MUNI
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Venous thrombosis

Normal Hemostasis

- A well regulated process
- Maintains blood in a fluid, clot free state in normal vessels
- Induces the rapid formation of a localized hemostatic plug at the site of vascular injury

Hemostasis

Primary haemostasis:

- Vasoconstriction (immediate)
- Platelet adhesion (within seconds)
- Platelet aggregation and contraction (within minutes)

Secondary haemostasis:

- Activation of coagulation factors (within seconds)
- Formation of fibrin (within minutes)

Fibrinolysis:

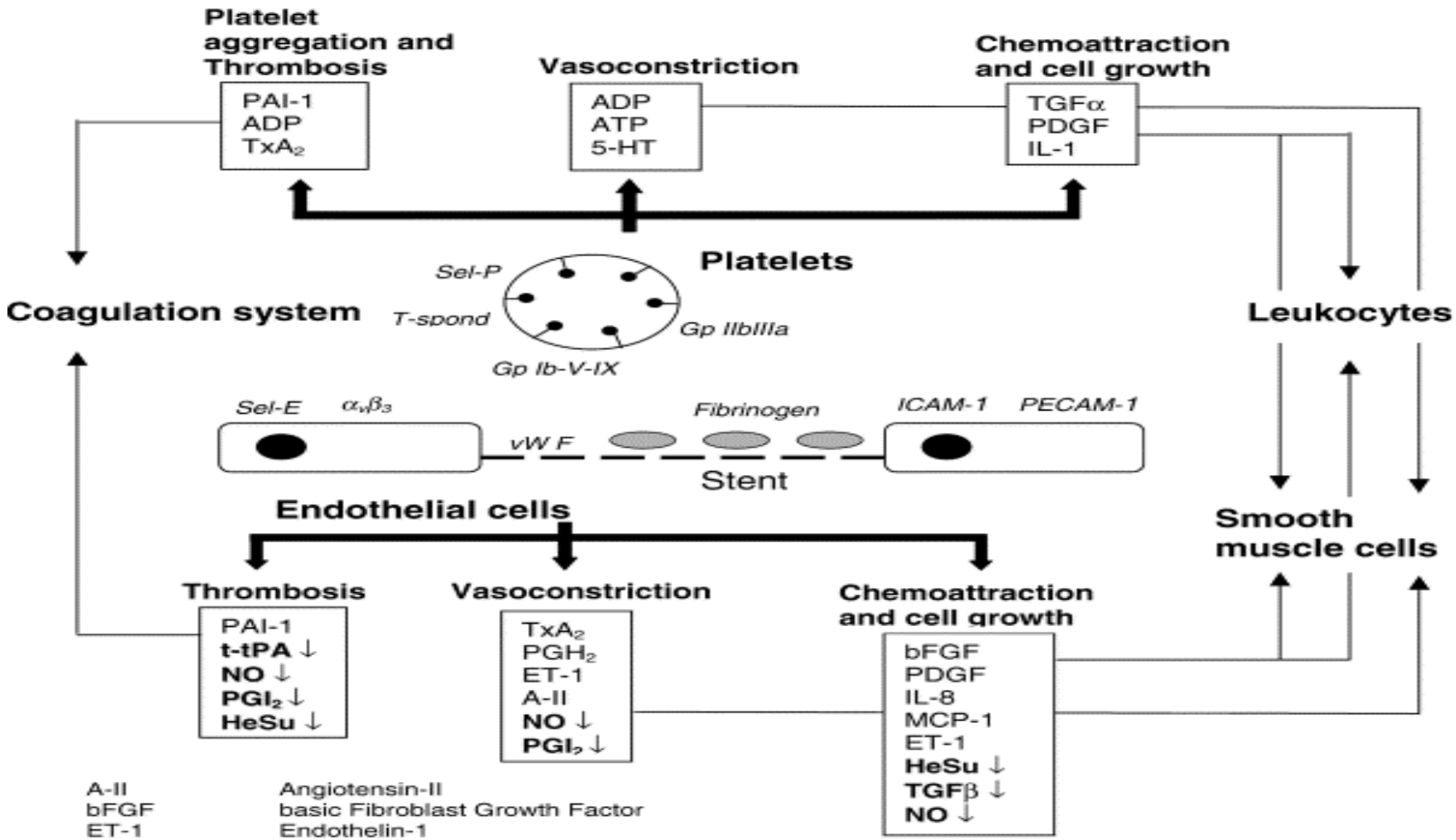
- Activation of fibrinolysis (within minutes)
- Lysis of the plug (within hours)

The Main Players in Hemostasis

- Endothelial cells
- Platelets
- Coagulation cascade

Endothelial Cells

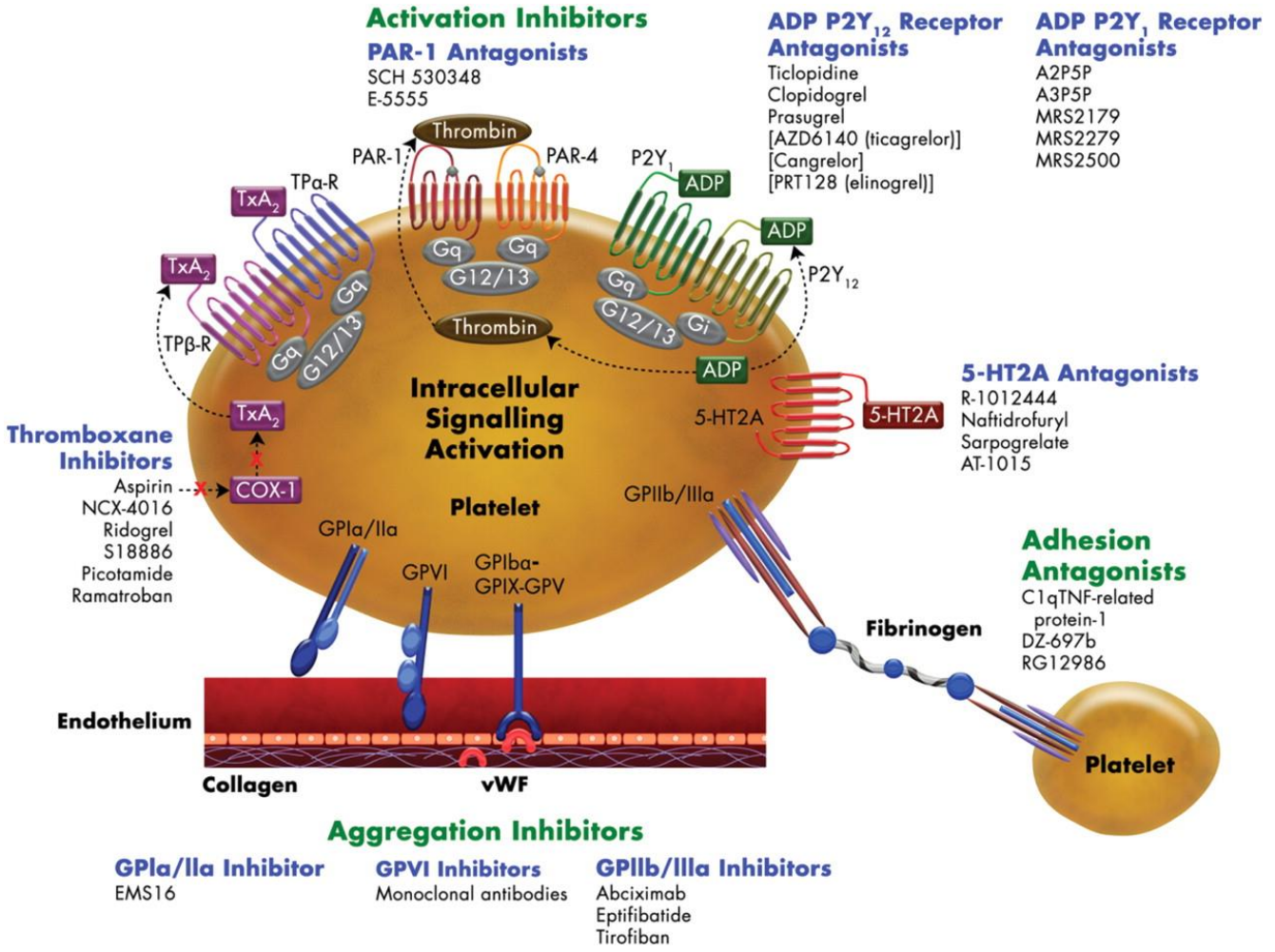
- Produce **vWF** (vonWillebrand factor)
  - A product of normal endothelium
  - found in the plasma in low concentration
  - essential for platelet binding to collagen and other surfaces
- Secrete **Tissue factor**
  - induced by cytokines (TNF, IL-1)
  - activates the ***extrinsic clotting pathway***



A-II	Angiotensin-II
bFGF	basic Fibroblast Growth Factor
ET-1	Endothelin-1
HeSu	Heparansulphates
ICAM-1	InterCellular Adhesion Molecule-1
IL-1 (-8)	Interleukin-1 (-8)
MCP-1	Monocyte Chemoattractant Factor-1
NO	Nitric Oxide
PAI-1	Plasminogen Activator Inhibitor-1
PDGF	Platelet Derived Growth Factor
PECAM-1	Platelet-endothelium Cell Adhesion Molecule-1
PGH_2	Prostaglandin H2
PGI_2	Prostaciclin
Sel-E (-P)	Selectin-E (-P)
TGFα (β)	Transforming Growth Factor α (β)
T-Spond	Thrombospondin
t-tPA	tissue-type Plasminogen Activator
TxA_2	Thromboxan A2
VWF	von Willebrand Factor
5-HT	Serotonin

Platelets

- Express **glycoprotein receptors** on membranes. Gp Ib,IIb/IIIa
- Have three types of granules
  - **Alpha granules**
    - Fibrinogen, fibronectin, factor V and VIII, PDGF, TGFb
  - **Dense bodies or delta granules**
    - ATP/ADP, ionized calcium, histamine, serotonin, epinephrine
  - **Lysosomal granules**



European Heart Journal

Platelets continued

- Upon encountering the ECM, platelets undergo ***three*** general reactions:

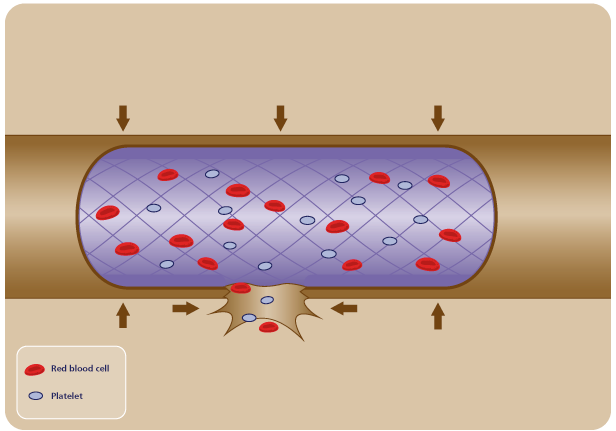
1. **Adhesion and shape change**
   mediated by vWF and glycoprotein Ib
2. **Secretion** (release reaction)
   - calcium required in coagulation cascade
   - ADP as mediator of platelet aggregation
   - Surface expression of phospholipid complex
     - Binding site for calcium ions and coagulation factors

Platelets continued

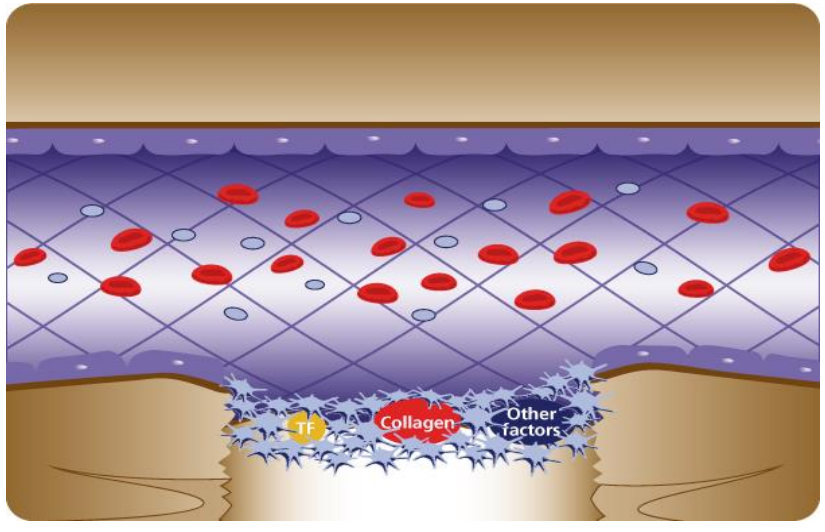
- 3. **Aggregation**
  - ADP and **TXA_2** (*vasoconstrictor thromboxane A_2*) are the stimuli for the formation of the primary hemostatic plug
    - Aspirin inhibits synthesis of TXA_2
  - Fused mass of platelets
    - Created by coagulation cascade that produces **thrombin**
    - Thrombin also converts **fibrinogen** to **fibrin** cementing platelets in place

Normal sequence of Hemostasis
(4 steps)

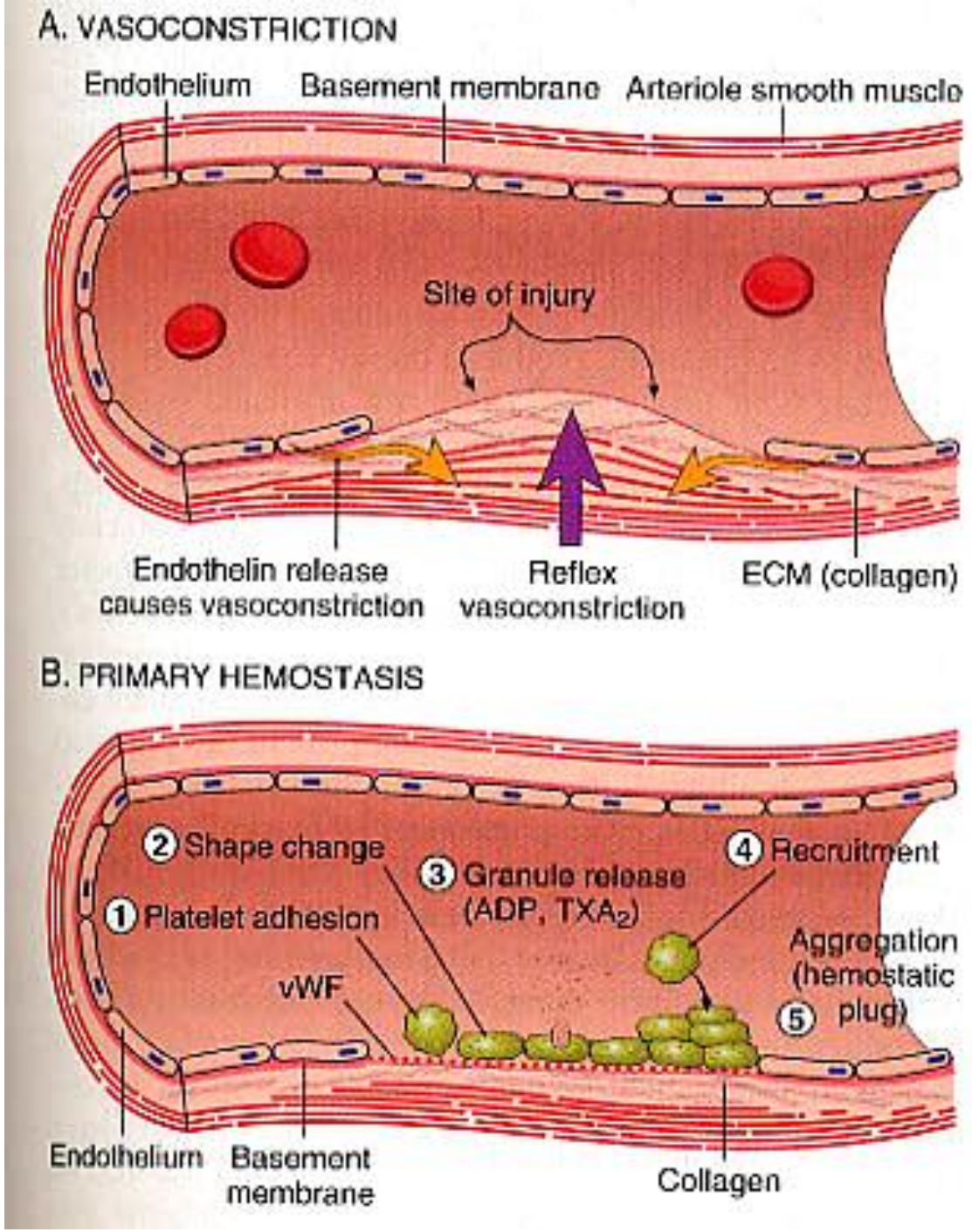
- **1. Arteriolar vasoconstriction (transient)**
  - Reflex neurogenic mechanisms
  - It is important for the activation of platelets or coagulation systems



- **2. Exposure of subendothelial ECM when there is endothelial injury**
  - ECM, especially collagen, is highly ***thrombogenic***
  - Platelets adhere and become activated
    - Change in shape
    - Release of secretory products
  - **<u>Aggregation</u>** of platelets forms **hemostatic plug**
  - **This is primary hemostasis**



First two steps of normal hemostasis



Secondary haemostasis

- Secondary haemostasis involves a series of interactions between coagulation factors which occur on the surface of tissue-factor-bearing cells and activated platelets
- This results in the generation of a thrombin burst and the formation of a haemostatic plug at the site of vascular injury
- Based on the "cell-based model", coagulation occurs in three overlapping phases – initiation, amplification and propagation

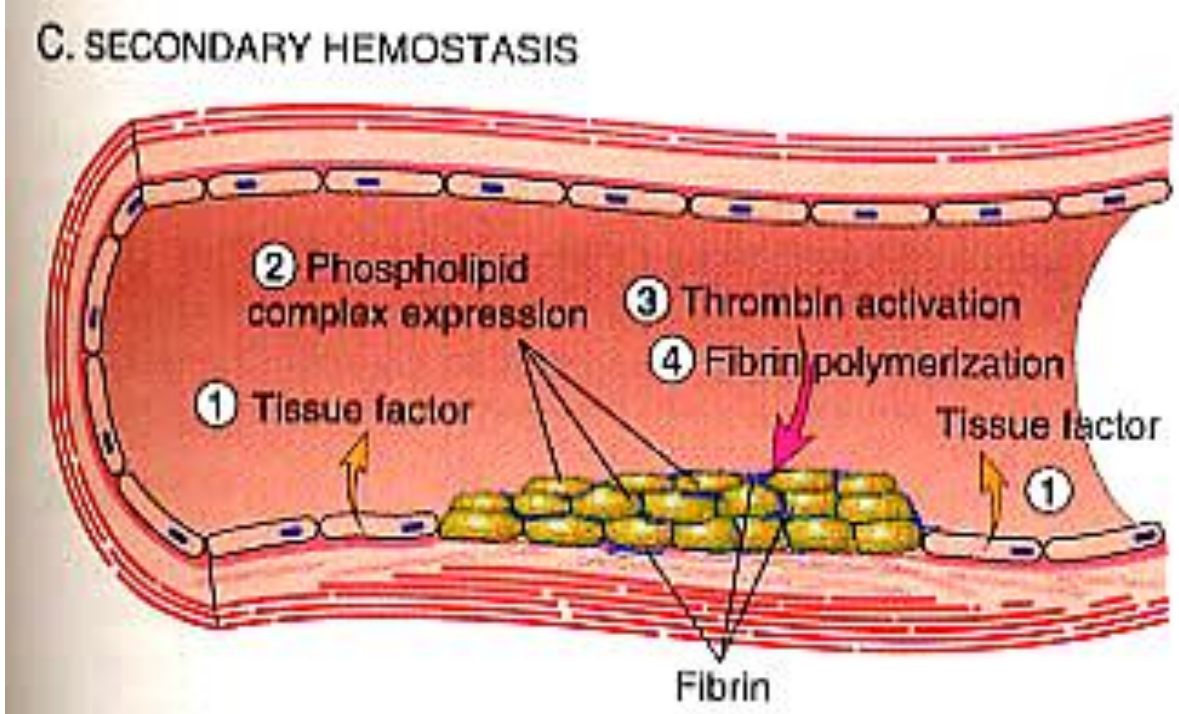
Normal hemostasis continued

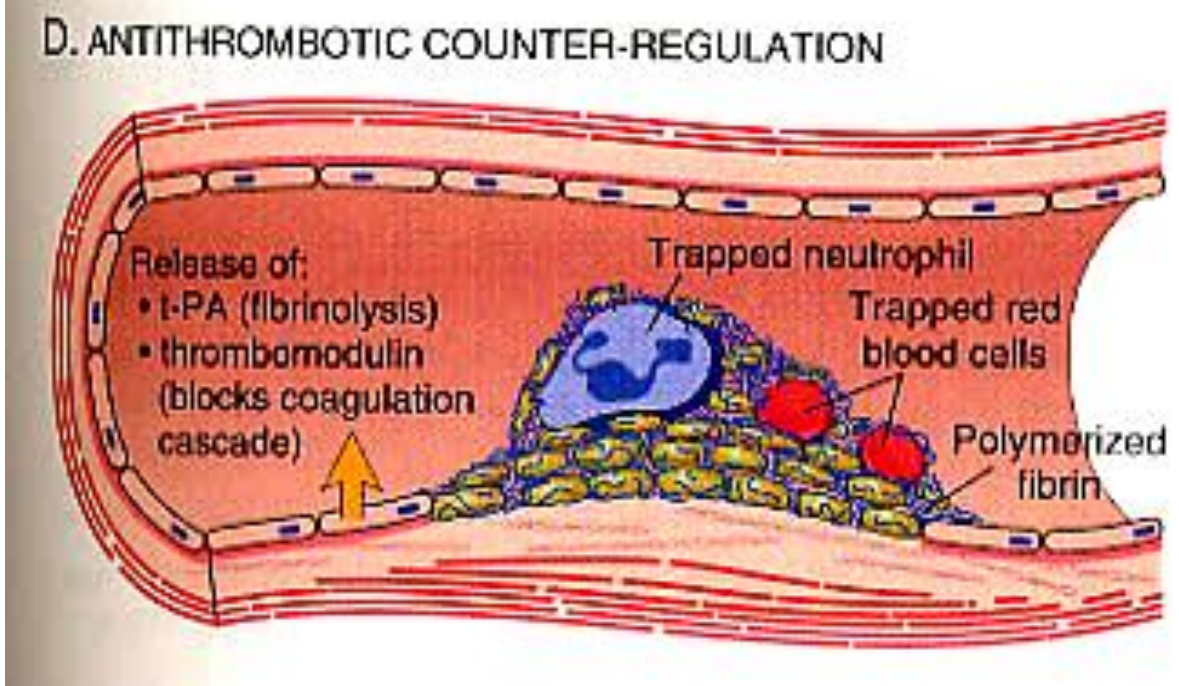
- **3. *Tissue factor* released at the site of injury** (by endothelial cells)
  - Works with secreted platelet factors
  - Activates **coagulation cascade**
    - A series of proteins where **thrombin** is activated
    - Induces further platelet recruitment and granule release
  - Ends in **fibrin deposition**
  - Called **secondary hemostasis**

Normal hemostasis continued

- **4. Formation of permanent plug**
  - Prevents further hemorrhage
  - Polymerized fibrin and platelet aggregation

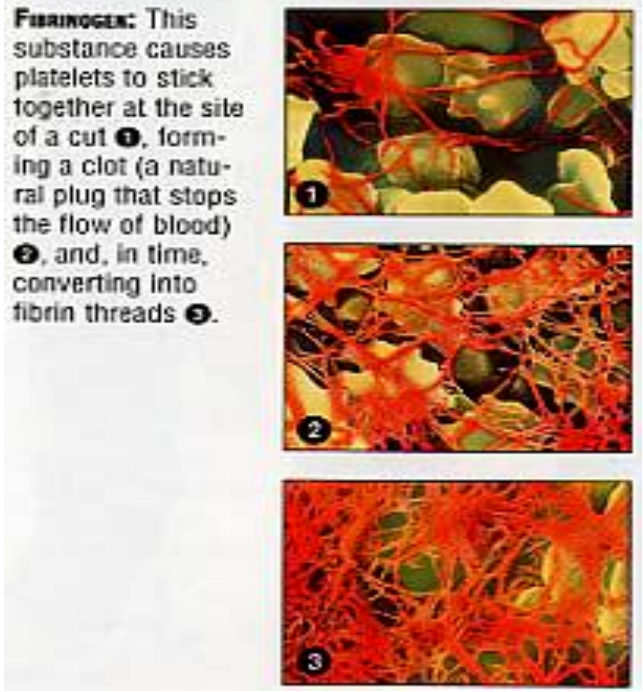
Steps 3 and 4


C. SECONDARY HEMOSTASIS
2 Phospholipid complex expression
3 Thrombin activation
4 Fibrin polymerization
1 Tissue factor
Tissue factor
1
Fibrin


D. ANTITHROMBOTIC COUNTER-REGULATION
Release of:
• t-PA (fibrinolysis)
• thrombomodulin (blocks coagulation cascade)
Trapped neutrophil
Trapped red blood cells
Polymerized fibrin

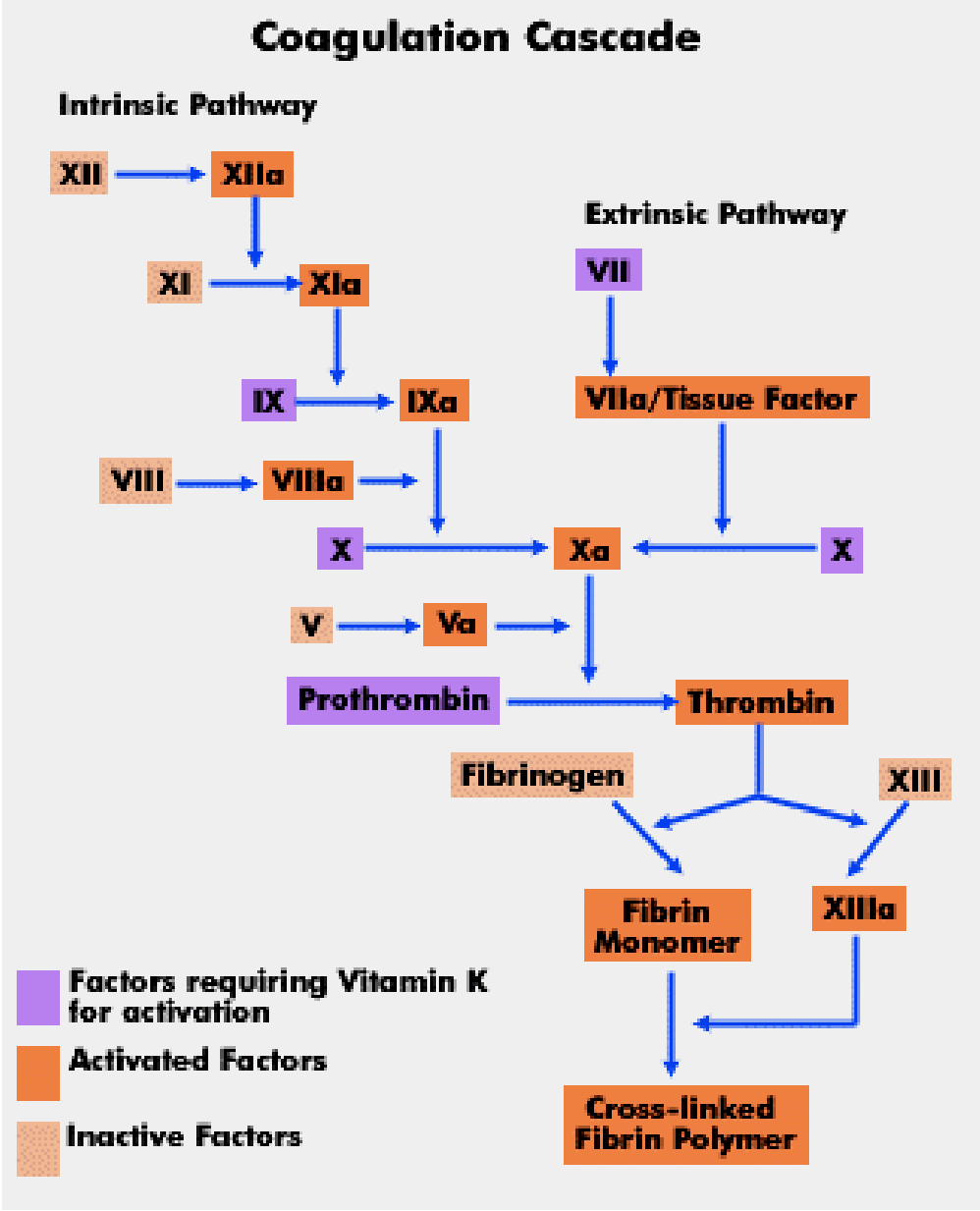
Coagulation Cascade

- A series of conversions of inactive proenzymes to activated enzymes,
  - culminating in the formation of **thrombin**
- Thrombin then coverts the soluble plasma protein **fibrinogen** to insoluble fibrous protein **fibrin**



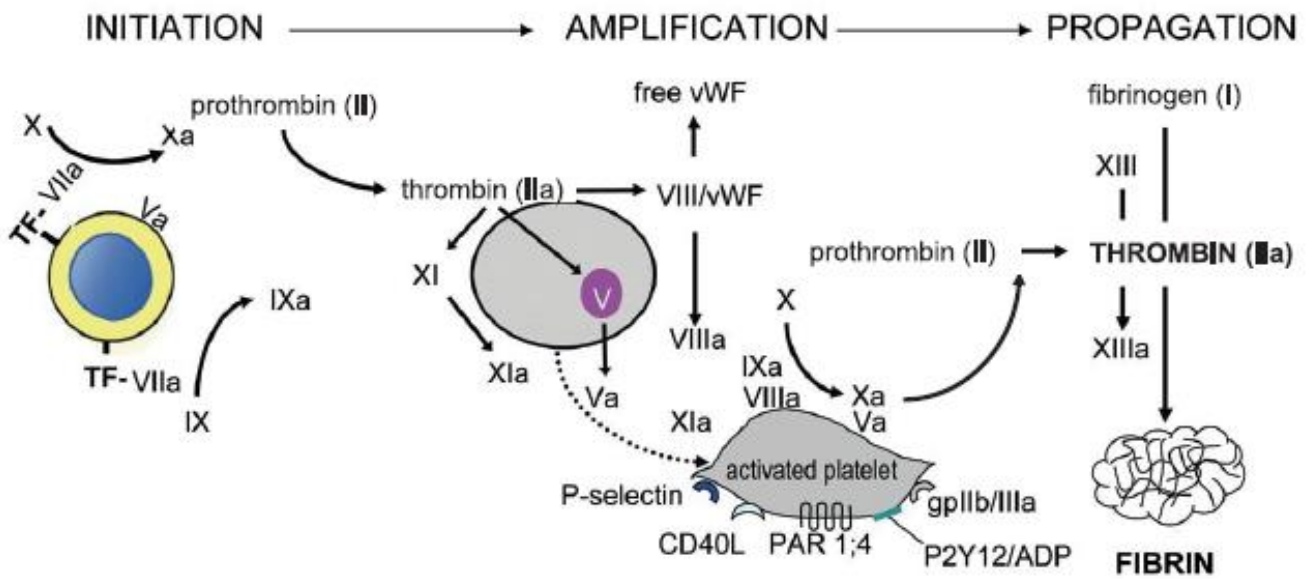
Two pathways of coagulation cascade

- **Intrinsic**
  - Surface contact
- **Extrinsic**
  - Tissue injury



Initiation phase

- Upon vessel wall injury, tissue factor (TF) is exposed to circulating endogenous factor VII/VIIa – leading to the TF/VIIa complex which initiates coagulation
- At the surface of TF-bearing cells the TF/VIIa complex activates:
  - Factor IX to IXa
  - Factor X to Xa
    - Factor Xa binds to factor Va on the cell surface



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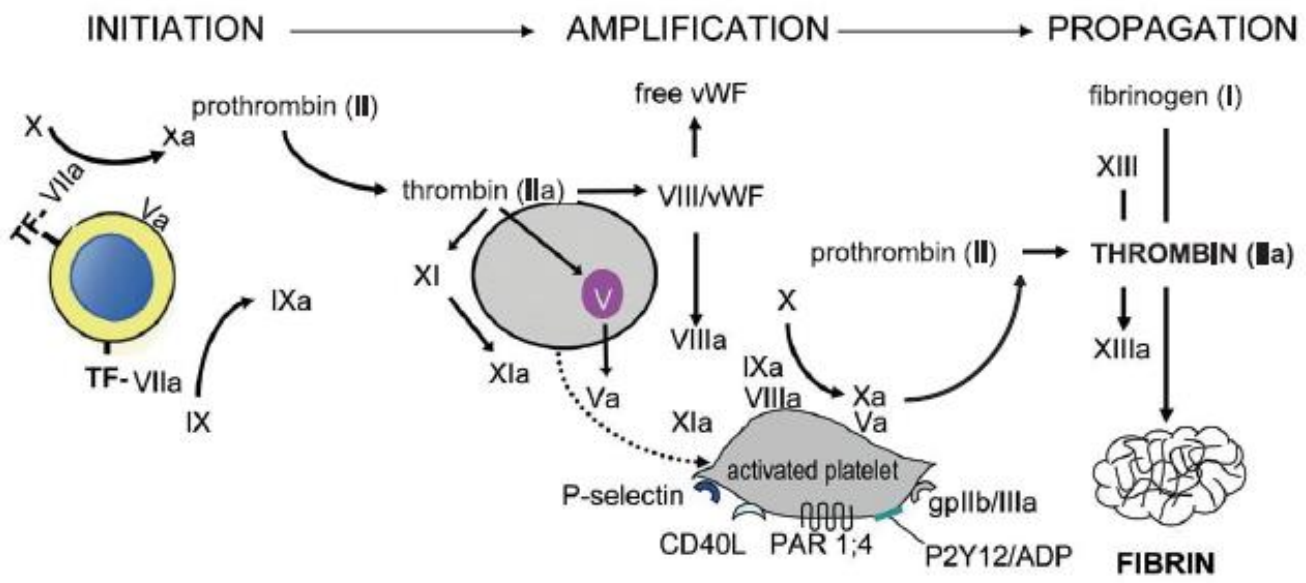
Amplification phase

- The factor Xa/Va complex activates small amounts of prothrombin to thrombin at the surface of subendothelial cells
- This limited amount of thrombin activates factors V, VIII and platelets
- The activated platelet binds factors Va, VIIIa and IXa



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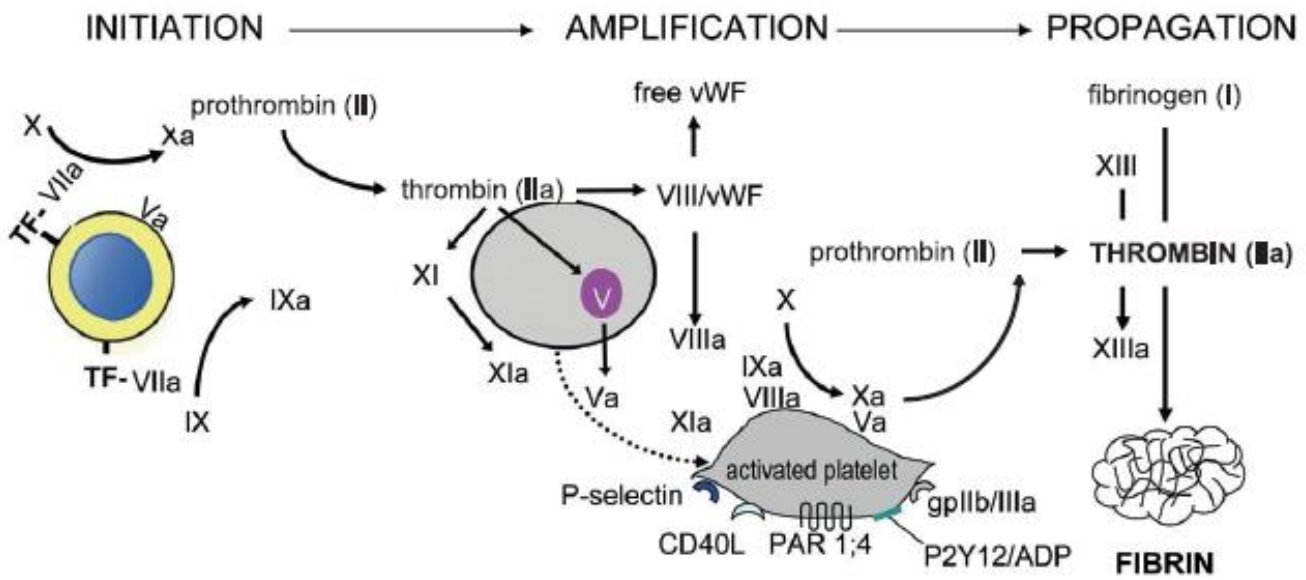
Propagation phase

- Thrombin-activated platelets change shape and expose negatively charged phospholipids to which the factor VIIIa/IXa complex binds
  - This results in factor X activation on the surface of activated platelets
- The factor Xa/Va complex activates large amounts of prothrombin resulting in a "thrombin burst" which:
  - Converts fibrinogen to fibrin
  - Activates fibrin-stabilising factor XIII
- The amount and rate of thrombin generation determines the strength of the haemostatic plug



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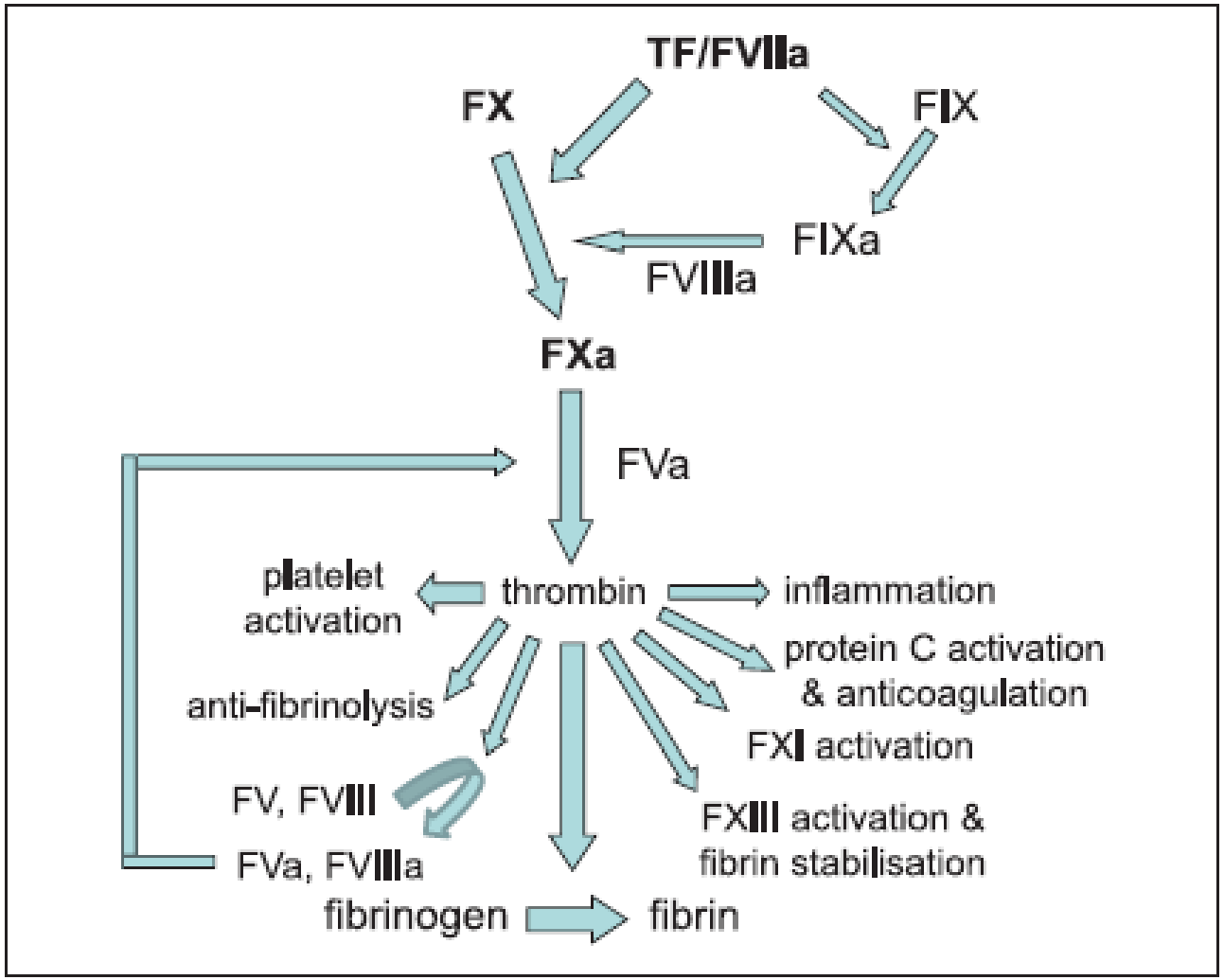
Trombin



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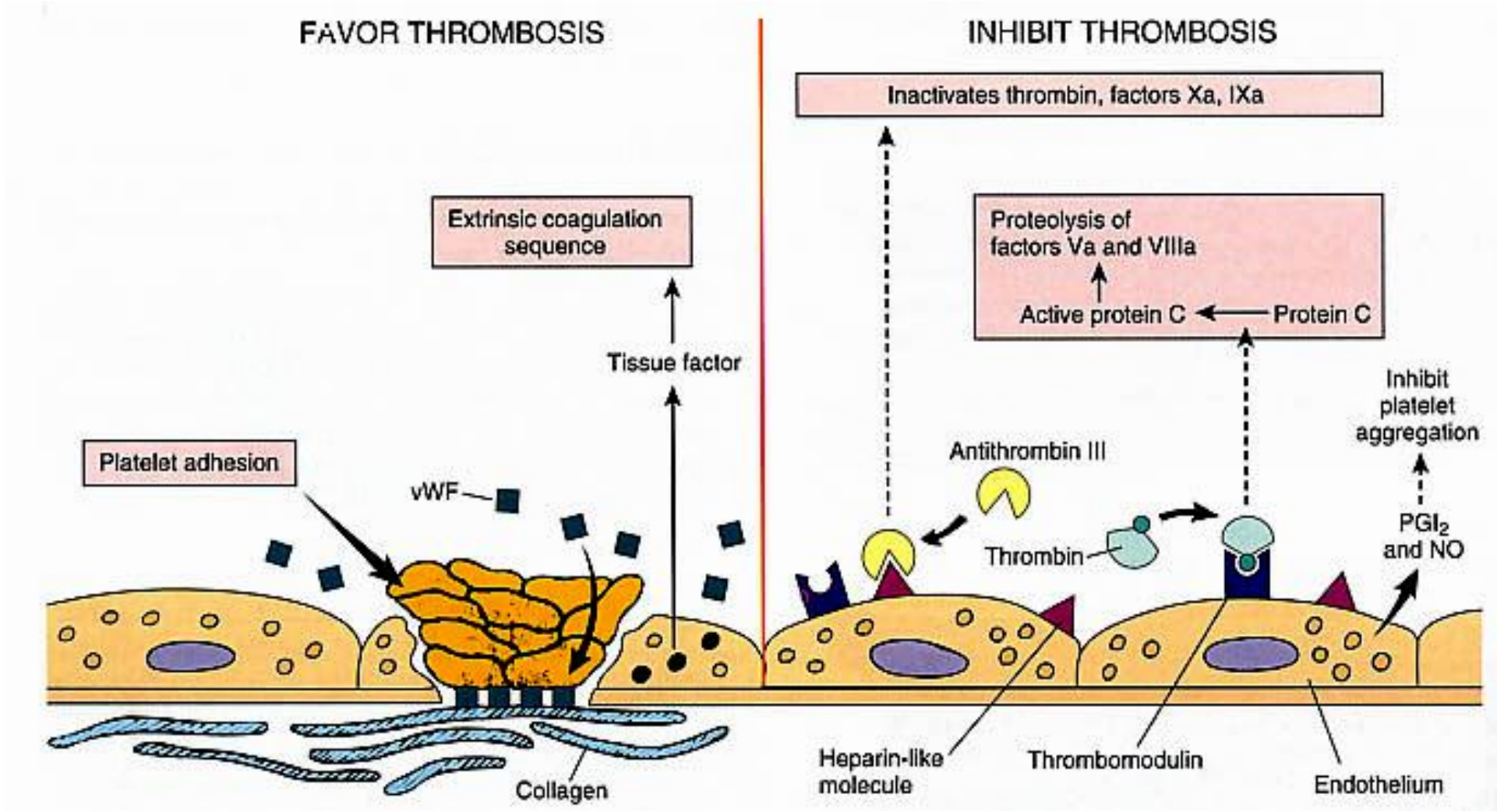
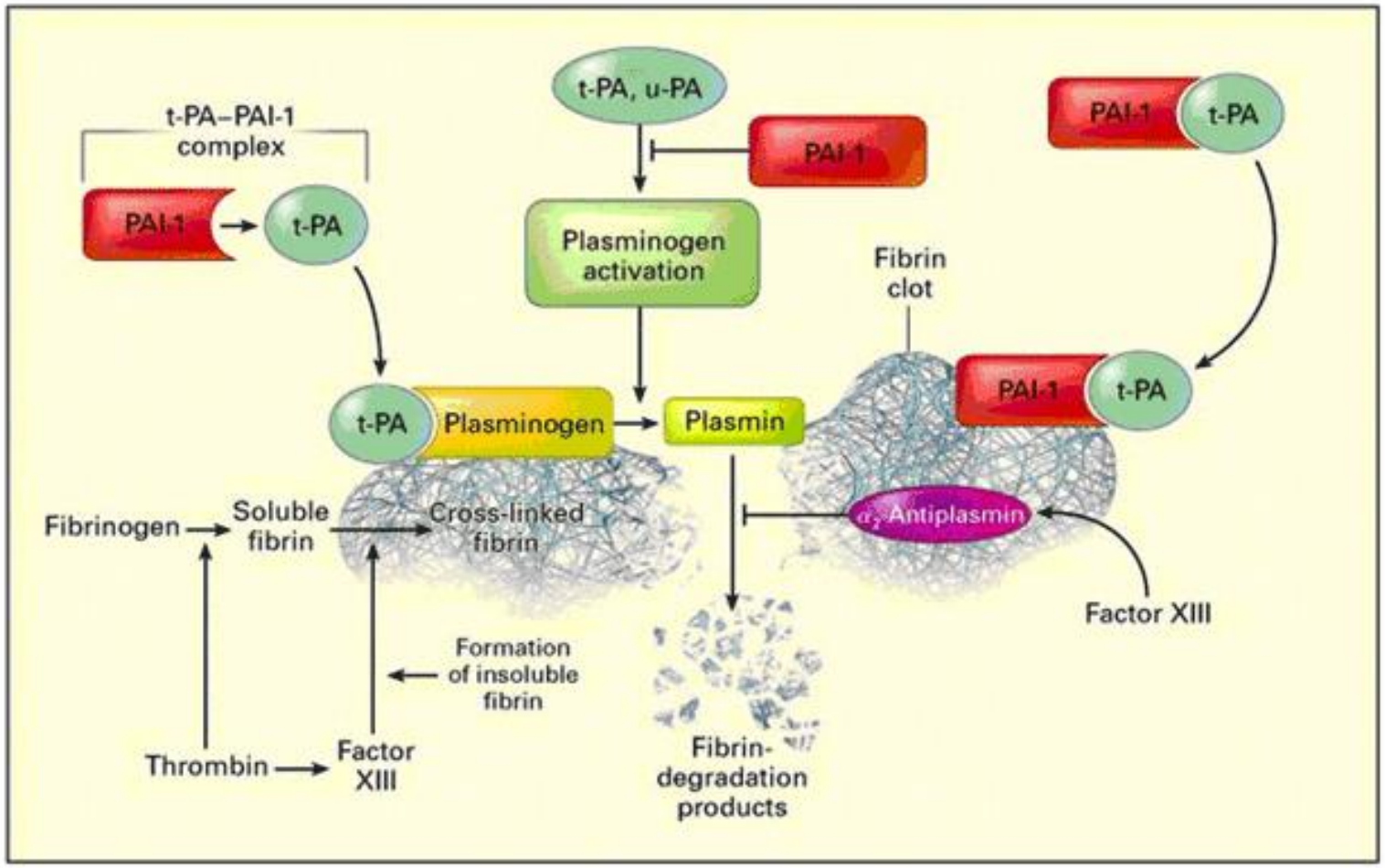
Control of cascade to prevent clotting elsewhere

- **Antithrombins**
  - activated by *heparin like* molecules on endothelial cells
    - Clinical administration of heparin minimizes thrombosis
- **Proteins C and S**
  - Vitamin K dependent
  - Inactivate cofactors Va and VIIIa
- **Plasminogen-plasmin system**
  - Breaks down fibrin and inhibits its polymerization
  - Products of split fibrin are anticoagulants

Factors that favor or inhibit thrombosis



Fibrinolytic system



Conditions Causing Bleeding

- Incomplete hemostasis is most common cause of bleeding.
- Vitamin K deficiency
  - severe coagulation defect
  - Required for synthesis of prothrombin and factors VII, IX and X
- Parenchymal diseases of the liver
  - Liver synthesizes several coagulation factors

Signs and Symptoms of 1º Hemostasis Problems

- Ecchymoses
- Petechiae
- Mucus membrane bleeding
- Hematoma
- Prolonged bleeding after minor surgery

Hereditary Vascular Problems

- Hereditary (spider) telangiectasis (Osler-Rendu-Weber): dilated superficial capillaries
- Ehlers-Danlos: collagen disorder
- Marfan syndrome: connective tissue
- Osteogenesis imperfecta

Acquired Vascular Problems

- Senile purpura (Bateman's): altered connective tissue support
- Cushing syndrome: metabolic
- Scurvy: abnormal collagen
- Allergy: vascular inflammation
- Viral infection

Quantitative Platelet Disorders

- Thrombocytopenia

<100,000/ml	BT prolonged
≈10,000	Bleeding in trauma or OR
<10,000	Spontaneous, CNS bleeding

- Thrombocytopenia due to destruction
  - ITP (acute in children, chronic in young women) with anti-glycoprotein
  - Drug reaction
  - Heparin induced thrombocytopenia
  - DIC and TTP

About Thrombotic Thrombocytopeneic Purpura (TTP)

- Disorder of systemic platelet aggregation in microvasculature
- Stimulus: unusually large vWf
- In children: likely to be deficiency in vWf metalloproteinase to break down vWf
- In adults: vWf metalloproteinase inhibited by autoantibodies
- Low PLT count, intravascular hemolysis, RBC fragmentation, high LDH

Quantitative Platelet Disorders

- Thrombocytopenia due to decreased production
  - Aplastic anemia (e.g., Fanconi's)
  - Fibrosis
  - Acute leukemia
  - Megaloblastic anemia
  - Hereditary (e.g., May-Hegglin, Wiscott-Aldrich, Bernard-Soulier)
- Splenic sequestration
- HELLP syndrome (hemolysis, elevated liver enzyme, low PLT) in pre-eclampsia
- Dilution (massive transfusion)

Quantitative Platelet Disorders

- Thrombocytosis
  - Primary with dysfunctions (e.g., CML, ET)
  - Post splenectomy: also see HJ, etc.
  - Hemolytic anemia
  - Acute hemorrhage and surgery

Hereditary deficiencies

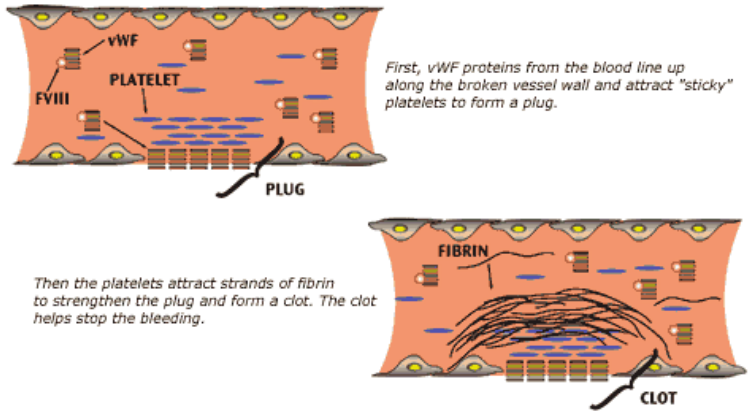
- **Hemophilia A--factor VIII deficiency**
  - Sex-linked recessive
  - 30% due to new mutations and don't have family link
  - Infuse patient with factor VIII from human blood or cryoprecipitate.
- **Hemophilia B--factor IX deficiency**
  - Clinically indistinguishable from Hemophilia A
  - Sex-linked recessive

Von Willebrand's Disease

Von Willebrand's Disease- Most common congenital bleeding disorder.

- Types I, II, and III.
- PT normal PTT normal or elevated
- Prolonged bleeding time
- **Type I** most common (70%)
- **Type III** causes most bleeding

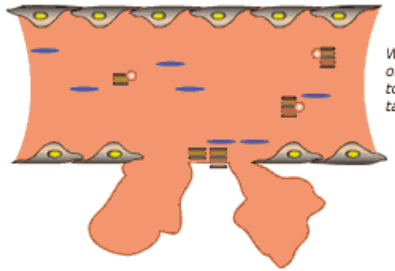
Figure 1. Normal Broken Blood Vessel



First, vWF proteins from the blood line up along the broken vessel wall and attract "sticky" platelets to form a plug.

Then the platelets attract strands of fibrin to strengthen the plug and form a clot. The clot helps stop the bleeding.

Figure 2. Broken Blood Vessel in vWD

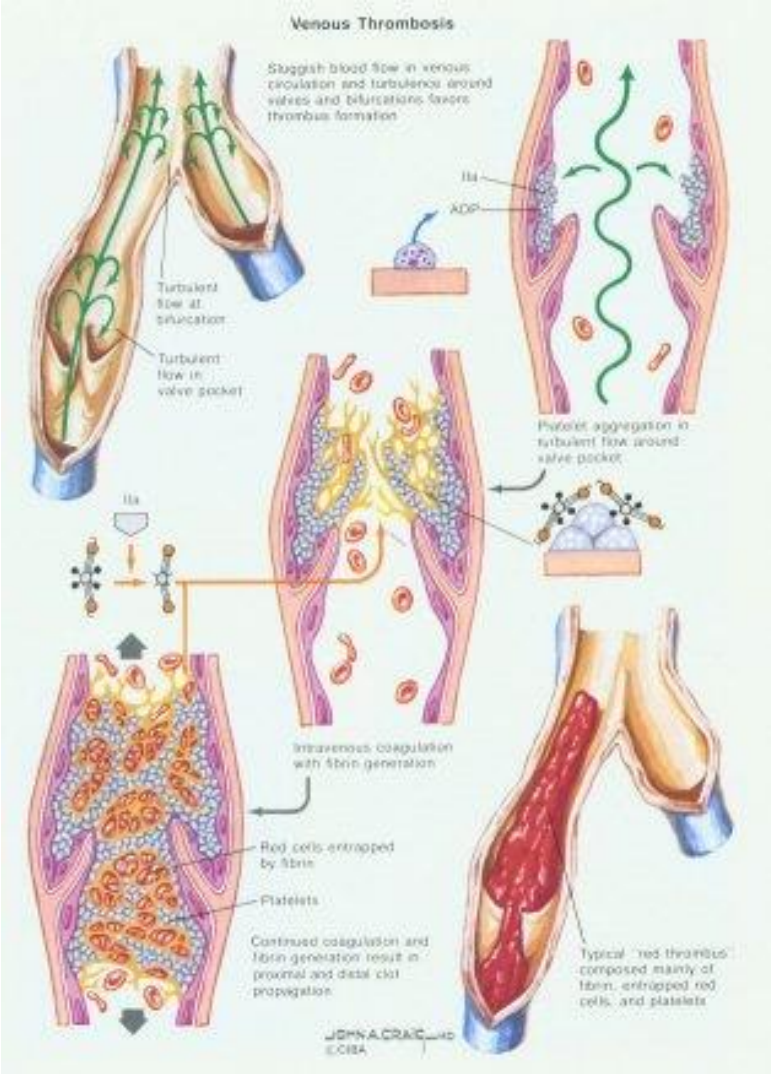


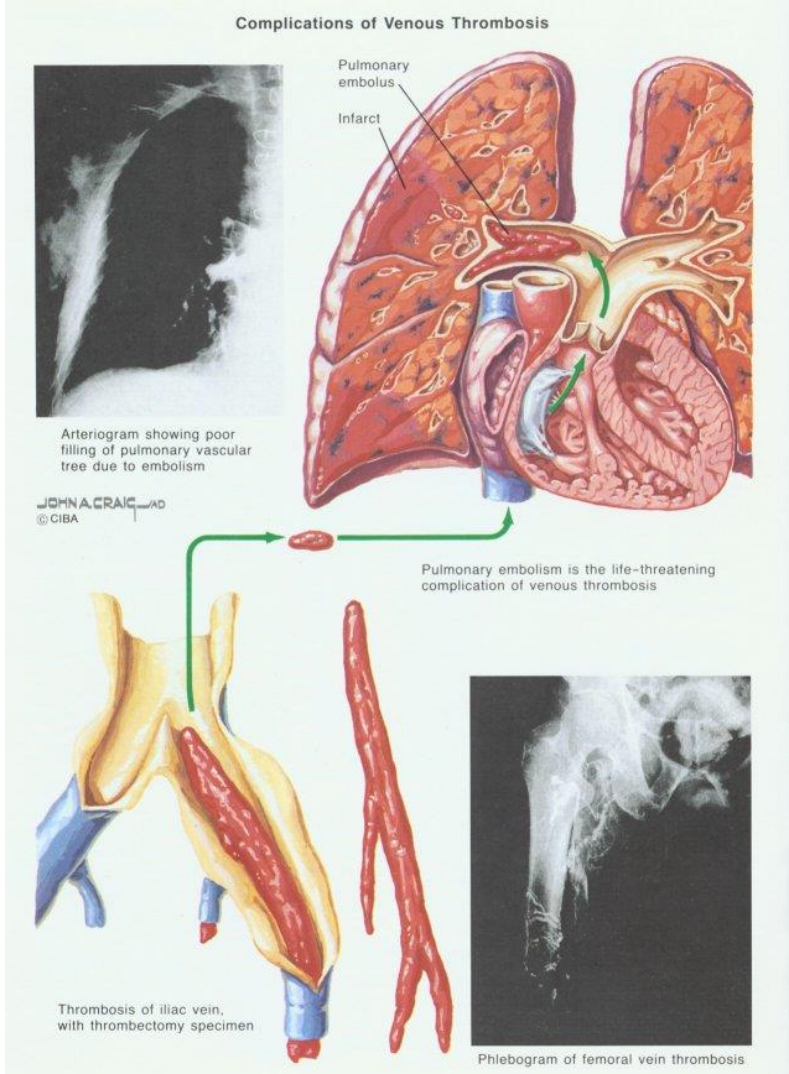
When a person has vWD, there isn't enough vWF or the vWF is damaged. The clot may take longer to form or not form properly, and bleeding make take longer to stop.

Thrombosis

- Pathological state
- Inappropriate activation of the normal hemostatic process
  - within the non-interrupted vascular system.
- Thrombus (blood clots) formation
  - Blocks blood flow to vital areas

DVT


Venous Thrombosis
Sluggish blood flow in venous circulation and turbulence around valves and bifurcations favors thrombus formation
IIa
ADP
Turbulent flow at bifurcation
Turbulent flow in valve pocket
Platelet aggregation in turbulent flow around valve pocket
IIa
Intravenous coagulation with fibrin generation
Red cells entrapped by fibrin
Platelets
Continued coagulation and fibrin generation result in proximal and distal clot propagation
Typical "red thrombus" composed mainly of fibrin, entrapped red cells, and platelets
JOHN A. CRAIG, MD
©CIBA


Complications of Venous Thrombosis
Pulmonary embolus
Infarct
Arteriogram showing poor filling of pulmonary vascular tree due to embolism
JOHN A. CRAIG, MD
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Pulmonary embolism is the life-threatening complication of venous thrombosis
Thrombosis of iliac vein, with thrombectomy specimen
Phlebogram of femoral vein thrombosis

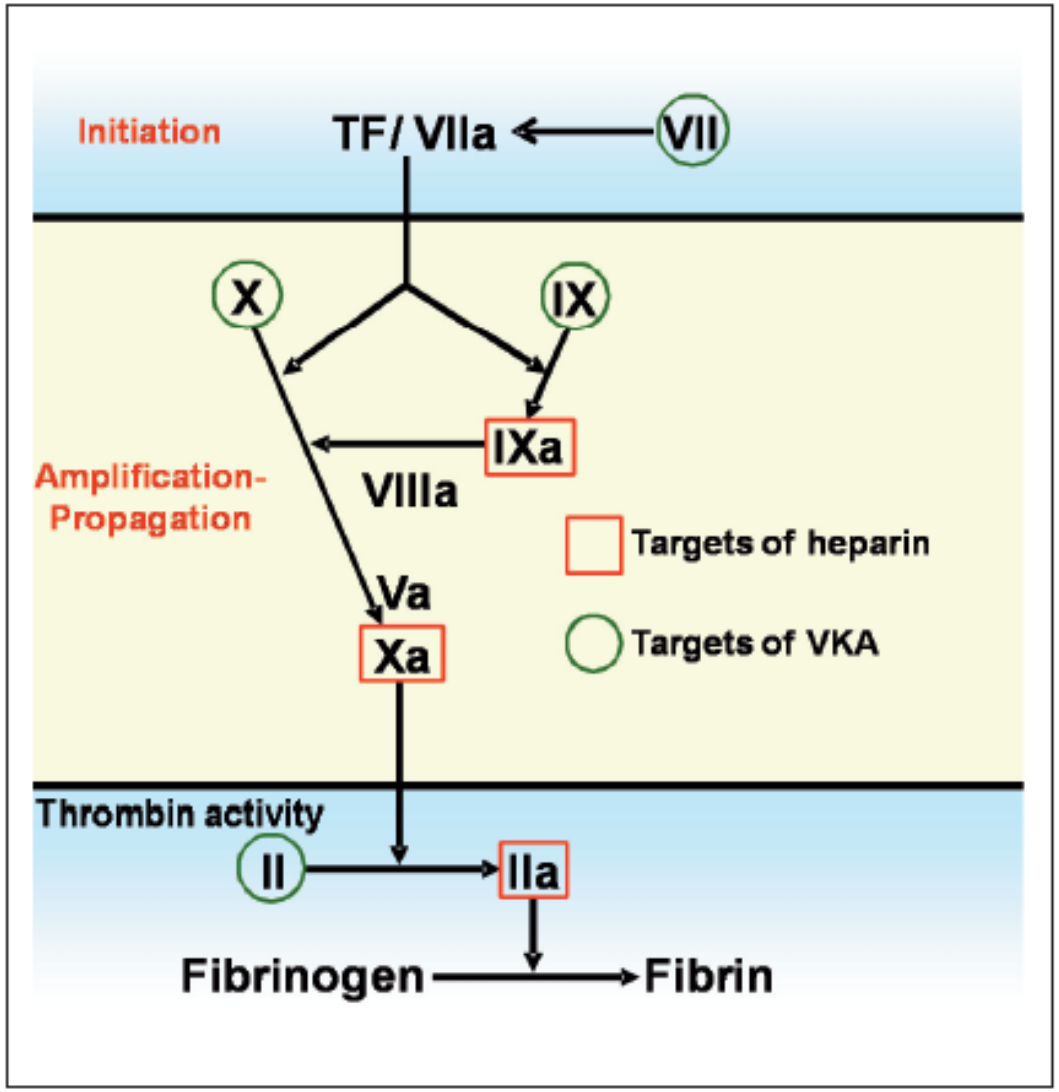
Hypercoagulability

- **Leiden Factor**- 30% spontaneous venous thrombosis.
- Most common congenital disorder.
- Resistance to Protein C, defect on factor V
- TX: heparin, warfarin.
- **Protein C, S deficiency**-5% venous thromboses. TX: heparin, warfarin.

Hypercoagulability

- **Antithrombin III** deficiency- 2-3% thrombosis. Heparin doesn’t work. Can develop after previous heparin exposure.

Heparin vs. Warfarin



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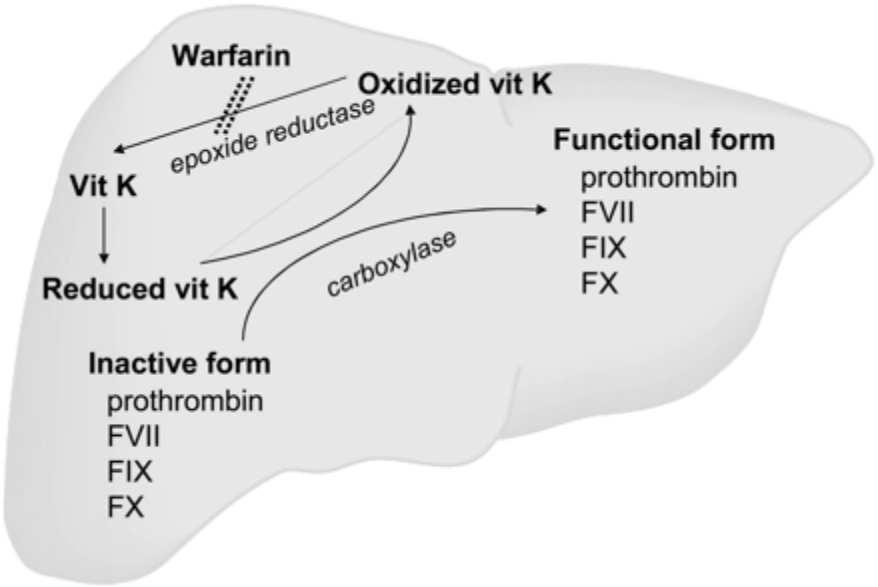
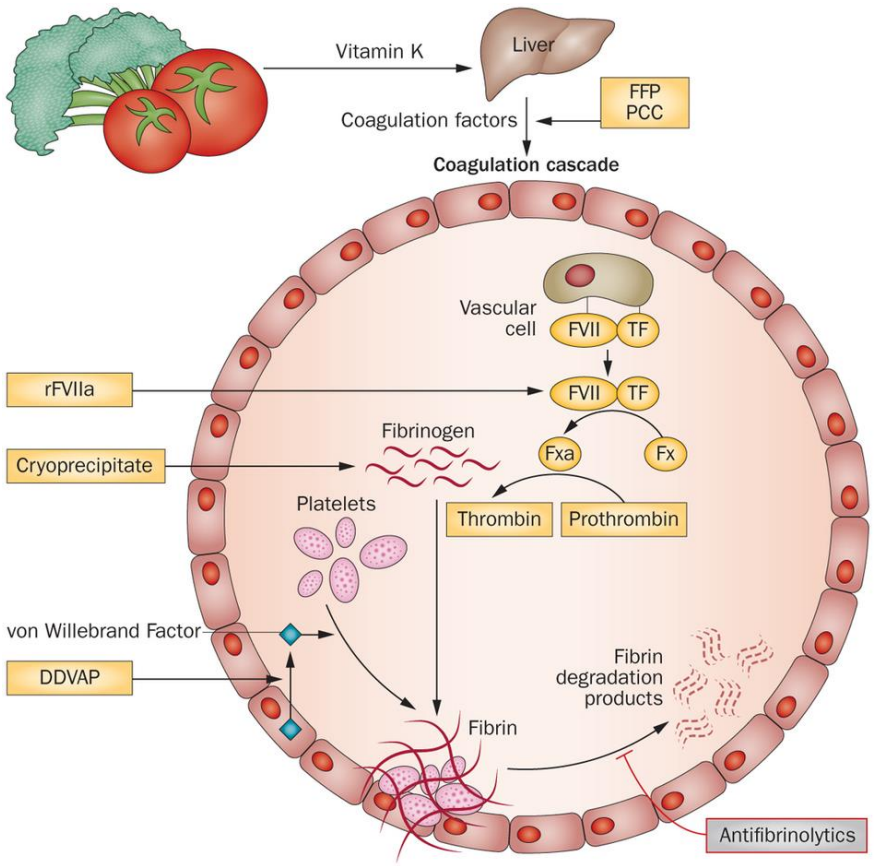
Warfarin activity



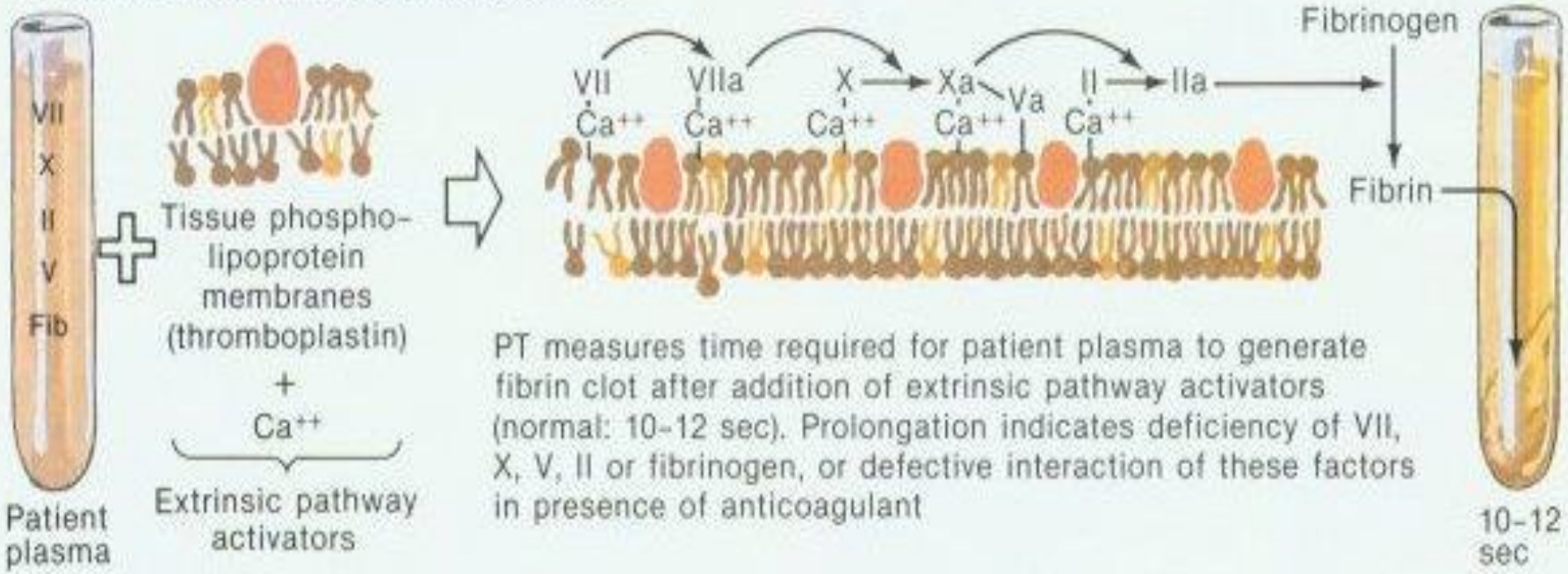
D-dimers


Vitamin K
Liver
FFP
PCC
Coagulation factors
Coagulation cascade
Vascular cell
FVII
TF
rFVIIa
FVII
TF
Fibrinogen
Cryoprecipitate
Fxa
Fx
Platelets
Thrombin
Prothrombin
von Willebrand Factor
DDVAP
Fibrin degradation products
Fibrin
Antifibrinolytics

Hemocoagulative examination

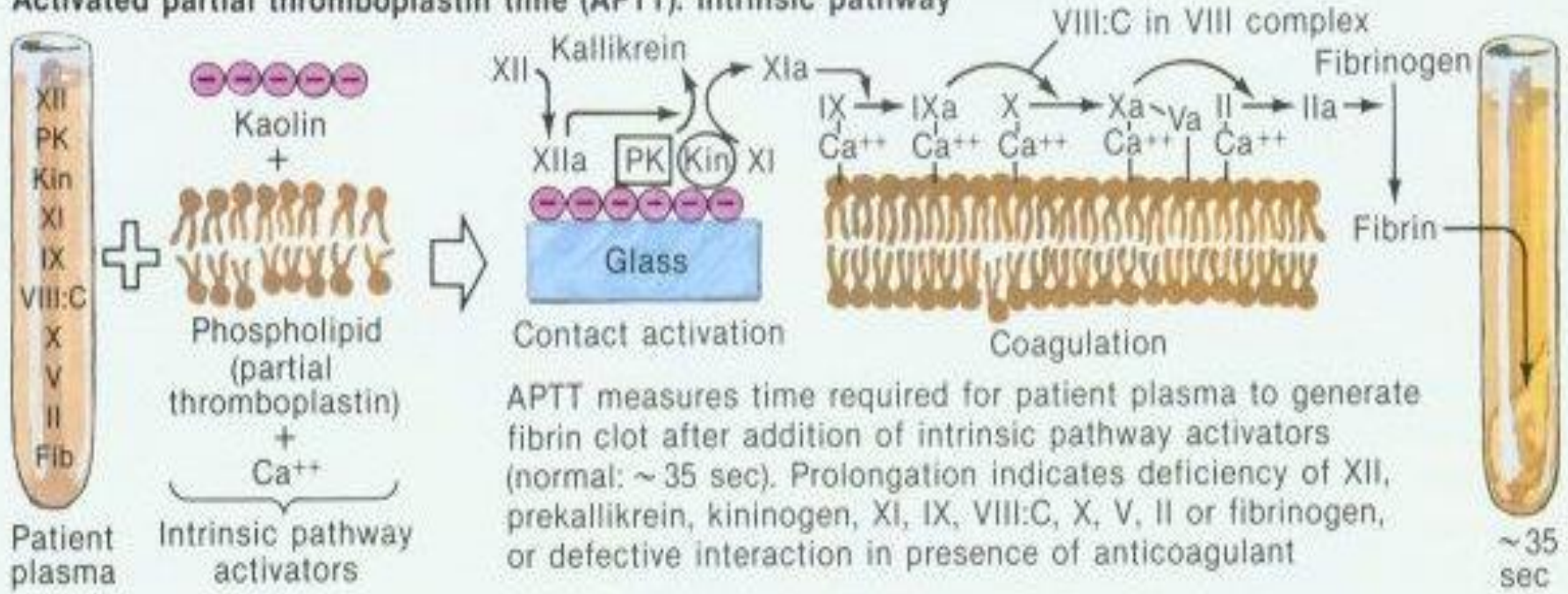
- aPTT = activate partial thromboplastin time
  - The partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT or APTT) is a performance indicator measuring the efficacy of both the "intrinsic" (now referred to as the contact activation pathway) and the common coagulation pathways.
  - Apart from detecting abnormalities in blood clotting, it is also used to monitor the treatment effects with heparin, a major anticoagulant.

Prothrombin time (PT): extrinsic pathway



PT measures time required for patient plasma to generate fibrin clot after addition of extrinsic pathway activators (normal: 10-12 sec). Prolongation indicates deficiency of VII, X, V, II or fibrinogen, or defective interaction of these factors in presence of anticoagulant

Activated partial thromboplastin time (APTT): intrinsic pathway



APTT measures time required for patient plasma to generate fibrin clot after addition of intrinsic pathway activators (normal: ~35 sec). Prolongation indicates deficiency of XII, prekallikrein, kininogen, XI, IX, VIII:C, X, V, II or fibrinogen, or defective interaction in presence of anticoagulant