Drugs affecting Blood

(2Lectures)

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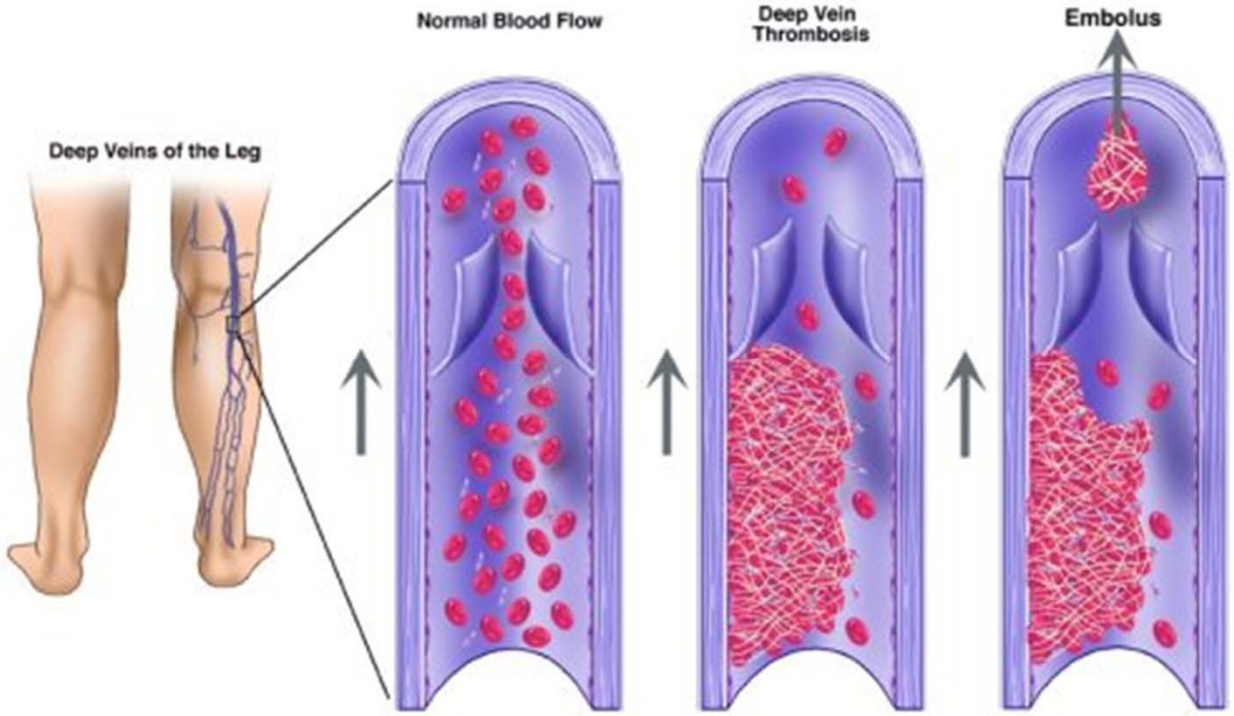
فرع الادوية والسموم

- 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.”

- All of them may occlude blood vessels and deprive tissues of oxygen and nutrients.



- Arterial thrombosis usually consists of a platelet-rich clot.
- Arterial thrombosis most often occurs in medium-sized vessels rendered thrombogenic by atherosclerosis.
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- Venous thrombosis typically involves a clot that is rich in fibrin, with fewer platelets than are observed with arterial clots.

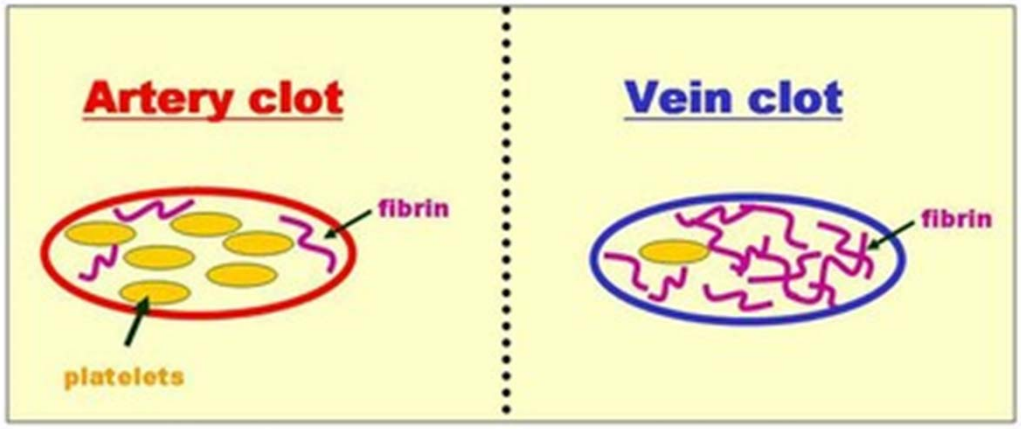
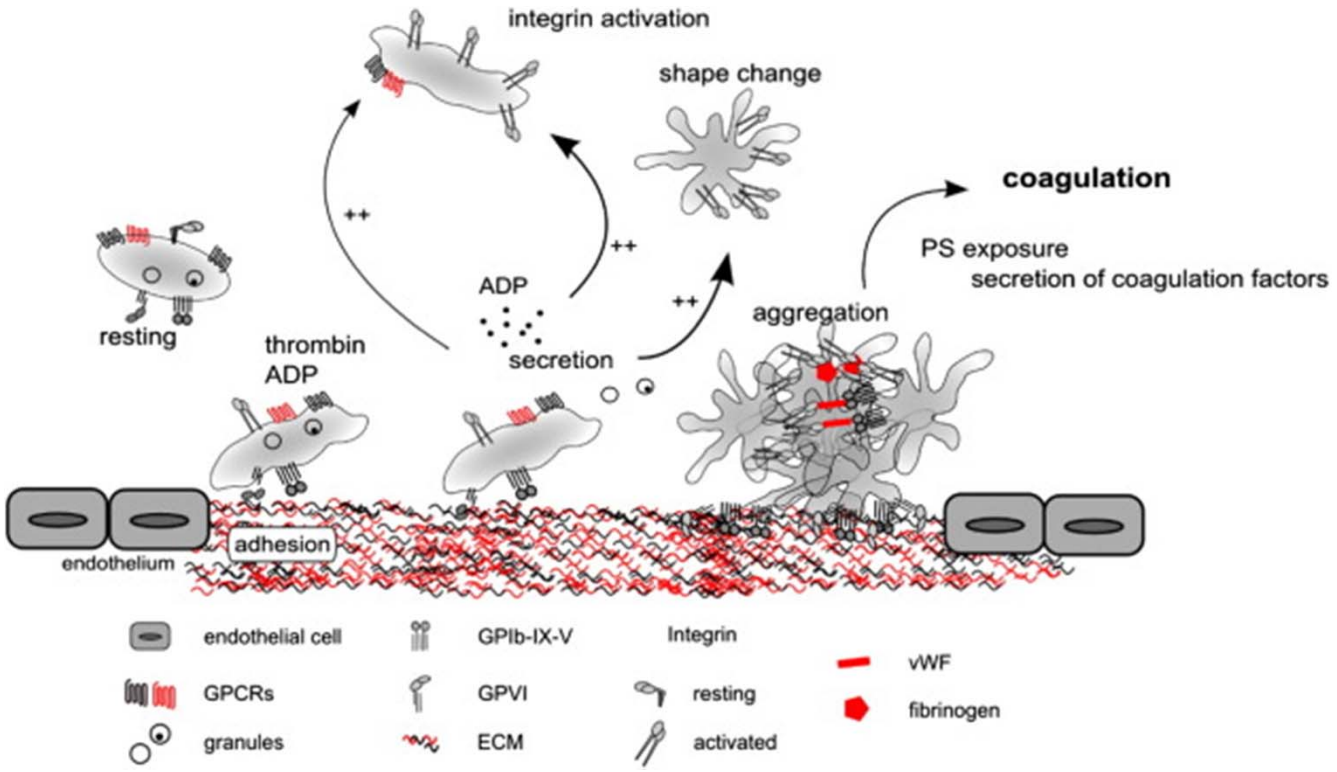


Figure 3 Figure 4

- A wound causes vasoconstriction, accompanied by:

✓ adhesion and activation of platelets

✓ formation of fibrin.



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.

PLATELET RESPONSE TO VASCULAR INJURY

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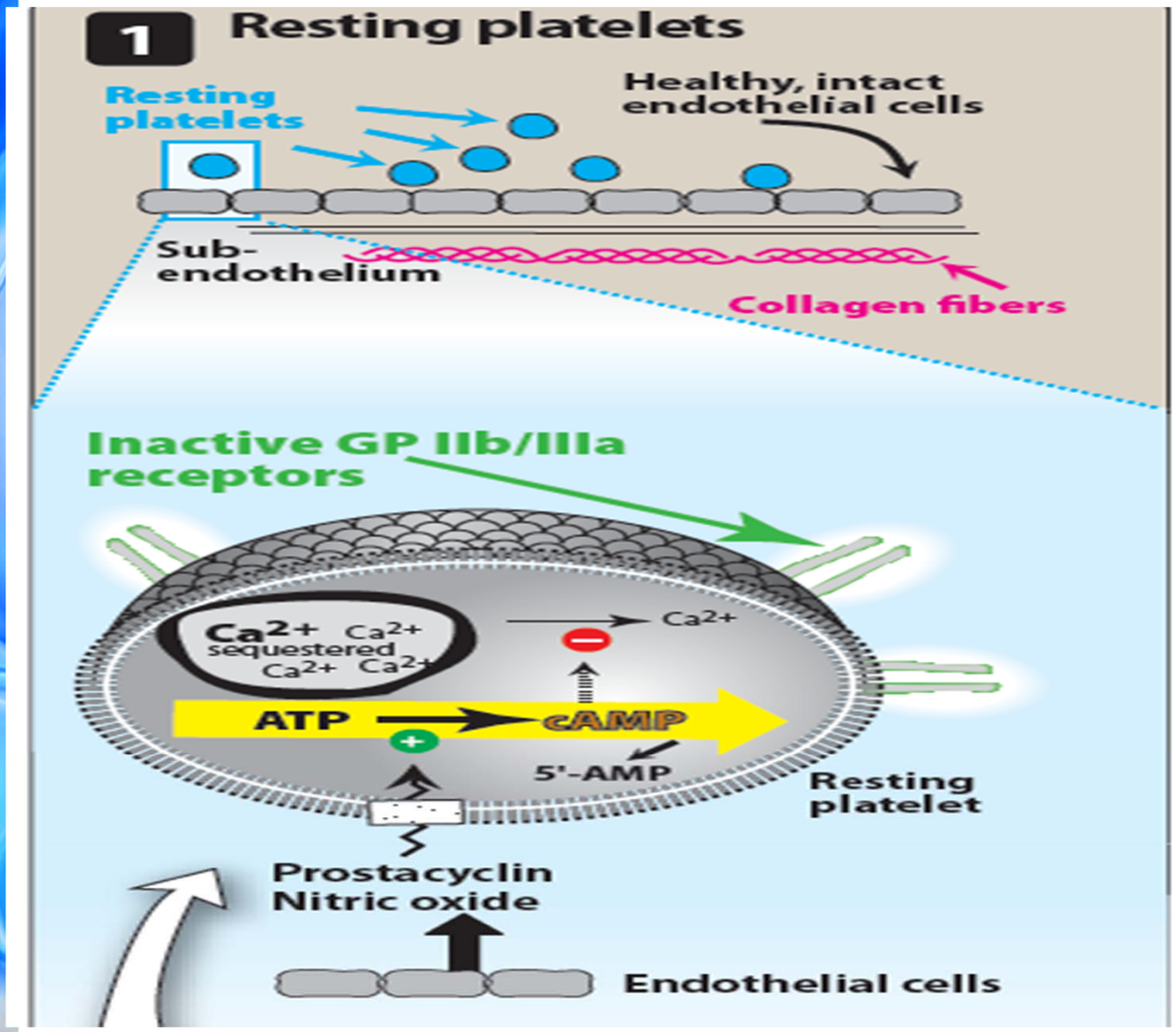
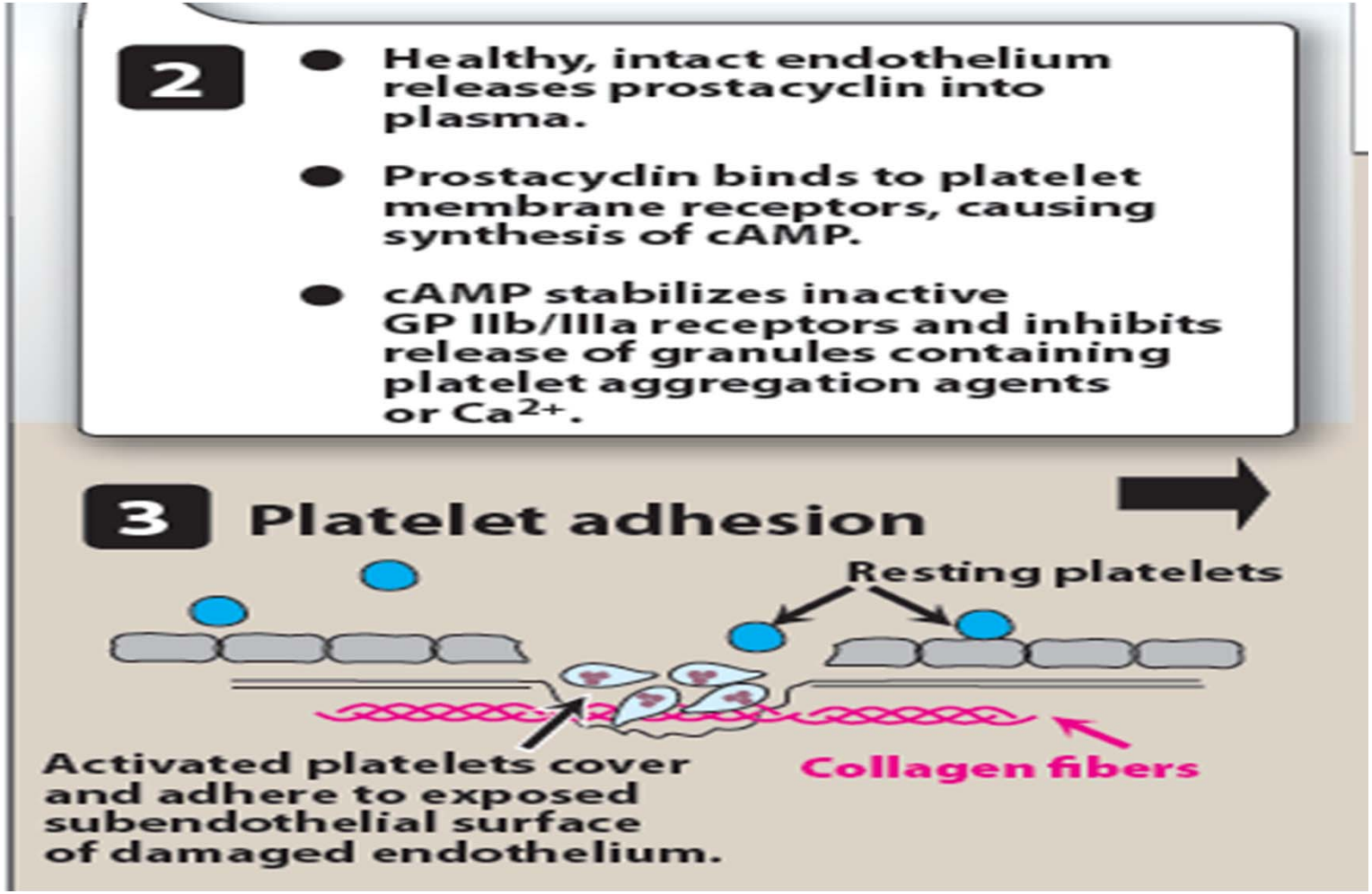
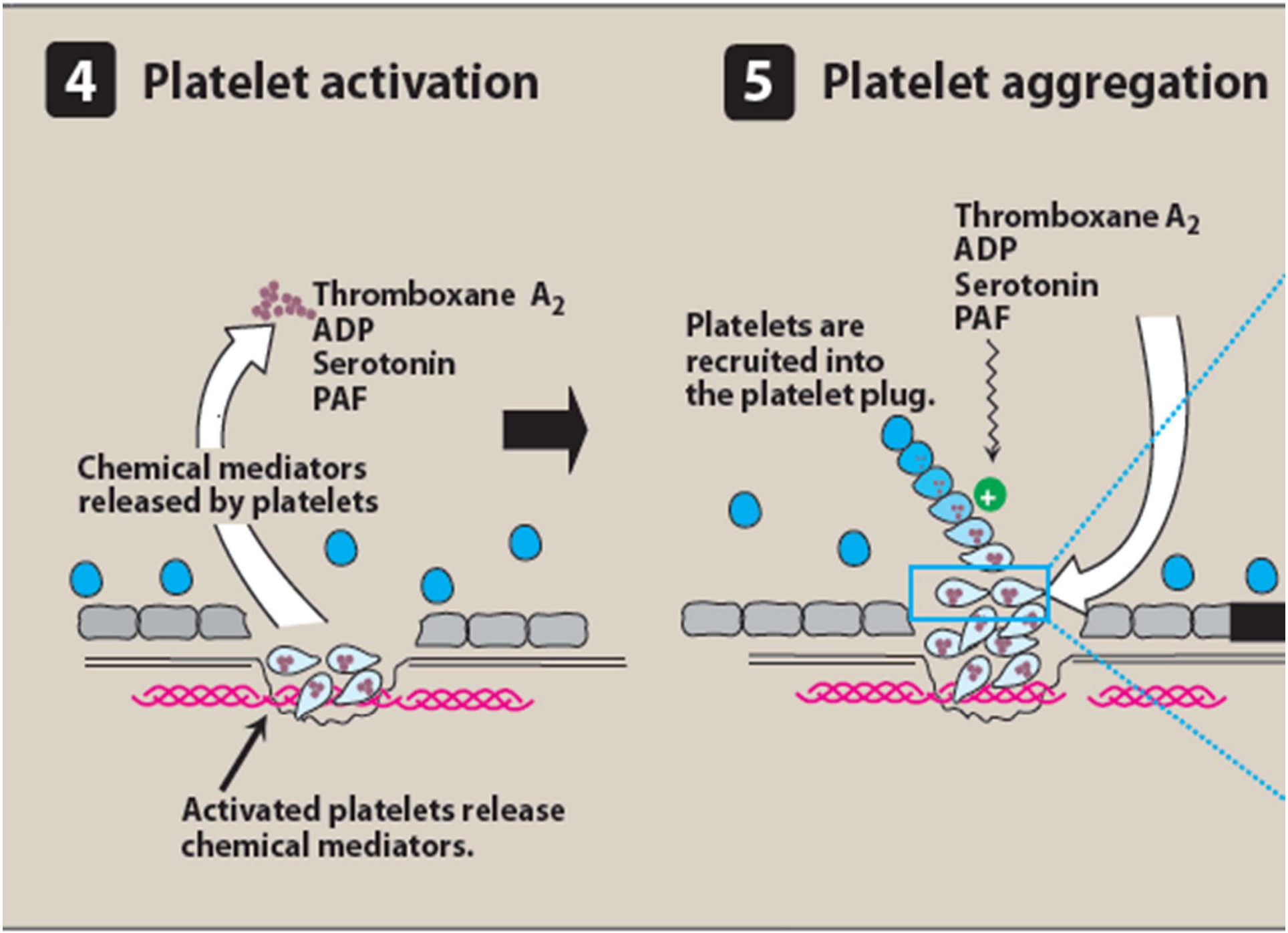
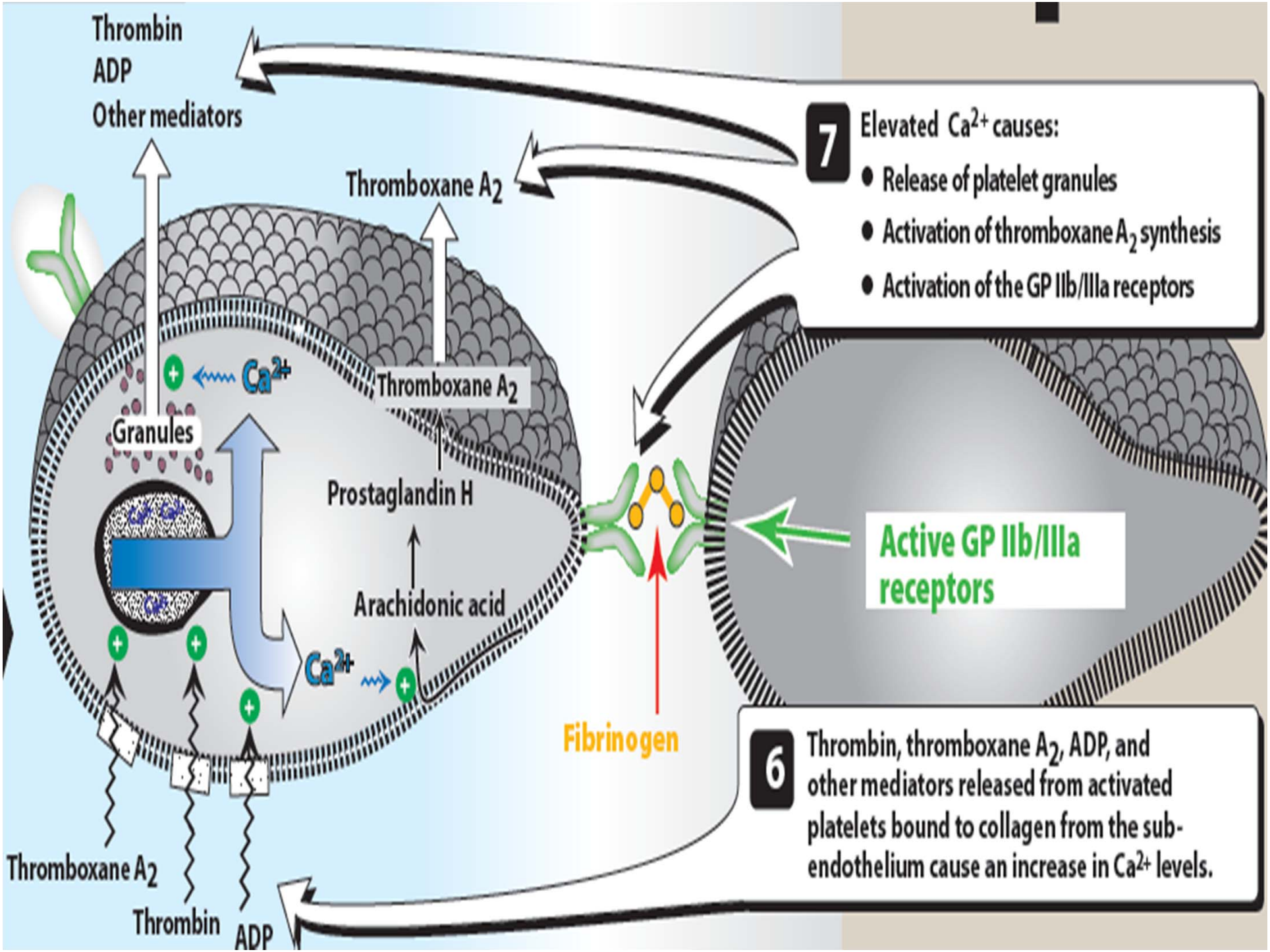
- These interactions lead to hemostasis or the cessation of blood loss from a damaged blood vessel.
- The creation of an unwanted thrombus involves many of the same steps as normal clot formation, except that the triggering stimulus is a pathologic condition in the vascular system rather than an external physical trauma.

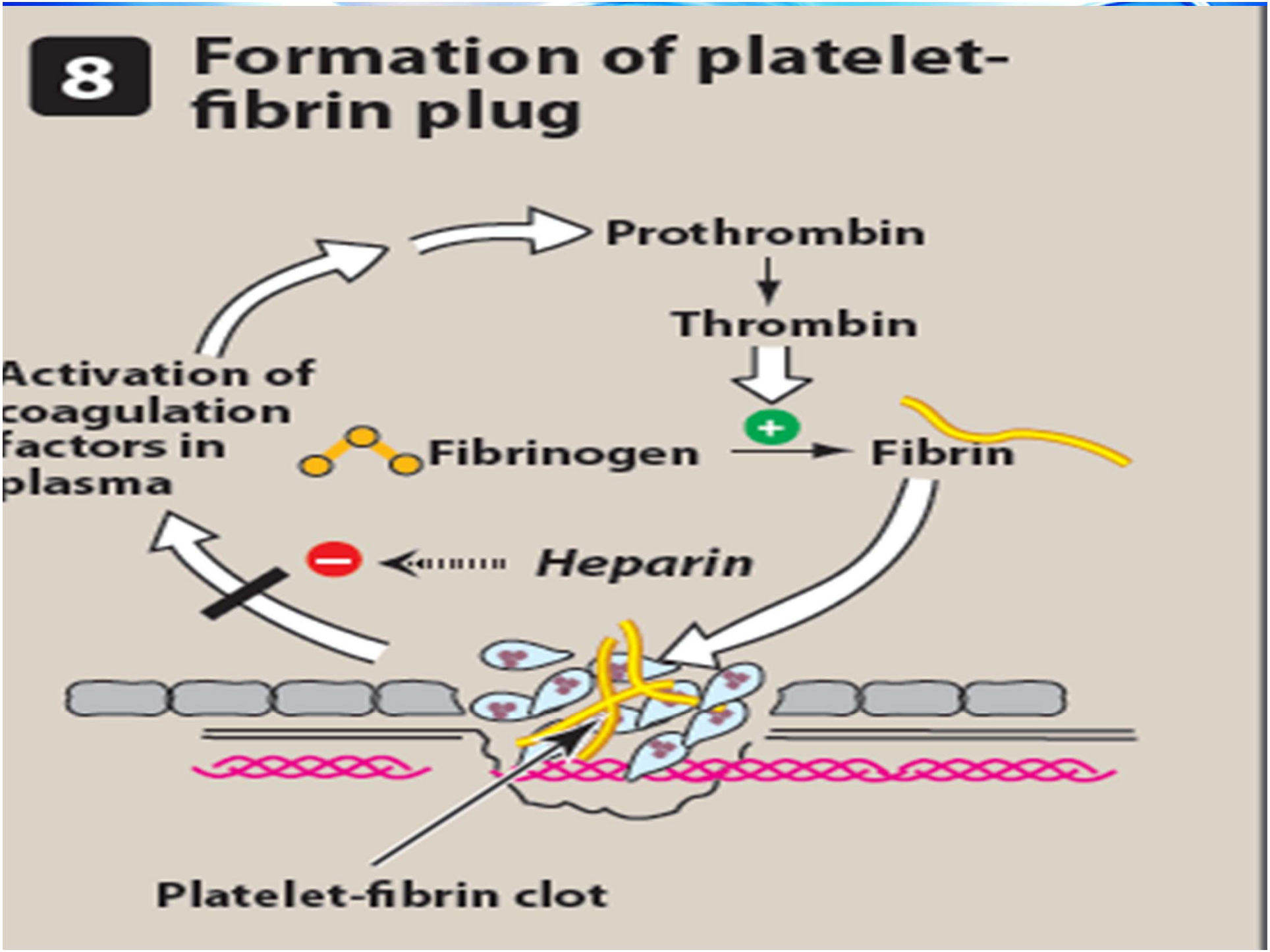

1 Resting platelets
Resting platelets
Healthy, intact endothelial cells
Sub-endothelium
Collagen fibers
Inactive GP IIb/IIIa receptors
Ca2+ Ca2+
sequestered
Ca2+ Ca2+
Ca2+
ATP
cAMP
5'-AMP
Resting platelet
Prostacyclin
Nitric oxide
Endothelial cells

- .
- The platelet membrane also contains receptors that can bind thrombin, thromboxanes,2 and exposed collagen.

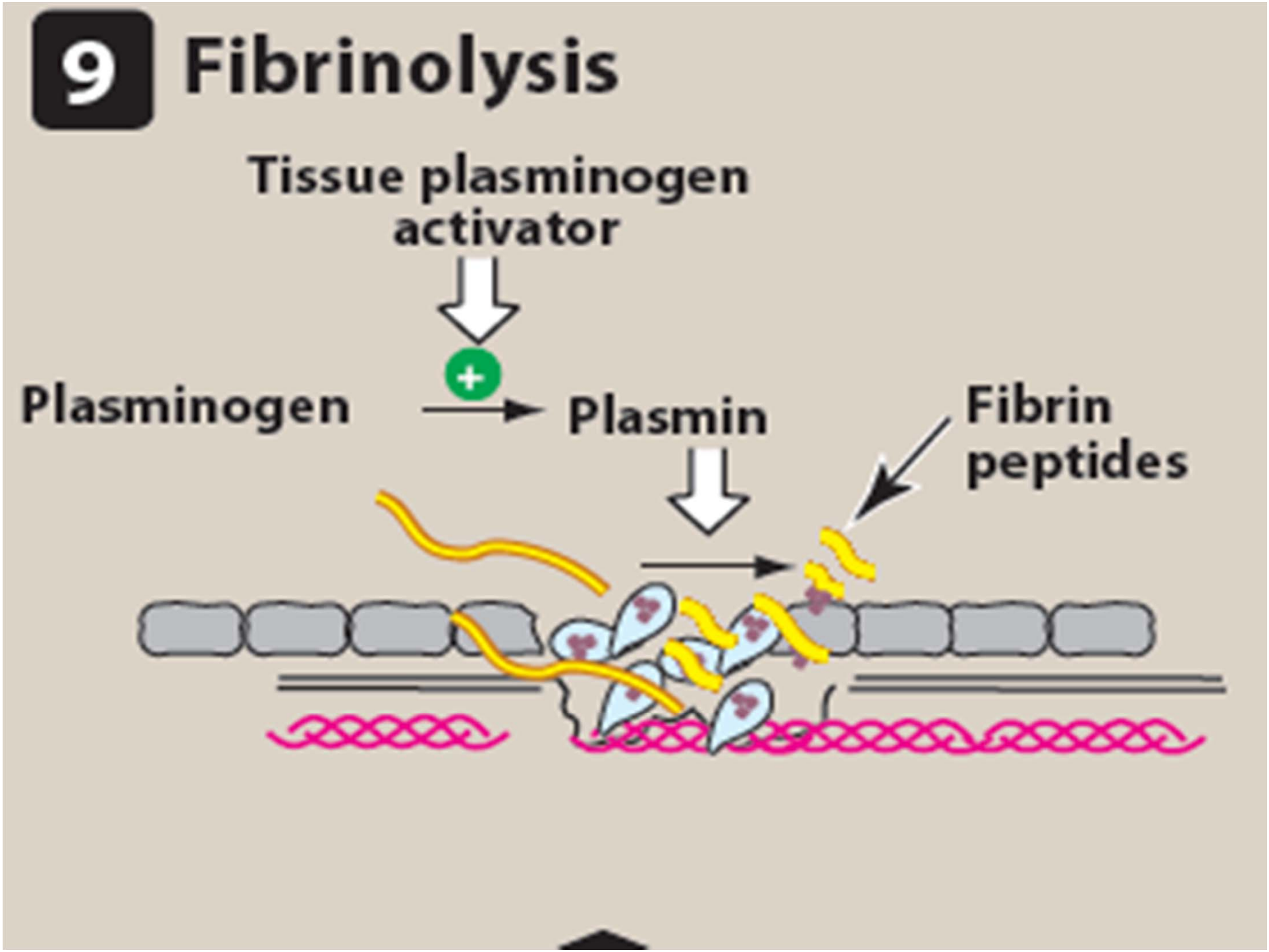



4 Platelet activation
Thromboxane A_2
ADP
Serotonin
PAF
Chemical mediators released by platelets
Activated platelets release chemical mediators.
5 Platelet aggregation
Thromboxane A_2
ADP
Serotonin
PAF
Platelets are recruited into the platelet plug.


Thrombin
ADP
Other mediators
Thromboxane A2
7
Elevated Ca2+ causes:
• Release of platelet granules
• Activation of thromboxane A2 synthesis
• Activation of the GP IIb/IIIa receptors
Ca2+
Granules
Thromboxane A2
Prostaglandin H
Arachidonic acid
Ca2+
Active GP IIb/IIIa receptors
Fibrinogen
6
Thrombin, thromboxane A2, ADP, and other mediators released from activated platelets bound to collagen from the sub-endothelium cause an increase in Ca2+ levels.
Thromboxane A2
Thrombin
ADP


8
Formation of platelet-fibrin plug
Prothrombin
Thrombin
Activation of coagulation factors in plasma
Fibrinogen
Fibrin
Heparin
Platelet-fibrin clot

9 Fibrinolysis



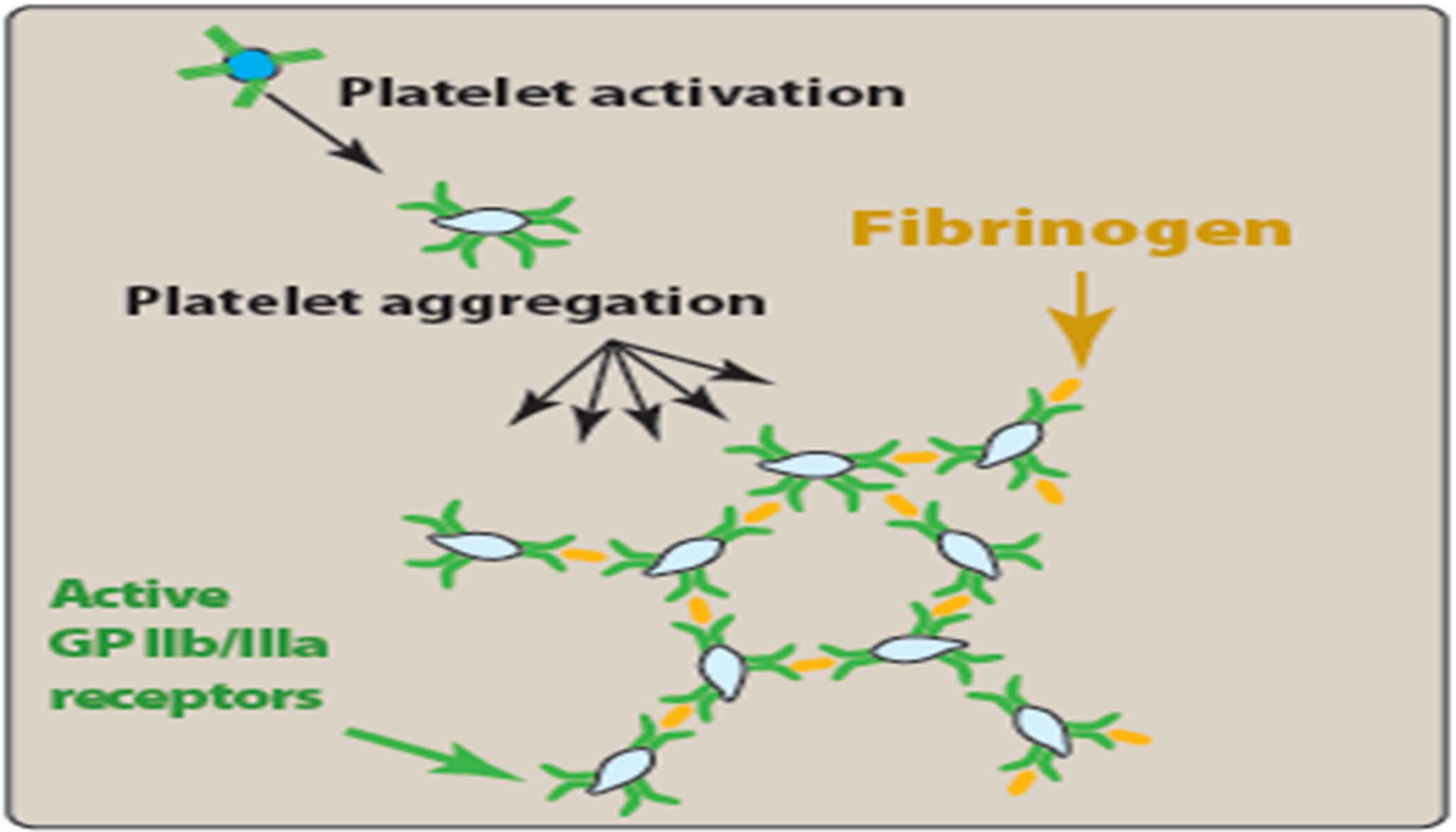


Figure 20.4
Activation and aggregation of platelets. GP = glycoprotein.

Chemical mediators synthesized by endothelial cells

- Prostacyclin is synthesized by intact endothelial cells and acts as an inhibitor of platelet aggregation.
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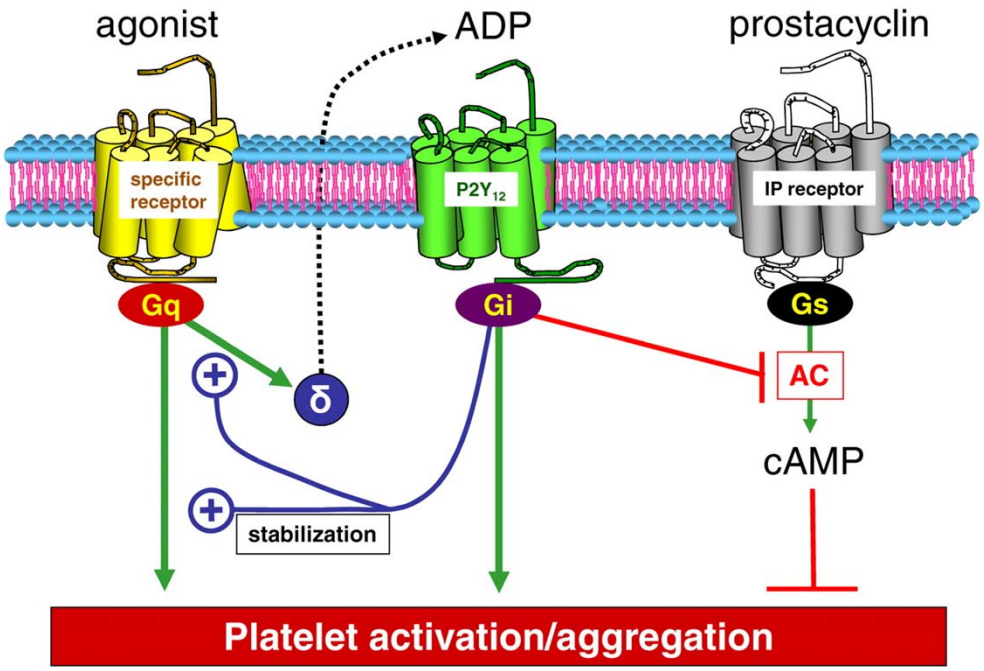
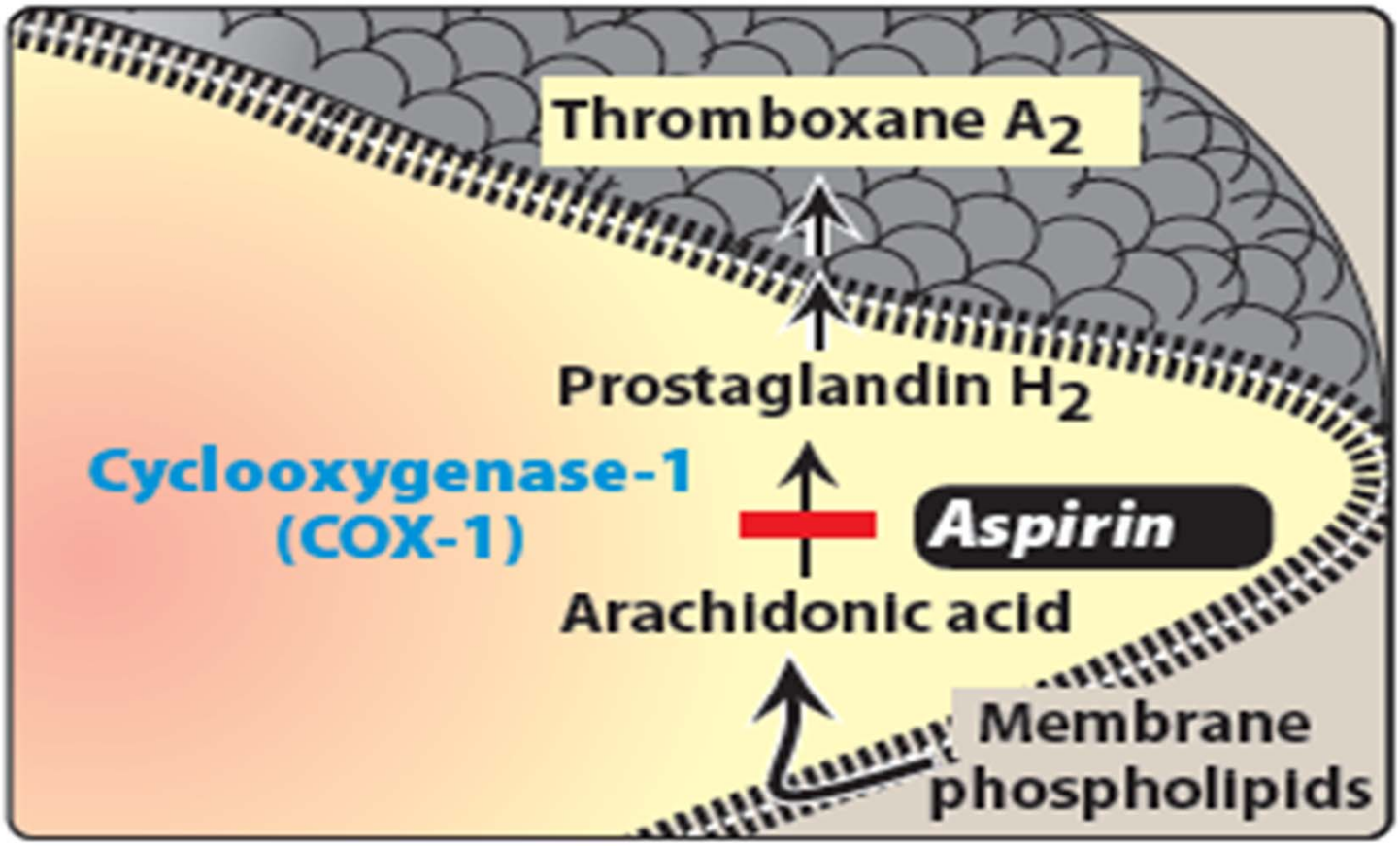
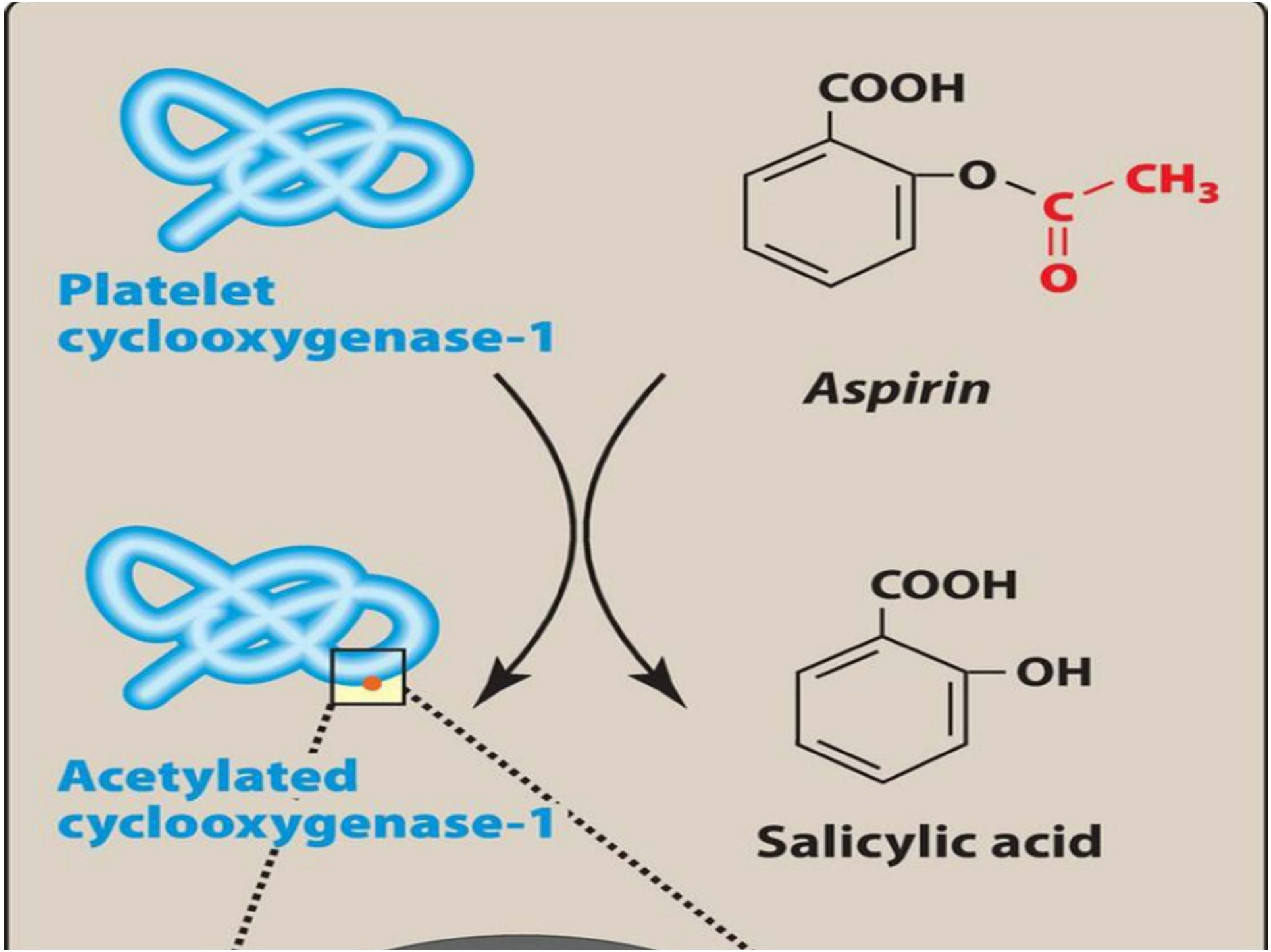


Aspirin

- Arachidonic acid is first converted to prostaglandin H2 by COX-1. Prostaglandin H2 is further metabolized to thromboxane A2, which is released into plasma.
- *Aspirin* inhibits irreversible inhibition of COX-1.



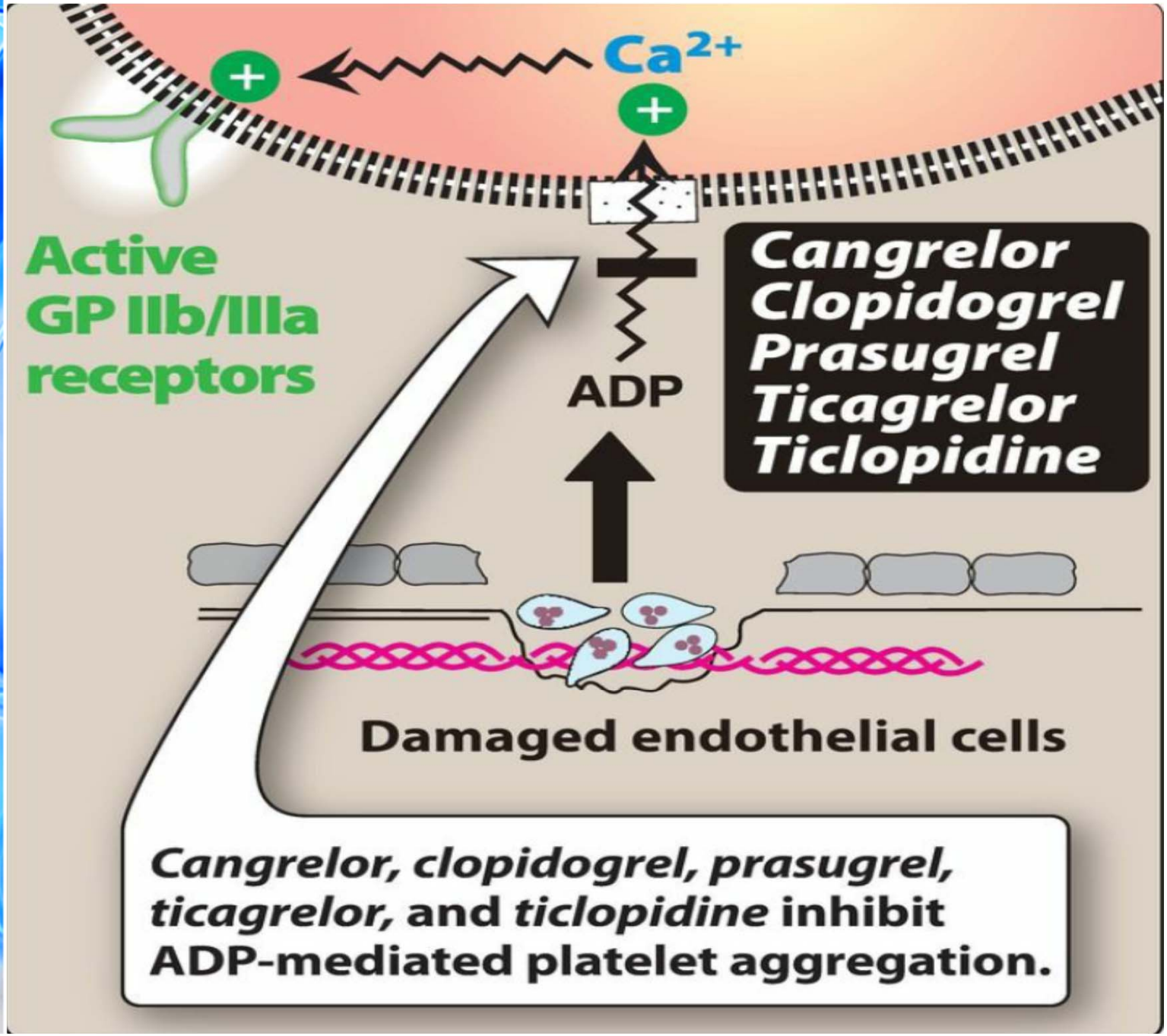

Platelet
cyclooxygenase-1
COOH
O
C
O
CH3
Aspirin
Acetylated
cyclooxygenase-1
COOH
OH
Salicylic acid

- The recommended dose of *aspirin* ranges from 50 to 325 mg, with side effects determining the dose chosen

- Nonsteroidal anti-inflammatory drugs, such as *ibuprofen*, inhibit COX-1 by transiently competing at the catalytic site.

- *Ibuprofen*, if taken within the 2 hours prior to *aspirin*, can obstruct the access of *aspirin* to the serine residue

P2Y12 receptor antagonists



- These drugs 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

- Ticagrelor and cangrelor bind to the P2Y12 ADP receptor in a reversible manner. The other agents bind irreversibly

- When treatment is suspended, the platelet system requires time to recover.

- *Clopidogrel* is approved for prevention of atherosclerotic events also approved for prophylaxis of thrombotic events in acute coronary syndromes

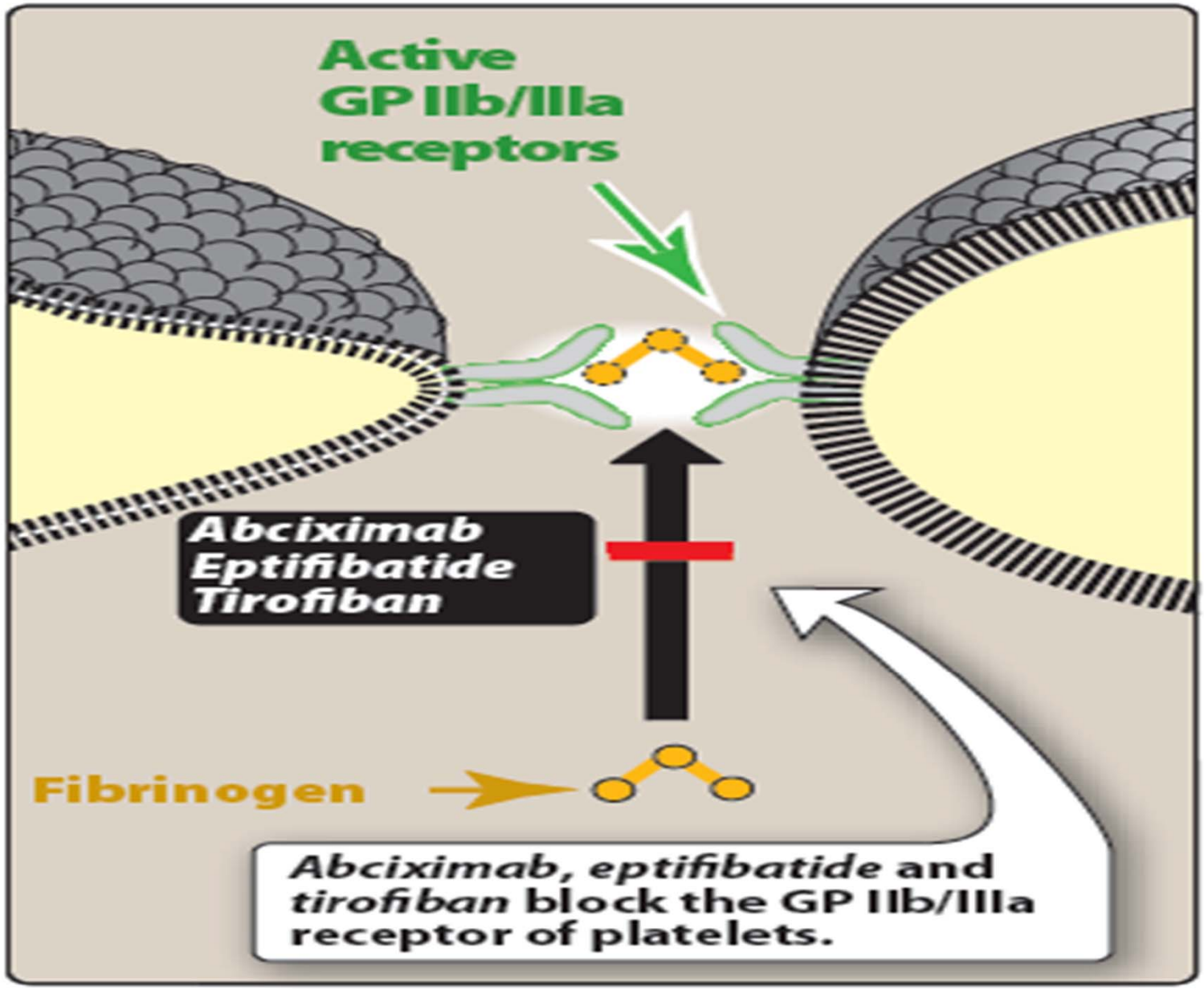
- Ticlopidine is similar in structure to clopidogrel. It is indicated for the prevention of transient ischemic attacks (TIA) and strokes in patients with a prior cerebral thrombotic event.

- Prasugrel is approved to decrease thrombotic cardiovascular events in patients with acute coronary syndromes (unstable angina, non–Stelevation MI, and ST-elevation MI managed with PCI).

Adverse effects

- prolonged bleeding
- Prasugrel is contraindicated in patients with history of TIA or stroke.
- Prasugrel, ticagrelor, and cangrelor carry black box warnings for bleeding.
- ticagrelor carries a black box warning for diminished effectiveness with concomitant use of aspirin doses above 100 mg.

Glycoprotein IIb/IIIa inhibitors



Eptifibatide and tirofiban

- *Eptifibatide* is a cyclic peptide that binds to GP IIb/IIIa at the site that interacts with the arginine-glycine-aspartic acid sequence of fibrinogen

- *Tirofiban* is not a peptide, but it blocks the same site as *eptifibatide*

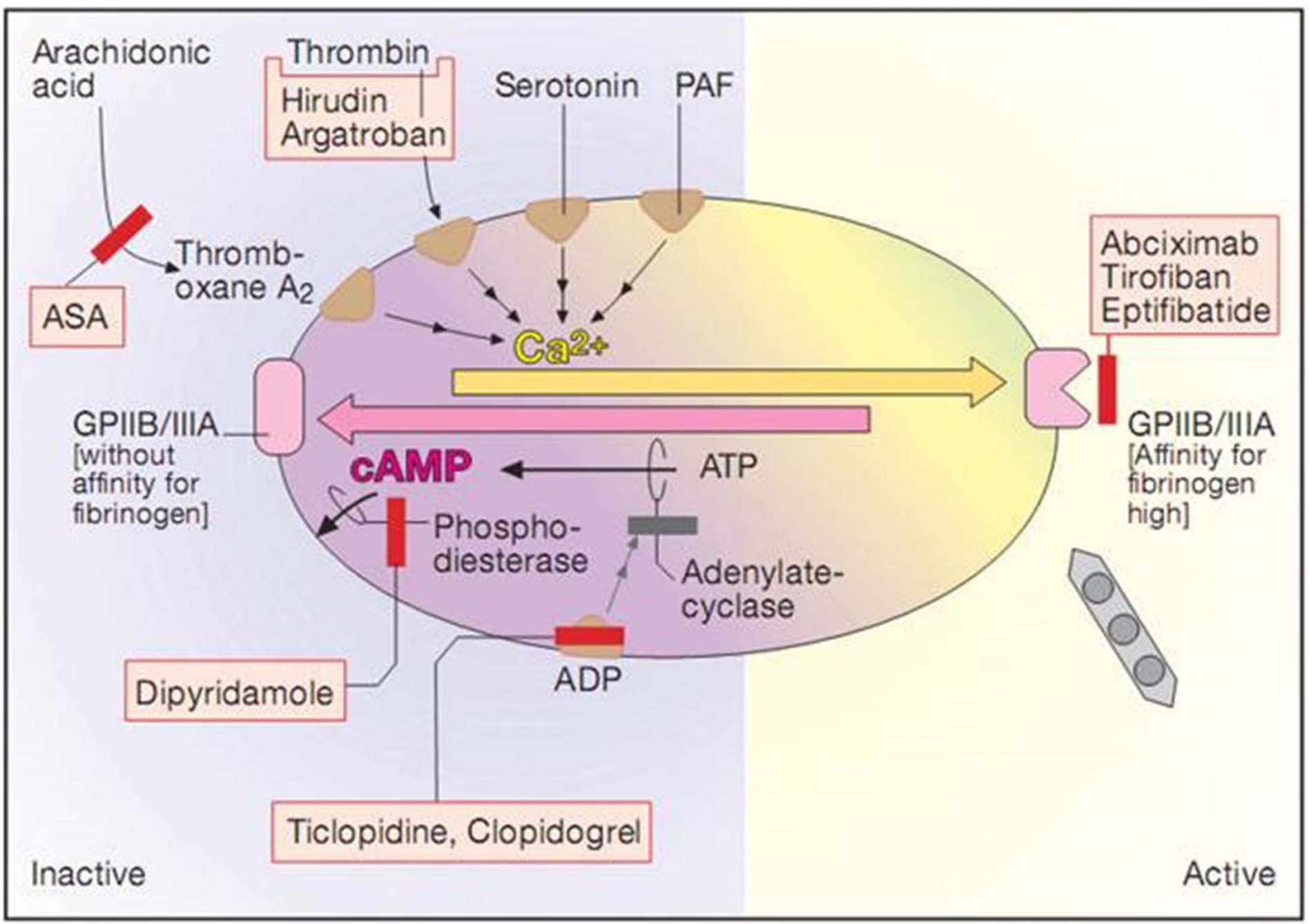
- Only IV formulations are available, because oral preparations of these GP IIb/IIIa blockers are too toxic. The major adverse effect of both drugs is bleeding.

Dipyridamole

- Coronary vasodilator, is used prophylactically to treat angina pectoris.
- It is usually given in combination with *aspirin* or *warfarin*.
- *Dipyridamole* increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase, resulting in decreased thromboxane A2 synthesis.
- It inappropriate for use in the elderly as a sole agent due to adverse GI and orthostatic hypotension.

Cilostazol

- Oral antiplatelet agent that also has vasodilating activity.
- reduce the symptoms of intermittent claudication.
- *Cilostazol* favorably alters the lipid profile, by causing a decrease in plasma triglycerides and an increase in HDL
- Headache and GI side effects (diarrhea, abnormal stools, dyspepsia, and abdominal pain).



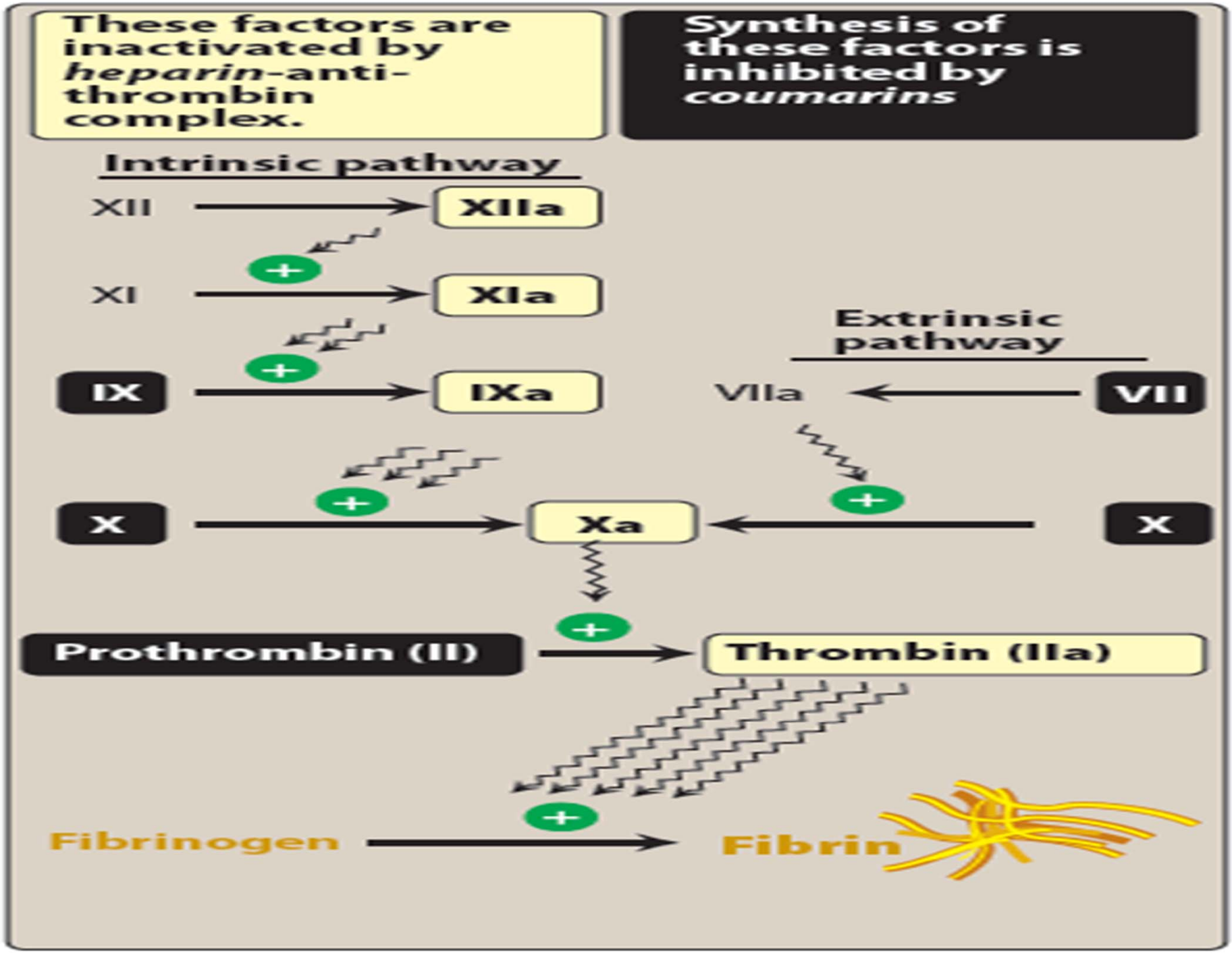
A. Inhibitors of platelet aggregation

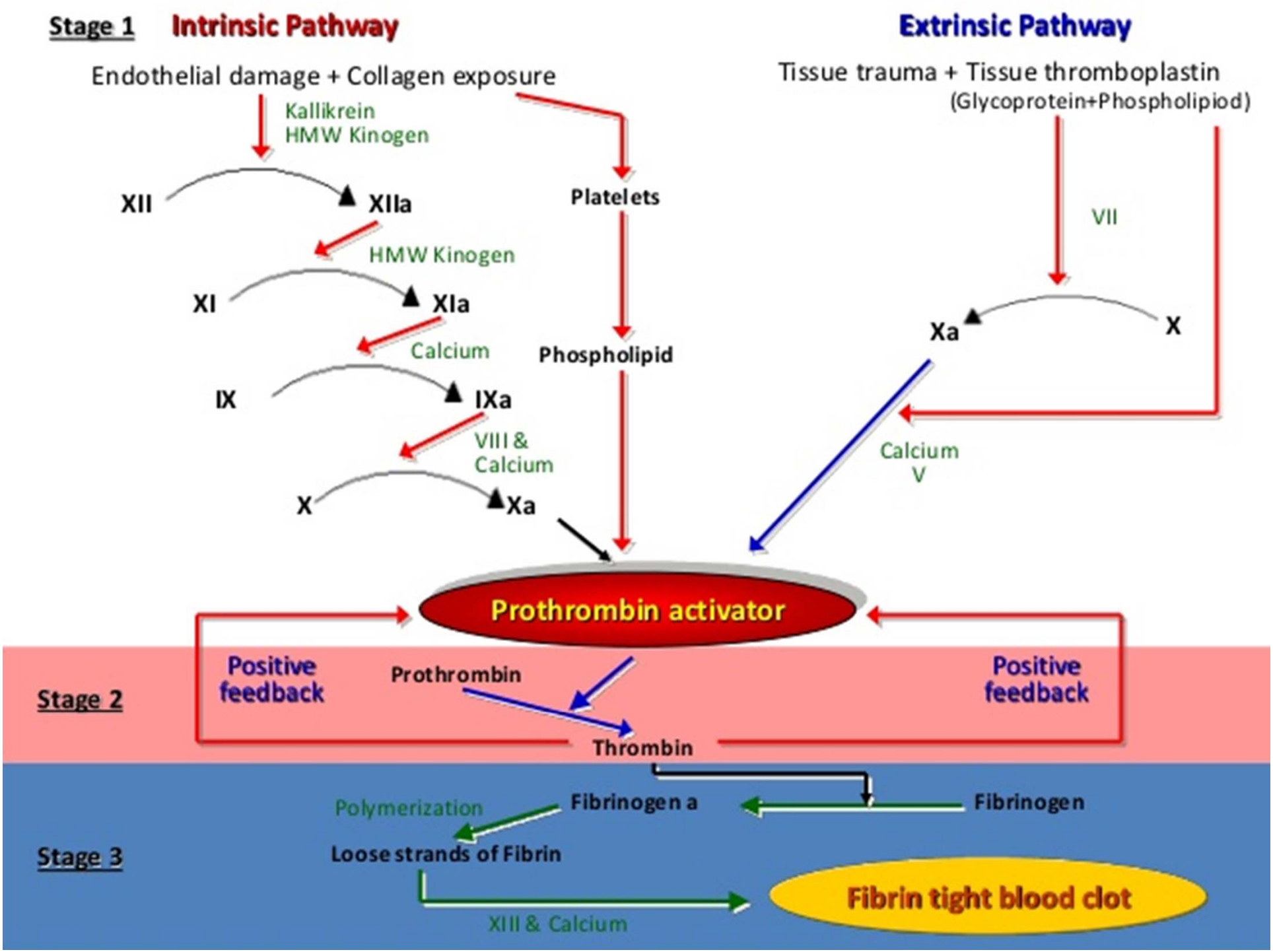
BLOOD COAGULATION

- The coagulation process that generates thrombin consists of two interrelated pathways,

- in response to vascular injury, tissue factor becomes exposed to blood.

- 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..


These factors are inactivated by *heparin*-anti-thrombin complex.
Synthesis of these factors is inhibited by *coumarins*
Intrinsic pathway
XII
XIIa
XI
XIa
IX
IXa
Extrinsic pathway
VIIa
VII
X
Xa
X
Prothrombin (II)
Thrombin (IIa)
Fibrinogen
Fibrin


Stage 1
Intrinsic Pathway
Endothelial damage + Collagen exposure
Kallikrein
HMW Kinogen
XII
XIIa
HMW Kinogen
XI
XIa
Calcium
IX
IXa
VIII &
Calcium
X
Xa
Platelets
Phospholipid
Extrinsic Pathway
Tissue trauma + Tissue thromboplastin
(Glycoprotein+Phospholipiod)
VII
Xa
X
Calcium
V
Prothrombin activator
Stage 2
Positive
feedback
Prothrombin
Thrombin
Positive
feedback
Stage 3
Polymerization
Fibrinogen a
Fibrinogen
Loose strands of Fibrin
XIII & Calcium
Fibrin tight blood clot

Formation of fibrin

- Both the extrinsic and the intrinsic systems involve a cascade of enzyme reactions that ultimately produce Factor Xa,
- which converts prothrombin (Factor II) to thrombin (Factor IIa,
- If thrombin is not formed or if its function is impeded (for example, by antithrombin III), coagulation is inhibited.

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).

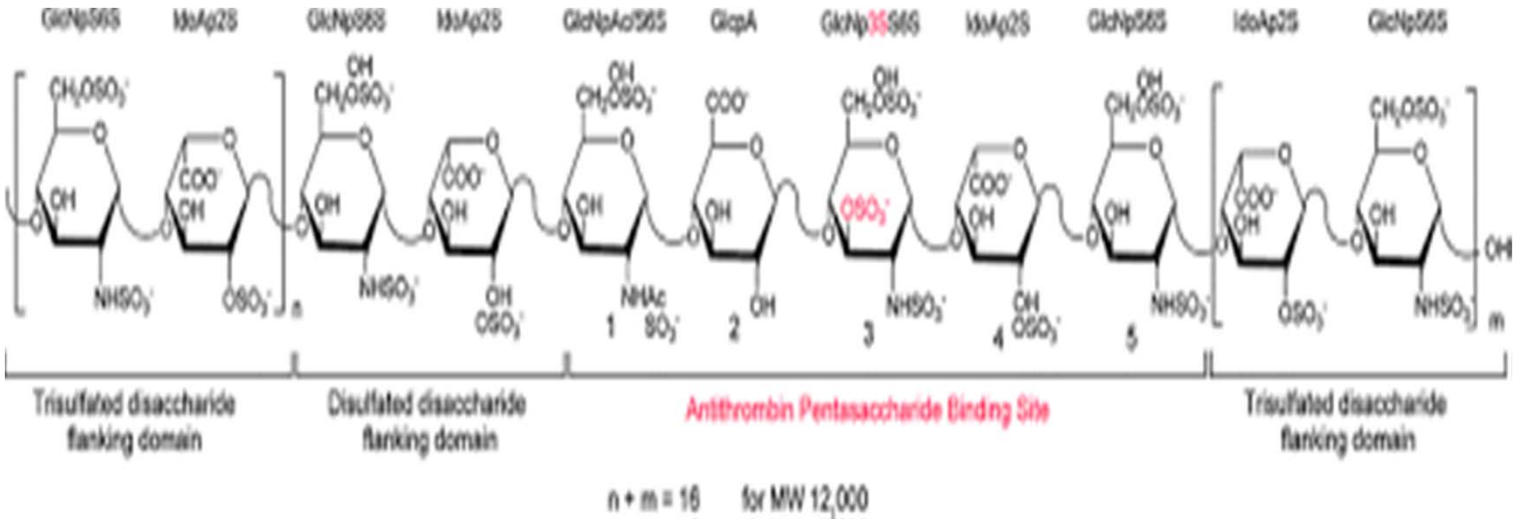
ANTICOAGULANTS

- The anticoagulant drugs inhibit either the action of the coagulation factors (such as *heparin* and *heparin*-related agents) or

- interfere with the synthesis of the coagulation factors (the vitamin K antagonists such as *warfarin.*

Thrombin inhibitors:
heparin and low-molecular-weight heparins

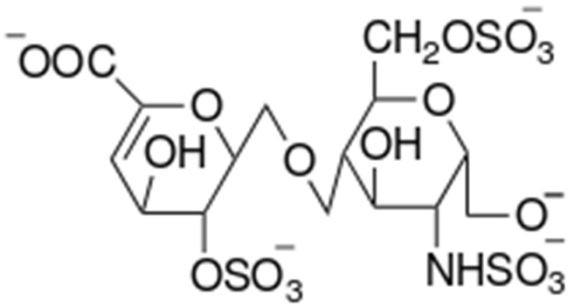
- *Heparin* is an injectable, rapidly acting anticoagulant that is often used acutely to interfere with the formation of thrombi.



Thrombin inhibitors:
heparin and low-molecular-weight heparins

- The *LMWHs* are heterogeneous compounds (one-third the size of unfractionated heparin) produced by the chemical or enzymatic depolymerization of unfractionated *heparin*

- *prevention of venous thrombosis and the treatment of a variety of thrombotic diseases, such as pulmonary embolism and acute myocardial infarction.*



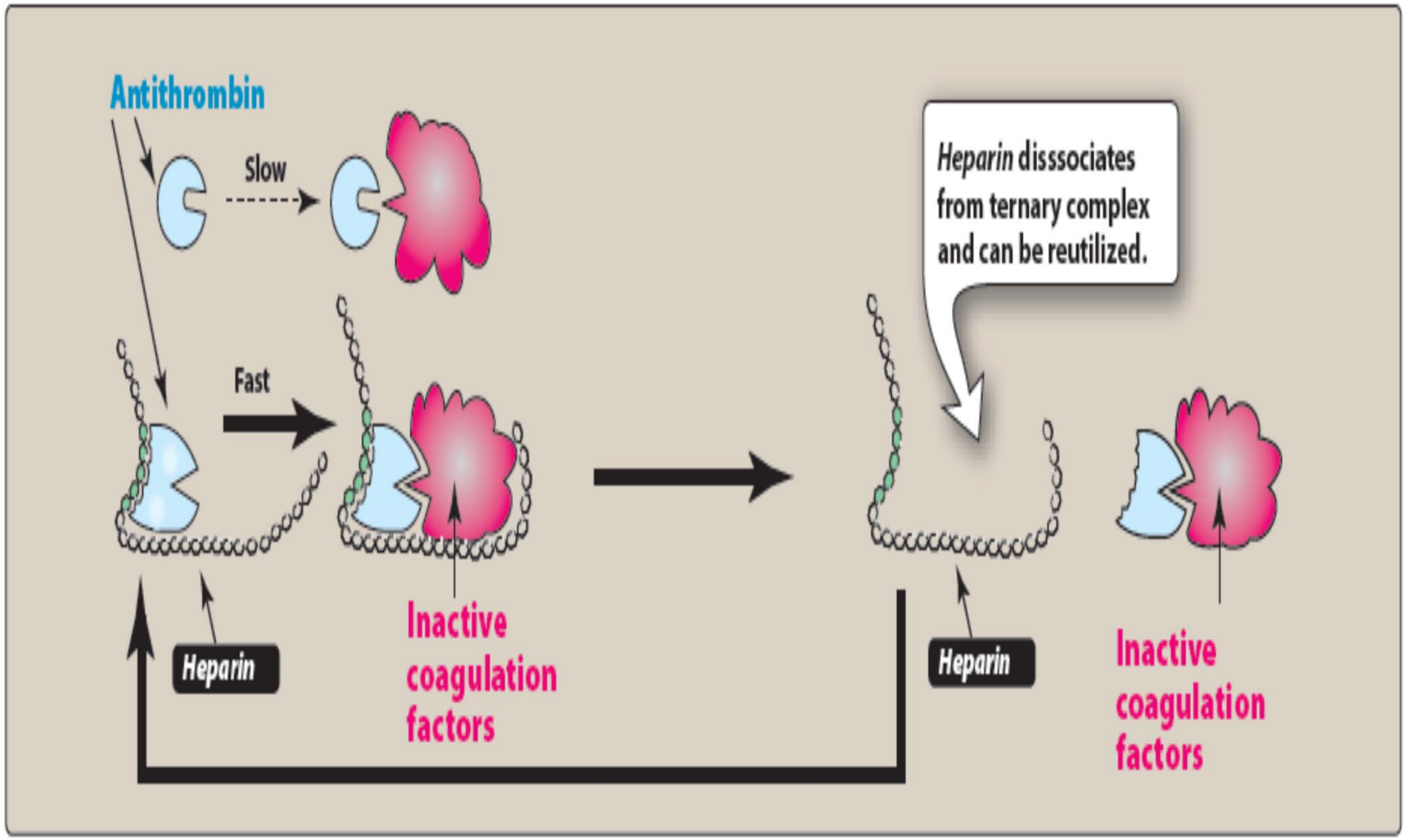
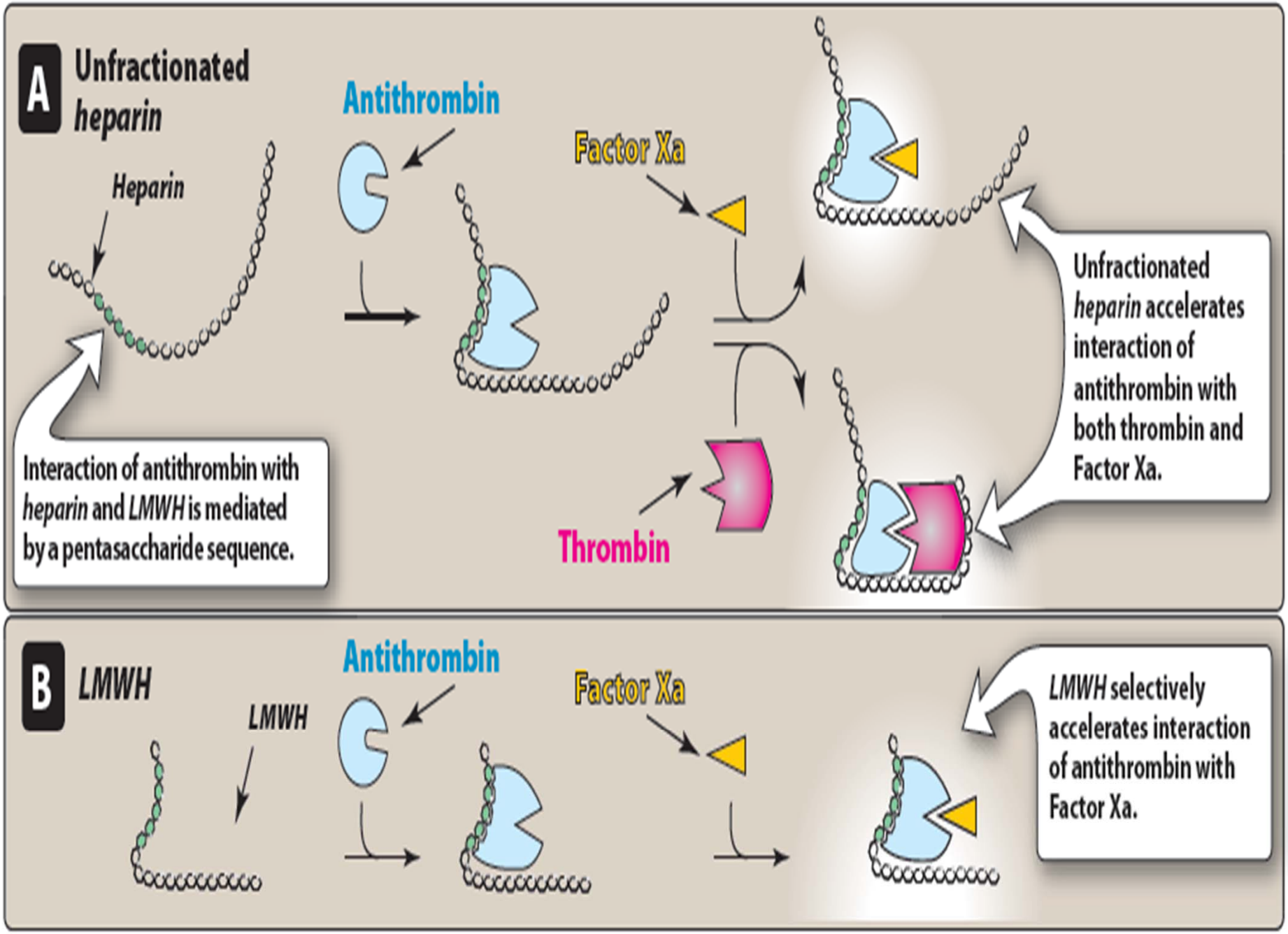


Figure 20.13
Heparin accelerates inactivation of coagulation factors by antithrombin.


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.

- Antithrombin III is an α-globulin. It inhibits serine proteases, including several of the clotting factors, most importantly, thrombin and Factor Xa

- In the absence of *heparin*, antithrombin III interacts very slowly with thrombin and Factor Xa.

- In contrast, *LMWHs* complex with antithrombin III and inactivate Factor Xa

Therapeutic uses:

- limit the expansion of thrombi by preventing fibrin formation.
- treatment of acute deep vein thrombosis and pulmonary embolism.
- is used prophylactically to prevent postoperative venous thrombosis
- One of the most advantage of LMWH (*enoxaparin* and *dalteparin)* these agents can be conveniently injected subcutaneously on a patient weight-adjusted basis, have predictable therapeutic effects, and have a more predictable pharmacokinetic profile.

Pharmacokinetics:

- 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
- *Heparin* must be given parenterally
- The *LMWHs* are administered subcutaneously

Adverse effects:

- Heparin and LMWH are similler anexceptions are thromboembolic problems, which are less common.

1- **Bleeding complications** (ceasing administration of the drug. or by treating with *protamine sulfate*)

2-**Hypersensitivity reactions:**, may be antigenic.chills, fever, urticaria, and anaphylactic shock.

3- **Thrombosis:**

4-*Heparin* may produce abnormal liver function tests, and osteoporosis has been observed in patients on long-term *heparin* therapy.

5-**Thrombocytopenia:**

Argatroban

- *Argatroban* is a synthetic parenteral anticoagulant that is derived from L-arginine
- *It is a direct thrombin inhibitor. Argatroban is used for the prophylaxis or treatment of venous thromboembolism*
- *Argatroban* is metabolized in the liver and has a half life of about 39 to 51 minutes.
- it may be used in patients with renal dysfunction, but it should be used cautiously in patients with hepatic impairment

Bivalirudin *and* desirudin

- *parenteral anticoagulants that are analogs of hirudin, a thrombin inhibitor derived from saliva of the medicinal leech*
- direct thrombin inhibitors that reversibly inhibit the catalytic site of both free and clot-bound thrombin.
- Like the others, bleeding is the major side effect of these agents.

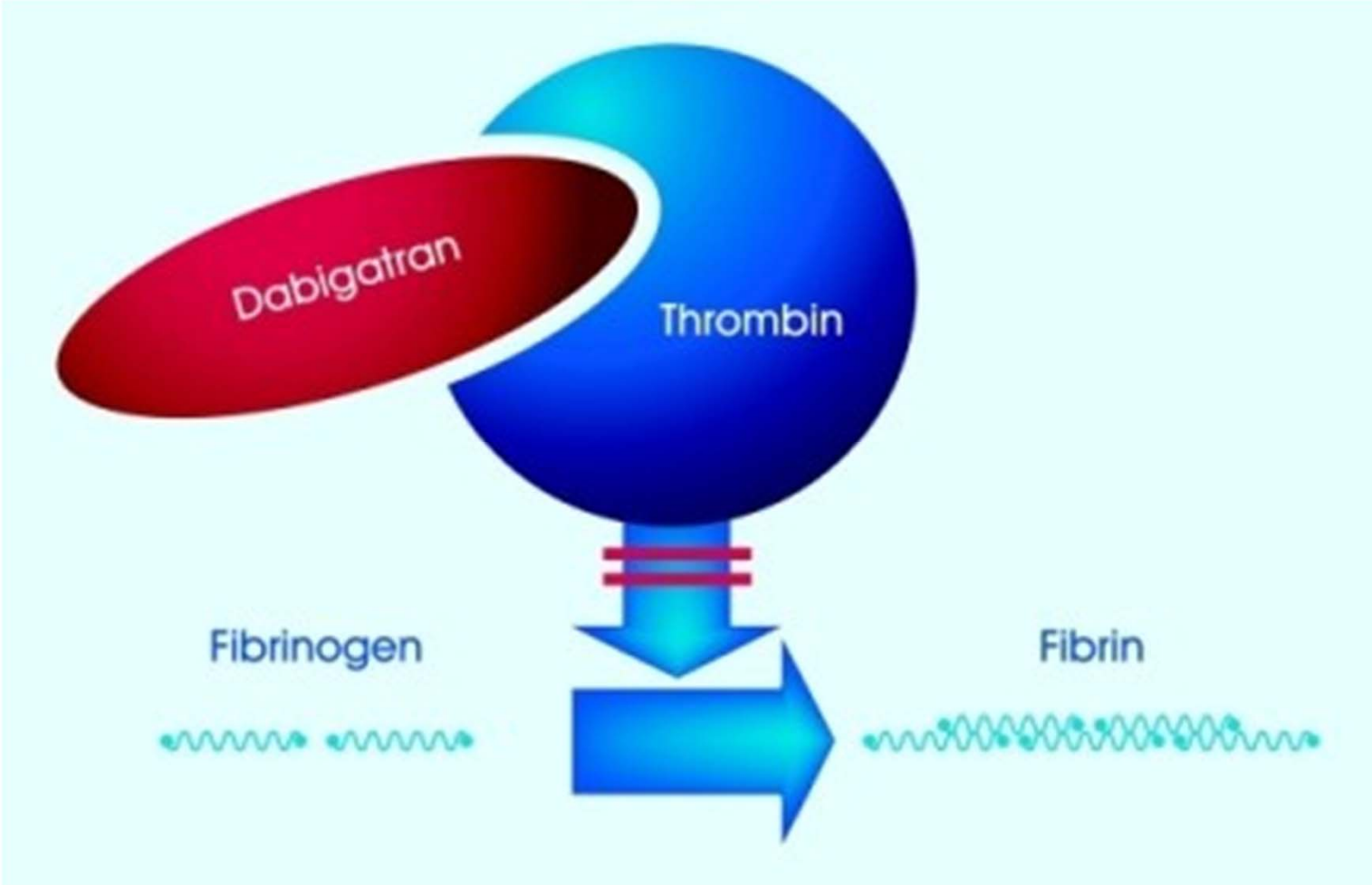
Fondaparinux:

- new class of pentasaccharide anticoagulants that is synthetically derived with no variable biologic activity.
- selectively inhibits only Factor Xa
- requires less monitoring than heparin.
- is eliminated in urine mainly as unchanged drug

Direct Oral Anticoagulants

Thrombin inhibitor: dabigatran etexilate

- Is the prodrug of the active moiety *dabigatran (estrase enz)*which is a direct thrombin inhibitor currently approved for prevention of stroke and systemic embolism in patients with atrial fibrillation.



Adverse effect: dabigatran etexilate

- *Dabigatran* should be used with caution in renal impairment or in patients over the age of 75, as the risk of bleeding is higher in these groups
- GI adverse effects are common with this drug and may include dyspepsia, abdominal pain, esophagitis, and GI bleeding.
- Abrupt discontinuation should be avoided, as patients may be at increased risk for thrombotic events.

Direct oral factor Xa inhibitors

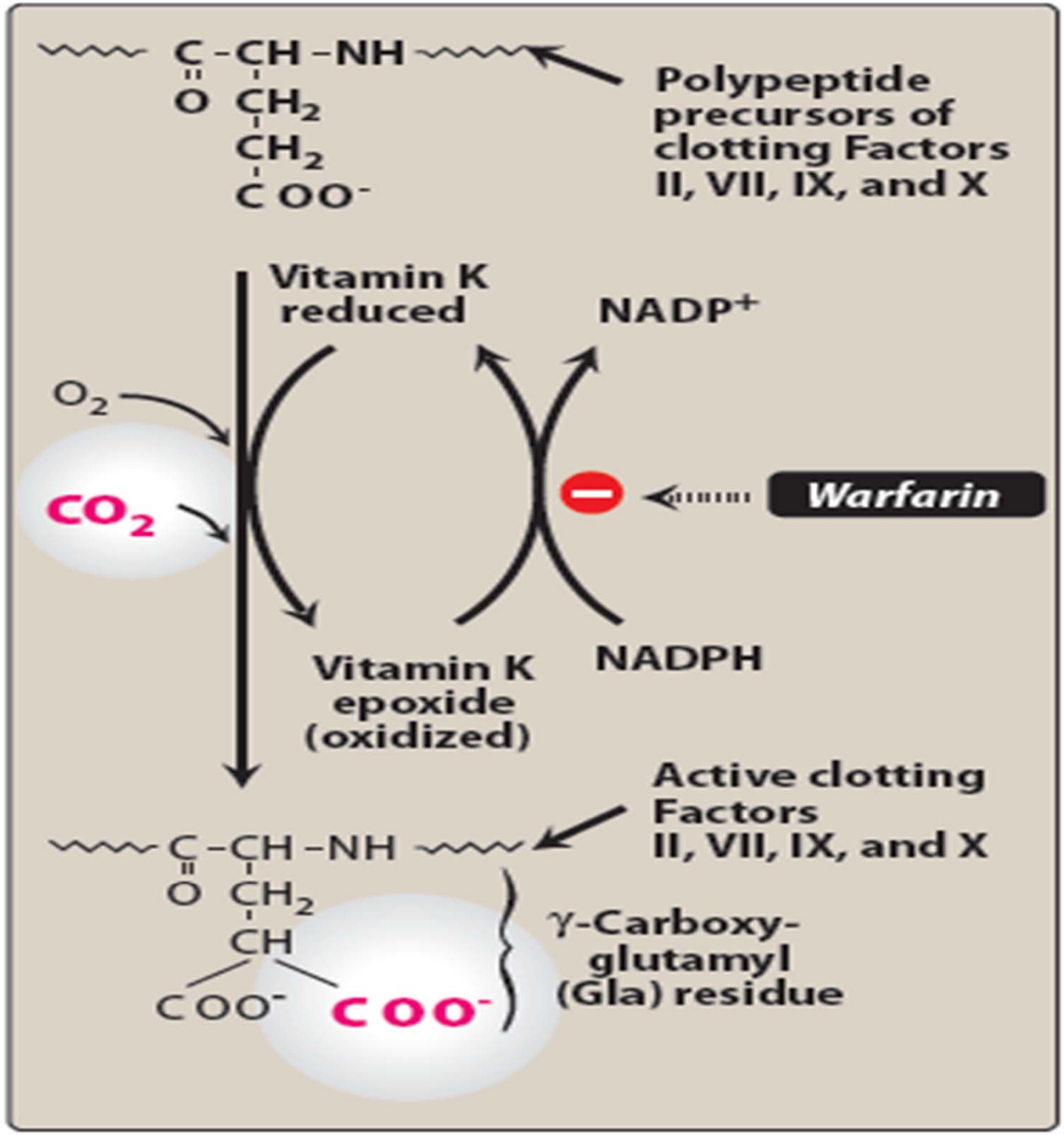
- Apixaban, betrixaban, edoxaban, and rivaroxaban are oral inhibitors of factor Xa. Inhibition of factor Xa reduces the production of thrombin (IIa) from prothrombin

- These agents are approved for prevention of stroke as well as the treatment of DVT and PE.

- Bleeding is the most serious adverse effect. Currently there is no antidote, but recombinant factor Xa products are in development.
- Abrupt discontinuation of the factor Xa inhibitors should be avoided.

Vitamin K antagonists

- The coumarin anticoagulants, which include commonly used *warfarin*, and rarely used *dicumarol*
- ability to antagonize the cofactor functions of vitamin K.
-
- The international normalized ratio (INR) was adopted to monitor *warfarin* concentration. Even careful monitoring to keep an INR of 2 to 3 for most patients does not prevent bleeding complications in many patients


Polypeptide precursors of clotting Factors II, VII, IX, and X
Vitamin K reduced
NADP+
O2
CO2
Warfarin
Vitamin K epoxide (oxidized)
NADPH
Active clotting Factors II, VII, IX, and X
γ-Carboxy-glutamyl (Gla) residue

Therapeutic uses:

- to prevent the progression or recurrence of acute deep vein thrombosis or pulmonary embolism after initial *heparin* treatment

- *Warfarin* is 99 % bound to plasma albumin,

- *Warfarin* readily crosses the placental barrier.

- The mean half-life of *warfarin* is approximately 40 hours, but this value is highly variable among individuals.

Adverse effects:

- Bleeding disorders: Minor bleeding may be treated by withdrawal of the drug and administration of oral *vitamin K1*, but severe bleeding requires that greater doses of the vitamin be given intravenously.
- Skin lesions and necrosis are rare complications of *warfarin* therapy and are observed primarily in women.
- Purple toe syndrome