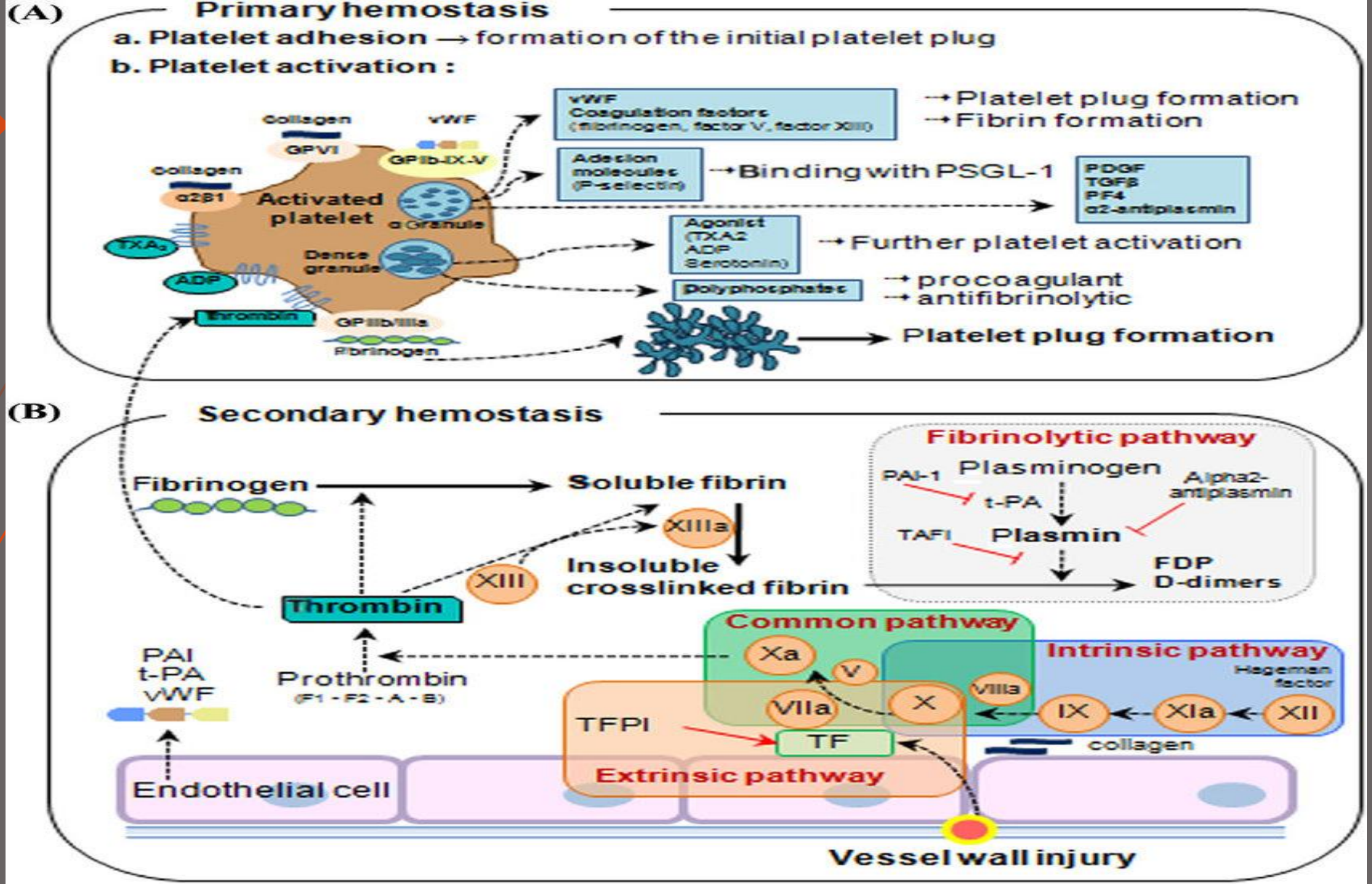
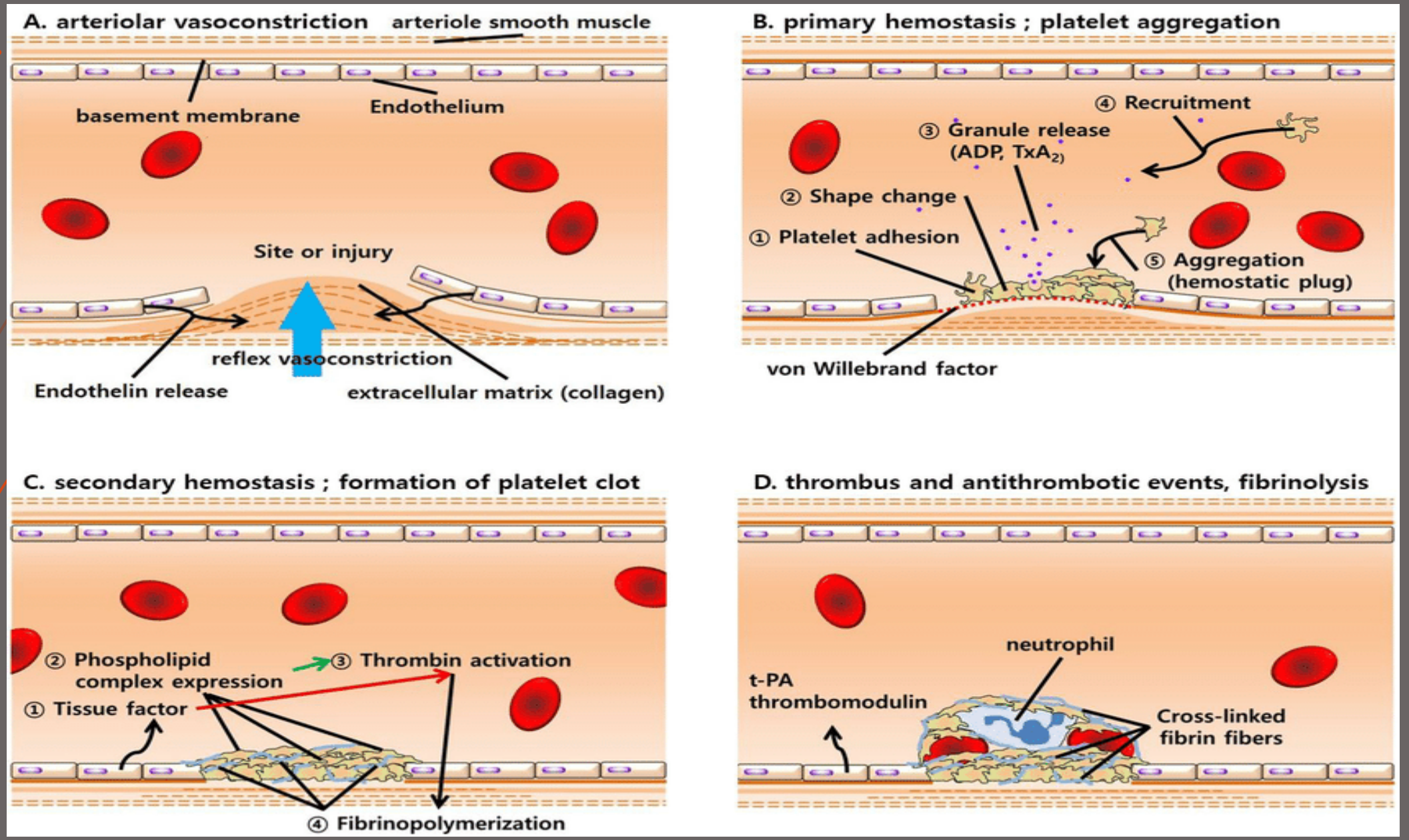
Approach to Bleeding Tendency

Simple and Direct

Causal Conditions

- Primary Hemostasias:
  - Purpuric disorders
- Secondary Hemostasias:
  - Disorder of Coagulation


(A)
Primary hemostasis
a. Platelet adhesion → formation of the initial platelet plug
b. Platelet activation :
Collagen
vWF
GPVI
GPIb-IX-V
Collagen
α2β1
Activated platelet
α Granule
Dense granule
TXA2
ADP
Thrombin
GPIIb/IIIa
Fibrinogen
vWF
Coagulation factors
(fibrinogen, factor V, factor XIII)
→ Platelet plug formation
→ Fibrin formation
Adesion molecules
(P-selectin)
→ Binding with PSGL-1
PDGF
TGFβ
PF4
α2-antiplasmin
Agonist
(TXA2
ADP
Serotonin)
→ Further platelet activation
Polyphosphates
→ procoagulant
→ antifibrinolytic
Platelet plug formation
(B)
Secondary hemostasis
Fibrinogen
Soluble fibrin
XIIIa
XIII
Insoluble crosslinked fibrin
Thrombin
Fibrinolytic pathway
PAI-1
Plasminogen
Alpha2-antiplasmin
t-PA
TAFI
Plasmin
FDP
D-dimers
Common pathway
Xa
V
Intrinsic pathway
Hegeman factor
VIIIa
VIIa
X
IX
XIa
XII
PAI
t-PA
vWF
Prothrombin
(F1 - F2 - A - B)
TFPI
TF
collagen
Extrinsic pathway
Endothelial cell
Vessel wall injury

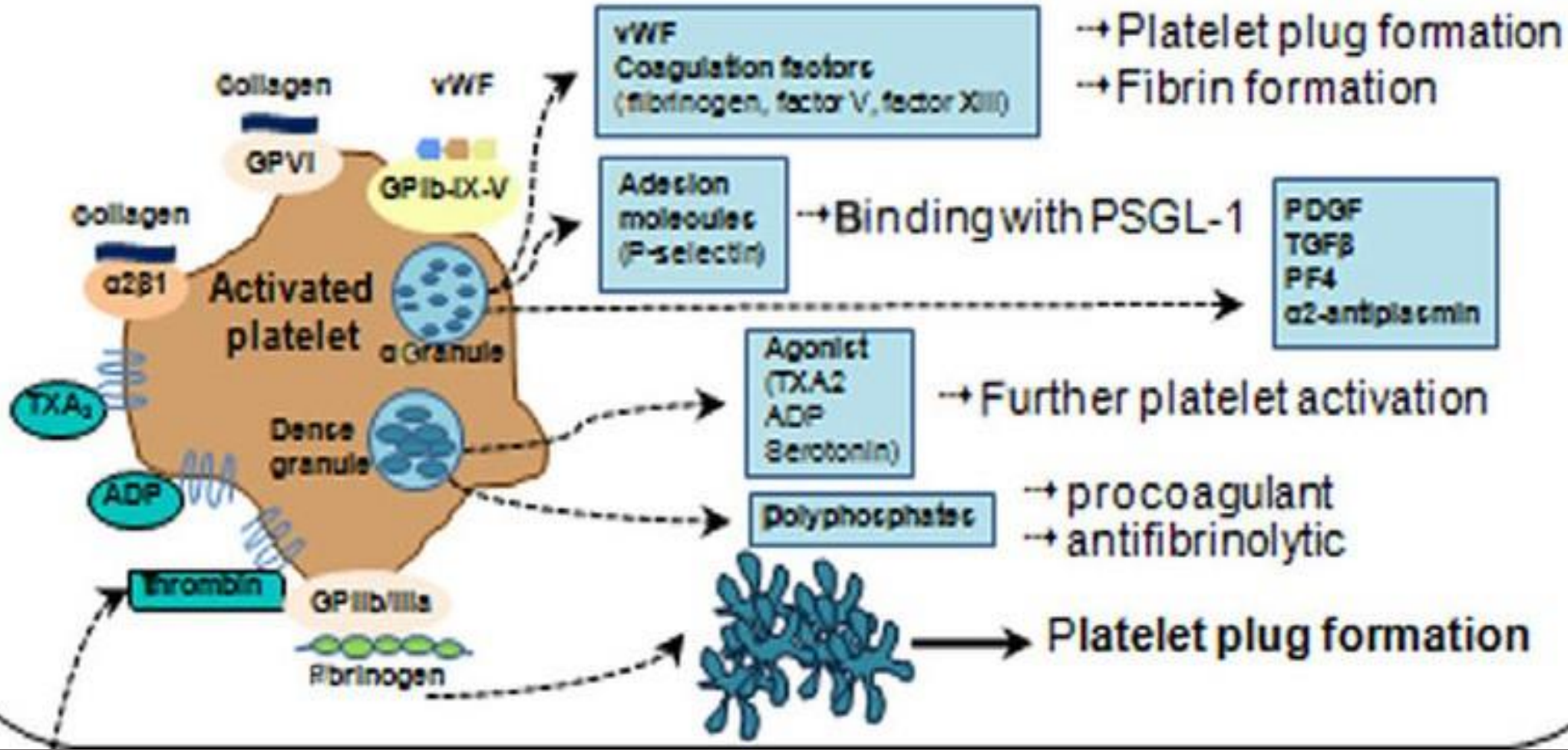

A. arteriolar vasoconstriction
arteriole smooth muscle
basement membrane
Endothelium
Site or injury
reflex vasoconstriction
Endothelin release
extracellular matrix (collagen)
B. primary hemostasis ; platelet aggregation
④ Recruitment
③ Granule release
(ADP, TxA2)
② Shape change
① Platelet adhesion
⑤ Aggregation
(hemostatic plug)
von Willebrand factor
C. secondary hemostasis ; formation of platelet clot
② Phospholipid
complex expression
③ Thrombin activation
① Tissue factor
④ Fibrinopolymerization
D. thrombus and antithrombotic events, fibrinolysis
neutrophil
t-PA
thrombomodulin
Cross-linked
fibrin fibers

Primary Hemostasis

Primary hemostasis

a. Platelet adhesion → formation of the initial platelet plug

b. Platelet activation :



Platelet number or function

- **Decreased number:**
- **Production problem**
  - Decreased megakaryopoesis (aplastic anemia, toxic)
  - Ineffective megakaryopoesis (B12/folate def., folate antagonist)
- **Accelerated destruction**
  - Non-immune (TTP/HUS, DIC, infection)
  - Immune (ITP, SLE, quinidine)
  - Sequestration (splenomegaly)

Platelet number or function

- **Abnormal platelets**
  - Congenital (Glanzmann's Thrombasthenia, Bernard-Soulier Syndrome)
  - Acquired (uremia, ASA, NSAID, anti-platelet agents)

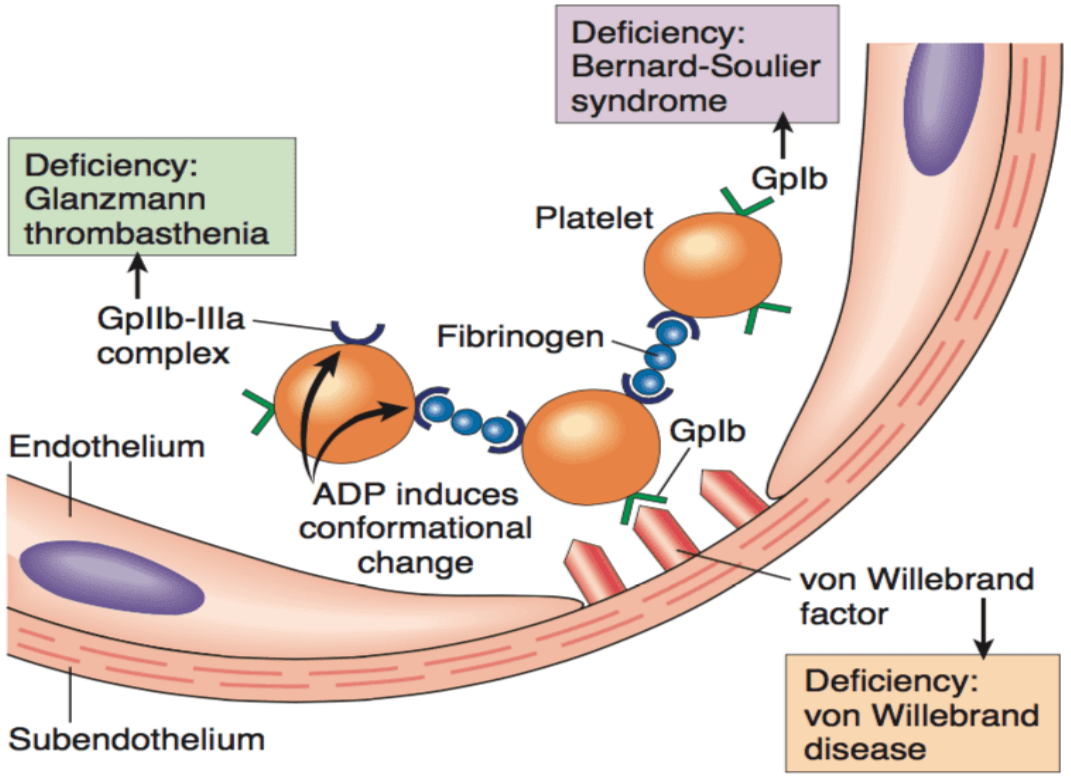


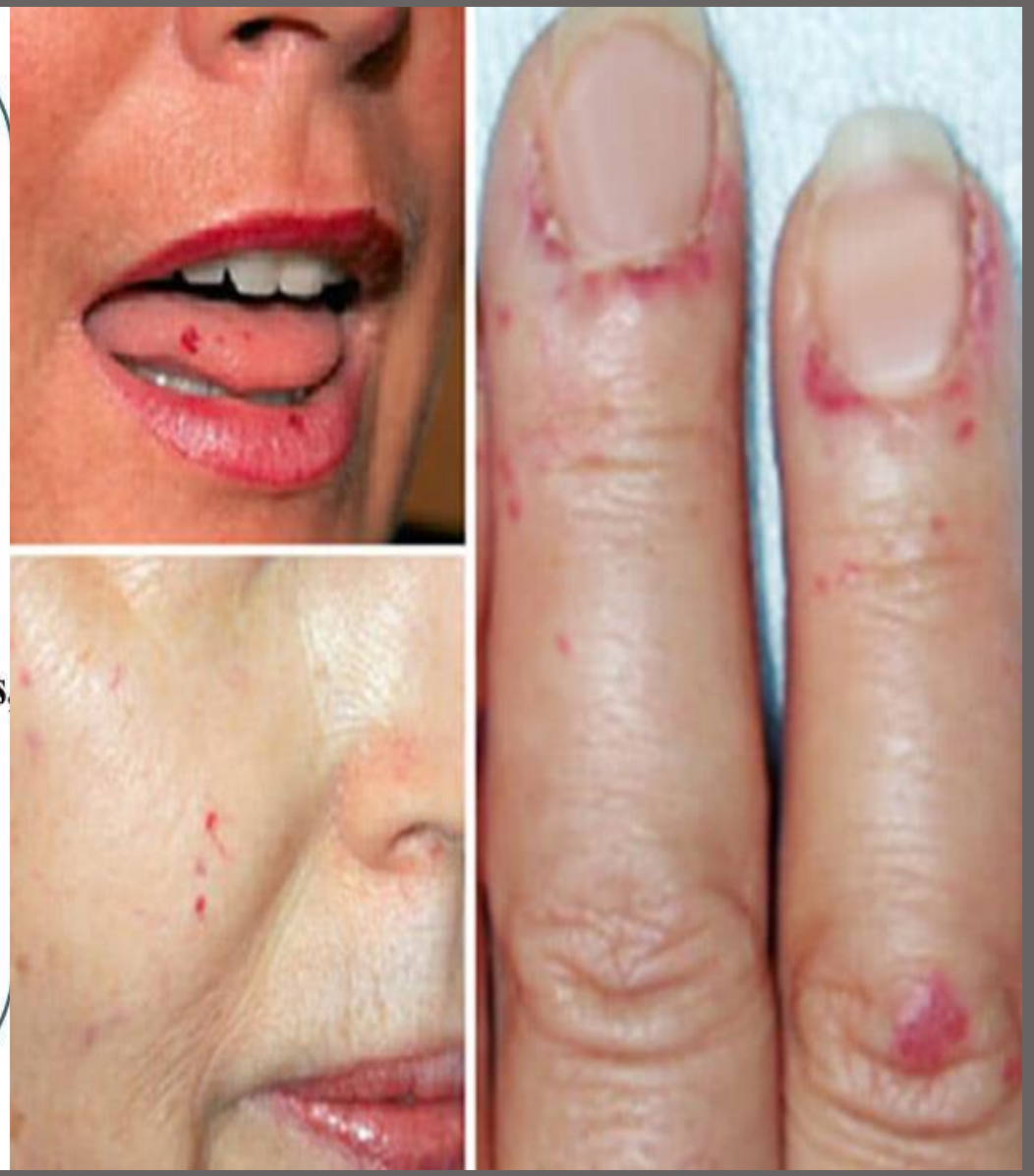
Figure 4-5 Platelet adhesion and aggregation. Von Willebrand factor functions as an adhesion bridge between subendothelial collagen and the glycoprotein Ib (GpIb) platelet receptor. Aggregation is accomplished by fibrinogen bridging GpIIb-IIIa receptors on different platelets. Congenital deficiencies in the various receptors or bridging molecules lead to the diseases indicated in the colored boxes. ADP, adenosine diphosphate.

Vessel Problem

- Congenital (collagen disease)
- Vitamin C deficiency (scurvy)
- Connective tissue disorders
- Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
- Acquired (vasculitis, steroids)

Hereditary Hemorrhagic Telangiectasia (Osler–Weber–Rendu Disease):

- HHT, a multisystem disease, genetically mediated disorder of fibrovascular tissue.
- The definitive diagnosis based on the Curaçao criteria, require presence of at least 3 of the following 4 clinical features:
- (1) Spontaneous, recurrent epistaxis.
- (2) Telangiectases at characteristic sites as lips, oral cavity, fingers, or nose
- (3) visceral lesions as cerebral or spinal AVMs, GI tract telangiectasias, pulmonary AVMs, hepatic AVMs
- (4) A family history of HHT in a first-degree relative.

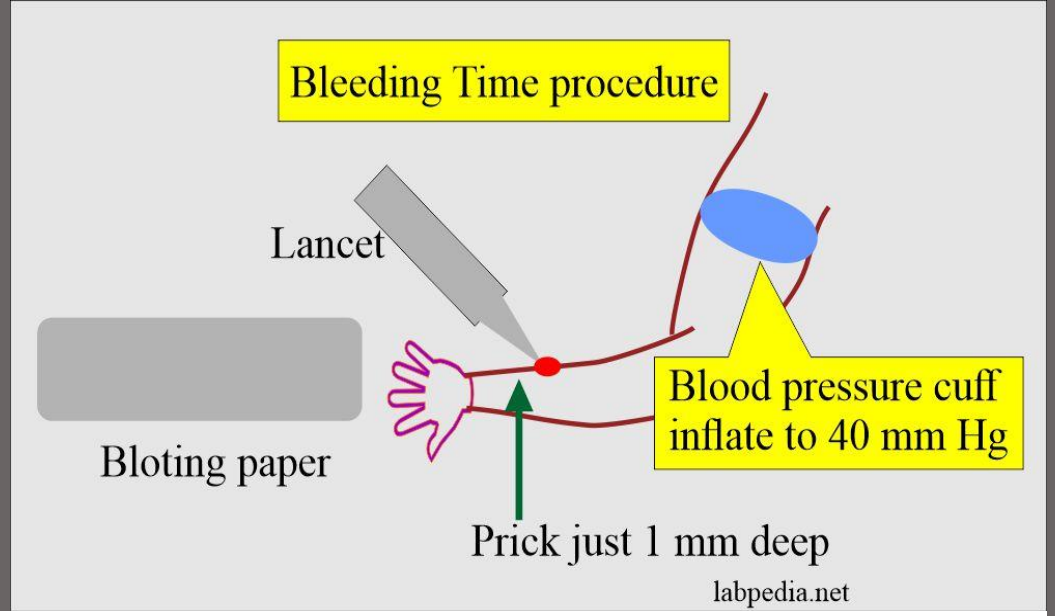


Signs and symptoms

- Petechia and purpura
- Spontaneous bleeding after trauma
- CNS bleeding (severe thrombocytopenia)
- Mucocutaneous bleeding
- Sever Menorrhagia

Laboratory exam

- Platelet count
- Peripheral blood study
- Prolonged bleeding time (BT)
- Abnormal tourniquet test(5 min pressure cuff between systolic and diastolic pressure, > 5 petechia in 2.5 cm2 of antecubital area)
- Prolonged Closure time (CT) (by PFA-100)
- Flowcytometry
- Bone marrow aspiration and biopsy



Abnormalities detected by PFA-100

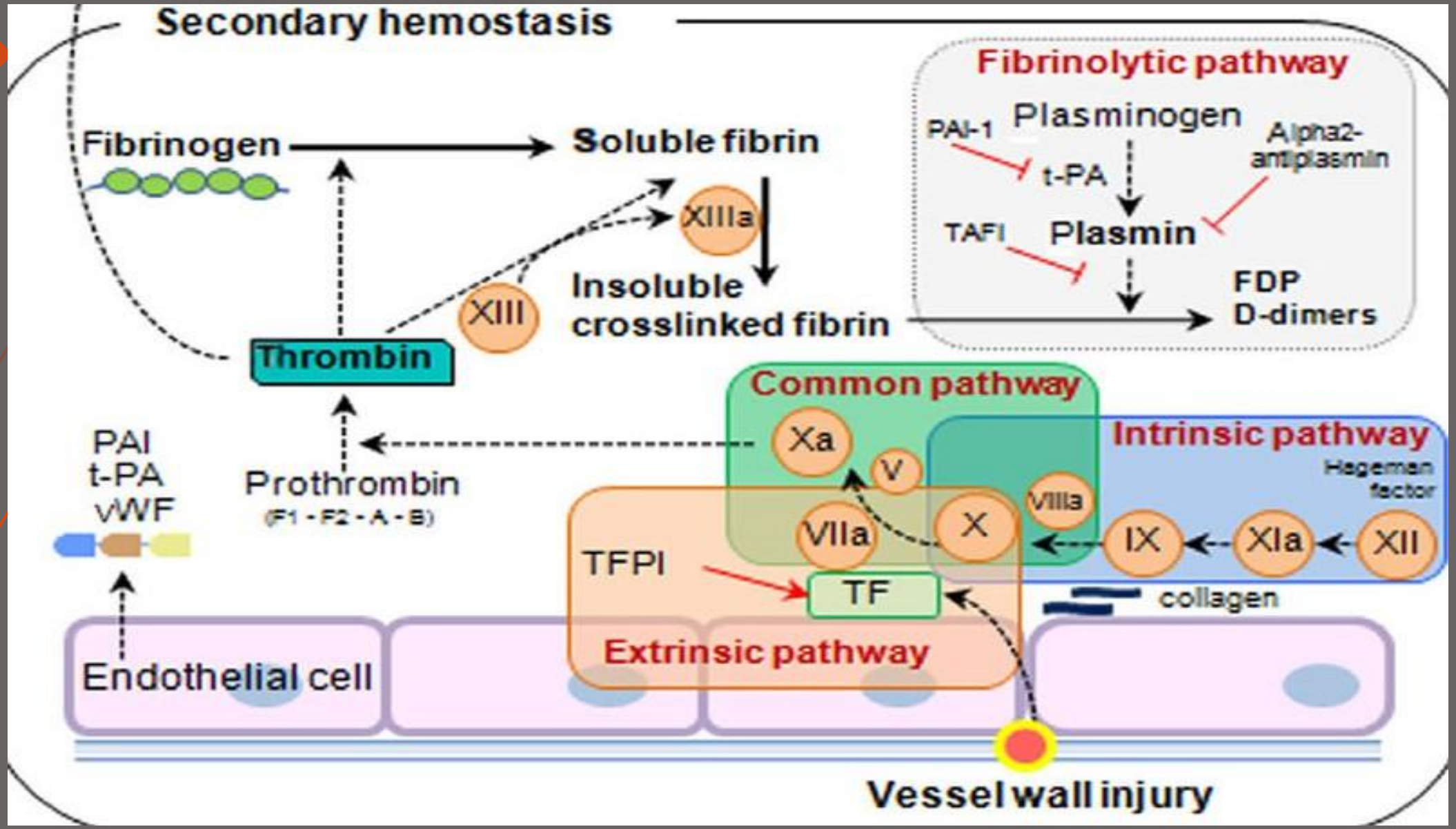
	CT	
	Col-ADP	Col-EPI
Normal	N	N
Aspirin and NSAIDs	N	↑
ADP receptor disorders including the use of Clopidogrel	N or ↑	N or ↑
BSS	↑	↑
GTT	↑	↑
VWD	↑	↑
Platelet-Type VWD	↑	↑
Dense Granule Deficiency	N or ↑	N or ↑
Primary Secretion Defects	N or ↑	N or ↑
Gray Platelet Syndrome	↑	↑
MYH9-related Disorders	N	↑
Scott Syndrome	N	N
MDS	N or ↑	N or ↑
Liver Disease	↑ [possibly as a result of ↓Hb]	↑ [possibly as a result of ↓Hb]
Uraemia	↑ [possibly as a result of ↓Hb]	↑ [possibly as a result of ↓Hb]

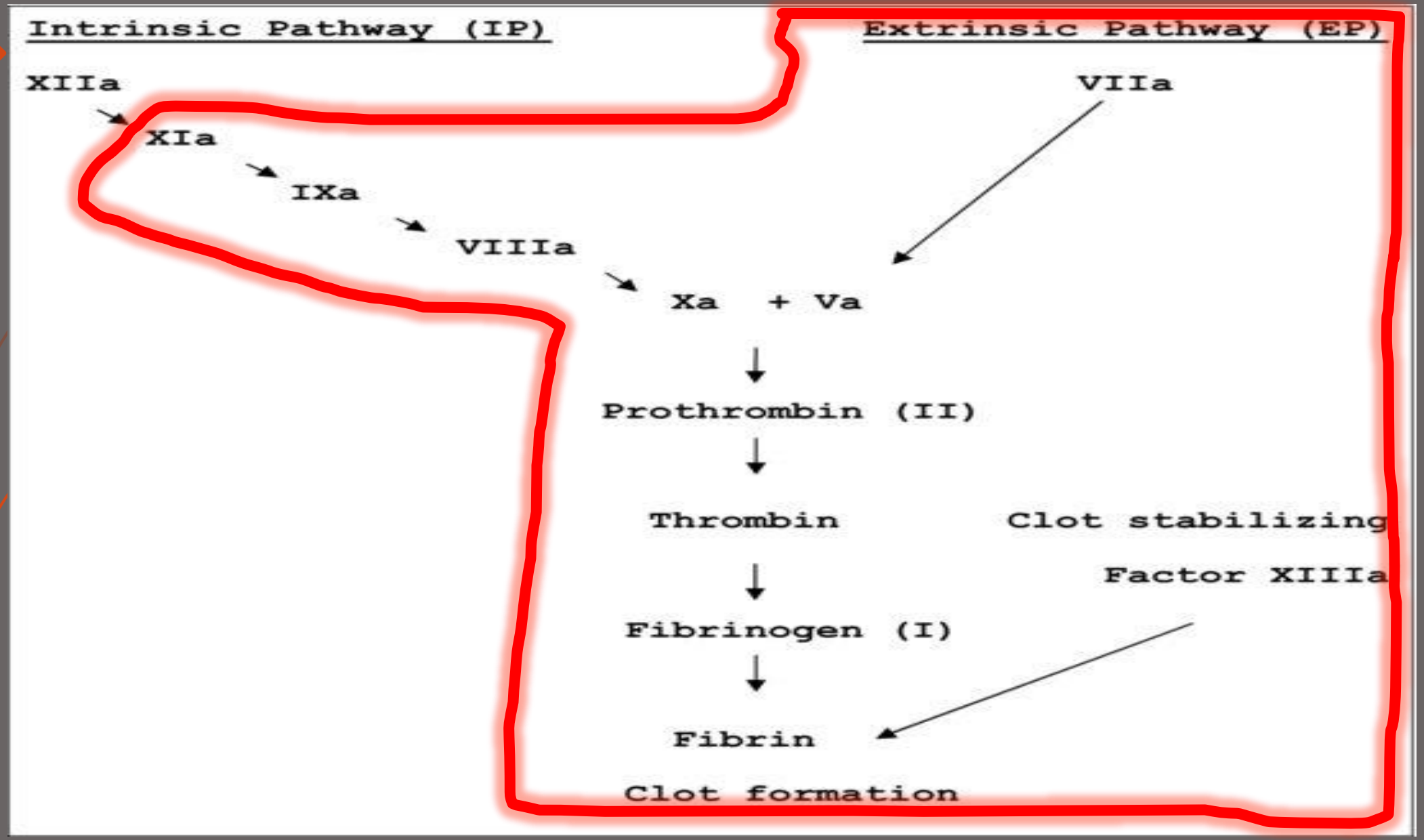
http://http://www.practical-haemostasis.com/

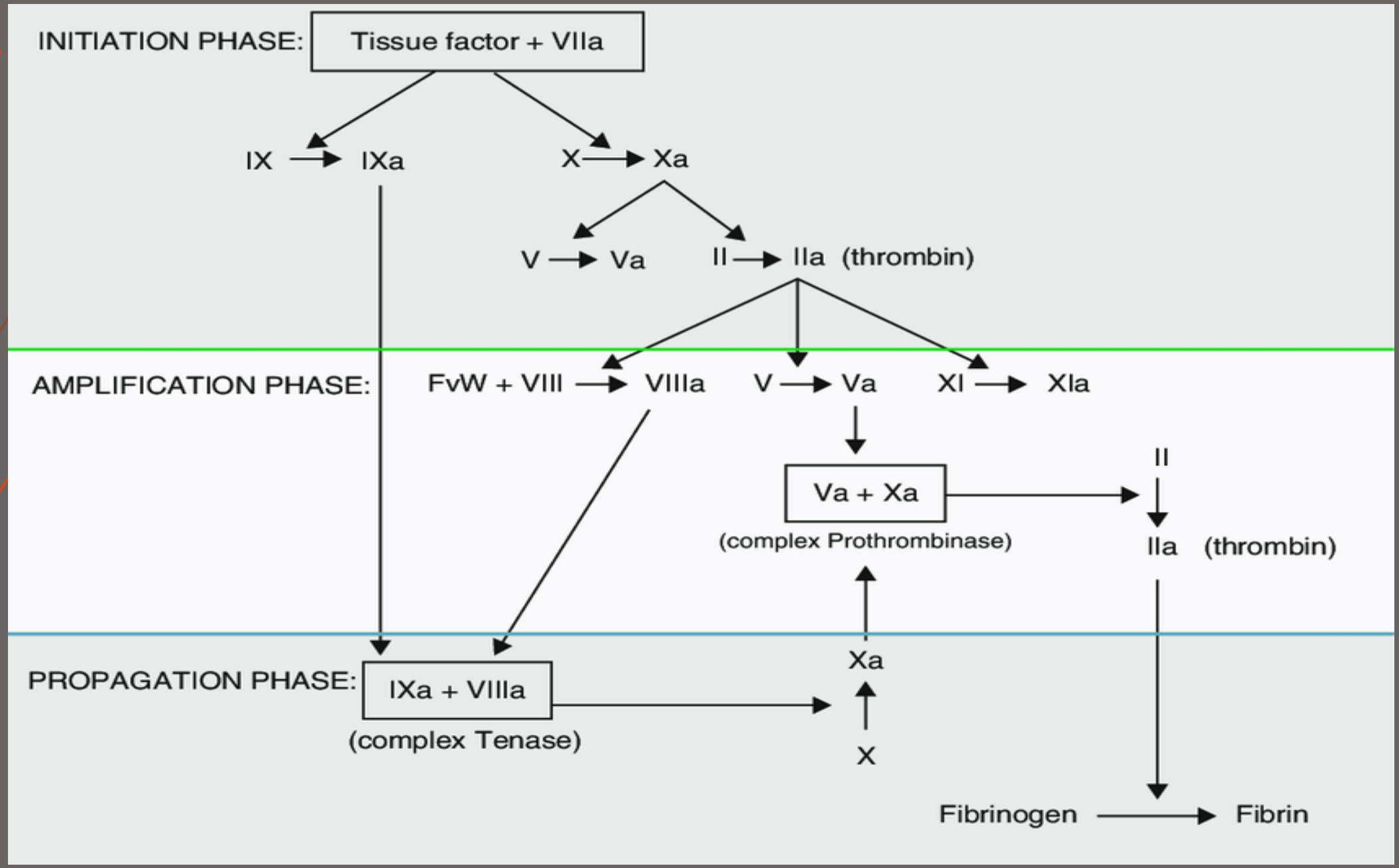
Treatment:

- **Production problem**
  - Decreased megakaryopoesis :PLT transfusion if active bleeding
  - Ineffective megakaryopoesis :therapy of causal factor
- **Accelerated destruction**
  - Non-immune :Plasmapheresis, plasma exchange
  - Immune : Steroid or IV IG or RhoGam (BM aspiration before steroid therapy)
- **Sequestration : splenectomy**
- **Abnormal platelets: PLT transfusion in the case of bleeding**

Secondary Hemostasis


Secondary hemostasis
Fibrinogen
Soluble fibrin
XIIIa
XIII
Insoluble
crosslinked fibrin
Thrombin
Prothrombin
(F1 - F2 - A - B)
PAI
t-PA
vWF
Fibrinolytic pathway
PAI-1
Plasminogen
Alpha2-
antiplasmin
t-PA
TAFI
Plasmin
FDP
D-dimers
Common pathway
Xa
V
VIIIa
VIIa
X
Intrinsic pathway
Hegeman
factor
IX
XIa
XII
TFPI
TF
collagen
Extrinsic pathway
Endothelial cell
Vessel wall injury


Intrinsic Pathway (IP)
Extrinsic Pathway (EP)
XIIa
VIIa
XIa
IXa
VIIIa
Xa + Va
Prothrombin (II)
Thrombin
Clot stabilizing
Factor XIIIa
Fibrinogen (I)
Fibrin
Clot formation


INITIATION PHASE:
Tissue factor + VIIa
IX
IXa
X
Xa
V
Va
II
IIa (thrombin)
AMPLIFICATION PHASE:
FvW + VIII
VIIIa
V
Va
XI
XIa
Va + Xa
(complex Prothrombinase)
II
IIa (thrombin)
PROPAGATION PHASE:
IXa + VIIIa
(complex Tenase)
Xa
X
Fibrinogen
Fibrin

Congenital

- **Factor VIII deficiency (Hemophilia A)**
- **Factor IX deficiency (Hemophilia B)**
- **Rare factor deficiency:**
  - X
  - V
  - XIII
  - I
  - XII
  - VII
  - II

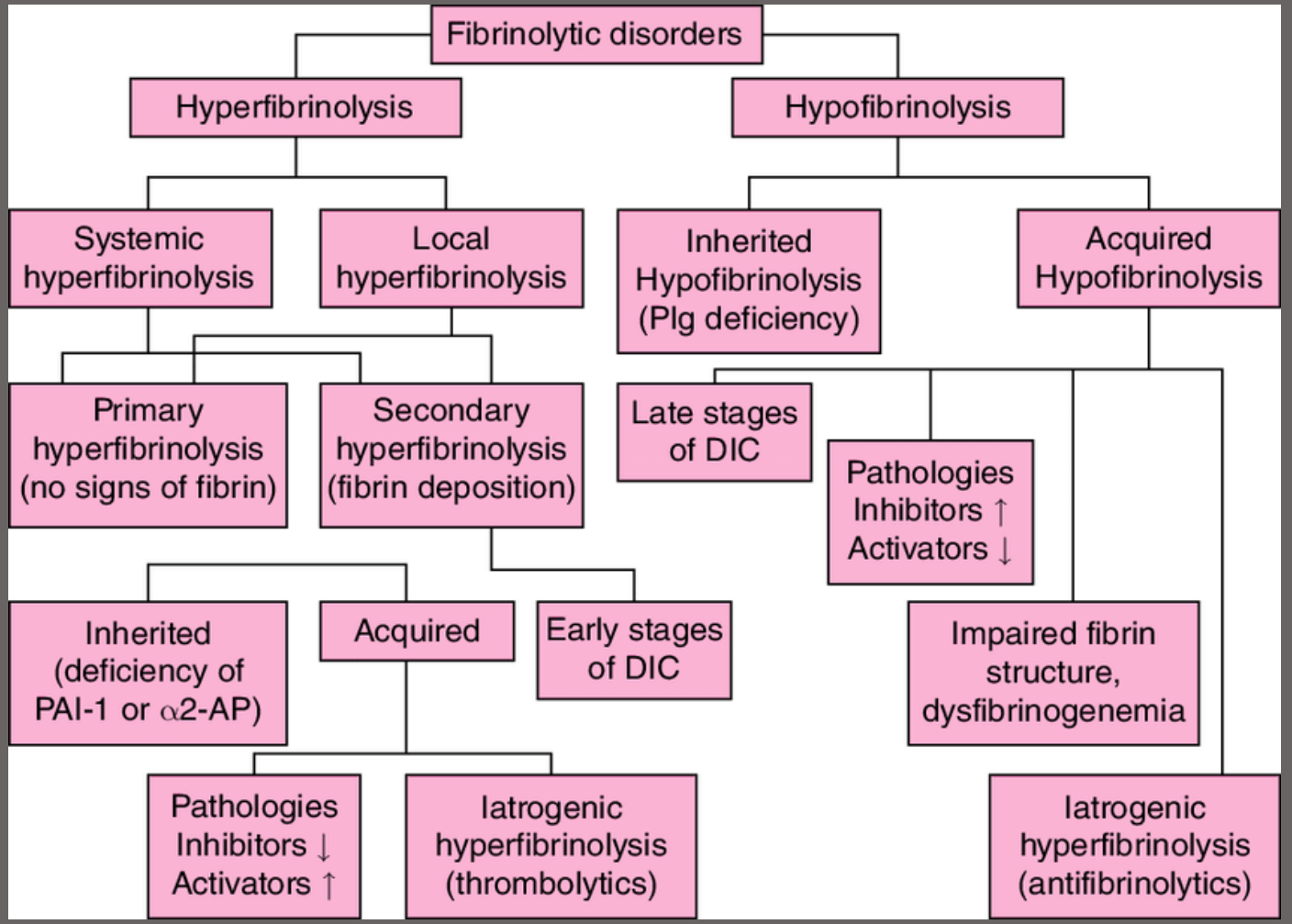
Acquired

- **Liver disease:**
  - Reduced synthesis of procoagulant proteins (FII, FV, FVII, FIX, FX, and FXI)
  - Fibrinogen levels are normal or increased, with acquired dysfibrinogenemia (50-75%)
  - Natural anticoagulant protein levels fall (Antithrombin, protein C and protein S)
  - Levels of plasminogen, α2antiplasmin, thrombin-activatable fibrinolysis inhibitor (TAFI), and FXIII levels are often reduced. (tPA are usually elevated)
- **Vitamin K deficiency:** Factors II, VII, IX, X, and protein C and protein S
- **Anticoagulants**
- **Inhibitors:** Collagen vascular disease, Cancer

Fibrinolysis disorders

(Bleeding tendency or Thrombophilia)

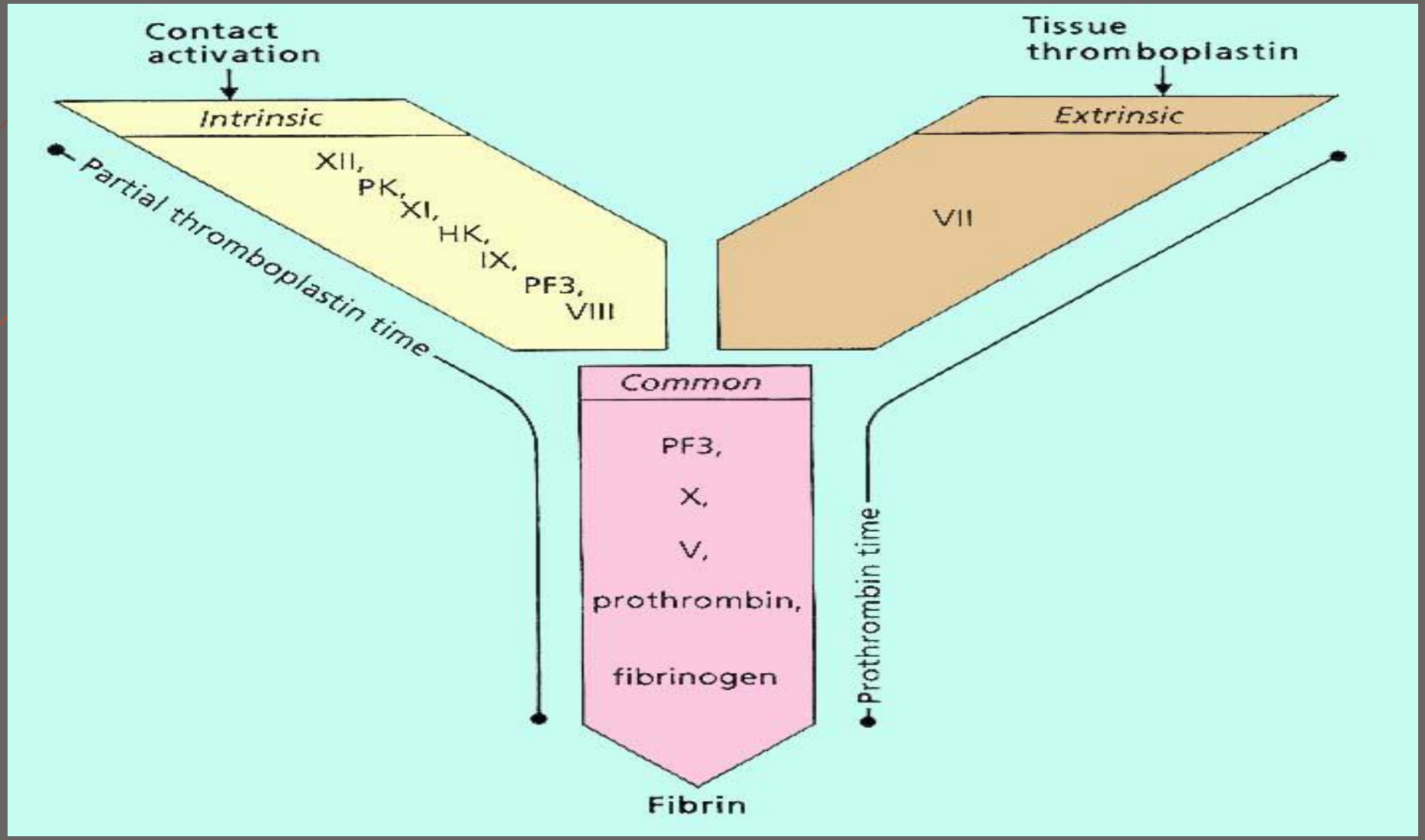
- liver cirrhosis
- Amyloidosis
- Acute promyelocytic leukemia
- Solid tumors
- Certain snake envenomation syndromes



Clinical presentation

- **Bleeding from large vessels into joints (hemarthroses)**
- **Bleeding from large vessels into muscles**
- **Deep soft tissues bleeding (hematomas, large ecchymoses)**
- **Onset - delayed after trauma**

Screening Tests of Blood Coagulation

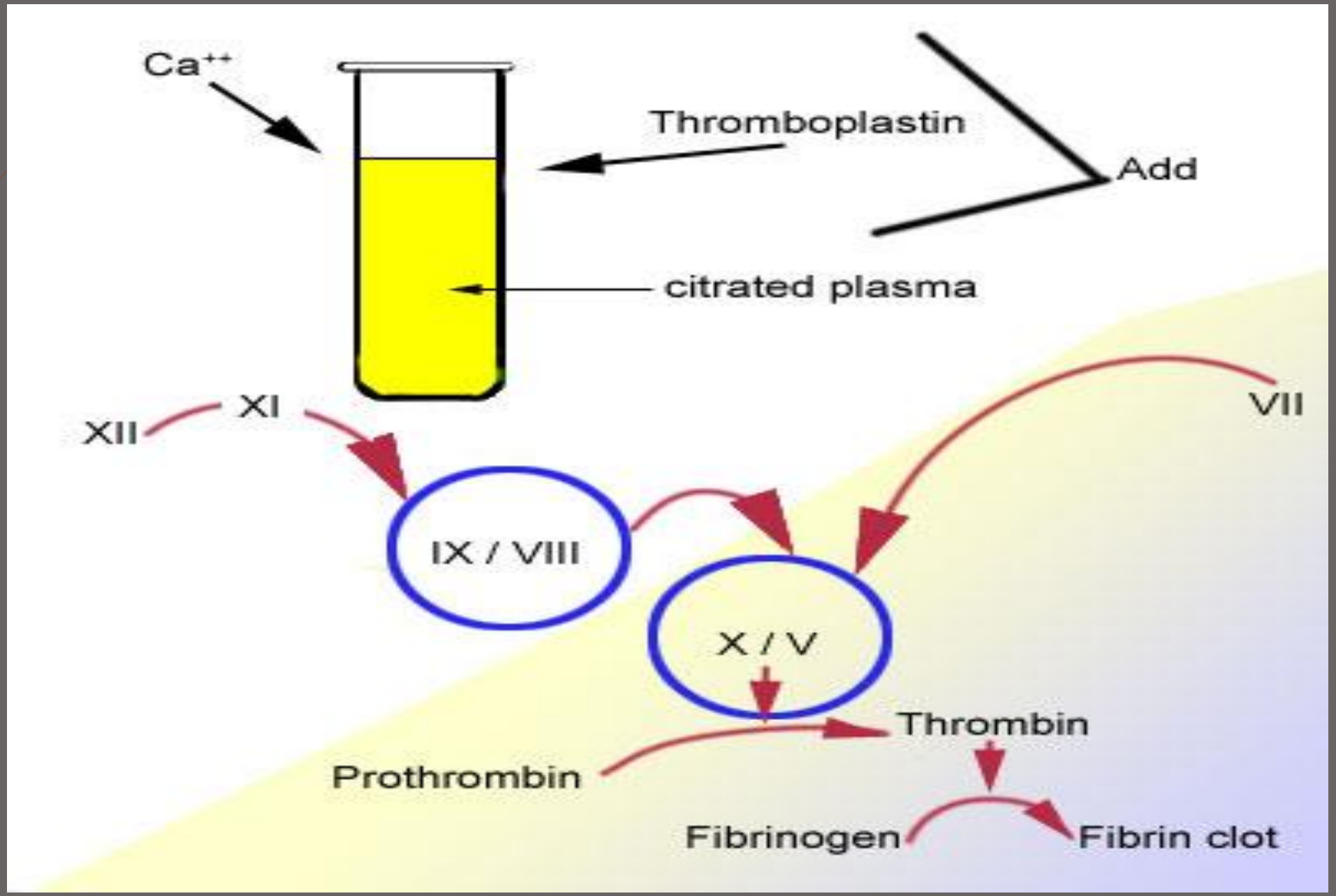


Laboratory findings

- **Normal bleeding time (BT) , Platelet count**
- **Prolonged prothrombin time (PT)**
- **Prolonged activated partial thromboplastin time (aPTT)**
- **Mixing studies - normal plasma corrects PT or aPTT**
- **Prolonged Thrombin time (TT)**

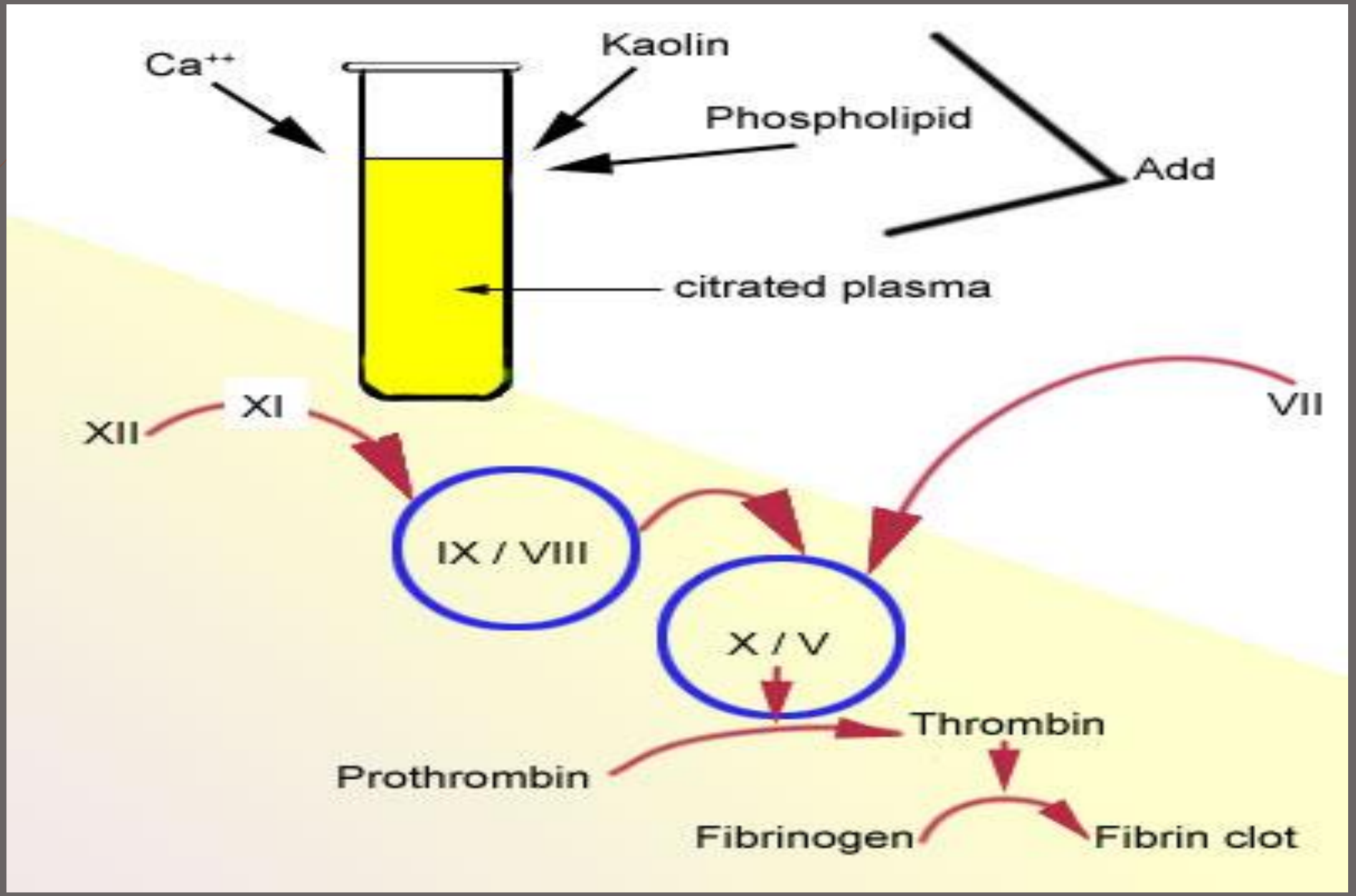
Laboratory findings

- **Prothrombin time (PT):**
- measures how long it takes blood to clot
- INR (international normalized ratio) stands for a way of standardizing the results
- normally takes about 25 to 30 seconds
- made longer by:
  - Blood-thinning medicine, such as warfarin.
  - Low levels, activity, absence of blood clotting factors.
  - Other substances, called inhibitors, that affect the clotting factors.
  - An increase in the use of the clotting factors (DIC)


Ca++
Thromboplastin
Add
citrated plasma
XII
XI
VII
IX / VIII
X / V
Thrombin
Prothrombin
Fibrinogen
Fibrin clot

Laboratory findings

- activated partial thromboplastin time (aPTT):
- investigate the cause of prolonged or excessive bleeding
- Normal results are typically 25 to 45 seconds
- prolonged PTT result may be due to:
  - deficiency of blood clotting factors (haemophilia A or B)
  - von Willebrand disease (a disorder that causes abnormal blood clotting)
  - disseminated intravascular coagulation
  - certain medications, such as the blood thinners heparin and warfarin
  - nutritional issues, such as vitamin K deficiency and malabsorption
  - antibodies including cardiolipin antibodies, lupus anticoagulants
  - leukemia
  - liver disease


Ca++
Kaolin
Phospholipid
Add
citrated plasma
XII
XI
VII
IX / VIII
X / V
Thrombin
Prothrombin
Fibrinogen
Fibrin clot

Laboratory findings

- **Mixing studies:**
- Used to investigate abnormal clotting time results
- Distinguish clotting time prolongation due to a coagulation factor deficiency or an inhibitor (specific or nonspecific)
- Direct further coagulation testing but it is not by itself diagnostic
- Mix patient plasma and normal pooled plasma and measure the clotting time that was initially prolonged

Laboratory findings

- **Thrombin Time**
- Assess the time that Thrombin convert Fibrinogen to an insoluble fibrin clot.
- Affected by
  - Abnormal Fibrinogen level or dysfibrinogenemia
  - Drug: Heparin or direct thrombin inhibitors

PT :normal; aPTT: prolong

Factor VIII, IX, XI, contact factor

Treatment

Factor replacement in factor VIII and IX deficiency

FFP in factor XI deficiency

No therapy for contact factor deficiency

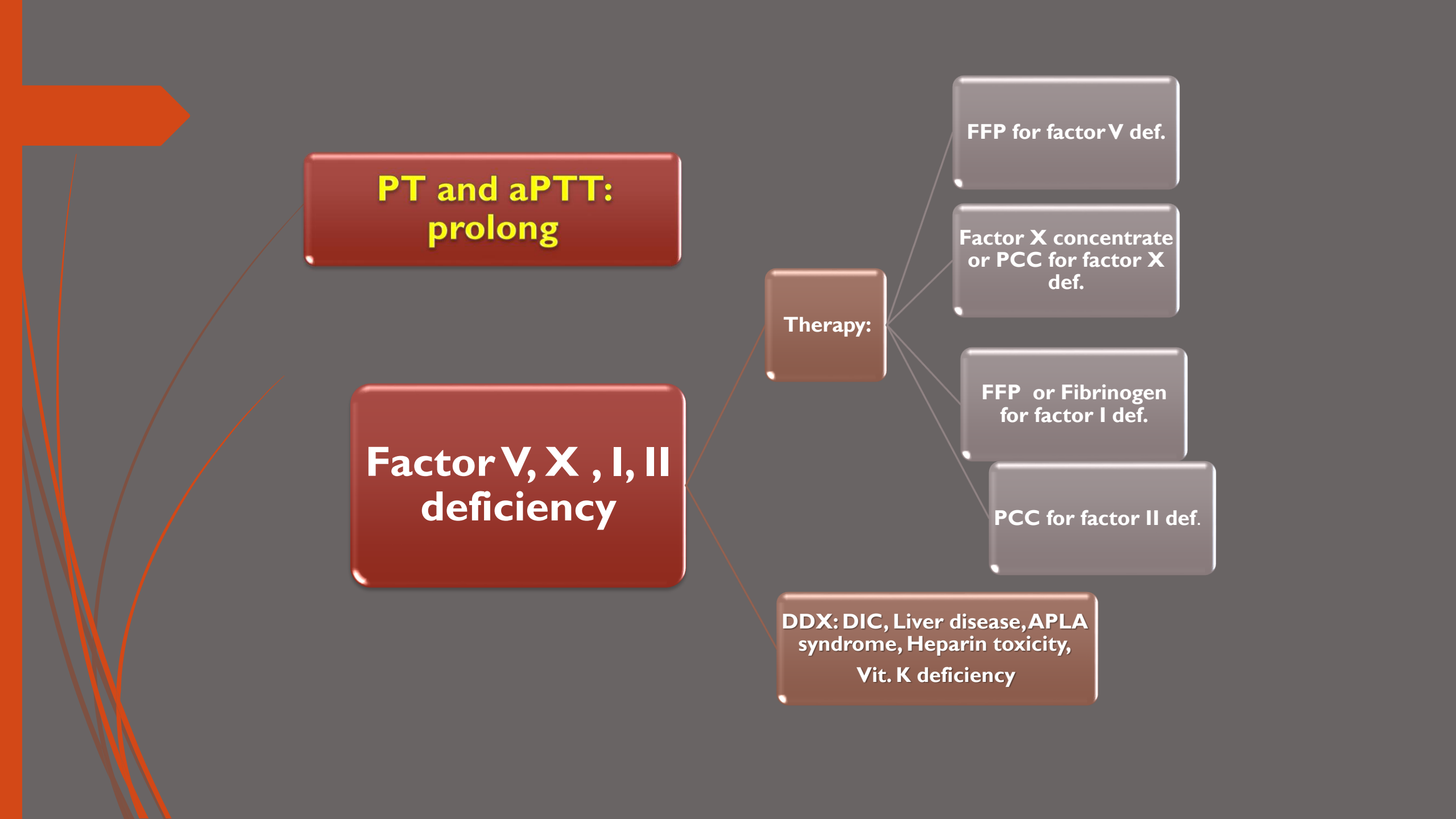
DDX: Antiphospholipid Syndrome, Heparin effect

PT: prolong ; aPTT :normal

Factor VII deficiency

Therapy :Factor replacement

DDX: Warfarin effect


PT and aPTT: prolong
Factor V, X , I, II deficiency
Therapy:
FFP for factor V def.
Factor X concentrate or PCC for factor X def.
FFP or Fibrinogen for factor I def.
PCC for factor II def.
DDX: DIC, Liver disease, APLA syndrome, Heparin toxicity, Vit. K deficiency

PT and aPTT: normal but bleeding tendency

Factor XIII deficiency

- Therapy: FFP
- Cryoprecipitate
- Factor XIII concentarte

PT and aPTT: normal but bleeding tendency

Mild Hemophilia A and B

Mild VWF deficiency

α2- antiplasminogn deficiency

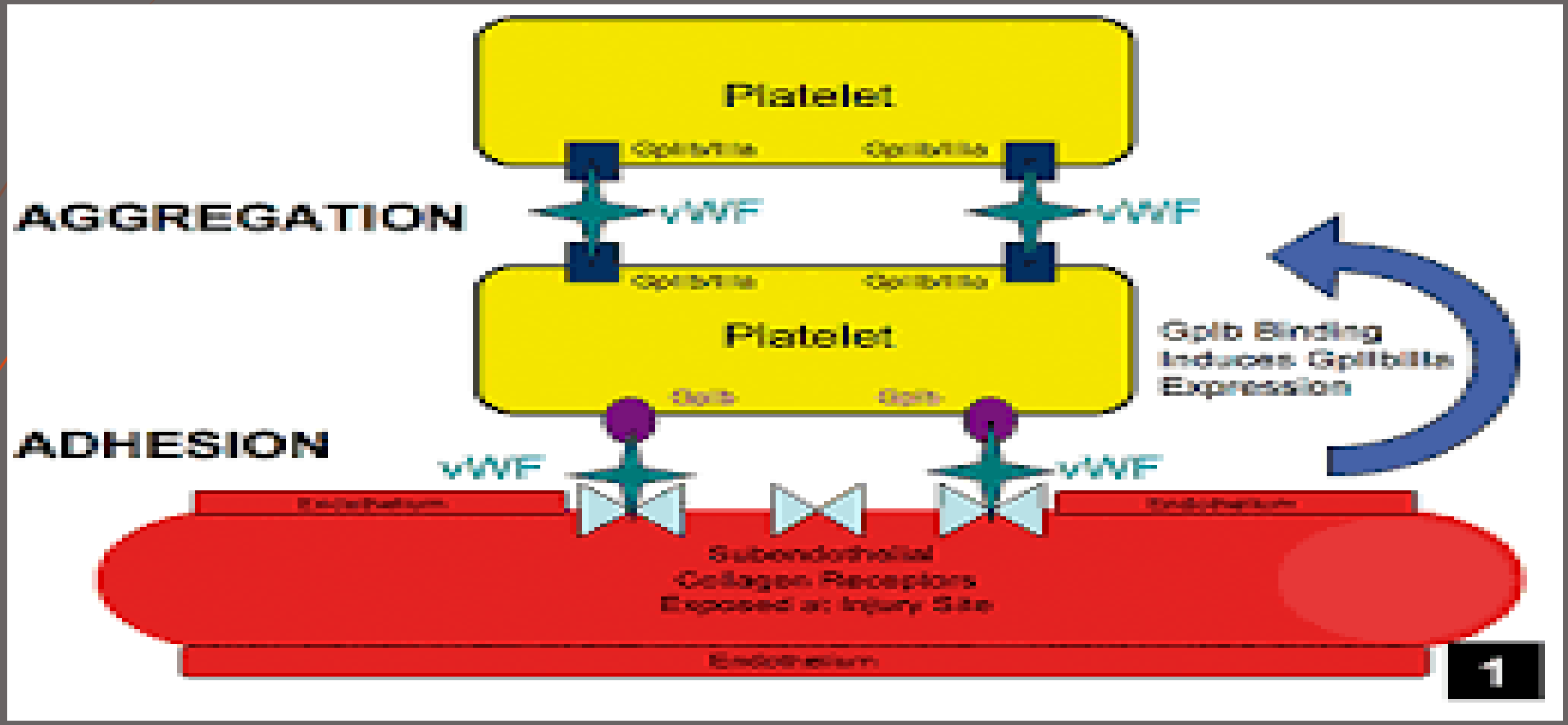
Plasminogen activator inhibitor deficiency

Combined Primary and Secondary Haemostatic Disorders

Disseminated Intravascular Coagulation

Thx: FFP, Cryoprecipitate, Fibrinogen concentrate

Von Willebrand's Disease



Von Willebrand's Disease

	Quantitative deficiency of VWF
Type 1	Partial quantitative deficiency of VWF
Type 3	Virtually complete deficiency of VWF
	Qualitative deficiency of VWF
Type 2	Qualitative deficiency of VWF
Type 2A	Qualitative variants with decreased platelet-dependent function associated with the absence of high and intermediate molecular weight VWF multimers
Type 2B	Qualitative variants with increased affinity for platelet GPIb
Type 2M	Qualitative variants with decreased platelet-dependent function not caused by the absence of high molecular weight VWF multimers
Type 2N	Qualitative variants with markedly decreased affinity for FVIII

Abbreviations: VWF, von Willebrand factor; GPIb, glycoprotein Ib; FVIII, factor VIII.

Von Willebrand's Disease

TYPE

- 1: Mild disease with mild symptom of bleeding tendency
- 3: Severe disease with severe symptom
- 2: Abnormal molecular structure moderate to severe presentation

Von Willebrand's Disease

Therapy

Type 1: DDAVP, concentrate factor (HUMATE-P, Wilate)

Type2: VWF concentrate Or DDAVP

Type 3: VWF concentrate

Von Willebrand's Disease

DDAVP
(Desmopressin)

- Vasopressin analog; stimulates VWF release from endothelium
- Intravenous administration (0.3 mcg/kg); intranasal (Stimate)
- Increased plasma VWF levels for 18-24 hours, enhanced platelet adhesiveness
- Effective in
  - Type I von Willebrand disease
  - Mild hemophilia A (some cases)
  - Other disorders of primary hemostasis (variable efficacy)
  - Reducing surgical blood loss (conflicting data)
- Can give q 24 hours with little tachyphylaxis
- Few side effects in adults (flushing, occasional hyponatremia, rare thromboembolism)

HUMATE-P®
Antihemophilic Factor/von Willebrand Factor Complex (Human)

Omid Reza Zekavat, ozekavat@gmail.com