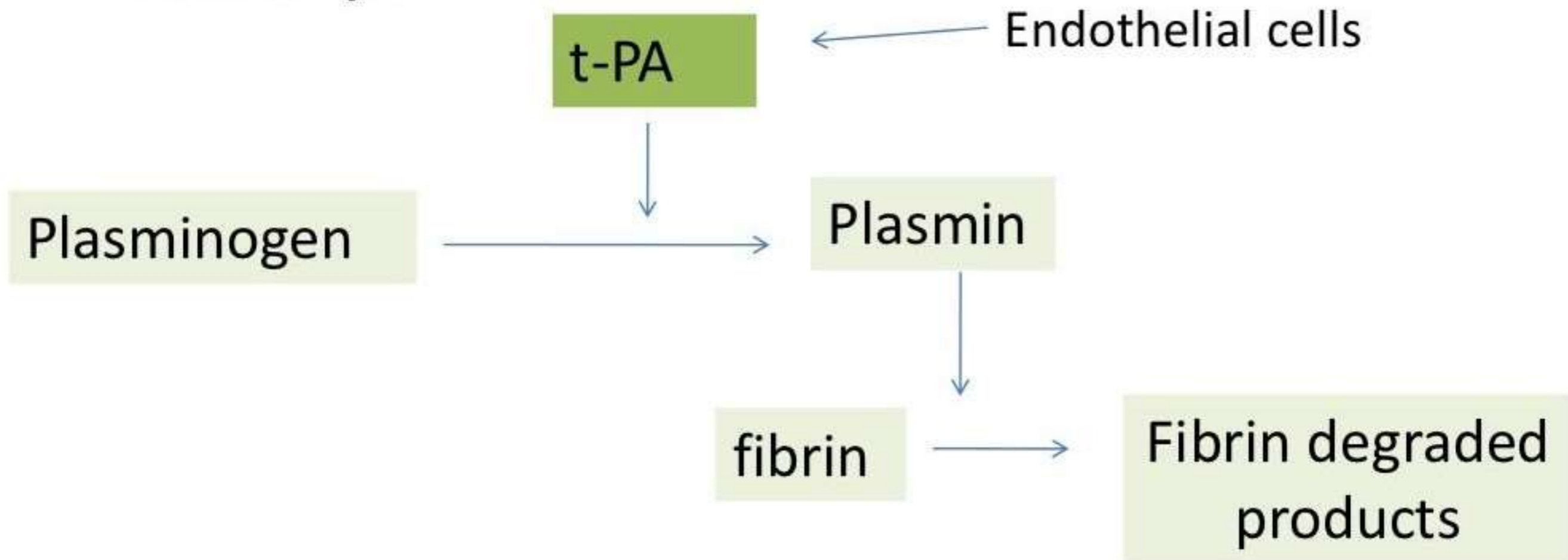
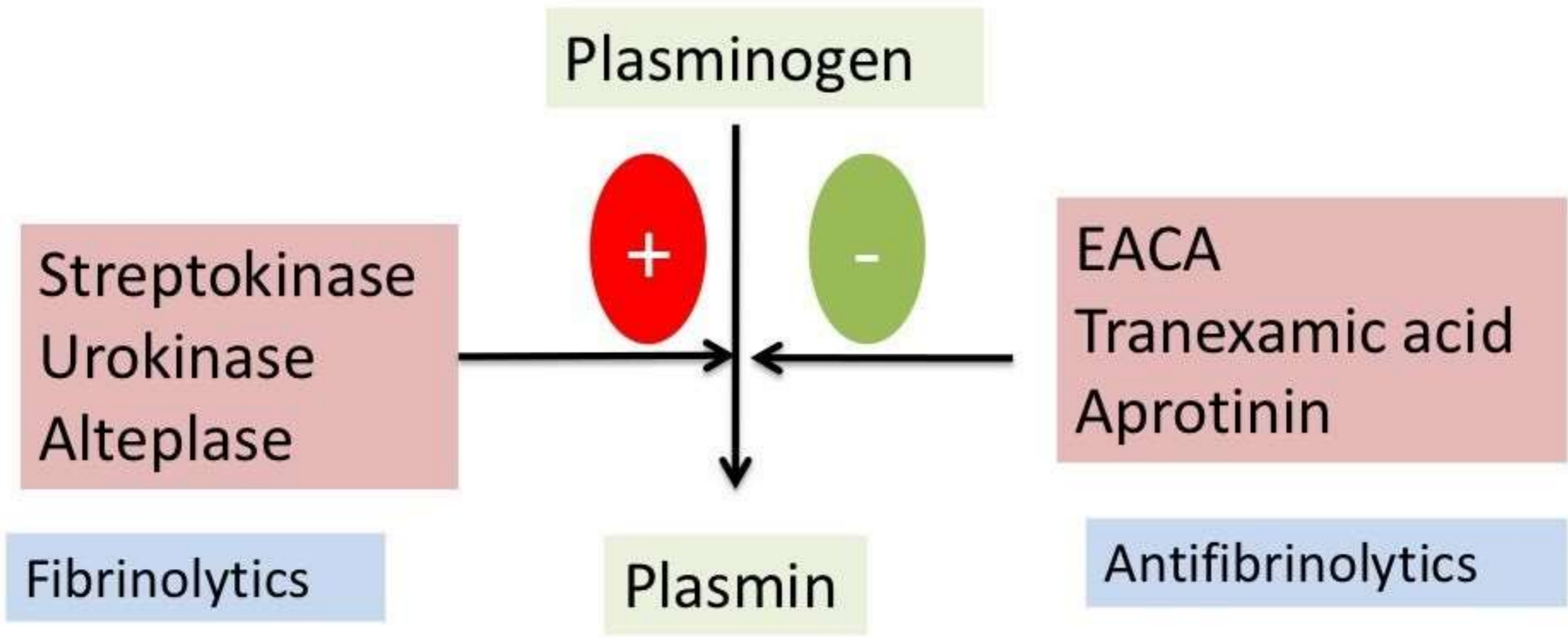


Fibrinolytics & Antiplatelets

Fibrinolytic system

- The process of dissolution of clot is called fibrinolysis



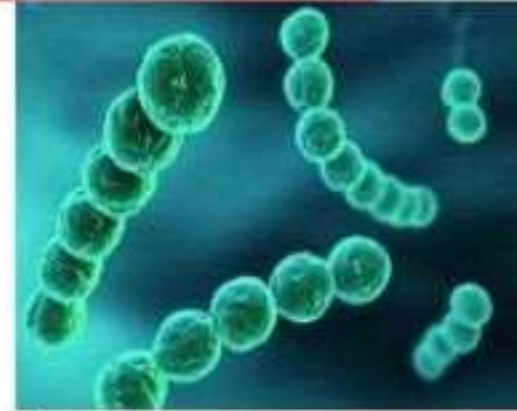


FIBRINOLYTICS

- Used to lyse the thrombi / clot to recanalize the occluded blood vessel (mainly coronary artery)
- Work by **activating the Fibrinolytic system**
 - **S**TREPTOKINASE
 - **U**ROKINASE
 - **R**ETEPLASE (analogue of alteplase)
 - **A**LTEPLASE (t- PA)
 - **T**ENECTEPLASE

Streptokinase

- Obtained from β -hemolytic streptococci
- Binds with circulating plasminogen to form complex that activates plasminogen to plasmin
- $t_{1/2} = 30 - 80$ min
- Antigenic ,Pyrogenic
- Destroyed by circulating antistreptococcal Antibodies
- Hypotension & arrhythmia can occur



Streptokinase

Uses

- Acute myocardial infarction
 - 7.5 to 15 lac IU; I.V over 1 hr period
- Deep vein thrombosis , Pulmonary embolism

Adverse effects

- Bleeding, hypotension, allergic reactions, fever, arrhythmias

Contraindications

- Recent trauma, surgery, abortion, stroke, severe hypertension, peptic ulcer, bleeding disorders

Urokinase

- Enzyme isolated from human urine, now prepared from cultured human kidney cells
- **Direct plasminogen activator**
- $t_{1/2}$ of 10 to 15 min
- **Non antigenic, Non allergenic**
- Fever can occur but hypotension rare
- Indicated in patients in whom streptokinase has been for an earlier episode

Alteplase

- recombinant tissue Plasminogen Activator(rt-PA)
- Selectively activates plasminogen bound to fibrin
- Non antigenic ,not destroyed by antibodies
- Rapid acting, more potent
- Superior in dissolving old clots
- Short half life 4-8 min
- Nausea, mild hypotension, fever may occur
- Expensive

Newer recombinant tissue plasminogen activators

- **Retepase :**
 - Modified rt-PA
 - Longer half life 15 -20 min, but less specific for fibrin bound plasminogen
- **Tenecteplase:**
 - **Genetically engineered** mutant form of alteplase
 - Higher fibrin selectivity and longer half life – 2 hrs
 - Single bolus dose 0.5 mg/kg sufficient
 - Very expensive

Uses of fibrinolytics

- Acute myocardial infarction
- Deep vein thrombosis
- Pulmonary embolism
- Peripheral arterial occlusion
- Ischemic Stroke

Antiplatelet drugs

Mechanism of platelet aggregation and inhibition

Platelet

Arachidonic acid

Cyclic endoperoxides

TXA₂

↓cAMP promotes adhesion of platelets

Endothelium

Arachidonic acid

Cyclic endoperoxides

PGI₂

↑cAMP inhibits adhesion of platelets & release of 5HT & ADP

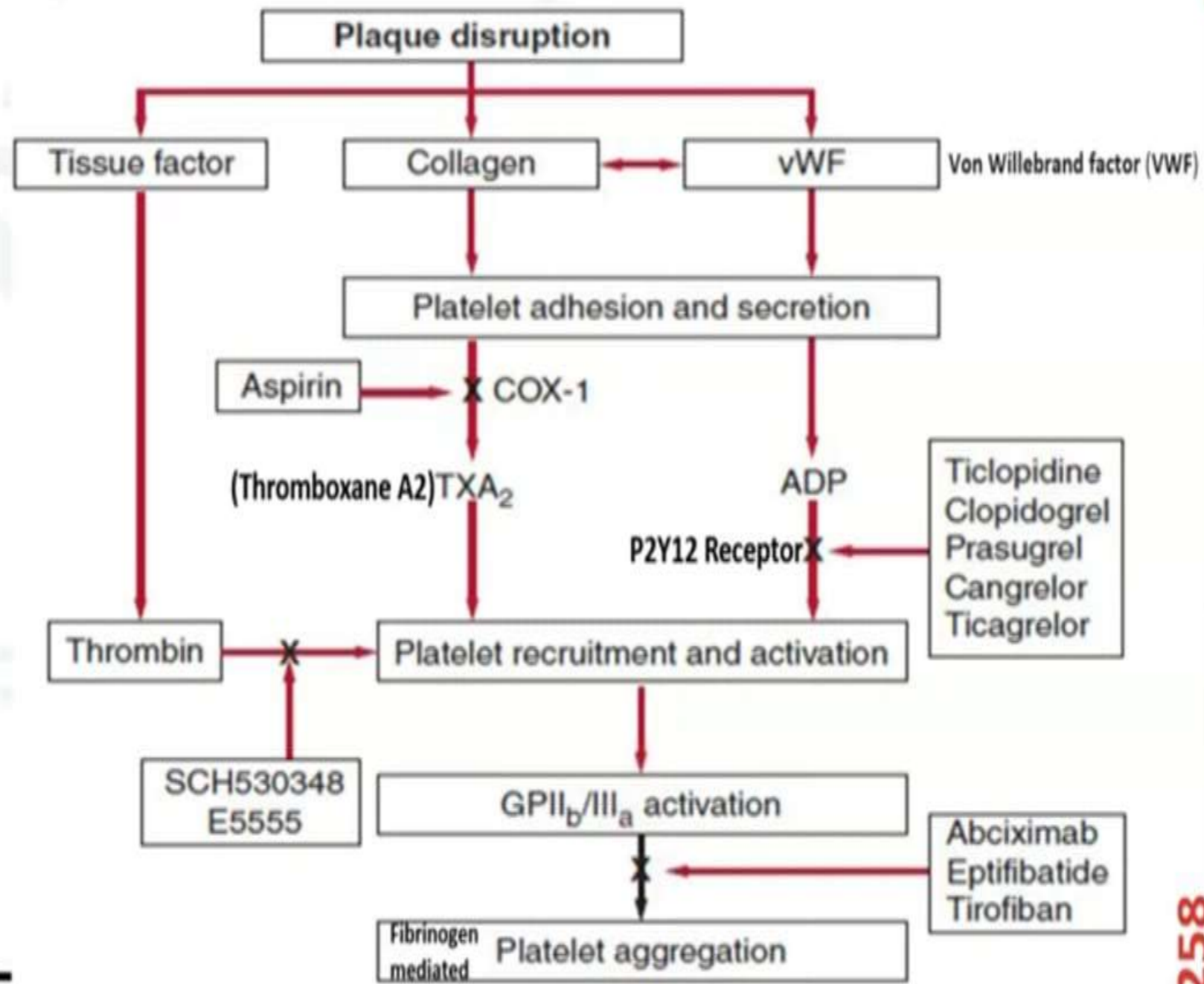
COX

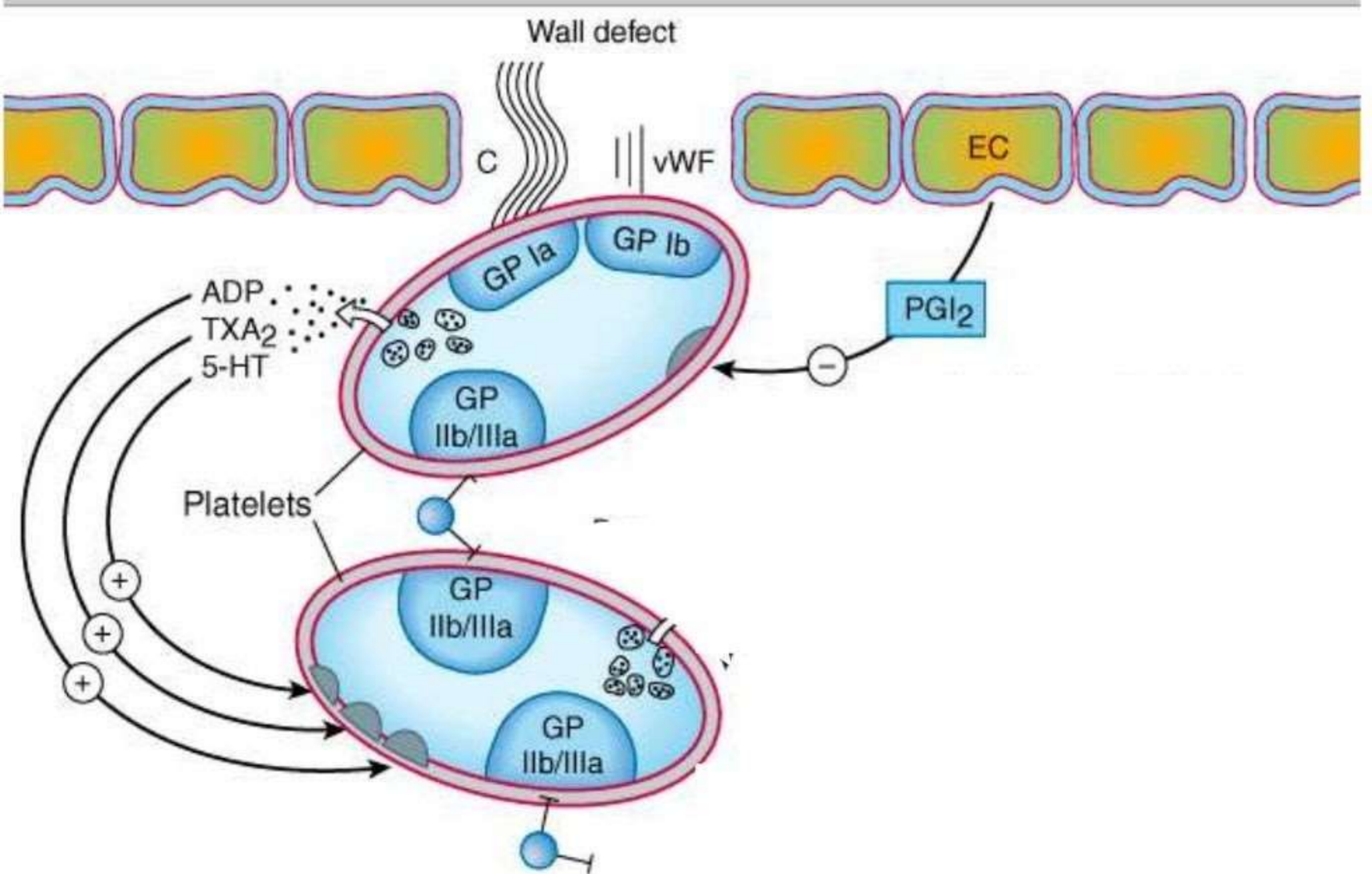
Prostacyclin synt

Adenylate cyclase

TX-synthetase

PLATELET AGGREGATION AND INHIBITION: MOA

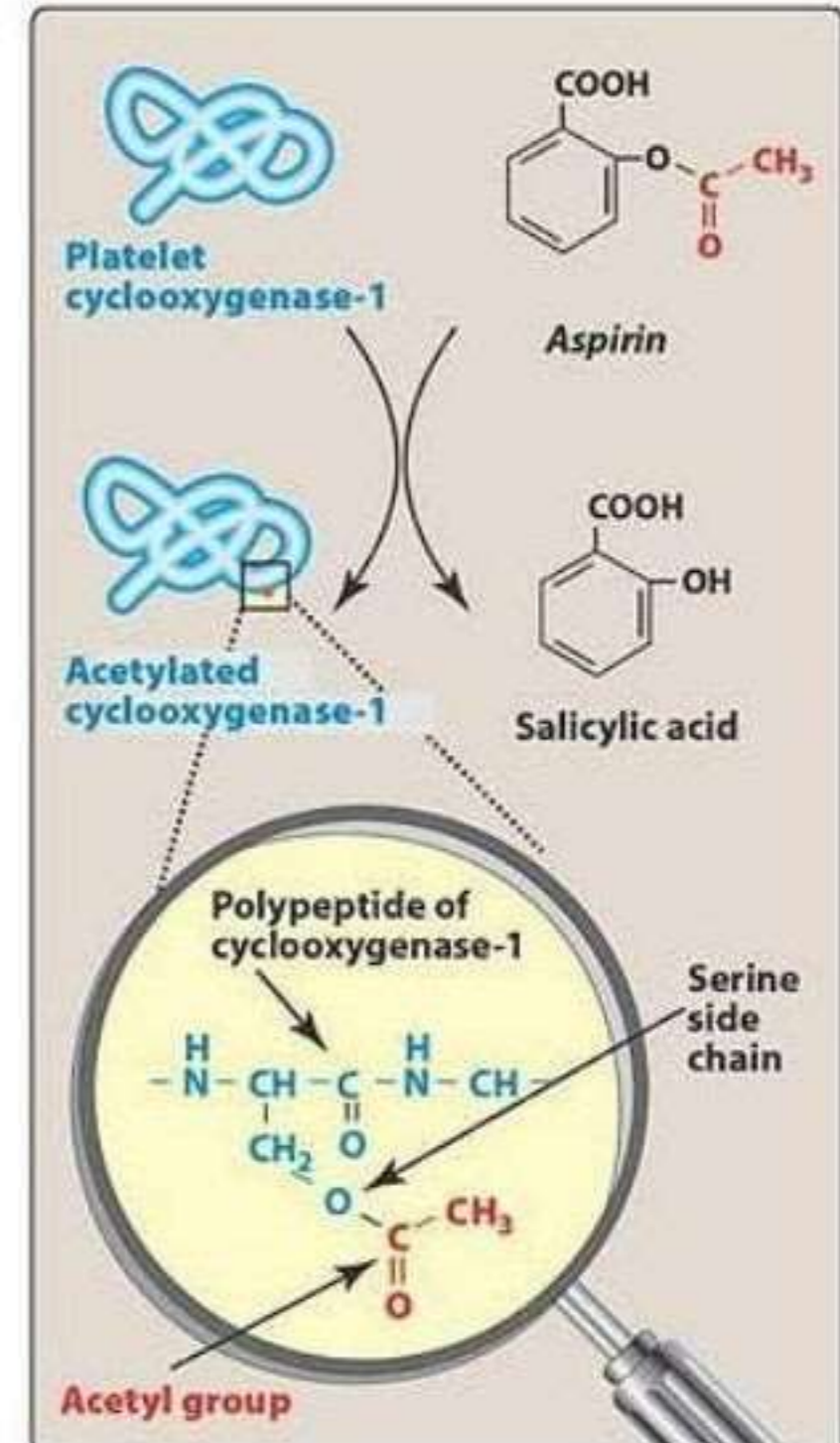
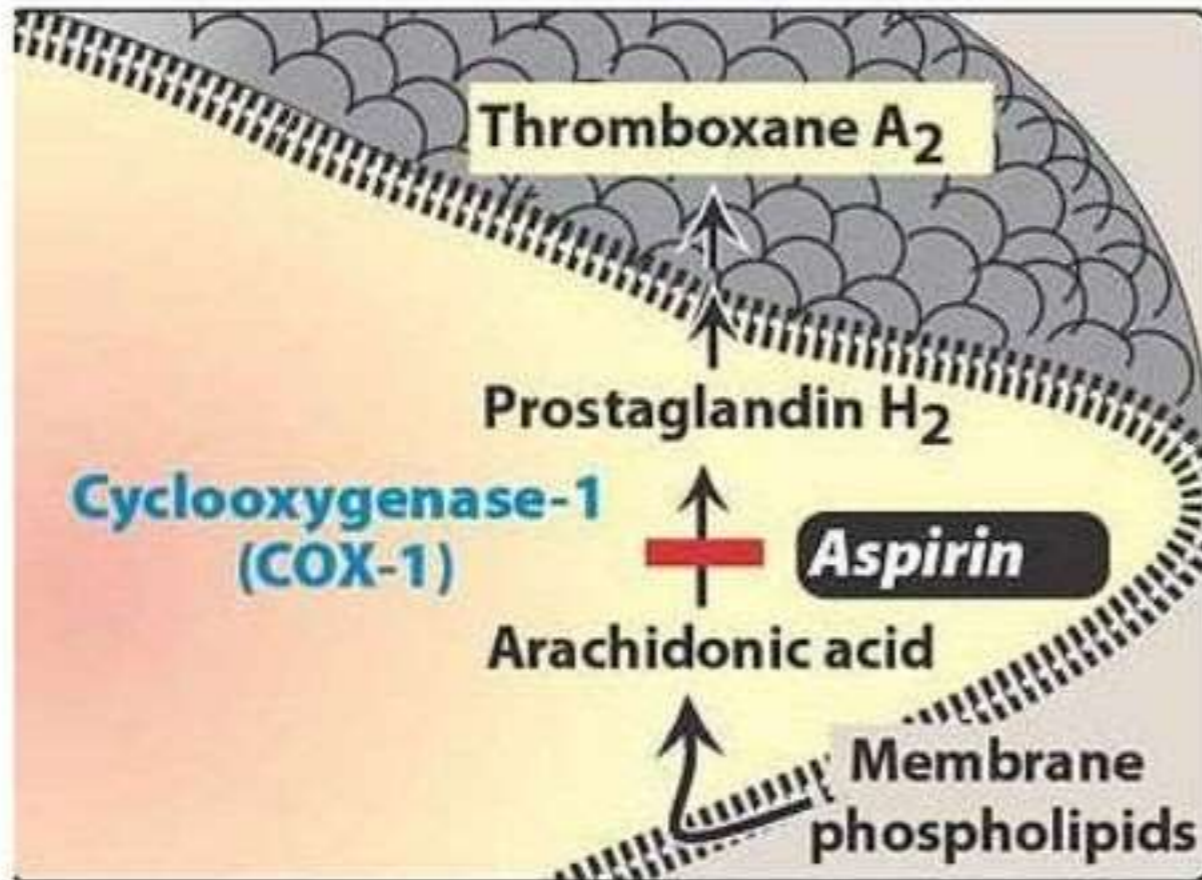




Antiplatelet drugs (Classification)

- TXA₂ synthesis inhibitor:
 - Low dose **aspirin**
- Phosphodiesterase inhibitor:
 - **Dipyridamole**, cilostazole
- Thienopyridine derivatives (ADP antagonists):
 - **Ticlopidine, clopidogrel**
- Gp-IIb/IIIa receptor antagonists
 - **Abciximab**, eptifibatide, tirofiban
- Others
 - PGI₂, daltroban, dazoxiben, clofibrate

Aspirin



Dipyridamole

- Coronary vasodilator and relatively weak antiplatelet drug
- Mechanism of action
 - Potentiates effect of endogenous prostacycline
 - In high conc inhibits Phosphodiesterase, so \uparrow cAMP
- Dose = 100 mg BD/TDS
- used with aspirin to prevent ischemic stroke in patients of TIA

Ticlopidipine & clopidogrel

- **ADP antagonists**, inhibit binding of ADP to its receptors **irreversibly**
- Also Inhibit fibrinogen induced platelet aggregation with out modifying GPIIb/IIIa
- Synergistic action with aspirin
- Both are prodrugs have long duration of antiplatelet effect
- Clopidogrel a congener of ticlodipine is safer and better tolerated

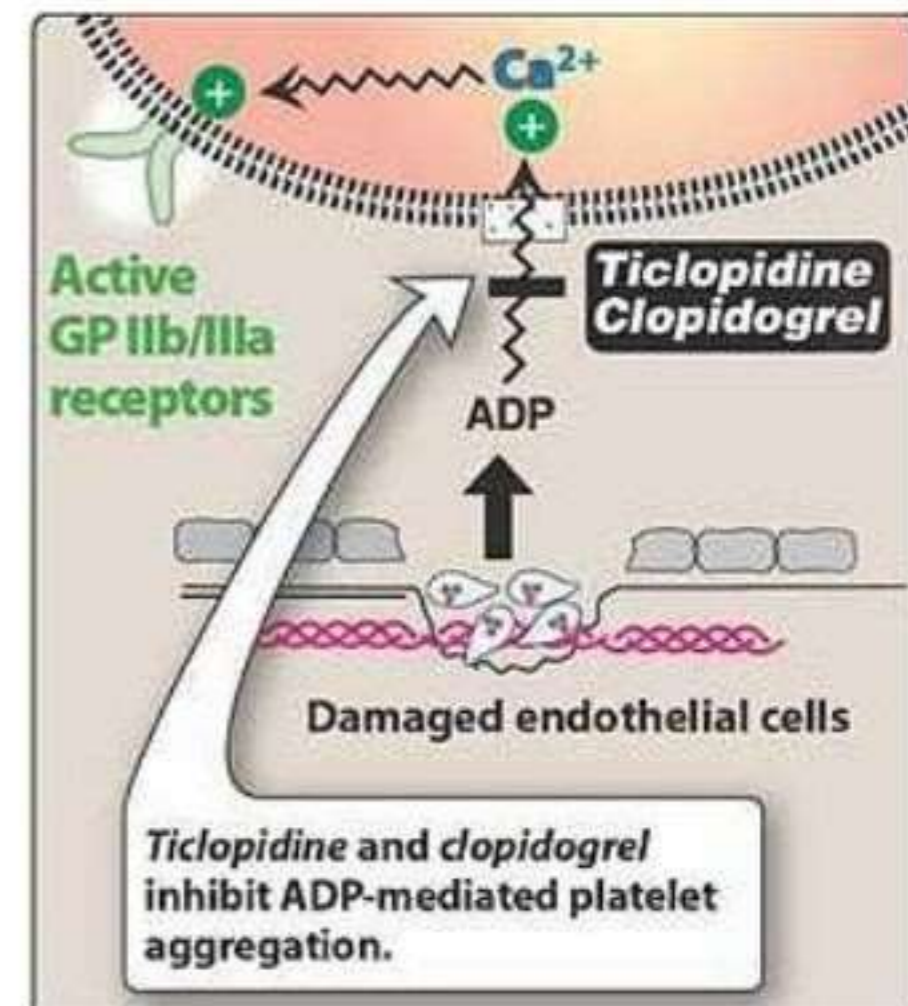
Ticlopidine Vs clopidogrel

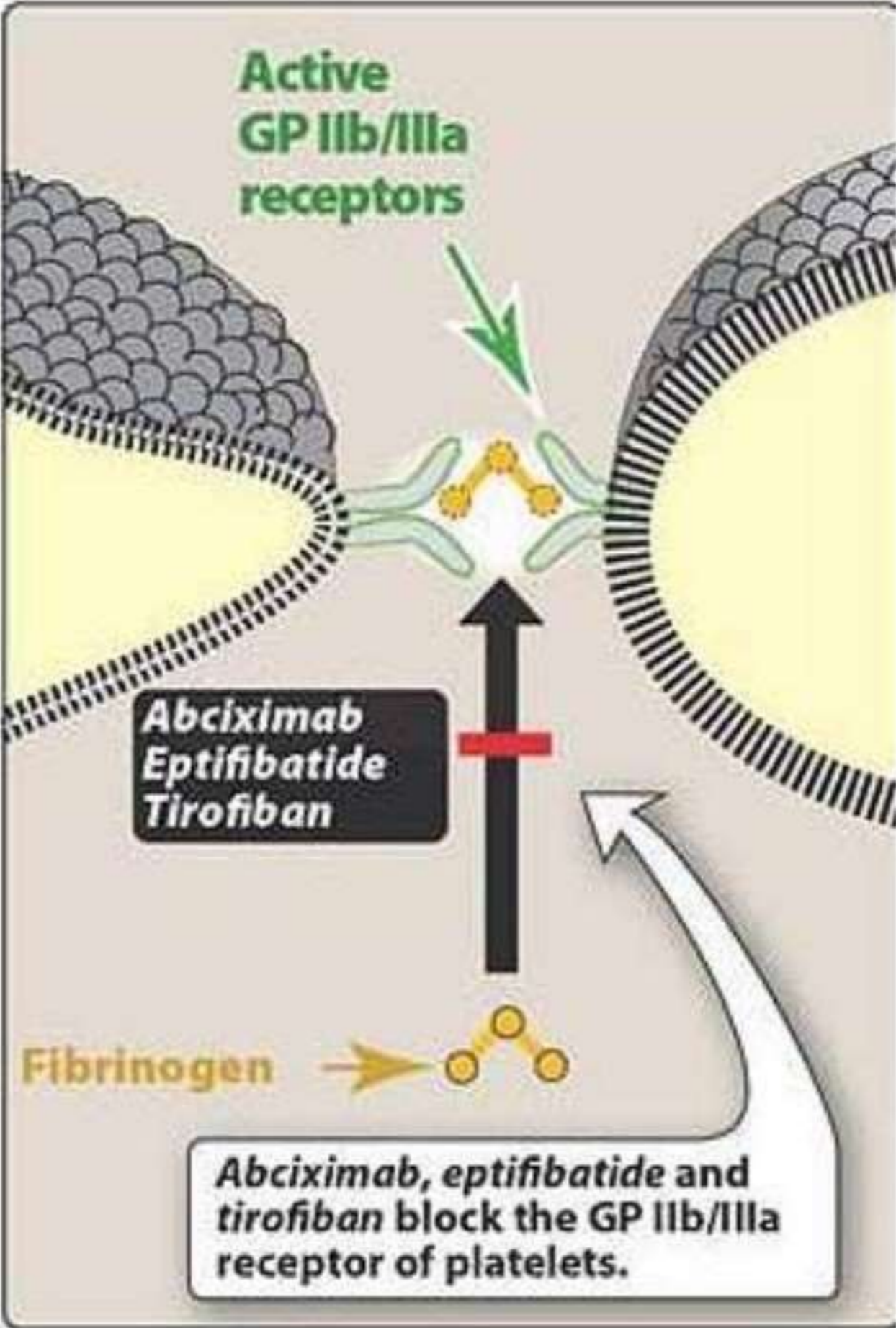
Ticlopidine

- Adverse effects:
 - Diarrhoea, vomiting, abdominal pain
 - Headache, tinnitus, skin rash
 - **Bleeding, neutropenia, thrombocytopenia**
- dose= 250 mg BD

Clopidogrel

- Adverse effects
 - Bleeding most IMP
 - Less bone marrow toxicity
 - Diarrhoea, epigastric pain, rashes
- Dose = 75 mg OD





Abciximab

- Fab fragment of Chimeric monoclonal antibody against GP-IIb/IIIa.
- Used to prevent platelet aggregation in patients having PCI, administered along with aspirin & heparin or LMW heparin
- Most common A/E is bleeding
- May cause thrombocytopenia, hypotension, bradycardia
- Non antigenic
- Dose: 0.25 mg/kg IV before PCI followed by 10 μ g/min for 12 hrs

Uses of antiplatelet drugs

- Prosthetic heart valves & A-V shunts
- Peripheral vascular disease
- Coronary artery diseases
 - Myocardial infarction
 - Unstable angina
 - Primary & secondary prevention of MI
- Coronary angioplasty, stents, bypass implants
- Cerebrovascular transient Ischemic attacks
- Venous thrombo-embolism