

# ***BLEEDING TENDENCY***



## 6<sup>th</sup> Lecture Objectives (BLEEDING TENDENCY)

1. To review the normal physiological aspects of coagulation process
2. To understand the definition of bleeding tendency and recognize its different types according to their etiology
3. To be able to approaches to patient with bleeding tendency (investigations and treatment)
4. To be able to recognize the complications of different types of bleeding tendency diseases and treating it

# Hemostatic mechanism

The normal haemostatic response to vascular damage depends on closely linked interaction between the blood vessel wall, circulating platelets and blood coagulation factors .

An efficient and rapid mechanism for stopping bleeding from sites of blood vessel injury is clearly essential for survival. Nevertheless, such a response needs to be tightly controlled to prevent extensive clots developing and to break down such clots once damage is repaired.

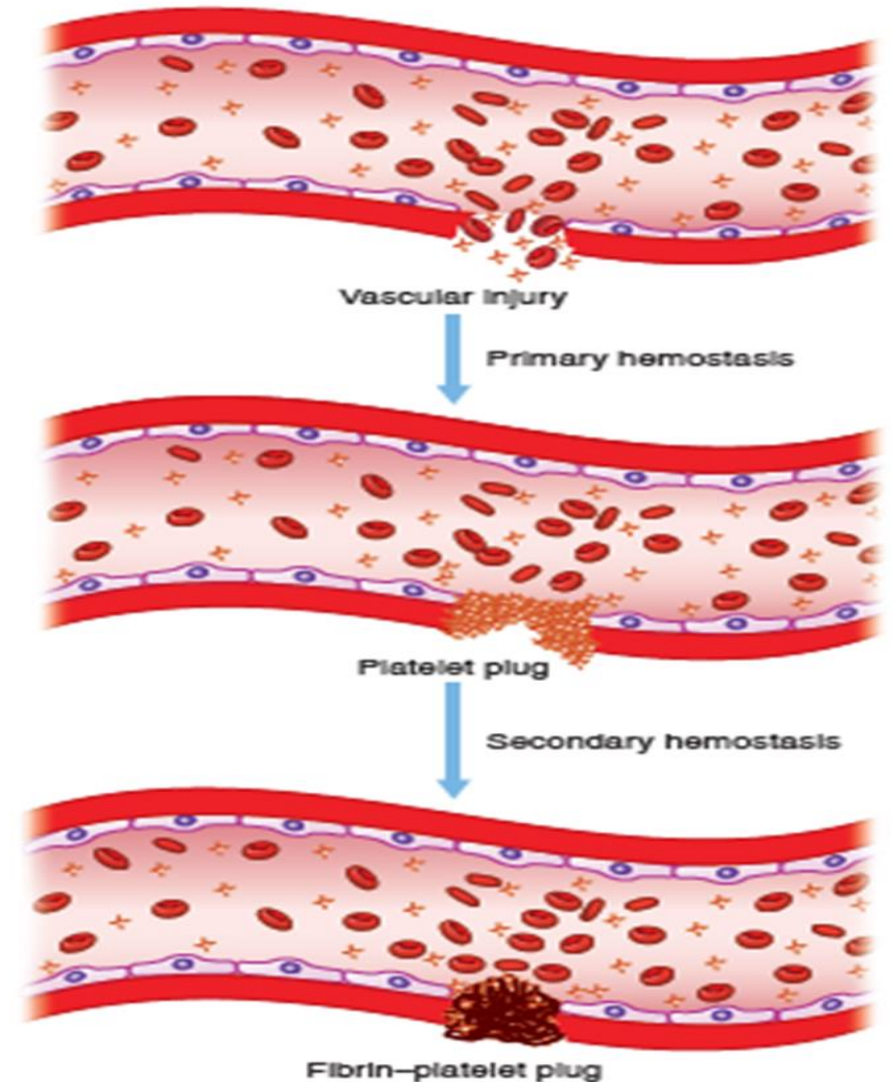
The haemostatic system thus represents a delicate balance between procoagulant and anticoagulant mechanisms allied to a process for fibrinolysis.

So, hemorrhage may result from deficiency or dysfunction of any of these elements.

- **Vasoconstriction,**
- **Platelet plug formation, and**
- **Fibrin thrombus formation**

Hemostasis occurs in stages called

**Primary hemostasis**  
**Secondary hemostasis**  
**Fibrinolysis**



**primary hemostasis**, the platelets interact with the injured vessels and with one another.

This interaction results in a mass of platelets known as the **primary hemostatic plug**, which temporarily arrests bleeding, but is fragile and easily dislodged from the vessel wall.

**secondary hemostasis** Subsequently, Generation of insoluble strands of Fibrin is formed by a series of complex biochemical reactions involving soluble plasma proteins (coagulation factors) as they interact with the injured blood vessels and the platelet plug fibrin become deposited on and within the primary platelet plug to reinforce and stabilize it and to allow the wound to heal without further blood loss.

The fibrin-reinforced plug, or thrombus , is called the **secondary hemostatic plug**. The blood has changed from a liquid to a semisolid gel at the site of injury .

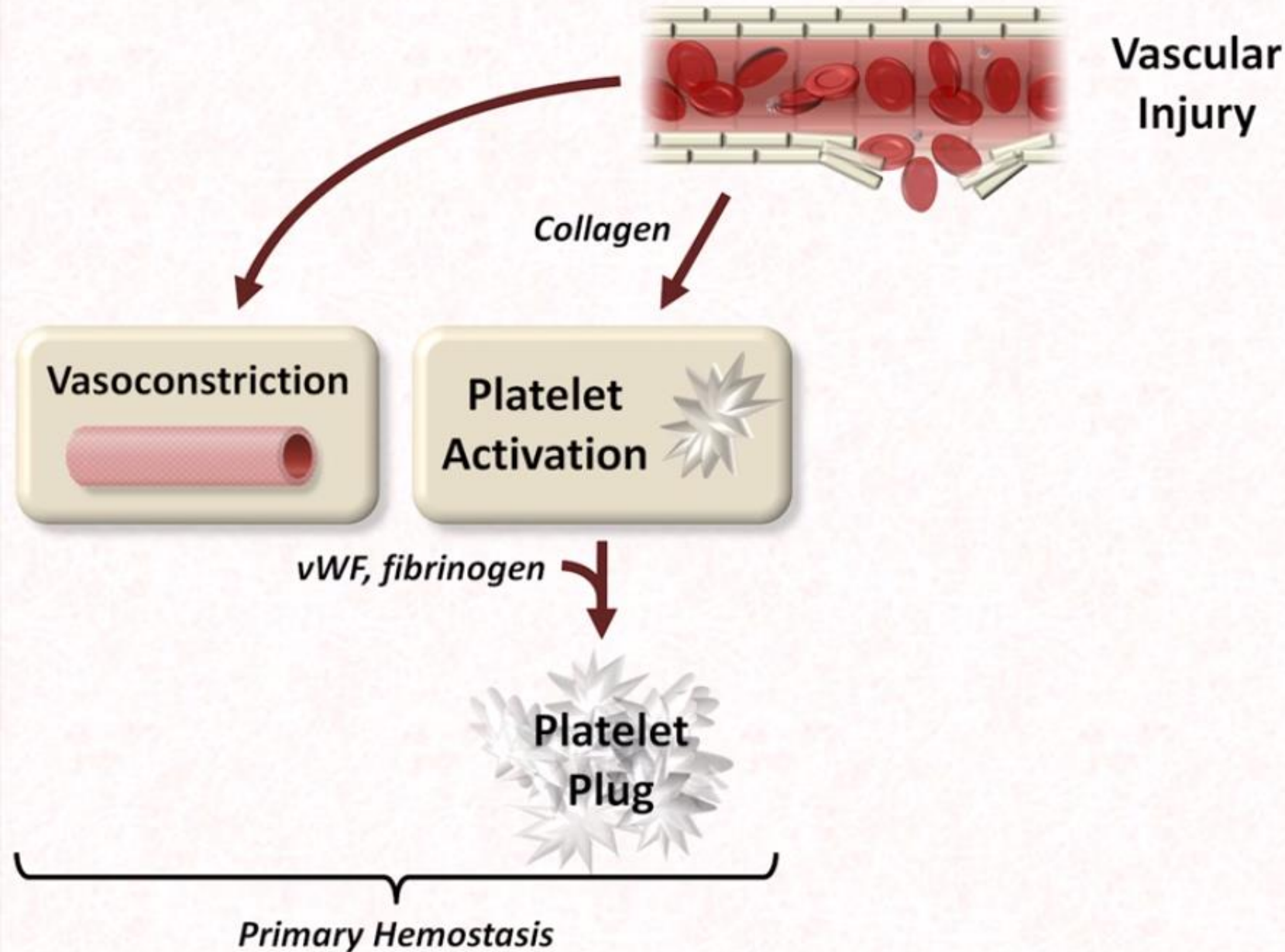
**the fibrinolytic stage** After the wound has healed, additional components of the hemostatic system break down and remove the clot during. Physiologic and biochemical inhibitors control all phases and components of the hemostatic system.



# Major Components of Hemostasis

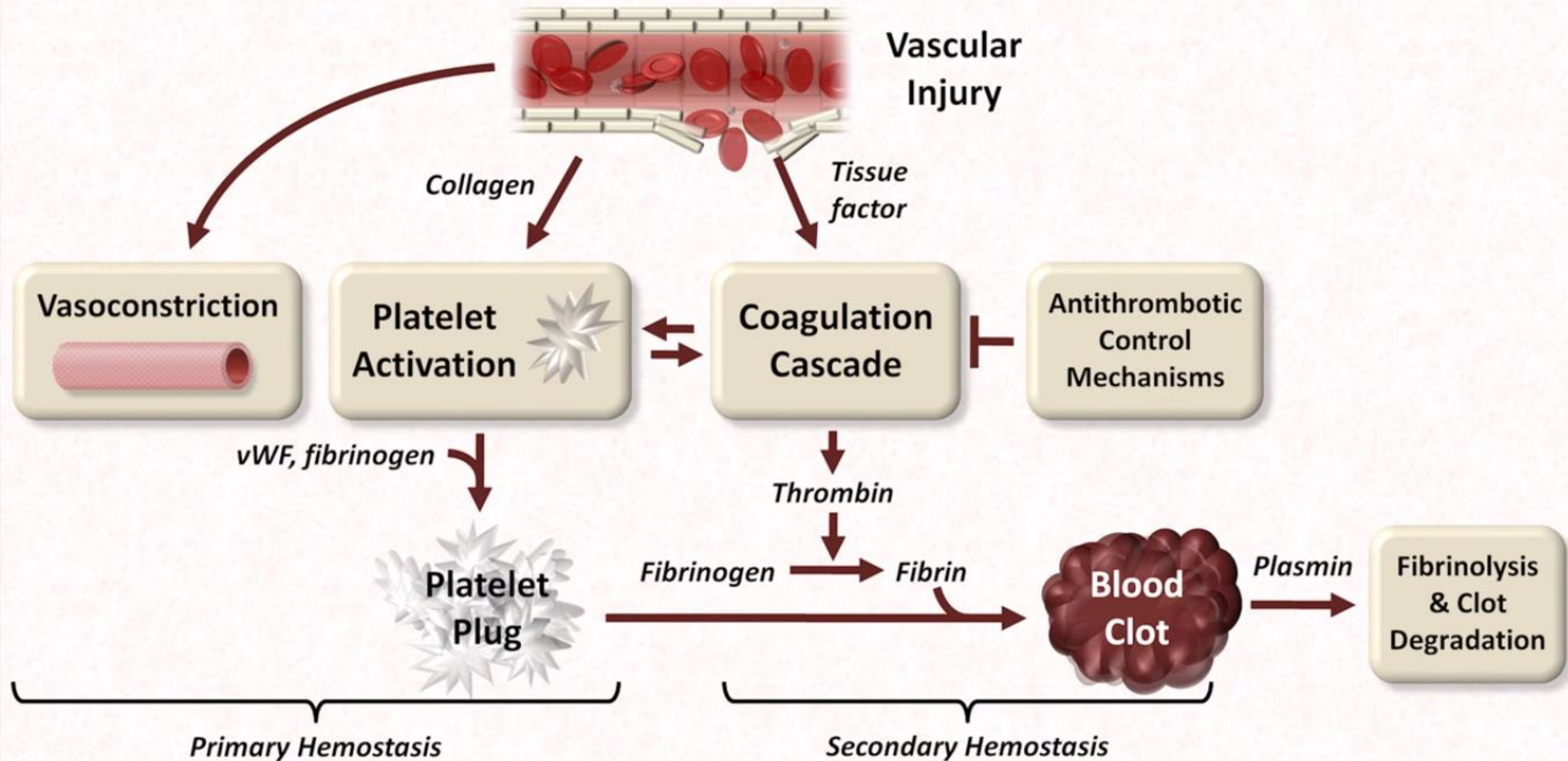
- Primary Hemostasis* {
- **Vasoconstriction**
  - **Platelet activation**
- Secondary Hemostasis* —
- **Coagulation cascade /  
Antithrombotic control mechanisms**
  - **Fibrinolysis**

# Major Components of Hemostasis





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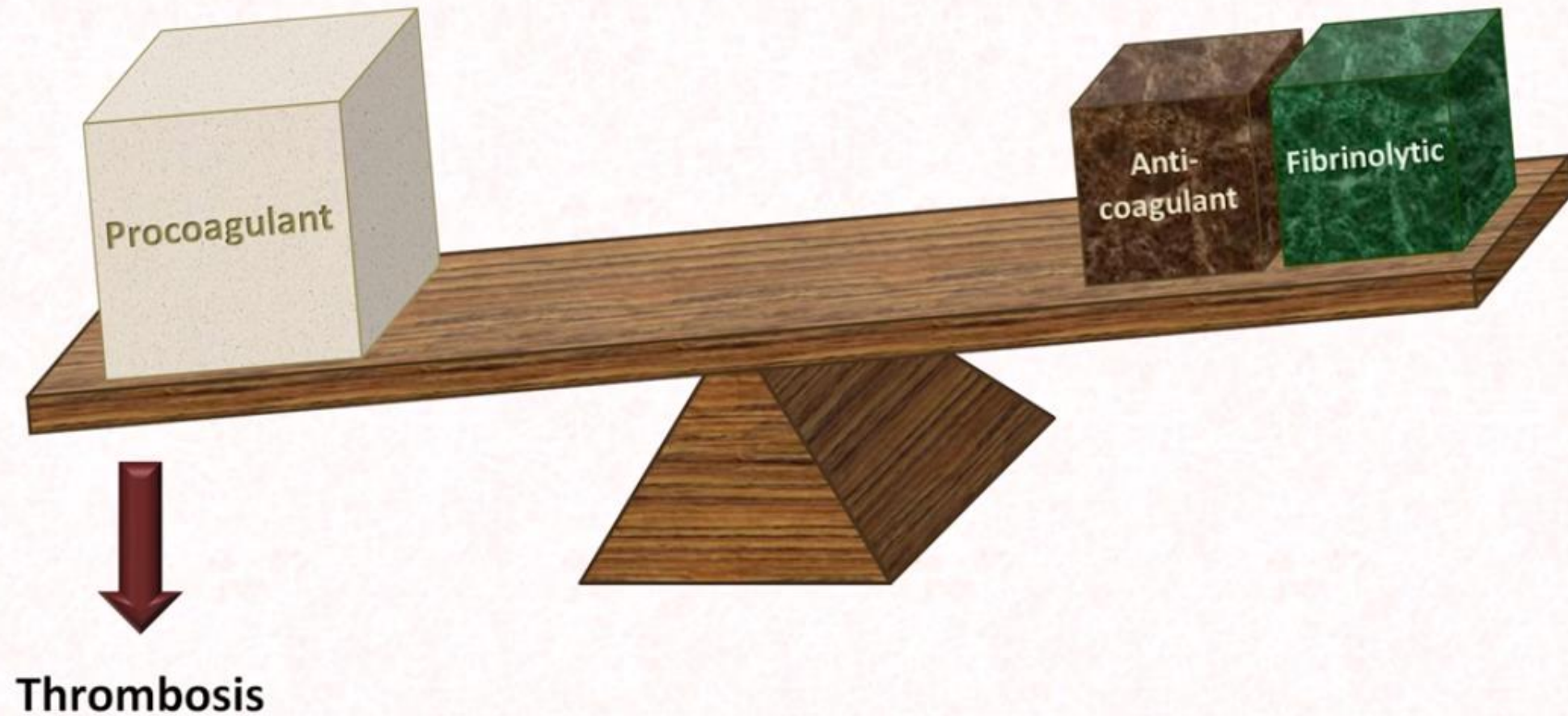




# Hemostatic Balance

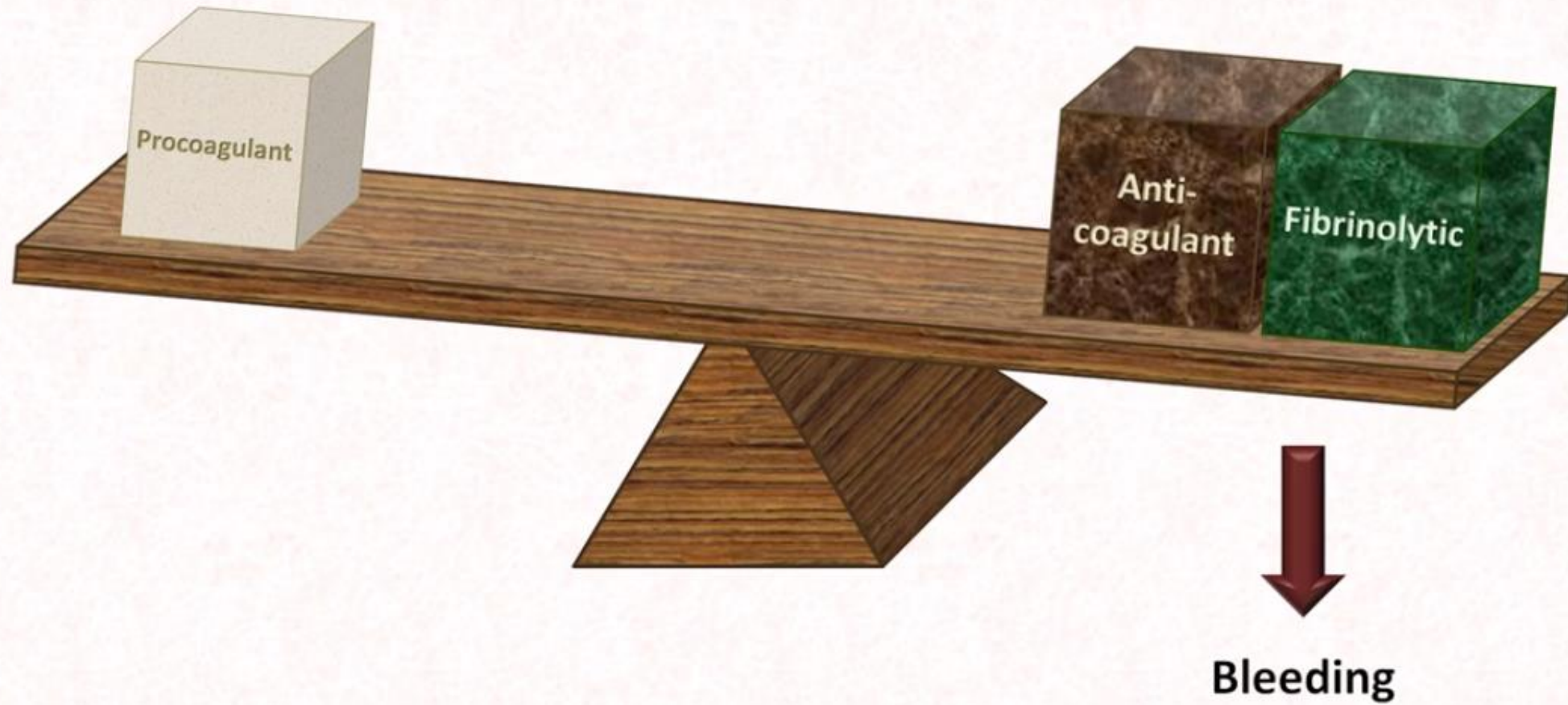


# Hemostatic Balance

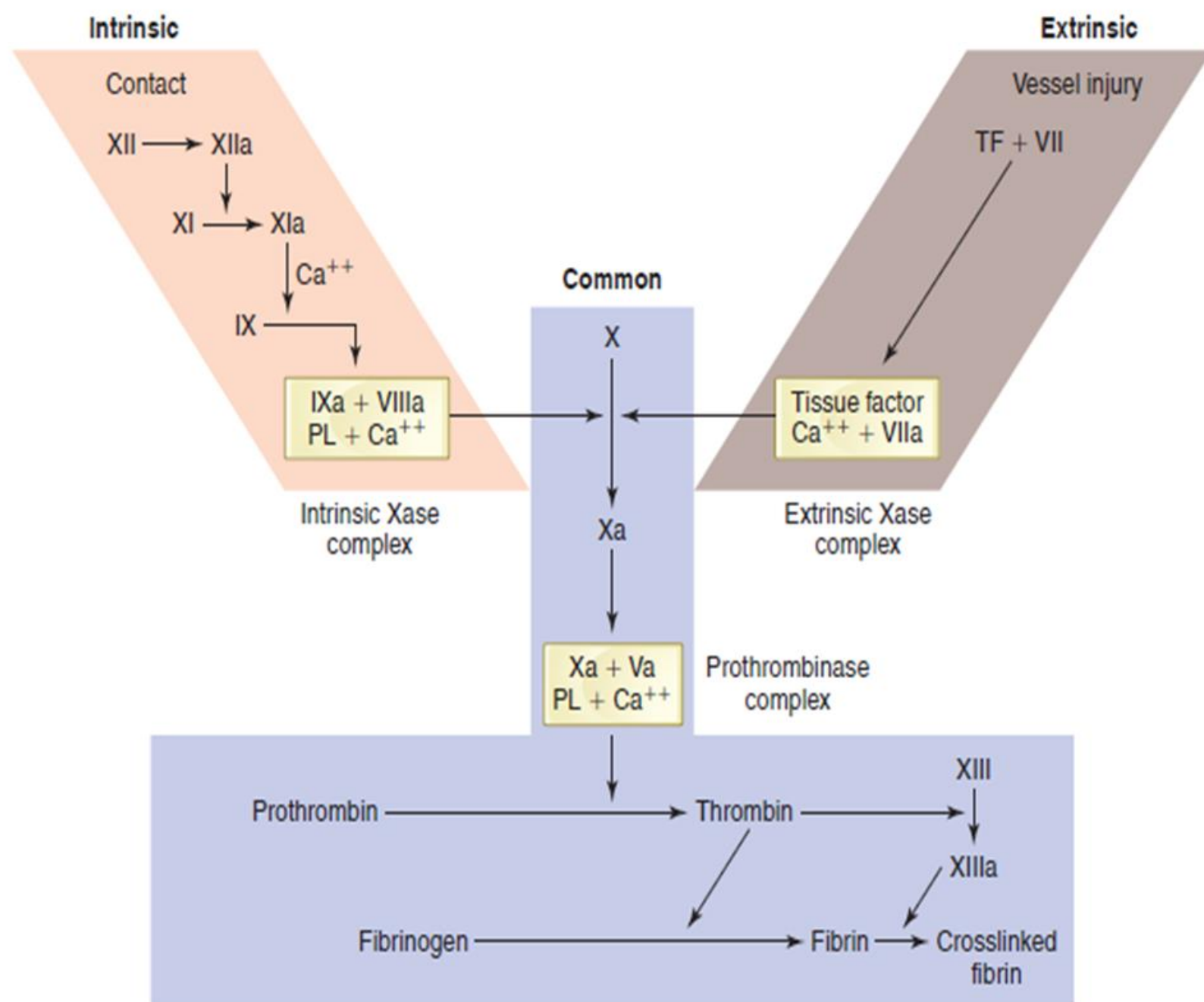




# Hemostatic Balance







**The clinical and laboratory  
evaluation of a patient with  
Bleeding tendency**

## **A)History:**

- site or sites of bleeding**
- severity and duration of bleeding**
- age of onset**
- was bleeding spontaneous or after trauma?**
- family history of similar problem**
- surgical history**
- drug history e.g aspirin,NSAID**



## **B)Physical Examination:**

-site of bleeding:platelet and blood vessel usually have mucous memberane bleeding e.g epistaxis,hematuria,GIT bleeding,and menorrhagia, while clotting factor deficiency(factor VIII,IX) cause muscle and joint bleeding with much more extensive ecchymoses and hematoma formation.

\*Haemorrhages into the skin *do not blanch* with pressure, which helps distinguish these from telangiectasia and erythema, which are due to dilated skin blood vessels.

- **Petechiae** : <2 mm in diameter
- **Purpuric spots**: 2-10 mm in diameter
  - palpable: vasculitis (e.g. Henoch-Schonlein purpura)
  - non palpable: thrombocytopenia
- **Ecchymoses** (larger bruises)
- **Haematoma** (tender elevation)





## C) Laboratory tests:

**1) Bleeding time:** assesses the function of platelets and their interaction with the vascular wall (bleeding stops within 4-8 min)

**2) Platelet count:**  $>50000/\text{mm}^3$  rarely have significant clinical bleeding.

**3) Activated partial thromboplastin time (aPTT):** normal level 30-40 sec, it measures the intrinsic clotting system.

**4) Prothrombin time (PT):** Normal range 10-13 sec, it measures the extrinsic clotting system.

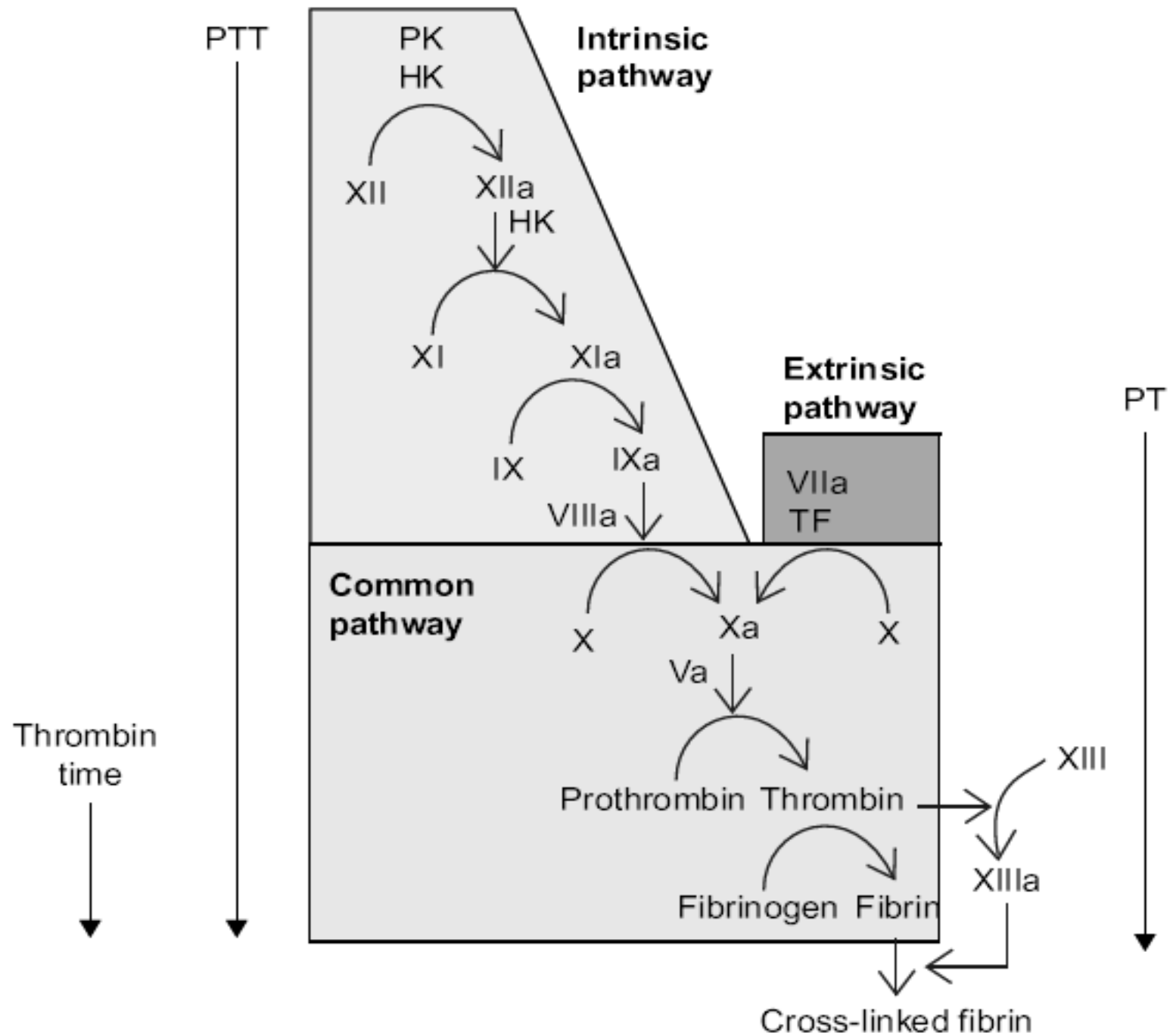
### **5) Clotting factor assays:**

Normal range 50-150 U/dl (50-150%)

Mild deficiency  $>5$  U/dl (but below the normal range) after significant trauma

Moderate deficiency 1-5 U/dl (mild trauma induce bleeding)

Severe deficiency  $<1$  U/dl (spontaneous bleeding)



# Laboratory Findings in Coagulation Disorders

Disorder	aPTT	PT	Bleeding time	Platelet count
Factor VIII,IX deficiency	prolonged	normal	normal	normal
Von Willebrand	prolonged	normal	prolonged	normal
Thrombocytopenia	normal	normal	prolonged	low
Platelet function defect	normal	normal	prolonged	normal
Vitamin K deficiency	prolonged	prolonged	normal	normal
DIC	prolonged	prolonged	prolonged	low

**(Clotting Factors Disorders)**

<b>Factor Numerical Designation</b>	<b>Alternative Name(s)</b>
I	Fibrinogen
II	Prothrombin
III	Tissue factor, thromboplastin
IV	Calcium
V	Proaccelerin, labile factor
VI (unassigned)	N/A
VII	Proconvertin, serum prothrombin conversion accelerator, stable factor
VIII	Antihemophilic factor
IX	Christmas factor, plasma thromboplastin component
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman (contact) factor
XIII	Fibrin-stabilizing factor



# Congenital clotting factor disorders

**Factor VIII deficiency (Hemophilia A)**

**Factor IX deficiency (Hemophilia B)**

## Genetics and classification:

Is x-linked recessive, with 85% having factor VIII deficiency and 10-15% having factor IX deficiency.

Some female carriers of hemophilia A or B will have sufficient reduction of their factor VIII or IX through lyonization of the X chromosome to produce mild bleeding.

## Clinical manifestations:

Both factors not crosses the placenta,thus bleeding symptoms may be present from birth or occur in the fetus.

Only about 30% of patients bleed with circumcision.

When a child begins to crawl and walk causes bruising, intramuscular hematoma and hemarthrosis.

The hallmark of hemophilia is the hemarthrosis (ankle,knee and the elbow joints)

Iliopsoas muscle bleeding leading to hypovolemic shock and inability to extend the hip.

Life- threatening bleeding in the hemophilic patient is CNS and upper air way bleeding.

## Laboratory findings :

- 1)prolonged aPTT (usually 2-3 times the upper limits of normal)
- 2)platelet count, bleeding time, PT,TT,are normal.
- 3)The specific assay for factor VIII,IX will confirm the diagnosis:

Normal range 50-150 U/dl(50-150%)

Mild deficiency >5 U/dl (but below the normal range)after significant trauma

Moderate deficiency 1-5 U/dl(mild trauma induce bleeding)

Severe deficiency <1U/dl (spontaneous bleeding)



# Treatment

## A. General measures

1) prevention of trauma. Although it is easy to advise parents that their child should avoid trauma, this advice is practically useless. Toddlers are active, and injure themselves easily. Effective measures include anticipatory guidance, including the use of car seats, seatbelts, and bike helmets, and the importance of avoiding high-risk behaviors.

2) avoid aspirin and other NSAID.

3) immunization against hepatitis B virus.

## B. Replacement therapy

In Mild factor VIII deficiency, the patient's endogenously produced factor VIII can be released by the administration of desmopressin acetate (by intranasal inhaler).

## Moderate and Severe factor VIII deficiency

recombinant factor VIII and recombinant factor IX.

Factor replacement therapy is the mainstay of hemophilia treatment. The degree of factor correction required to achieve hemostasis is largely determined by the site and nature of the particular bleeding episode.

## C. PROPHYLAXIS

Is usually provided every 2-3 days to maintain a measurable plasma level of clotting factor (1-2%) when assayed just before the next infusion.

- **Cryoprecipitate** contains **(1, 8, 13, and VWF)**
- **FFP** effective in treating factors **2, 5, 10, 11** deficiency, not effective in treating factors **7, 8, 9** deficiency

## Chronic complications:

- 1) chronic joint destruction.
- 2) risk of transfusion-transmitted infections (HIV, Hepatitis B or C).
- 3) development of an inhibitors to either factor VIII or IX.

# Factor XI deficiency(Hemophilia C)

Is autosomal disease with mild to moderate bleeding, more in Ashkenazi Jews.

- PTT is longer than it is in hemophilia A or B.
- treated with FFP.



# Von Willebrand disease

Is the most common hereditary bleeding disorder(1-2% of the general population).

Is inherited autosomally, but is more in women (menorrhagia is a major symptom).

## Pathophysiology:

VWF is a large multimeric glycoprotein that is synthesized in megakaryocytes and endothelial cells.

It is responsible for the normal interaction with the subendothelial matrix and platelets, and serves as the carrier protein for plasma factor VIII.

## Classification:

Type 1 VWD:the protein is reduced but not absent.

Type 2 VWD:qualitatively abnormal.

Type 3 VWD:the protein is absent.

## Clinical manifestations:

- Mucocutaneous bleeding(bruising,epistaxis,menorrhagia and postoperative hemorrhage particularly after mucosal surgery such as tonsillectomy).

## Laboratory findings

1. prolong bleeding time.
2. prolong PTT.
3. Both may be normal in Type 1VWD.
4. quantitative assay for VWF antigen, VWF activity.
5. plasma factor VIII activity.
6. determination of VWF structure.
7. platelet count.

## Treatment

Type 1 VWD: desmopressin (DDAVP) induces the release of VWF from the endothelial cells.

In some patients with type 2 VWD, desmopressin may be similarly effective, but in other circumstances the released VWF is dysfunctional.

Replacement therapy: plasma derived VWF containing concentrates that also contain factor VIII.

# Acquired clotting factor disorders



## Vitamin K deficiency:

### Causes:

1. lack of oral intake of vit. K.
2. alteration in the gut flora due to long term use of broad-spectrum antibiotics.
3. malabsorption of vitamin K (cystic fibrosis or biliary atresia).
4. hemorrhagic disease of the newborn.

# Hemorrhagic Disease of the Newborn

## classic form

A moderate decrease in factors II, VII, IX, and X normally occurs in all newborn infants by **48-72 hr** after birth, rare in term infants and more frequent in premature infants, accentuation and prolongation of this deficiency between the **2nd and 7th days** of life result in spontaneous and prolonged bleeding with a gradual return to birth levels by **7-10 days** of age. This transient deficiency of vitamin K-dependent factors is probably due to lack of free vitamin K from the mother and absence of the bacterial intestinal flora normally responsible for the synthesis of vitamin K and is responsive to and prevented by vitamin K therapy. Breast milk is a poor source of vitamin K, so hemorrhagic complications are more frequent in breast-fed than in formula-fed infants.

### Early-onset (onset from birth to 24 hr)

life-threatening vitamin K deficiency-induced bleeding also occurs if the mother has been treated with drugs (phenobarbital, phenytoin) that interfere with vitamin K function.

Late onset (>2 wk) is often associated with vitamin K malabsorption, as noted in neonatal hepatitis or biliary atresia .

## **Liver disease:**

Since all the clotting factors are produced *exclusively* in the liver(except factor VIII),coagulation abnormalities are very common in patients with severe liver disease.

Treatment: FFP or cryoprecipitate+Vitamin K.

# **Disseminated Intravascular Coagulation (consumptive coagulopathy)**

Are a heterogeneous group of conditions including DIC that result in consumption of clotting factors, platelets, and anticoagulant proteins.

Consequences of this process include widespread intravascular deposition of fibrin leading to tissue ischemia, necrosis, generalized hemorrhagic state and hemolytic anemia.



## **Causes:**

- 1. Infection:e.g meningococemia.**
- 2. Tissue injury:like massive burn.**
- 3. Malignancy:acute promyelocytic leukaemia.**
- 4. Venom or toxin:snake bites.**
- 5. GIT disorders:fulminant hepatitis.**

## Laboratory findings:

- 1)prolongation of PT,PTT,and TT.
- 2)decrease factor II,V,VIII,fibrinogen and platelet.
- 3)Blood smear: fragmented ,burr and helmet-shaped RBC (schistocytes).
- 4)FDP(fibrin degredation product),D-dimers are appear in the blood.

## Treatment:

### **A)general measures:**

- treat the trigger that caused the DIC
- restore normal hemostasis by correcting the shock, acidosis and hypoxia.

**B)replacement therapy:** platelet infusions, cryoprecipitate, and /or FFP.

**(Platelet Disorders)**

**\*Platelets circulate with a life-span 10-14 days.**

**\*Normal platelet count is(150-450X10<sup>9</sup>/L)**

**Causes of thrombocytopenia(<150X10<sup>9</sup>/L)**

**1)decreased production (congenital or acquired).**

**2)increased destruction (immune or nonimmune).**



## **IMMUNE THROMBOCYTOPENIC PURPURA (ITP)**

**Is the most common cause of acute onset of thrombocytopenia.**

**Etiology:**

1-4 weeks after exposure to a common viral infection(e.g.Epstein-Barr virus), a small number of children develop an autoantibody directed against the platelet surface.

## Clinical manifestations:

- \*there is a history of a preceding viral infection.
- \*a healthy (1-4 yr)old child who has a sudden onset of generalized petechiae, purpura, and mucous membrane bleeding.

## Prognosis:

- ❖ 70-80% of children with acute ITP have a spontaneous resolution within 6 months.
- ❖ 10-20% develop chronic ITP.
- ❖ less than 1% develop intracranial hemorrhage.

## Laboratory findings:

- 1. severe thrombocytopenia( $<20 \times 10^9/L$ ).**
- 2. Hb, WBC, are normal. (Hb may be decreased due to profuse bleeding).**
- 3. B.M: increase number of megakaryocytes.**

## Treatment:

\*Platelet transfusion in ITP is usually contraindicated unless life-threatening bleeding is present.

- 1) Intravenous immunoglobulin(IVIG):dose 0.8-1 g/kg/day(1-2 days).
- 2) Prednisone:1-4 mg/kg/day(for 2-3 weeks).
- 3) i.v anti-D therapy: dose 50Mg/kg.
- 4) Splenectomy:indicated in
  - a- older child >4 year with severe ITP last >1 year.
  - b- life threatening hemorrhage(intracranial hemorrhage).

## (Disorders of Blood Vessels)

1) **Henoch-Schonlein purpura** :an IgA-mediated vasculitis, presents with palpable purpura on the lower extremities and buttocks, renal insufficiency, arthritis, and abdominal pain. platelet count is normal.

2) **Scurvy (vit. C deficiency)**: causes impaired collagen synthesis that results in weakened blood vessels.

3) Inherited disorders of collagen synthesis (e.g. **Ehlers-Danlos syndrome**).

4) Malnutrition and corticosteroids may weaken the collagen supporting vessels.