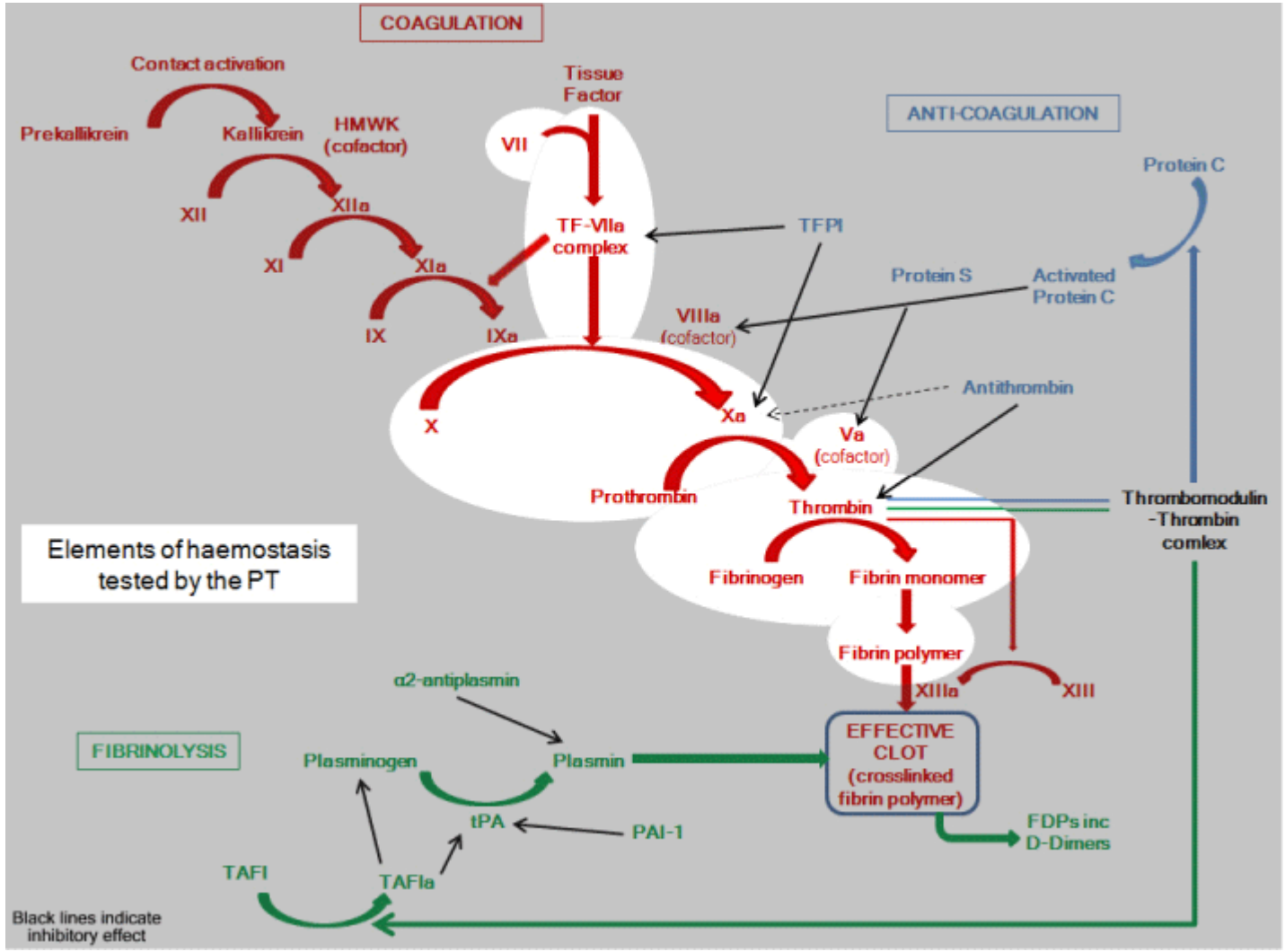
	SCORE				
SYMPTOMS (up to the time of diagnosis)	0[a]	1[a]	2	3	4
Epistaxis	No/trivial	- > 5/year or - more than 10 minutes	Consultation only*	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy (use of hemostatic blood components and rFVIIa) or desmopressin
Cutaneous	No/trivial	For bruises 5 or more (> 1cm) in exposed areas	Consultation only*	Extensive	Spontaneous hematoma requiring blood transfusion
Bleeding from minor wounds	No/trivial	- > 5/year or - more than 10 minutes	Consultation only*	Surgical hemostasis	Blood transfusion, replacement therapy, or desmopressin
Oral cavity	No/trivial	Present	Consultation only*	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy or desmopressin
GI bleeding	No/trivial	Present (not associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia)	Consultation only*	Surgical hemostasis, antifibrinolytic	Blood transfusion, replacement therapy or desmopressin
Hematuria	No/trivial	Present (macroscopic)	Consultation only*	Surgical hemostasis, iron therapy	Blood transfusion, replacement therapy or desmopressin
Tooth extraction	No/trivial or none done	Reported in ≤25% of all procedures, no intervention**	Reported in ≥25% of all procedures, no intervention**	Resuturing or packing	Blood transfusion, replacement therapy or desmopressin
Surgery	No/trivial or none done	Reported in ≤25% of all procedures, no intervention**	Reported in ≥25% of all procedures, no intervention**	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy or desmopressin
Menorrhagia	No/trivial	Consultation only* or - Changing pads more frequently than every 2 hours or - Clot and flooding or - PBAC score>100#	- Time off work/school > 2/year or - Requiring antifibrinolytics or hormonal or iron therapy	- Requiring combined treatment with antifibrinolytics and hormonal therapy or - Present since menarche and > 12 months	- Acute menorrhagia requiring hospital admission and emergency treatment or - Requiring blood transfusion, Replacement therapy, Desmopressin, or - Requiring dilatation & curretage or endometrial ablation or hysterectomy)
Post-partum hemorrhage	No/trivial or no deliveries	Consultation only* or - Use of syntocin or - Lochia > 6 weeks	- Iron therapy or - Antifibrinolytics	- Requiring blood transfusion, replacement therapy, desmopressin or - Requiring examination under anaesthesia and/or the use of uterin balloon/package to tamponade the uterus	- Any procedure requiring critical care or surgical intervention (e.g. hysterectomy, internal iliac artery legation, uterine artery embolization, uterine brace sutures)
Muscle hematomas	Never	Post trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	Never	Post trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
CNS bleeding	Never			Subdural, any intervention	Intracerebral, any intervention
Other bleedings^	No/trivial	Present	Consultation only*	Surgical hemostasis, antifibrinolytics	Blood transfusion or replacement therapy or desmopressin

When are basic coagulation tests useful?

- Major haemorrhage (include fibrinogen)
- INR for warfarin monitoring
  - NB normal PT/APTT does not exclude significant level of anticoagulation with DOAC

Prothrombin Time

- PPP, tissue factor (phospholipids) with excess of calcium at 37

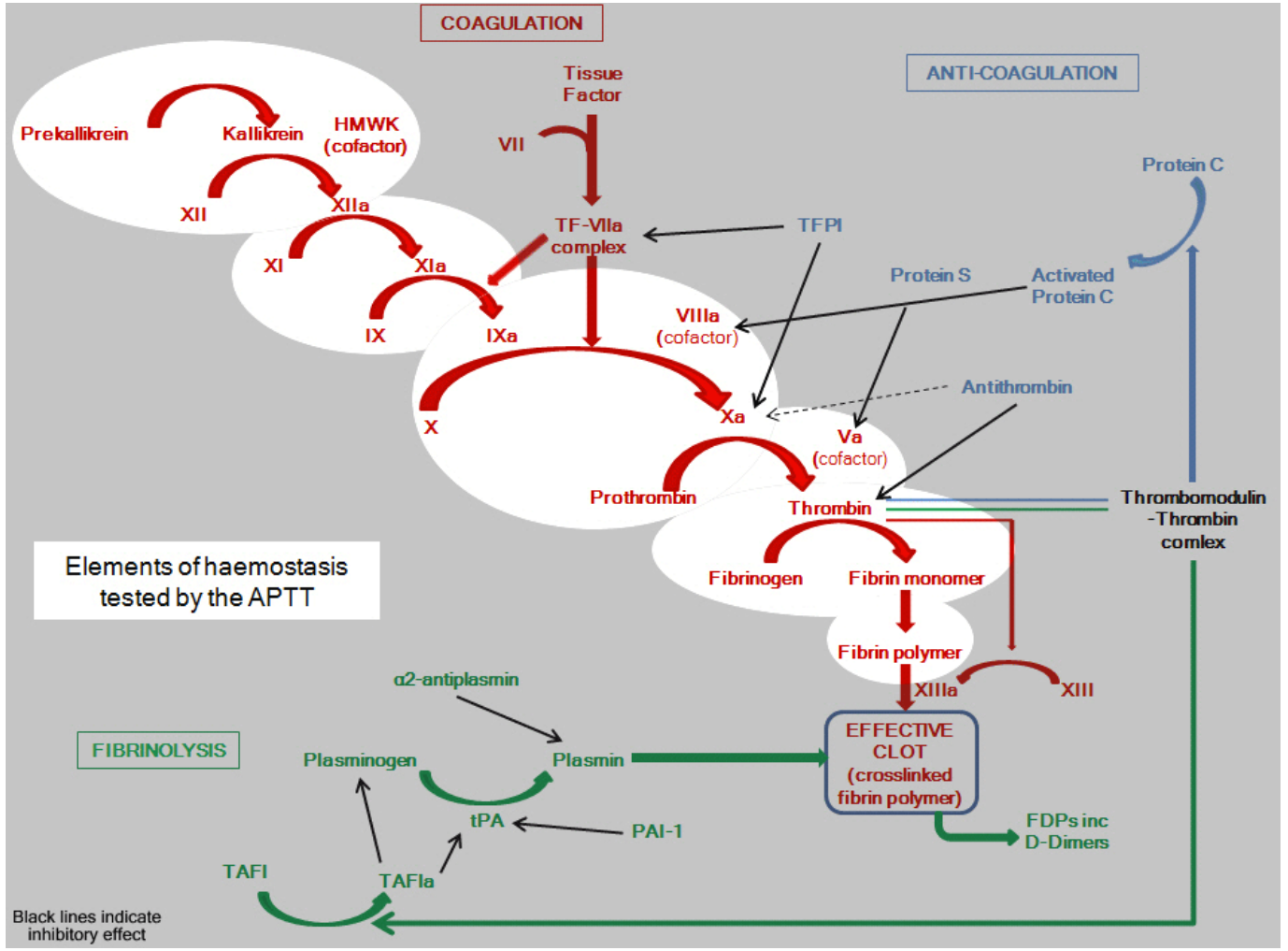


Courtesy: Practical Haemostasis

Prolonged PT

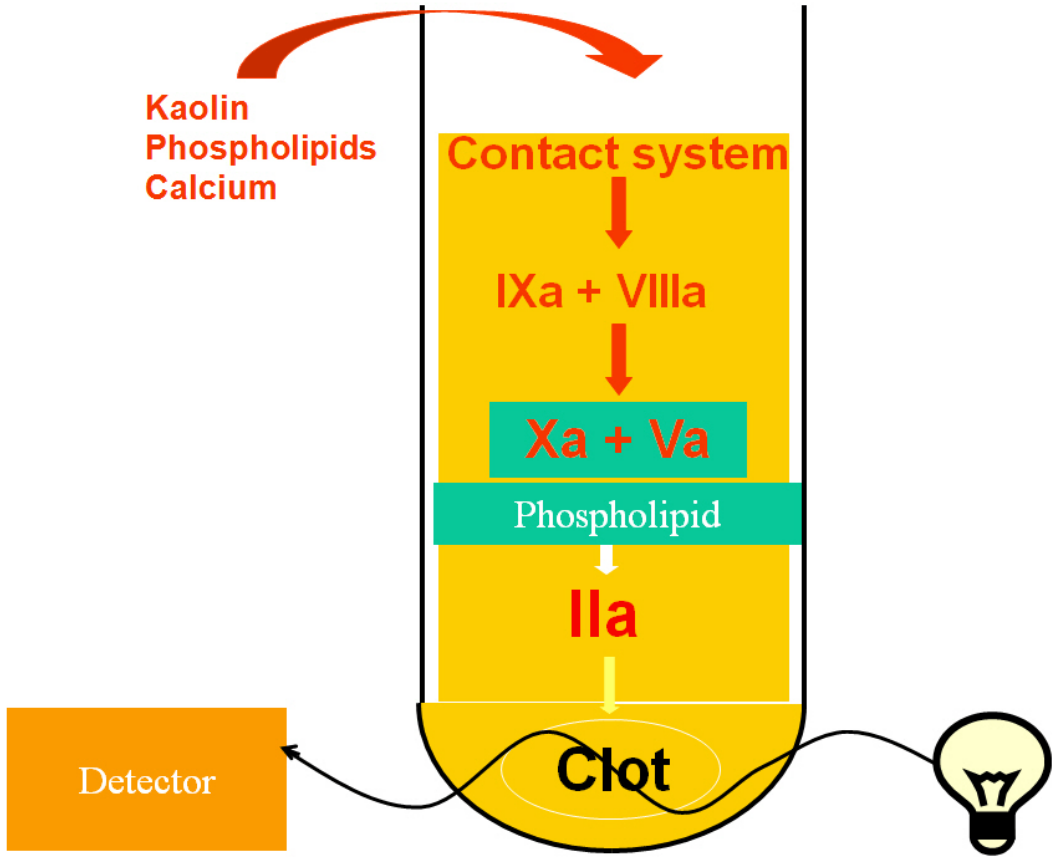
- Isolated: Factor VII deficiency
- Vitamin K deficiency
  - Vitamin K antagonists e.g. warfarin, phenindione, rodenticides
  - Liver disease
  - Malabsorption (leading to vitamin K deficiency)
- High concentrations of unfractionated heparin
- Direct thrombin inhibitors e.g. Lepirudin, argatroban
- Afibrinogenaemia and dysfibrinogenemia
- Dilutional coagulopathy e.g. massive blood transfusion
- Multiple clotting factor deficiencies e.g. FV and FVIII deficiency

APTT: Activated Partial Thromboplastin Time



Courtesy: Practical Haemostasis

APTT


Kaolin
Phospholipids
Calcium
Contact system
IXa + VIIIa
Xa + Va
Phospholipid
IIa
Clot
Detector

Cases……

4 year old boy….head injury, subdural bleed….

Test	Patient	Reference Range
PT	12s	11-14s
APTT	95s	23-35s
Fibrinogen (Clauss)	3.9g/L	1.5-4.0g/L
Thrombin Time	13s	10-13s

45 year old woman, space occupying lesion, pre- operative assessment……

Test	Patient	Reference Range
PT	12s	11-14s
APTT	95s	23-35s
Fibrinogen (Clauss)	3.9g/L	1.5-4.0g/L
Thrombin Time	13s	10-13s

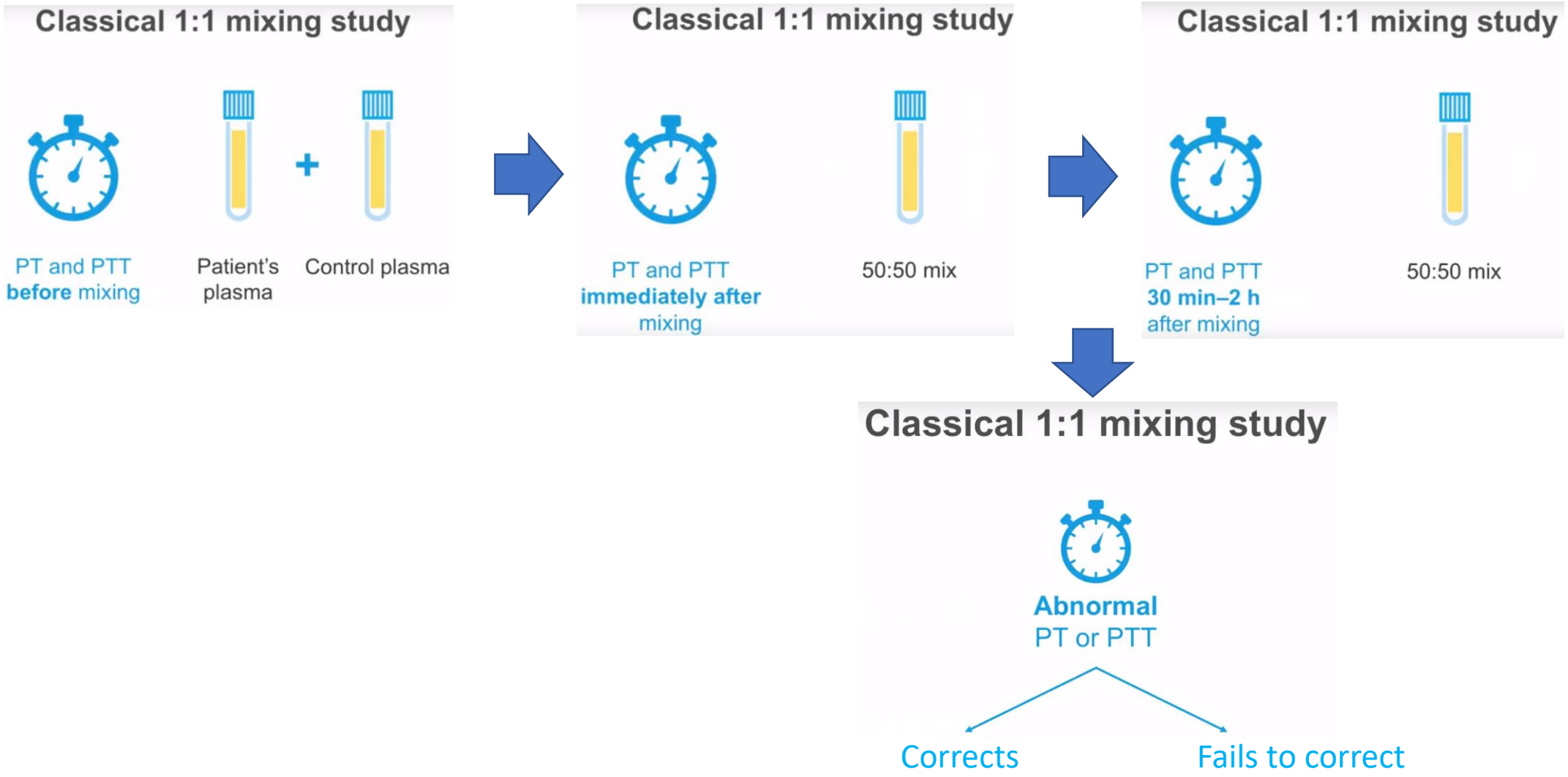
70 year old, colon cancer, for biopsy of ring enhancing lesion

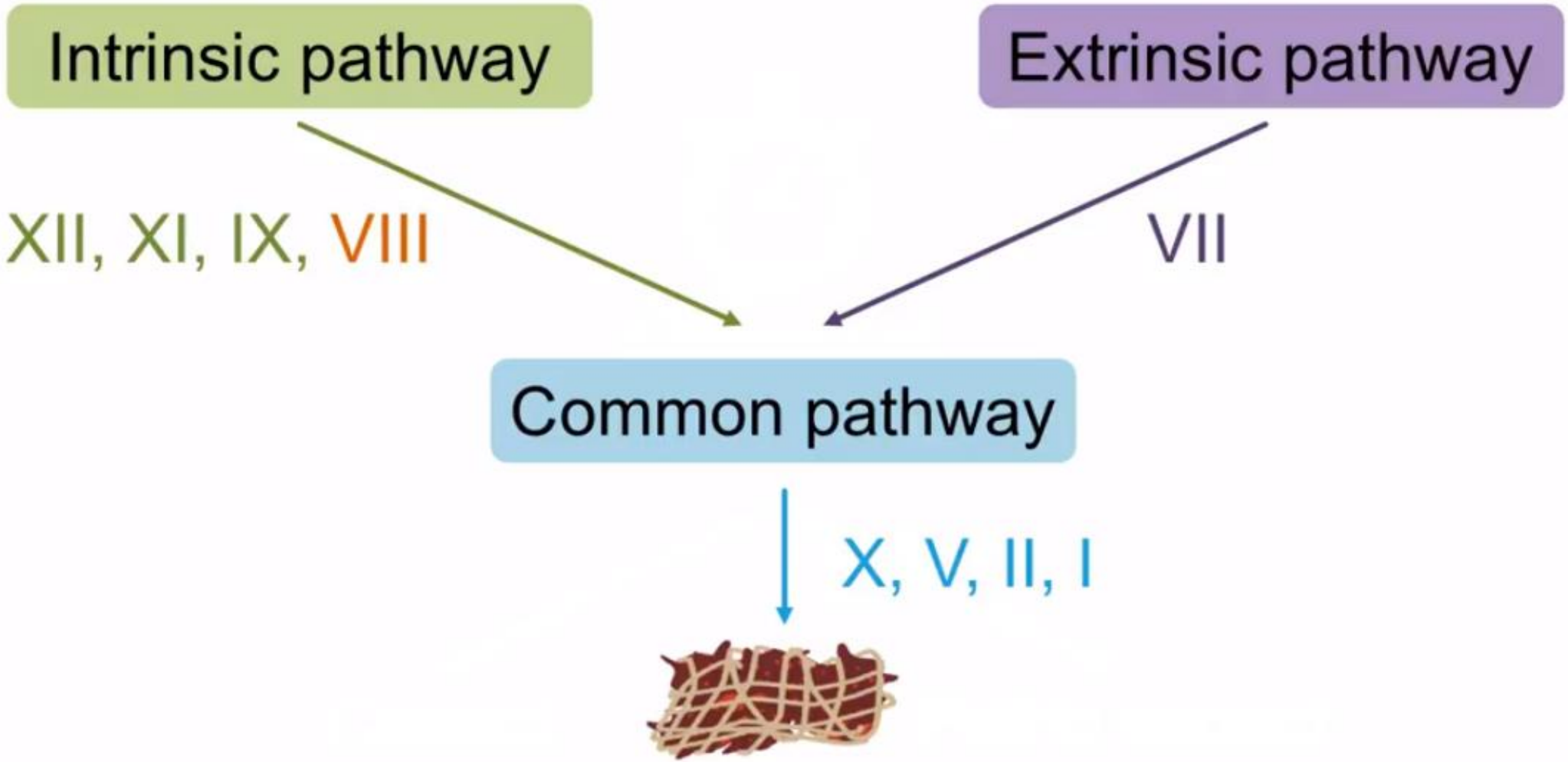
Test	Patient	Reference Range
PT	14s	11-14s
APTT	76s	23-35s

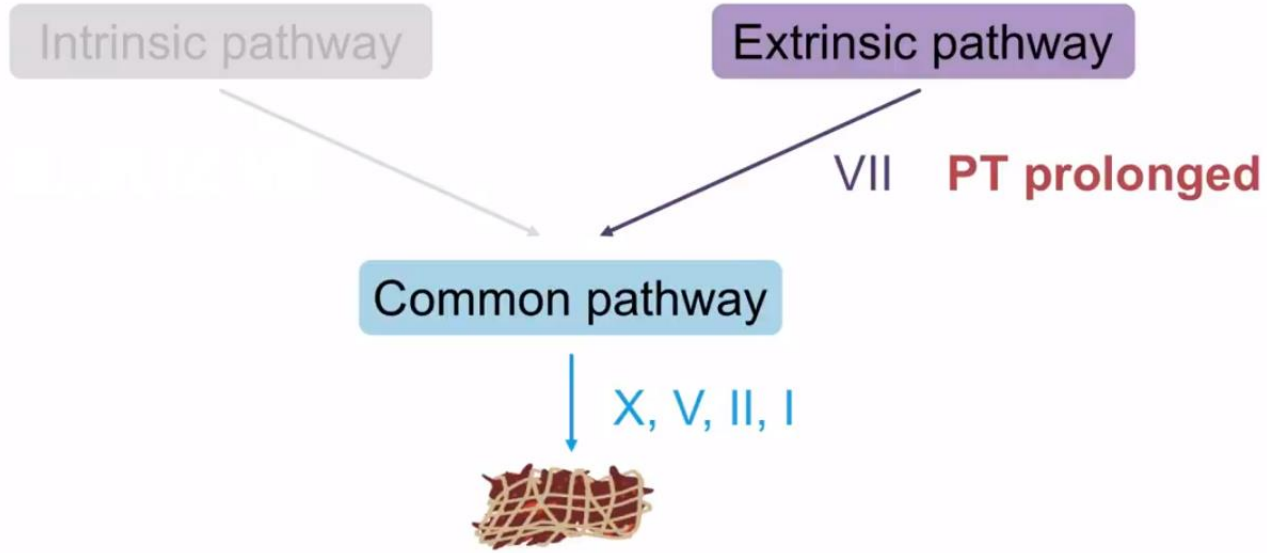
Approach

- Repeat the test
- Recheck drug history, personal bleeding history and FH
- If still raised: either an inhibitor or a clotting factor deficiency
  - How to tell the difference?

Mixing studies




Intrinsic pathway
Extrinsic pathway
XII, XI, IX, VIII
VII
Common pathway
X, V, II, I



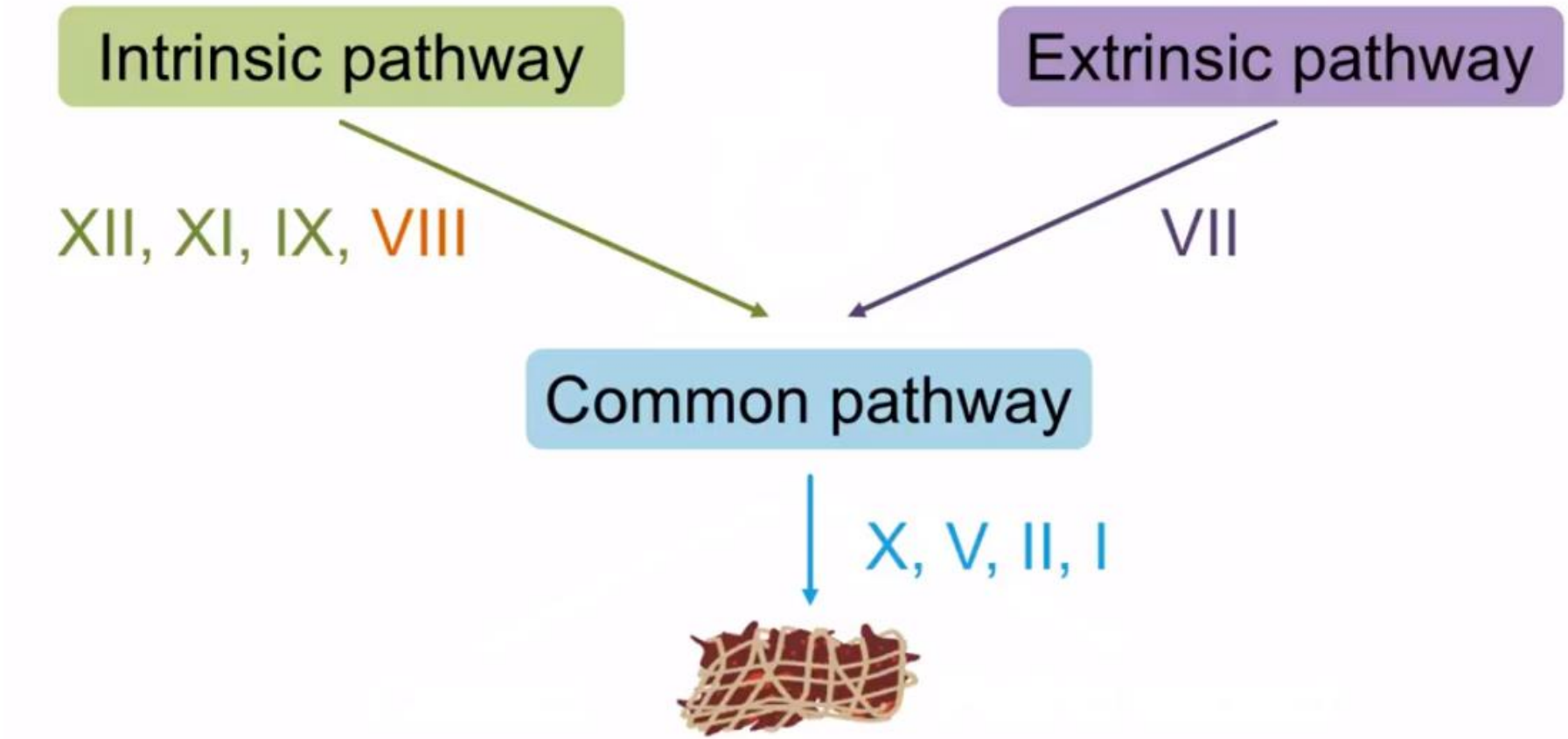
PT mixing study

PT **normalizes**

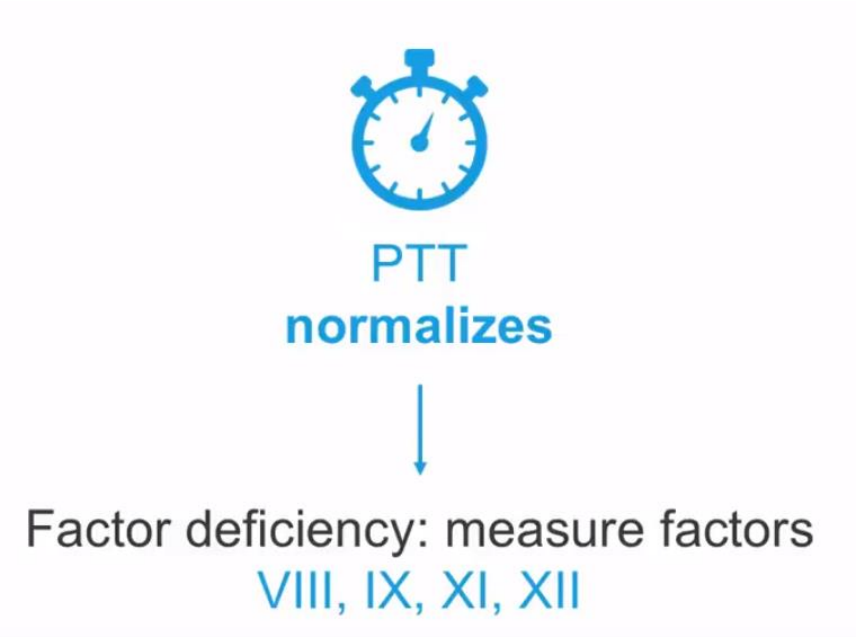
Factor deficiency: measure factors I, II, V, VII, X

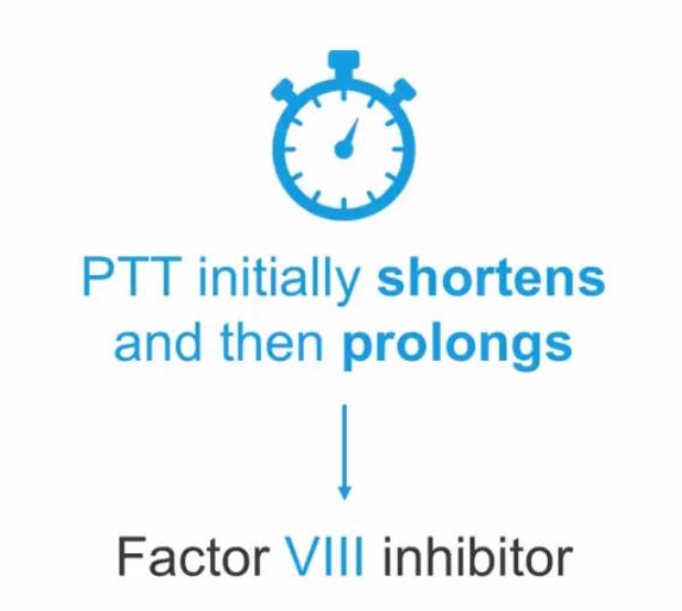
PT does **not normalize**

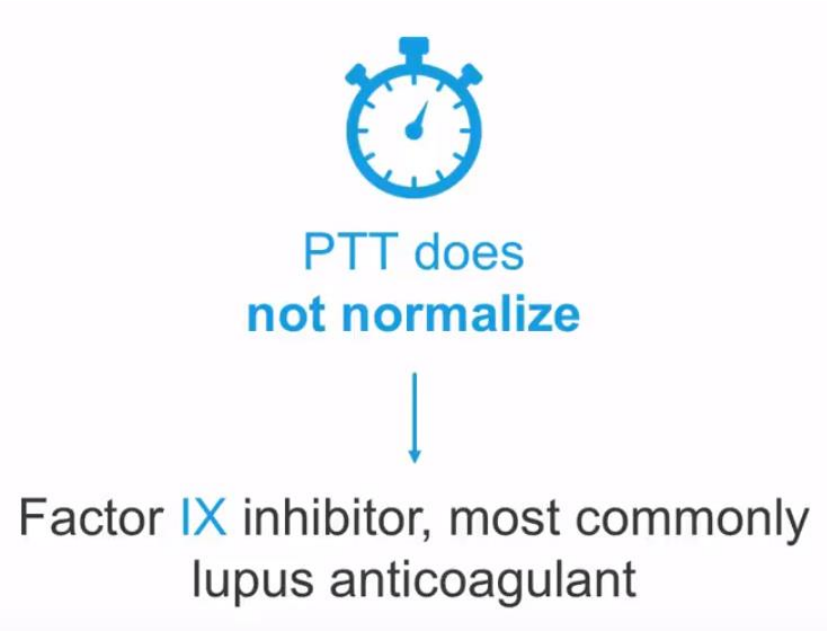
Factor V inhibitor


Intrinsic pathway
Extrinsic pathway
XII, XI, IX, VIII
VII
Common pathway
X, V, II, I

APTT mixing studies-interpretation







APTT abnormalities

Abnormality	Interpretation
Isolated Prolonged APTT	Deficiencies of either XII, XI, IX & VIII. However, the APTT can be normal with mild deficiencies of these clotting factors. In general the deficient factor has to be less than 20-40% of normal before the APTT is prolonged [but see comments regarding APTT incubation times.] Contact factor deficiency e.g. pre-kallikrein deficiency [In multiple clotting factor deficiencies the APTT becomes prolonged with less severe reductions in factor levels] Acquired clotting factor inhibitors - these are most commonly directed against FVIII and may occur as either autoantibodies [e.g. acquired Haemophilia A] or alloantibodies (in individuals with severe Haemophilia A following exposure to exogenous factor VIII e.g. the use of factor VIII concentrate to treat a bleed). Inhibitors against other clotting factors are rare but do occur e.g. Factor V . Lupus anticoagulant [LA] - a LA targets phospholipid and so can result in an isolated prolongation of the APTT. Although the PT requires phospholipid the concentration of PL in the PT reagents is high and so it frequently neutralises the LA and so the PT is not prolonged.

APTT and PT abnormalities

Prolonged APTT + Prolonged PT	Vitamin K deficiency Liver disease due to: - Malabsorption of vitamin K [a fat soluble vitamin] and which leads to decreased gamma carboxylation of the vitamin K dependent clotting factors - Decreased synthesis of clotting factors - An acquired dysfibrinogenemia due to changes in the sialic acid content of the fibrinogen. This is similar to the effect seen in the newborn infant - the so-called 'fetal fibrinogen.' Direct thrombin inhibitors DIC - due to the consumption of clotting factors Massive blood transfusion leading to a dilutional coagulopathy In patients receiving thrombolytic therapy, the APTT may be prolonged due to a reduction in fibrinogen levels. In multiple clotting factor deficiencies the APTT becomes prolonged with less severe reductions in factor levels. Combined deficiency of clotting factors e.g. Factors V and VIII 'Common Pathway' clotting factor deficiences - FV, F, FII [Prothrombin] and Fibrinogen.
Increased APTT ± Prolonged PT	Unfractionated heparin [UFH]: UFH significantly prolongs the APTT but the PT usually shows little prolongation. In cases of significant over anticoagulation with UFH the PT will be prolonged. Antiphospholipid antibodies [In some cases the PT can be prolonged although this is unusual due to the high PL concentration in PT reagents] Acquired clotting factor inhibitors e.g. FV, FX
Prolonged PT ± Prolonged APTT	Warfarin - the APTT may be only prolonged by a few seconds in patients who are stably anticoagulated on warfarin - but in patients who are overdosed the APTT may be significantly prolonged.

4 year old boy….head injury, subdural bleed….

Test	Patient	Reference Range
PT	12s	11-14s
APTT	95s	23-35s
Fibrinogen (Clauss)	3.9g/L	1.5-4.0g/L
Thrombin Time	13s	10-13s

45 year old woman, space occupying lesion, pre- operative assessment……

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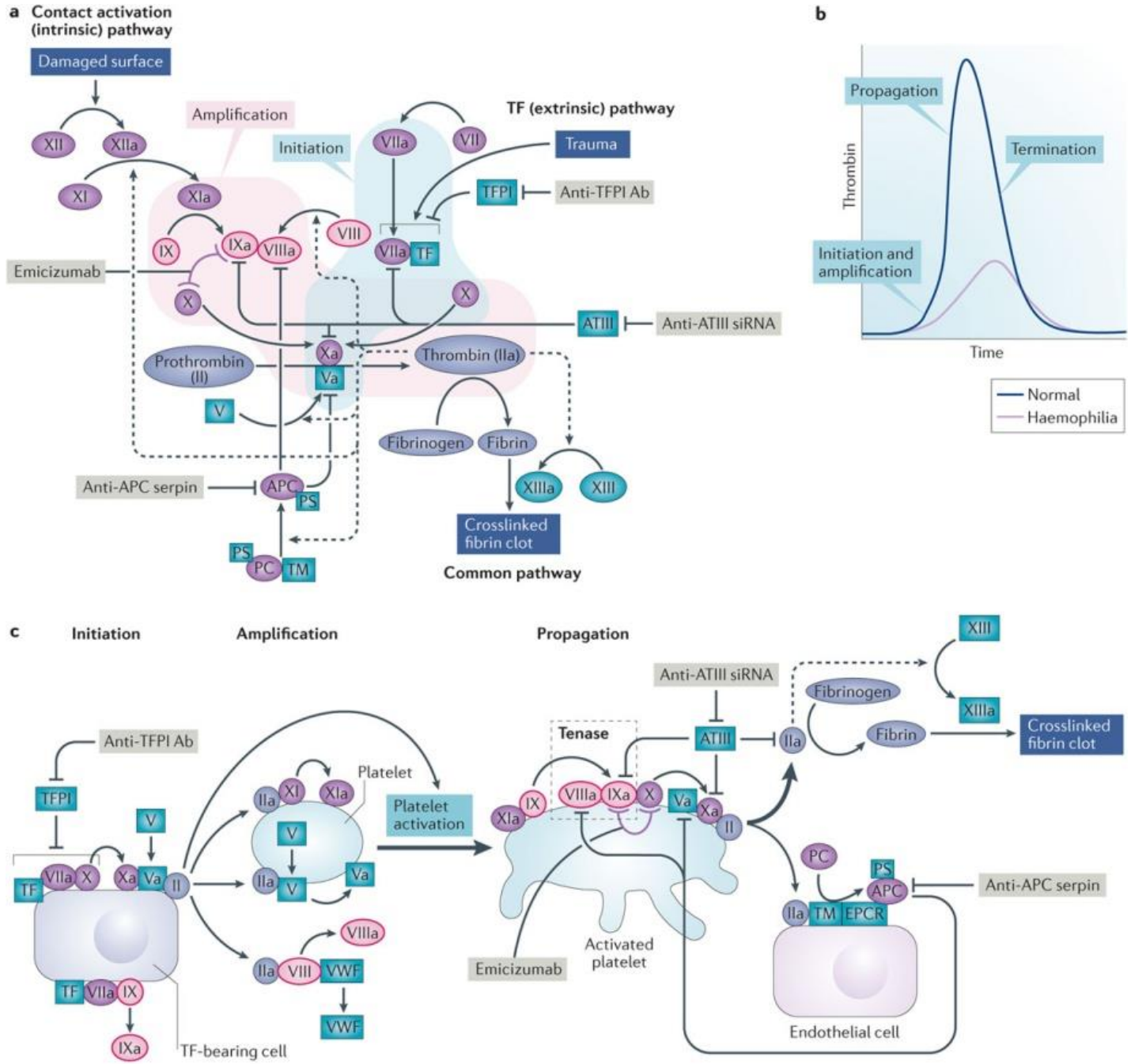
Inherited deficiencies of the coagulation cascade

- Seek advice from haematologist….tertiary centre
- Plan elective procedures
- Treatment options vary:
  - DDAVP- mild haemophilia and vWD
  - Factor replacement, gene therapy trials
  - Some patients have inhibitors requiring bypass therapy/immune tolerance

Table 3 | **Summary of alternative (non-factor replacement) therapies that inhibit the anticoagulant pathways**

Antithrombotic target	Molecule (sponsor)	Modality	Clinical stage	Refs
Antithrombin III	Fitusiran (Alnylam)	siRNA	Phase III initiated	49
TFPI (Kunitz-2 domain)	Concizumab (Novo Nordisk)	mAb	Phase II	10
TFPI (Kunitz-1 and Kunitz-2 domains)	PF-06741086 (Pfizer)	mAb	Phase II	47
TFPI (interface of Kunitz-1 and Kunitz-2 domains)	BAY1093884 (Bayer)	mAb	Phase I	48
Activated protein C	SerpinPC (Apcintex)	Modified α1-antitrypsin	Preclinical	11

mAb, monoclonal antibody; siRNA, small interfering RNA; TFPI, tissue factor pathway inhibitor.


a Contact activation (intrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
Amplification
Initiation
IX
IXa
VIIIa
VIII
Emicizumab
X
Xa
Va
V
Prothrombin (II)
Thrombin (IIa)
TF (extrinsic) pathway
Trauma
VIIa
VII
TFPI
Anti-TFPI Ab
VIIa TF
X
ATIII
Anti-ATIII siRNA
Fibrinogen
Fibrin
XIIIa
XIII
Crosslinked fibrin clot
Anti-APC serpin
APC
PS
PS
PC
TM
Common pathway
b
Propagation
Termination
Thrombin
Initiation and amplification
Time
Normal
Haemophilia
c
Initiation
Amplification
Propagation
Anti-TFPI Ab
TFPI
V
TF
VIIa
X
Xa
Va
II
TF
VIIa
IX
IXa
Platelet
XI
XIa
IIa
V
Va
VIIIa
IIa
VIII
VWF
VWF
TF-bearing cell
Platelet activation
Tenase
VIIIa
IXa
X
Va
IX
XIa
Xa
II
Emicizumab
Activated platelet
Anti-ATIII siRNA
ATIII
IIa
Fibrinogen
Fibrin
XIII
XIIIa
Crosslinked fibrin clot
PC
PS
APC
Anti-APC serpin
IIa
TM
EPCR
Endothelial cell

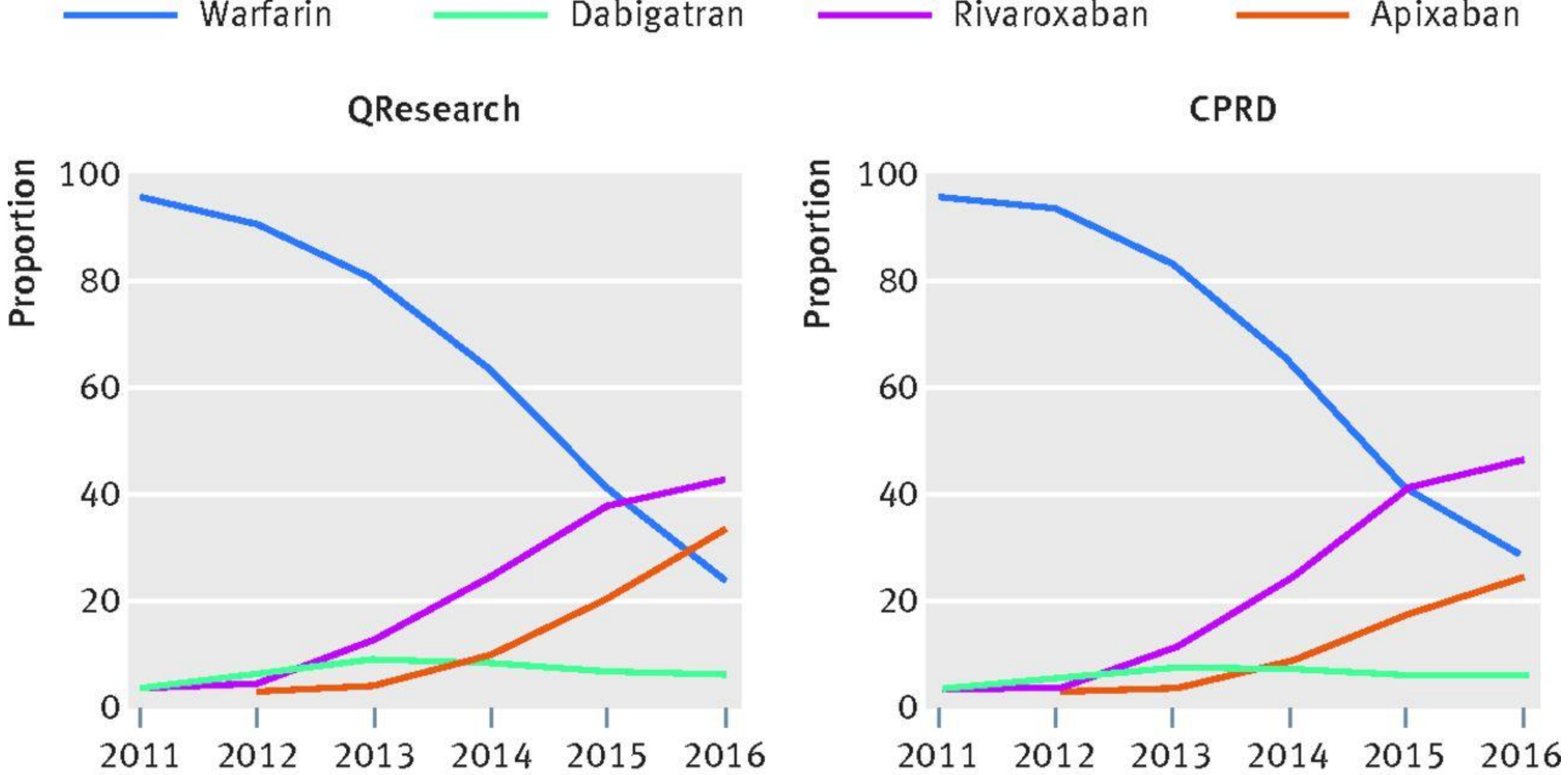
Von Willebrand's Disease

- APTT can be normal!

Types	Features
1	Partial deficiency of VWF
2	Qualitative VWF defects
2A	VWF variants with loss of high-molecular-weight multimers and decreased VWF-dependent platelet adhesion
2B	VWF variants with loss of high-molecular-weight multimers caused by increased affinity for platelet glycoprotein Ib
2M	VWF variants with decreased VWF-dependent platelet adhesion not associated with the loss of high-molecular-weight multimers
2N	VWF variants with decreased binding affinity for FVIII
3	Severe deficiency of VWF

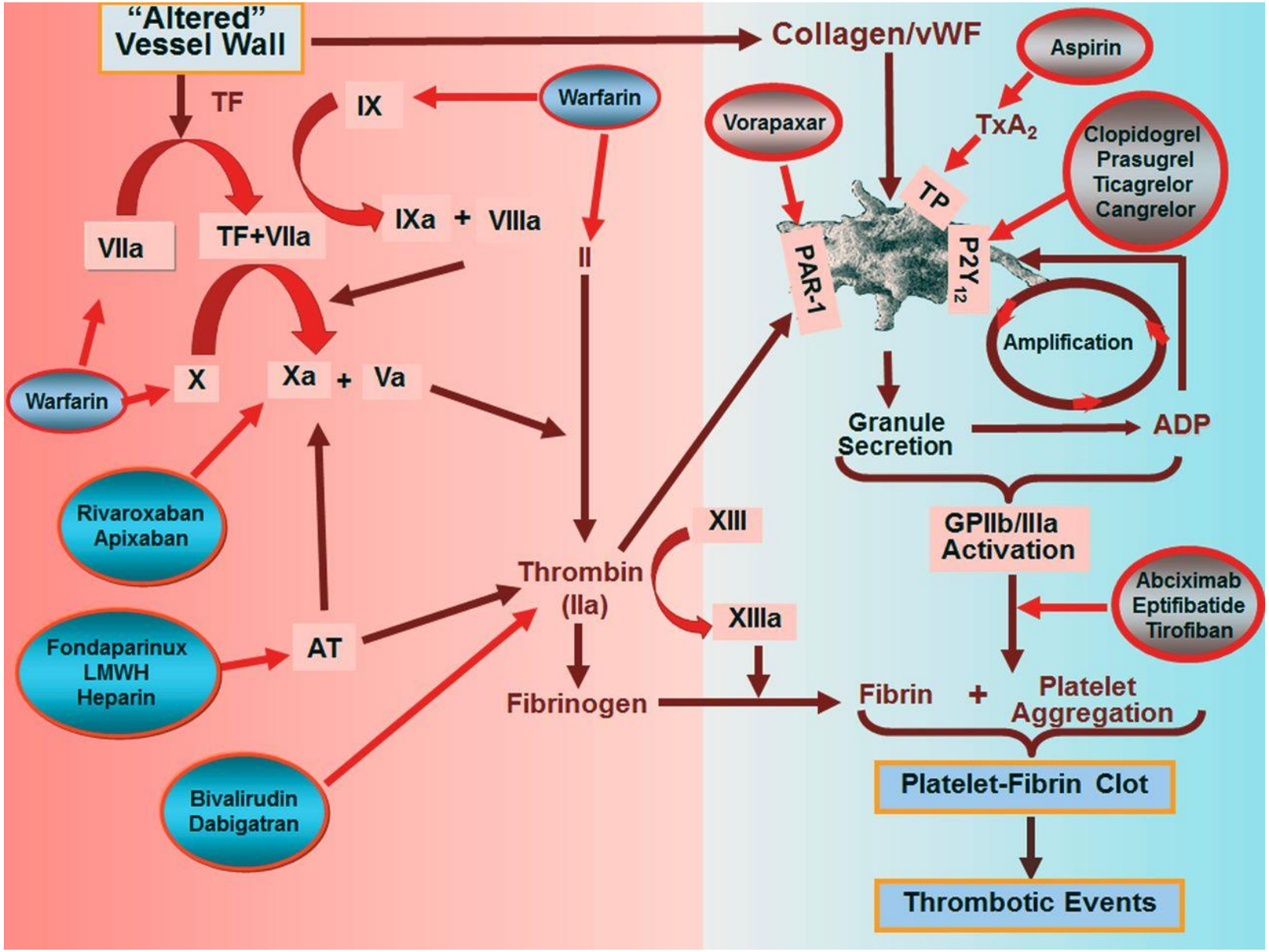
Acquired disorders of the coagulation cascade

- Autoimmune/alloimmune conditions
- Systemic disease: liver disease/prematurity/malabsorption
- Drugs



QResearch, version 42

Clinical Practice Research Datalink (CPRD), November 2016



Paul A. Gurbel, and Udaya S. Tantry JCHF 2014;2:1-14

Emergency reversal of warfarin-ICH

- Discontinue medication
- Reverse anticoagulation immediately and BEFORE INR RESULTS ARE BACK with 4 factor Prothrombin Complex Concentrate (PCC) AND Vitamin K (phytomenadione) 5-10mg IV

Weight	Dose of PCC
less than 60kg	1500 units
60-75kg	2000 units
76-90kg	2500 units
greater than 90kg	3000 units

- Immediately after PCC has been given, repeat the clotting screen and assess degree of correction of INR

Elective Surgery and DOACS

	Consider bridging with full treatment dose heparin in
VTE	Patients with a VTE within previous 3 months. Very high risk patients such as patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3.5.
AF	Patients with a previous stroke/TIA in last three months. Patients with a previous stroke/TIA and three or more of the following risk factors: • Congestive cardiac failure • Hypertension (greater than 140/90 mmHg or on medication) • Age over 75 years • Diabetes mellitus
MHV	All Mechanical Heart Valve patients except those with a bileaflet aortic valve and no other risk factors (AF, prior stroke or TIA, hypertension, diabetes, congestive cardiac failure or age over 75 years)

Discontinuation of DOACs for elective procedures

Renal Function eGFR (ml/min)	Low bleeding risk	High bleeding risk
Dabigatran		
80 or more	24 hours	48 hours
50 to 79	24-48 hours	48-72 hours
30 to 49	48-72 hours	96 hours
Dabigatran is not licensed for use with an eGFR below 30ml/min		
Apixaban, Rivaroxaban and Edoxaban		
30 or more	24 hours	48 hours
15-29	48 hours	72 hours
Apixaban, rivaroxaban and edoxaban are not licensed for use with an eGFR below 15ml/min		

Following minor or low risk procedures in patients with low bleeding risk: recommence 6-12 hours post procedure

Following high risk procedures and in patients with an increased bleeding risk or in any situation where bleeding unacceptable: do not restart full dose DOACS for 48 hours. If high thrombosis risk consider prophylactic LMWH until DOAC considered appropriate

Emergency reversal of DOACs

- Standard clotting tests may not detect DOACs
- Do not provide an accurate or reliable indication of the intensity of anticoagulation
- A normal activated partial thromboplastin time (APTT) and prothrombin time (PT) do not exclude the presence of significant concentrations of a DOAC

Management of critical bleeding

Usefulness of standard clotting tests

Dabigatran	Thrombin time (TT) is the most sensitive measure of Dabigatran. If TT normal dabigatran levels very low or absent. At therapeutic levels APTT usually 1.5-2 x baseline but can be normal. No effect on PT.
Rivaroxaban	At therapeutic levels APTT and PT 1-1.5 x baseline
Apixaban	At therapeutic levels APTT and PT will often be normal
Edoxaban	Changes observed in APTT or PT at the expected therapeutic dose are subject to a high degree of variability and are not useful in monitoring the anticoagulation effect of edoxaban

- Measure DOAC levels: do not wait for the results to guide treatment!
- Check APTT, PT, LFTs and renal function
- Need to account for last dose and time to guide treatment
- Tranexamic acid 1g IV
- Apixaban/Rivoroxaban: FEIBA/PCC 50 IU/kg

DOAC trough and peak levels (micrograms/L)

	Trough	Peak
Rivaroxaban 20mg od	22 (4-96)	223 (160-360)
Apixaban 5mg bd	103 (41-230)	171 (91-321)
Dabigatran 150mg bd	90 (31-225)	184 (64-443)

5-95% confidence intervals presented from trial data.
Individual patient values may vary

Specific antidotes

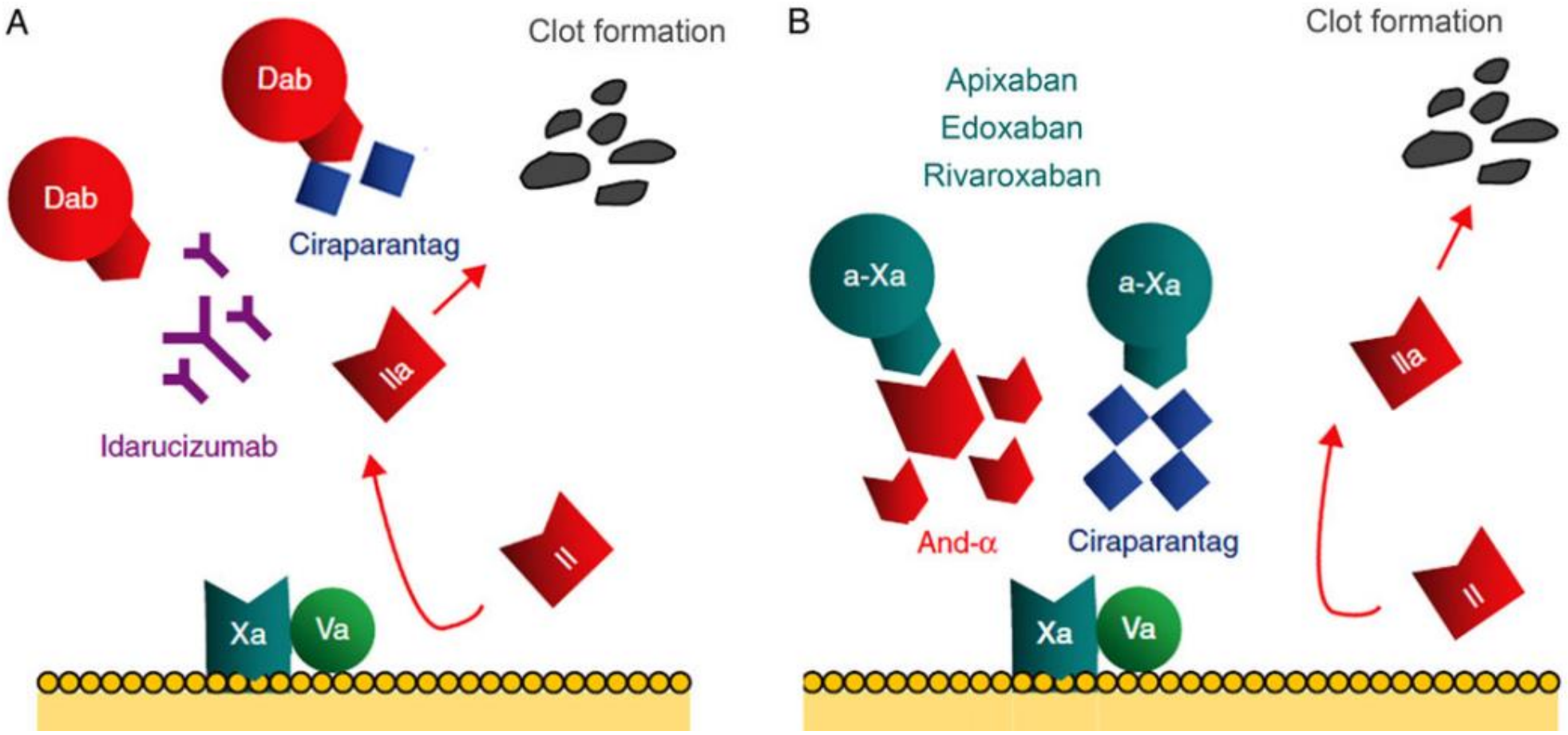
- Idaricuzimab: 5 g IV: dabigratran

Table 2 **New reversal agents for non-vitamin K antagonist oral anticoagulants**

	Idarucizumab	Andexanet	Ciraparantag (PER977)
Target	Dabigatran	Oral direct factor Xa-inhibitors, low-molecular-weight heparins and fondaparinux	Oral direct factor Xa and IIa inhibitors, low-molecular-weight heparins, un-fractionated heparin and fondaparinux
Structure	Humanized Fab fragment	Human rFXa variant	Synthetic small molecule
Immediate onset of reversal (<10 min)	Yes	Yes	Yes
Duration of effect	(12 to) 24 h	2 h	24 h
Re-administration possible	Yes, after 24 h	Unknown	Currently tested (NCT02207257)
Tested in healthy volunteers	Yes (NCT020287809)	Yes	Yes (NCT01826266, NCT02207257)
Elderly	Yes	Yes (NCT022207725)	No
Renally impaired	Yes	No	No
Tested in patients	Successful reversal of the specific effect of dabigatran (NCT02104947)	Ongoing (NCT02329327)	No
Pro-coagulation signals	No	Decrease of tissue factor pathway inhibitor activity	No

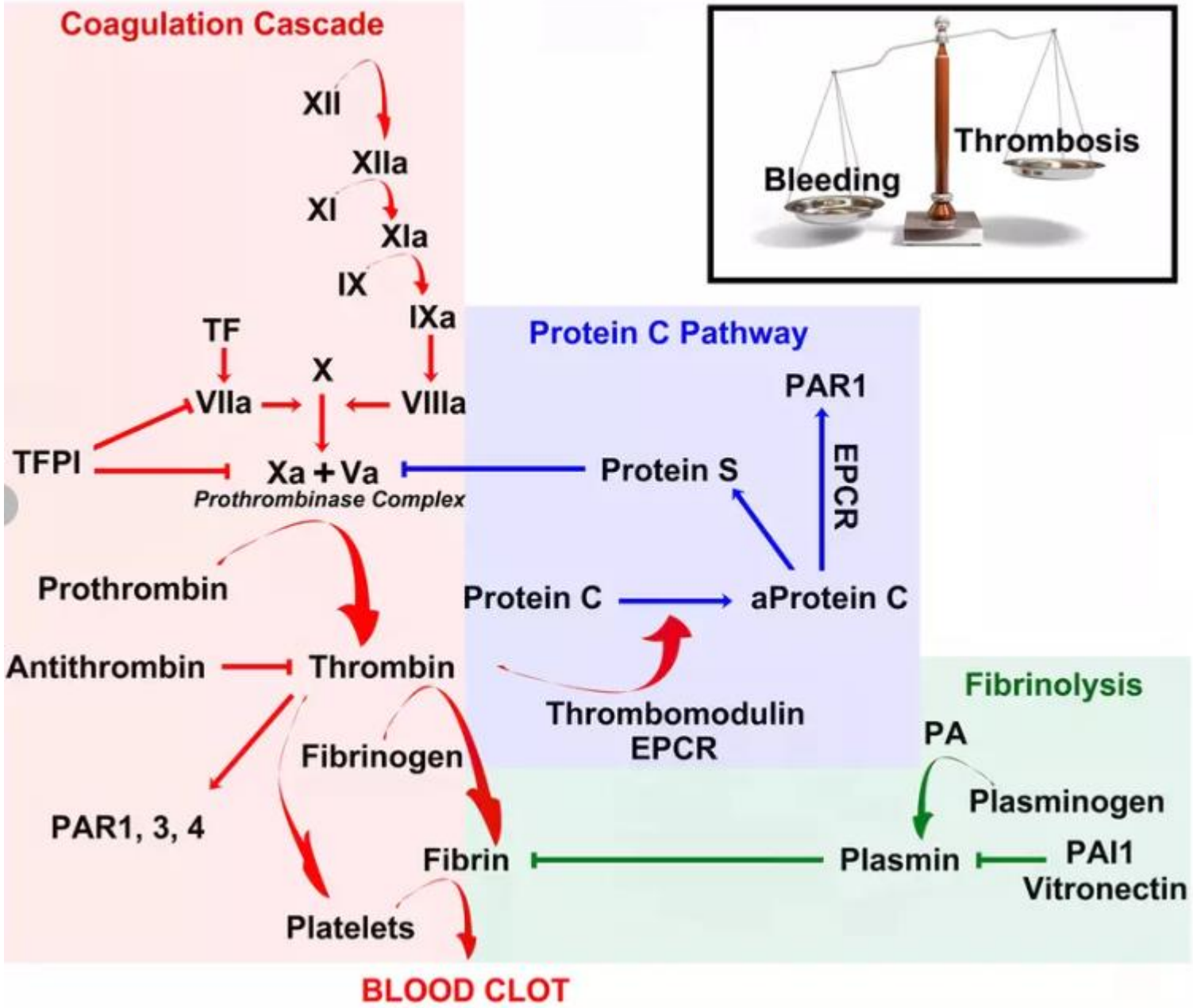
The clinical development program for Ciraparantag is currently at the Phase II stage, it is not possible to comment on the dose that will be studied in the Phase III trial and which is therefore more likely to be approved for clinical use.

Monoclonal abs, decoy molecules, small molecules with high affinity for DOACS



Niessner et al.

Balance


Coagulation Cascade
XII
XIIa
XI
XIa
IX
IXa
TF
X
VIIa
VIIIa
TFPI
Xa + Va
Prothrombinase Complex
Prothrombin
Antithrombin
Thrombin
PAR1, 3, 4
Fibrinogen
Fibrin
Platelets
BLOOD CLOT
Protein C Pathway
PAR1
EPCR
Protein S
Protein C
aProtein C
Thrombomodulin
EPCR
Fibrinolysis
PA
Plasminogen
Plasmin
PAI1
Vitronectin
Bleeding
Thrombosis

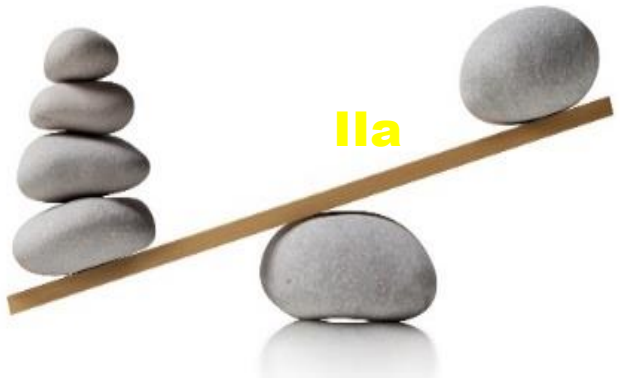
- Prothrombin gene mutation G20210
- AT deficiency
- Protein c and S deficiency
- Factor V Leiden mutation: associated with ischaemic stroke in children

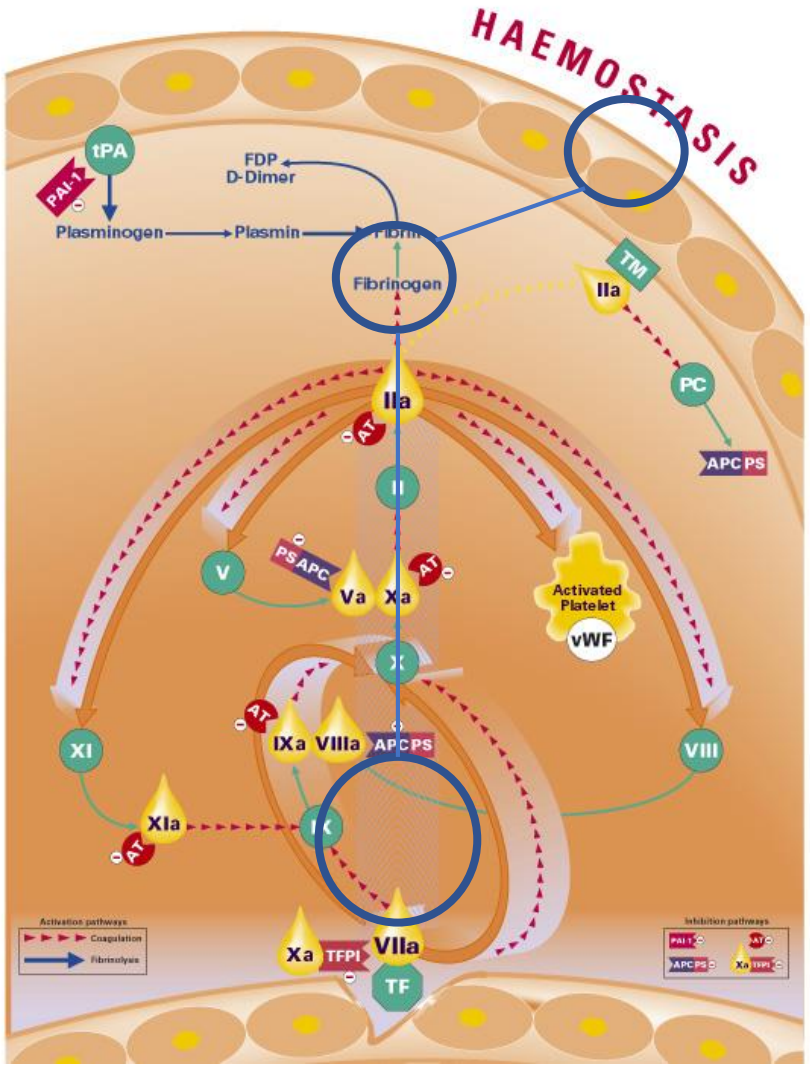
Central: Thrombin Generation

- Procoagulant initiated by TF
  - Triggers thrombin formation
- Anticoagulant initiated by thrombin
  - AT and α2Macroglobulin

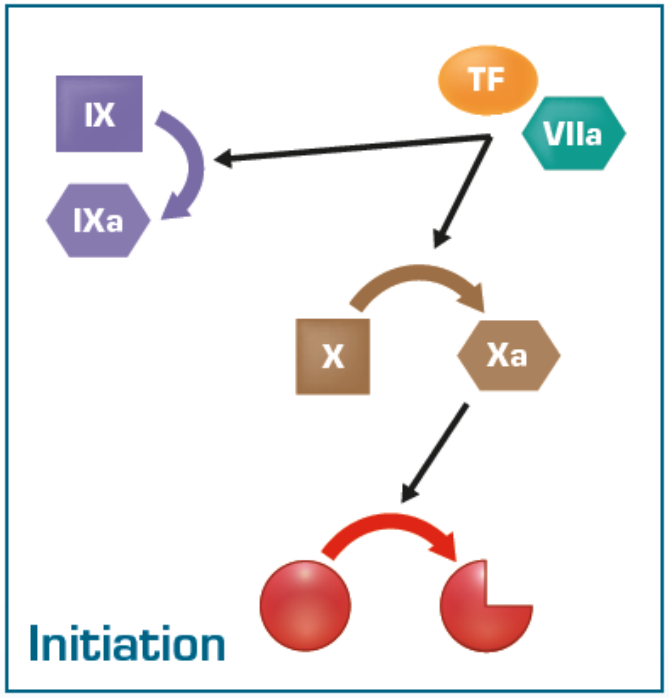
Excess:
Risk of thrombosis

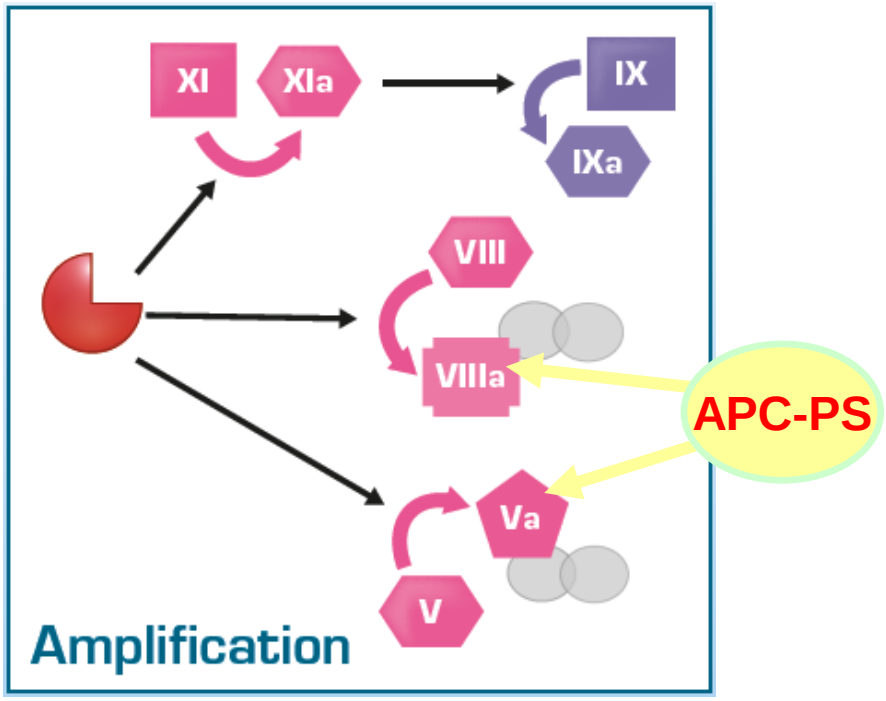
Lack:
Risk of bleeding

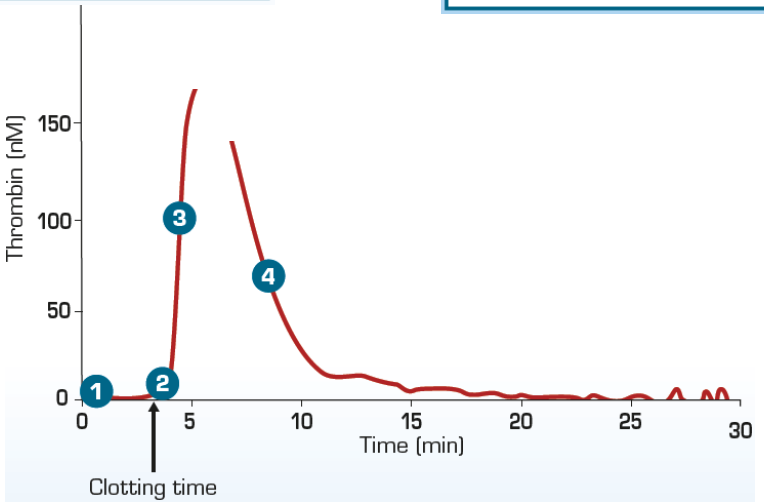




- Phase 1&2: Initiation & Amplification

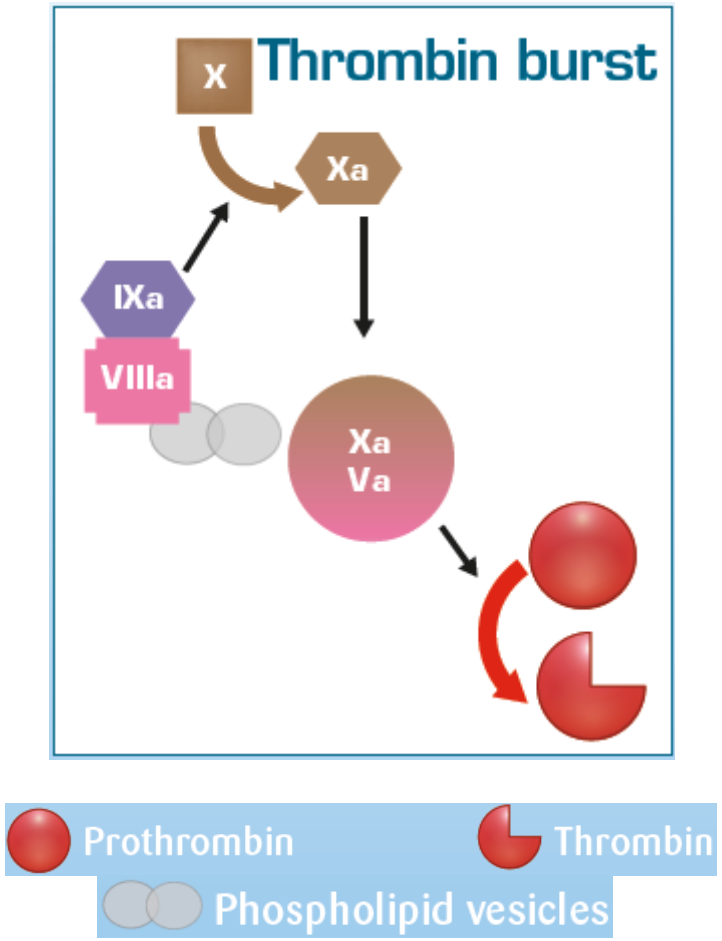


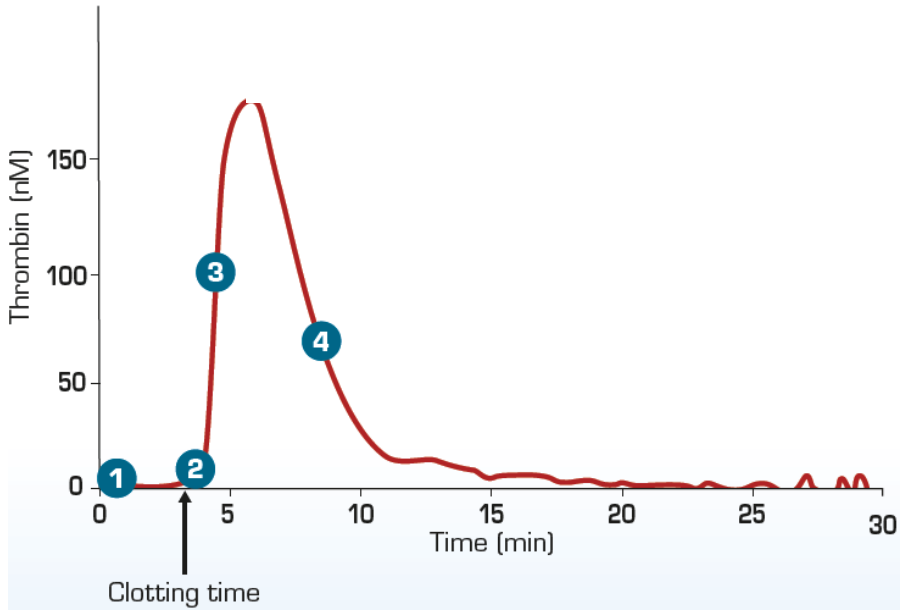




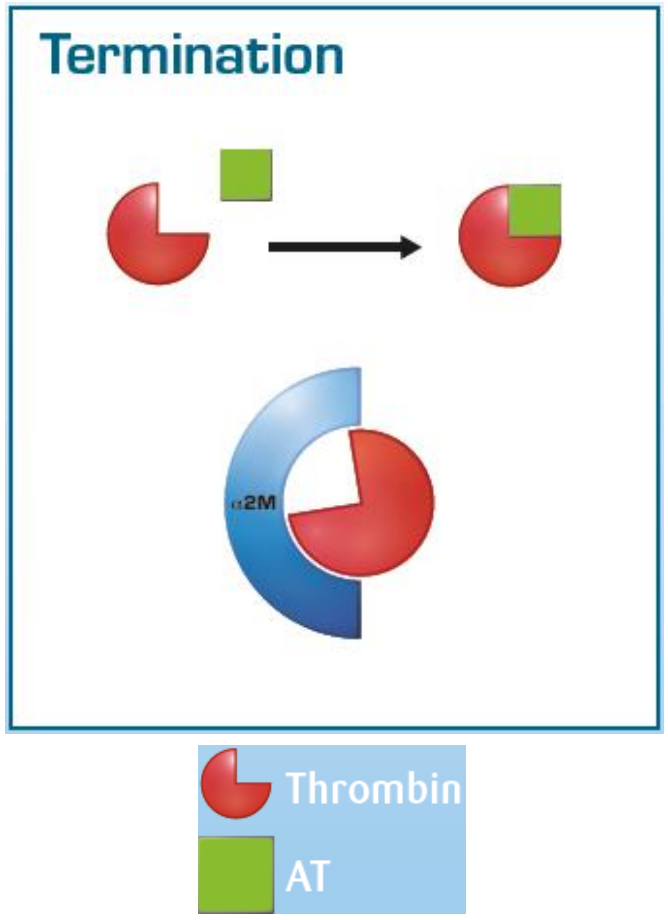
Thrombin
Phospholipid vesicles

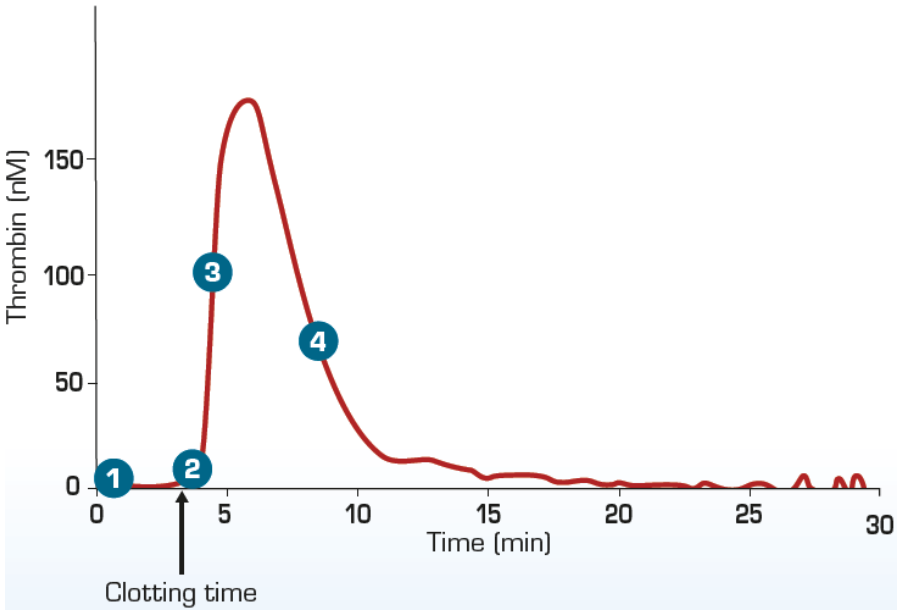
- Phase 3: Thrombin burst



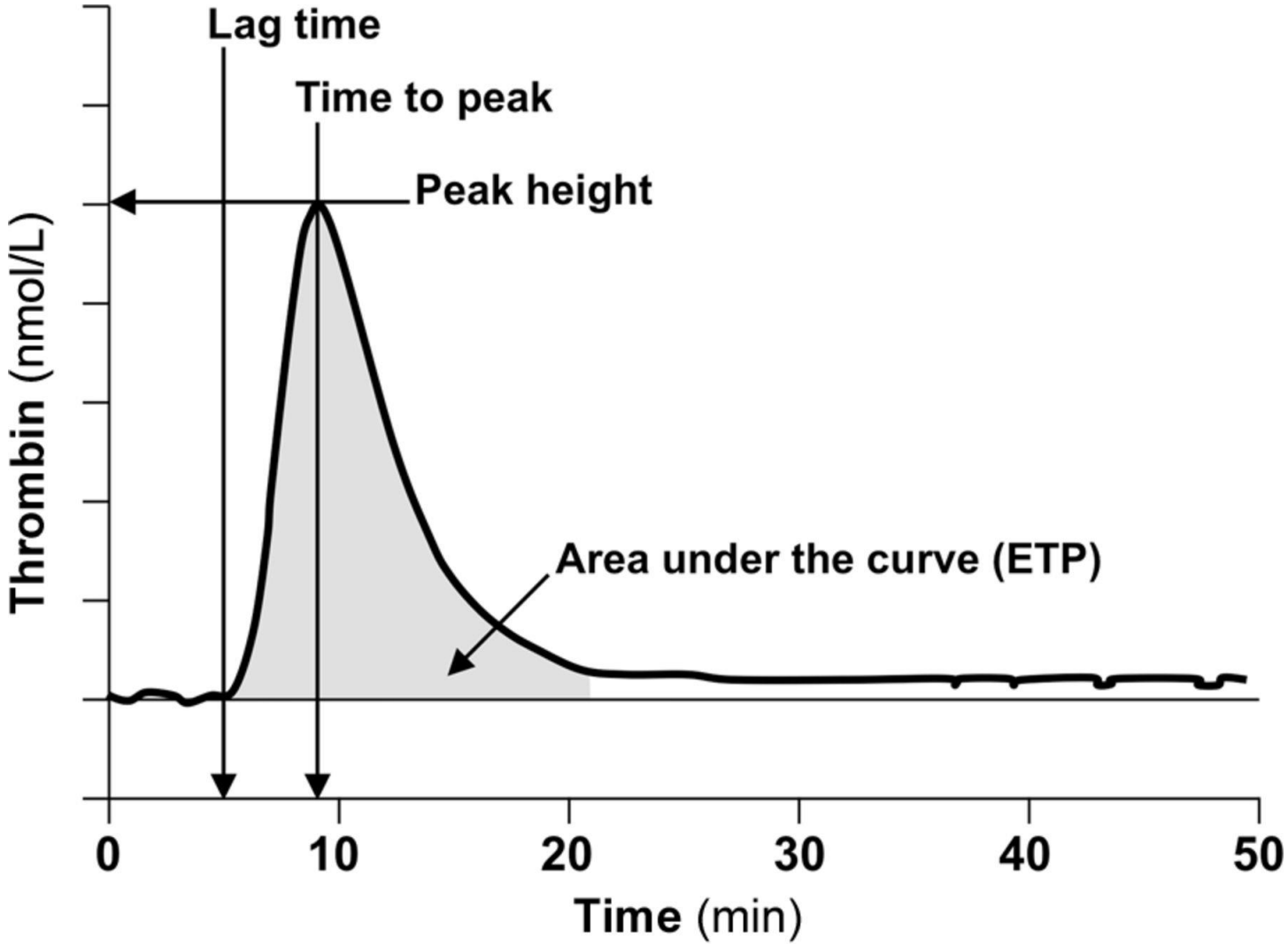


Phase4. Termination



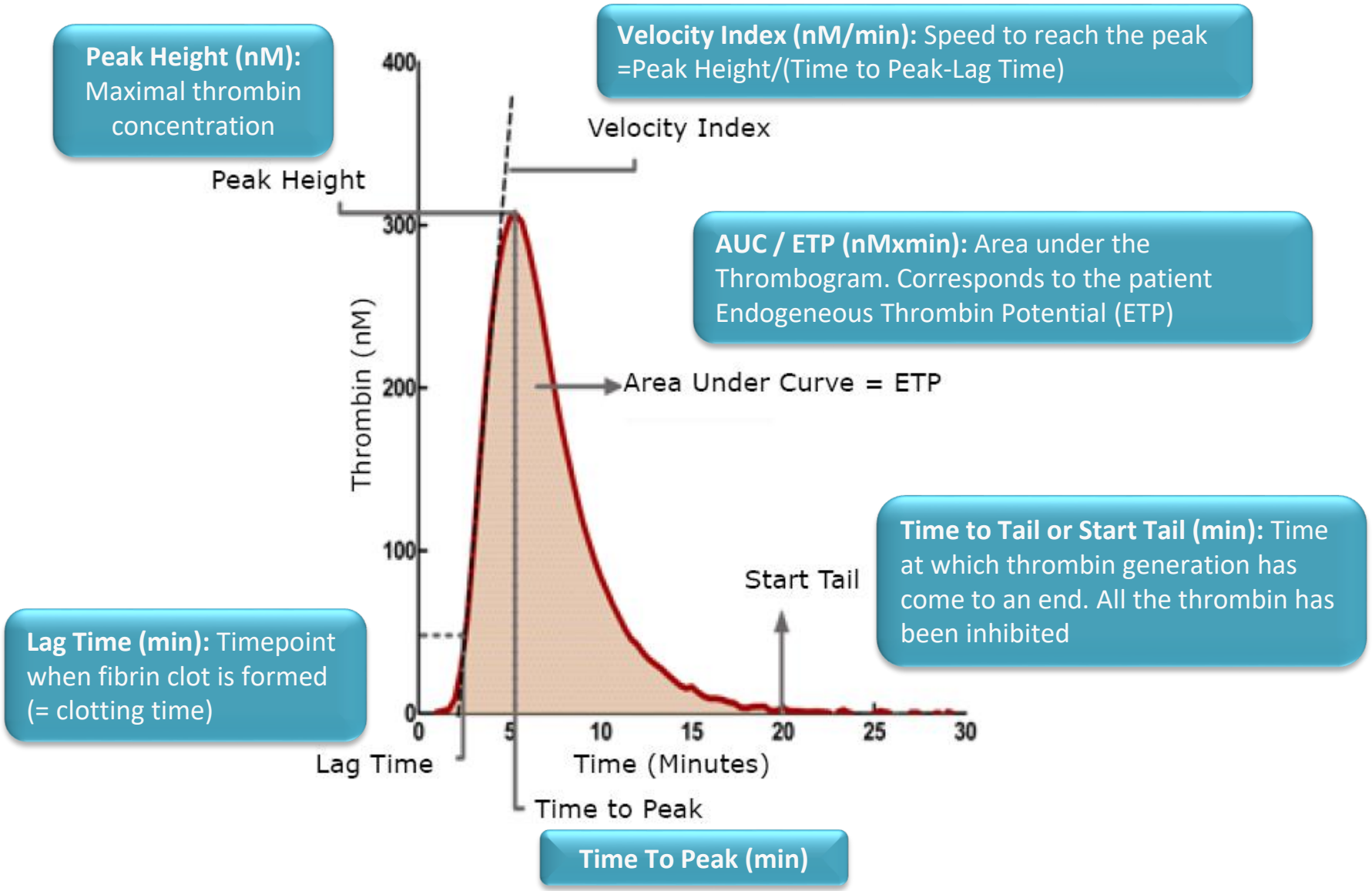


Thrombin generation



Peak Height (nM): Maximal thrombin concentration

Velocity Index (nM/min): Speed to reach the peak =Peak Height/(Time to Peak-Lag Time)



AUC / ETP (nMxmin): Area under the Thrombogram. Corresponds to the patient Endogeneous Thrombin Potential (ETP)

Time to Tail or Start Tail (min): Time at which thrombin generation has come to an end. All the thrombin has been inhibited

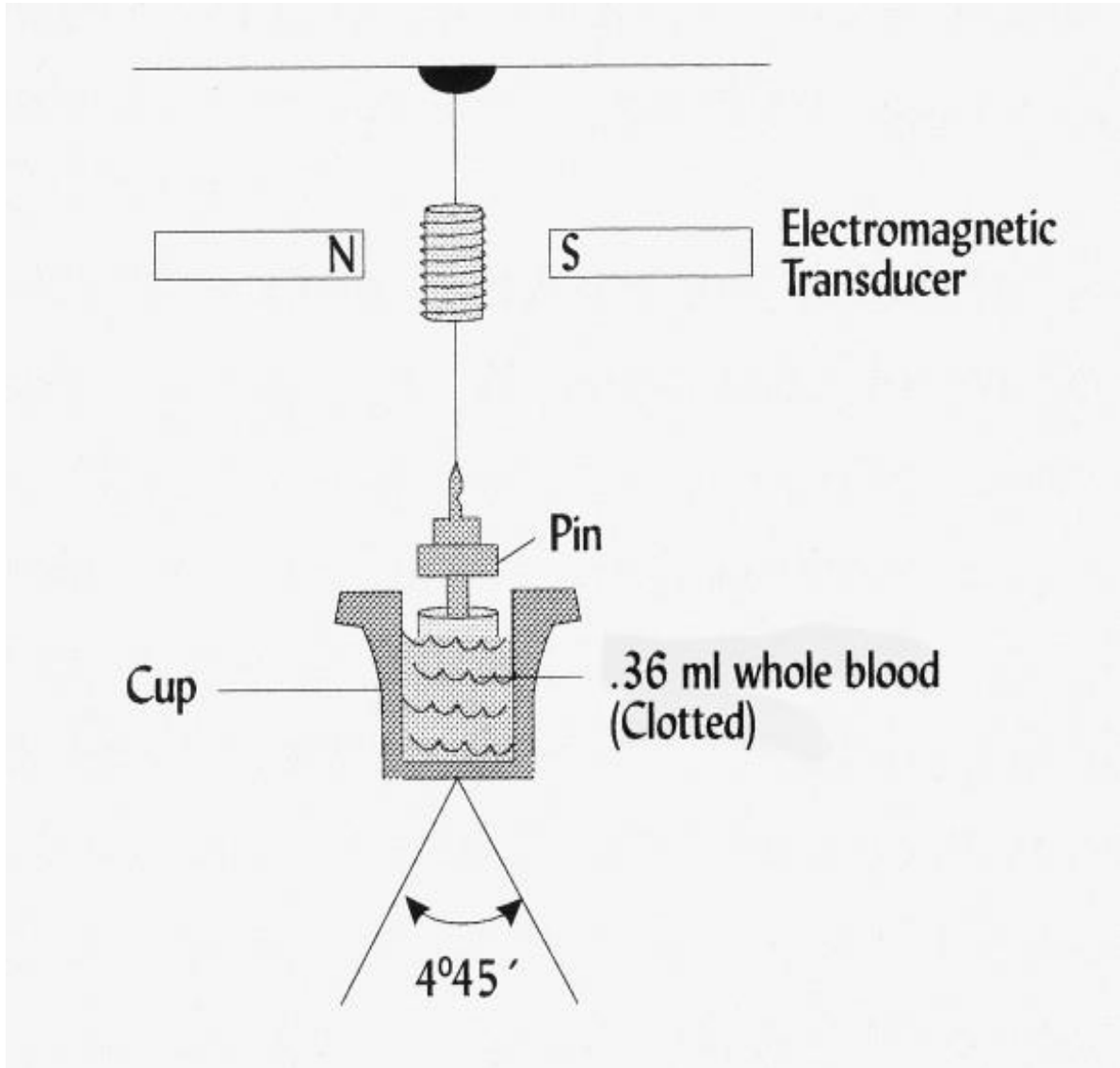
Lag Time (min): Timepoint when fibrin clot is formed (= clotting time)

Time To Peak (min)

The thromboelastogram (TEG)

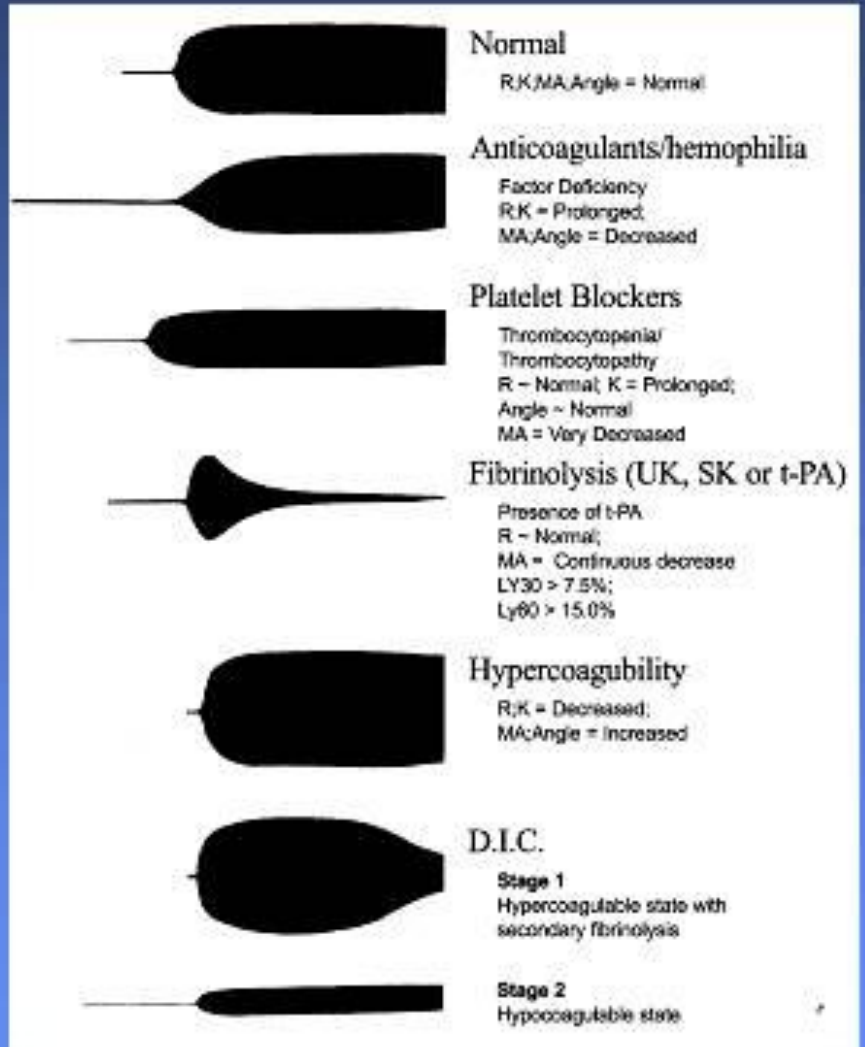
- Whole blood in cuvette
- Developed for use with celite activator
- Measures changes in clot strength
- Includes all phases of haemostatic mechanism including fibrinolysis.

TEG sample cup design



THROMBOELATOGRAPHY

Qualitative analysis



Summary

- Useful concept-several models
- Screening assays: PT, APTT, TT, fibrinogen
- Cannot be taken in isolation: must consider the other contributions of Virchow's Triad, the patient's personal bleeding history
- Prolonged PT/APTT
- Repeat assays/ Check history
- Mixing studies- discern between inhibitors vs. factor deficiencies
- Interventional procedures for patients with Inherited haemophillias:
  - Liase with tertiary centres caring for the patient
  - Treatment dependent on severity of deficiency and bleeding risk with procedures
- Drugs affecting the coagulation cascade:
- Xa inhibitors/Direct thrombin inhibitors/LMWH, Heparin/Warfarin
  - Reversal of agents
  - Elective management
- Increasing development of global assays of coagulation