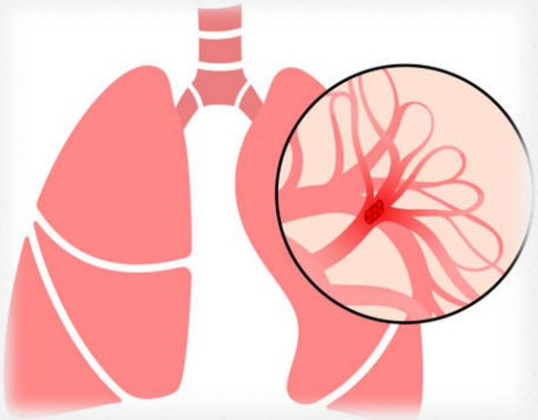
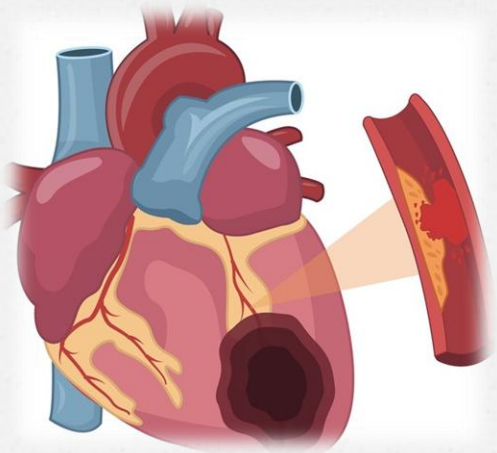
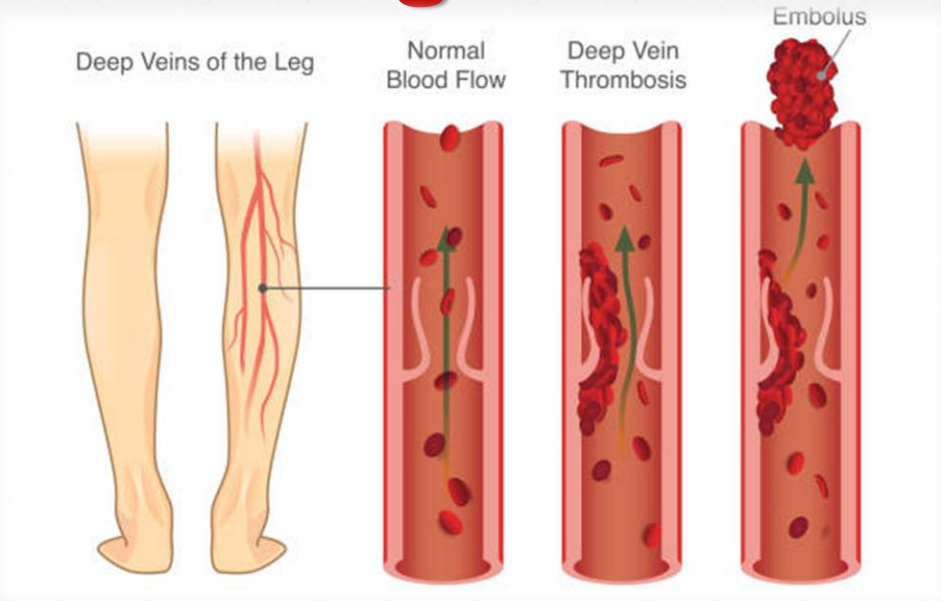
Anticoagulants, thrombolytic & antiplatelet drugs





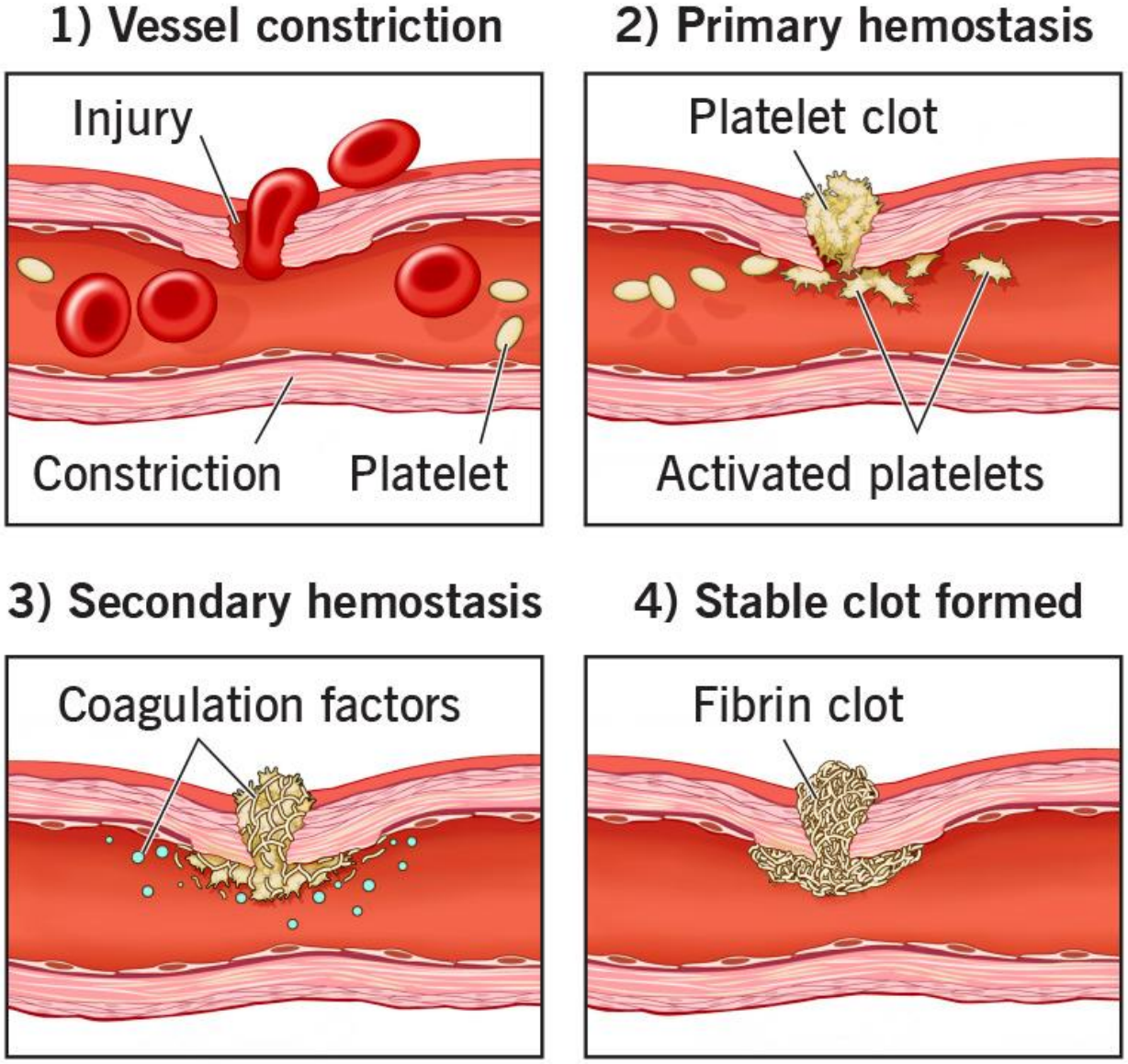


Dr Lobna Aly Abdelzaher
Associate Professor of Pharmacology
Faculty of Medicine

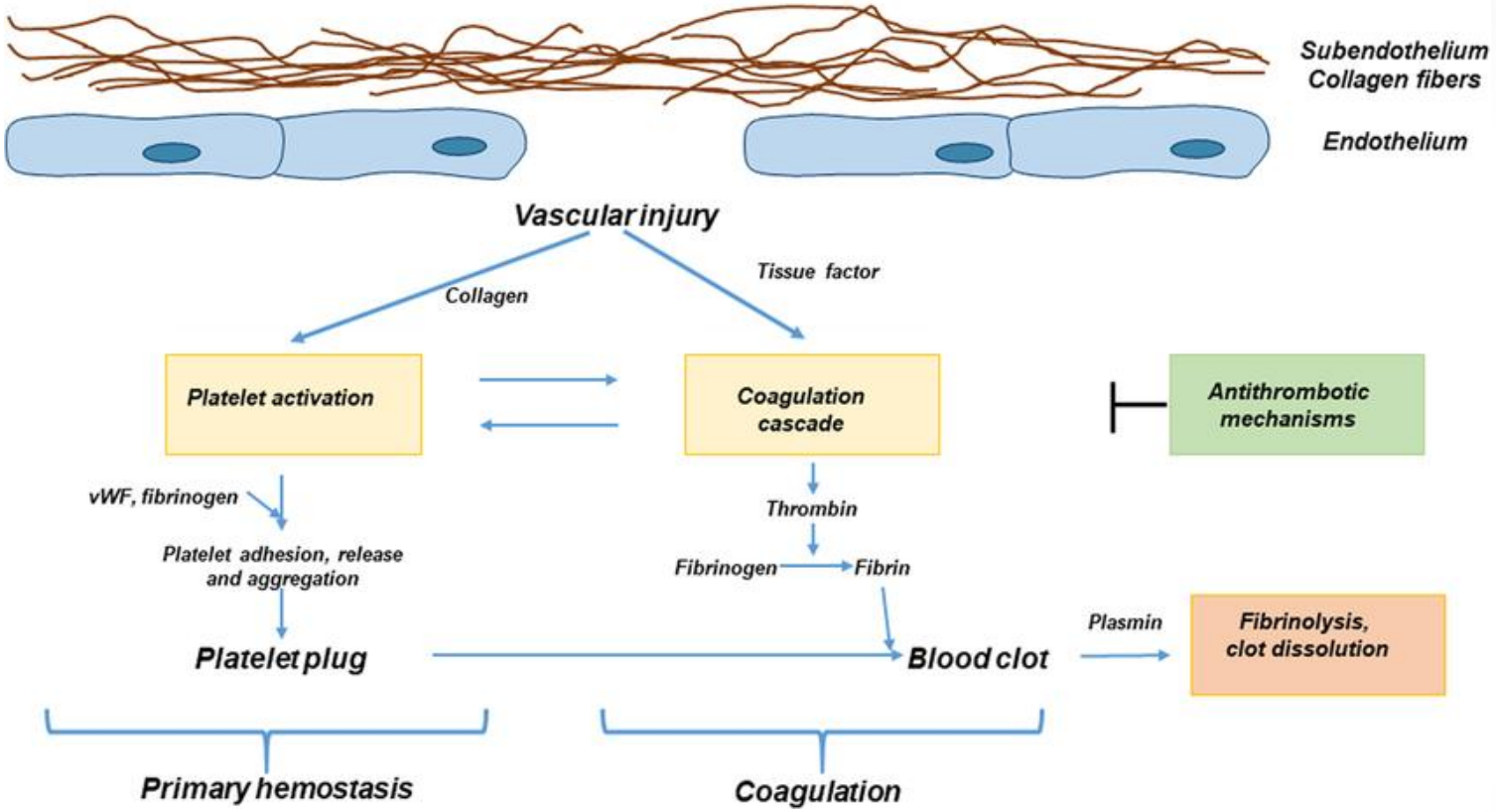
Intended learning outcomes (ILOs)

- To provide the **basic knowledge** about the commonly used anticoagulant, thrombolytic and antiplatelet drugs as regard the **mechanism of action** and **therapeutic uses**.
- To clarify the **basic pharmacokinetics** that has vital role in tailoring the therapeutic regimen.
- To be familiar with the **starting doses** of oral anticoagulant drugs and **how to monitor** the dose.
- To understand **limitations of using these drugs**, as regards **adverse effects**, **contraindications**, and **drug interactions**.
- To predict the **risk/benefit ratio** as a base to **initiate, discontinue or avoid drug administration**.
- To know **how to reverse the effects of anticoagulant drugs**.
- Understand the **importance of anticoagulation in reducing morbidity and mortality in atrial fibrillation and venous thromboembolism**.
- To clarify the role of **aspirin as antithrombotic drugs in the prophylaxis of myocardial infarction, stroke and peripheral vascular thromboses**.
- Appreciate the importance of giving patients adequate information about their proposed therapy.

Hemostasis

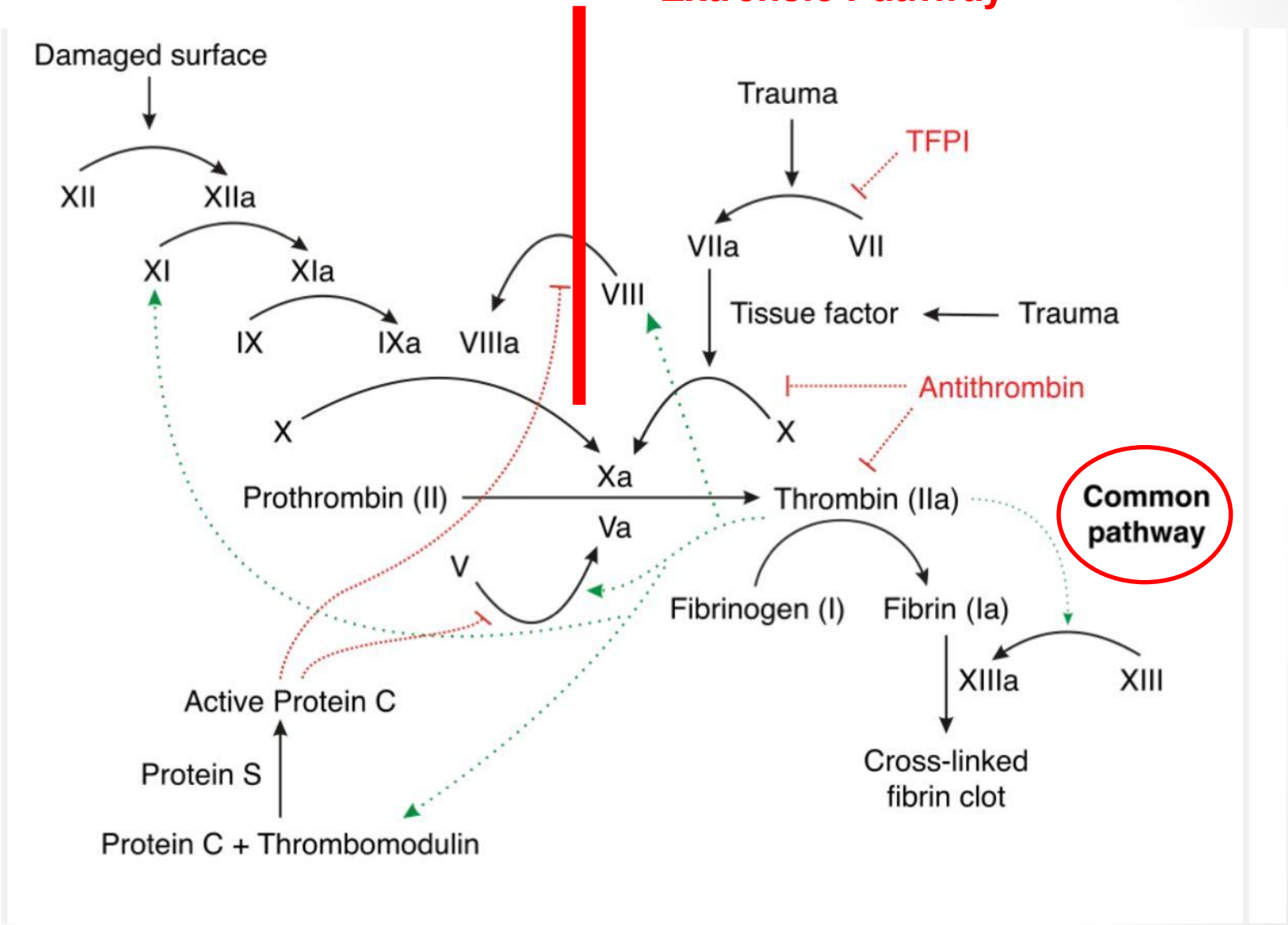

1) Vessel constriction
Injury
Constriction
Platelet
2) Primary hemostasis
Platelet clot
Activated platelets
3) Secondary hemostasis
Coagulation factors
4) Stable clot formed
Fibrin clot

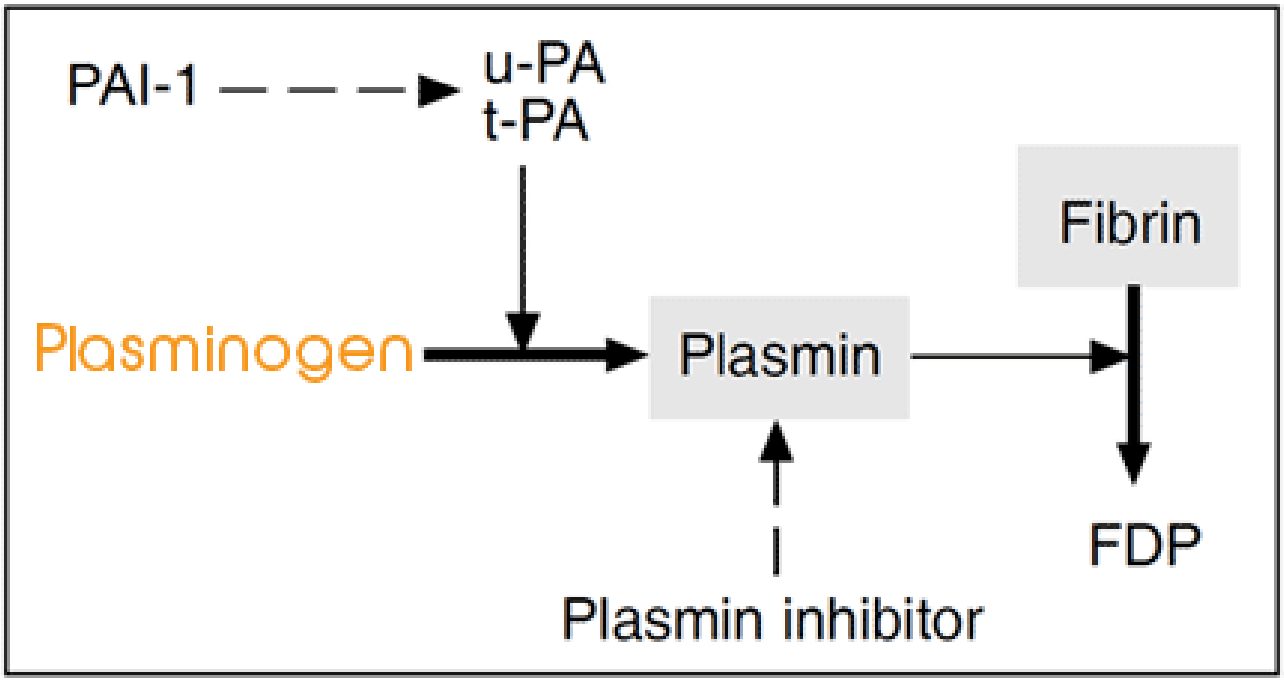
Hemostasis


Subendothelium
Collagen fibers
Endothelium
Vascular injury
Collagen
Tissue factor
Platelet activation
Coagulation cascade
Antithrombotic mechanisms
vWF, fibrinogen
Platelet adhesion, release and aggregation
Thrombin
Fibrinogen
Fibrin
Plasmin
Fibrinolysis, clot dissolution
Platelet plug
Blood clot
Primary hemostasis
Coagulation

Intrinsic Pathway

Extrensic Pathway




PAI-1
u-PA
t-PA
Fibrin
Plasminogen
Plasmin
FDP
Plasmin inhibitor

Pharmacologic Therapy

General approach

- **The acute phase** (~7 days) requires rapidly-acting anticoagulants (UFH, **LMWH**, fondaparinux, rivaroxaban) to prevent thrombus extension and embolization.
- **The early maintenance phase** (7 days to 3 months) consists of continued anticoagulation ,**warfarin**, to reduce risk of long-term sequelae (eg, postthrombotic syndrome) by allowing formed clot to be slowly dissolved by endogenous thrombolysis.
- Anticoagulation **beyond 3 months is aimed at long-term secondary prevention of recurrent VTE**.

I- Heparin

I-Unfractionated Heparin (UFH)

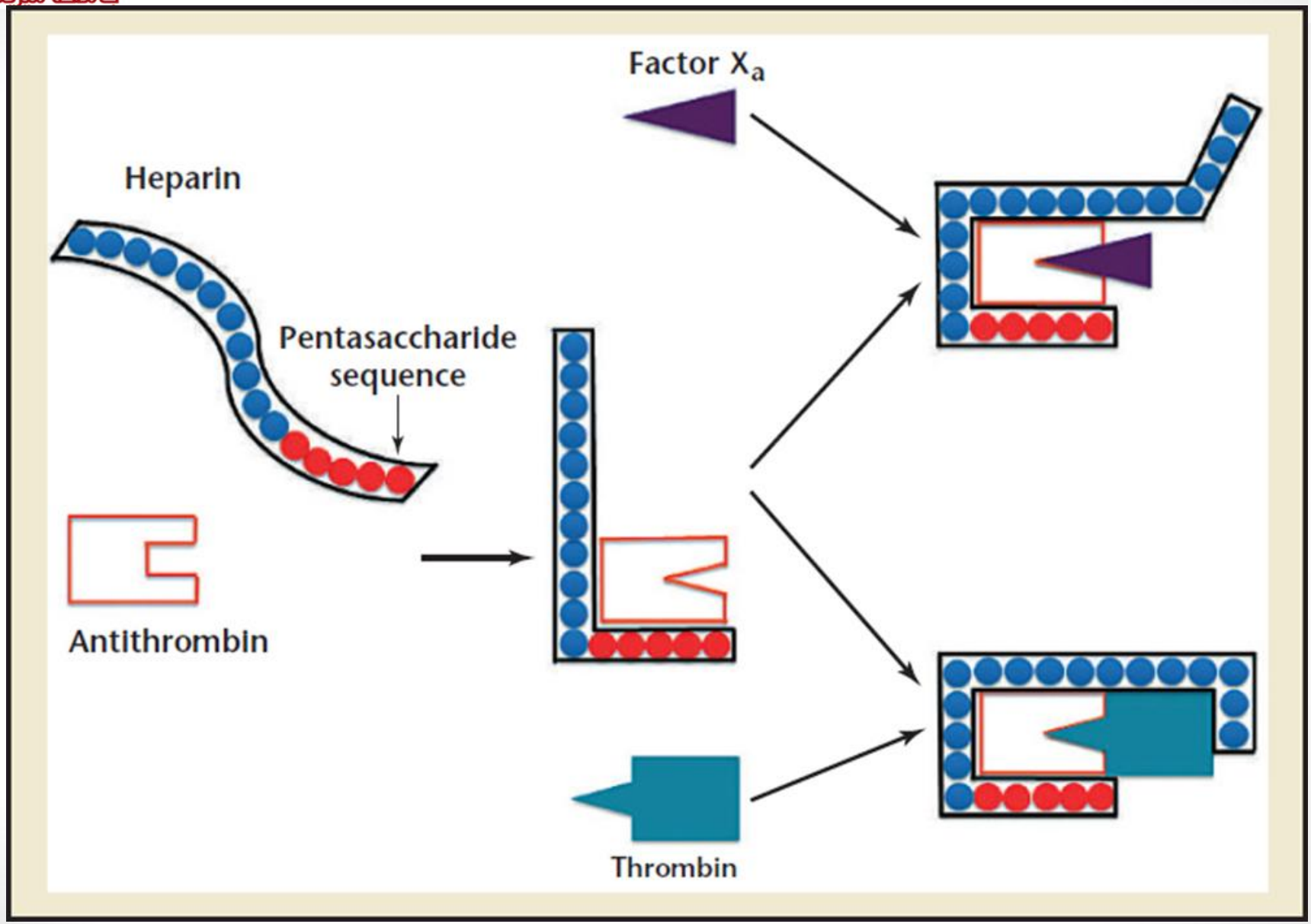
II-Low molecular weight heparin (LMW)

Unfractionated Heparin (UFH)

- **Unfractionated Heparin (UFH)** is a **large sulfated polysaccharide polymer** obtained from animal sources.
  - Each batch contains molecules of varying size, with an **average molecular weight of 15,000–20,000 (Da)**.
  - Heparin is highly acidic and can be **neutralized by basic molecules (eg, protamine)**.
  - Heparin is given **IV** or **SC** to avoid the risk of hematoma associated with intramuscular injection.
  - Unfractionated heparin (UFH) **prevents growth and propagation of a formed thrombus and allows endogenous thrombolytic systems to degrade the clot**.
  - The activated partial thromboplastin time (aPTT) with a therapeutic range of 1.5 to 2.5 times the mean normal control value is used for monitoring.

Mechanism of action

- Unfractionated heparin **binds to endogenous antithrombin III** (ATIII) via a key pentasaccharide sequence.
- The **heparin–ATIII complex combines** with and irreversibly inactivates **thrombin** and several other factors, particularly **factor Xa**.
- In the presence of heparin, ATIII proteolyzes thrombin and factor Xa approximately 1000-fold faster than in its absence.
- **Heparin provides anticoagulation immediately after administration**. The action of heparin is monitored with the activated partial thromboplastin time (aPTT) laboratory test.
- **LMW heparins** and **fondaparinux**, like unfractionated heparin, bind ATIII. These complexes have the **same inhibitory effect on factor Xa however fail to affect thrombin**.


Factor X_a
Heparin
Pentasaccharide sequence
Antithrombin
Thrombin

Low molecular weight Heparin (LMWH)

- ***Enoxaparin (Clexan; S.C.)***, ***nadroparin*** and ***dalteparin***.
- They are ***fragments*** of unfractionated heparin with **low molecular weights of 2000–6000 (Da).**
- Have **greater bioavailability and longer durations of action** than unfractionated heparin; thus, doses can be given less frequently (e.g, once or twice a day).
- Promote inhibition of ***factor Xa*** by antithrombin with little effect on thrombin.
- Have ***longer t½*** , so they are used S.C. once or twice / day.
- They have ***predictable anticoagulant effect***, so no need for routine lab monitoring or dose adjustment.
- They have ***lesser side effects*** as thrombocytopenia, osteoporosis and bleeding.
- Their effect is ***incompletely*** neutralized by protamine sulphate.
- They are ***monitored by antifactor Xa activity*** but not by aPTT.

Therapeutic Uses

- Treatment of **DVT, pulmonary embolism, and acute myocardial infarction**.
- **For revascularization** in combination **with thrombolytics.**
- In combination **with glycoprotein IIb/IIIa inhibitors during angioplasty and placement of coronary stents**.
- It **is the drug of choice when an anticoagulant must be used in pregnancy**.

Adverse effects

Bleeding

- **Discontinue** the drug and **give IV protamine sulfate by slow IV infusion over 10 minutes (1 mg/100 units of UFH infused; maximum 50 mg**).
- **Protamine only partially reverses the effects of LMW heparins and does not affect the action of fondaparinux**.

Thrombocytopenia

- UFH causes **moderate transient thrombocytopenia in many patients** and severe thrombocytopenia and thrombosis in a small percentage of patients.
- LMW heparins and fondaparinux are less likely to cause this immune-mediated thrombocytopenia.

Alopecia, hyperkalemia & osteoporosis (UFH)

Fondaparinux

- Synthetic pentasaccharide binding strongly to antithrombin with high specific activity against factor Xa i.e., **inhibits factor Xa like LMWH**.
- **Has long half-life (15 h)** allowing once daily dosage.
- No cross reactivity with heparin-antibodies, so it is recommended in HIT.

II-Warfarin

- **Warfarin sodium (Dendivan or Marivan).**
- It is the widely used **cumarin** (dicumarol is a second cumarin derivative).

Mechanism of action:

- It acts only in vivo by by **inhibiting the enzyme vitamin K epoxide reductase** which is responsible for synthesis of vitamin K-dependent coagulation factors (II, VII, IX and X).
- **Delayed onset** because the effect depends on the t½ of the clotting factors (3 days).

Laboratory control:

- By measuring prothrombin time **PT** and calculation of **INR (**1-1.5).
- It is given 10 mg at bed time for 3 days, then 5 mg / day as maintenance dose.

Pharmacokinetics:

1- Complete absorption after oral or parenteral use (oral (F) is near 100%), but parenteral use does not alter the speed of anticoagulant effect.
2- High binding to plasma proteins (99%), so it has low Vd.
3- Delayed onset of action (after 1-3 days) till metabolism of the already present clotting factors.
4- t½ is 40 h., duration of action is 2-5 days (due to enterohepatic circulation + long t ½ + long time needed for resynthesis of clotting factors).
5- Metabolized in liver and kidney to inactive metabolites and excreted in urine and stool.

Side effects:

1- ***Bleeding:*** is the most serious one.
2- ***Osteoporosis*** due to deficiency of Vit K
3- ***Teratogenic effect:*** as bone defect, bleeding of fetus and abortion.
4- ***Hypersensitivity reactions*** (fever and dermatitis) and alopecia.
5- ***Skin necrosis and purple toe syndrome*** (painful bluish discoloration of sides and planter surfaces of toes), which is decreased by elevation of legs, it appears after 3-8 weeks of treatment, may be due to release of cholesterol emboli from atheroma.
6- ***GIT manifestations***: anorexia, nausea, vomiting, diarrhea and abdominal cramps

Reversal of anticoagulant activity (Antidote):

- In cases of mild bleeding: stop the drug + vitamin **K1 (Phytonadion**) orally is given.
- In cases of severe bleeding: **vitamin K1 by slow I.V.** (to avoid hypotension) and **fresh frozen plasma** (rich in clotting factors) are given.

Indications of warfarin:

1- **Prevention of progression or recurrence of deep venous thrombosis** (for 3 months) or pulmonary embolism (for 6 months) after initial course of heparin.

2- **Prevention of systemic embolization** in patients with:

- Acute myocardial infarction.
- Dilated cardiomyopathy.
- Prosthetic heart valves.
- Chronic atrial fibrillation.

3- **Prevention of venous thromboembolism in high risk patients** as after orthopedic or gynecological surgery.

Property	Heparins	Warfarin
Structure	Large acidic polysaccharide polymers	Small lipid-soluble molecule
Route of administration	Parenteral	Oral
Site of action	Blood	Liver
Onset of action	Rapid (minutes)	Slow (days); limited by half-lives of preexisting normal factors
Mechanism of action	Activate antithrombin III, which inactivates coagulation factors including thrombin and factor Xa	Impairs post-translational modification of factors II, VII, IX and X
Monitoring	aPTT for unfractionated heparin but not LMW heparins	Prothrombin time
Antidote	Protamine for unfractionated heparin; protamine reversal of LMW heparins is incomplete	Vitamin K_1, plasma, prothrombin complex concentrates
Use	Mostly acute, over days	Chronic, over weeks to months
Use in pregnancy	Yes	No

III-Direct Thrombin Inhibitors

1- **Oral direct thrombin inhibitor: e.g., Dabigatran etexilate mesylate (Pradaxa):**

- Predictable anticoagulant effect (no monitoring requirement).
- Rapid therapeutic effect compared to warfarin.
- No need for platelet monitoring (no thrombocytopenia).
- Fewer drug interactions in comparison with warfarin.
- Dabigatran antidote is available (***idarucizumab***) developed at 2015 under the trade name "praxbind".
- Used in **heparin-induced thrombocytopenia**.

2- Parentral drugs: e.g., Hirudin, Argatroban, Lepirudin (Refludan), Bivalirudin (Angiomax):

- Hirudin is a specific, irreversible thrombin inhibitor from leech saliva that is now available in recombinant form as lepirudin.
- Its action is independent of antithrombin, which means it **can reach and inactivate fibrin bound thrombin in thrombi.**

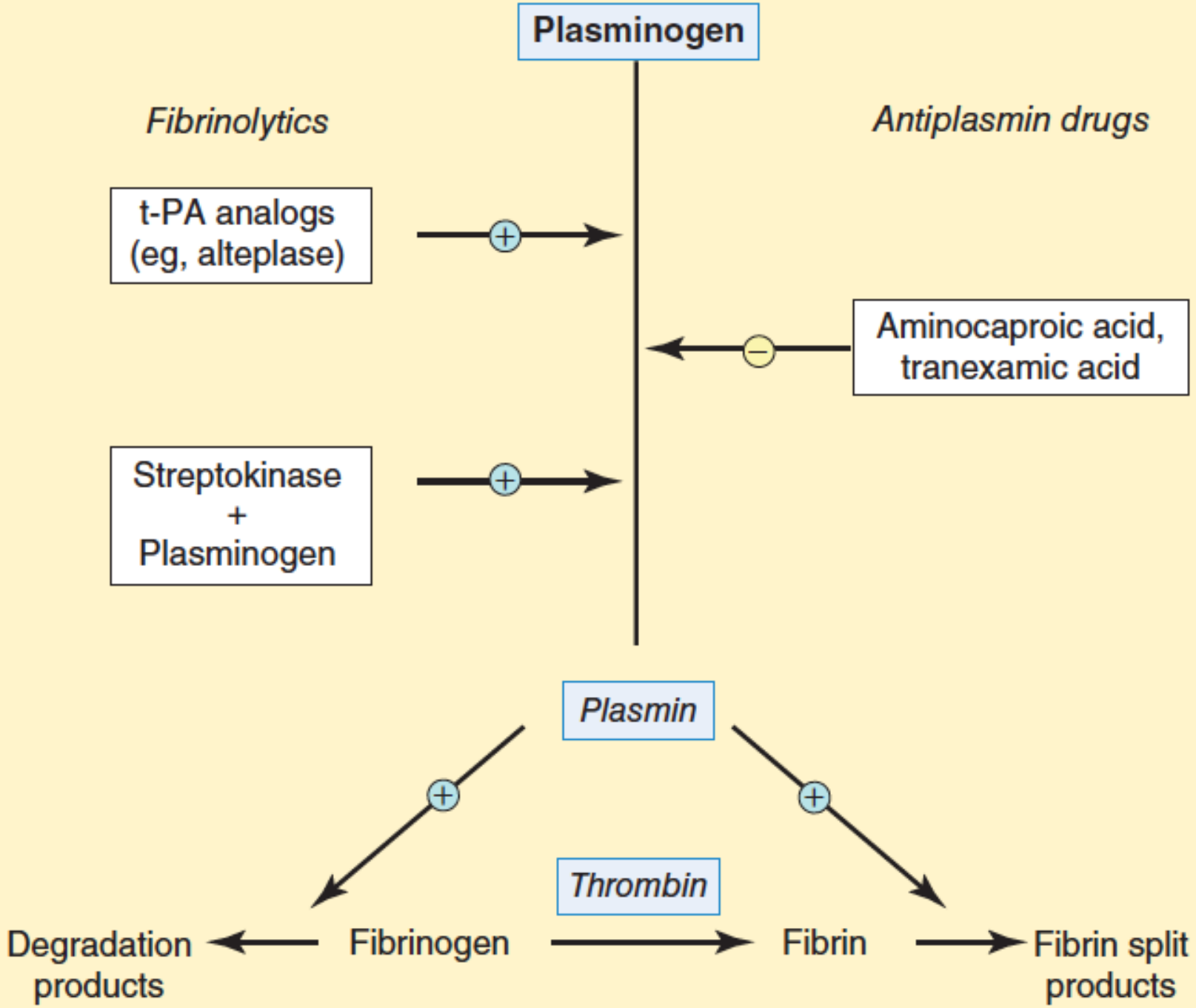
IV-Direct Factor X Inhibitors

Several factor Xa inhibitors, such as **rivaroxaban, apixaban and edoxaban**, have been approved for certain conditions, and are also in clinical development for other indications

V-Thrombolytics

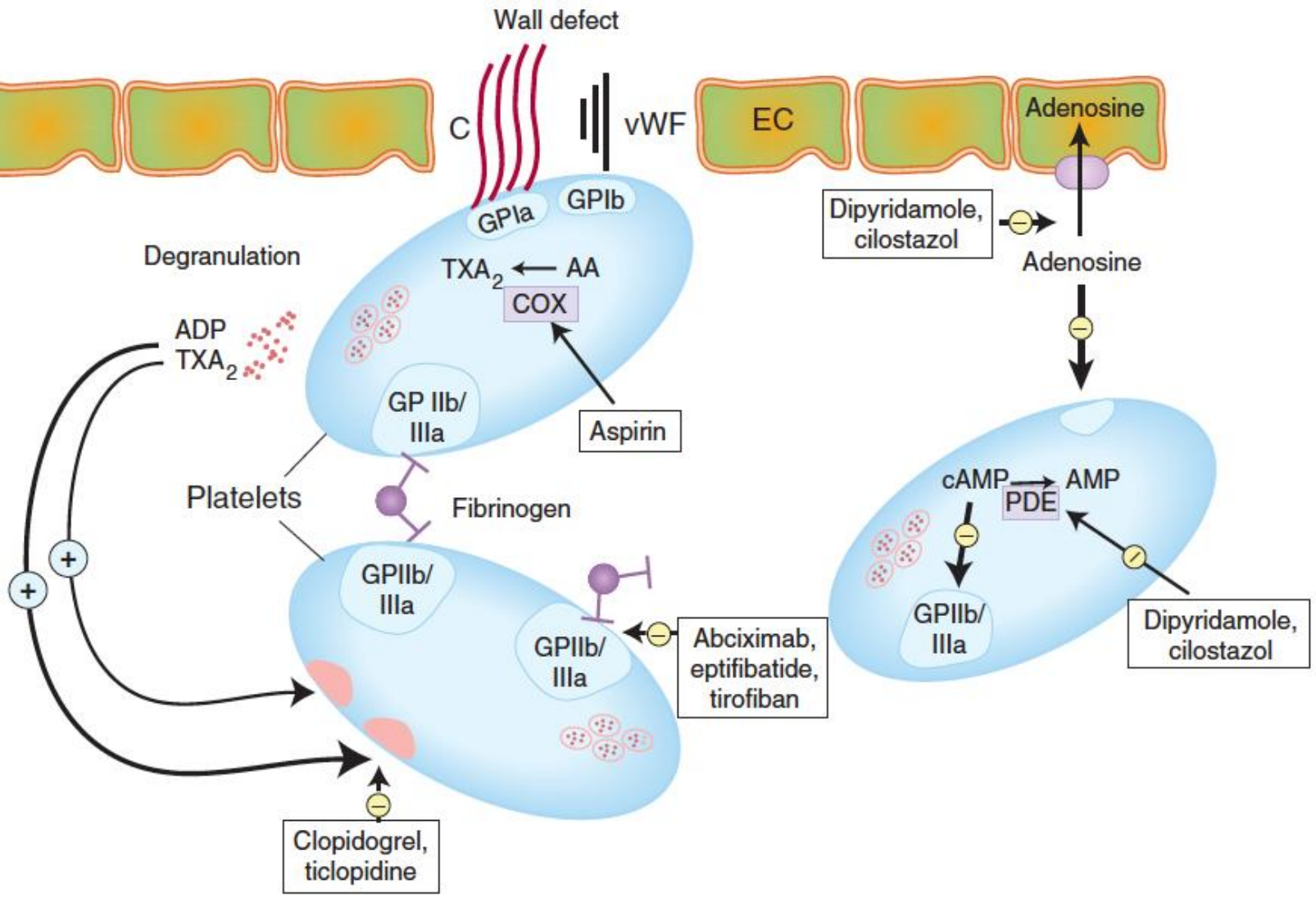
- Thrombolytic agents are **proteolytic enzymes that enhance conversion of plasminogen to plasmin, which subsequently degrades the fibrin matrix** an alternative to percutaneous coronary angioplasty in the emergency treatment of coronary artery thrombosis. Dosage regimens of thrombolytic agents for treatment of DVT and/or PE:

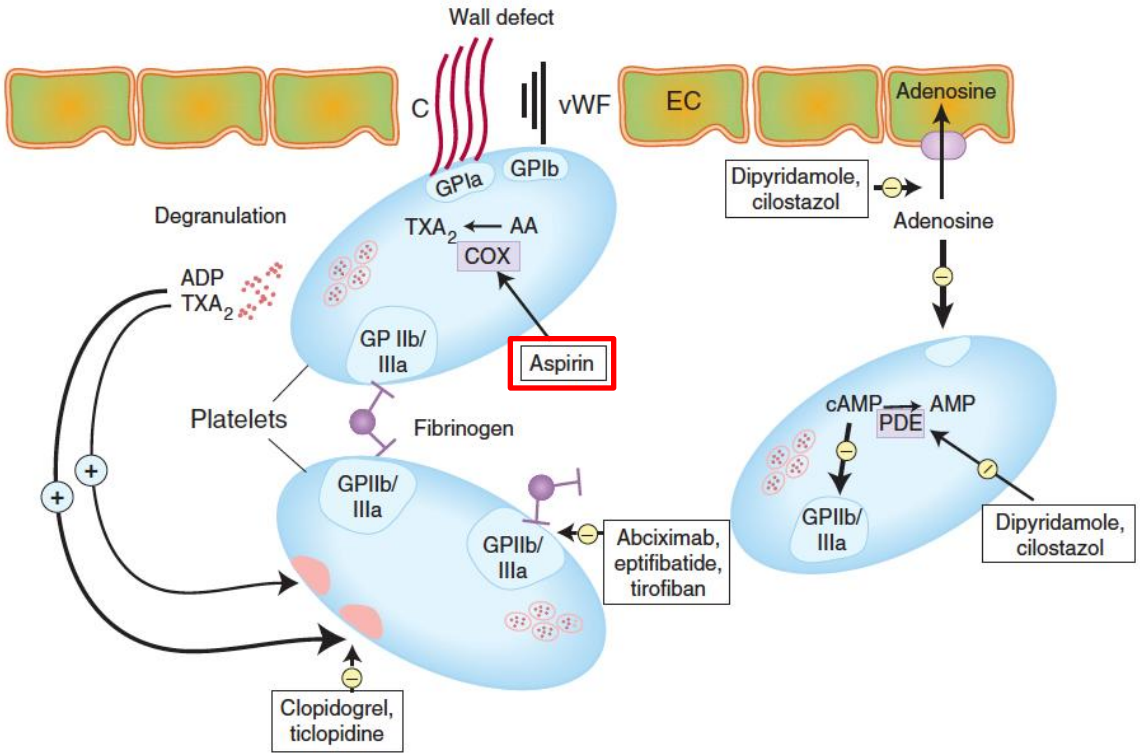
- **Alteplase** (Activase): For PE, 100 mg by IV infusion over 2 hours
- **Streptokinase** (Streptase): 250,000 units IV over 30 minutes, followed by a continuous IV infusion of 100,000 units/h for 24 hours (PE) or 24 to 72 hours (DVT)
- **Urokinase** (Abbokinase): For PE, 4400 IU/kg IV over 10 minutes, followed by 4400 IU/kg/h for 12 to 24 hours


Plasminogen
Fibrinolytics
Antiplasmin drugs
t-PA analogs
(eg, alteplase)
Aminocaproic acid,
tranexamic acid
Streptokinase
+
Plasminogen
Plasmin
Thrombin
Degradation
products
Fibrinogen
Fibrin
Fibrin split
products

VI-Antiplatelet Drugs

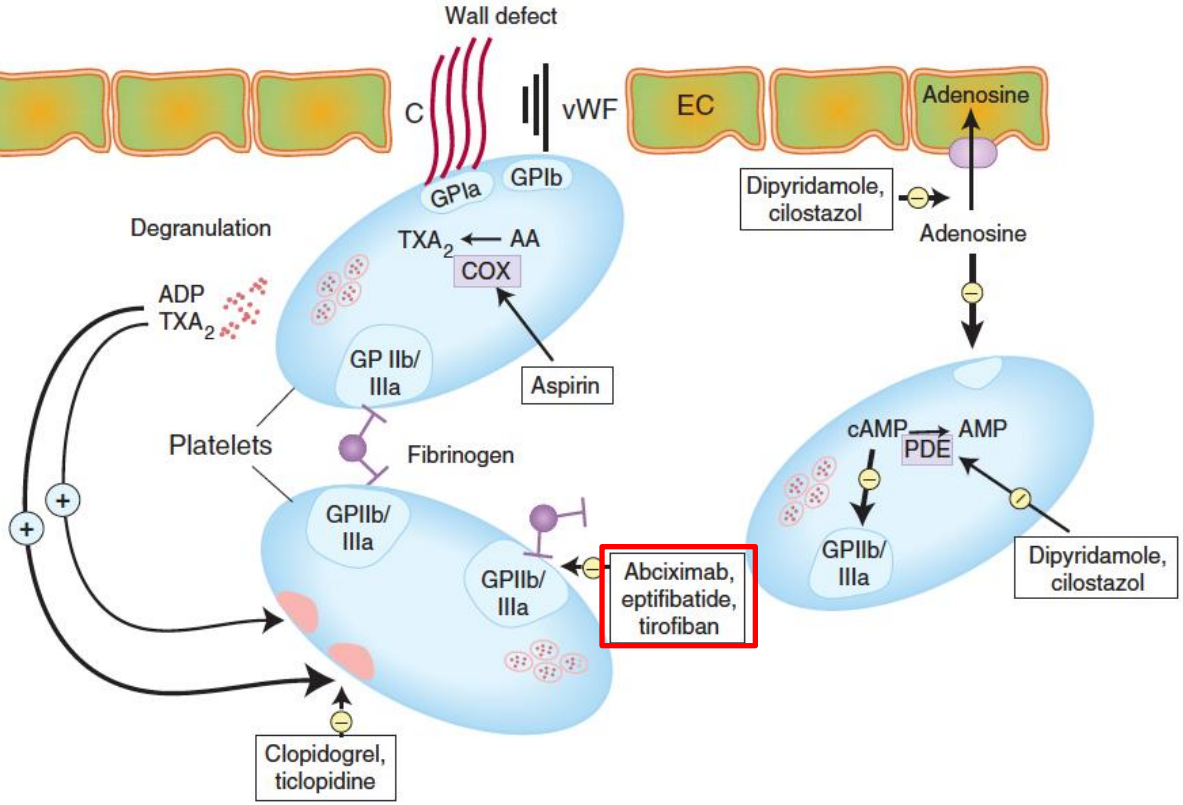
- Nonsteroidal anti-inflammatory drugs (NSAIDs), glycoprotein IIb/IIIa receptor inhibitors (abciximab , tirofiban , and eptifibatide), antagonists of ADP receptors (clopidogrel, prasugrel , and ticlopidine), and inhibitors of phosphodiesterase 3 (dipyridamole and cilostazol).


Wall defect
C
vWF
EC
Adenosine
GPIa
GPIb
Dipyridamole, cilostazol
Adenosine
Degranulation
TXA2 ← AA
COX
ADP
TXA2
GP IIb/ IIIa
Aspirin
Platelets
Fibrinogen
cAMP → AMP
PDE
GPIIb/ IIIa
GPIIb/ IIIa
Abciximab, eptifibatide, tirofiban
GPIIb/ IIIa
Dipyridamole, cilostazol
Clopidogrel, ticlopidine



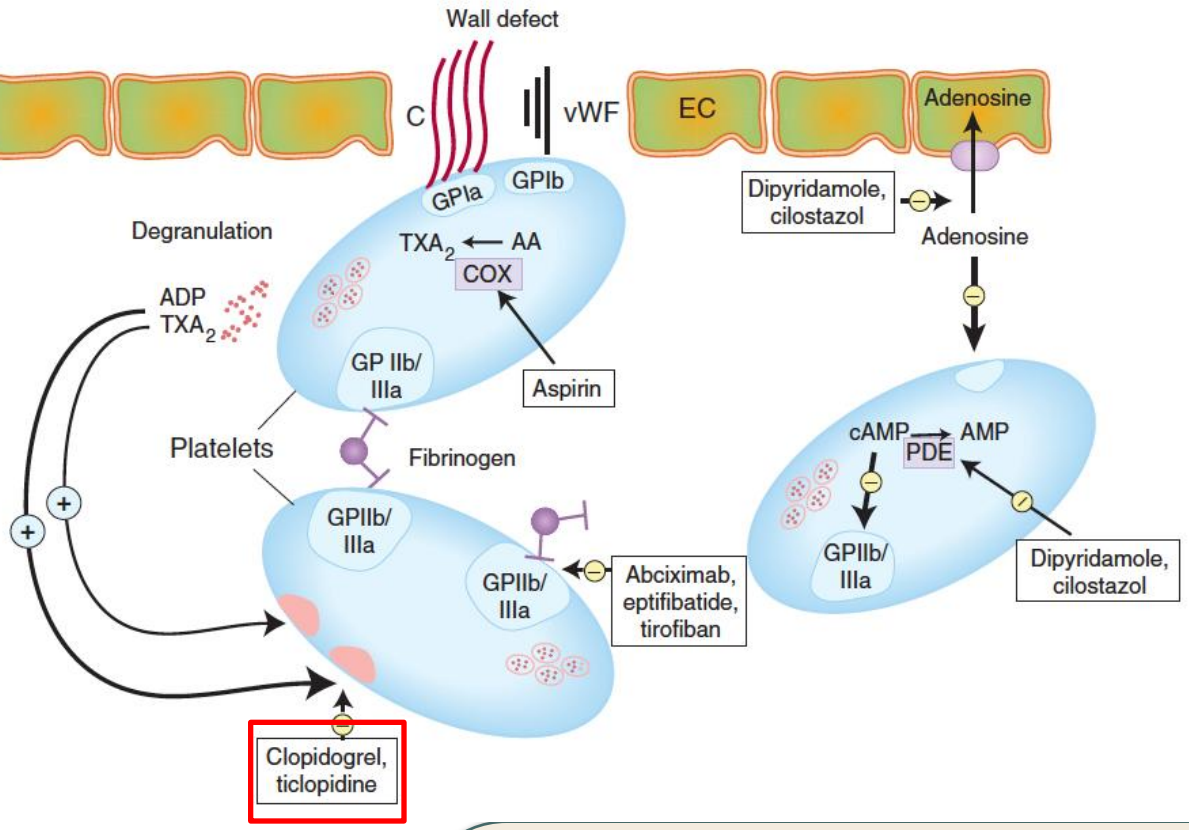
Aspirin

- Aspirin and other NSAIDs **inhibit thromboxane synthesis by blocking the enzyme cyclooxygenase (COX).**



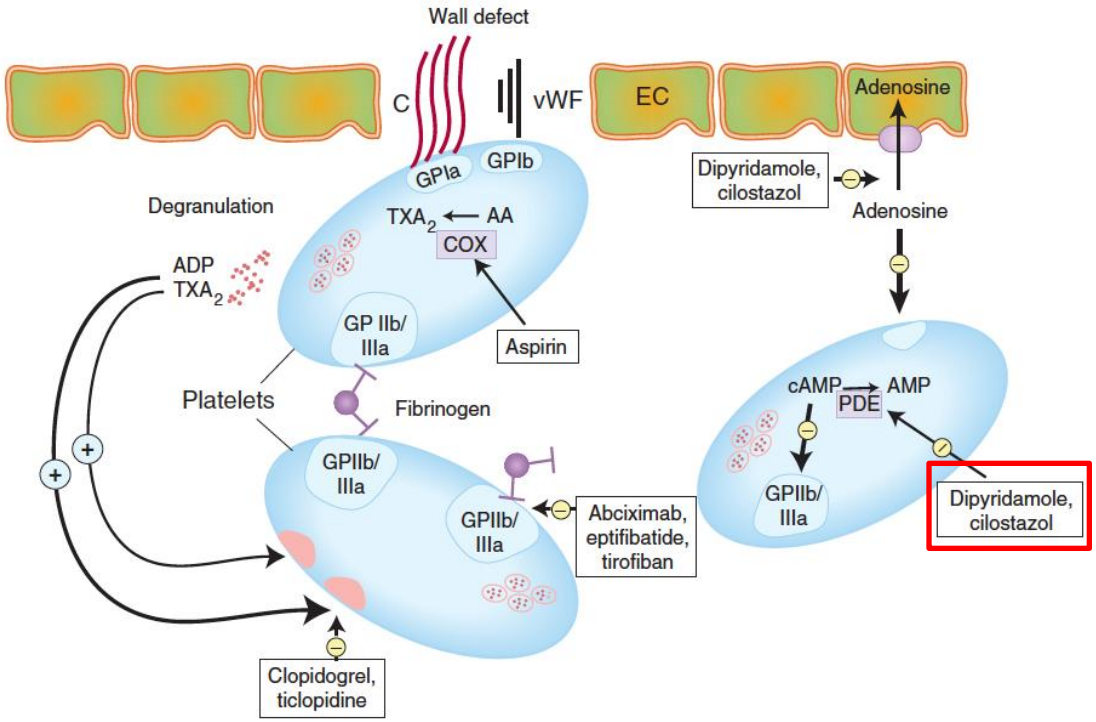
Abciximab

- Monoclonal antibody that reversibly **inhibits the binding of fibrin and other ligands to the platelet glycoprotein IIb/IIIa receptor** , a cell surface protein involved in platelet cross-linking.
- Eptifibatide and tirofiban also reversibly block the glycoprotein IIb/IIIa receptor.



Clopidogrel

- Clopidogrel, prasugrel, and the older drug ticlopidine are converted in the liver to active metabolites that **irreversibly inhibit the platelet ADP receptor and thereby prevent ADP-mediated platelet aggregation**.
- Ticagrelor, newer drug, reversibly inhibits the platelet ADP receptor.



Dipyridamole

- Dipyridamole and the newer cilostazol appear to have a dual mechanism of action.
  - They **prolong the platelet-inhibiting action of intracellular cAMP by inhibiting phosphodiesterase enzymes**.
  - They **also inhibit the uptake of adenosine by endothelial cells and erythrocytes and thereby increase the plasma concentration of adenosine, thus increase platelet cAMP and inhibit aggregation.**

Dr Lobna Aly Abdelzaher

Clinical Uses

- **Aspirin** is used to **prevent further myocardial infarcts**, prevent transient ischemic attacks (TIAs), ischemic stroke, and other thrombotic events.
- The **glycoprotein IIb/IIIa inhibitors** **prevent restenosis after coronary angioplasty** and are used in acute coronary syndromes (eg, unstable angina).
- **Clopidogrel** and **ticlopidine** are effective in **preventing TIAs and ischemic strokes,** especially in patients who cannot tolerate aspirin.
- **Dipyridamole** is approved as:
  - An adjunct to warfarin in the **prevention of thrombosis in those with cardiac valve replacement.**
  - **in combination with aspirin for secondary prevention of ischemic stroke**.
- **Cilostazol** is used to treat **intermittent claudication, a manifestation of peripheral arterial disease**.

DRUGS USED IN BLEEDING DISORDERS

Dr Lobna Aly Abdelzaher

2025-2026

DRUGS USED IN BLEEDING DISORDERS

1- Vitamin K1 (phytonadione) & Vitamin K2 (Menaquinone)

- Used in warfarin toxicity and also in hemorrhagic disorders of neonates.

2- Plasma fractions

- Recombinant factor VIIa.
- Desmopressin acetate: increase factor VII activity
- Cryoprecipitate: are used in bleeding particularly with hemophilia.

3- AMINOCAPROIC ACID

 It is a fibrinolysis antagonist.

 It acts by blocking of the binding of plasmin to fibrin. It used by I.V. injection.

Therapeutic uses:

- Control bleeding caused by thrombolytic therapy.
- Adjunctive therapy in hemophilia.
- Prophylaxis for rebleeding from intracranial aneurysms.
- Decrease postsurgical GIT bleeding and postprostatectomy bleeding.
- Decrease bladder bleeding secondary to radiation or drug-induced cystitis.

Side effects:

- It may cause intravascular thrombosis, hypotension, myopathy, abdominal discomfort, diarrhea and nasal stuffiness.

Contraindications:

- Disseminated intravascular coagulation and upper genitourinary bleeding.

4- TRANEXAMIC ACID:

- It is analog of aminocaproic acid and used as fibrinolytic antagonist.
- It acts by blocking of the binding of plasmin to fibrin.
- It used by I.V. injection.

Thank You