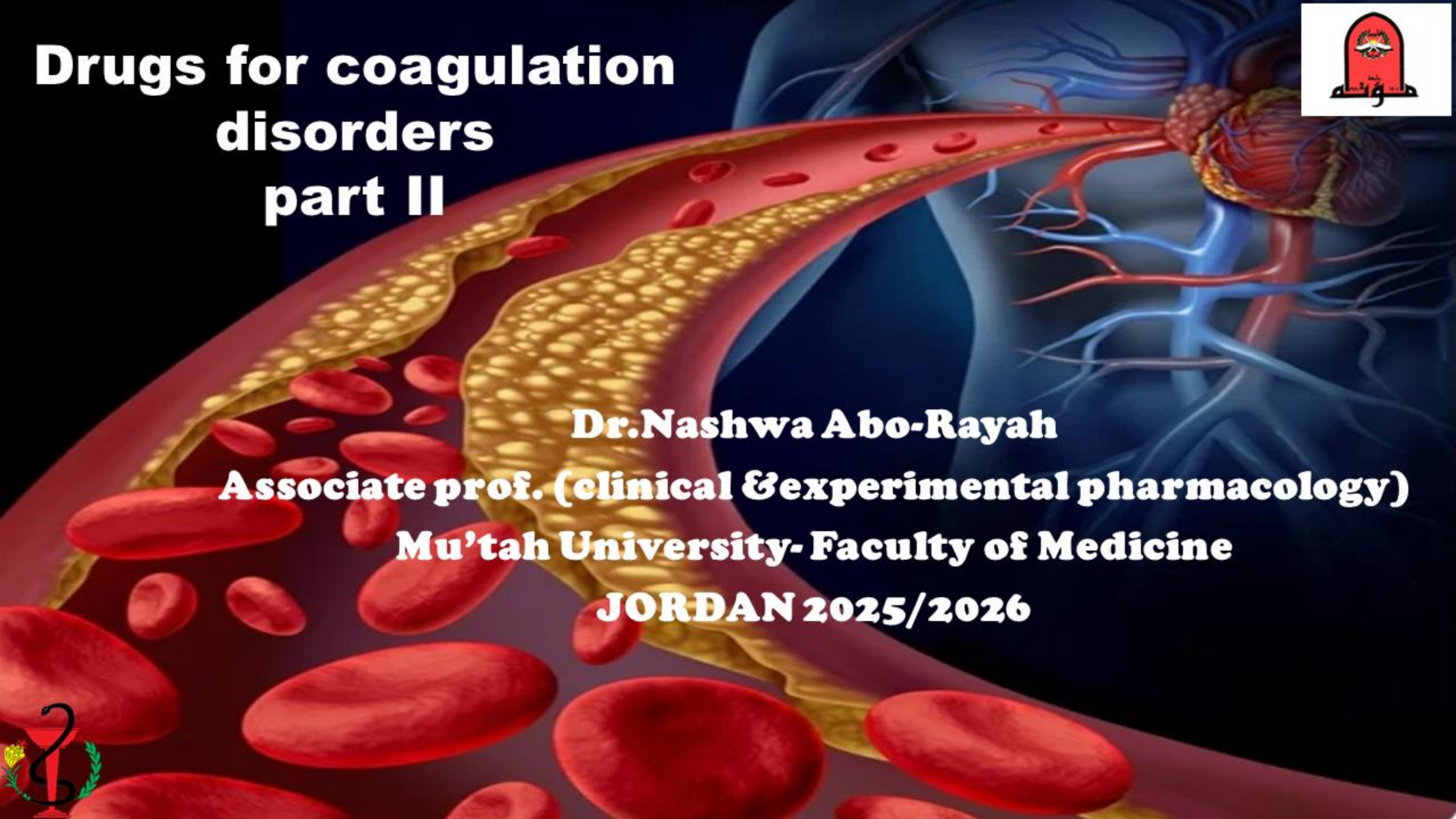
Drugs for coagulation disorders part II



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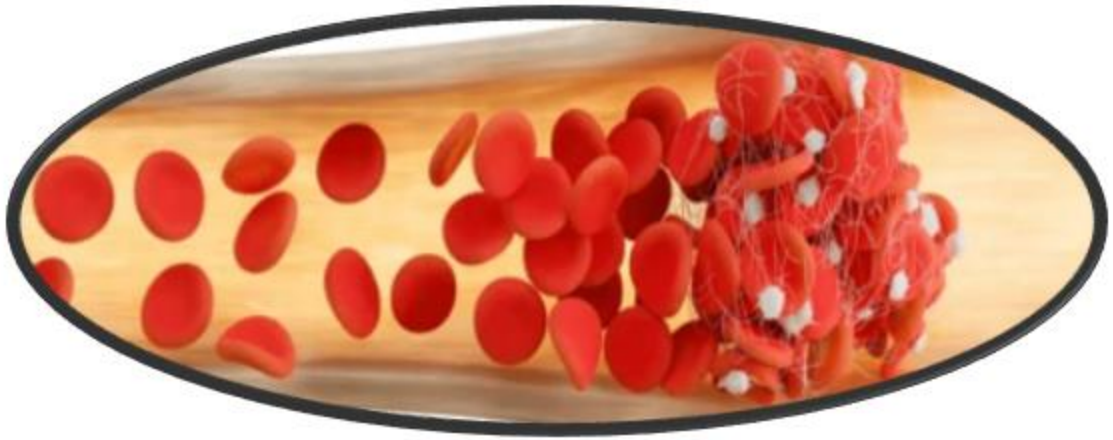
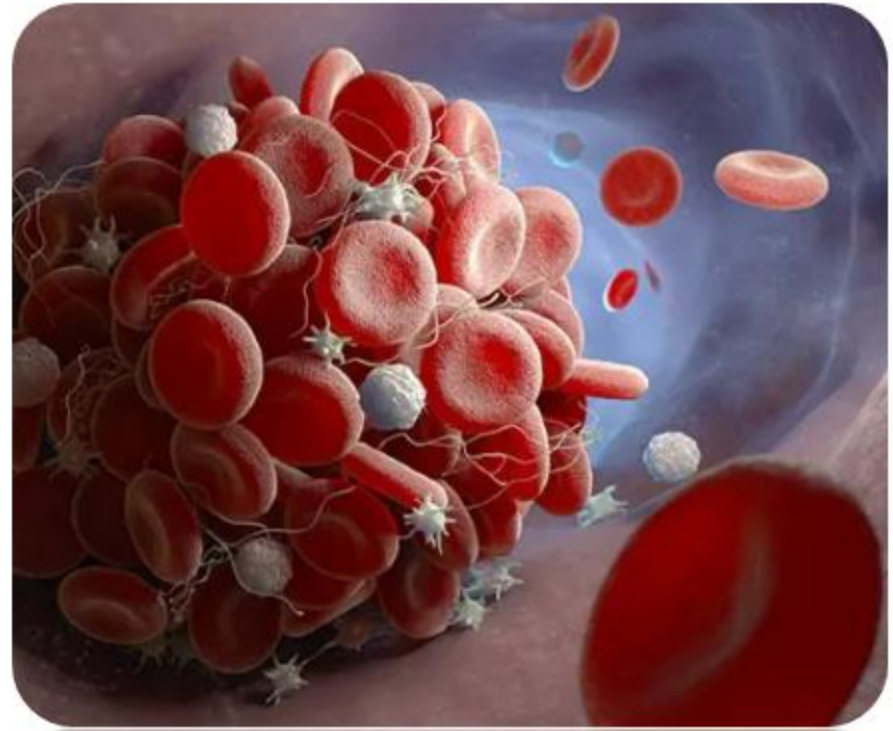
JORDAN 2025/2026

II- Anti-platelets

- **A blood clot is** a solid, gel-like aggregate formed to stop bleeding
- Consisting of a fibrin mesh network trapping red blood cells and platelets
- **Principal components of thrombus include** fibrin, platelets, red blood cells (RBCs),





Classification of antiplatelet drugs (antithrombotic)

Platelet aggregation inhibitors	Phosphodiesterase (PDE) Inhibitors	Protease-activated receptor-1 (PAR) antagonists
1. Cyclooxygenase (COX) Inhibitors: **Aspirin (Acetylsalicylic acid)** The most common antiplatelet agent; it **irreversibly** inhibits COX-1, decreasing the synthesis of thromboxane A2 (TXA2) **2. Adenosine Diphosphate (ADP) Receptor Inhibitors (P2Y12 Inhibitors):** These drugs block the P2Y12 ADP receptor on the platelet surface, preventing activation: ▪ **Irreversible**: Clopidogrel , Prasugrel, Ticlopidine. ▪ **Reversible**: Ticagrelor **3. Glycoprotein (GP) IIb/IIIa Inhibitors**: strong inhibition by blocking the final step of platelet aggregation (binding of fibrinogen to GPIIb/IIIa receptors): ▪ Abciximab ▪ Eptifibatide ▪ Tirofiban	4. **Cilostazol** : Inhibits PDE-3, increasing cAMP, resulting in decreased platelet aggregation and vasodilation. • **Dipyridamole:** • non-specific inhibitor of PDE	**5. Vorapaxar** : ▪ Blocks thrombin-induced platelet activation.

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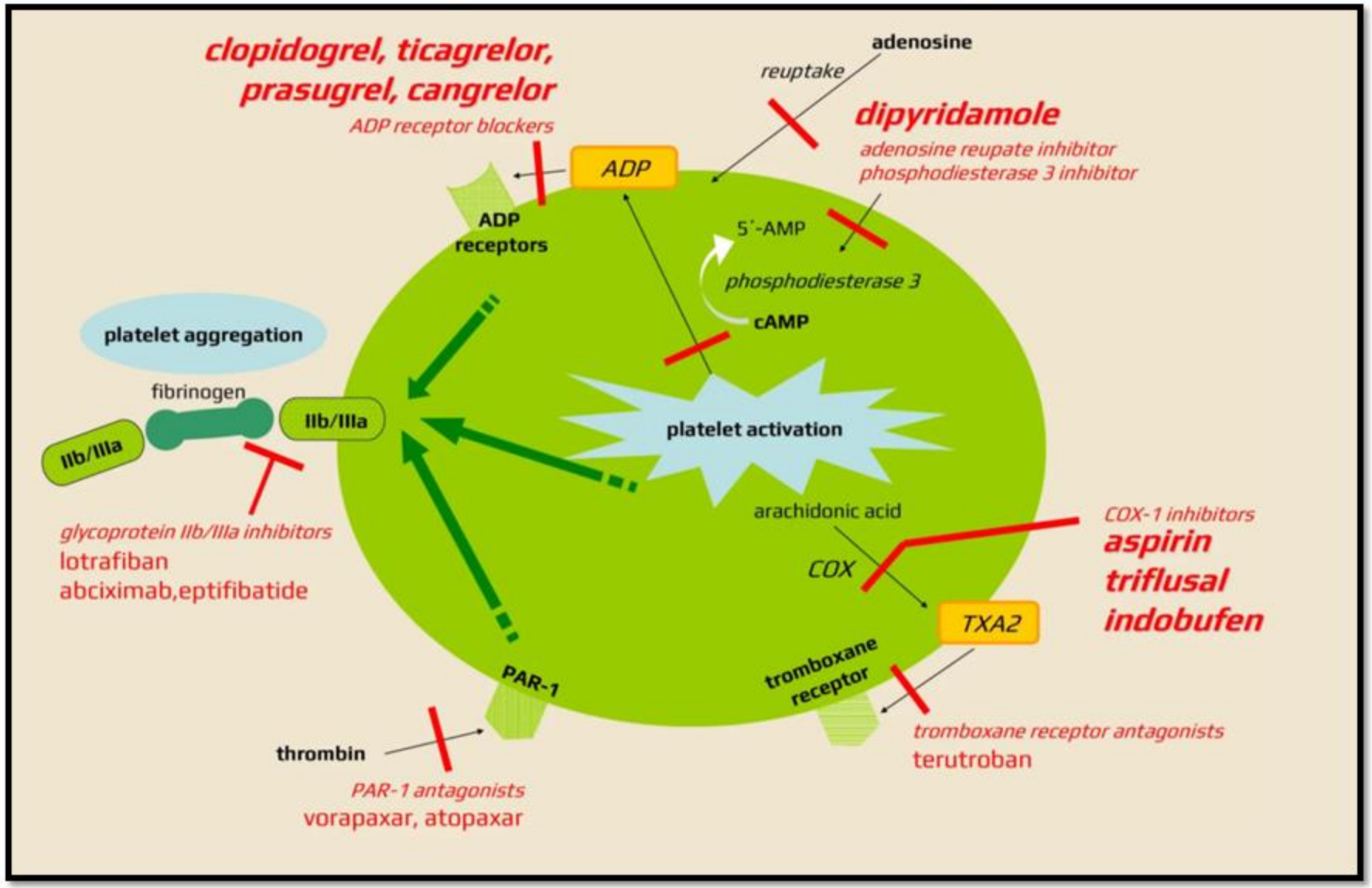


General adverse effects of antiplatelets

- **Excessive Bleeding**: The most significant risk, including prolonged bleeding from minor cuts, easy bruising (ecchymosis), nosebleeds (epistaxis), and heavy menstruation.
- **Gastrointestinal (GI) upset**: Stomach pain, nausea, heartburn, gastritis, and severe GI bleeding or ulcers.
- **Intracranial Hemorrhage**: less common than GI bleeding.

General contraindications of antiplatelets

- **Active Bleeding: Absolute contraindication** in patients with active gastrointestinal (GI) ulcers or intracranial hemorrhage.
- **Bleeding Disorders**: Hemophilia or significant thrombocytopenia.
- **Recent Trauma/Stroke**: High-risk patients with recent stroke (e.g., within 30 days) or major injury.
- **Hepatic/Renal Impairment**: specifically for certain P2Y12 inhibitors like ticagrelor.
- **Allergy/Asthma**: Known hypersensitivity to the drug or NSAID-induced asthma/urticaria.

Platelet aggregation inhibitors:1- Aspirin

Mechanism of antiplatelet effect of aspirin:

* **Thromboxane A_2 (platelet aggregating agent)**.
* The **low dose aspirin (75-150 mg, 81 mg) irreversibly inhibits thromboxane A2 synthesis** through **inactivation of platelet COX-1** resulting in: **suppression of platelet aggregation last for the life of the platelets "approximately 7 to 10 days" .**
* **The anti-platelet effect is cumulative with 'low dose' aspirin.**

Low Dose Aspirin - Major Uses: (prophylaxis)

- Secondary prevention of transient ischaemic attack (TIA), ischaemic stroke and myocardial infarction.
- Prevention of MI in patients with angina pectoris.
- Prevention of coronary artery bypass graft (CABG) occlusion.

1- Aspirin

Aspirin adverse effects

- **Risk of GI adverse events (ulceration and bleeding)**
- **Allergic reactions and intolerance in some asthmatics**
- **Lack of response in some patients (aspirin resistance).**
- **Advantages of aspirin:**
- **Although it is not very effective antithrombotic drug, it is widely used because of its ease of use, low cost and availability**

Precautions:

- **Aspirin must be stopped (7-14 days) before surgical operation to avoid bleeding.**
- **NSAIDs e.g., Ibuprofen,** if taken concomitantly with, or 2 hours prior to aspirin, can obstruct the access of aspirin COX 1 and antagonize the platelet inhibition by aspirin.
- Therefore, aspirin should be taken at least 30 minutes before other NSAIDs as ibuprofen or at least 8 hours after ibuprofen.
- **COX-2 inhibitors (Coxibs e.g., celecoxib) do not have antiplatelet effects** and may contribute to cardiovascular events by increasing activity of thromboxane A_2 (prothrombotic) i.e., the patients taking coxibs still need low-dose aspirin for cardiovascular protection.

Dose of Aspirin:

the dose 75-150 mg per day.

2- Ticlodipine, clopedogril

- **Adverse effects**

1. Prolonged bleeding for which there is no antidote.
2. Inhibition of cytochrome P450 (enzyme inhibitor)→ interfere with the metabolism of drugs such as phenytoin, tolbutamide, warfarin, and tamoxifen if taken concomitantly.
3. Serious hematological adverse effects "neutropenia, thrombocytopenia, and aplastic anemia) limit ticlopidine usefulness.

- **Indications:**

1- Prevention of coronary stent occlusion (usually combined with aspirin).

2- In combination with aspirin to prevent MI and stroke.

2- Ticlodipine, clopedogril

- **Clopidogrel is the preferred agent - Why?**
  - **Clopidogrel is more effective** in ischemic heart disease events.
  - **Clopidogrel is safer than** Ticlopidine due to haematological adverse effects of Ticlopidine " *neutropenia,* thrombocytopenia and aplastic anemia" although clopidogrel still causes thrombocytopenia**.**
  - **Food interferes with the absorption of ticlopidine** but not with clopidogrel.

New ADP antagonists:

- **Prasugrel: More rapid onset of action than clopidogrel**
- **Ticagrelor: reversible (contraindicated in renal and hepatic impairment)**

3- GP IIb/IIIa inhibitors

- **Mechanism of action:**
- **Glycoprotein IIb/IIIa is a platelet surface receptor for fibrinogen needed for platelet aggregation.**
- **Stimulation of GPIIb/IIIa receptors produces platelet aggregation while blocking of these receptors prevents platelet aggregation.**
- **Available only for intravenous administration.**
- **GP IIb/IIIa blockers:**

1. **Monoclonal antibody: abciximab**
2. **Peptide Antagonists :Eptifibatide**
3. **Non-peptide Antagonists Tirofiban**

4- Phosphodiesterase inhibitors

○ Dipyridamole

- **Coronary vasodilator with weak antiplatelet effect.**
- **Indications: in combination** with **aspirin** or **warfarin** in coronary ischemia (not used alone).
- **Mechanism of action:**
- Increases intracellular levels of cAMP by inhibiting phosphodiesterase (non-specific)→ ↓ thromboxane A_2 synthesis, decreasing cGMP (vasodilatation).
- **Cilostazol** is a phosphodiesterase 3 (PDE3) inhibitor that increases cAMP levels, leading to antiplatelet, vasodilation, and potentially protective vascular effects.
- **Indication**: orally to improve walking distance in patients with intermittent claudication (leg pain caused by poor circulation).

5- Protease-activated receptor-1 (PAR 1) antagonists

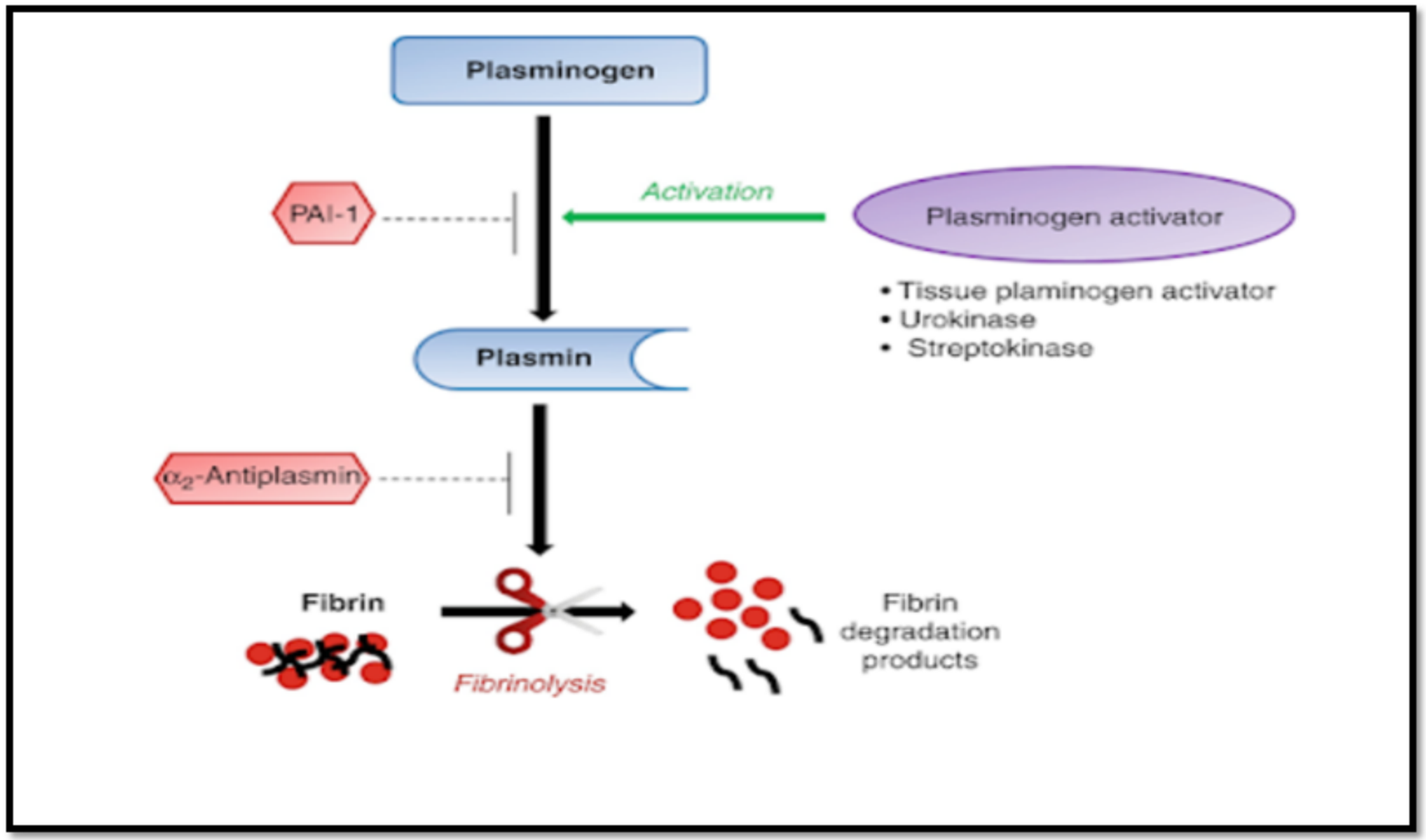
- **Mechanism of action:**
- Antiplatelet effect by inhibiting **thrombin-related platelet aggregation**.
- **Vorapaxar**: **oral** potent PAR 1antagonists
- **For prevention of MI in ischemic heart diseases**
- **The most significant adverse effect of vorapaxar** is an increased risk of bleeding,potentially intracranial hemorrhage
- **Contraindicated in** patients with a history of stroke or transient ischemic attack (TIA).
- **Other potential adverse effects include:**
- Pale skin
- Cool hands and feet

III- Thrombolytic Agents (Fibrinolytic) (Clot busters)

III- Thrombolytic Agents (Fibrinolytic)

- **Emergency medications** that dissolve dangerous blood clots by converting plasminogen to plasmin, which breaks down fibrin, restoring blood flow
- **Indications: administered IV only**
- Acute ischemic stroke
- Pulmonary embolism
- Acute myocardial infarction
- DVT
- **Contraindications**: Active bleeding, recent surgery, severe uncontrolled high blood pressure, or a history of stroke.
- **Adverse effects**: hypotension- allergy (antigenic)- bleeding tendency
- **Antidote: anti-firinolytic drugs**

Mechanism of action of thrombolytic agents (fibrinolytic)



Classification of thrombolytic drugs

Fibrin-Specific Agents (Second/Third Generation):

- **Activate plasminogen bound to fibrin within a clot.**
- **Alteplase (tPA):** Recombinant tissue-plasminogen activator identical to natural human tPA.
- **Reteplase (r-PA):**
- Faster action and longer duration, improved fibrin penetration.
- **Tenecteplase (TNK-tPA):**
- Highly fibrin-specific with a longer half-life, allowing for bolus administration.

Non-Fibrin-Specific Agents (First Generation)

- **Activate plasminogen systemically, causing increased systemic fibrinolysis with a higher risk of bleeding**
- **Streptokinase:** Extracted from Streptococcus B; not widely used due to antigenicity and lower clot selectivity.
- Relatively inexpensive to other thrombolytics
- **Urokinase:**
- Extracted from human urine
- used for peripheral vascular clots and catheter clearance.

Thrombolytic Agents (Fibrinolytic)

❑ Urokinase:

- **The same action of streptokinase but differs in:**
  - **Originally isolated from human urine**
  - **More expensive than streptokinase.**
  - **Non allergic (Non-immunogenic).**
  - **Lower recurrence rate of thrombosis.**

❑ Fibrin-Specific Agents

- **Newly advanced agents & fibrin specific.**
- **Include:**
  - **Alteplase:** short-acting: IV infusion
  - **Reteplase: Rapid with longer duration:** IV bolus injection, 2 doses: 30 min. apart
  - **Tenecteplase: The fastest lytic IV bolus injection used in MI, single dose**
- **Both Reteplase and Tenecteplase are:**
  - Longer half-lives than alteplase.

* **All drugs are similar in efficacy & safety.**

* **They are very expensive.**

Clinical Indications & contraindications of Thrombolytics

1. **Acute myocardial infarction (acute MI):**
   - **within 6-12 h of starting infarction.**
   - **Best results if intervention within 1-1.5 H**
   - **The use of small dose of aspirin (75-150 mg) with thrombolytics improves their efficacy.**
   - **Angioplasty with or without stent placement is superior to thrombolytic therapy: (PCI) percutaneous coronary intervention.**
   - **The shorter the door-to- needle time (DNT), the better the prognosis**
2. **Acute Pulmonary embolism:**
   - **Thrombolytics improves pulmonary embolism if used within the first 24 h of embolism.**
3. **Acute arterial thrombosis**
4. **Acute deep vein thrombosis**
5. **Acute ischemic stroke (not haemorrhagic).**

- **Contraindications of thrombolytic drugs**

- **Internal bleeding: active bleeding in brain, eye,…**
- **Hemorrhagic Stroke or history within 3 months**
- **Uncontrolled hypertension**
- **Surgery or trauma within the past 2 months**
- **Aortic dissection:** breaks down blood clots that are sealing the damaged aorta, leading to **fatal aortic rupture**

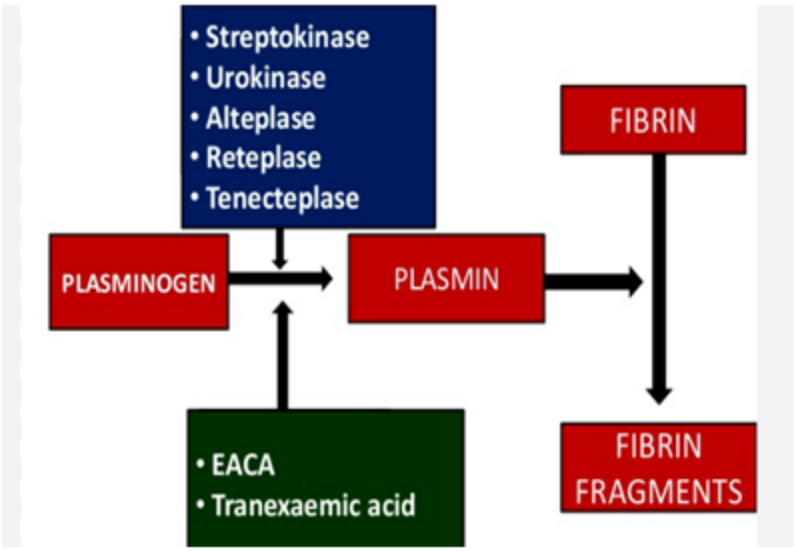
Anti-fibrinolytic drugs

Anti-fibrinolytic drugs

- **Drugs that prevent the breakdown of blood clots (fibrinolysis) by inhibiting the enzyme plasmin, thereby reducing bleeding**

- **Mechanism of action:**
- Competitive blocking of plasminogen activation by covering and protecting plasminogen: inhibiting activation of plasminogen to plasmin, thereby stopping the breakdown of fibrin and preserving the fibrin meshwork.
- **Aminocaproic acid (Oral and IV) and tranexamic acid (IV) : inhibit fibrinolysis.**

- **Indications:**
- **1- Stop bleeding induced by fibrinolytic drugs: antidote**
- **2- Prevent bleeding in tissues rich in plasminogen:**
- **After lung and prostate surgery**
- **Menorrhagia:** heavy menstruation
- **Ocular trauma**



Contraindications of antifibrynolytic drugs

- **Active Thromboembolic Disease**: Active deep vein thrombosis (DVT), pulmonary embolism (PE), cerebral thrombosis, or acute myocardial infarction.
- **Active Intravascular Clotting**: Conditions such as Disseminated Intravascular Coagulation (DIC), unless the fibrinolytic process is the primary cause and the patient is receiving heparin.
- **Subarachnoid Hemorrhage**: Use is generally avoided due to risks of cerebral edema and infarction.
- **Hypersensitivity** to the drug
- **Macroscopic Hematuria**: Active bleeding from the upper urinary due to the risk of ureteric obstruction by clots.
- **Concomitant Use of Combination Hormonal Contraceptives**: Due to increased risk of thrombotic events.

Classification of anti-fibrinolytic drugs

Lysine Analogues (Synthetic)

- Synthetic derivatives of the amino acid lysine.
- **Act by:** binding to lysine sites on plasminogen, preventing its activation into plasmin
- **Tranexamic Acid (TXA):** A highly potent antifibrinolytic
- **Aminocaproic Acid**: Similar in action to TXA, but less potent.

Serine-derivatives

- Broad-spectrum inhibitors that directly inhibit the action of plasmin.
- **Aprotinin**: A naturally occurring compound (originally derived from bovine tissue)
- Its systemic use is heavily restricted or banned in many areas due to its nephrotoxic and cardiotoxic effects

Drugs used in bleeding disorders

Drugs used in bleeding disorders

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

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

2- Factor Replacement Therapies (Hemophilia A & B):

- **These replace the missing clotting factor (Factor VIII for A, Factor IX for B).**
- **They can be plasma-derived or recombinant (lab-made).**

3- Monoclonal Antibodies/Bypassing Agents (Hemophilia A):

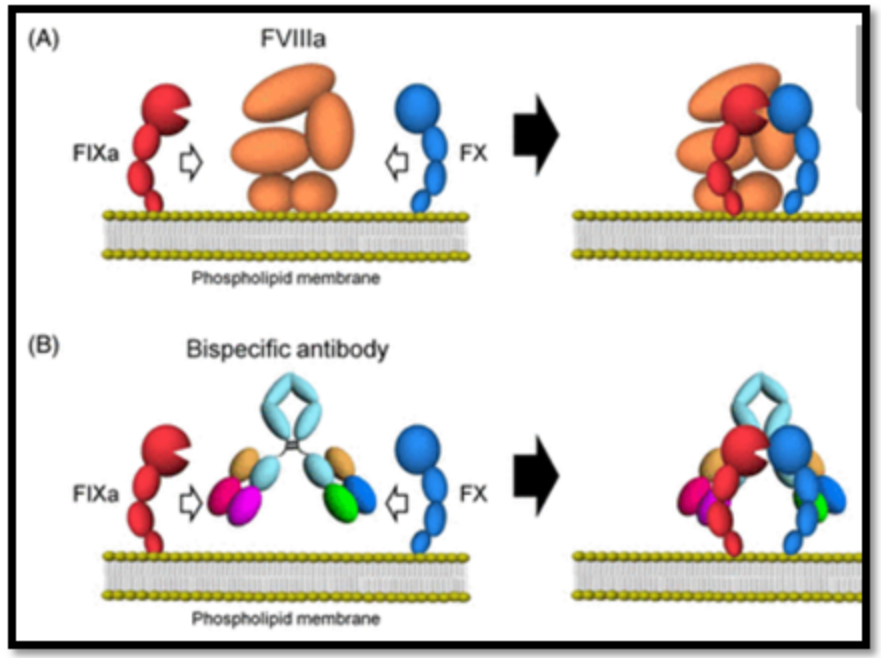
- **Emicizumab**: A bispecific antibody that mimics Factor VIII, bridging Factors IX and X to allow blood to clot.
- **Recombinant Factor VIIa**
- **Plasma-derived**

4- Antifibrinolytics (Clot Stabilizers)

5- Desmopressin:

A synthetic hormone that releases stored Factor VIII, used for mild hemophilia A and von Willebrand disease (vWD)

Mechanism of action of emicizumab



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Thank you