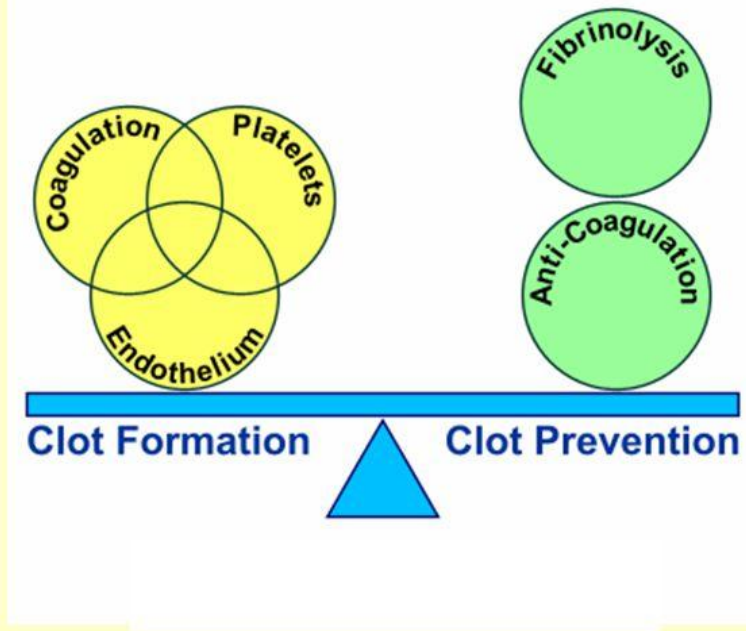
Introduction to Bleeding Disorders

HK

Objectives

- Physiology of hemostasis
- Hemostasis :Process of clot formation
- Classification of bleeding disorders
- Clinical approach to bleeding disorders
  - Case study -1 (hereditary bleeding disorder)
  - Case study -2 (acquired bleeding disorder)
- Interpretation of coagulation tests (?)



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Bleeding tendency = hemophilia = hypo-coagulable state

Thrombosis tendency = thrombophilia = hypercoagulable state

Blood is the essence of vitality; it must remain in constant motion to sustain every part of the body.
When blood ceases to flow,
life ends.

Interrelated process

- **STOP (natural anticoagulants)**
- **START (endothelium + platelets)**

  Platelet plug
- **MAKE (coagulation cascade)**

  Fibrin clot
- **STOP (natural anticoagulants)**
- **CLEAN (fibrin-o-lysis)**

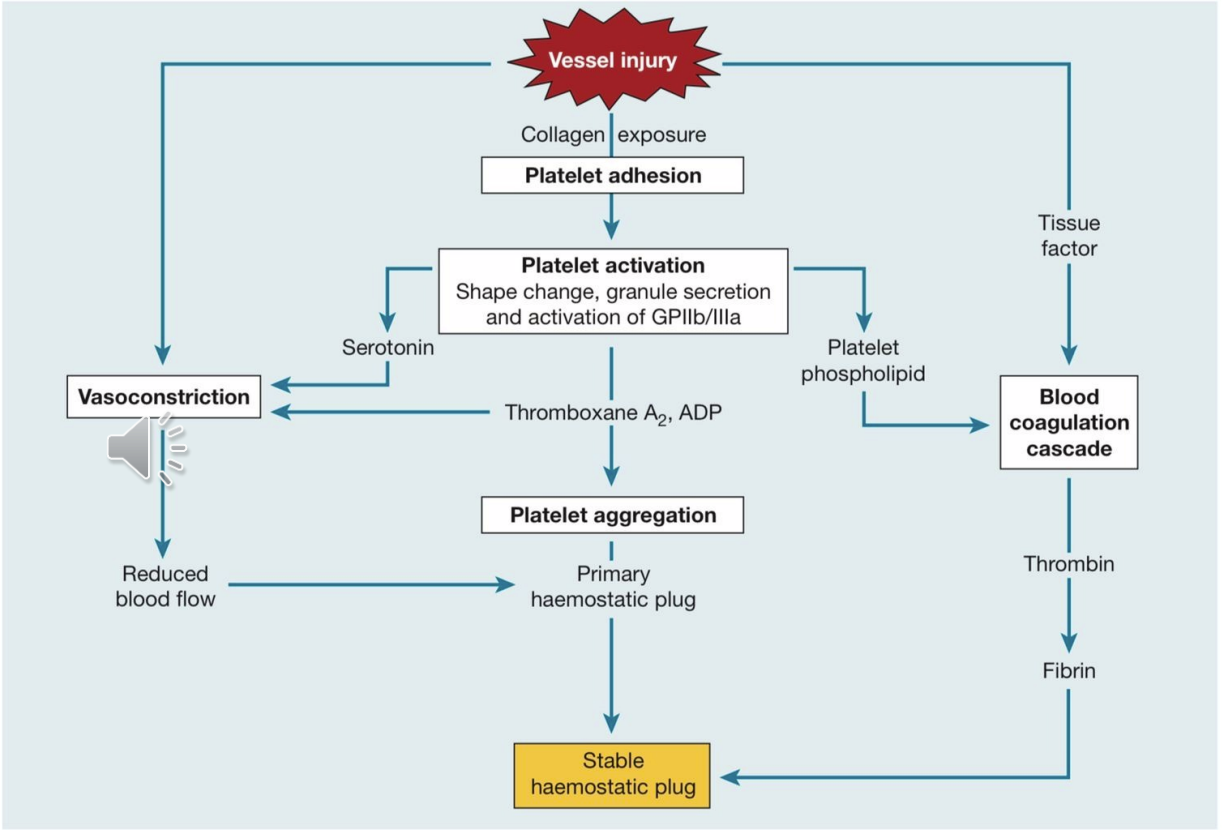


Figure 24.1 The involvement of blood vessels, platelets and blood coagulation in haemostasis. ADP, adenosine diphosphate.

Hemostasis is a process

- **START (endothelium + platelets)**

  Platelet plug

- **MAKE (coagulation cascade)**

  Fibrin clot

- **STOP (natural anticoagulants)**

- **CLEAN (fibrin-o-lysis)**

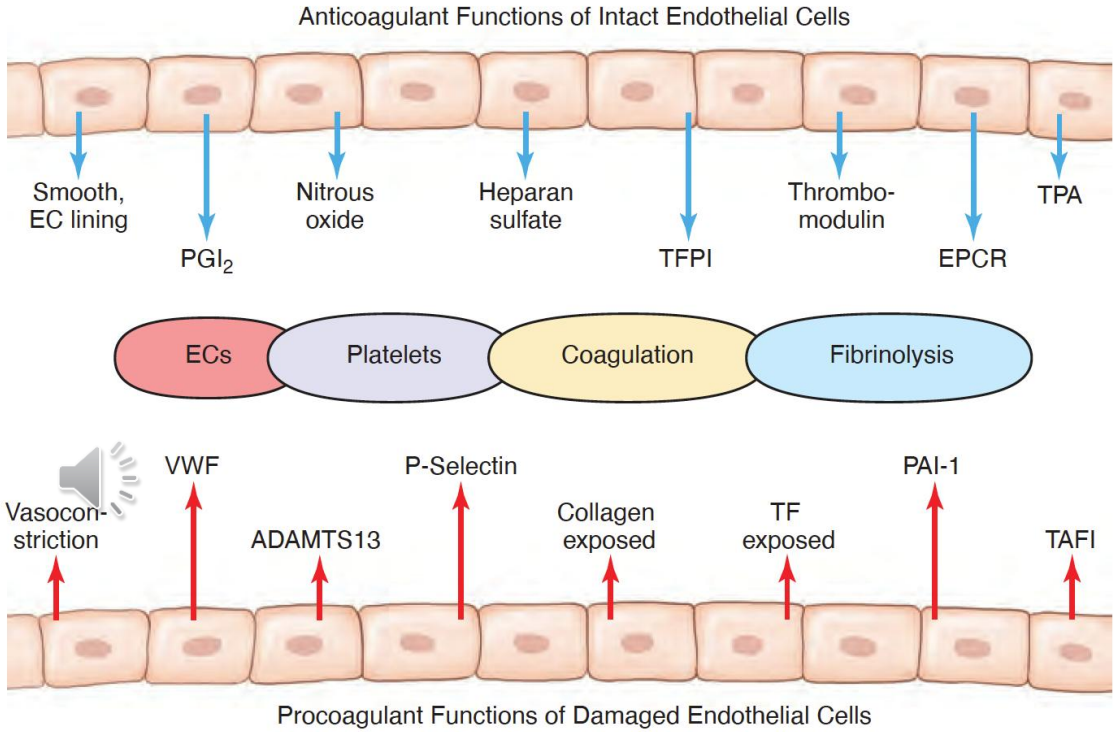


Figure 35.1 Hemostatic Properties of Endothelial Cells that Line the Inner Surface of All Blood Vessels. Depicted in this cartoon are the anticoagulant properties associated with normal intact endothelial cells and the procoagulant properties associated with damaged endothelial cells as they relate to the functions of the hemostatic system listed in the center. *ADAMTS13,* A disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13; *ECs,* endothelial cells; *EPCR,* endothelial cell protein C receptor; *PAI-1,* plasminogen activator inhibitor-1; *PGI_2,* prostacyclin or prostaglandin I_2; *TAFI,* thrombin activatable fibrinolysis inhibitor; *TF,* tissue factor; *TFPI,* tissue factor pathway inhibitor; *TPA,* tissue plasminogen activator; *VWF,* von Willebrand factor.

START

Endothelial injury→ release of TF , Collagen

Vascular muscle contraction

Platelet's activations→

Adhesion (vWF,Collagen)

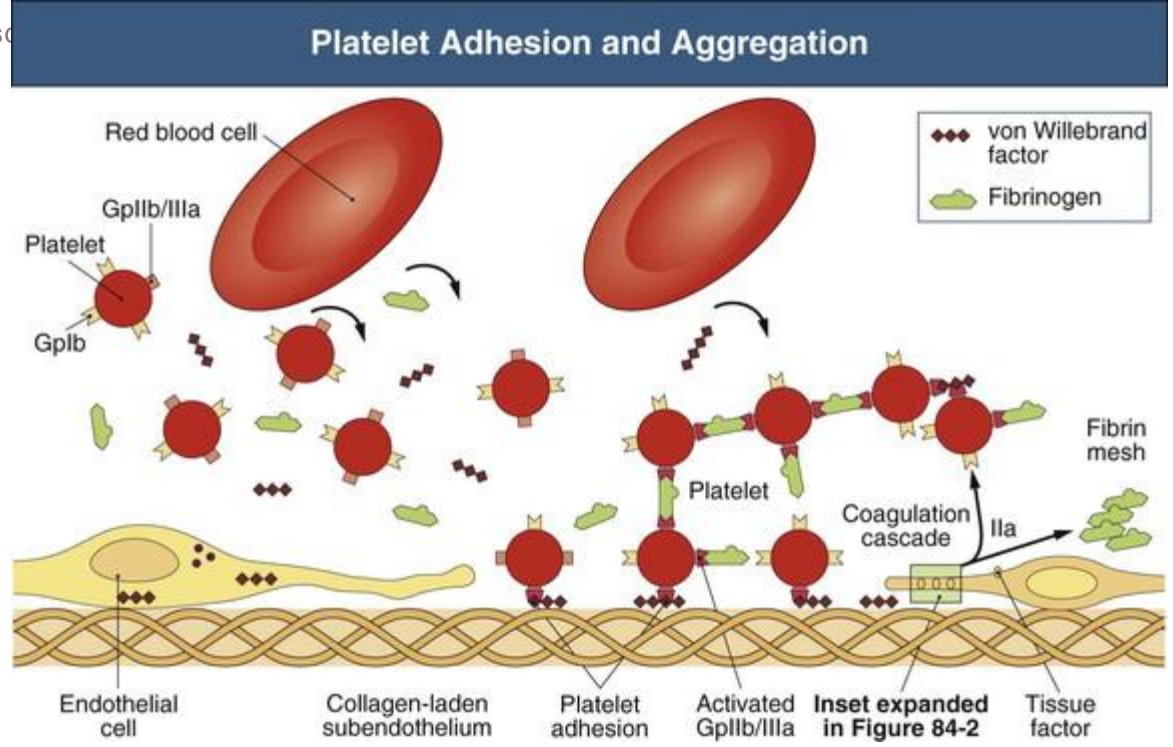
Aggregation (Fibrinogen)

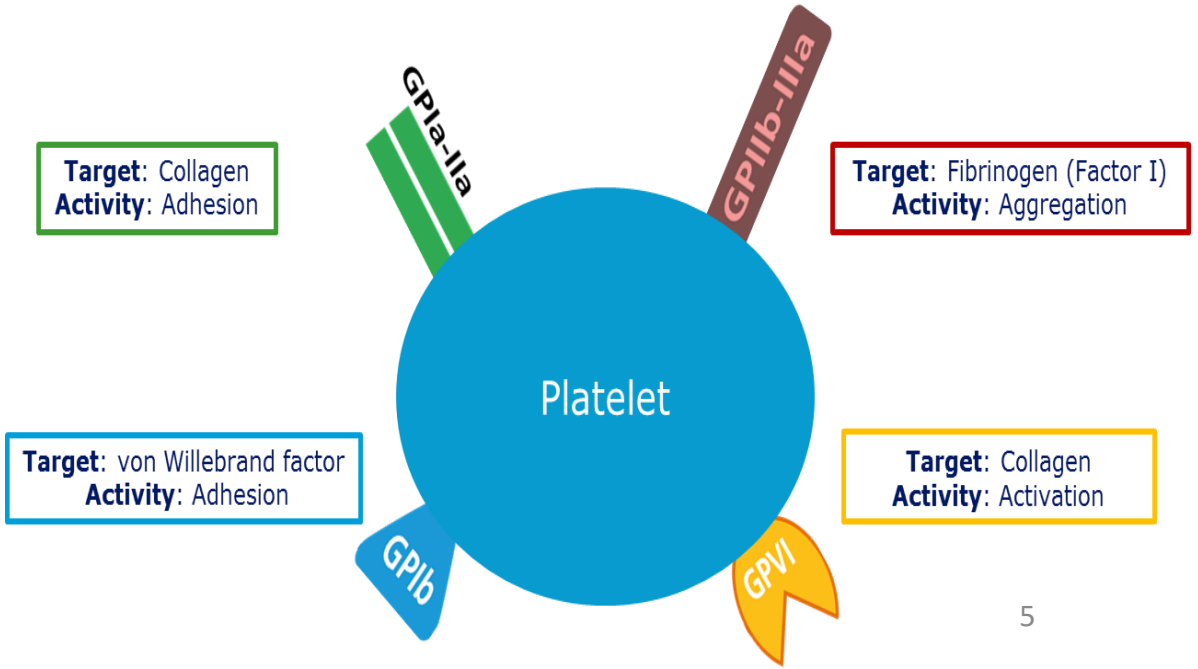
Secretion (Ca++, ADP, serotonin, etc) + PL

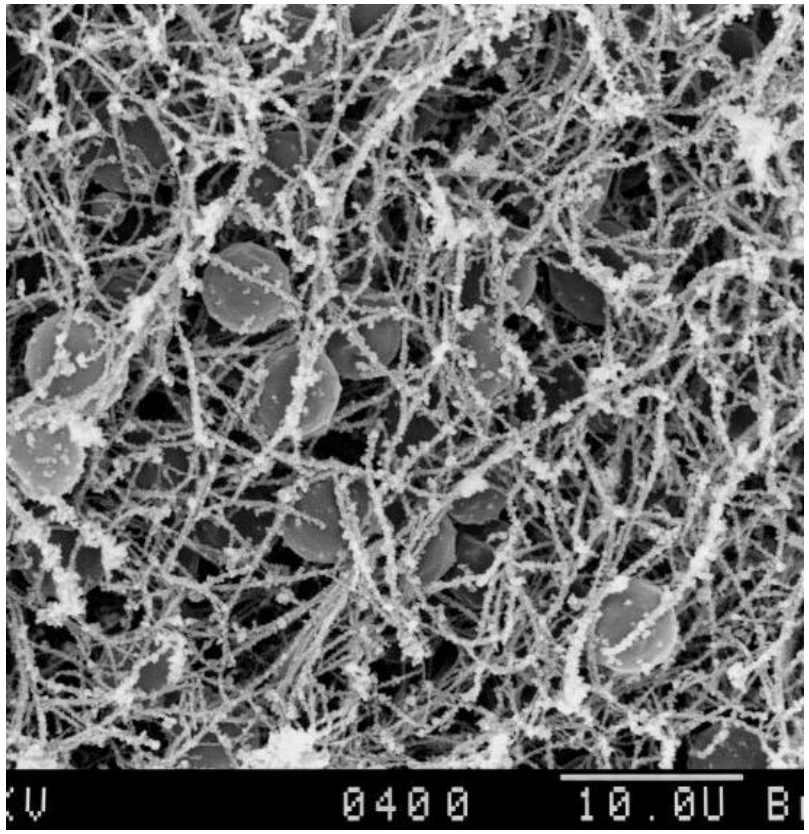
Set the stage for the Make (ing) of the clot

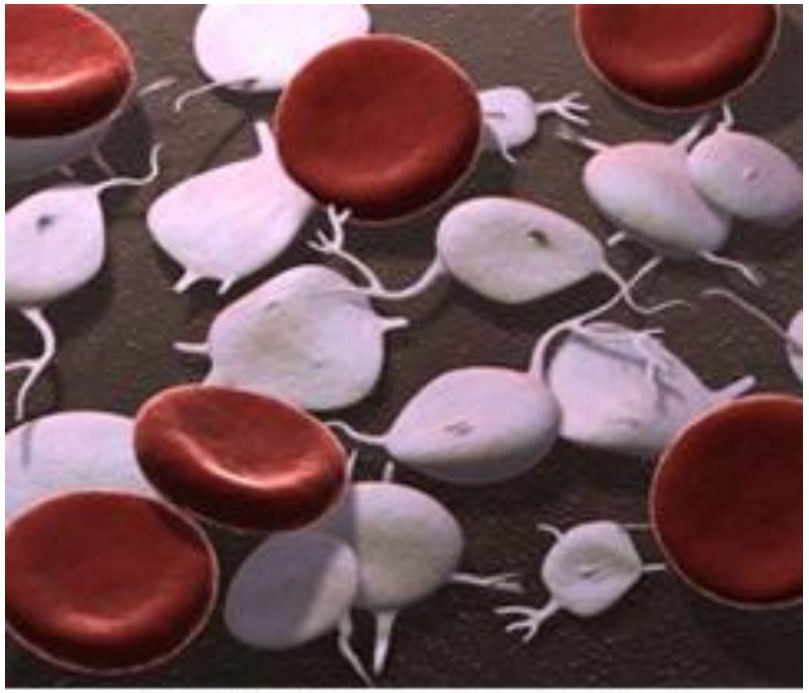
III = Tissue factor = thromboplastin

PL= Phospholipid







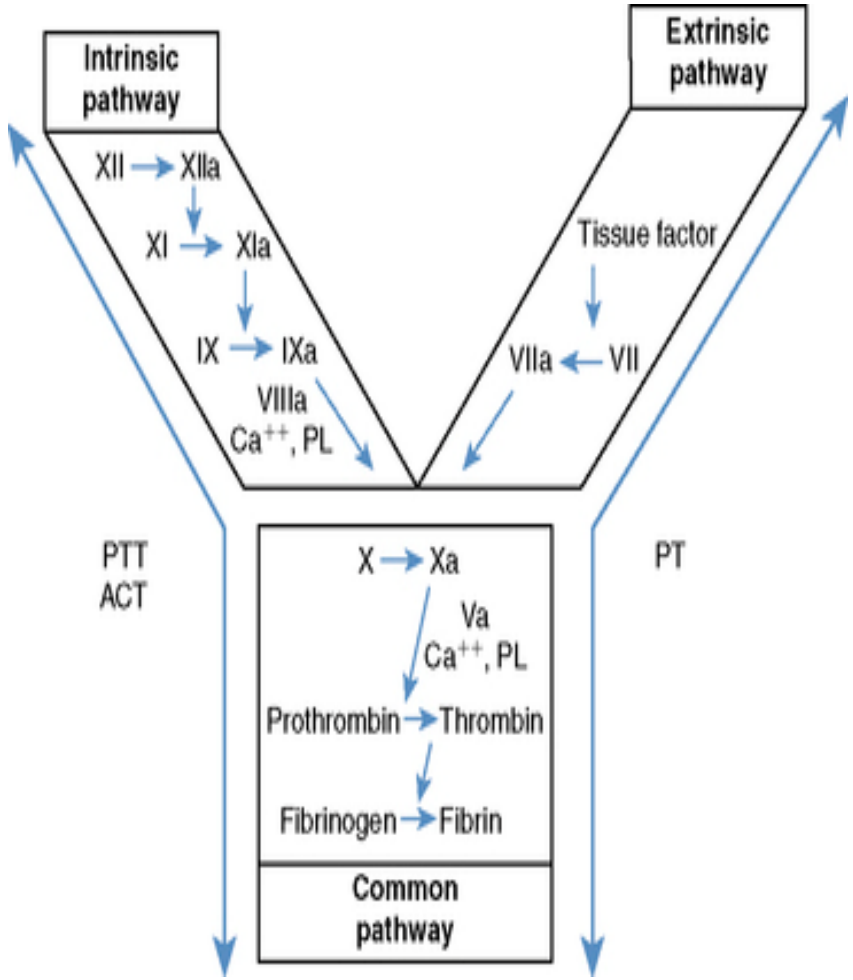


Platelets come together to form a platelet plug

Make the clot (old theory)

- Platelets plug is not enough.
- This stage happens at the platelets plug surface
- Activations of coagulation factors /co-factors
- **X:V activate prothrombin**
- **Prothrombin** (II)→ **Thrombin** (IIa)
- **Fibrinogen**(I) → **Fibrin** clot

1. TF + FVII
2. TF:FVIIa activate X in presence of V
3. X:V activate prothrombin
4. Thrombin convert Fibrinogen into fibrin clot



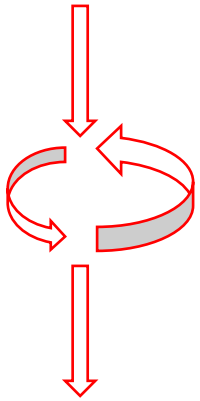
1. Contact system →XII+XI (12+11) → IX + VIII (8+9) → X:V
2. X:V (5;10)activate prothrombin
3. Thrombin convert Fibrinogen into fibrin clot (2:1)

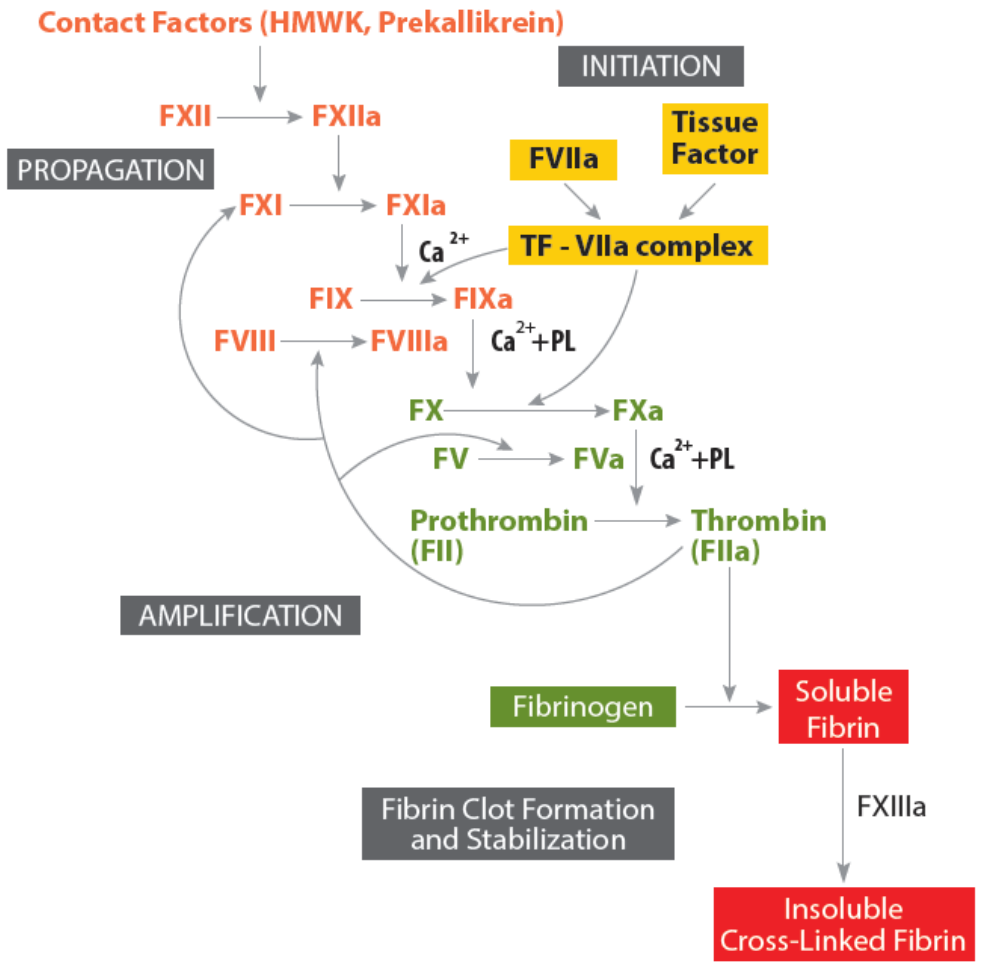
Make the clot (new)

- Loop reaction
- This stage happens at the platelets plug surface
- X:V activate prothrombin
- Prothrombin (II)→ Thrombin (IIa) | Not enough
- Fibrinogen(I) → Fibrin clot

?

- Instead, thrombin will activate more Factor V , VIII and IX





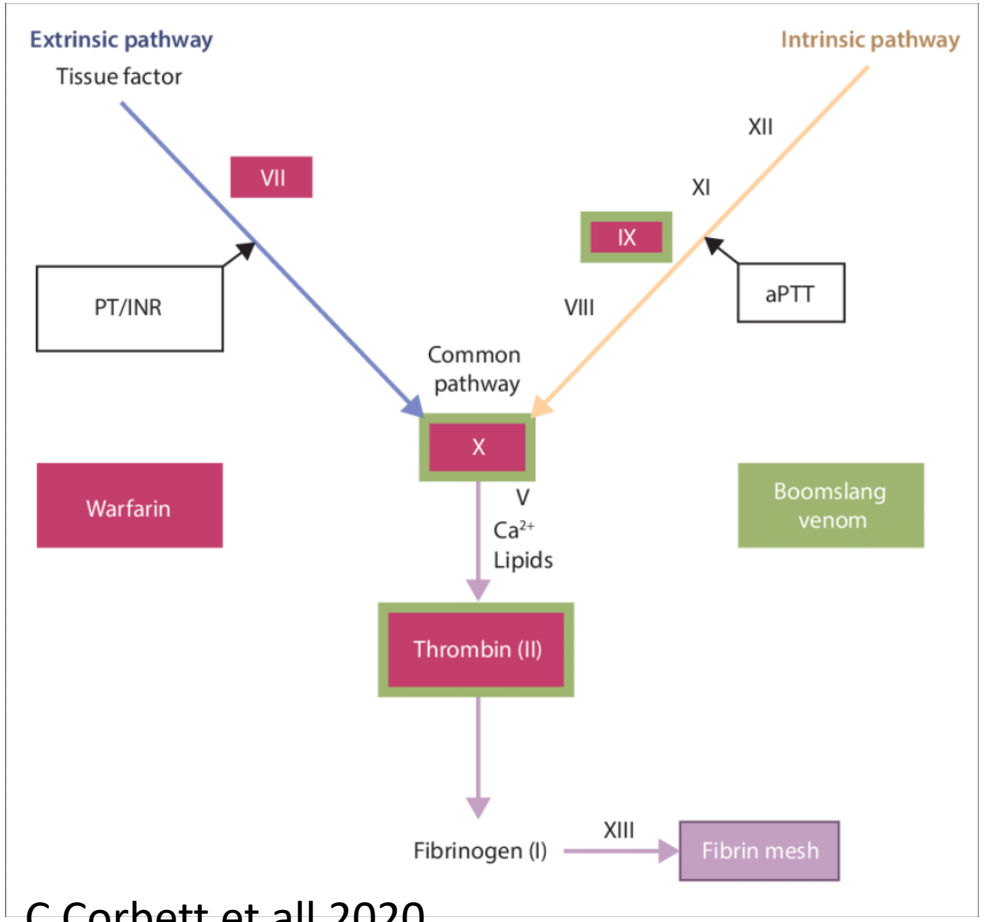
1. TF + FVII
2. TF:FVIIa activate X in presence of V
3. X:V activate prothrombin
4. Thrombin not enough to convert Fibrinogen into fibrin clot
5. So we need an AMPLIFICATION phase….Thrombin → intrinsic pathway(8,9)—COMMON→ THROMBIN BURST

Coagulation simplified

- Vitamin K (1972) :
  - 10,9,7,2

- (8) 9, **10** 7 (3)
- **(5)**

- 2 (Prothrombin)→ 2a(thrombin)
- 1 (fibrinogen) → 1a (fibrin)



C.Corbett et all,2020

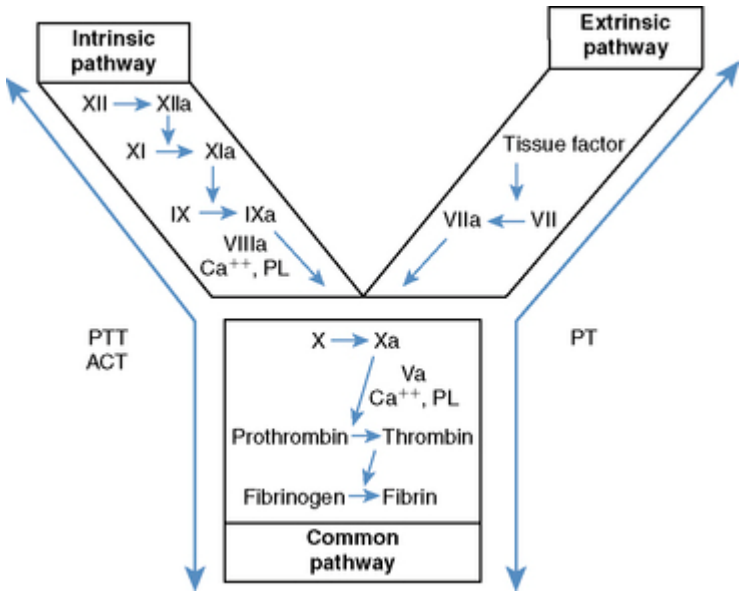


Table 8.1 Blood coagulation factors

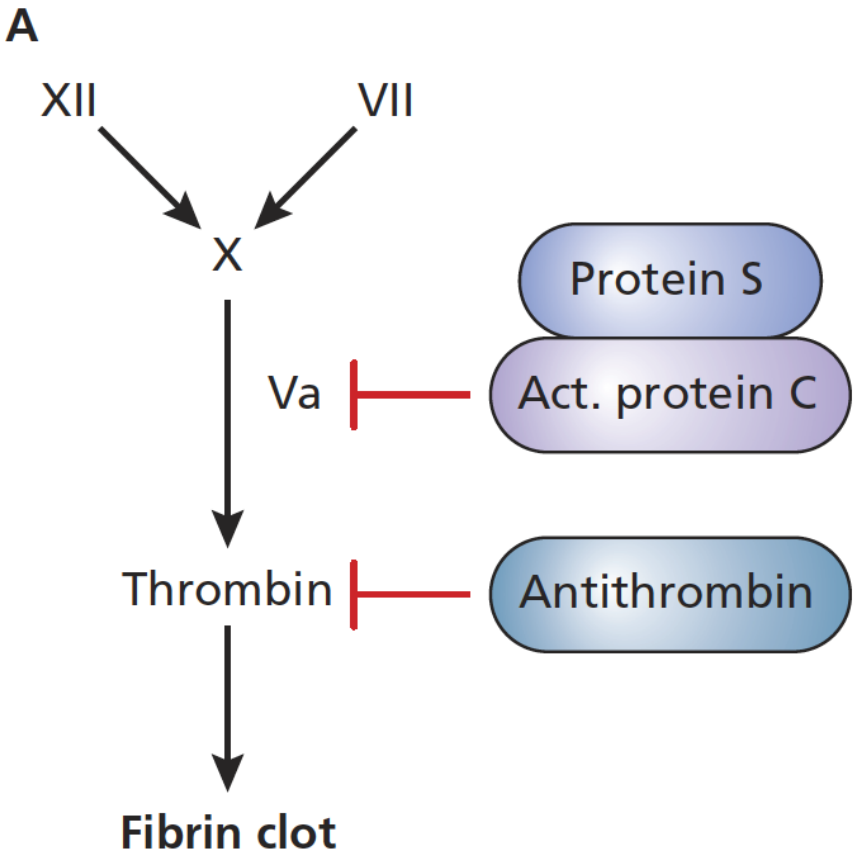
Factor	Name
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
IV	Calcium
V	Proaccelerin
VI	–
VII	Proconvertin
VIII	Antihaemophilic factor
IX	Christmas factor (plasma thromboplastin component)
X	Stuart–Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin-stabilizing factor
Fitzgerald factor	High-molecular-weight kininogen
Fletcher factor	Prekallikrein

Stop (termination phase)

- Switch off the hemostasis cascade in order to limit the reaction to the site of injury

Natural anticoagulants :

1. TFPI (Tissue factor pathway inhibitor)
2. Protein S
3. Protein C
4. Anti thrombin



Clean (Fibrinolysis)

- Activation of plasminogen
- plasmin
- Fibrin → FDP

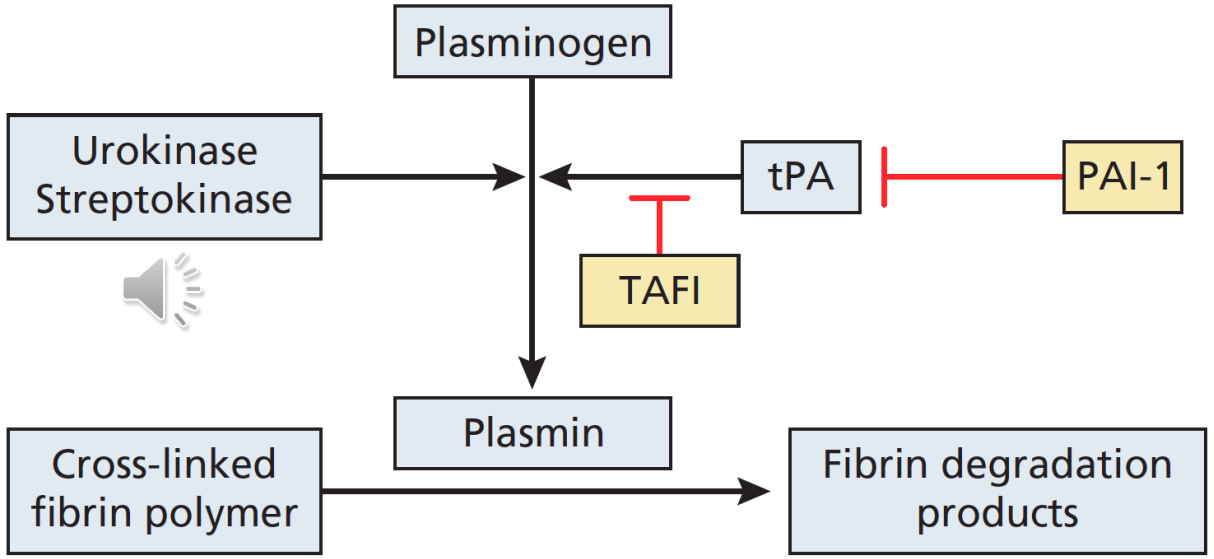


Figure 9-4 Fibrinolysis. TAFI, thrombin-activatable fibrinolysis inhibitor; tPA, tissue plasminogen activator.

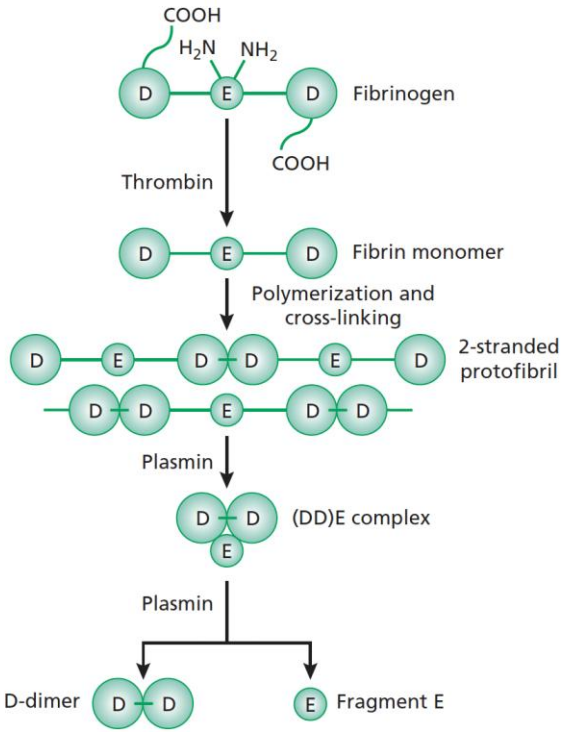


Figure 10-3 Fibrin formation and degradation. Fibrinogen has a trinocular structure with a central E and 2 D domains. Thrombin cleaves fibrinopeptides A and B (not depicted), located in the E domain. The resultant fibrin monomers polymerize nonenzymatically forming fibrin polymers. Factor XIIIa cross-links the D domains of nearby fibrin monomers. Plasmin degrades cross-linked fibrin, thereby generating (DD)E complexes composed of an E fragment noncovalently bound to D-dimer. With further plasmin attack, the (DD) E complex is degraded into fragment E and D-dimer.