

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)



HLS Physiology | MID 8

Hemostasis



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بسم الله الرحمن الرحيم،

نرجو منكم الدعاء لزميلنا في الدفعة
عون العدوان، الذي وافته المنية.

اللهم ارحمه واغفر له، وأسكنه فسيح جناتك، وأنر قبره وأنس وحشته، واجعل قبره روضةً من رياض
الجنة.

اللهم اجبر قلوب أهله وذويه، وارزقهم الصبر والسلوان، وألهمهم جميل الصبر وحسن العزاء.

رحمه الله رحمةً واسعةً وأسكنه الفردوس الأعلى من الجنة...

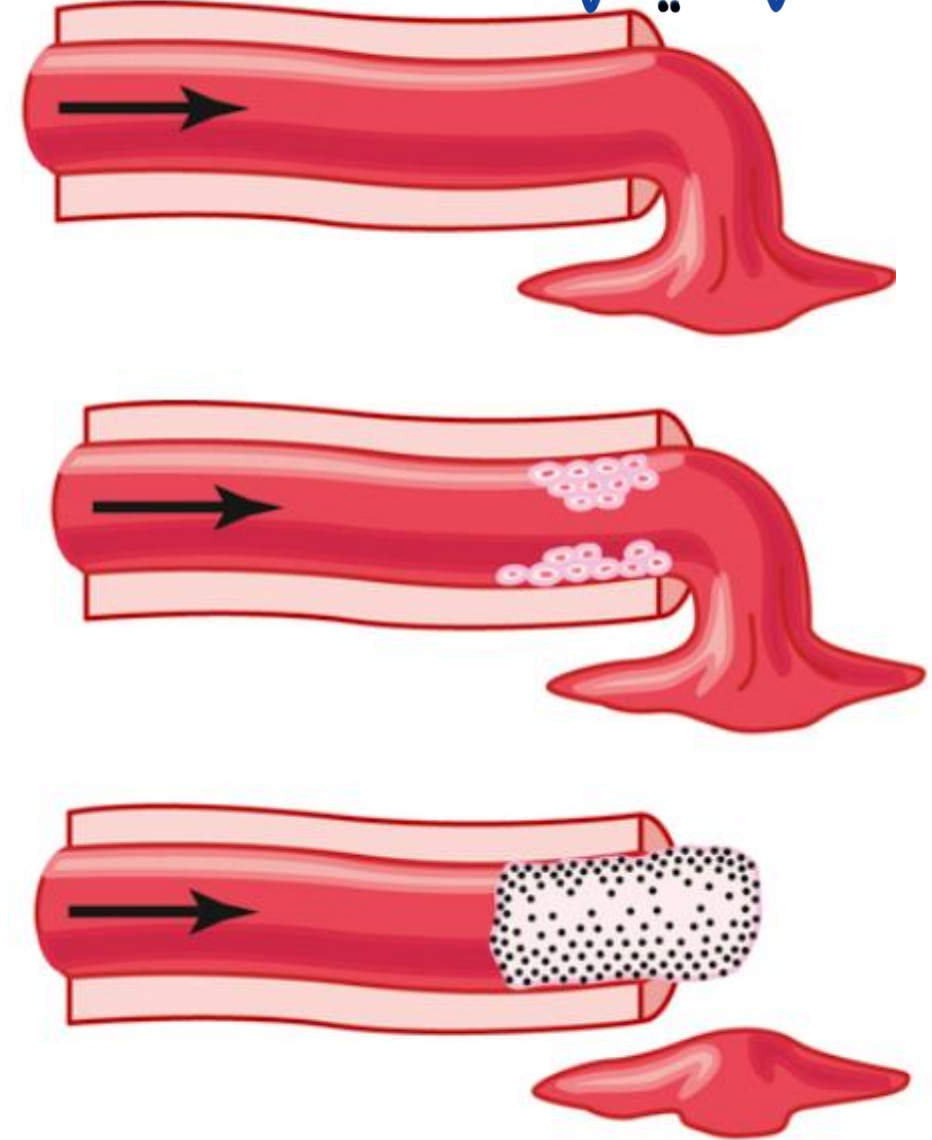
Hemostasis

Events of hemostasis

Hemostasis means prevention of blood loss and includes the following events:

- (1) Vascular constriction.
- (2) Formation of a platelet plug.
- (3) Formation of a blood clot as a result of blood coagulation.
- (4) Fibrous organization or dissolution of the blood clot**

رَبِّ اشْرَحْ لِي صَدْرِي
وَيَسِّرْ لِي أَمْرِي



The body normally maintains homeostasis, meaning that physiological processes are regulated to preserve normal conditions.

The same principle applies to hemostasis.

When a blood vessel is injured, the body must stop the bleeding. However, the resulting clot should not remain permanently.

Therefore, hemostasis involves both:

- Clot formation: Prevents blood loss.
- Clot removal or organization: Allows tissue repair and restoration of normal function

After the clot has fulfilled its function, two outcomes are possible:

- The clot is dissolved and normal tissue is restored.
- The clot becomes organized into connective tissue, potentially producing a scar.

What determines the outcome?

The final outcome depends on the size and depth of the injury.

- Small or superficial injury: The clot may dissolve, followed by restoration of the normal tissue and endothelial lining.
- Deeper injury: The body may recruit fibroblasts to produce connective tissue, leading to scar formation.

Hemostasis

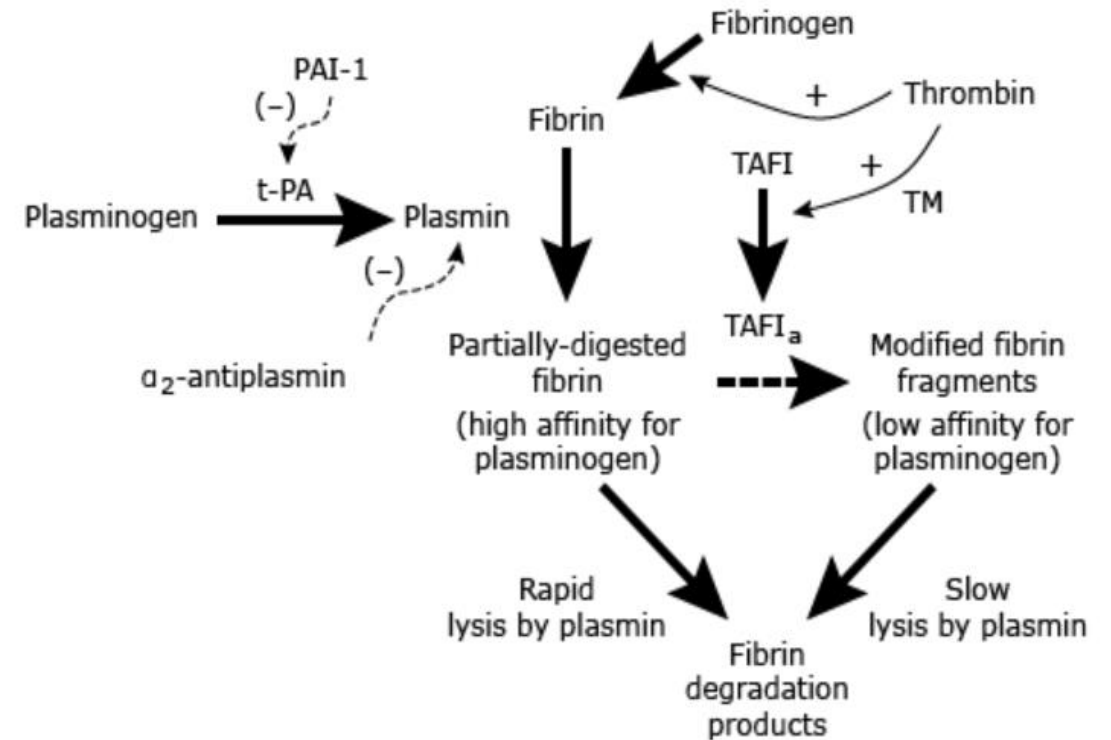
Dissolution of clot

– Regulation of Coagulation and Fibrinolysis

- Most coagulation factors are produced by the liver and circulate in their inactive forms.
- Under normal physiological conditions, blood remains fluid because **anticoagulant mechanisms predominate over procoagulant mechanisms**.
- During hemostasis, clot formation must remain **localized to the site of injury** to prevent unnecessary extension into the surrounding circulation.
- The body maintains a balance between clot formation and clot dissolution, ensuring that the clot performs its function without persisting unnecessarily.

Plasminogen is converted into plasmin by tissue plasminogen activator (t-PA). Plasmin then degrades fibrin.

The detailed mechanism of fibrinolysis is explained in Slide 5.



لَا إِلَهَ إِلَّا اللَّهُ الْعَظِيمُ الْحَلِيمُ
لَا إِلَهَ إِلَّا اللَّهُ رَبُّ الْعَرْشِ الْعَظِيمِ
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وَرَبُّ الْعَرْشِ الْكَرِيمِ

****Plasminogen is a plasma protein, when activated, becomes a substance called plasmin (or fibrinolysin).**

When a clot is formed, a large amount of plasminogen is trapped in the clot along with other plasma proteins.

The injured tissues and vascular endothelium very slowly release a powerful activator called tissue plasminogen activator few days later, after the clot has stopped the bleeding. t-PA eventually converts plasminogen to plasmin. which in turn removes the remaining unnecessary blood clot.

****If clots were not removed after they performed their hemostatic function, their accumulation would eventually obstruct the vessels**

**** A clot is not meant to be a permanent solution to vessel injury. It is a transient device to stop bleeding until the vessel can be repaired.**

Think!

There is genetically engineered tissue plasminogen activator (t-PA) available.

When can you use tPA ?

Recombinant tissue plasminogen activator can be used as a thrombolytic medication to dissolve certain pathological blood clots.

Clinical applications include:

- Selected patients with acute ischemic stroke.
- Selected patients with acute myocardial infarction, particularly STEMI when timely primary PCI is unavailable.
- Selected patients with severe pulmonary embolism.

Thrombosis versus bleeding

Hemostasis must remain balanced.

If coagulation is excessive or occurs abnormally, it can cause thrombosis.

Thrombosis refers to the formation of a pathological clot inside a blood vessel.

If coagulation is insufficient, or if platelet numbers or functions are impaired, excessive bleeding may occur.

Therefore:

- Excessive coagulation → thrombosis.
- Insufficient hemostasis → bleeding.

Myocardial Infarction (MI)

Myocardial infarction may develop through the following sequence:

1. **Atherosclerotic changes:** Cholesterol plaques develop within the coronary arteries, accompanied by inflammation.
2. **Thrombus formation:** Disruption of the affected vascular surface activates platelets and the coagulation cascade, leading to thrombus formation.
3. **Vascular occlusion:** A sufficiently large thrombus may completely obstruct the coronary artery.
4. **Reduced oxygen supply:** Blood flow is interrupted, preventing adequate oxygen delivery to the heart muscle.
5. **Myocardial infarction:** Prolonged interruption of blood flow results in myocardial cell death.

Management of Myocardial Infarction

A. Catheterization (Preferred Approach When Available and Appropriate)

- A catheter is introduced through an artery in the arm or leg and advanced toward the coronary arteries.
- The obstructed artery is reopened using catheter-based intervention.
- A **stent** may be inserted to maintain blood flow.
- Drug-coated stents are used to reduce the risk of subsequent narrowing.

B. Pharmacological Treatment

- When timely catheter-based intervention is unavailable, **thrombolytic therapy** may be considered in eligible patients.
- Genetically engineered **tPA** is one of the medications used to dissolve the thrombus.
- Its administration requires specific precautions because of the associated bleeding risk.

Key point: tPA promotes clot dissolution by activating plasminogen into plasmin, which degrades fibrin. It may therefore be used in selected thrombotic conditions, including eligible cases of ischemic stroke and myocardial infarction.

Hemostasis

Fibrous organization

The clot can become invaded by **fibroblasts**, which subsequently form **connective tissue** all through the clot (promoted at least partially by **growth factor** secreted by **platelets**)

** The aggregated platelets secrete a chemical that helps promote the invasion of fibroblasts from the surrounding connective tissue into the wounded area of the vessel. Fibroblasts form a scar at the vessel defect..

****Early clot retraction is caused by platelet contraction. Tissue repair requires living cells: endothelial cells restore the lining, inflammatory cells clear damage and coordinate healing, and fibroblasts rebuild damaged connective tissue.”

Prevention

Normal Intravascular Anticoagulants

Under normal physiological conditions, blood remains in a **fluid state** due to the presence of natural anticoagulant mechanisms that prevent unnecessary clot formation:

- **Endothelial surface factors**
- **Antithrombin action of fibrin and antithrombin III.**
- **Heparin.**

More than 50 important substances that cause or affect blood coagulation have been found in the blood and in the tissues—some that promote coagulation, called procoagulants, and others that inhibit coagulation, called anticoagulants. Whether blood will coagulate depends on the balance between these two groups of substances. In the blood stream, the anticoagulants normally predominate, so the blood does not coagulate while it is circulating in the blood vessels. However, when a vessel is ruptured, procoagulants from the area of tissue damage become activated and override the anticoagulants, and then a clot does develop.

Prevention

Endothelial Surface Factors

- 1) the smoothness of the endothelial cell surface
- 2) a layer of **glycocalyx** on the endothelium
- 3) a protein bound with the endothelial membrane, **thrombomodulin**, which binds **thrombin**.
- The **thrombomodulin-thrombin** complex also activates a plasma **protein C**, with protein S as a cofactor, acts as an anticoagulant by **inactivating** activated **Factors V and VIII**.
- 4) Intact endothelial cells also produce other substances such a **prostacyclin and nitric oxide (NO)** that inhibit **platelet aggregation** and initiation of blood clotting

** Therefore, an intact vessel provides both a physical barrier and active inhibitory signals.

When the endothelial wall is damaged, **its smoothness and its glycocalyx-thrombomodulin layer are lost, which activates both **Factor XII** and the **platelets**, thus setting off the intrinsic pathway of clotting. If Factor XII and platelets come in contact with the **subendothelial collagen**, the activation is even **more powerful**.

**Notice that thrombin has different effects depending on its setting. At the injury, it promotes platelet activation and fibrin formation. When bound to thrombomodulin on endothelium, it helps activate an anticoagulant pathway

Prevention

Antithrombin Action of Fibrin and Antithrombin III.

- Among the most important anticoagulants in the blood are those that remove thrombin from the blood.
 - (1) the **fibrin fibers** that are formed during the process of clotting (85 to 90%)
 - (2) The thrombin that does not adsorb to the fibrin fibers soon combines with **antithrombin III**. (an alpha-globulin)

"يقول ابن تيمية: والله إن المسألة تُغلق في وجهي، فأستغفر الله ألف مرة فتفتح لي. ثق بأن الإستغفار يفتح لك أبواب الخير والنجاح والفلاح."

1. Antithrombin Action of Fibrin Fibers (85–90%)

- During blood coagulation, thrombin promotes the formation of **fibrin fibers**.
- These fibrin fibers adsorb approximately **85–90% of the thrombin** formed during clotting.
- Although thrombin normally promotes coagulation through positive-feedback mechanisms, its adsorption onto fibrin fibers helps **localize thrombin activity to the site of clot formation**.
- This prevents excessive thrombin activity from spreading into the surrounding circulation.

2. Antithrombin III (ATIII)

- **Antithrombin III** is a plasma protein belonging to the **alpha-globulin** fraction.
- Thrombin that is not adsorbed onto fibrin fibers can combine with antithrombin III.
- This interaction contributes to the inactivation of thrombin and prevents further propagation of coagulation.

Importance of Thrombin Regulation

- Thrombin promotes clot formation and amplifies coagulation through positive feedback.
- Therefore, its activity must remain localized to the injured region.
- **Fibrin fibers and antithrombin III** help prevent thrombin from promoting unnecessary clot formation outside the site of injury.

Fibrin fibers adsorb thrombin, helping retain its activity within the developing clot rather than allowing it to spread freely through the circulation.

Prevention

Heparin

- Highly negatively charged conjugated polysaccharide
- Powerful anticoagulant, but its concentration in the blood is normally low.
- Widely used as a pharmacological agent **and can be administered by injection.**
- Increases effectiveness of antithrombin III.
- Inhibits **thrombin**, activated factors XII, XI, **X** and IX.
- Produced in basophil and mast cells.

*Factor X is particularly important because it is a component of the **prothrombinase complex**.*

Prevention

Anticoagulants (Outside body)

- When blood is collected in a glass test tube normally clots in about 6 minutes.
- **Siliconized containers** often does not clot for 1 hour or more. silicone prevents contact **activation of platelets and Factor XII**.
- **Heparin** → when blood must be passed through a heart-lung machine or artificial kidney machine and then back into the person.
- **Soluble oxalate, citrate ion** → decreases the ionic calcium level → blood coagulation is blocked

Citrate, oxalate, and EDTA bind calcium ions.

Calcium is essential for several steps in the coagulation cascade.

Reducing the availability of **ionized calcium (Ca^{2+})** prevents blood coagulation.

Heparin

- Heparin is an anticoagulant that acts rapidly and has a relatively short duration of action.
- It is particularly useful when blood must circulate outside the body through artificial tubing and subsequently return to the patient's circulation.

Clinical applications:

A. Hemodialysis (Artificial Kidney Machine)

- During hemodialysis, blood is withdrawn from the patient's circulation, passed through an artificial kidney machine, and returned to the body.
- Because the blood comes into contact with artificial surfaces rather than normal vascular endothelium, coagulation may occur.
- **Heparin is administered to prevent clot formation within the extracorporeal circuit.**
- A hemodialysis session may last approximately **4 hours**.
- Because heparin has a relatively short duration of action, its anticoagulant effect gradually decreases after administration is stopped, provided no additional doses are given.

B. Cardiopulmonary Bypass (Heart-Lung Machine)

- During cardiopulmonary bypass, blood circulates through an external heart-lung machine.
- Contact with the artificial tubing and surfaces can activate coagulation.
- Heparin is administered to maintain blood in a fluid state during extracorporeal circulation.

Comparison with Warfarin

- **Heparin:** Has a rapid onset of anticoagulant action and a relatively short duration of action.
- **Warfarin:** Has a delayed onset of anticoagulant action.

Thromboembolic Conditions

Causes

- A thrombus → an abnormal clot that develops in a blood vessel.
- An embolus → freely flowing clots.
- Emboli that originate in large arteries or in the left side of the heart → brain, kidneys, or elsewhere.
- Emboli that originate in the venous system or in the right side of the → lungs (pulmonary embolism).

Deep vein thrombosis (DVT) may occur during late pregnancy or after prolonged sitting without movement. These situations can cause stagnation of blood flow, leading to the accumulation of clotting factors and promoting thrombus formation in the leg.

The affected leg may develop swelling and erythema.

However, the most dangerous complication occurs when a piece of the thrombus breaks off and travels through the venous circulation to the heart and then to the lungs, causing a pulmonary embolism, which can be fatal.

- If an embolus originates in the heart, it may travel through the arterial circulation and obstruct blood vessels in organs such as the brain or kidneys.

Thromboembolic Conditions

Causes

- **Cause of Thromboembolic Conditions**

(1) Any roughened endothelial surface of a vessel—as may be caused by arteriosclerosis, infection, or trauma—is likely to initiate the clotting process.

- In atherosclerosis, cholesterol accumulates in the arterial wall, forming plaques that may damage the endothelium.
- Any factor that damages the endothelium can promote thrombus formation.
- Inflammation and tissue damage may also contribute to this process.

(2) Blood often clots when it flows very slowly through blood vessels, where small quantities of thrombin and other procoagulants are always being formed.

Anything that disrupts normal blood flow can increase the risk of thrombus formation.

For example, a patient with **atherosclerosis** may have narrowing of the blood vessel, which can disturb blood flow.

Cardiac arrhythmias, such as atrial fibrillation, can disrupt normal blood flow within the heart, causing blood stasis and increasing the risk of thrombus formation.

A thrombus formed in the heart may detach and become an **embolus**. If it enters the systemic circulation, it may travel to the brain and cause a stroke.

These factors may be associated with tissue damage, which can initiate the clotting process. They are considered potential **intrinsic factors** according to the lecture.

SLIDES NOTES:

Several factors, acting independently or simultaneously, can cause *thromboembolism*:

- (1) Roughened vessel surfaces associated with atherosclerosis can lead to thrombus formation
- (2) Imbalances in the clotting–anticlotting systems can trigger clot formation.
- (3) Slow-moving blood is more apt to clot, probably because small quantities of fibrin accumulate in the stagnant blood, for example, in blood pooled in varicose leg veins or pooled in ineffectively pumping atria during atrial fibrillation
- (4) Widespread clotting is occasionally triggered by release of tissue thromboplastin into the blood from large amounts of traumatized tissue. Widespread clotting can occur in **septicemic shock**, in which bacteria or their toxins initiate the clotting cascade.

- **Disseminated Intravascular Coagulation**
- This often results from the presence of **large amounts of traumatized tissue** in the body that releases **great quantities of tissue factor** into the blood.
- **Septicemia**, in which either circulating bacteria or bacterial toxin
- Plugging of small peripheral vessels greatly diminishes delivery of oxygen and other nutrients to the tissues.
- Bleeding → The reason for this is that so many of the clotting factors are removed by the widespread clotting

The doctor's explanation of the previous slide:

❑ **Disseminated Intravascular Coagulation (DIC)**

Severe bacterial infection spreading into the bloodstream and causing extensive tissue damage may lead to the release of large amounts of tissue factor, activating the extrinsic coagulation pathway. This can lead to Disseminated Intravascular Coagulation (DIC), a serious complication characterized by widespread clot formation throughout the circulation.

DIC is a critical condition associated with a high mortality rate, and its treatment can be challenging.

❑ **Why do patients with DIC develop both clotting and bleeding?**

Clotting: Excessive activation of coagulation leads to widespread thrombus formation.

Bleeding: Clotting factors and platelets are consumed during widespread clot formation. The liver cannot synthesize and replace the consumed clotting factors quickly enough, resulting in an increased risk of bleeding.

This makes treatment challenging because anticoagulants may worsen the bleeding.

*Warfarin acts as a vitamin K antagonist, reducing the synthesis of functional vitamin K-dependent clotting factors by the liver.

What happens when different components fail?

- If platelet number or function is impaired →
the rapid seal at small vascular injuries becomes less effective. This commonly produces **mucocutaneous bleeding**: petechiae, nosebleeds, gingival bleeding, or heavy menstrual bleeding.

Small tiny bleedings



Hemostasis

Hemophilia A: Factor VIII deficiency. 85%

Hemophilia B: Factor IX deficiency. 15%

Both are **X-linked recessive disorders** and can cause significant bleeding.

Clinical features:

Prolonged bleeding: Bleeding may continue for a long time after an injury and may require medical intervention to stop.

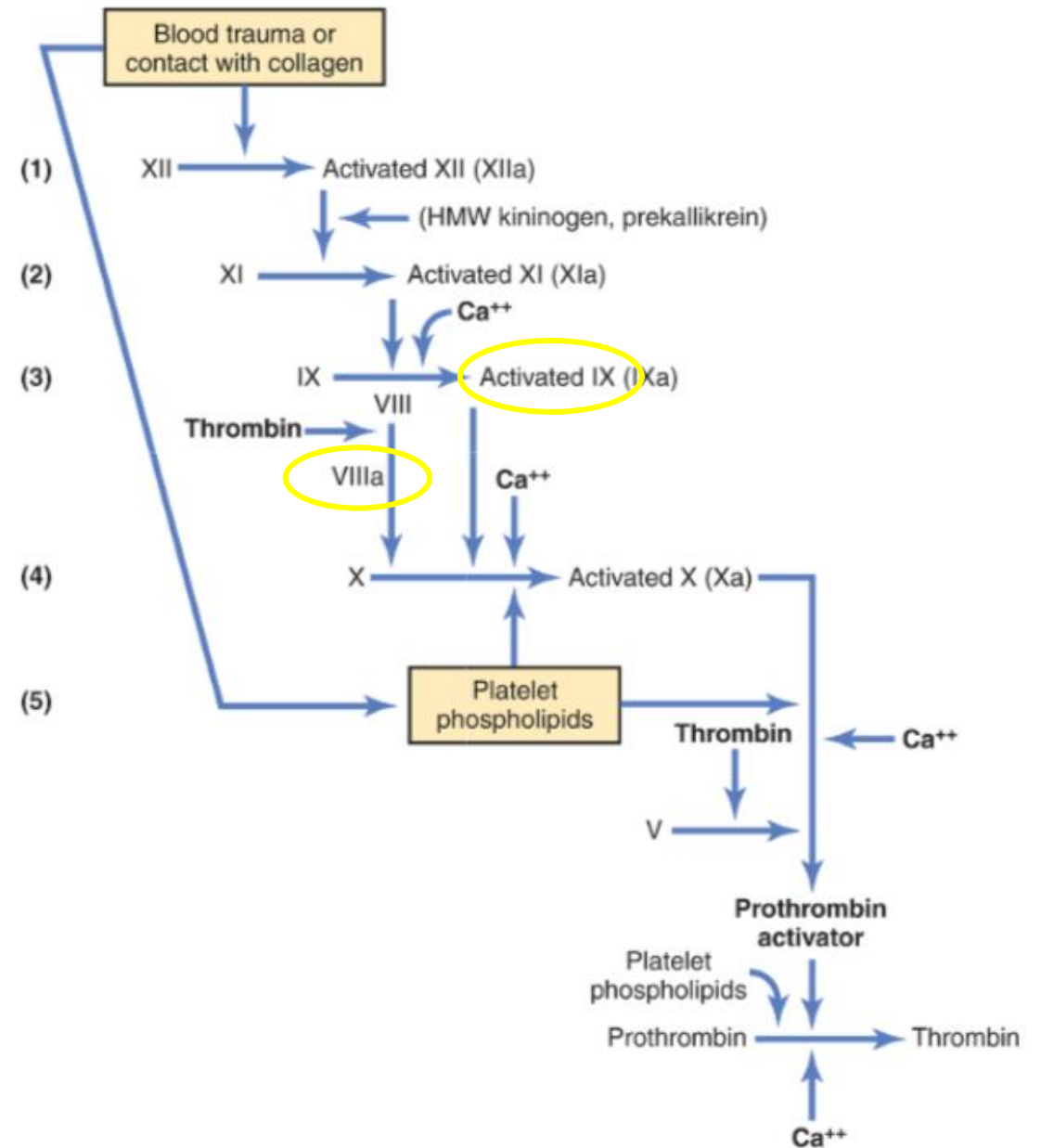
Circumcision: Persistent bleeding after circumcision in a newborn boy may be an early sign of hemophilia.

Bruising: As the child grows and experiences falls or minor injuries, bruising may occur.

Hemarthrosis: Repeated bleeding into joints can cause blood to accumulate within the joint space.

Hematomas: Blood may accumulate beneath the skin, forming hematomas.

These findings are associated with impaired blood coagulation due to clotting factor deficiency.



- ** Hemophilia A and B are X-linked disorders that predominantly affect males.
- ** Patients with more severe hemophilia are more likely to have spontaneous bleeding.
- ** Immediate and delayed bleeding after trauma is common
- ** Common sites of bleeding in newborns include the central nervous system, and sites of medical interventions including circumcision, heel sticks, and venipunctures.
- ** **Children** – Bruising, joint bleeds, and other sites of musculoskeletal, and oral bleeding.
- ** ** **factor XII** is activated by coming into contact with either exposed collagen in an injured vessel or a foreign surface such as a glass test tube

What happens when different components fail?

- If platelet number or function is impaired →
the rapid seal at small vascular injuries becomes less effective. This commonly produces **mucocutaneous bleeding**: petechiae, nosebleeds, gingival bleeding, or heavy menstrual bleeding.
- If coagulation factors are deficient →
the initial platelet plug may form, but fibrin reinforcement is impaired. Severe factor deficiencies more typically produce **deep bleeding**, including muscle hematomas and bleeding into joints

PT and aPTT

Time to form a fibrin clot in citrated, platelet-poor plasma

	PT It is used to monitor the anticoagulant effect of warfarin.	aPTT (often called PTT)
Full name	Prothrombin time	Activated partial thromboplastin time
Reagents added	Tissue factor, phospholipid + calcium	Contact activator, phospholipid + calcium
Pathways assessed	Extrinsic + common	Intrinsic + common
Factors assessed	VII + X, V, II, I	XII, XI, IX, VIII + X, V, II, I
Typical prolongation	Factor VII deficiency	Hemophilia A or B
Range	12-14 seconds	25-30 seconds

****INR is a calculated standardized expression of PT, not another independently measured clotting time and not derived from aPTT.**

**** INR Without warfarin: approximately 1.0**

Common warfarin target: 2.0–3.0

The target depends on the indication

رسالة من الفريق العلمي:

اللهم بارك لنا في وقتنا وعلمنا، وافتح علينا فتوح العارفين، وارزقنا فهم النبيين
وحفظ المرسلين، ووفقنا لما تحب وترضى، واجعل هذا العلم حجةً لنا لا علينا،
وانفعنا به وانفع بنا، يا رب العالمين

For any feedback, scan the code or click on it.



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			