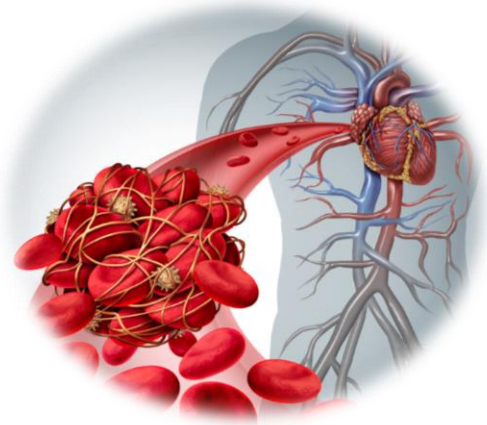
Mustansiriyah University
College of Pharmacy
Depart. of Pharmacology and Toxicology

Anticoagulants and Antiplatelet Agents



Pharmacology 4th Stage

October , 2023

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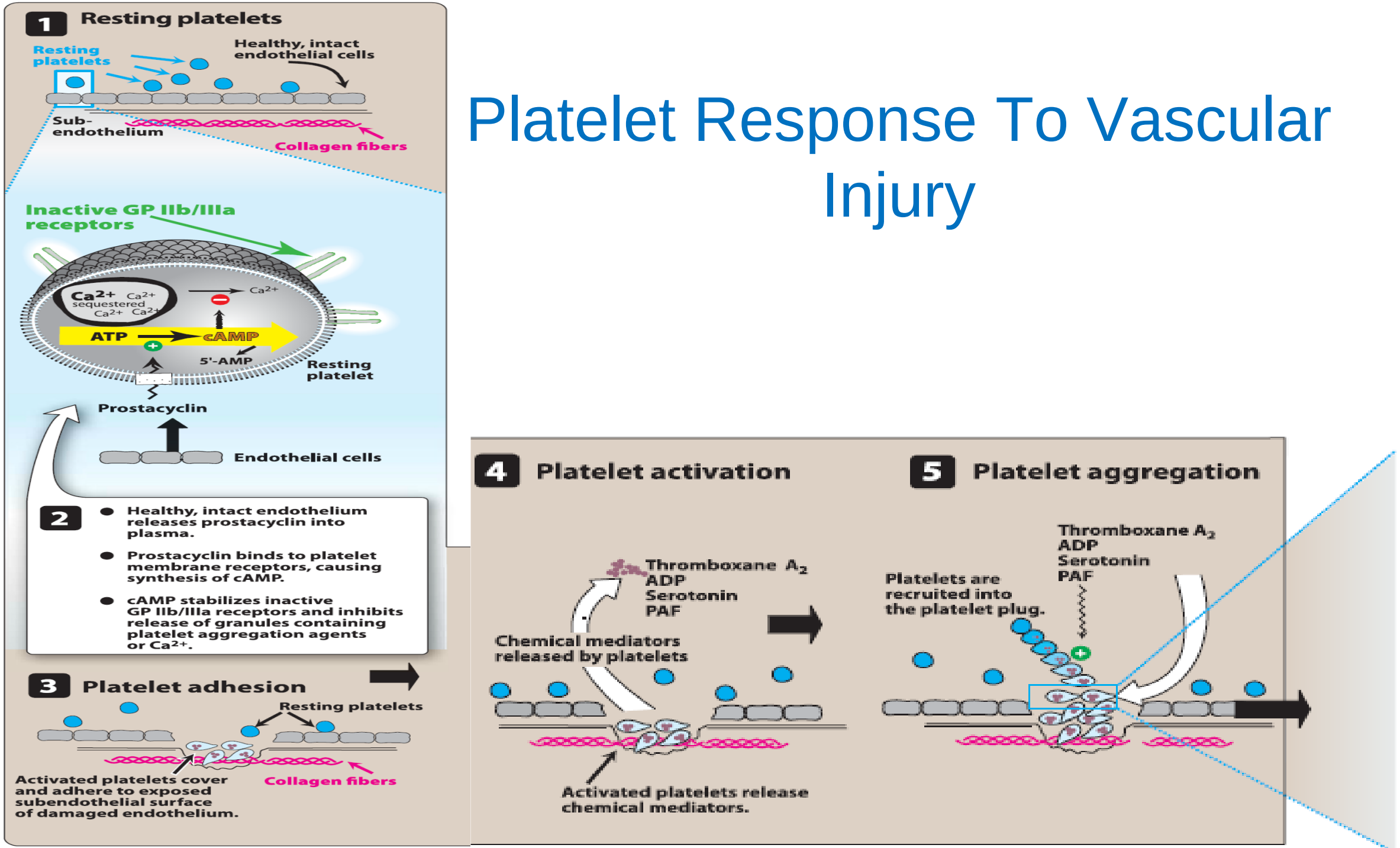
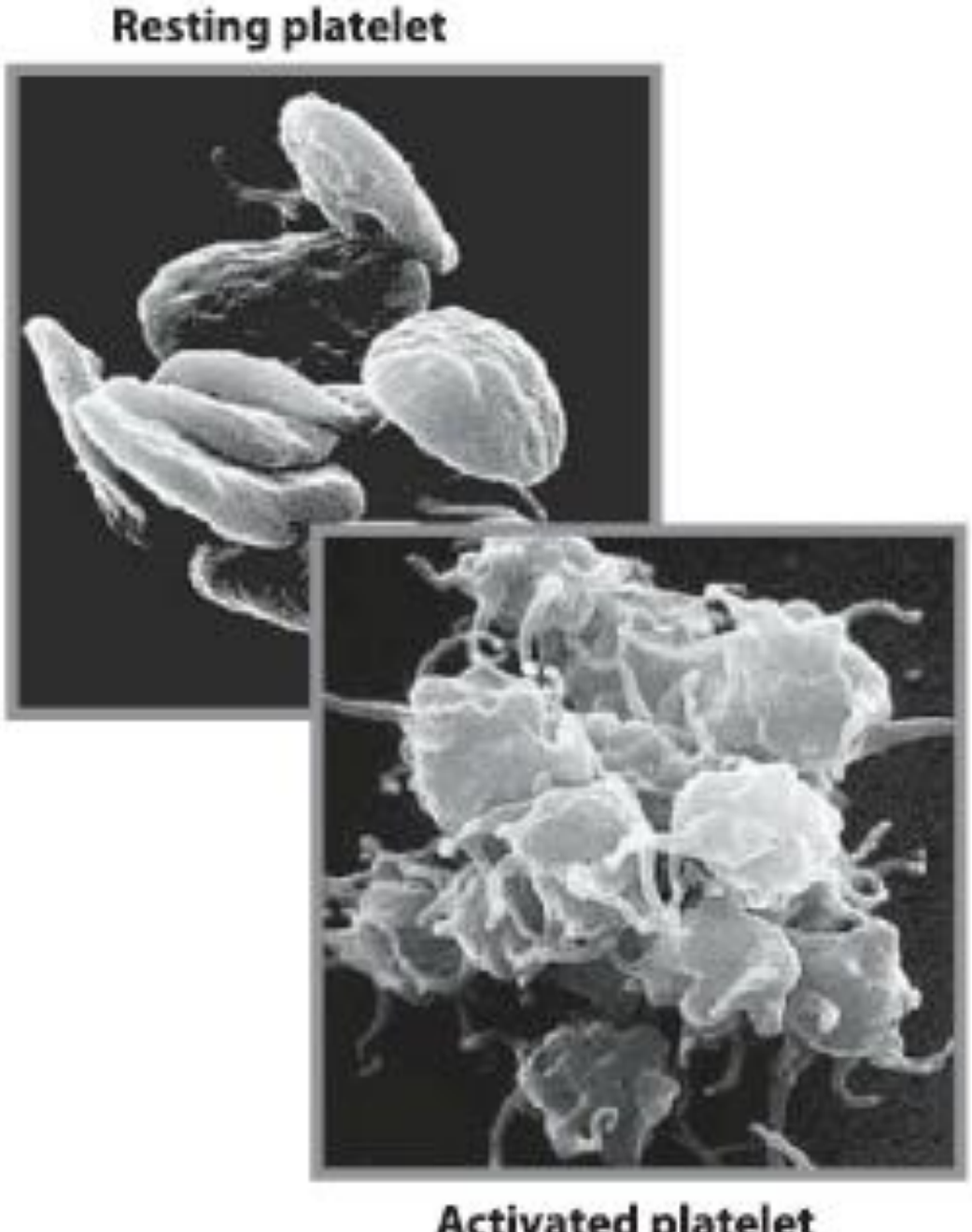
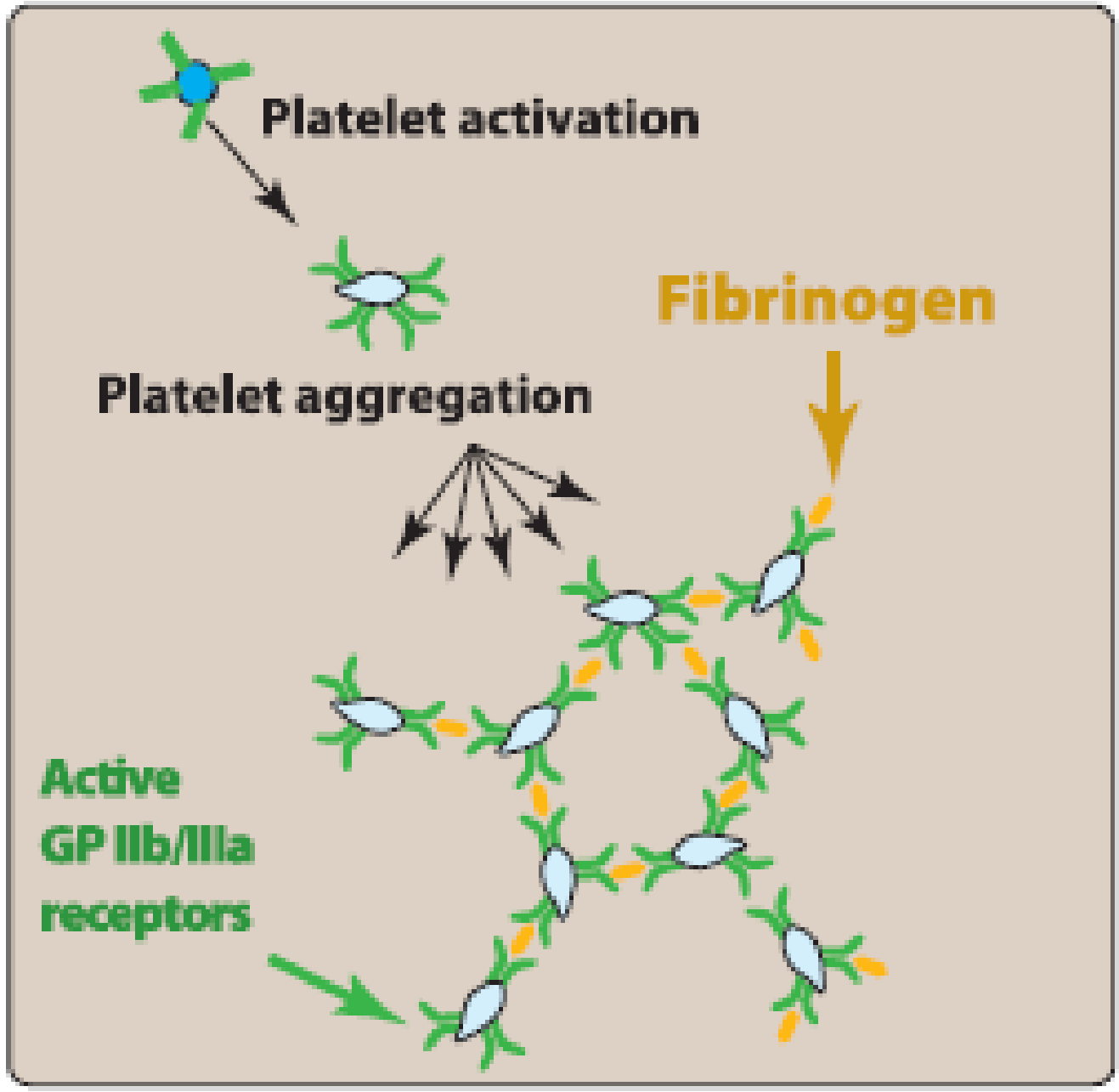
Thrombus Versus Embolus

- 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 mediumsized 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).

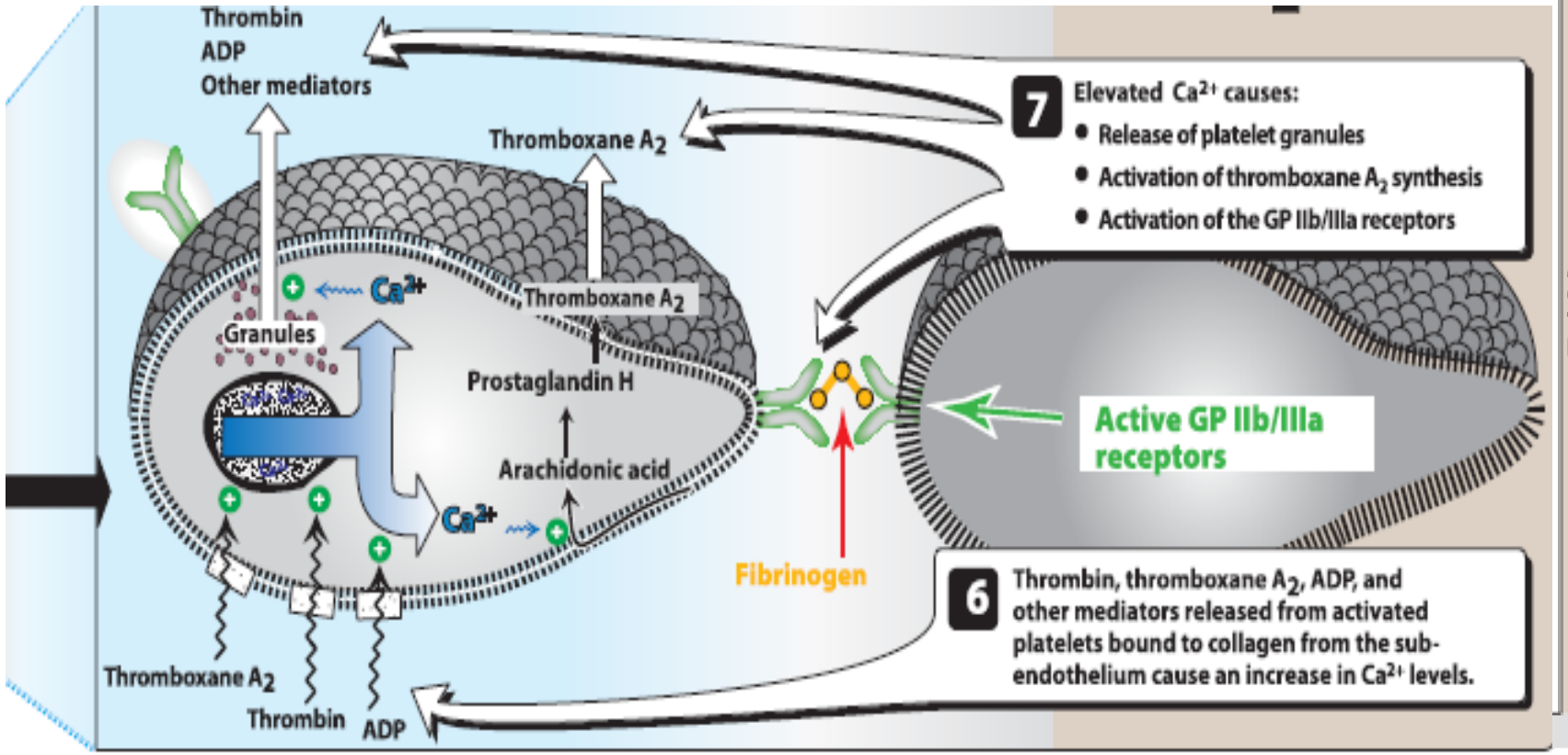
Platelet Response To Vascular Injury

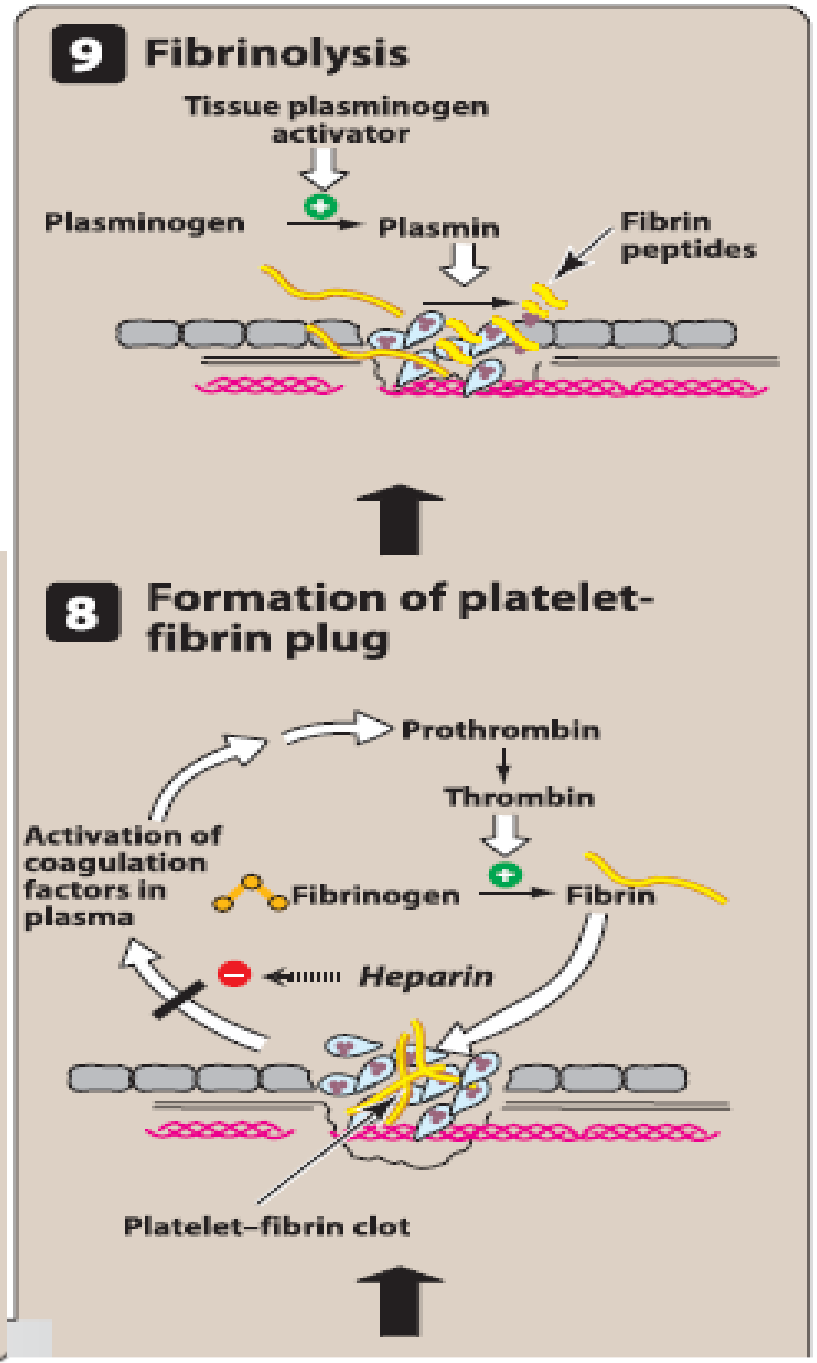



Resting platelet
Activated platelet


Platelet activation
Fibrinogen
Platelet aggregation
Active
GP IIb/IIIa
receptors

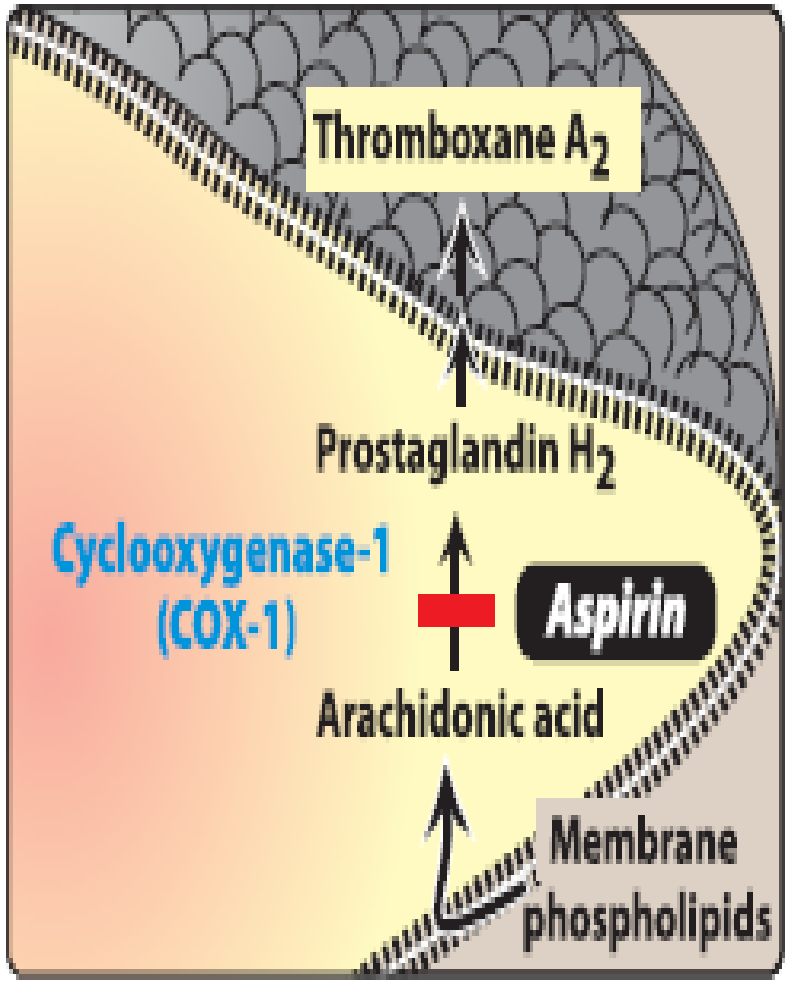
Platelet Response To Vascular Injury Cont..





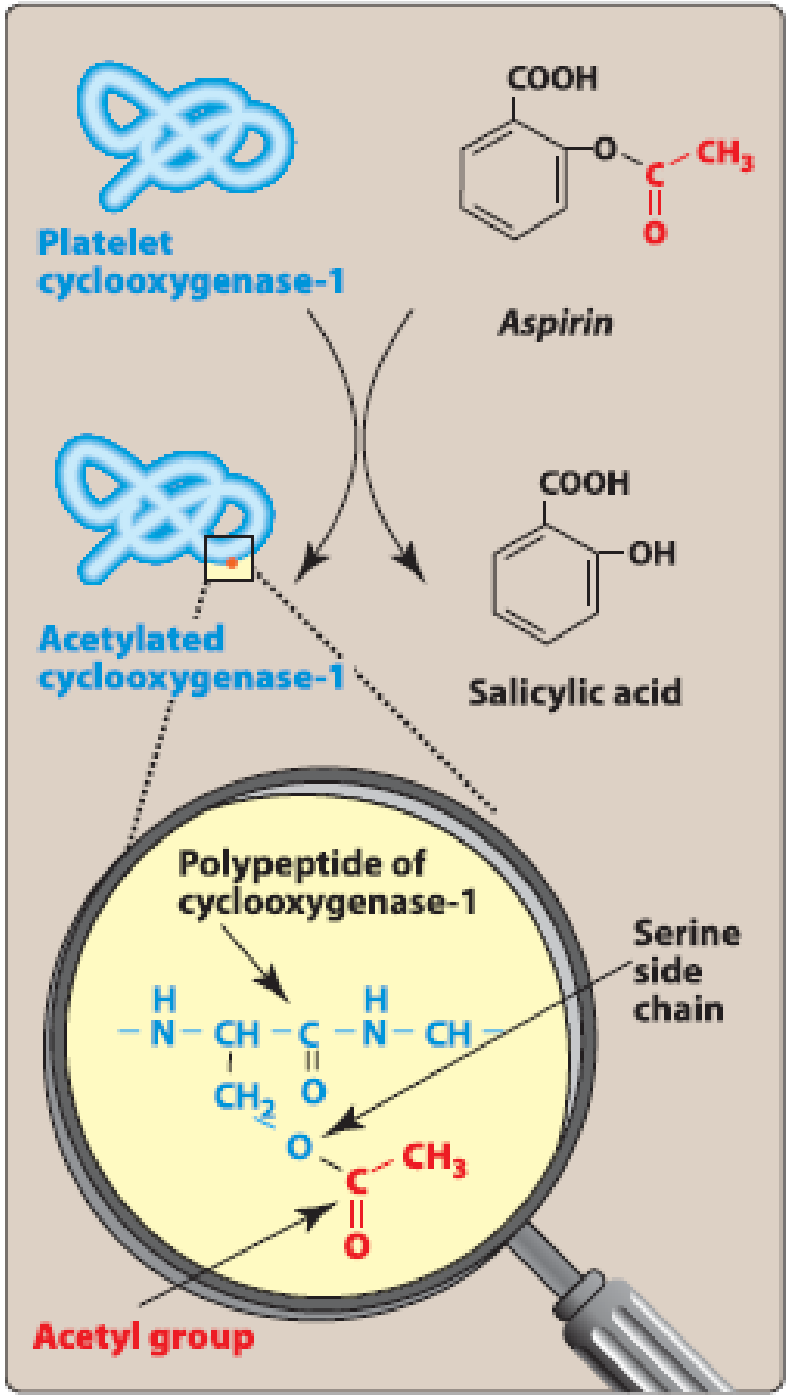
Platelet Aggregation Inhibitors

- Cyclooxygenase-1 inhibitors (COX-1)
- GP lib/lila 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).


Platelet cyclooxygenase-1
COOH
O
CH3
C
O
Aspirin
Acetylated cyclooxygenase-1
COOH
OH
Salicylic acid
Polypeptide of cyclooxygenase-1
Serine side chain
H
N
CH
C
H
N
CH
CH2
O
O
CH3
C
O
Acetyl group

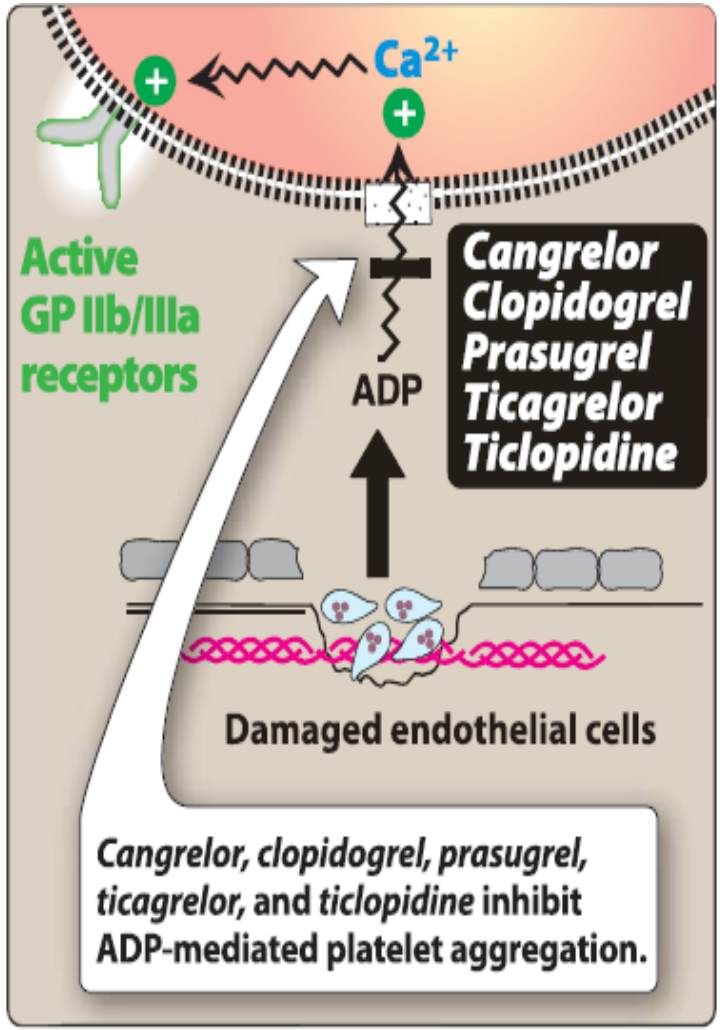
1- Aspirin Cont..

- **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? SA? T1/2 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 lib/lila receptors required for platelets to bind to fibrinogen and to each other. When treatment is suspended, the platelet system requires time to recover. Reversibility?
- **Uses:** prevention of atherosclerotic events in patients with a recent Ml or stroke and peripheral arterial disease. prophylaxis of thrombotic events in acute coronary syndromes and percutaneous coronary intervention (PCI).

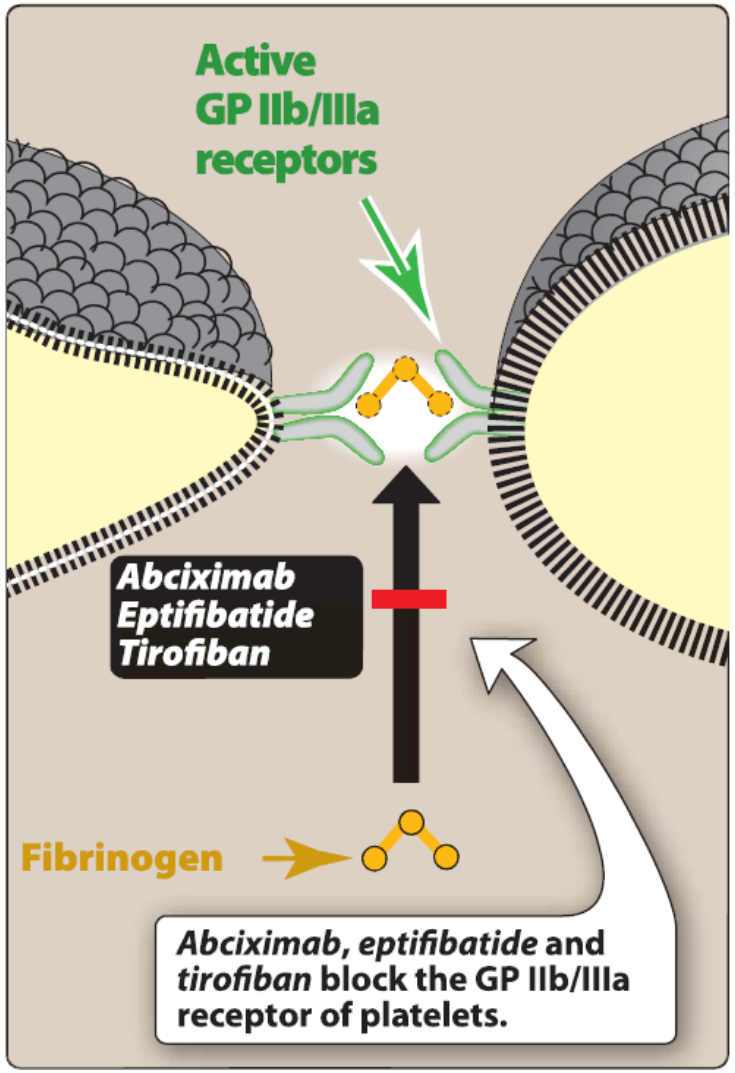


2- P2Y12 receptor antagonists Cont..

- **PK**: loading dose?? food interfere? ptn binding? Metabolites (CYP P450)? Elimination? Prodrug? Genetic polymorphism of CYP 2C19 !!! Which drug ?
- **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 lib/lila receptor complex. By binding to GP lib/lila, 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 Ill, 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 Gl side effects (diarrhea, abnormal stools, dyspepsia, and abdominal pain). Rarely, thrombocytopenia or leukopenia. Cilostazol is contraindicated in patients with heart failure.

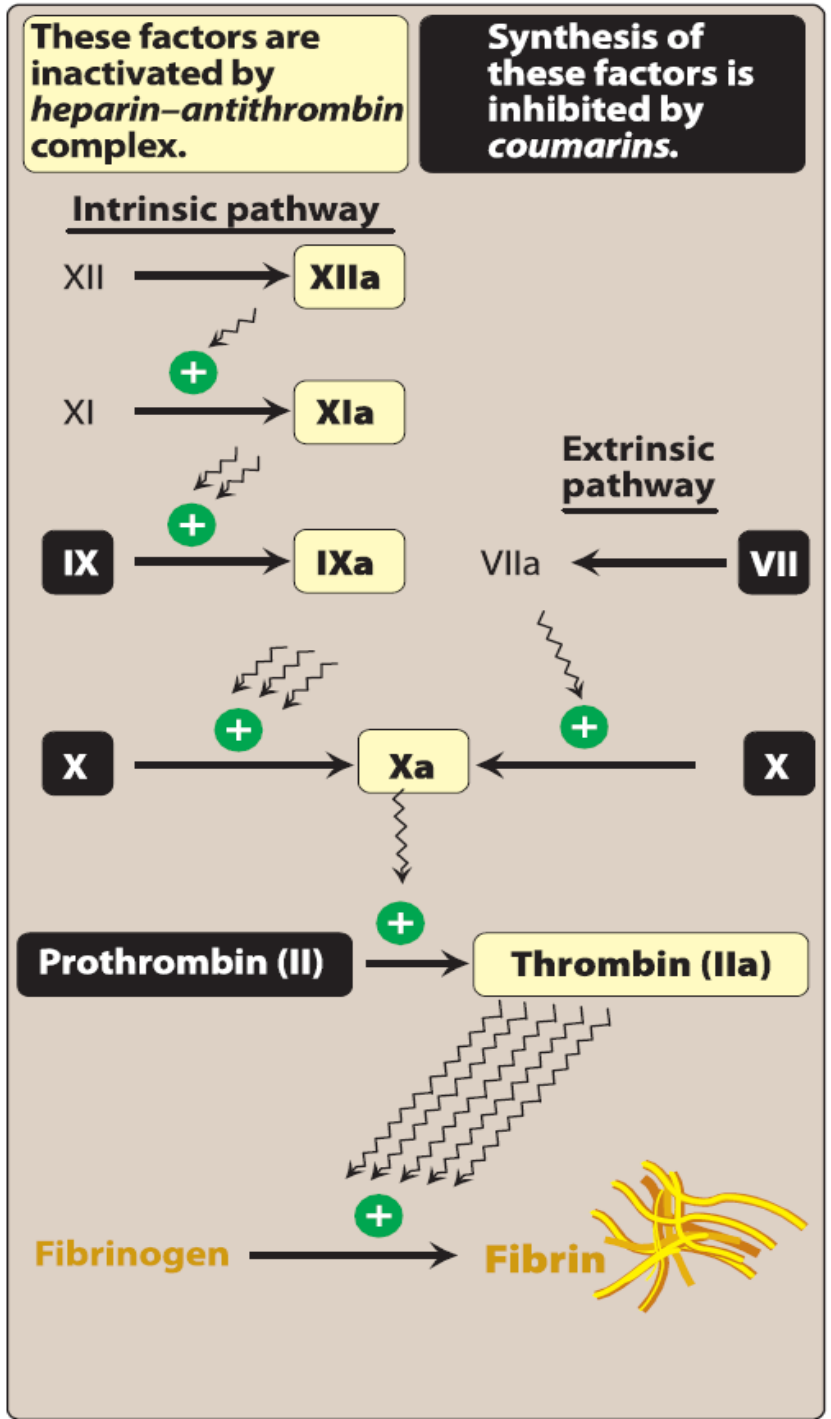
6- Vorapaxar (new)

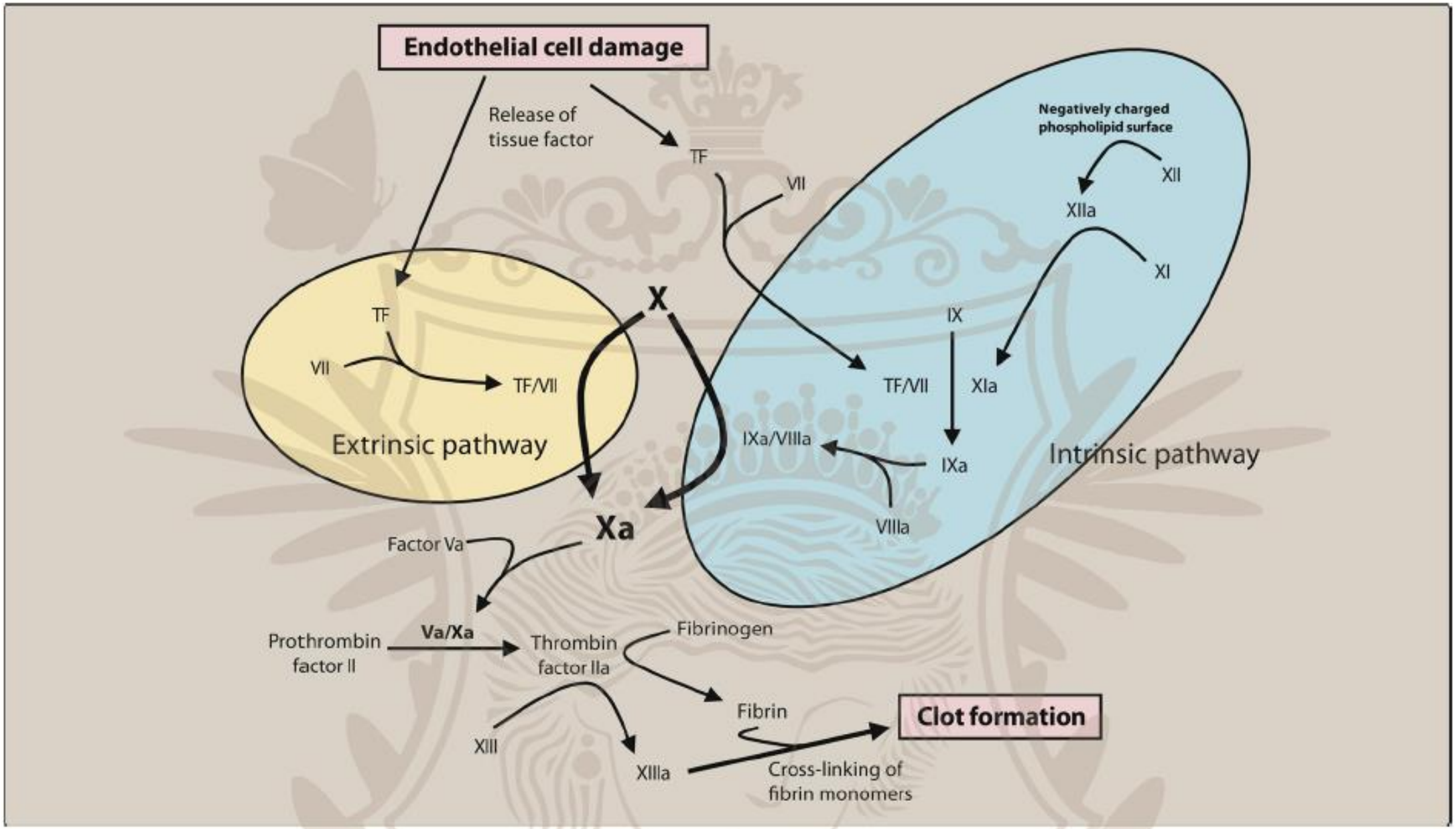
- Vorapaxar is an antagonist of the protease-activated receptor-1 (a thrombin receptor) expressed on platelets. Although it binds reversibly, it has a long half-life and an extended duration of action (4 weeks after discontinuation) .
- Given orally in conjunction with aspirin or clopidogrel to reduce 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:			
Aspirin	Angioedema Bleeding Bronchospasm GI disturbances Reye syndrome SJS	Anticoagulants, P2Y12 inhibitors, NSAIDs—increased bleeding *cidofovir*—nephrotoxicity *probenecid*—decreased uricosuric effects	CBC LFT
Cilostazol	Bleeding GI disturbances Headache Peripheral edema SJS	Food (administer on empty stomach)	CBC
Clopidogrel	Bleeding SJS	Strong CYP2C19 inhibitors reduce antiplatelet effect (e.g., *omeprazole*)	CBC LFT
Dipyridamole	Bleeding Dizziness GI discomfort Rash	Salicylates—increased bleeding Thrombolytic agents—increased bleeding	None for oral administration
Prasugrel	Angioedema Bleeding Headache Hyperlipidemia Hypertension	Anticoagulants—increased bleeding Other antiplatelets—increased bleeding	CBC
Ticagrelor	Bleeding Dyspnea Headache Raised SCr	Strong CYP3A4 inhibitors (e.g., *ketoconazole*)—increased bleeding Strong CYP3A4 inducers (e.g., *rifampin*)—decreased efficacy	CBC LFT
Injectable Agents:			
Abciximab *Eptifibatide* *Tirofiban*	For all agents: Hypotension Nausea Vomiting Thrombocytopenia	For all agents: Increased bleeding: *Ginkgo biloba* Antiplatelets Salicylates SSRIs and SNRIs	For all agents: APTT clotting time H/H platelet count thrombin time

Blood Coagulation

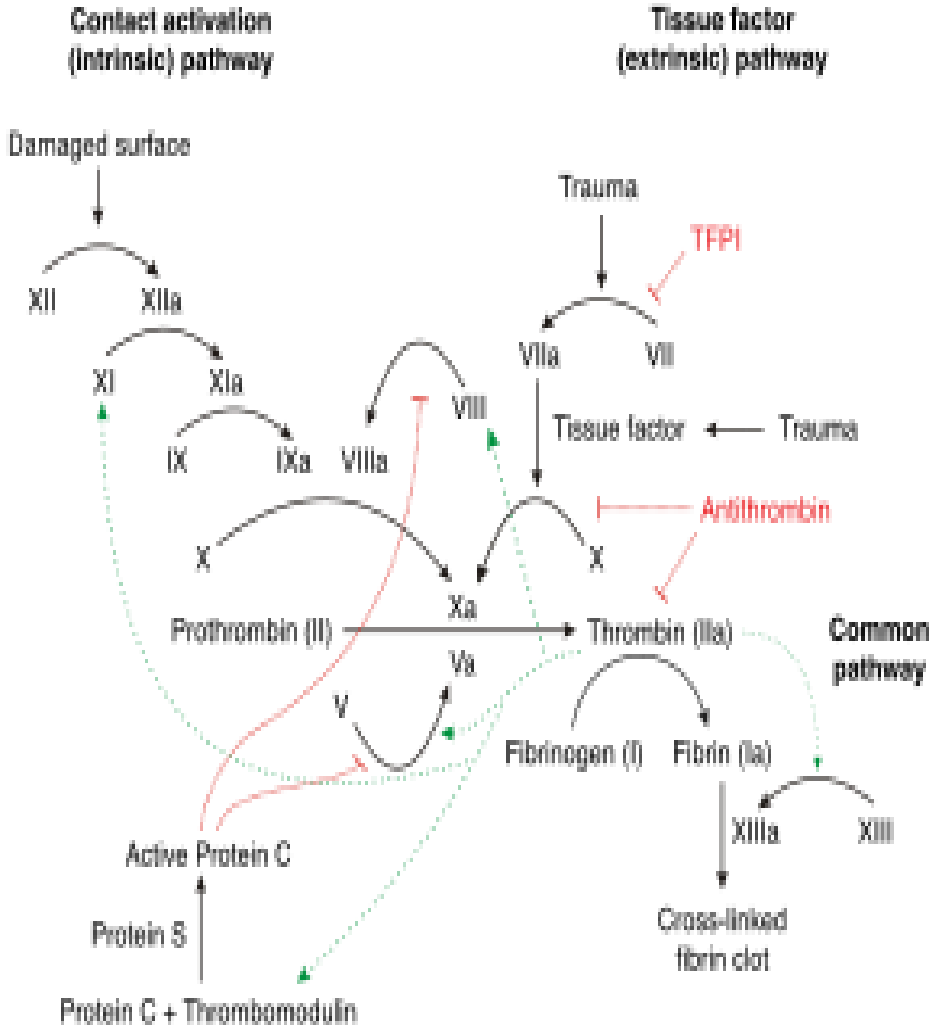
- The coagulation process consists of two interrelated pathways, the extrinsic and the intrinsic systems.
- The extrinsic system is initiated by the activation of clotting factor VII by tissue factor (also known as thromboplastin).
- The intrinsic system is triggered by the activation of clotting factor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




Endothelial cell damage
Release of tissue factor
TF
VII
Negatively charged phospholipid surface
XII
XIIa
XI
X
TF
VII
TF/VII
Extrinsic pathway
IX
TF/VII
XIa
IXa/VIIIa
IXa
VIIIa
Intrinsic pathway
Xa
Factor Va
Prothrombin factor II
Va/Xa
Thrombin factor IIa
Fibrinogen
Fibrin
Clot formation
XIII
XIIIa
Cross-linking of fibrin monomers

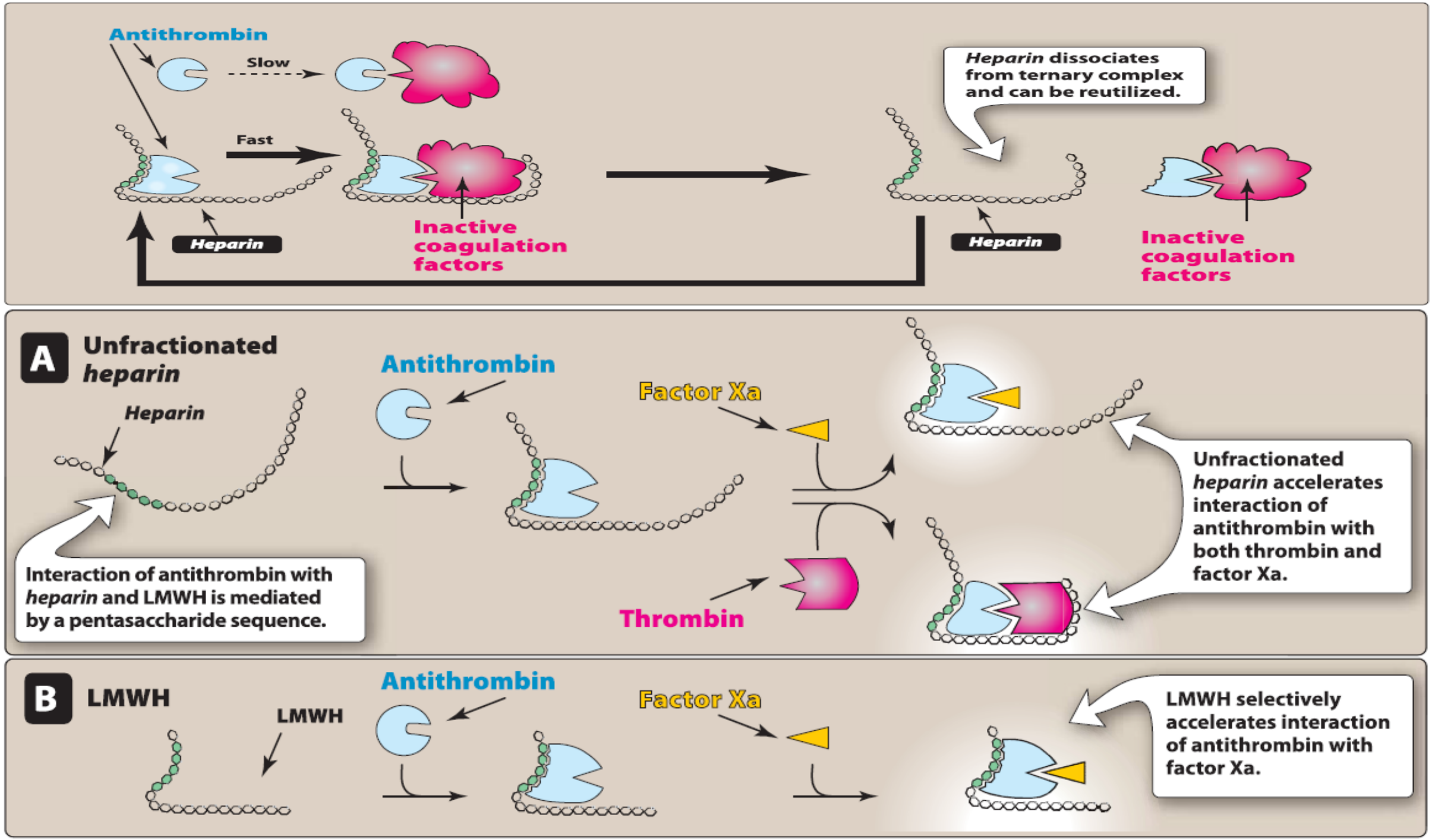
Inhibitors of coagulation

- 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).



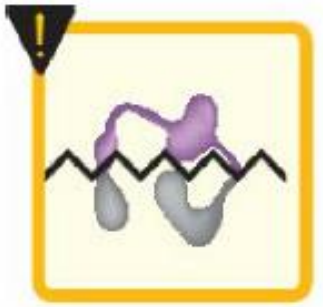
Anticoagulants 1- Heparin & LMWHs

- 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 Ill, with the subsequent rapid inactivation of coagulation factors by 1000-fold. Antithrombin Ill is an a globulin that inhibits serine proteases of thrombin (factor lla) and factor Xa. LMWHs complex with antithrombin Ill and inactivate factor Xa (including that located on platelet surfaces)


Antithrombin
Slow
Fast
Heparin
Inactive coagulation factors
Heparin dissociates from ternary complex and can be reutilized.
Heparin
Inactive coagulation factors
A
Unfractionated heparin
Heparin
Antithrombin
Factor Xa
Thrombin
Interaction of antithrombin with heparin and LMWH is mediated by a pentasaccharide sequence.
Unfractionated heparin accelerates interaction of antithrombin with both thrombin and factor Xa.
B
LMWH
LMWH
Antithrombin
Factor Xa
LMWH selectively accelerates interaction of antithrombin with factor Xa.

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?? MOA and dose?), hypersensitivity (chills, fever, urticaria, and anaphylactic shock) Heparin-induced thrombocytopenia (HIT) (is immune mediated and risk of vebous and arterial embolism) LMWHs can have cross-sensitivity and not used in HIT, osteoporosis with long use heparin, C.I. ?



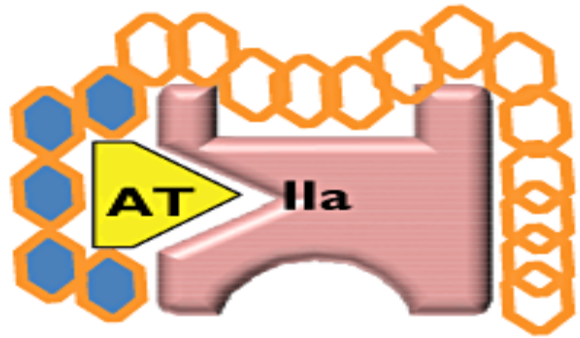
P. Anticoagulants 2- Argatroban

- 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.

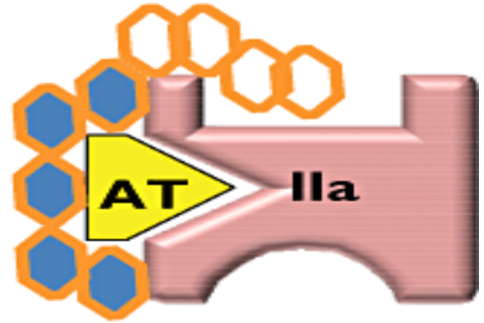
P. Anticoagulants: 3- Bivalirudin and Desirudin

- 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** t1/2 25 min, excretion? ,

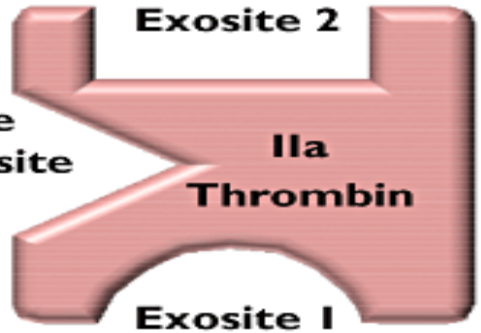
Unfractionated heparin



Low molecular weight heparin



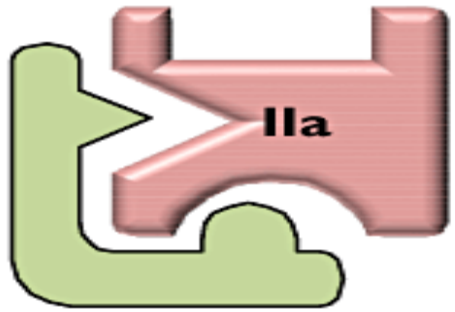
Thrombin



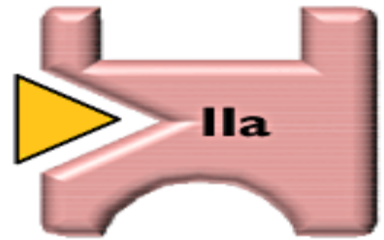
Exosite I
Fibrin binding site

Exosite 2
Heparin binding site

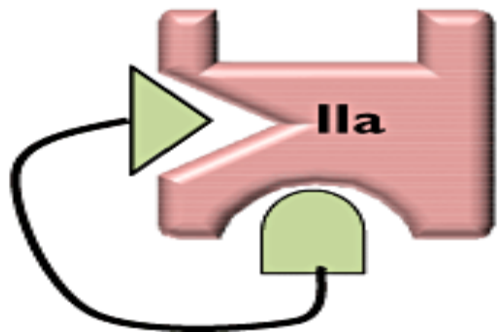
Lepirudin/ Desirudin



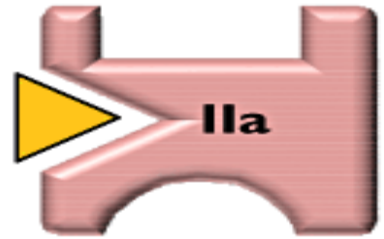
Argatroban



Bivalirudin



Dabigatran

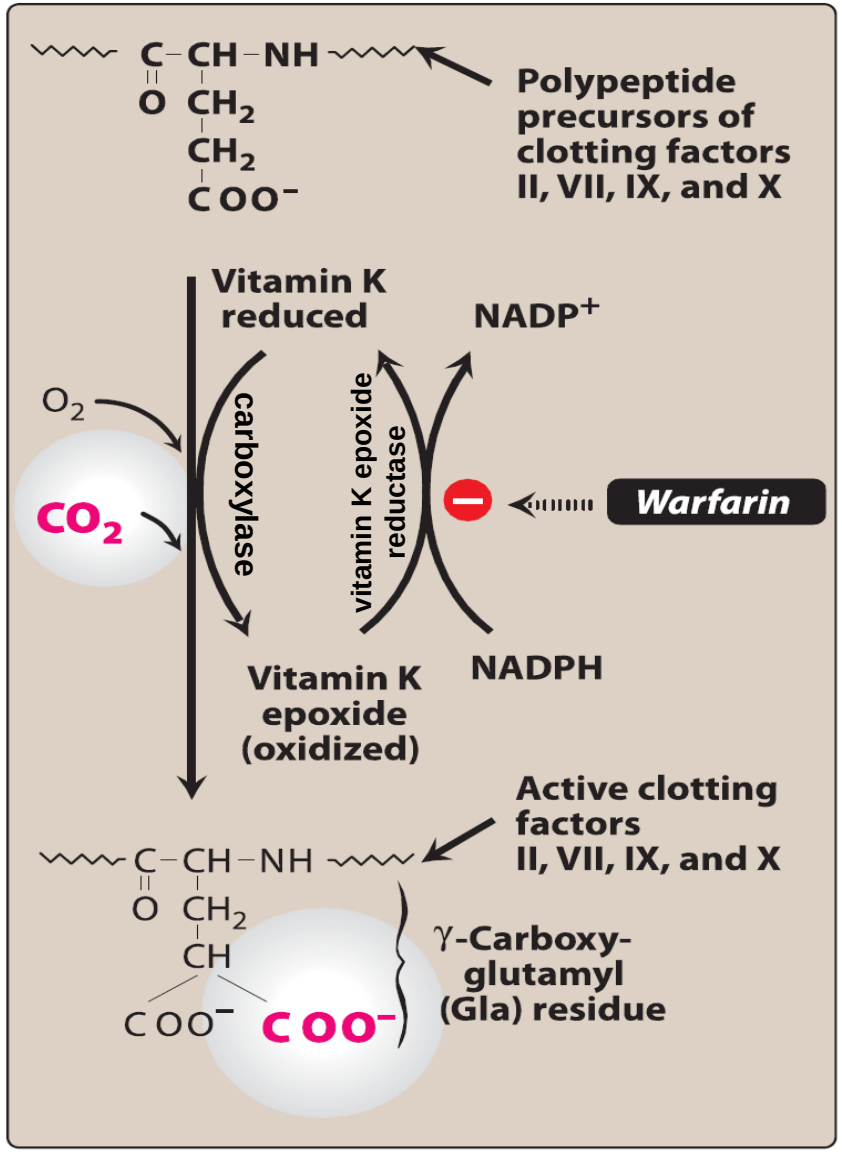


P. Anticoagulants: 4- Fondaparinux

- Fondaparinux is a synthetically derived pentasaccharide anticoagulant that selectively inhibits factor Xa.
- **MOA**: By selectively binding to antithrombin Ill, fondaparinux potentiates (300-to 1000-fold) the innate neutralization of factor Xa by antithrombin Ill.
- **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? t1/2 18 hr. renal impairment? .
- **A.E**: Bleeding (no antidote). HIT is less than heparin

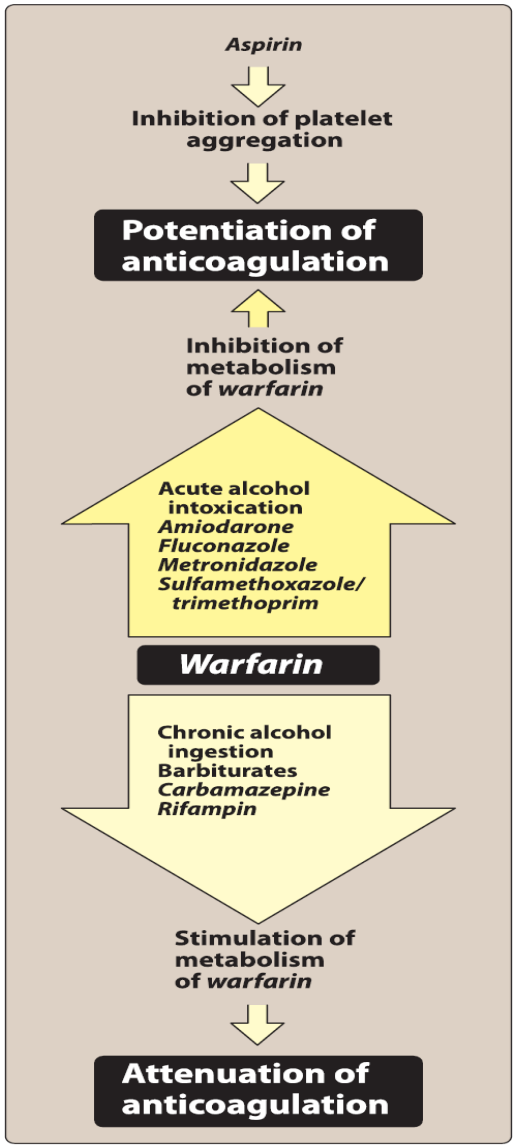
Vitamin K Antagonists: Warfarin

- 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? T1/2=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

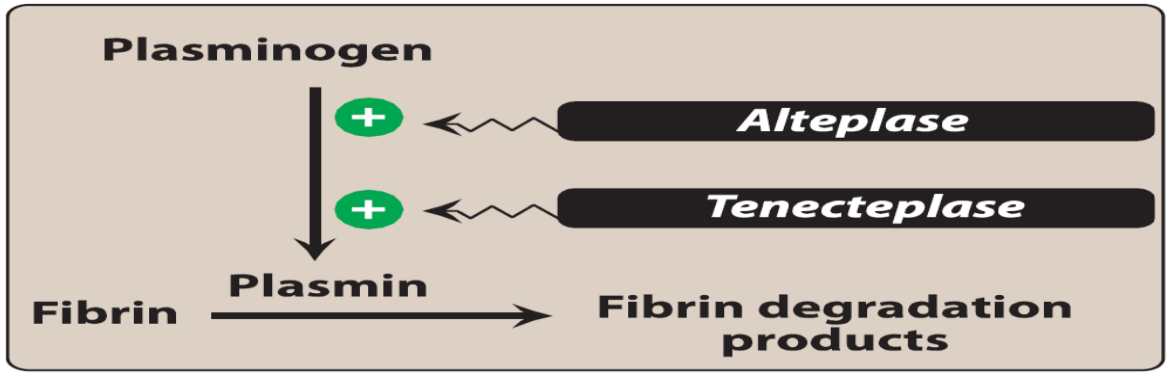
- **MOA**: oral direct thrombin inhibitor. Both clot-bound thrombin and free thrombin are inhibited by dabigatran.
- **Uses**: Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Treatment and prophylaxis of DVT and PE in patients who have already received parenteral 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 Gl 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 (lla) 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.

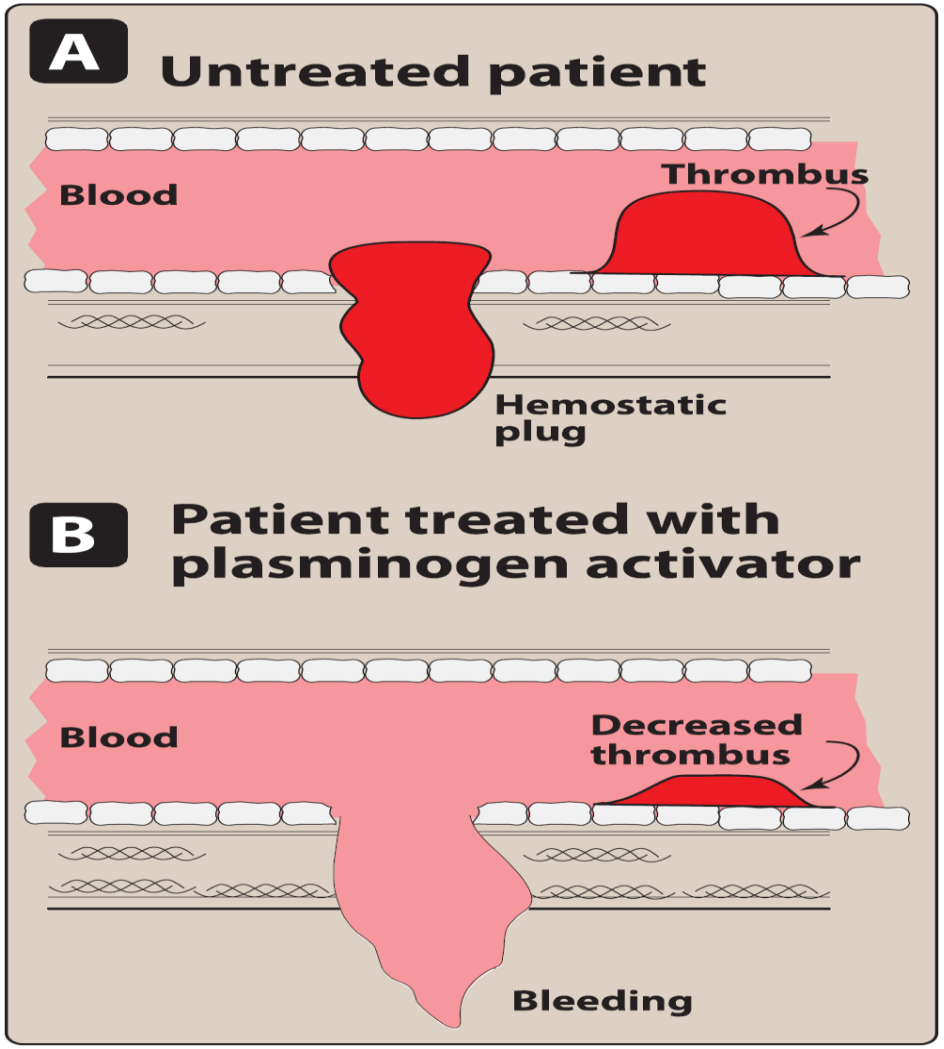
Thrombolytic Drugs: Alteplase and Tenecteplase

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



Alteplase and Tenecteplase Cont..

- **A.E**: hemorrhage is a major adverse effect. Why? 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: production? Affinity to plasminogen? Uses? T1/2? Administration? Unique S.E



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
Aminocaproic acid *Tranexamic acid*	Fibrinolytic state	Muscle necrosis Thrombosis CVA Seizure	CBC Muscle enzymes Blood pressure
Idarucizumab	*Dabigatran*	Hypokalemia Thrombosis	aPTT Clotting time Thrombin time
Protamine sulfate	*Heparin*	Flushing Nausea/vomiting Dyspnea Bradyarrhythmia Hypotension Anaphylaxis	Coagulation monitoring Blood pressure Heart rate
Vitamin K1	*Warfarin*	Skin reaction Anaphylaxis	PT/INR