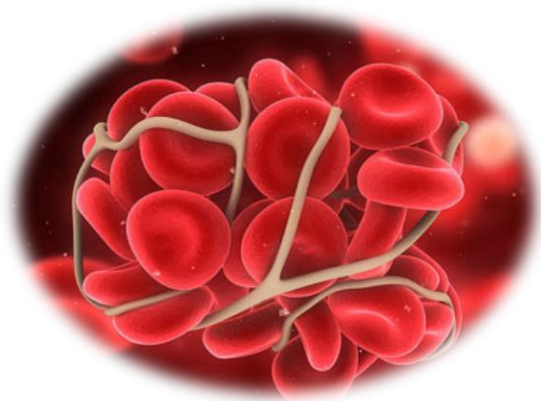




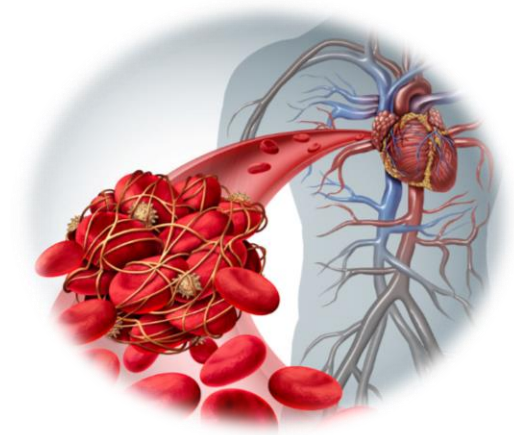
Mustansiriyah University
College of Pharmacy
Depart. of Pharmacology and Toxicology



Anticoagulants and Antiplatelet Agents



Pharmacology 4th Stage
November , 2024

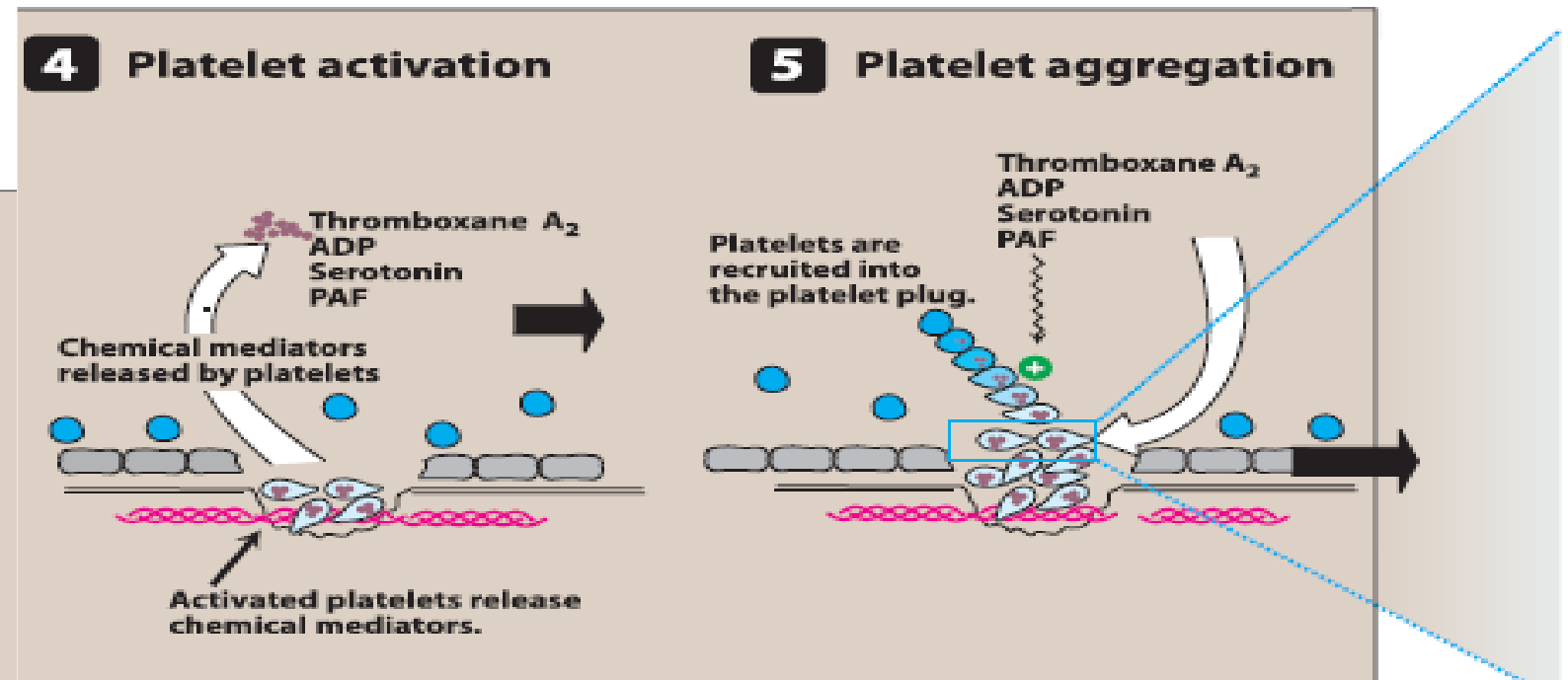
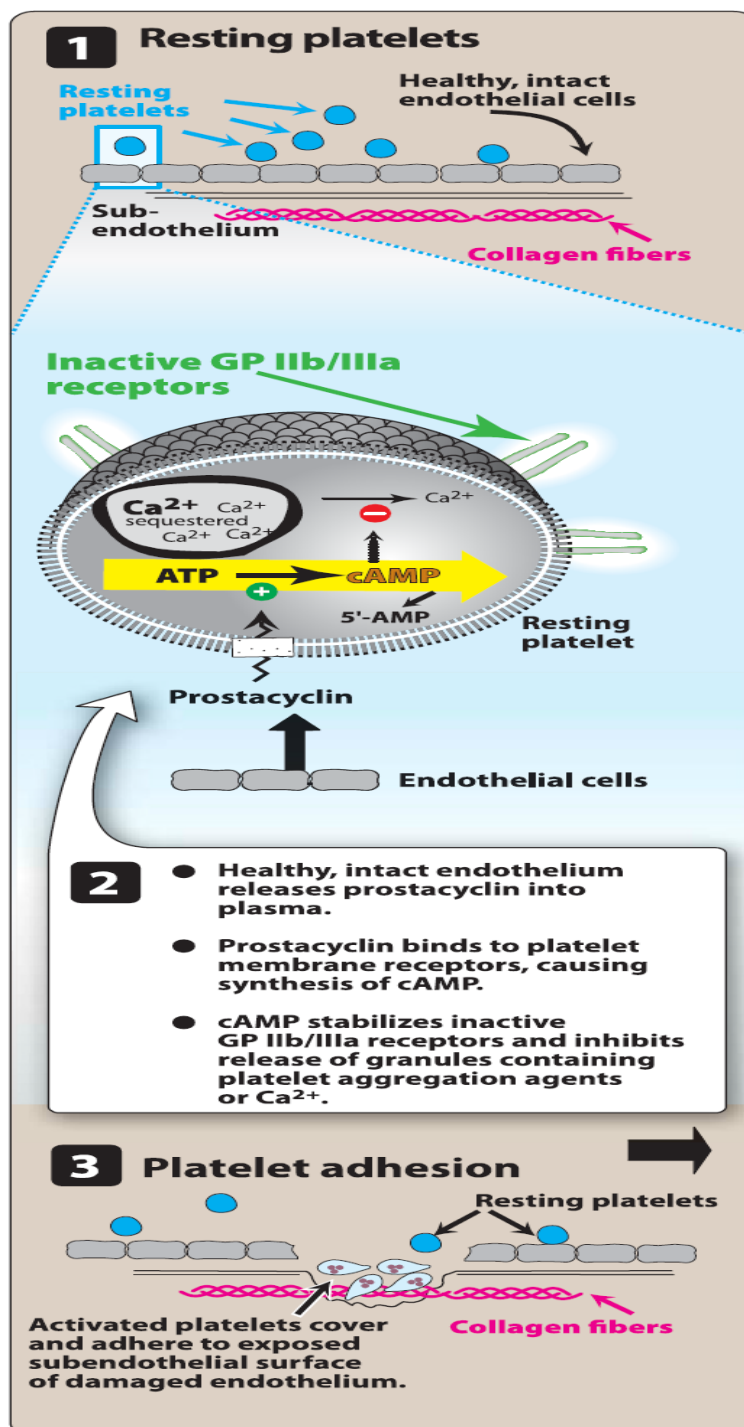


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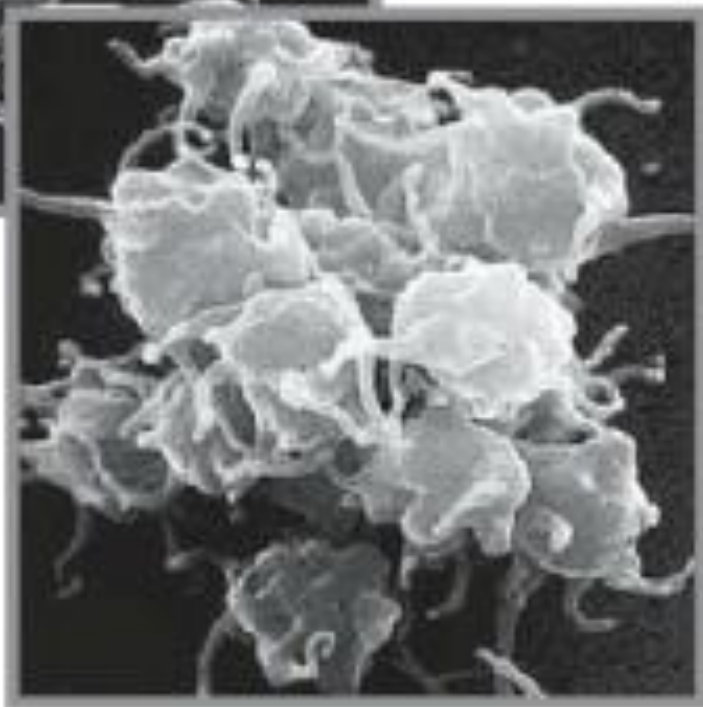
Thrombus Versus Embolus

- Clot that adheres to a vessel wall is called a thrombus: whereas an intravascular clot that floats in the blood is termed an embolus
- Detached thrombus becomes an embolus. Both may occlude blood vessels and deprive tissues of oxygen and nutrients.
Arterial thrombosis most often occurs in medium sized vessels rendered thrombogenic by atherosclerosis.
- **Arterial thrombosis** usually consists of a platelet-rich clot. In contrast, **venous thrombosis** is triggered by blood stasis or inappropriate activation of the coagulation cascade (fibrin with fewer platelets).

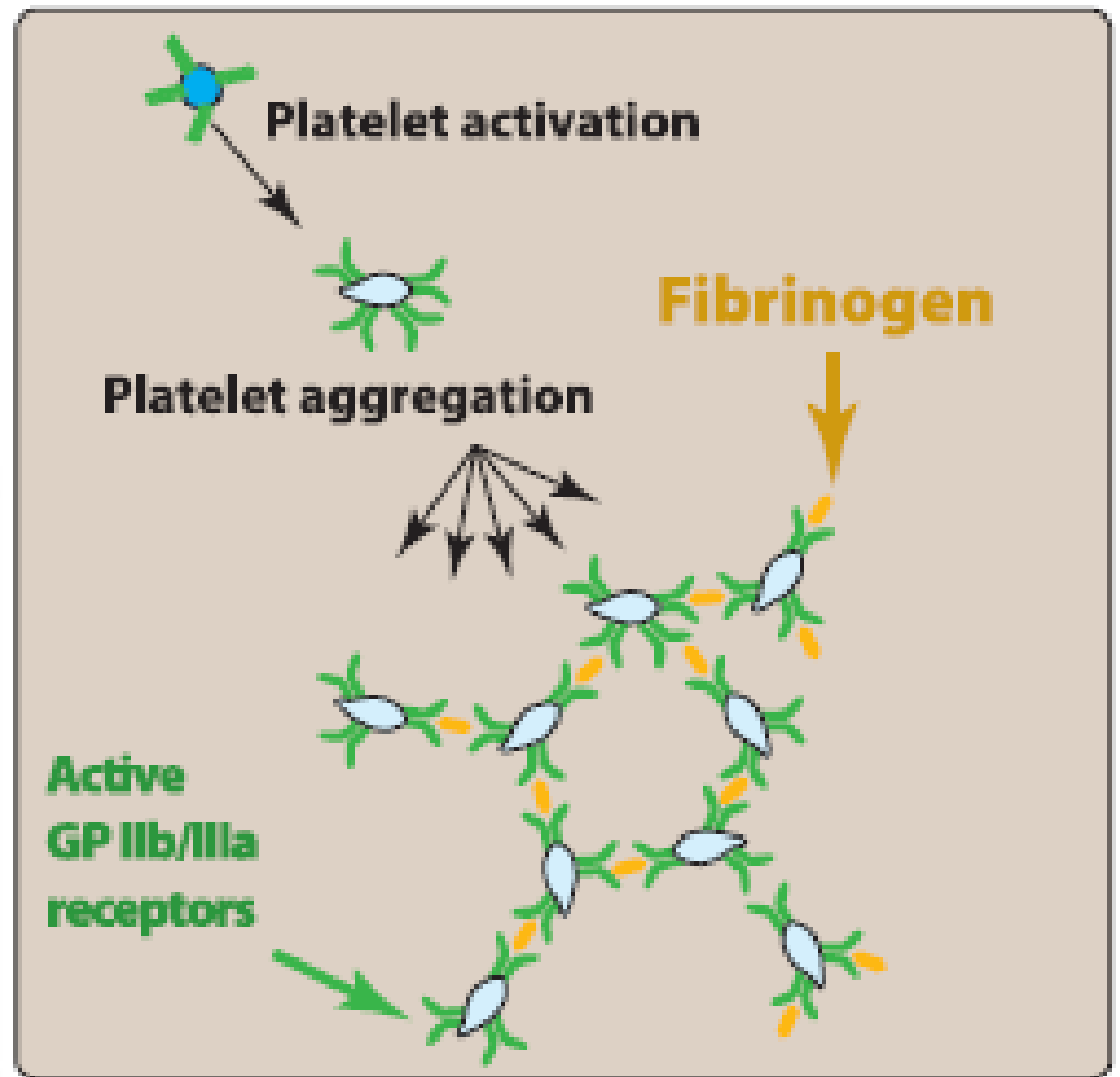
Platelet Response To Vascular Injury



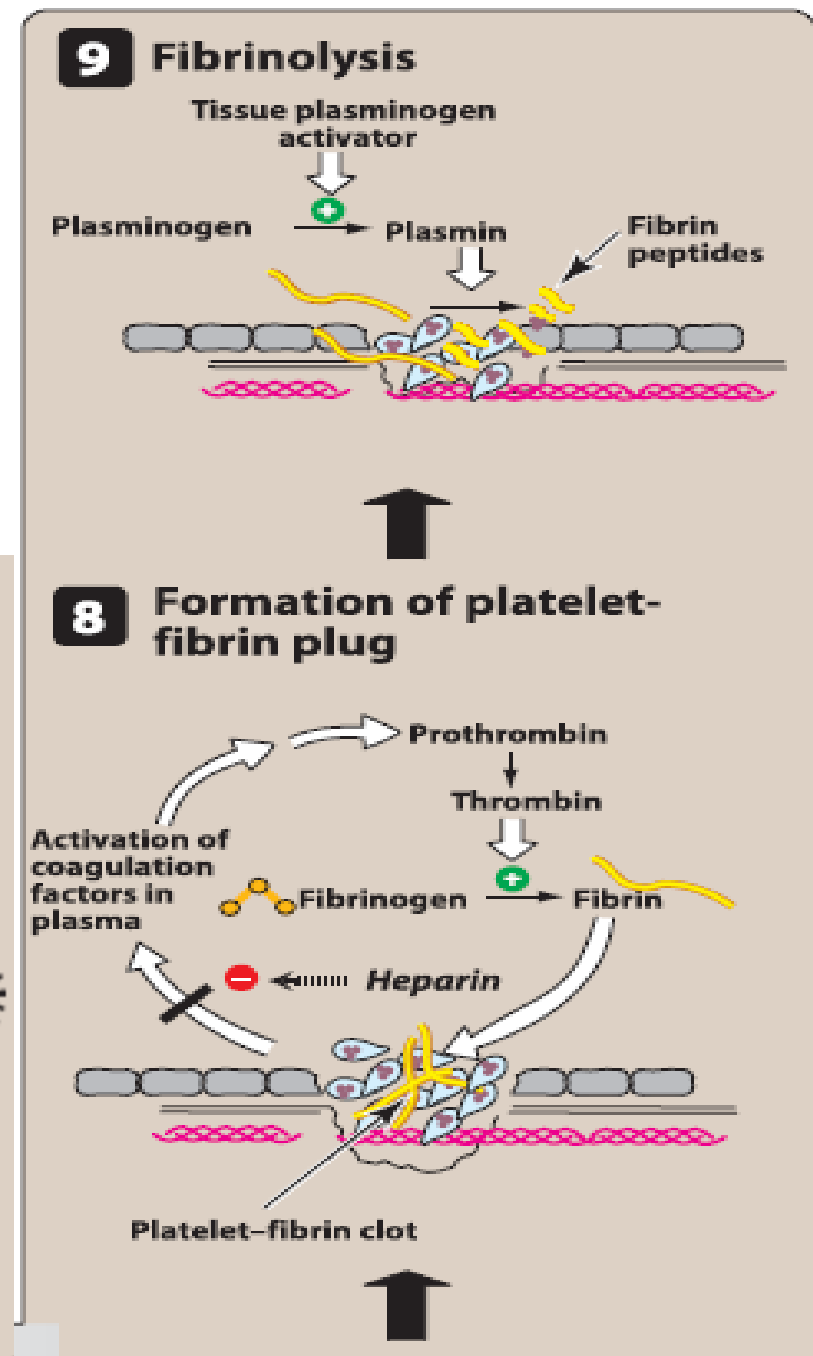
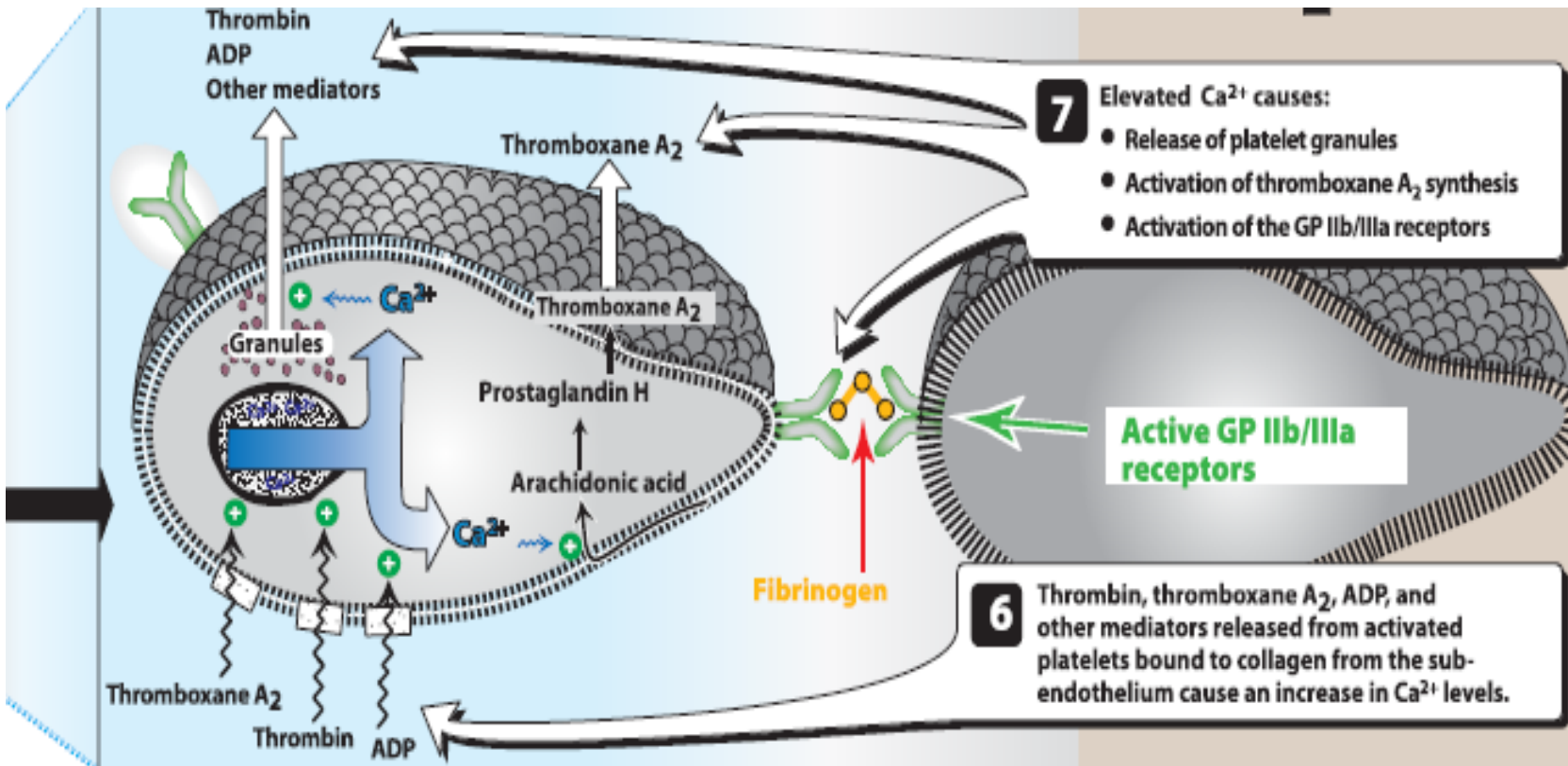
Resting platelet



Activated platelet



Platelet Response To Vascular Injury Cont..

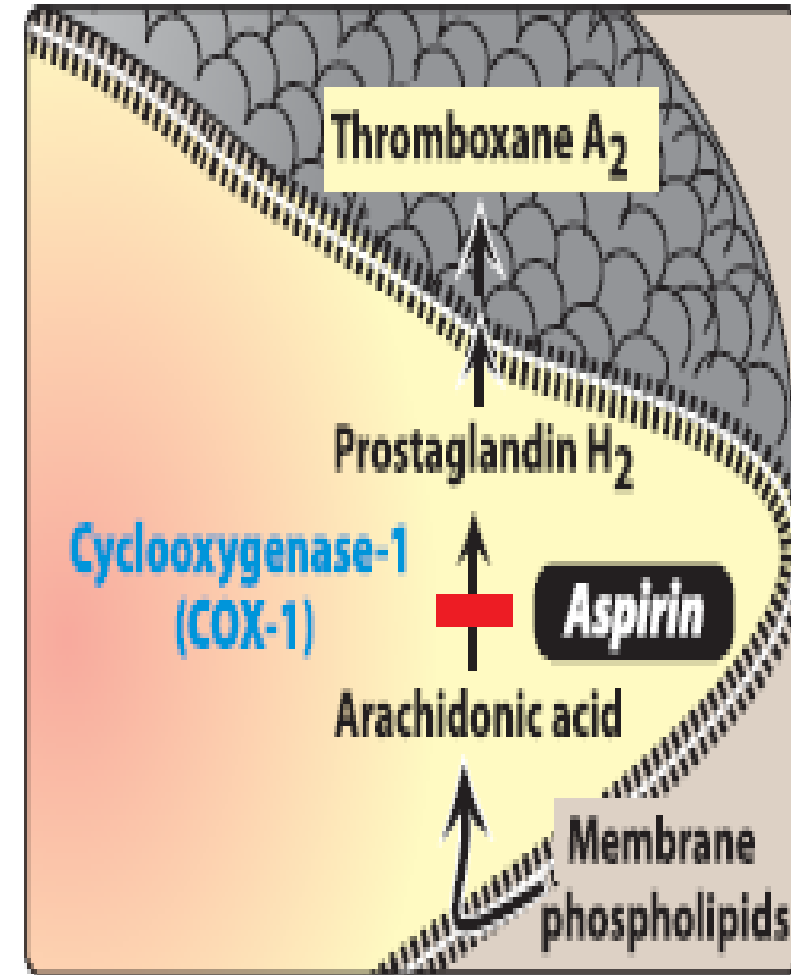


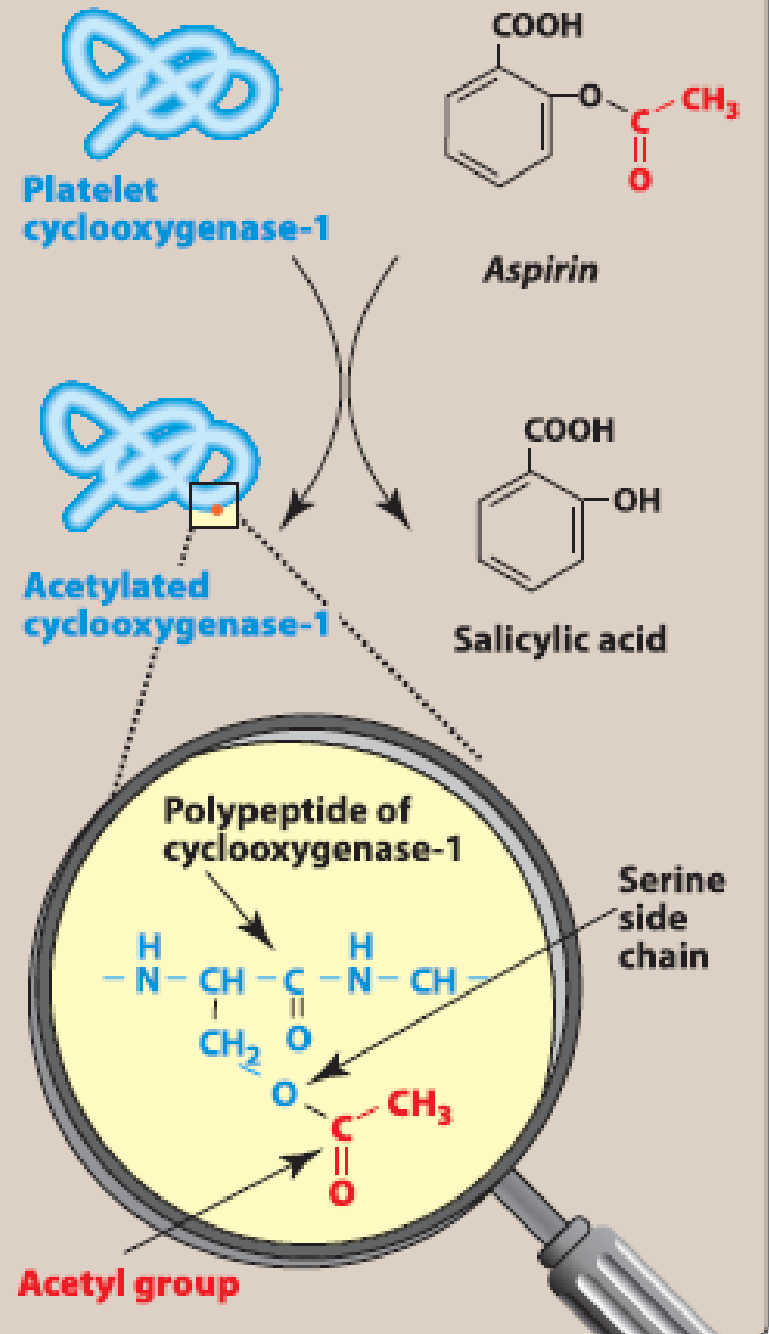
Platelet Aggregation Inhibitors

- Cyclooxygenase-1 inhibitors (COX-1)
- GP IIb/IIIa blocking
- ADP receptors blocking

1- Aspirin

- MOA: 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. Suppression of platelet aggregation last for the life of the platelet (7 to 10days).



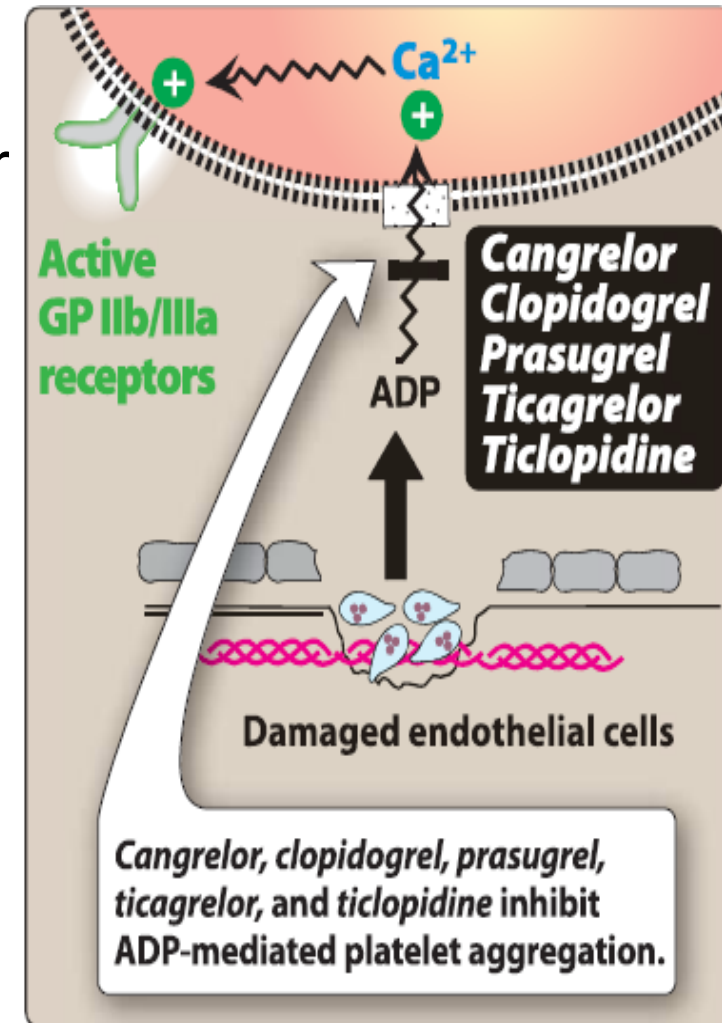


1- Aspirin Cont..

- **Therapeutic use:** prophylactic treatment of transient cerebral ischemia, recurrent MI, and to decrease mortality in the setting of primary and secondary prevention of MI. The recommended antiplatelet dose of *aspirin* ranges from 50 to 325 mg daily.
- **PK:** metabolism? S.Acid? $T_{1/2}$ each? Excretion?
- **Adverse effects:** high dose can increase bleeding time and cause hemorrhagic stroke and gastrointestinal (GI) bleeding. NSAID, such as ibuprofen, inhibit COX-1 by transiently competing at the catalytic site which antagonize platelet inhibition by aspirin.

2- P2Y₁₂ receptor antagonists

- **Ticlopidine, clopidogrel, prasugrel, ticagrelor, and cangrelor (IV).**
- **MOA:** inhibit the binding of ADP to the P2Y₁₂ receptor on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other. When treatment is suspended, the platelet system requires time to recover.
- **Uses:** prevention of atherosclerotic events in patients with a recent MI or stroke and peripheral arterial disease. prophylaxis of thrombotic events in acute coronary syndromes and percutaneous coronary intervention (PCI).

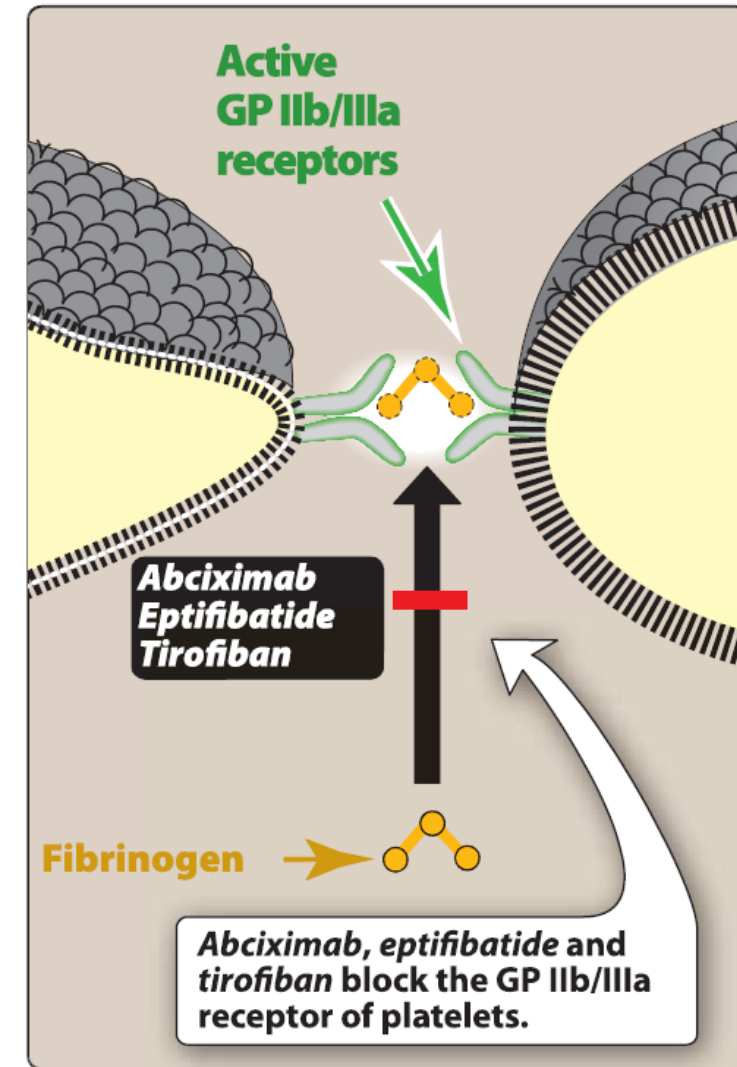


2- P2Y₁₂ receptor antagonists Cont..

- **PK:** loading dose? food interfere? ptn binding? Metabolites (CYP P450)? Elimination? Prodrug? Genetic polymorphism of CYP 2C19
- **Adverse effects:** Prolonged bleeding (no antidote). Ticlopidine is associated skin agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia. TTP has been reported as an adverse effect for both clopidogrel and prasugrel. Contraindication and black box warning?

3- Glycoprotein IIb/IIIa inhibitors

- **Abciximab (mAb), Eptifibatide, and Tirofiban**
- **MOA:** inhibits the GP IIb/IIIa receptor complex. By binding to GP IIb/IIIa, abciximab blocks the binding of fibrinogen and von Willebrand factor and, consequently, aggregation does not occur.
- **Uses:** These agents are given intravenously, along with heparin and aspirin, as an adjunct to PCI for the prevention of cardiac ischemic complications.
- **PK:** Route? Onset peak? Speed of platelet function recovery? Excretion?
- **Adverse effects:** bleeding, especially if used with anticoagulants.



4- Dipyridamole

- **MOA:** Dipyridamole is a coronary vasodilator, increases intracellular levels of cAMP by inhibiting phosphodiesterase, resulting in decreased thromboxane A₂ synthesis. The drug may potentiate the effect of prostacyclin and, therefore, decrease platelet adhesion to thrombogenic surfaces
- **Uses:** for stroke prevention and is given in combination with another antiplatelet agent since it has weak antiplatelet effects on its own.
- **PK:** oral? protein bound? Metabolism and excretion? .
- **Adverse effects:** headache and dizziness and can lead to orthostatic hypotension(especially if administered IV). Not used in patient with unstable angina !!

5- Cilostazol

- **MOA:** inhibit phosphodiesterase type II, which prevents the degradation of cAMP, thereby increasing levels of cAMP in platelets and vascular tissues. The increase in cAMP prevents platelet aggregation and promotes vasodilation of blood vessels,.
- **Uses:** reduce the symptoms of intermittent claudication.
- **PK:** oral , metabolism? CYP 3A4 and 2C19 ? elimination ?
- **A.E:** Headache and GI side effects (diarrhea, abnormal stools, dyspepsia, and abdominal pain). Rarely, thrombocytopenia or leukopenia. Cilostazol is contraindicated in patients with heart failure .

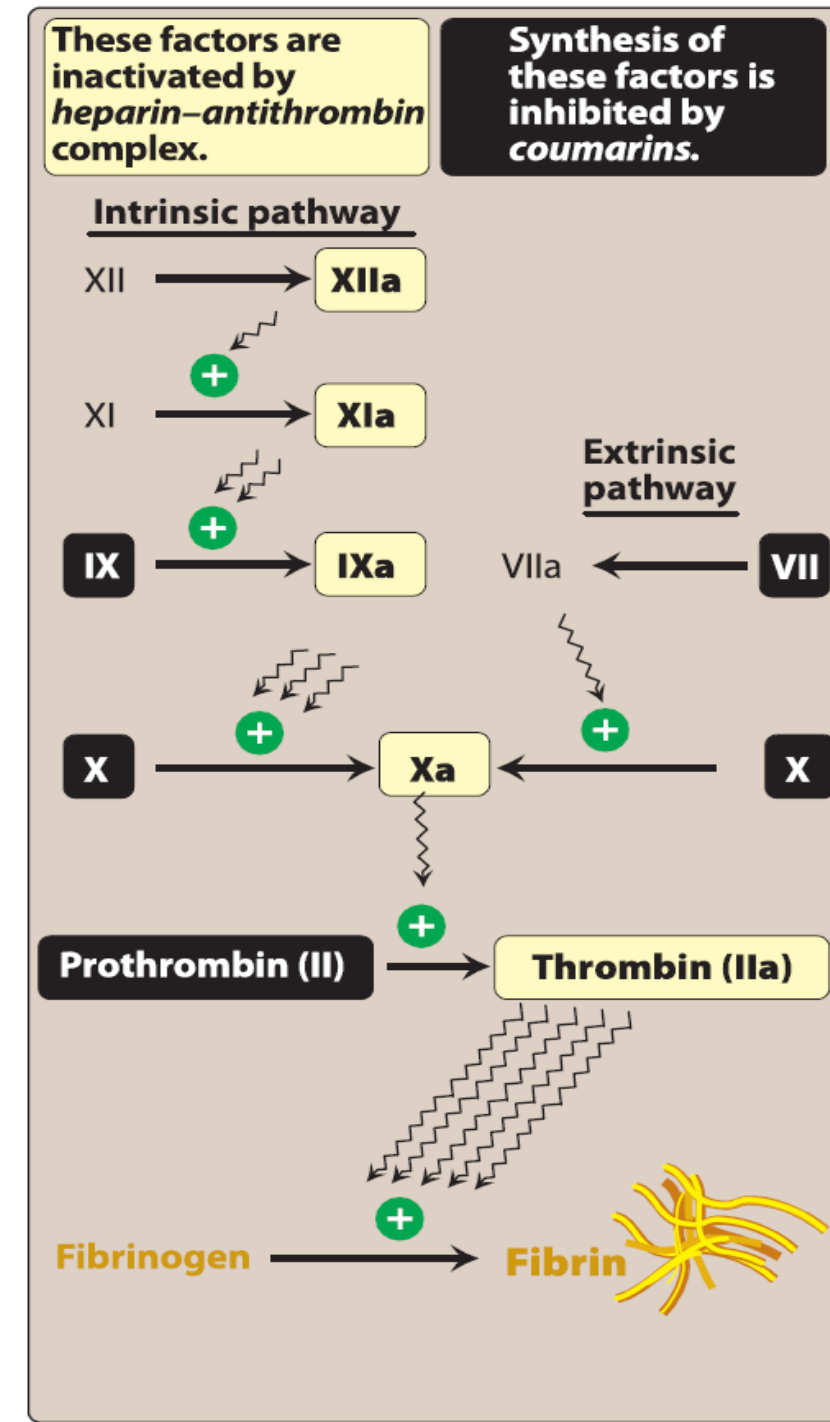
6- Vorapaxar (new)

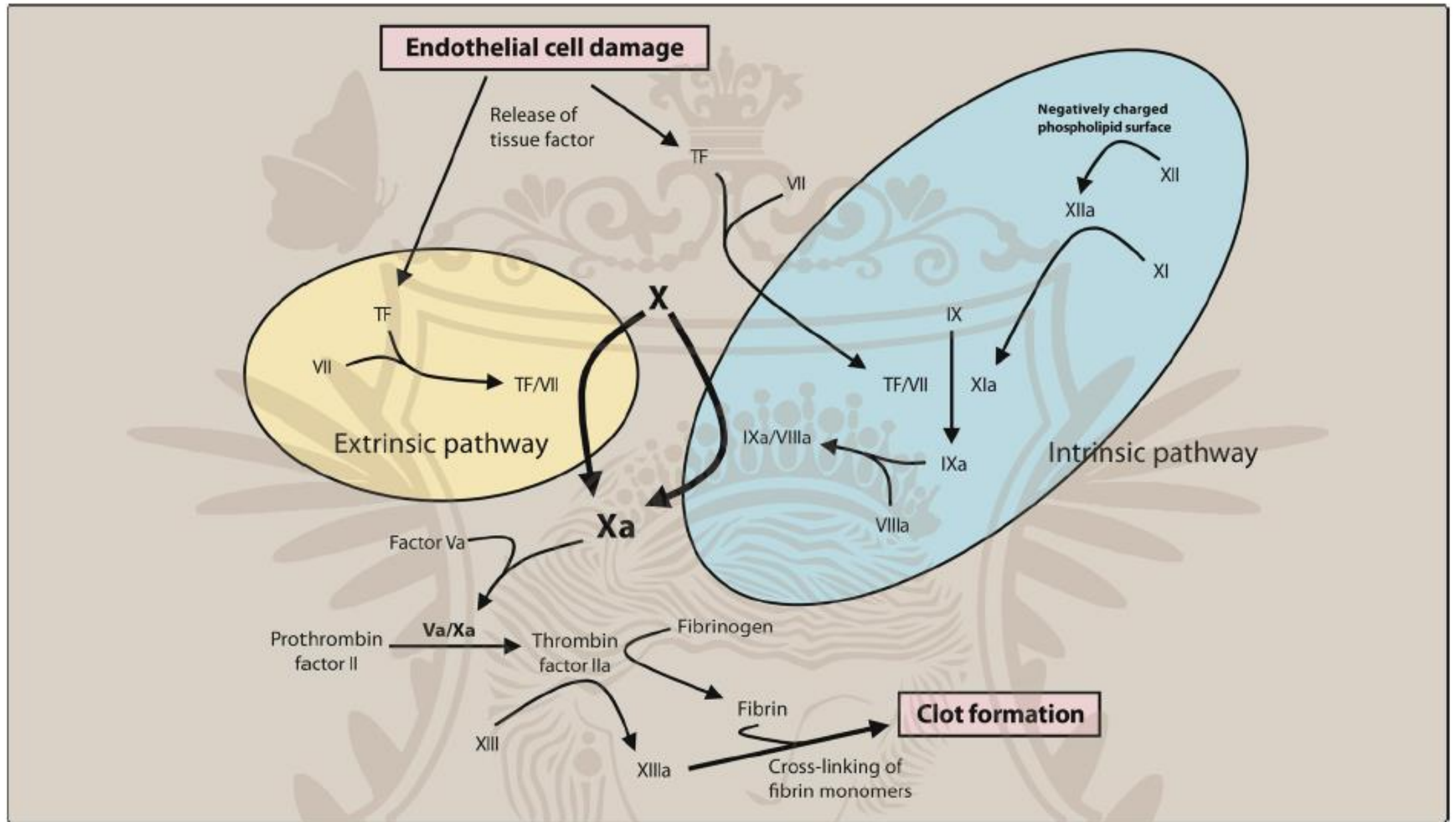
- **Vorapaxar** is an antagonist of the protease-activated receptor-1 (a thrombin receptor) expressed on platelets. Although it binds reversibly, it has a long half-life and an extended duration of action (4 weeks after discontinuation).
- **Uses:** Given orally in conjunction with aspirin or clopidogrel to reduce cardiovascular events in patients with a history of MI or with peripheral artery disease.
- It should not be given to patients with a high risk of bleeding, including patients with a history of stroke, transient ischemic attack, or intracranial hemorrhage.

Medication	Adverse Effects	Drug Interactions	Monitoring Parameters
Oral Agents:			
<i>Aspirin</i>	Angioedema Bleeding Bronchospasm GI disturbances Reye syndrome SJS	Anticoagulants, P2Y12 inhibitors, NSAIDs —increased bleeding <i>cidofovir</i> —nephrotoxicity <i>probenecid</i> —decreased uricosuric effects	CBC LFT
<i>Cilostazol</i>	Bleeding GI disturbances Headache Peripheral edema SJS	Food (administer on empty stomach)	CBC
<i>Clopidogrel</i>	Bleeding SJS	Strong CYP2C19 inhibitors reduce antiplatelet effect (e.g., <i>omeprazole</i>)	CBC LFT
<i>Dipyridamole</i>	Bleeding Dizziness GI discomfort Rash	Salicylates—increased bleeding Thrombolytic agents—increased bleeding	None for oral administration
<i>Prasugrel</i>	Angioedema Bleeding Headache Hyperlipidemia Hypertension	Anticoagulants—increased bleeding Other antiplatelets—increased bleeding	CBC
<i>Ticagrelor</i>	Bleeding Dyspnea Headache Raised SCr	Strong CYP3A4 inhibitors (e.g., <i>ketoconazole</i>)—increased bleeding Strong CYP3A4 inducers (e.g., <i>rifampin</i>)—decreased efficacy	CBC LFT
Injectable Agents:			
<i>Abciximab</i>	For all agents:	For all agents:	For all agents:
<i>Eptifibatide</i>	Hypotension Nausea Vomiting Thrombocytopenia	Increased bleeding: <i>Ginkgo biloba</i> Antiplatelets Salicylates SSRIs and SNRIs	APTT clotting time H/H platelet count thrombin time
<i>Tirofiban</i>			

Blood Coagulation

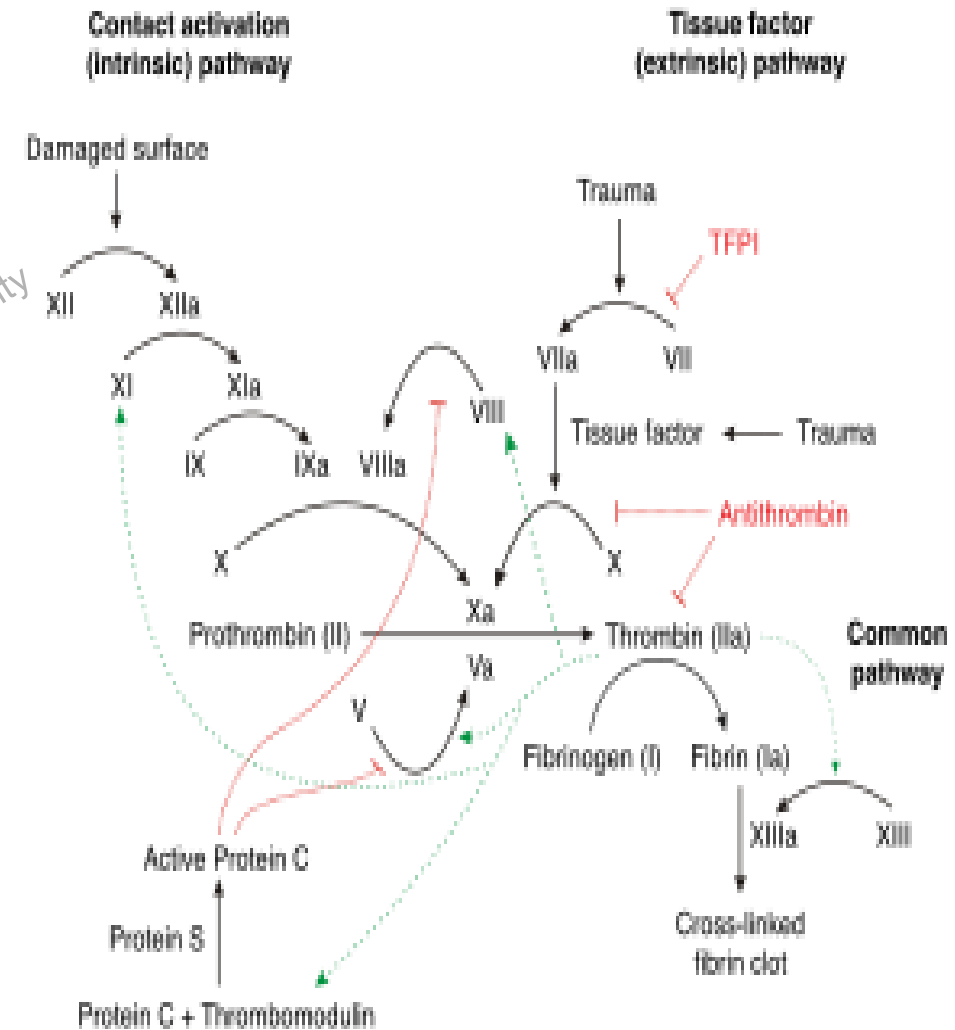
- The coagulation process consists of two interrelated pathways, the extrinsic and the intrinsic systems.
- **The extrinsic system** is initiated by the activation of clotting factor VII by tissue factor (also known as thromboplastin).
- **The intrinsic system** is triggered by the activation of clotting factor XII by negatively charged phospholipid surface. This occurs when blood comes into contact with the collagen in the damaged wall of a blood vessel.





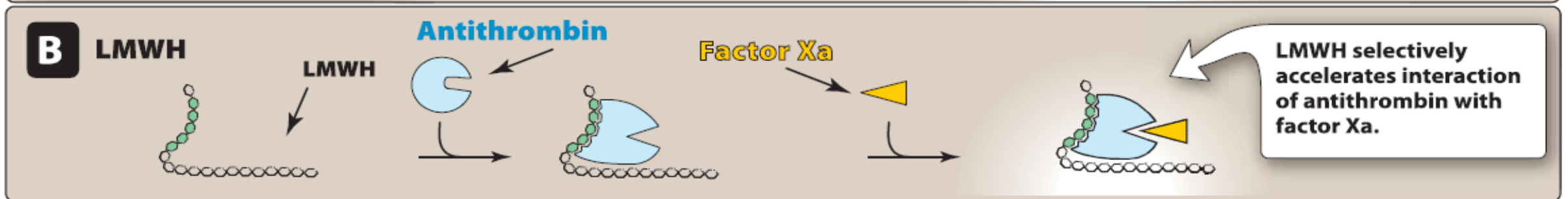
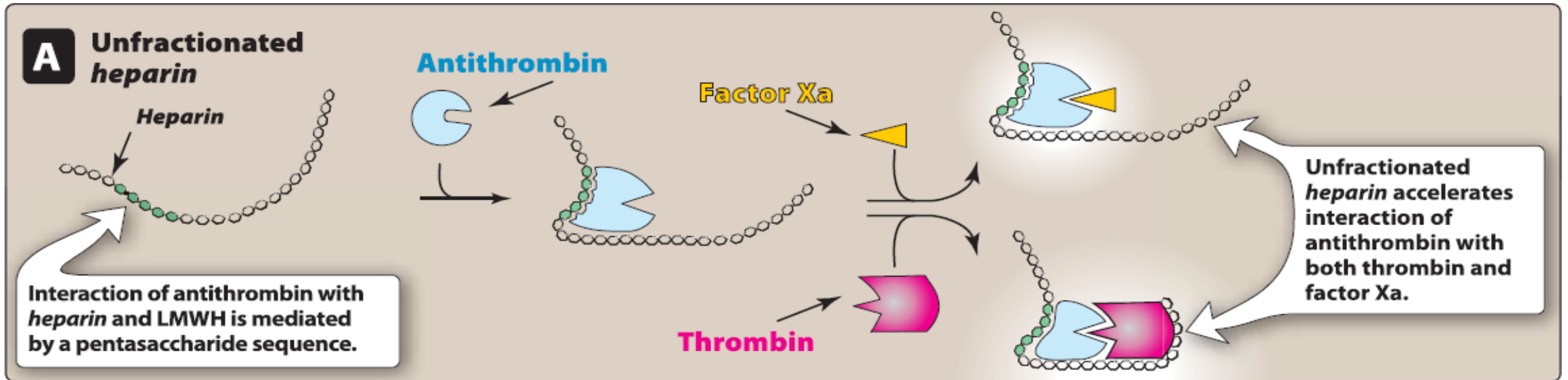
Inhibitors of coagulation

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



Anticoagulants 1- Heparin & LMWHs

- **Heparin** is an injectable, rapidly acting anticoagulant occurs naturally as a macromolecule complexed with histamine in mast cells.
- **Unfractionated heparin** is a mixture of straight-chain, anionic glycosaminoglycans with a wide range of molecular weights.
- **LMWHs** (**enoxaparin** and **dalteparin**) produced by depolymerization of unfractionated heparin. The LMWHs are heterogeneous compounds about one-third the size of unfractionated heparin.
- **MOA:** anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors by 1000-fold. Antithrombin III is an a globulin that inhibits serine proteases of thrombin (factor IIa) and factor Xa. LMWHs complex with antithrombin III and inactivate **factor Xa** (including that located on platelet surfaces)



Parenteral Anticoagulants 1- Heparin & LMWHs Cont..

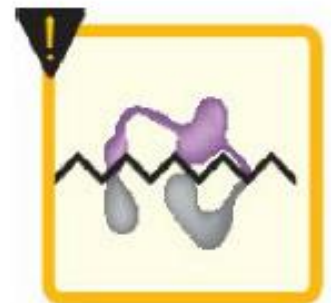
- **Uses:** for prophylaxis (patients undergoing surgery and acute MI) and treatment of acute venous thromboembolism (DVT or PE). Anticoagulants of choice for treating pregnant women? LMWHs prefer over Heparin?
- **PK:** route? Heparin not oral !!, bolus dose? Need aPTT anti-Xa level tests in which drug ? IV vs SC ? Ptn binding and excretion?
- **Adverse effects:** bleeding (protamine sulfate as antidote), hypersensitivity (chills, fever, urticaria, and anaphylactic shock) Heparin-induced thrombocytopenia (HIT) (is immune mediated and risk of venous and arterial embolism) LMWHs can have cross-sensitivity and not used in HIT, osteoporosis with long use heparin,
- **C.I. ?**



Bleeding



Hypersensitivity



Thrombo-
cytopenia

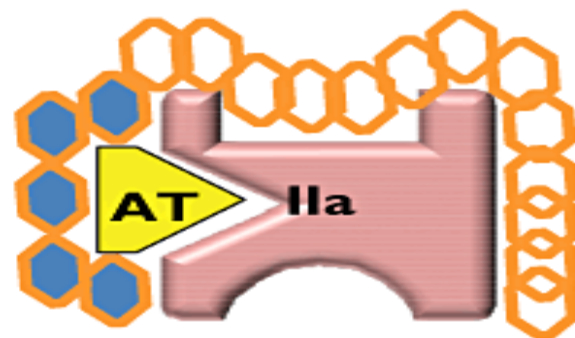
P. Anticoagulants 2- Argatroban

- **Argatroban** is a synthetic !!! parenteral anticoagulant that is derived from L-arginine. It is a direct thrombin inhibitor.
- **Uses:** prophylaxis or treatment of venous thromboembolism in patients with HIT, and during PCI in patients who have or are at risk for developing HIT.
- **PK:** metabolism? half-life? Excretion? Monitoring?
- **A.E:** Bleeding.

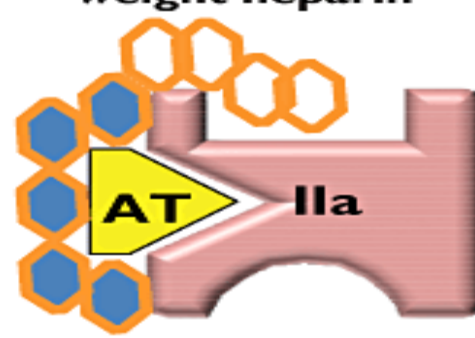
P. Anticoagulants: 3- Bivalirudin and Desirudin

- Are analogs of hirudin, a thrombin inhibitor derived from saliva of the medicinal leech
- **MOA:** selective direct thrombin inhibitors that reversibly inhibit the catalytic site of both free and clot-bound thrombin.
- **Uses:** DVT, alternative to heparin in patients undergoing PCI who have or are at risk for developing HIT and also in patients with unstable angina undergoing angioplasty.
- **PK** $t_{1/2}$ 25 min, excretion? ,

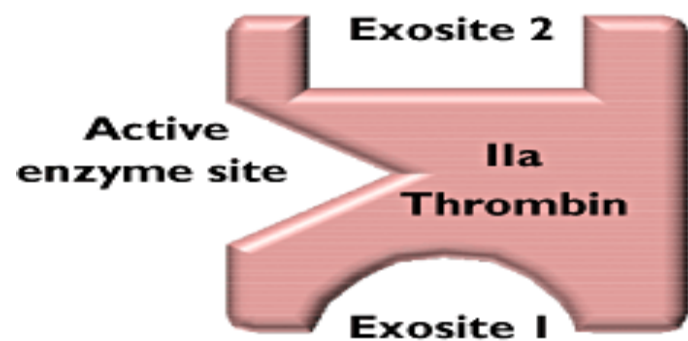
Unfractionated heparin



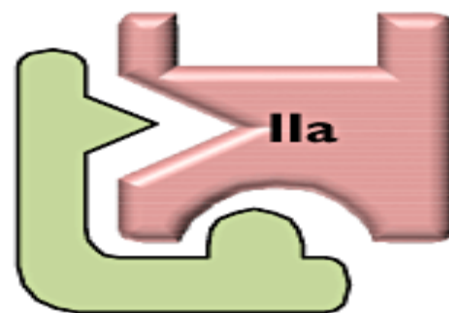
Low molecular weight heparin



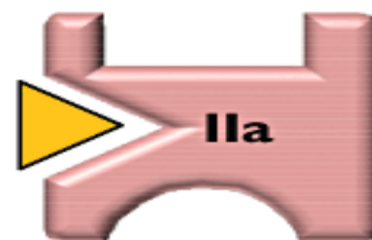
Thrombin



**Lepirudin/
Desirudin**



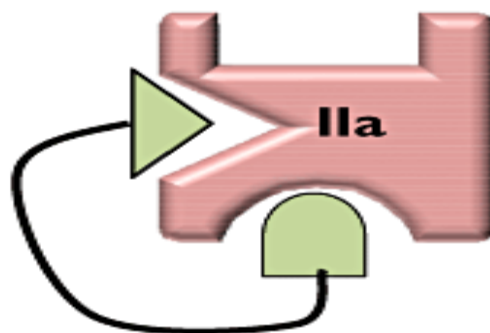
Argatroban



Exosite 1
Fibrin binding site

Exosite 2
Heparin binding site

Bivalirudin



Dabigatran

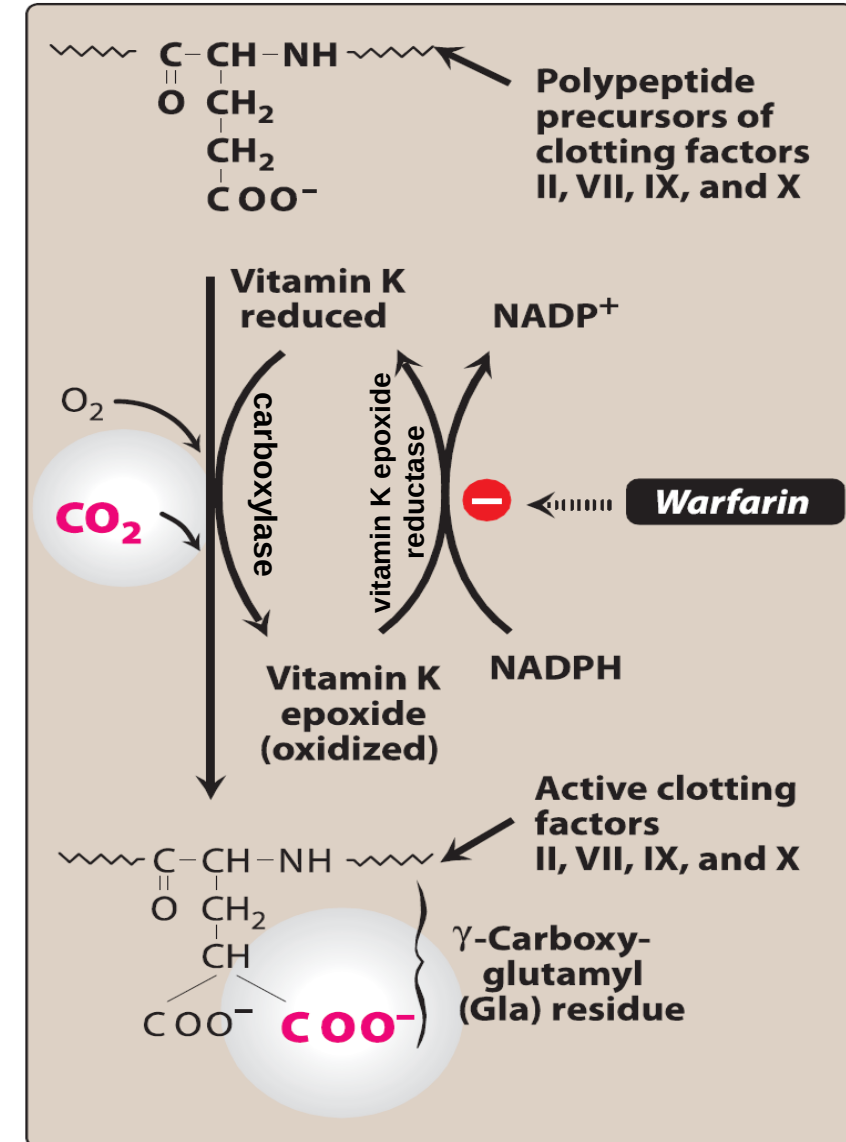


P. Anticoagulants: 4- Fondaparinux

- Fondaparinux is a synthetically derived pentasaccharide anticoagulant that selectively inhibits factor Xa.
- **MOA:** By selectively binding to antithrombin III, fondaparinux potentiates (300-to 1000-fold) the innate neutralization of factor Xa by antithrombin III.
- **Uses:** treatment of DVT and PE, prophylaxis of venous thromboembolism in the setting of orthopedic and abdominal surgery.
- **PK:** route? predictable pharmacokinetic profile! Monitoring? Excretion? $t_{1/2}$ 18 hr. renal impairment? .
- **A.E:** Bleeding (no antidote). HIT is less than heparin

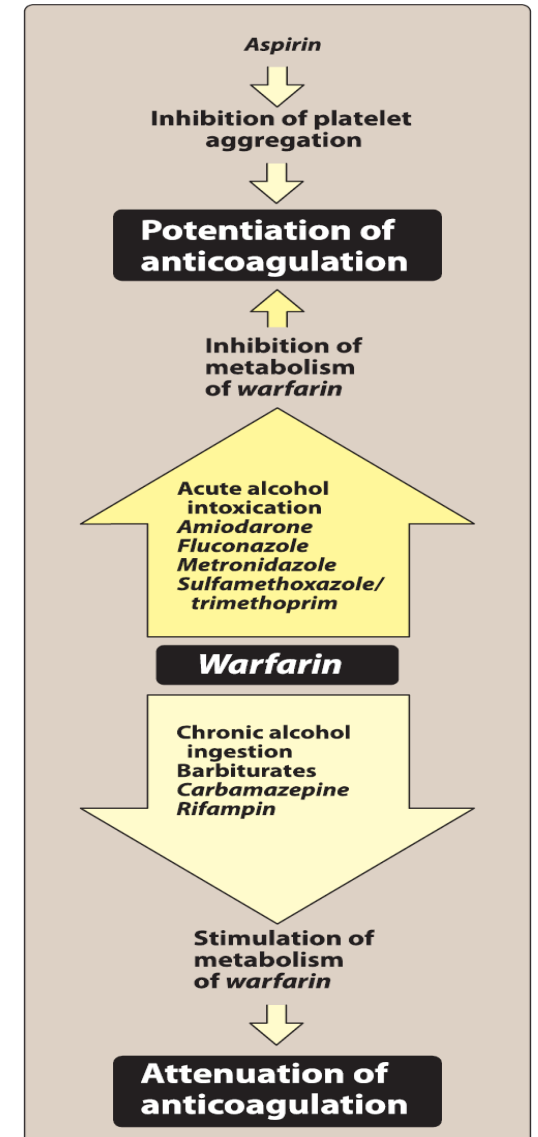
Vitamin K Antagonists: Warfarin

- Warfarin is Coumarin anticoagulants that antagonize the cofactor functions of vitamin K.
- **MOA:** warfarin inhibits vitamin K epoxide reductase enzyme result in blocking the Vitamin K regeneration. Warfarin treatment results in the production of clotting factors with diminished activity (10% to 40% of normal), due to the lack of sufficient γ -carboxyglutamyl side chains.



Vitamin K Antagonists: Warfarin

- **Uses:** prevention and treatment of DVT and PE, stroke prevention, stroke prevention in the setting of atrial fibrillation and/or prosthetic heart valves, protein C and S deficiency, and antiphospholipid syndrome.
- **PK:** NTI, international normalized ratio (INR) for monitoring, oral (100%), ptn. binding affect distribution? $T_{1/2}=40$ hrs. variable among individuals, Metabolism CYP2C9, Active or ? DDI ?
- **A.E:** bleeding (stop, V. K antidote oral or IV, whole blood, frozen plasma, and plasma concentrates of blood factors). Rare: Skin lesions and necrosis, Purple toe syndrome. Warfarin is teratogenic



Direct Oral Anticoagulants: 1- Dabigatran etexilate

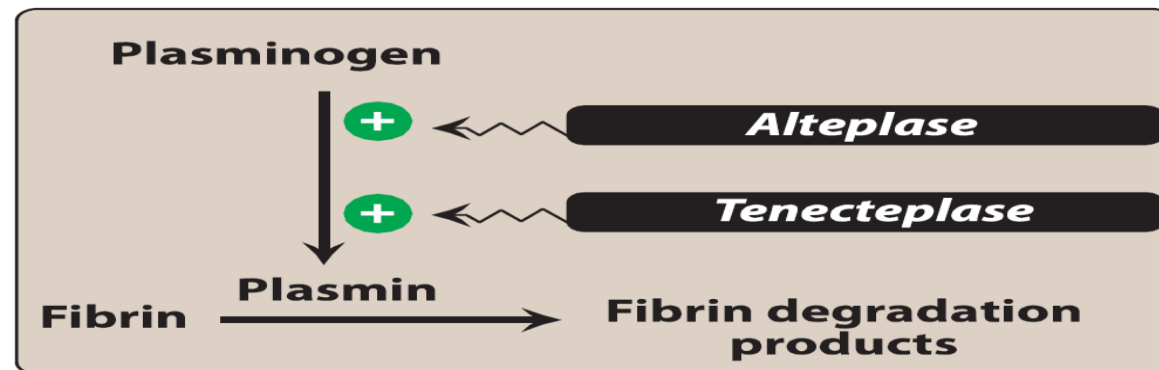
- **MOA:** oral direct thrombin inhibitor. Both clot-bound thrombin and free thrombin are inhibited by dabigatran.
- **Uses:** Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Treatment and prophylaxis of DVT and PE in patients who have already received parenteral anticoagulants. Not recommended in patients with bioprosthetic heart valves.
- **PK:** prodrug? Which enzyme? P-gp? Excretion?
- **A.E:** bleeding (darucizumab as antidote), dyspepsia, abdominal pain, esophagitis, and GI bleeding. Avoid abrupt discontinuation

Direct Oral Anticoagulants: 2- factor Xa inhibitors

- **Apixaban, betrixaban, edoxaban, and rivaroxaban**
- **MOA:** Inhibition of factor Xa reduces the production of thrombin (IIa) from prothrombin.
- **Uses:** except betrixaban, prevention of stroke in nonvalvular atrial fibrillation, and treatment of DVT and PE. They use as prophylaxis to prevent or reduce the risk of recurrence of DVT and PE.
- **PK:** metabolism active or? CYP P450 for each drug? Excretion? P-gp?
- **A.E:** bleeding (Factor Xa may use as antidote), renal dysfunction can increase risk of bleeding, avoid abrupt discontinuation to prevent thrombotic events.

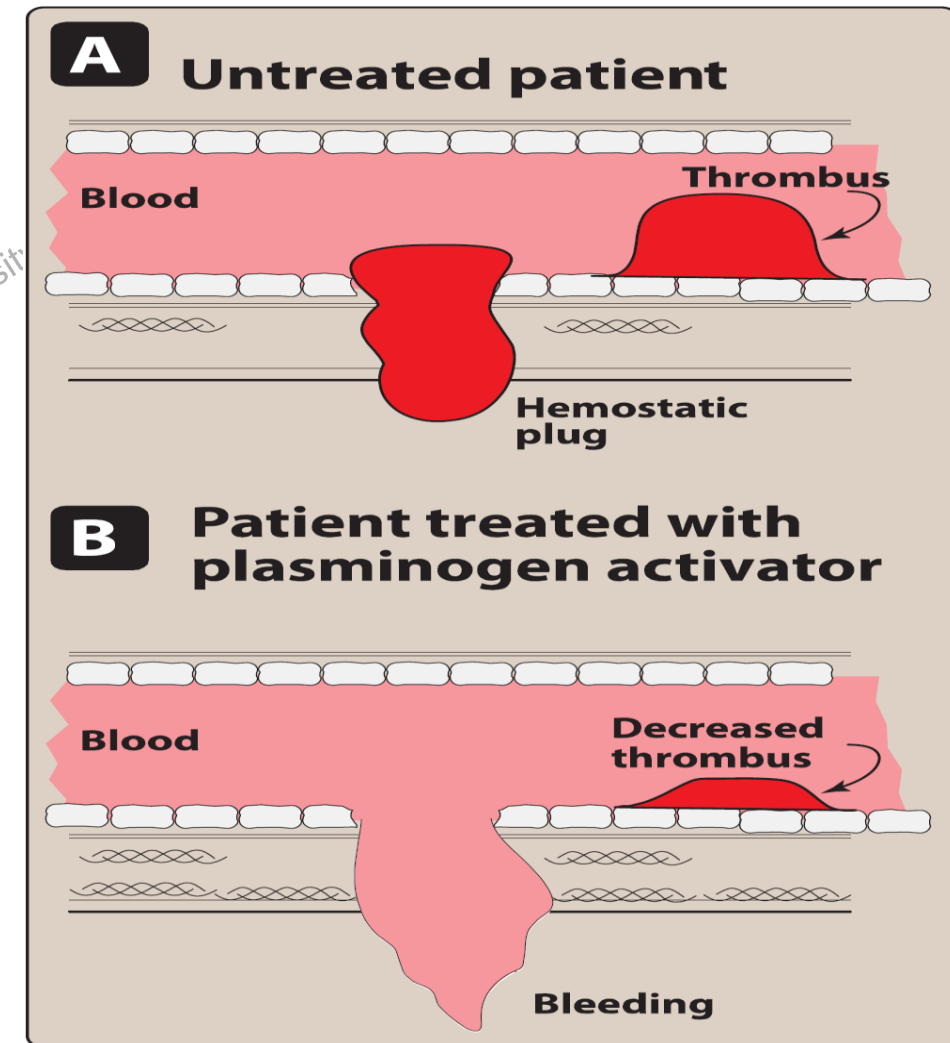
Thrombolytic Drugs: Alteplase and Tenecteplase

- **MOA:** act either directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi. The effect occurs with a higher frequency when therapy is initiated early. Increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis.
- **Uses:** Now used less for DVT and PE due to serious bleeding. For MI, intracoronary delivery of the drugs to achieve recanalization but not used widely. Instead used IV for clots with strokes, restoring catheter and shunt function.



Alteplase and Tenecteplase Cont..

- **A.E:** hemorrhage is a major adverse effect. Increase bleeding in pre-exist gastric ulcer (figure right) . C.I in pregnancy and patient with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.
- **Alteplase Vs Tenecteplase:**



Drugs Used To Treat Bleeding

- Bleeding either naturally (hemophilia), fibrinolytic states that may arise after surgery, or anticoagulating uses. In addition to antibleeding drugs, concentrated preparations of coagulation factors or blood transfusion are available from human donors (but high risky).
- **1- Aminocaproic acid and tranexamic acid:** Both agents are synthetic, orally active, excreted in the urine, and inhibit plasminogen activation. Uses for controlling fibrinolytic states. Tranexamic acid is 10 times more potent than aminocaproic acid.
- **2- Protamine sulfate:** antagonizes the anticoagulant effects of heparin. This protein is derived from fish sperm or testes and is high in arginine content, which explains its basicity. The positively charged protamine interacts with the negatively charged heparin, forming a stable complex without anticoagulant activity.

Drugs Used To Treat Bleeding Cont..

- 3- **Vitamin K:** stop bleeding problems due to warfarin by increasing the supply of active vitamin K1. It may be administered via the oral, subcutaneous, or intravenous route (slow IV infusion). SC less effective than oral and IV. The response to vitamin K1 is slow, requiring about 24 hours to reduce INR (fresh frozen plasma for emergency).
- 4- **Idarucizumab:** monoclonal antibody fragment used to reverse bleeding caused by dabigatran through neutralization process. IV use with rapidly eliminated for emergency situations

Medication	Antidote for Bleeding Caused by	Adverse Effects	Monitoring Parameters
<i>Aminocaproic acid</i> <i>Tranexamic acid</i>	Fibrinolytic state	Muscle necrosis Thrombosis CVA Seizure	CBC Muscle enzymes Blood pressure
<i>Idarucizumab</i>	<i>Dabigatran</i>	Hypokalemia Thrombosis	aPTT Clotting time Thrombin time
<i>Protamine sulfate</i>	<i>Heparin</i>	Flushing Nausea/vomiting Dyspnea Bradycardia Hypotension Anaphylaxis	Coagulation monitoring Blood pressure Heart rate
<i>Vitamin K1</i>	<i>Warfarin</i>	Skin reaction Anaphylaxis	PT/INR