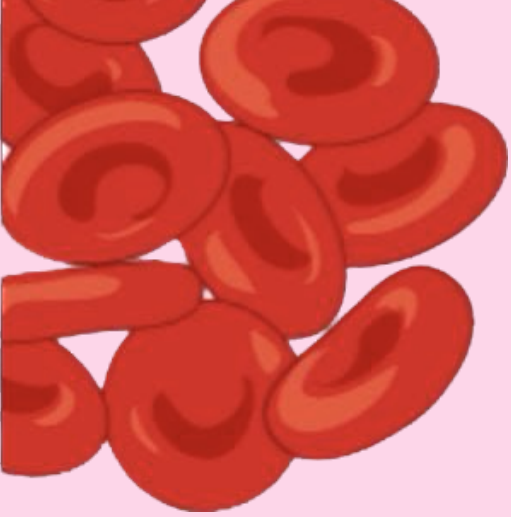


النادي الطبي

HEMATOPOIETIC & LYMPHATIC SYSTEM

-HAYAT BATCH-

SUBJECT : Pharma

LEC NO. : 3

DONE BY : Abdi

وَقُل رَّبِّ زِدْنِي عِلْمًا

DRUG THERAPY OF THROMBOSIS

Thrombosis:

- Thrombosis is a pathological condition resulting from inappropriate activation of the hemostatic mechanisms i.e. platelet aggregation & coagulation (fibrin formation).

→ thrombi have the ability to cause occlusions in the blood vessels which reduces blood supply to tissues leading to infarctions.

MECHANISMS OF BLOOD COAGULATION:

A. In the absence of injury of vesseles:

- Resting platelets circulate freely and platelet activation and aggregation are not initiated due to:

1. **Chemical mediators** (synthesized by endothelial cells):

   - Prostacyclin (PGI_2): binds to its platelet membrane receptors → ↑ intracellular cAMP → ↓ free intracellular Ca^{++} ('used as vasodilator')

     ↳ ↓ intracellular Ca^{++} locks platelets granules preventing their release & inactivates fibrinogin receptors thus prevents clots formation.

   - Nitric oxide (NO): binds to its platelet membrane receptors → ↑ intracellular cGMP → ↓ free intracellular Ca++

     → PGI_2 & NO cause also vasodilitation which gives platelets more space thus prevents them from contact with each other.

     - ↓ free intracellular Ca^{++} →
       - Inhibits release of platelet aggregation agents from granules
       - Stabilizes inactive GPIIb/IIIa receptors.

         ↳ fibrinogen receptors
       - ↓ synthesis of TXA_2

2. **The intact endothelium** covers subendothelial collagen and circulating **levels of thrombin and TXA_2** are low.

   ↳ if get uncovered start coagulation cascade

B. In response to vascular injury:

1. **Vasospasm** of injured blood vessel.

   ↳ Squeeze platelet together get them close to one another

2. **Platelets functions:**

   - **Platelets adhesion:** platelets stick to collagen and von Willebrand factor (vWf) released at area of injury → a complex series of chemical reactions → platelet activation.

- **Platelets activation:** - Activated platelets release chemicals such as:
  - ADP →↓ intracellular cAMP → ↑ free intracellular Ca^{++} → platlets activation and aggregation
    ↳ Activates fibrinogen receptors GPIIb/IIIa fibrinogen starts to bind with fibrinogen receptors forming a mesh work that connects platelets (plug)
  - $Thromboxane_{A2}$ (synthesized by COX-I enzyme) → platlets aggregation.
    ↳ Causes vasoconstriction
  - Serotonin → further potentiates vasoconstriction
  - PAF "platelet activating factor"

  - Activated platelets also express on their surface:
    - Certain proteins (receptors) that attach to:
      - vWf (synthesized by the endothelium of blood vessels)
      - fibrinogen (glycoprotein IIb/IIIa)
      - collagen (glycoprotein Ia)
    - A crucial clotting protein called thrombin.
      ↳ turns soluble fibrinogen to insoluble fibrin
- **Platelets aggregation:**

  - The activation of platelets → release of sequestered Ca^{++} stores → ↑ free intracellular Ca^{++} →
    - Release of platelet aggregation agents from granules
    - Active of GPIIb/IIIa receptors that bind fibrinogen
    - Activation of TXA2
  - Fibrinogen (a soluble plasma GP) → binds to GPIIb/IIIa receptors on two separate platelets (Connecting them) → platelet cross-linking and platelet aggregation → each activated platelet can recruit other platelets
- **Platelets plug**: platelets loss their individual membrane forming gelatinous mass → arrest bleeding.
  → platelet plug must be reinforced to remain stable as it can stop bleeding but can be taken off easily

3. Fibrin clott:.

- Tissue factors (from the injured tissue) + mediators (on the surface of platelets) → local stimulation of the clotting cascade → formation of thrombin (factor lla) → hydrolysis of fibrinogen to fibrin → the platelet plug is reinforced by fibrin.

- Subsequent cross-linking of the fibrin strands stabilizes the clot.

→ Thrombin:
- turns fibrinogen to fibrin thus stablize platelets plug
- Also activates factor XIII "fibrin stabilizing factor"
  ↑ clot strength

4. Fibrinolysis: Tissue plasminogen activator (t-PA) → activation of plasminogen to plasmin → splits fibrin and fibrinogen into fragments → clot dissolution.

→ Takes time → infarction before restoring blood supply

There are 2 types of thrombus:

1. **White thrombus**: formed in arteries due to platelets adhesion. High pressure circulation leads to vessels injury.

   ↳ Main component is platelets thus treated by Antiplatelets

   - Risk factors: smoking, hypertension, hyperlipidemia, diabetes mellitus, cholesterol emboli

     ↳ ↑tension on the wall ↑ risk of bv injury

   - e.g. coronary thrombosis, cerebral thrombosis, peripheral artery thrombosis/ embolism.

     ↗ Angina & may cause mycardial infarction

     ↳ Cerebral infarction

   - Treated mainly by antiplatelet drugs & fibrinolytics.

     ↗ Prevention of further clotting

     ↳ breaks clot

2. **Red thrombus:** formed in veins due to venous stasis which triggers fibrin network formation through which red cells are enmeshed forming the red thrombus.

   - Risk factors: pregnancy, immediate post-childbirth period, use of oral contraceptives or estrogen replacement therapy, high dose corticosteroid therapy, immobilization (bone fracture, knee, hip, abdominal surgery, and catheters).

     ↗ uterus enlargment ↓ venous blood flow

     ↳ ↑ formation of coagulation factors

   - It increases in size with time forming long tail. This tail can be detached easily forming emboli e.g. pulmonary embolism.

   - Treated mainly by anticoagulants.(fibrinolytics may be used)

DRUG THERAPY OF THROMBOSIS

Anticoagulants	Antiplatelets	Fibrinolytics
• Interfere with coagulation factors & thrombus formation.	• Interfere with aggregation of platelets & thrombus formation.	• Induce lysis of fibrin (thrombus).

Antiplatelets

PGs analogues

PDE inhibitor

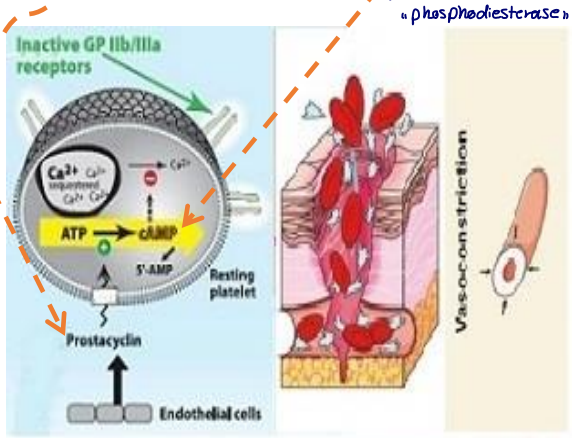
breaks cAMP «phosphodiesterase»

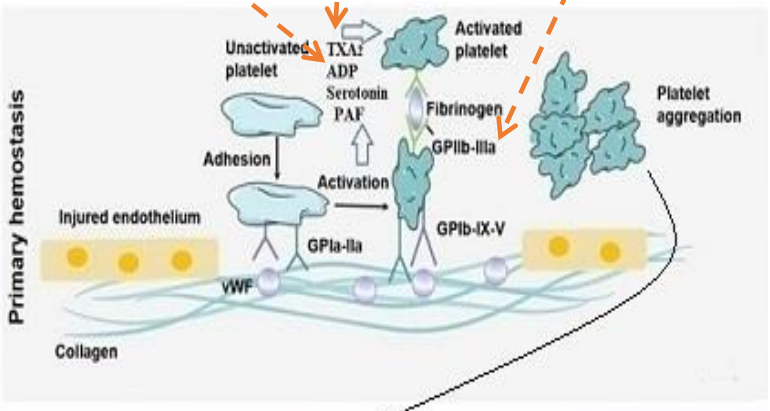
ADP receptor blockers

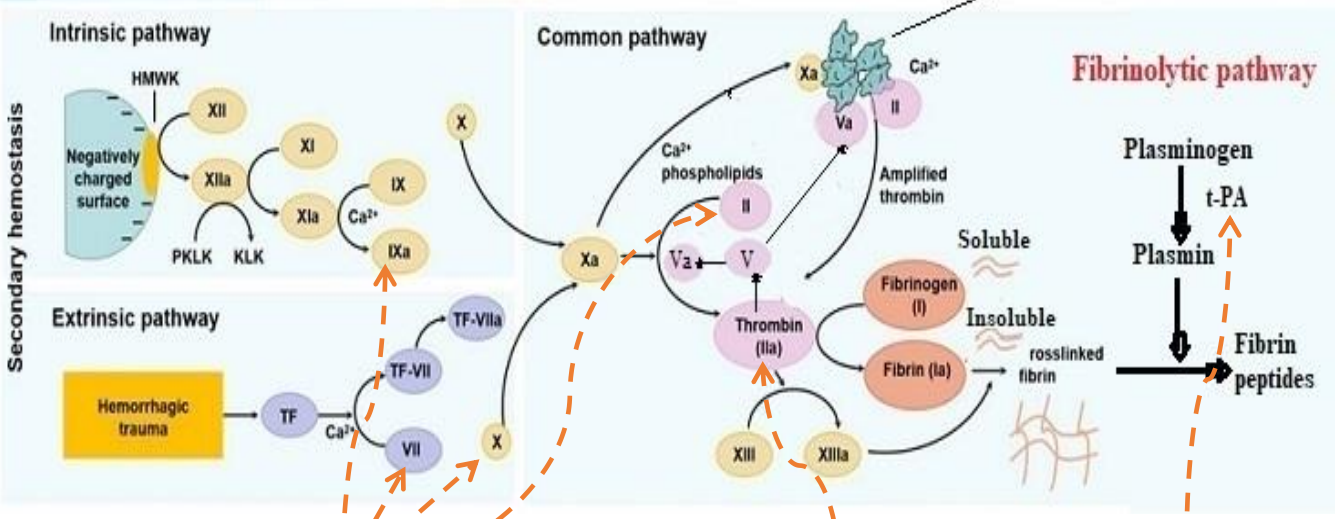
COX-I inhibitors

Aspirin

GPIIb/IIIa receptor blockers







Oral Anticoagulants (Warfarin & NOAC)

Parenteral Thrombin Inhibitors (Indirect & Direct)

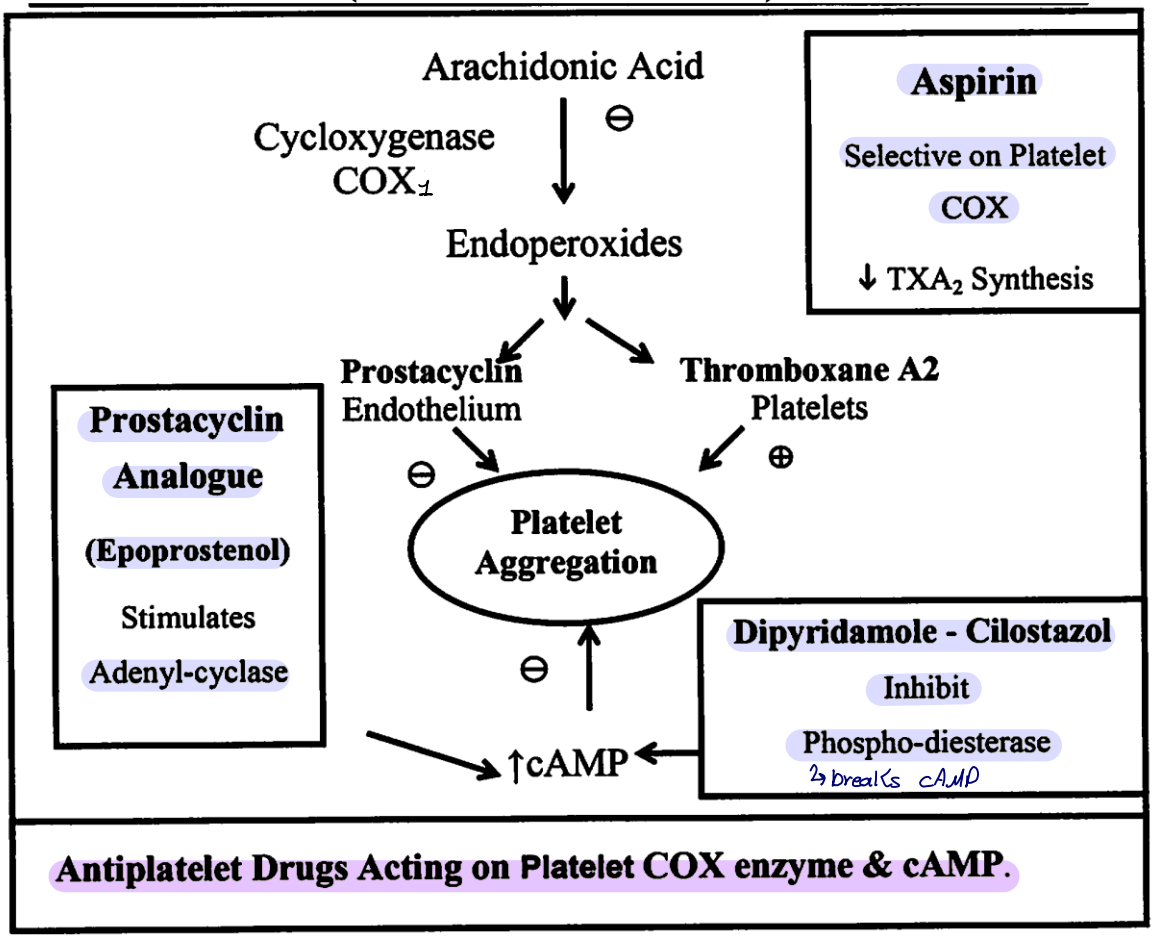
recombinant t-PA

Fibrinolytics

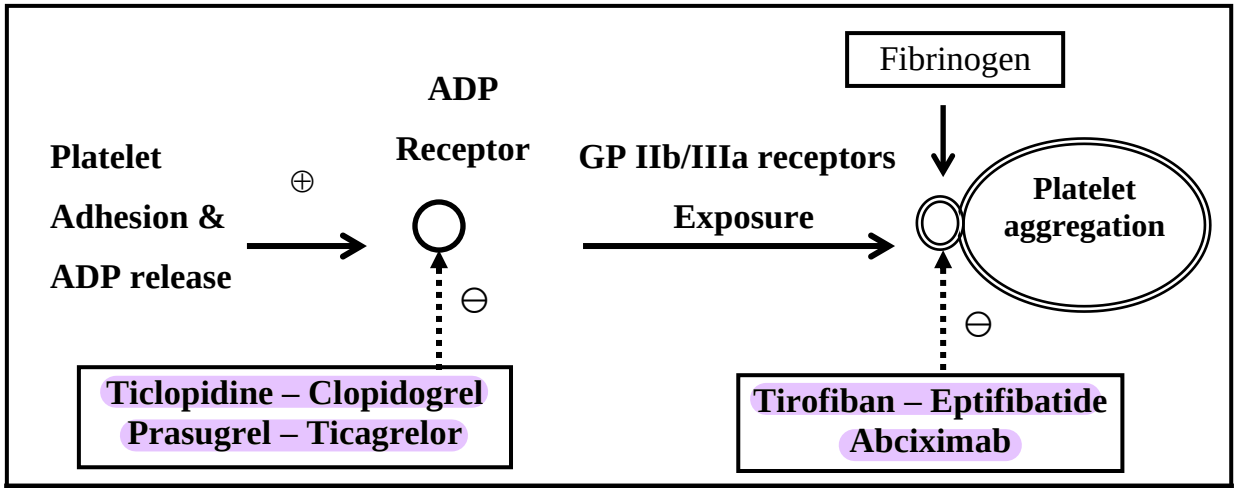
Anticoagulants

ANTIPLATELET DRUGS

(ANTITHROMBOTICS)



Antiplatelet Drugs Acting on Platelet COX enzyme & cAMP.



Platelet Aggregation & Site of action of AntiplateleDrugs Acting on platelet Receptors

Classification of antiplatelets according to mechanism of Action

I. Drugs Acting on Platelet COX Enzyme

Acetylsalicylic acid (Aspirin)

- Prototype antithrombotic
- Low (infantile) (small)-dose aspirin **(75 - 325 mg/day oral):** inhibits platelet thromboxane A2 synthesis by inhibiting (**irreversible** acetylation) of COX-I enzyme.
  ↳ The only irreversible COX-1 inhibitor
- Aspirin is the main antiplatelet drug used. (Clopidogrel or dipyridamole may be combined to it or given to the patients intolerant to it).
- Low dos aspirin is selective on platelets (why??)

II. Drugs Increasing cAMP

1. PGI_2 analogue (epoprostenol)

- Stimulates adenyl cyclase → ↑cAMP.
- Potent antiplatelet & vasodilator.
- Very short duration (minutes)→ given by IVI. → thus can't be used as prophylactic treatment
- **Uses**: **hemodialysis-cardiopulmonary bypass- pulmonary hypertension**

2. Dipyridamole & Cilostazol (oral)

- Inhibit phosphodiesterase →↓ cAMP breakdown → ↑cAMP.
- Vasodilator & antiplatelet.
- Dipyridamole is a weak antiplatelet →combined with warfarin or aspirin. (prefered to aspirin for combination with warfarin due to less bleeding).
- **Cilostazol is used** in **intermittent claudication**
  ↳ Pain in lower body part muscles due to atherosclerosis ↑ by exercise & stops when resting

↳ As combining warfarin & aspirin may induce bleeding so using dipyridamole & warfarin is safer

III. Drugs acting on platelet Receptors

1. Drugs inhibiting ADP receptors

- They inhibit **(irreversibly)** the binding of ADP to its receptors →inhibit expression of fibrinogen receptors
- **Ticlopidine- clopidogrel - prasugrel – ticagrelor**
- Are given orally, maximum effect is achieved after 3-5 days (loading dose is required to achieve rapid maximal effect)

2. Drugs blocking GP IIb/IIIa (Fibrinogen) Receptor

- **Tirofiban, eptifibatide, abciximab** (mono-clonal antibody)
- All are given IVI; short term therapy.
- They block platelet GP IIb/IIIa receptors (activation of this receptor complex is the "final common pathway" for platelet aggregation)
- **Abciximab** consists of monoclonal antibodies which bind to receptors.
- **Eptifibatide,** and **tirofiban** are analogues to delta chain of fibrinogen which mediates binding of fibrinogen to GP IIb/IIIa receptors on platelets.

Therapeutic uses of antiplatelet drugs (mainly in arterial thrombosis)

1. High risk of myocardial infarction (AMI): e.g., previous attack or angina.
2. Acute coronary syndrome. thrombosis in coronary artery causes angina
3. Coronary bypasses grafting, angioplasty & stent insertion (clopidogrel is routinely used). ↳ Coronary artery occlusion thus we make different blood route
4. Prosthetic heart valves: thrombo-embolism.
5. Transient ischemic attacks (TIAs)- thrombotic stroke.

Adverse effects of antiplatelet drugs:

↳ Stroke can be caused by either bleeding or thrombosis

A. Common: increased risk of bleeding

B. Individual:

1. **Aspirin (oral once /day)**:
   - GIT: gastric irritation, bleeding ulcers.
   - Precipitating attack of bronchial asthma. ↑IL
2. **Epoprostenol (IVI)**: Flushing, headache, hypotension.
3. **Dipyridamole (oral): Steal phenomena** (↑cAMP → VD → shift blood from atherosclerotic vessels to healthy vessels) -dizziness- headache- GIT disturbance. ↳ Thus ↓ blood supply to atherosclerotic vessel causing ischemia
4. **Cilostazol (oral):**
   - Headache, dizziness - GIT upset: dyspepsia, diarrhea
   - VD → Tachycardia, palpitations, peripheral edema.
5. **Ticlopidine (oral):** bone marrow depression → **neutropenia**

6. **Prasugrel: (oral)**
   - Increased risk of bleeding (CI: in patients with history of TIA or stroke) bleeding stroke
7. **Clopidogrel (oral once /day)** (preferred to ticlopidine; less risk of neutropenia)
   - Rash - Gastric irritation- diarrhea.
   - Clopidogrel is a prodrug → avoid with PPIs e.g. omeprazole as it inhibits its activation in liver by CYP450

protein pump inhibitors

8. **Ticagrelor:** shortness of breath
9. **Abciximab (IVI)**: thrombocytopenia, arrhythmia.

ANTICOAGULANTS

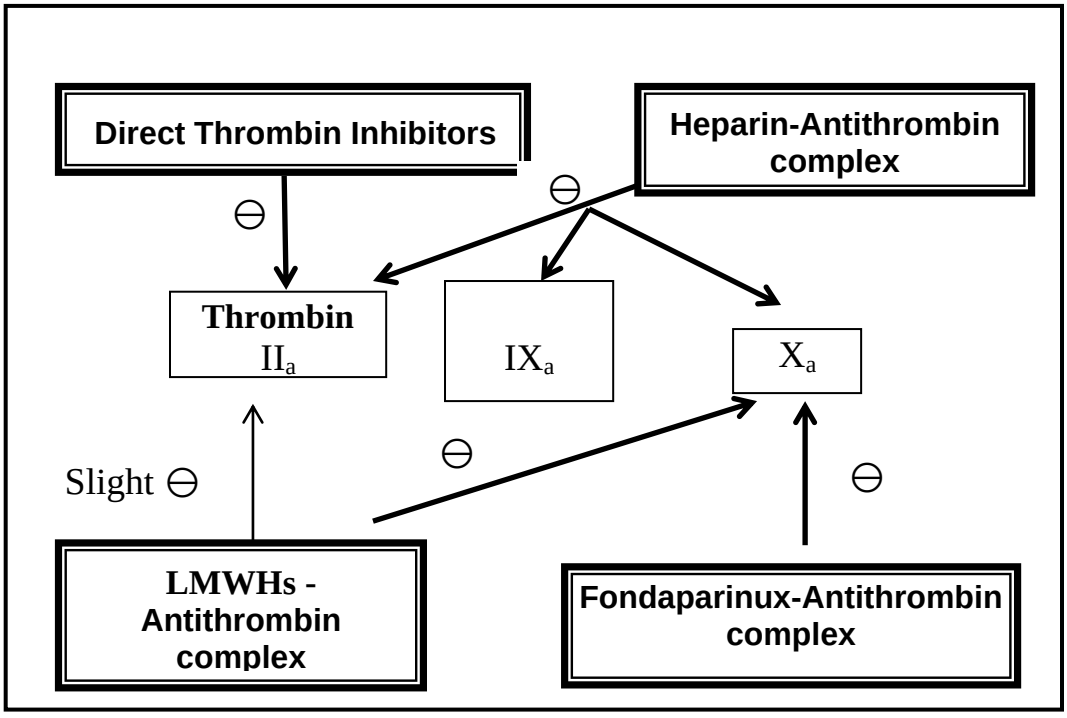
A. Parenteral Anticoagulants:

I. Indirect thrombin inhibitors: Heparin - low molecular weight heparins (LMWHs) - fondaparinux.

II. Direct thrombin inhibitors: Bivalirudin - Argatroban.

B. Oral anticoagulants: Warfarin – New oral anticoagulants (NOAC).

A.PARENTERAL ANTICOAGULANTS



Site of action of Indirect & Direct Thrombin Inhibitors