Pharmacology

Dentistry Department

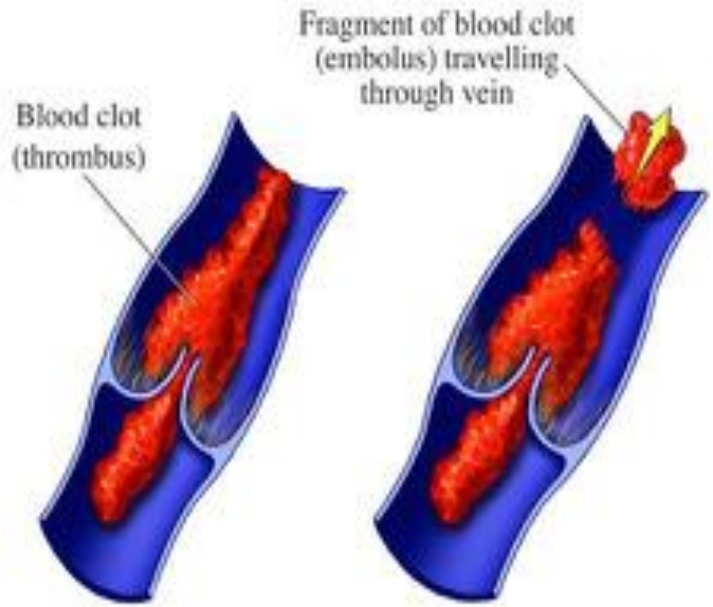
3rd Grade

Anticoagulant and Antiplatelet Agents

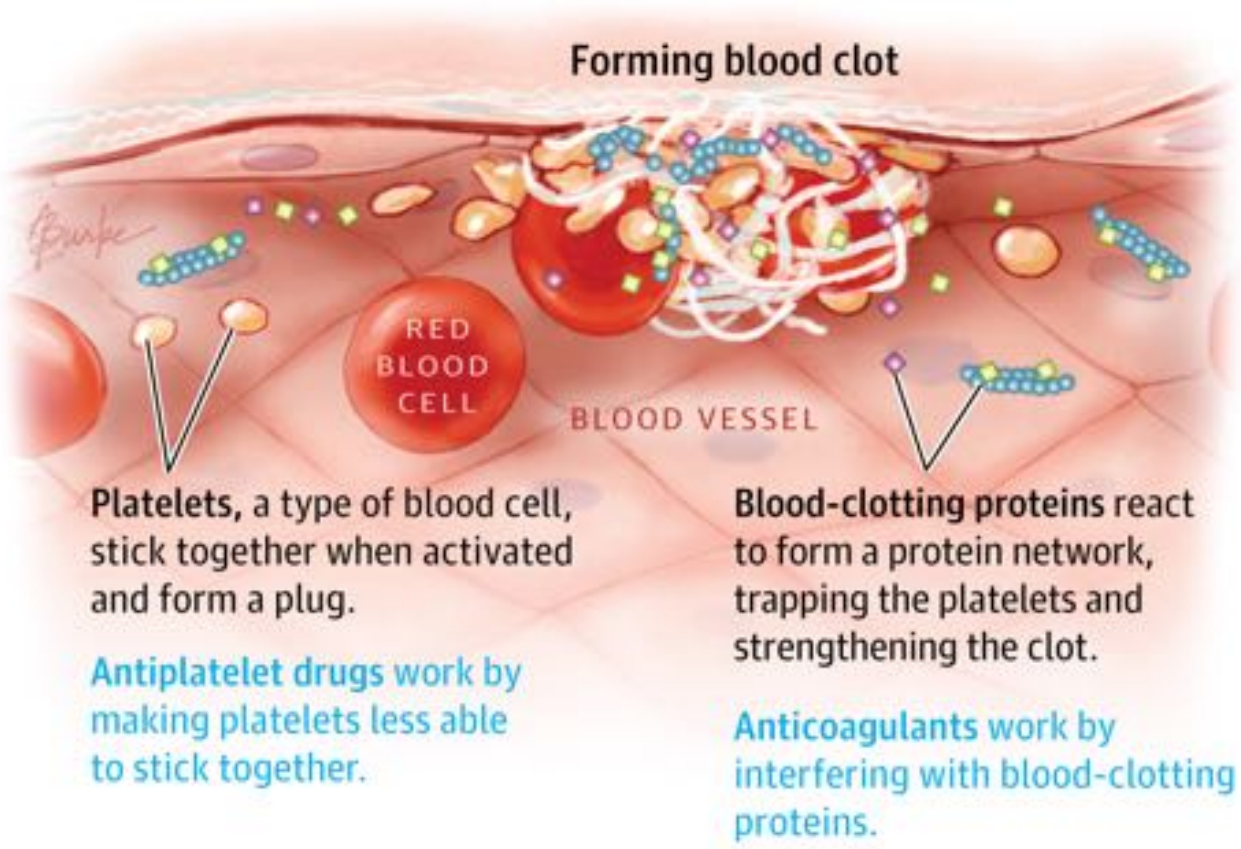
Dr. Ali Al-Athari

OVERVIEW:

- **Thrombosis:** is the **formation of an unwanted clot within a blood vessel**, and it is the most common abnormality of hemostasis.
- **Thrombotic disorders include acute myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary embolism (PE), and acute ischemic stroke.**
- A **clot that adheres to a vessel wall is called a "thrombus,"** whereas an ***intravascular clot that floats in the blood is termed an "embolus."*** Thus**, a detached thrombus becomes an embolus.**
- Both thrombi and emboli are dangerous, because they may **occlude blood vessels and deprive tissues of oxygen and nutrients.**

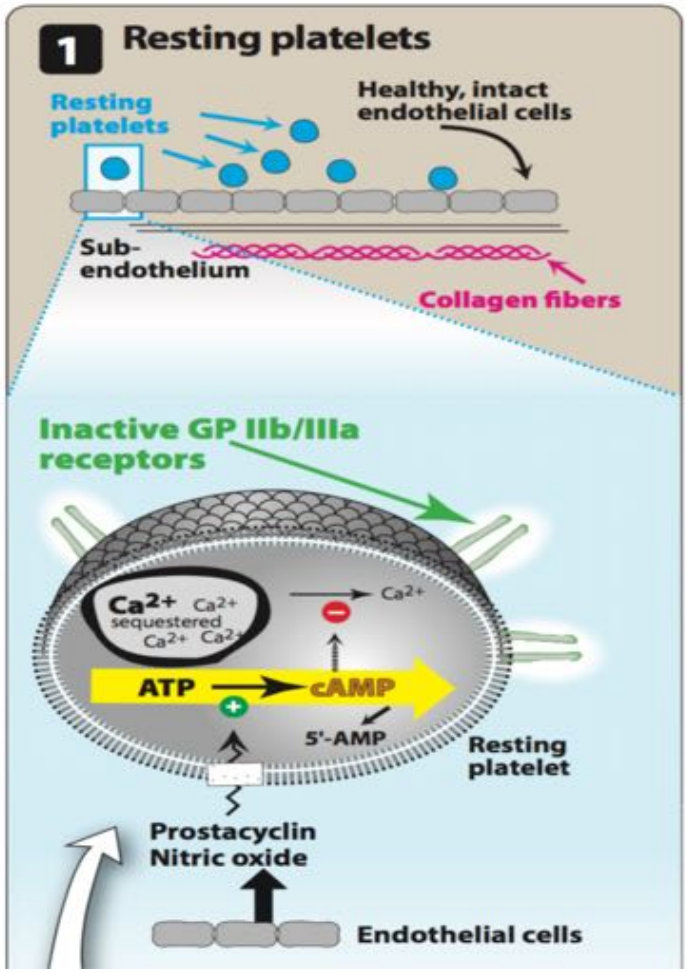


Antiplatelets and Anticoagulants Drugs



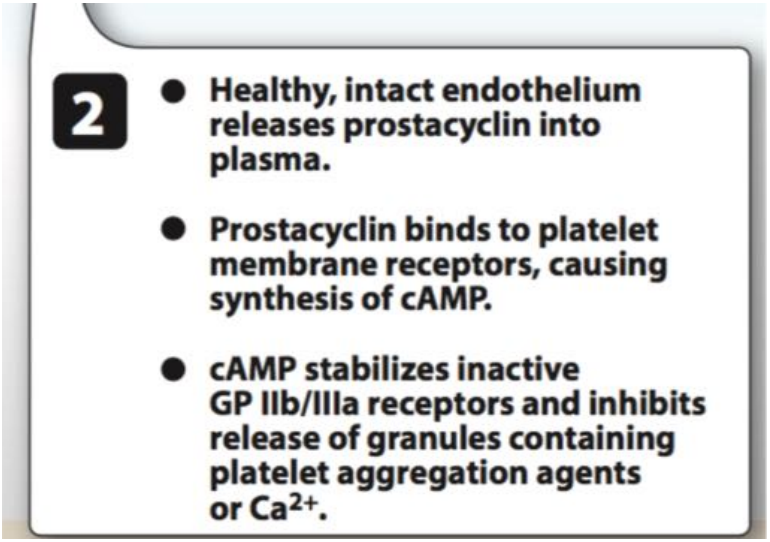
PLATELET RESPONSE TO VASCULAR INJURY:

- **Physical trauma to the vascular system**, such as a puncture or a cut, initiates a complex series of interactions between **platelets, endothelial cells, and the coagulation cascade.** These interactions lead to **hemostasis or the cessation of blood loss from a damaged blood vessel**. Platelets are central in this process.
- Initially, there is **vasospasm** of the damaged blood vessel to prevent further blood loss.
- The next step involves the formation of a **platelet–fibrin plug** *at the site of the puncture.*
- The creation of an **unwanted thrombus** involves many of the same steps as normal clot formation, **except that the triggering stimulus is a pathologic condition in the vascular system, rather than external physical trauma.**



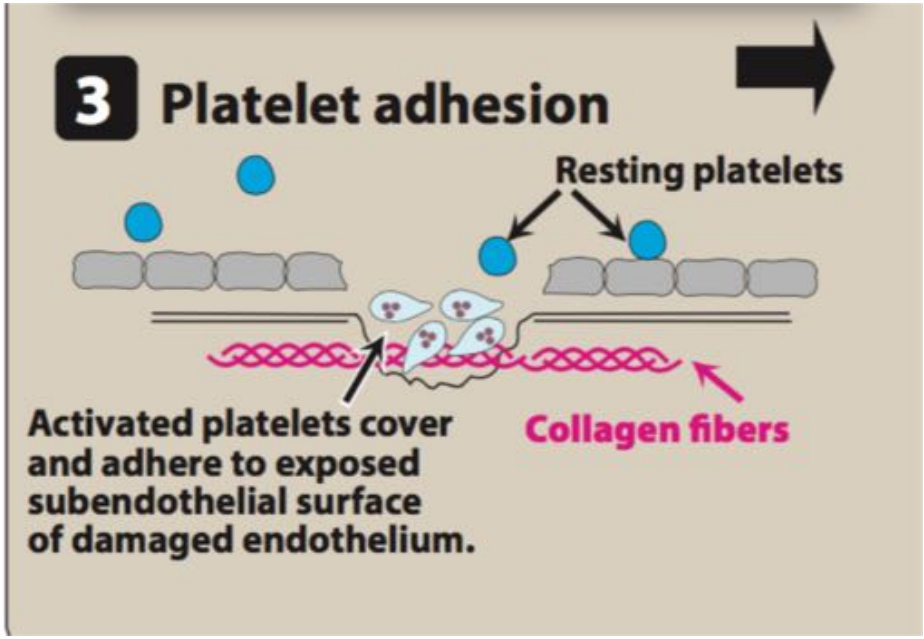
A. Resting platelets:

- **Platelets** act as vascular sentries, monitoring the **integrity of the vascular endothelium**.
- **In the absence of injury**, resting platelets circulate freely, because: In the normal vessel the **intact endothelium covers the collagen** in the subendothelial layers and the healthy, intact endothelium **releases prostacyclin** into plasma.



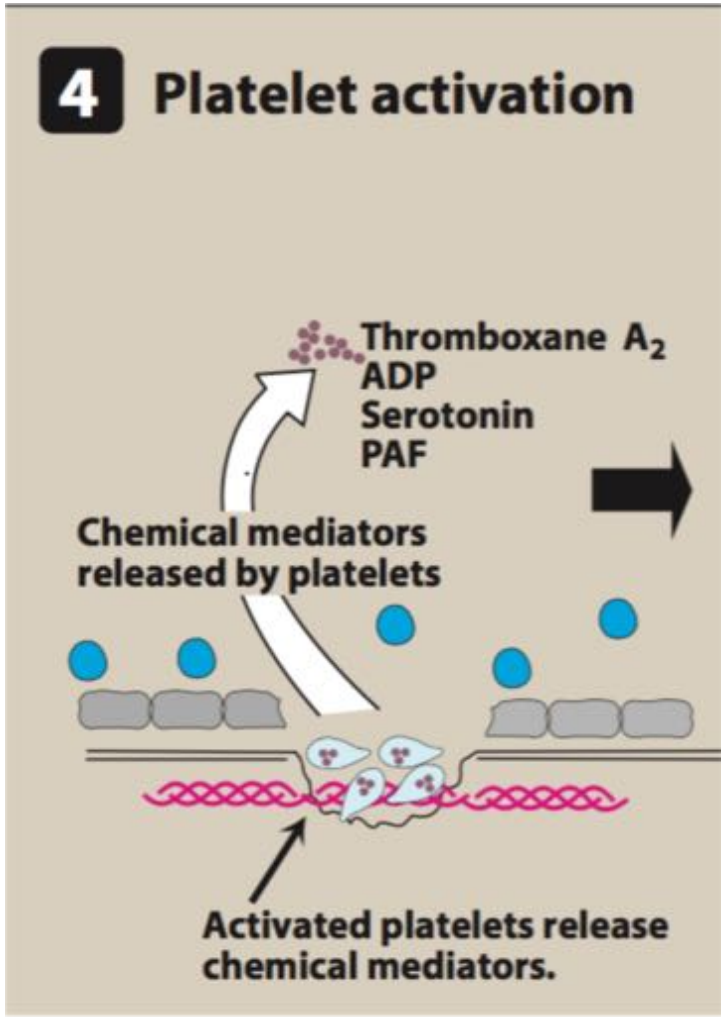
B. Platelet adhesion

- When **the endothelium is injured**, **platelets adhere to the exposed collagen of the sub-endothelium** .
- This triggers a complex series of chemical reactions, resulting in ***platelet activation***.



C. Platelet activation

- **Receptors on the surface of the adhering platelets are activated by the collagen of the underlying connective tissue**.
- This causes morphologic changes in platelets and the release of platelet granules containing chemical mediators, such as **adenosine diphosphate (ADP), thromboxane A2, serotonin, platelet activation factor, and thrombin.**
- These signaling molecules bind to **receptors in the outer membrane of resting platelets circulating nearby.** These receptors function as **sensors that are activated by the signals sent from the adhering platelets. The previously dormant platelets become activated and start to aggregate.**
- These actions are mediated by several messenger systems that ultimately result **in elevated levels of calcium and a decreased concentration of cAMP within the platelet.**



D. Platelet aggregation:

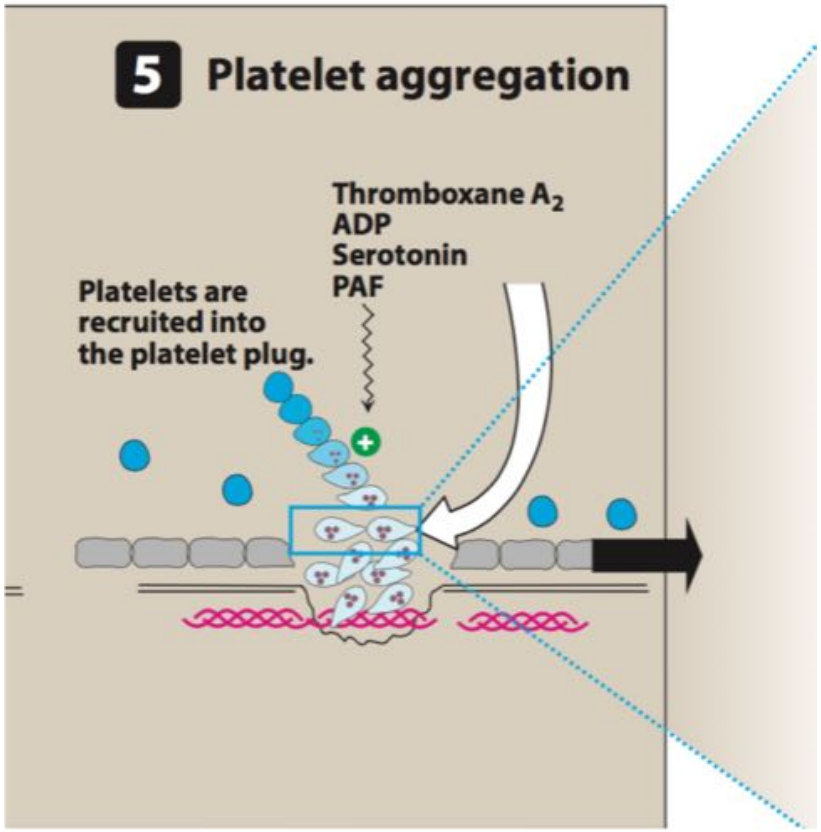
The increase in cytosolic calcium accompanying activation is due to a release of sequestered stores within the platelet which leads to:

1) the **release of platelet granules** containing mediators, such as **ADP and serotonin that activate other platelets**.

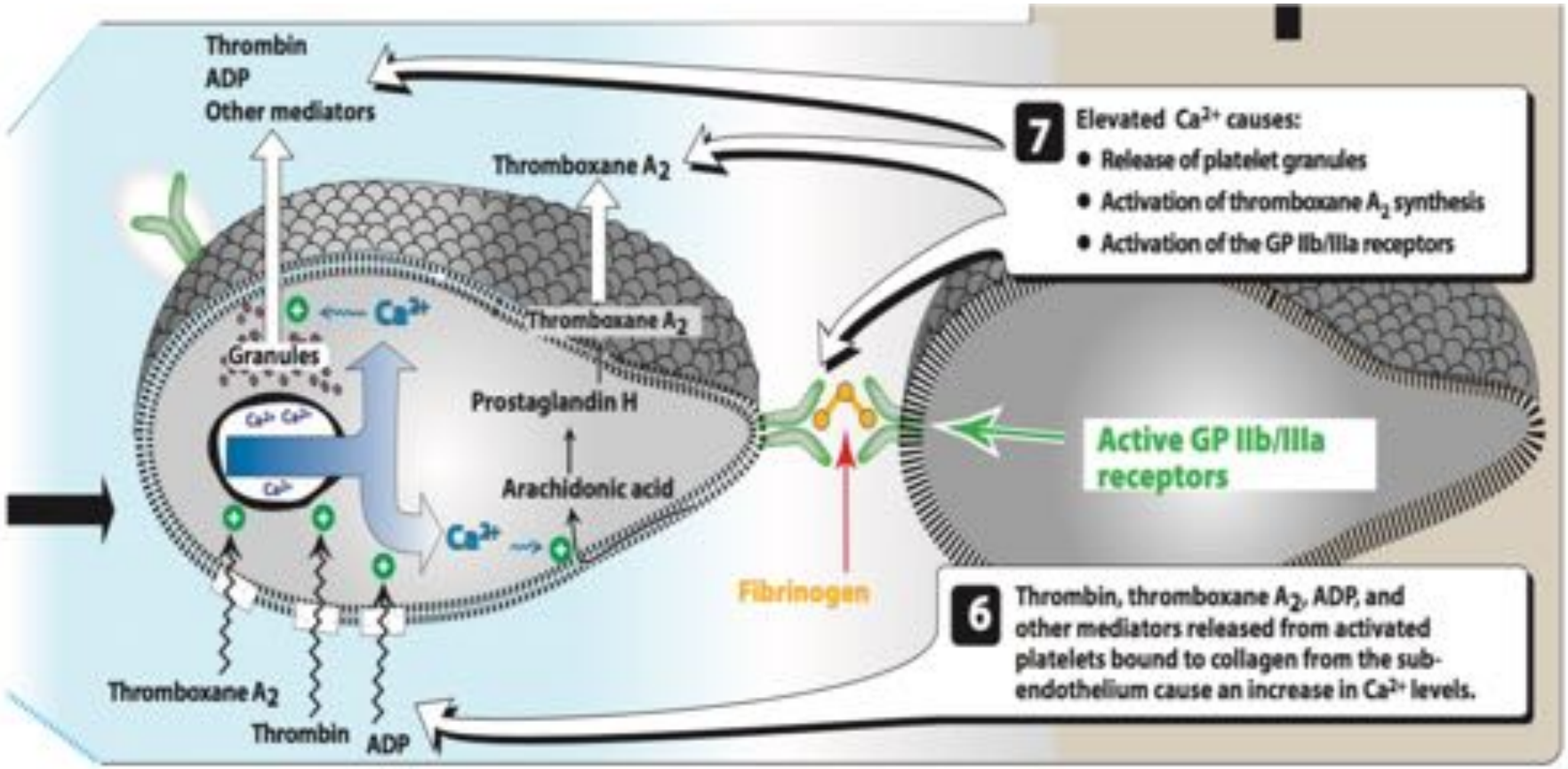
2) activation of **thromboxane A2 synthesis**.

3) **activation of glycoprotein (GP) IIb/IIIa receptors** that **bind fibrinogen and, ultimately, regulate platelet–platelet interaction** and thrombus formation.

- **Fibrinogen,** a soluble plasma GP**, simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and platelet aggregation.** This leads to an avalanche of platelet aggregation, because each activated platelet can recruit other platelets.

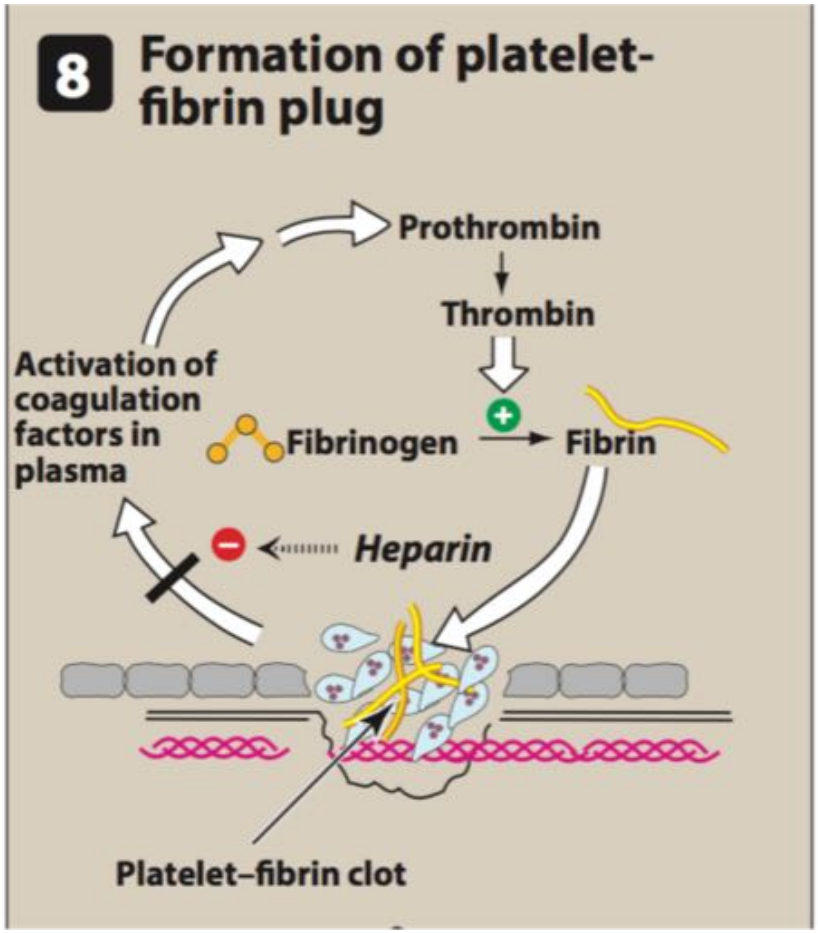


D. Platelet aggregation:



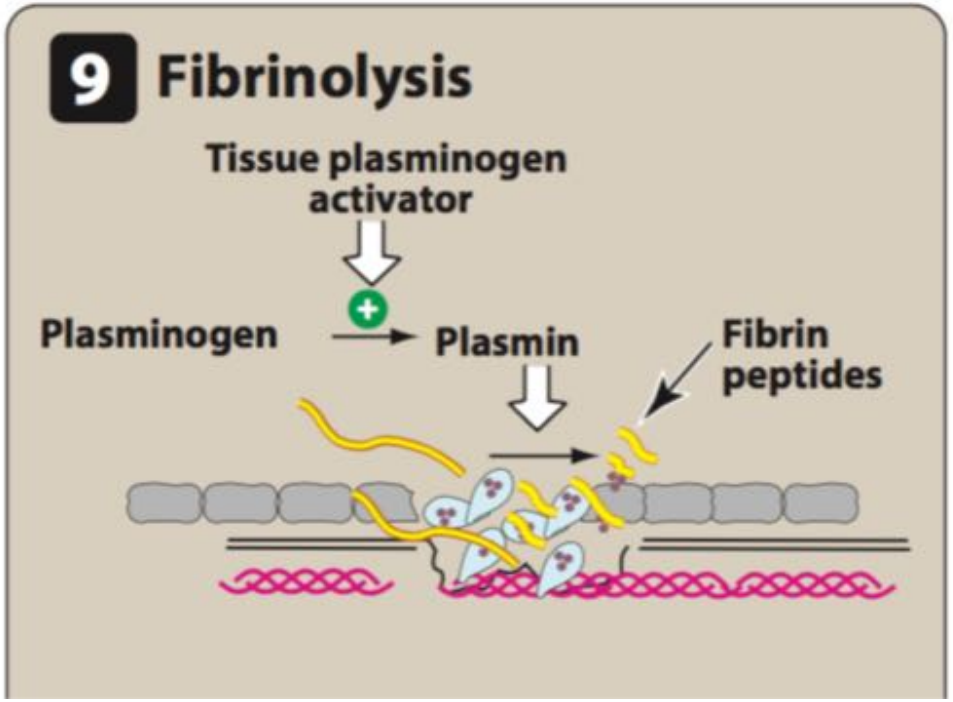
E. Formation of a clot

- **Local stimulation of the coagulation cascade by tissue factors released from the injured tissue and by mediators on the surface of platelets results in the formation of thrombin (factor IIa).**
- In turn, **thrombin, a serine protease, catalyzes the hydrolysis of fibrinogen to fibrin, which is incorporated into the clot**. Subsequent **cross-linking of the fibrin strands stabilizes the clot** and forms a hemostatic **platelet–fibrin plug**



F. Fibrinolysis

- During clot formation, the fibrinolytic pathway is locally activated. **Plasminogen** is enzymatically processed to **plasmin (fibrinolysin)** by **plasminogen activators in the tissue** .
- ***Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal***.



PLATELET AGGREGATION INHIBITORS

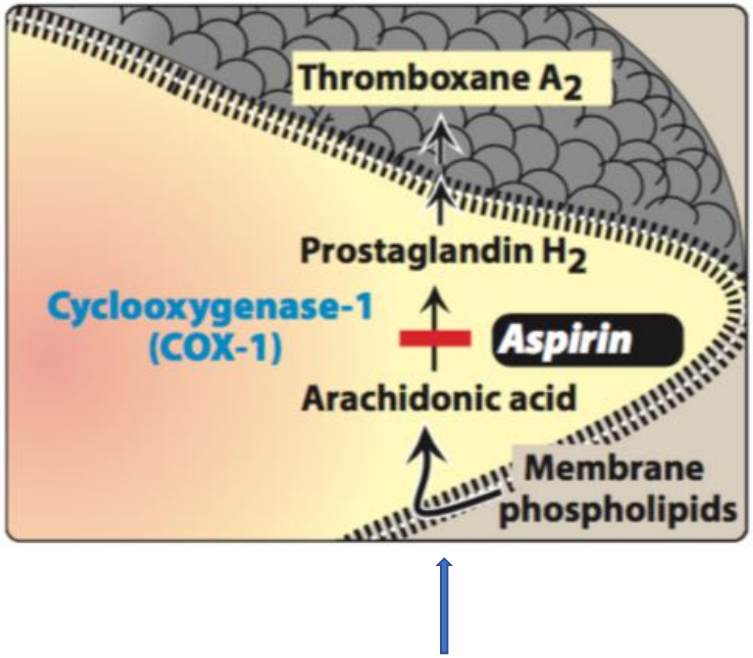
- Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation.
- The platelet aggregation inhibitors **inhibit cyclooxygenase-1 (COX-1)** or **block GP IIb/IIIa or ADP receptors**, thereby interfering with the signals that promote platelet aggregation.
- Because these agents have different mechanisms of actions**, synergistic or additive** effects may be achieved when agents from different classes are combined.
- These agents are beneficial in the prevention and treatment of **occlusive cardiovascular diseases**.

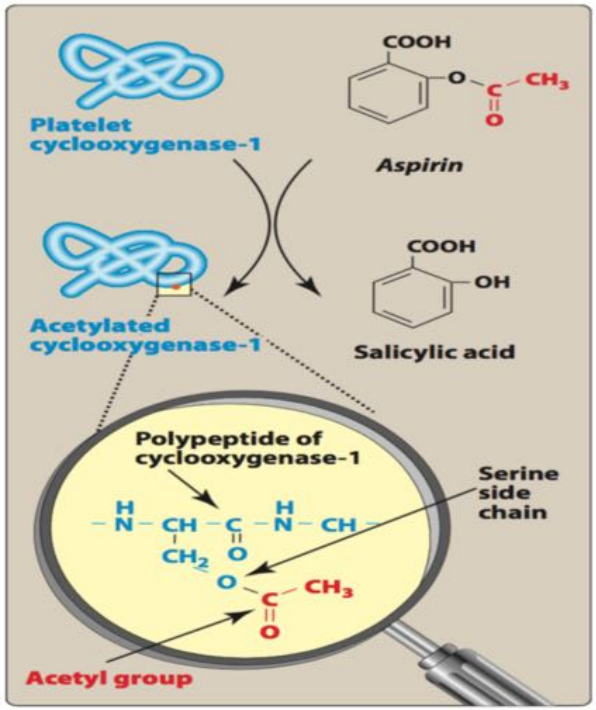
A. Aspirin

Mechanism of action:

- Stimulation of platelets by **thrombin**, **collagen**, and **ADP** results in activation of platelet membrane **phospholipases** that liberate **arachidonic acid from membrane phospholipids**.
- **Arachidonic acid** is first converted to **prostaglandin H2 by COX-1 Prostaglandin H2** is further metabolized to **thromboxane A2**, which is released into plasma.
- **Thromboxane A2 promotes the aggregation process** that is essential for the rapid formation of a hemostatic plug.
- ***Aspirin*** inhibits **thromboxane A2 synthesis by acetylation of a serine residue on the active site of COX-1**, **thereby irreversibly inactivating the enzyme.**
- This shifts the balance of chemical mediators to favor the antiaggregatory effects of **prostacyclin**, thereby preventing platelet aggregation.

- The inhibitory effect is rapid, and ***aspirin*-induced suppression of thromboxane A2 and the resulting suppression of platelet aggregation last for the life of the platelet, which is approximately 7 to 10 days.**
- ***Aspirin*** is the **only antiplatelet agent that irreversibly inhibits platelet function.**





Therapeutic use:

- *Aspirin* is used in the **prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent MI, and to decrease mortality in the setting of primary and secondary prevention of MI.**
- Complete inactivation of platelets occurs with **75 mg of *aspirin*** given daily. The recommended dose of *aspirin* ranges from **50 to 325 mg daily**.

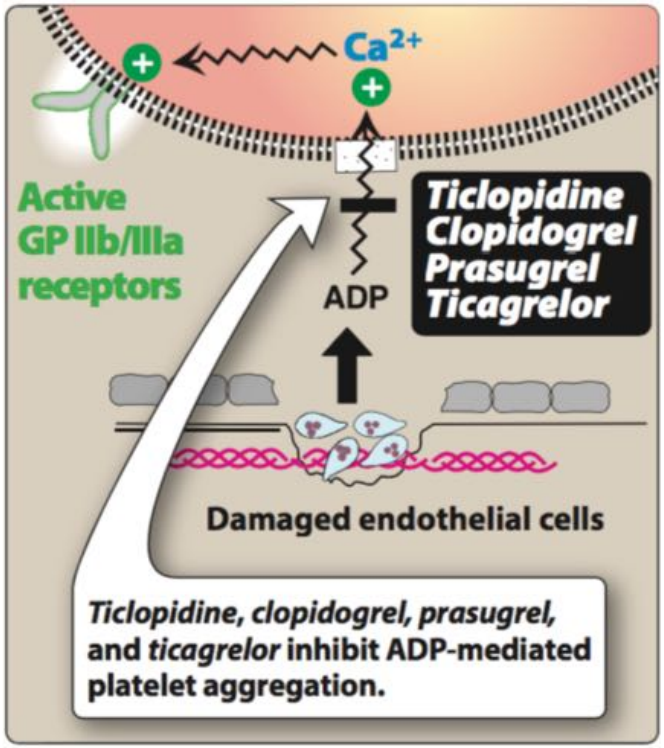
Adverse effects:

- **Higher doses of *aspirin*** increase drug-related toxicities as well as the probability that *aspirin* **may also inhibit prostacyclin production**.
- **Bleeding time is prolonged by *aspirin* treatment**, causing complications that include an increased incidence **of hemorrhagic stroke and gastrointestinal (GI) bleeding,** especially at higher doses of the drug.

B. Ticlopidine, clopidogrel, prasugrel, and ticagrelor

Mechanism of action:

- These drugs **inhibit the binding of ADP to its receptors on platelets** (P2Y12 **ADP receptors**) and, thereby, **inhibit the activation of the GP IIb/IIIa receptors** required for platelets to bind to fibrinogen and to each other .
- **The maximum inhibition of platelet aggregation** is achieved in 3 to 4 days with *ticlopidine*, and **3 to 5 days with *clopidogrel*.** When treatment is suspended, the platelet system requires time to recover.



Therapeutic use:

- *Clopidogrel* is approved for prevention of atherosclerotic events in patients with a recent **MI or stroke**. It is also approved for prophylaxis of thrombotic events in acute coronary syndromes **(unstable angina or MI).**
- *Ticlopidine* is similar in structure to *clopidogrel*. It is indicated for the prevention of **transient ischemic attacks (TIA) and strokes** in patients with a prior **cerebral thrombotic event.**

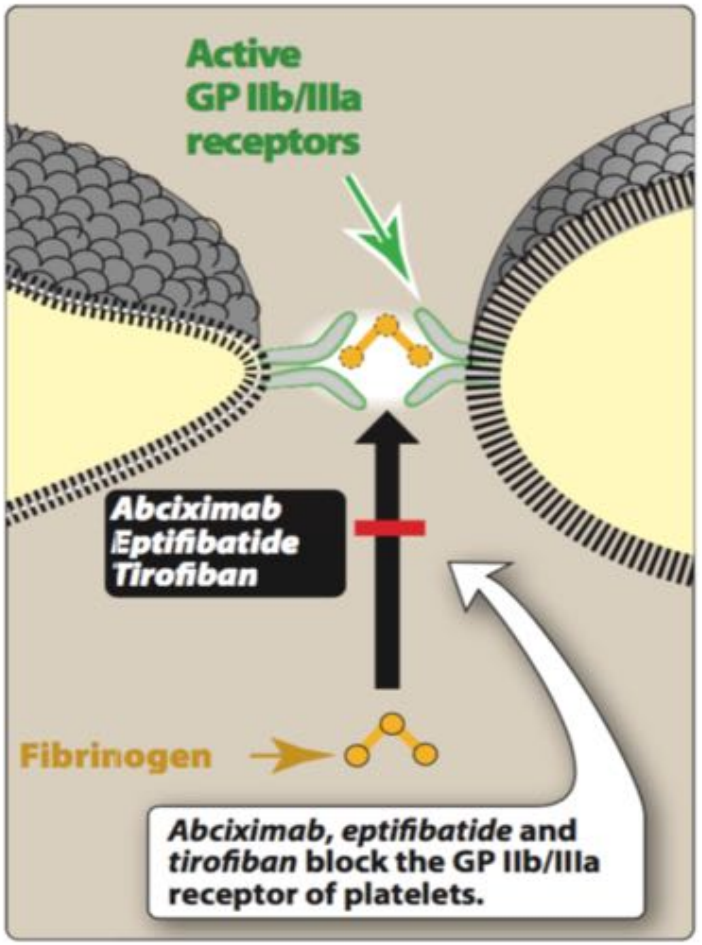
Adverse effects:

- These agents can cause prolonged bleeding for which there is no antidote.
- *Ticlopidine* is associated with **severe hematologic reactions that limit its use, such as agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia.**
- *Clopidogrel* causes fewer adverse reactions, and the incidence of neutropenia is lower.

C. Abciximab, eptifibatide, and tirofiban

Mechanism of action:

- The **GP IIb/IIIa receptor** plays a key role in stimulating **platelet aggregation. abciximab eptifibatide, and tirofiban inhibits the GP IIb/IIIa receptor complex**. By binding to **GP IIb/IIIa** these agents **blocks the binding of fibrinogen and, consequently, aggregation does not occur.**
- These agents are given intravenously, along with *heparin* and *aspirin* for **the prevention of cardiac ischemic complications.**
- The **major adverse effect** of these agents is **bleeding,** especially if used with anticoagulants.

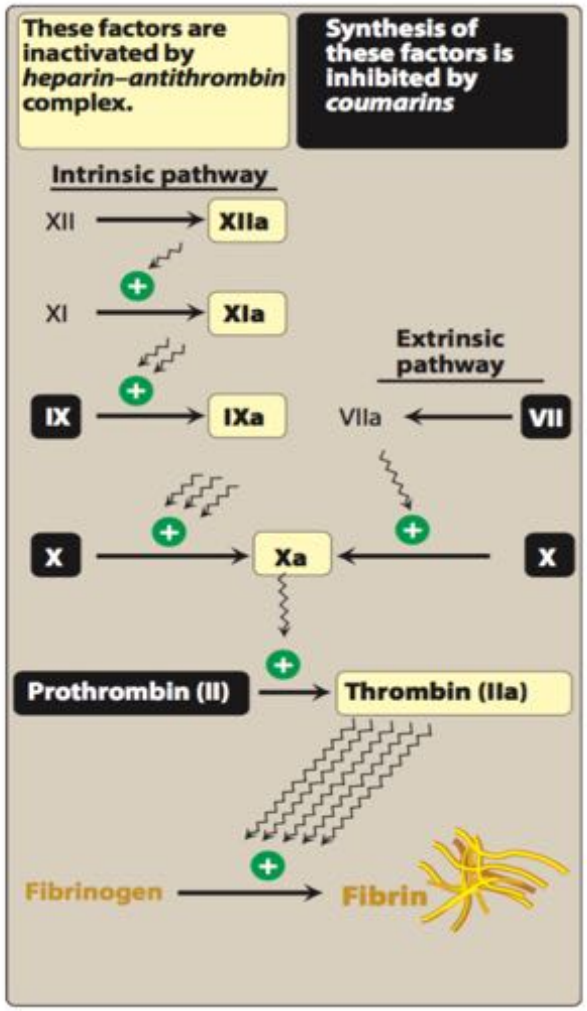


D. Dipyridamole

- *Dipyridamole is* a coronary vasodilator, **increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase**, thereby resulting in **decreased thromboxane A2 synthesis**. The drug may **potentiate the effect of prostacyclin to antagonize platelet stickiness and, therefore, decrease platelet adhesion to thrombogenic surfaces.**
- *Dipyridamole* is used for **stroke prevention** and is usually given in **combination with *aspirin***.
- **Patients with unstable angina should not use *dipyridamole*** because of its **vasodilating properties, which may worsen ischemia (coronary steal phenomenon).**
- *Dipyridamole* commonly causes headache and can lead to orthostatic hypotension (especially if administered IV).

BLOOD COAGULATION

- The coagulation process that generates **thrombin** consists of two inter- related pathways, the **extrinsic and the intrinsic systems**.
- **The extrinsic system is initiated by the activation of clotting factor VII by tissue factor (also known as thromboplastin)**. Tissue factor is a membrane protein that is normally separated from the blood by the endothelial cells that line the vasculature. However, in response to vascular injury, tissue factor becomes exposed to blood. There it can bind and activate factor VII, initiating the extrinsic pathway.
- **The intrinsic system is triggered by the activation of clotting factor XII**. This occurs when blood comes into contact with the collagen in the damaged wall of a blood vessel.



A. Formation of fibrin

- Both the extrinsic and the intrinsic systems involve a cascade of enzyme reactions that sequentially transform various plasma factors (proenzymes) to their active (enzymatic) forms. **Ultimately, factor Xa is produced, which converts prothrombin (factor II) to thrombin (factor IIa)** .
- **Thrombin plays a key role in coagulation, because it is responsible for generation of fibrin**, which forms the mesh-like matrix of the blood clot. If thrombin is not formed or if its function is impeded (for example, by **antithrombin III**), coagulation is inhibited.

B. Inhibitors of coagulation

- It is important that coagulation is restricted to the local site of vascular injury. Endogenously, there are several inhibitors of coagulation factors, **including protein C, protein S, antithrombin III, and tissue factor pathway inhibitor**.
- The mechanism of action of several **anticoagulant agents, including *heparin* and heparin-related products, involves activation of these endogenous inhibitors (primarily antithrombin III).**

ANTICOAGULANTS

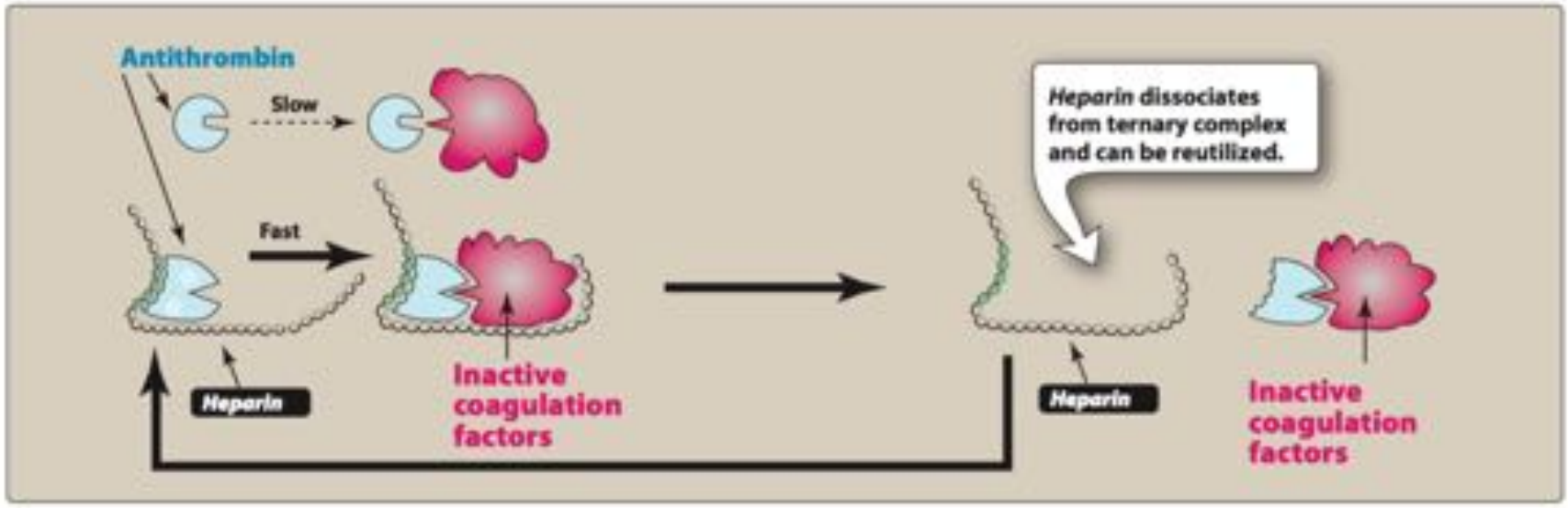
- The anticoagulant drugs **inhibit either the action of the coagulation factors (for example, *heparin*) or interfere with the synthesis of the coagulation factors (for example, vitamin K antagonists such as *warfarin*).**

A. Heparin and low molecular weight heparins:

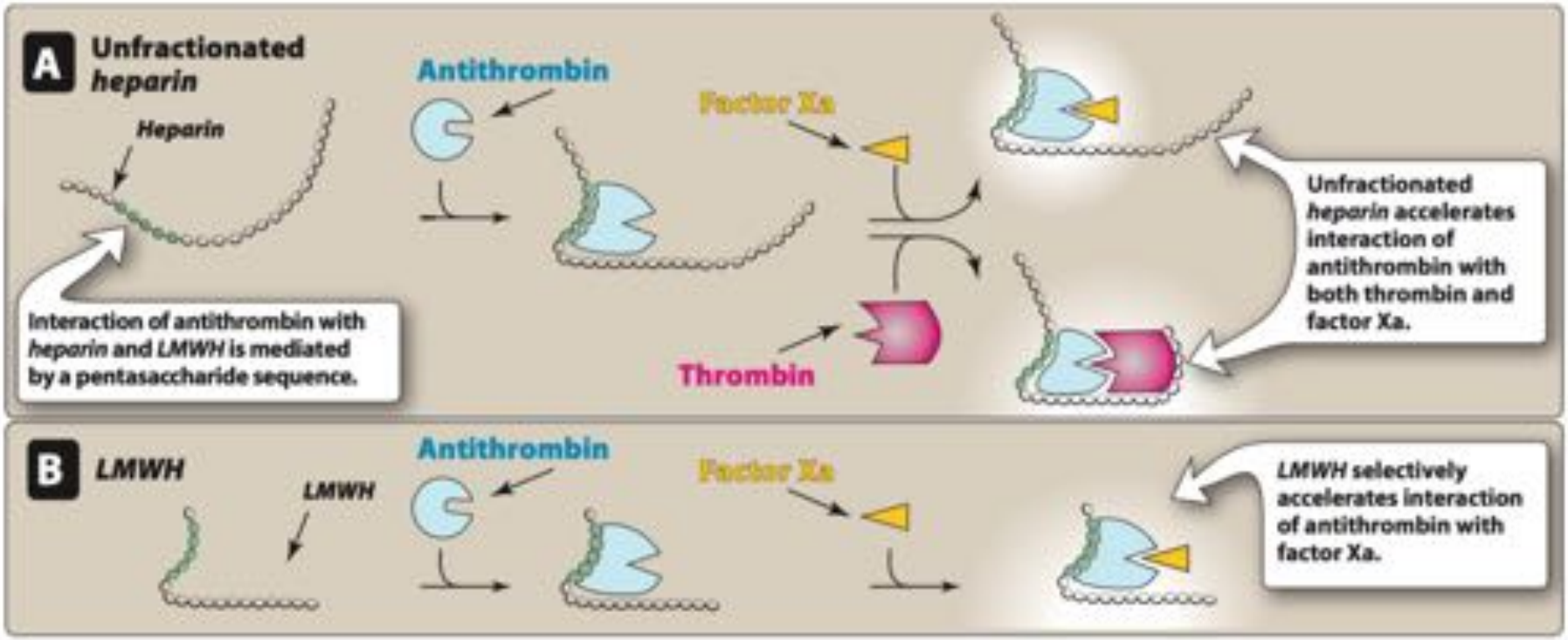
- *Heparin* is an injectable, **rapidly acting anticoagulant** that is often used acutely to interfere with the formation of thrombi.
- *Heparin* **occurs naturally as a macromolecule** complexed with histamine in mast cells, where its physiologic role is unknown.
- It is extracted for commercial use from **porcine intestinal mucosa**. **Unfractionated *heparin* is a mixture of** straight-chain, anionic glycosaminoglycans with **a wide range of molecular weights.**
- The realization that **low molecular weight forms of *heparin* (*LMWHs*)** can also act as anticoagulants led to the isolation of ***enoxaparin*** ,produced by enzymatic depolymerization of unfractionated *heparin*. Other LMWHs include ***dalteparin*** and ***tinzaparin*** .
- The *LMWHs* are about one-third the size of unfractionated *heparin*.

Mechanism of action:

- Heparin anticoagulant effect is a consequence of binding to **antithrombin III**, with the subsequent **rapid inactivation of coagulation factors.**
- **Antithrombin III** is an α globulin **that inhibits serine proteases of thrombin (factor IIa) and factor Xa .** In the absence of *heparin*, antithrombin III interacts very slowly with thrombin and factor Xa**. When *heparin* molecules bind to antithrombin III, a conformational change occurs that catalyzes the inhibition of thrombin about 1000-fold**



- ***LMWHs*** complex with **antithrombin III and inactivate factor Xa** (including that located on platelet surfaces) **but do not bind as avidly to thrombin.**



Therapeutic use:

- *Heparin* and the *LMWHs* **limit the expansion of thrombi by preventing fibrin formation. These agents are used for the treatment of acute venous thromboembolism (DVT or PE).**
- *Heparin* and *LMWHs* are also used for **prophylaxis of postoperative venous thrombosis in patients undergoing surgery** (for example, hip replacement) and those with acute MI.
- These drugs are the **anticoagulants of choice for treating pregnant women, because they do not cross the placenta, due to their large size and negative charge.**
- ***LMWHs* do not require the same intense monitoring as *heparin*, thereby saving laboratory costs and nursing time.** These advantages make *LMWHs* useful for both inpatient and outpatient therapy.

Pharmacokinetics:

- *Heparin* must be administered subcutaneously or intravenously, because the drug does not readily cross membranes .The *LMWHs* are administered subcutaneously.

- *Heparin* is often initiated as an intravenous bolus to achieve immediate anticoagulation. This is followed by lower doses or continuous infusion of *heparin*, **titrating the dose so that the activated partial thromboplastin time (aPTT) is 1.5- to 2.5-fold** that of the normal control.
- [Note: The **aPTT is the standard test used to monitor the extent of anticoagulation with *heparin***.]

- Whereas the **anticoagulant effect with *heparin* occurs within minutes of IV administration (or 1 to 2 hours after subcutaneous injection)**, **the maximum anti–factor Xa activity of the *LMWHs* occurs about 4 hours after subcutaneous injection.**

Pharmacokinetics:

- **It is usually not necessary to monitor coagulation values with *LMWHs* because the plasma levels and pharmacokinetics of these drugs are more predictable.** However, in renally impaired, pregnant, and obese patients, monitoring of factor Xa levels is recommended with *LMWHs*.
- In the blood, *heparin* binds to many proteins that neutralize its activity, causing unpredictable pharmacokinetics. *Heparin* binding to plasma proteins is variable in patients with thromboembolic diseases. Although generally restricted to the circulation, ***heparin* is taken up by the monocyte/macrophage system**, and it undergoes depolymerization and desulfation to inactive products. The inactive metabolites, as well as some of the parent *heparin* and *LMWHs*, are excreted into the urine.

Adverse effects:

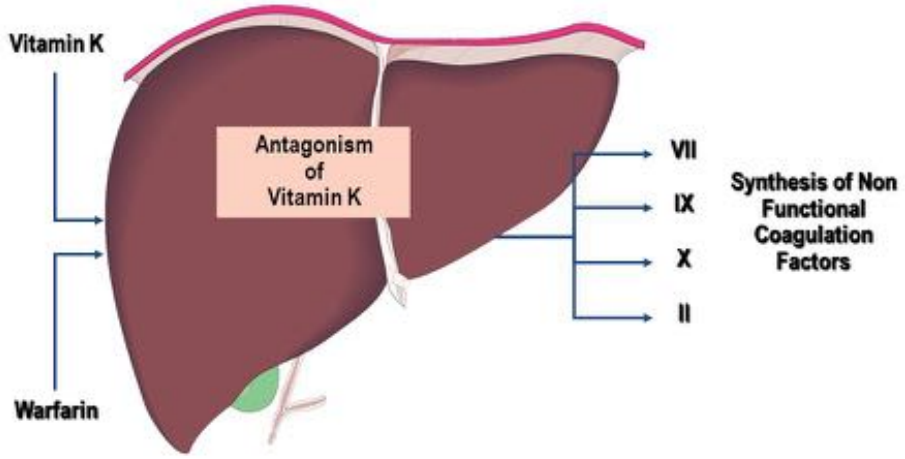
- The chief complication of *heparin* and *LMWH* therapy is **bleeding**. Careful monitoring of the patient and laboratory parameters is required to minimize bleeding. **Excessive bleeding** may be managed by **discontinuing the drug** or by **treating with *protamine sulfate***. When infused slowly, the latter **combines ionically with *heparin* to form a stable, 1:1 inactive complex**. It is very important that the dosage of *protamine sulfate* is carefully titrated (1 mg for every 100 units of *heparin* administered), because ***protamine sulfate* is a weak anticoagulant, and excess amounts may trigger bleeding episodes or worsen bleeding potential.**
- *Heparin* preparations are obtained from **porcine sources** and, therefore, may be **antigenic**. Possible adverse reactions include **chills, fever, urticaria, and anaphylactic shock.**
- *Heparin*-induced **thrombocytopenia (HIT)** is a serious condition, in which circulating blood contains an abnormally low number of platelets. This reaction is immune-mediated and carries a risk of venous and arterial embolism.
- ***Heparin* and *LMWHs* are contraindicated in patients** who have **hypersensitivity to *heparin*, bleeding disorders, alcoholism, or who have had recent surgery of the brain, eye, or spinal cord.**

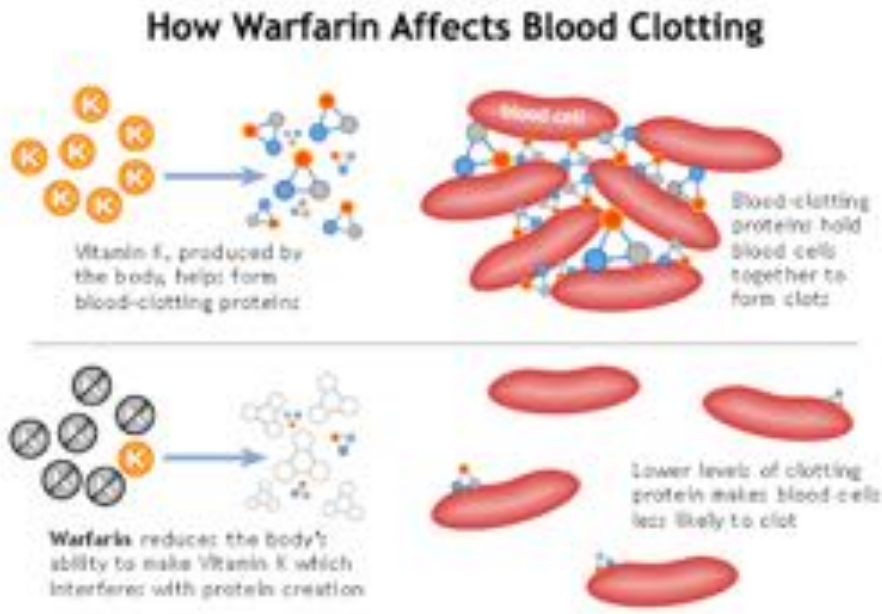
B-Warfarin:

- The **coumarin anticoagulants** owe their action to the ability to **antagonize the cofactor functions of vitamin K.** The only therapeutically relevant coumarin anticoagulant is ***warfarin*** .Initially used as a rodenticide, *warfarin* is now widely used clinically as an oral anticoagulant.
- The international normalized ratio (**INR)** is the **standard by which the anticoagulant activity of *warfarin* therapy is monitored**. The goal of ***warfarin* therapy is an INR of 2 to 3** for most indications.
- ***Warfarin* has a narrow therapeutic index**. Therefore, it is important that the INR is maintained within the optimal range as much as possible, and frequent monitoring may be required.

Mechanism of action:

- **Factors II, VII, IX, and X require vitamin K as a cofactor for their synthesis by the liver.**
- ***Warfarin* inhibit vitamin K regeneration in the liver by inhibiting the the enzyme vitamin K epoxide reductase.**





Mechanism of action:

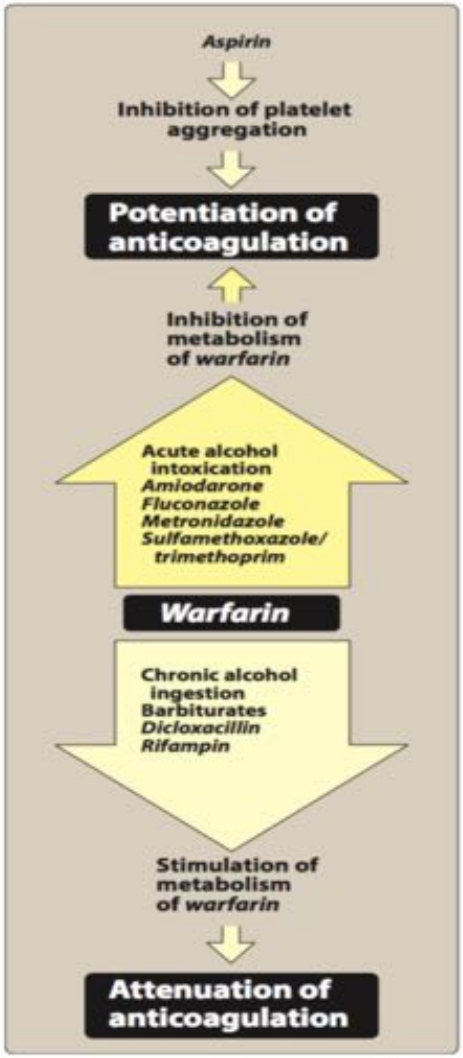
- *Warfarin* treatment results in the production of **clotting factors with diminished activity (10% to 40% of normal)**.
- **Unlike *heparin*, the anticoagulant effects of *warfarin* are not observed immediately after drug administration**. Instead, peak effects may be **delayed for 72 to 96 hours**, which is the time required to deplete the pool of circulating clotting factors.
- **The anticoagulant effects of *warfarin* can be overcome by the administration of *vitamin K*.** However, reversal following administration of *vitamin K* takes **approximately 24 hours** (the time necessary for degradation of already synthesized clotting factors).

Therapeutic use:

- *Warfarin* is used in the prevention and treatment of **DVT and PE, and stroke prevention.**
- It is also used for prevention of **venous thromboembolism during orthopedic or gynecologic surgery.**

Pharmacokinetics:

- *Warfarin* is **rapidly absorbed after oral administration** (100% bioavailability with little individual patient variation).
- ***Warfarin* is highly bound to plasma albumin**, which prevents its diffusion into the cerebrospinal fluid, urine, and breast milk. However, **drugs that have a greater affinity for the albumin-binding site, such as sulfonamides, can displace the anticoagulant and lead to a transient, elevated activity.**
- ***Warfarin* is metabolized by the CYP450 system to inactive components.** After conjugation to glucuronic acid, the inactive metabolites are excreted in urine and feces. **Agents that affect the metabolism of *warfarin* may alter its therapeutic effects.**
- *Warfarin* has numerous drug interactions that may potentiate or attenuate its anticoagulant effect.



Adverse effects:

- The principal adverse effect of *warfarin* is **hemorrhage**, and the agent has a black box warning for bleeding risk. Therefore, it is important to **frequently monitor the INR and adjust the dose of *warfarin*.**
- **Minor bleeding may be treated by withdrawal of the drug or administration of oral *vitamin K1,*** but **severe bleeding may require greater doses of *vitamin K* given intravenously. Whole blood, frozen plasma, and plasma concentrates of blood factors may also be used for rapid reversal of *warfarin*.**
- ***Warfarin* is teratogenic and should never be used during pregnancy.** If anticoagulant therapy is needed during pregnancy, *heparin* or *LMWH* may be administered.


Thank
you!