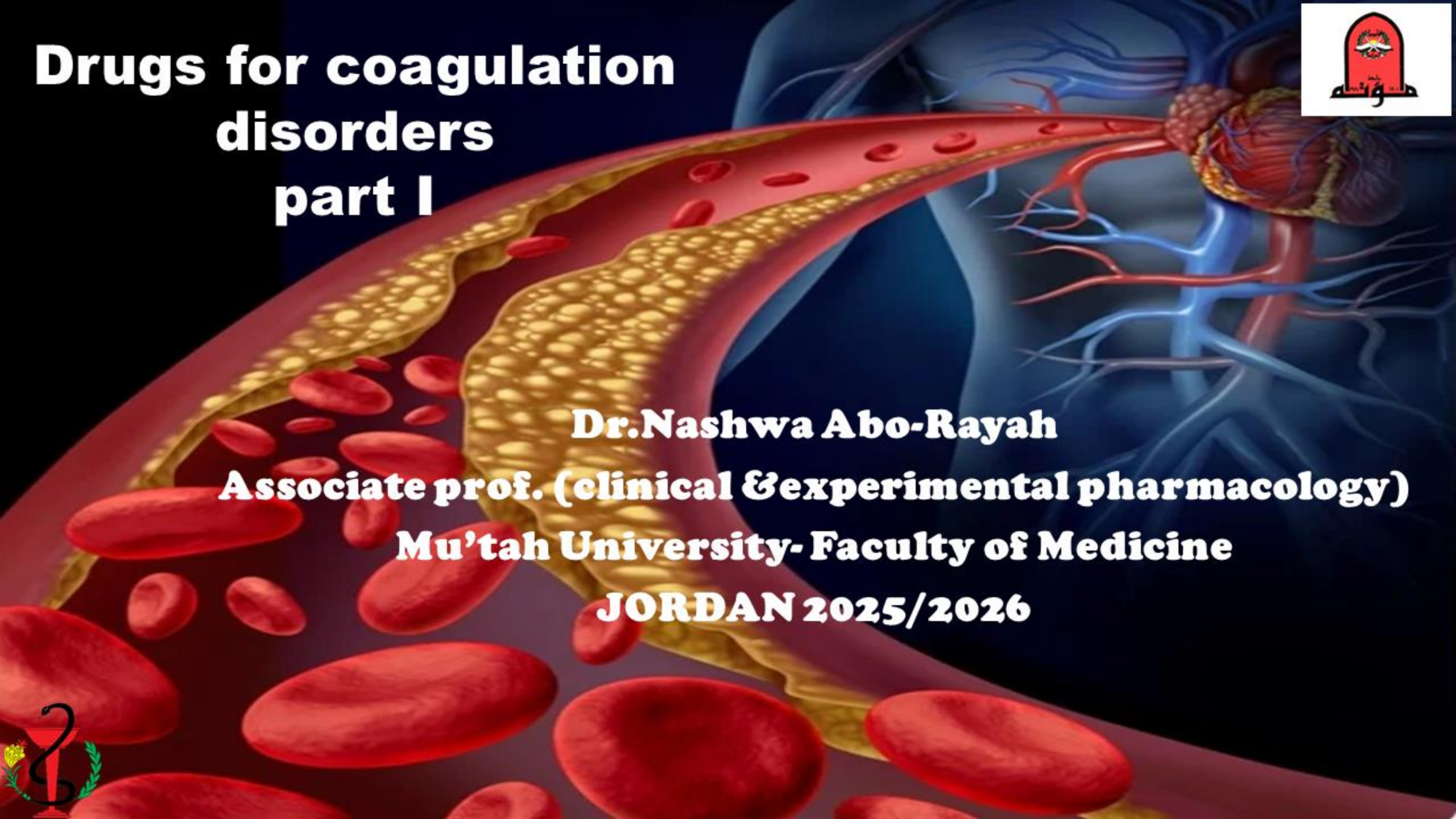
Drugs for coagulation disorders part I



Dr.Nashwa Abo-Rayah

Associate prof. (clinical &experimental pharmacology)

Mu'tah University- Faculty of Medicine

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Objectives

- Coagulation disorders
- Coagulation cascade
- What are blood thinners?
- Classification of anticoagulant drugs
- Indications & contraindications of anticoagulant therapy
- Indirect thrombin inhibitors
- Oral anticoagulants: Warfarin sodium (Dendivan or marivan)
- Direct Oral Anticoagulants (DOACs)
- Newer Parenteral Anticoagulants (Thrombin inhibitors)

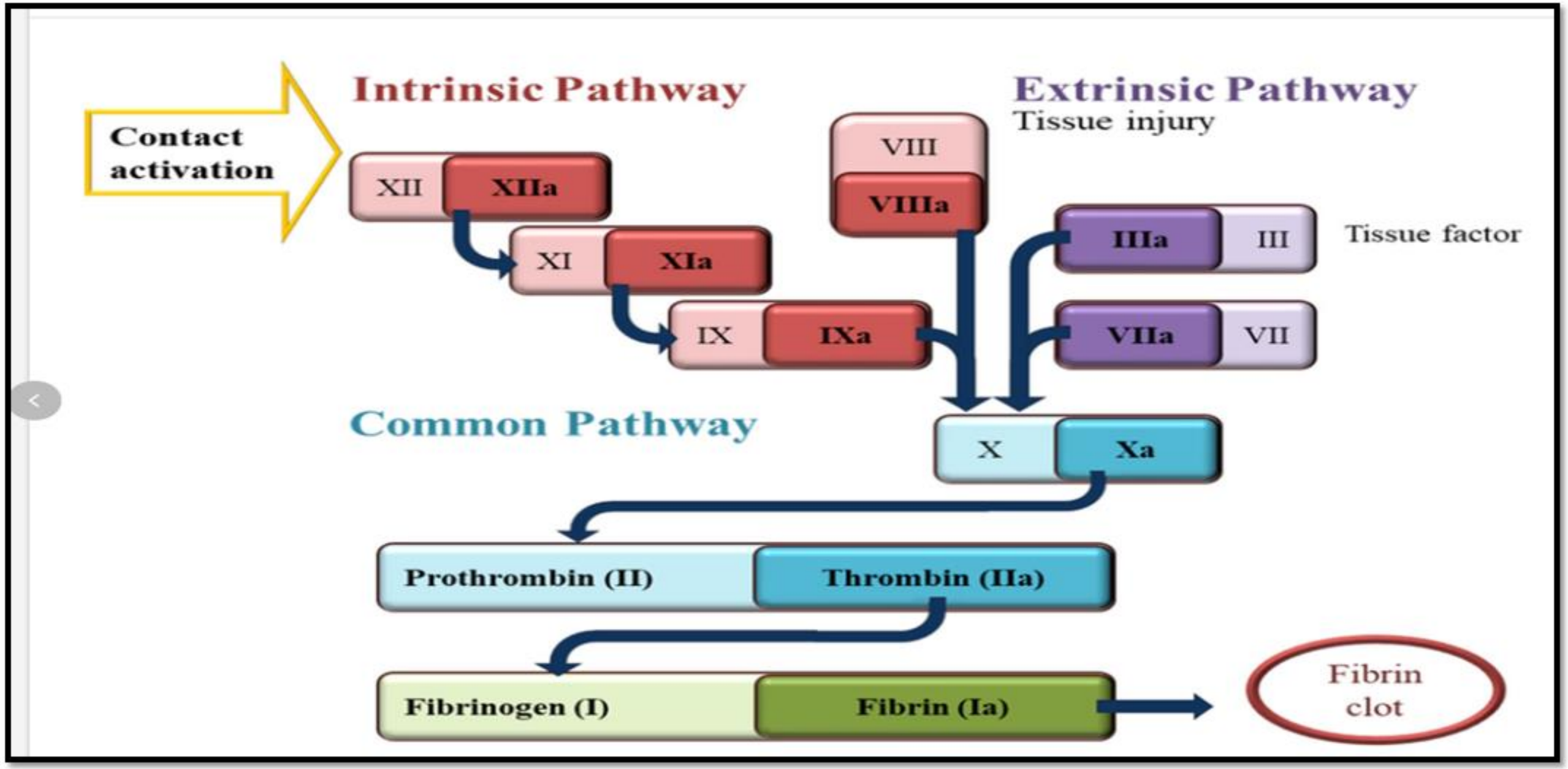
Coagulation disorders

- Coagulations disorders are **conditions that affect the blood's clotting activities.**
- **Increased coagulability**: DVT, stroke, MI, pulmonary emboli, DIC, Estrogen therapy,……
- **Bleeding disorders**: when the blood lacks certain clotting factors
- Hemophilia
- Vitamin K diffeciency
- Von Willebrand disease

Thrombosis (increased coagulation)

- **Thrombi & emboli are the most common & serious abnormalities of blood disorders.**
  - ***Thrombosis*: formation of an unwanted clot within a blood vessel.**
  - ***A thrombus*: A clot that adheres to a vessel wall.**
  - ***Embolus*: is an intravascular clot that floats in the blood i.e., a detached thrombus.**
- **<u>Both thrombi and emboli are dangerous, because they may block blood vessels and deprive tissues of oxygen and nutrients.</u>**

Pathway of blood coagulation: coagulation cascade (secondary hemostasis)



Blood thinners

- **Drugs which stop blood coagulation or clotting**
- **Including:**
- **Anticoagulants**: interfering with clotting factors to lengthen the time it takes to form a blood clot
- **Anti-platelet drugs**: prevent platelets from clumping together to form a clot.
- **Both types of drugs are effective** in keeping a clot from forming or stopping the growth of a clot.
- **Anticoagulants are considered more aggressive** drugs than antiplatelet drugs.
- Anticoagulants are recommended primarily for cases with a high risk of stroke, atrial fibrillation, DVT and pulmonary embolism
- Antiplatelet primarily used to prevent arterial thrombosis, such as in patients with coronary artery disease.

Anticoagulants

Oral anticoagulants

- **1-Vitamin K antagonists:**
- Warfarin: stop the production of vitamin K-dependent clotting factors
- **2- Direct Oral Anticoagulants (DOACs) (NOACs: Newer oral anticoagulants):**
- **A. Direct thrombin inhibitors** : e.g. Dabigatran
- **B. Direct factor Xa inhibitors**: e.g., Betrixaban, rivaroxaban

Parenteral (injectable)

- **1- Indirect thrombin inhibitors:**
- **A. Heparins (unfractionated heparin 'UFH' & Low molecular weight heparin "LMW"): enoxaparin** :
- **B. Synthetic pentasaccharide**: e.g., **fondaparinux.**
- **2- Newer parenteral direct thrombin inhibitors (DTIs)**
- **Rudin-endig +argatroban**

Indications of anticoagulant therapy

- **1- Atrial Fibrillation (AF):** To reduce the risk of stroke in patients with non-valvular or valvular AF.
- **2- Venous Thromboembolism (VTE):** Treatment and prevention of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE).
- **3- Prosthetic Heart Valves**: Essential for preventing clotting on mechanical heart valves.
- **4- Acute Coronary Syndromes (ACS):** Used in myocardial infarction to prevent clot propagation.
- **5- Hypercoagulable States**: Patients with conditions like antiphospholipid syndrome.
- **6- Prophylaxis**: In hospitalized patients with acute medical illnesses or undergoing high-risk orthopedic surgeries (e.g., hip/knee replacement).
- **7- Left Ventricular (LV) Thrombus**: Following a major myocardial infarction.

Contra-indications to anticoagulant therapy

- **Active bleeding**
- **Previous bleeding**: Gastro-intestinal bleed during previous 2 weeks
- Intracranial bleed during previous 3 months
- Head injury in the previous 3 months
- **Acute stroke**
- **Pericarditis or acute bacterial endocarditis**
- **Uncontrolled systolic hypertension** > 200mmHg
- **Previous surgery or procedures:**
- Neurosurgery or spinal surgery in the previous 3 months
- Intra-ocular disease or eye surgery in the previous 3 months
- Lumbar puncture, epidural or spinal analgesia during previous 24 hours
- Recent surgery or organ biopsy with high risk of bleeding (e.g. liver biopsy): wait for 2 weeks
- **Untreated inherited bleeding disorders,** e.g. haemophilia
- **Thrombocytopenia**
- **Previous heparin-induced thrombocytopenia (for heparins only)**
- **Drug hypersensitivity**

1- Indirect thrombin inhibitors

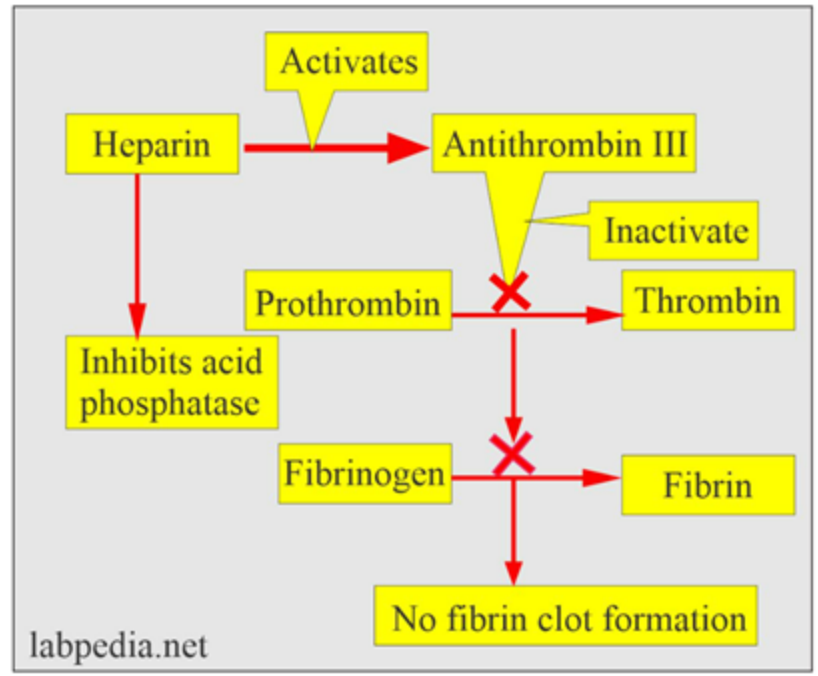
A) Unfractionated Heparin (UFH) (Heparin) :

- **Pharmacokinetics of Heparin:**

* Due to highly negative charge (ionized) of heparin and its large molecular size, **it is not given orally. It is given parenterally**
* **I.V.** →immediate onset of action (5 hours duration): indicated in emergency: **in hospital**
* **Deep S.C.** → delayed onset (1-2h): indicated for long-term maintenance: at home:
* Choose a different site for each injection, such as the abdominal fat layer at least 2 inches away from the umbilicus.
* Do Not Rub: Do not rub the injection site after administering, as this can increase the risk of bruising.
* **I.M. injection must be avoided (cause painful hematomas).**
* **Half life:** 1-1.5 hours (short acting)
* **NOT Passing BBB and placenta**
* **Elimination: liver and kidney**

Mechanism of action of heparin

- **Heparin**, **LMWHs**, and **fondaparinux** have **no intrinsic anticoagulant activity**.
- These agents **bind to antithrombin-III (protease)**: naturally occurring inhibitor of clotting factors: **2**, 9,**10**, 11, 12.
- **Heparin inhibits both thrombin and factor Xa equally.**
- **Factor Xa inhibition is more specific than thrombin inhibition**.
- **Fondaparinux**: **has only antifactor Xa activity**



Heparin mode of action

Monitoring of heparin anticoagulant Therapy

- Monitoring of **aPTT (activated partial thromboplastin time)** is necessary in case of heparin administration either S.C. or I.V. (Very important in I.V.).
- **Therapeutic goal:** aPTT should be **1.5-2.5 times normal** control value.
- Normal aPTT: 30-40 sec.
- aPTT in heparin therapy: 60-100 sec.

Adverse Effects of Unfractionated Heparin

1. **Bleeding:**

- **Dose-dependent & dosage adjustment based on aPTT monitoring reduces the incidence of bleeding.**

- **Protamine sulfate** (a mixture of basic **(positively charged)** polypeptides isolated from salmon sperm) is used to overcome bleeding because it binds tightly **(electrostatic bond)** to heparin and neutralizes its anticoagulant effect.

- **Dose** : (1 mg protamine/100 units heparin) required to neutralize the heparin present in the plasma.

N.B. Protamine binds only long heparin molecules. Therefore, protamine **only partially** reverses the anticoagulant activity of LMWHs and **has no effect on that of fondaparinux**.

Adverse Effects of Unfractionated Heparin

2. **Heparin-Induced Thrombocytopenia (HIT- immune-based reactions):**

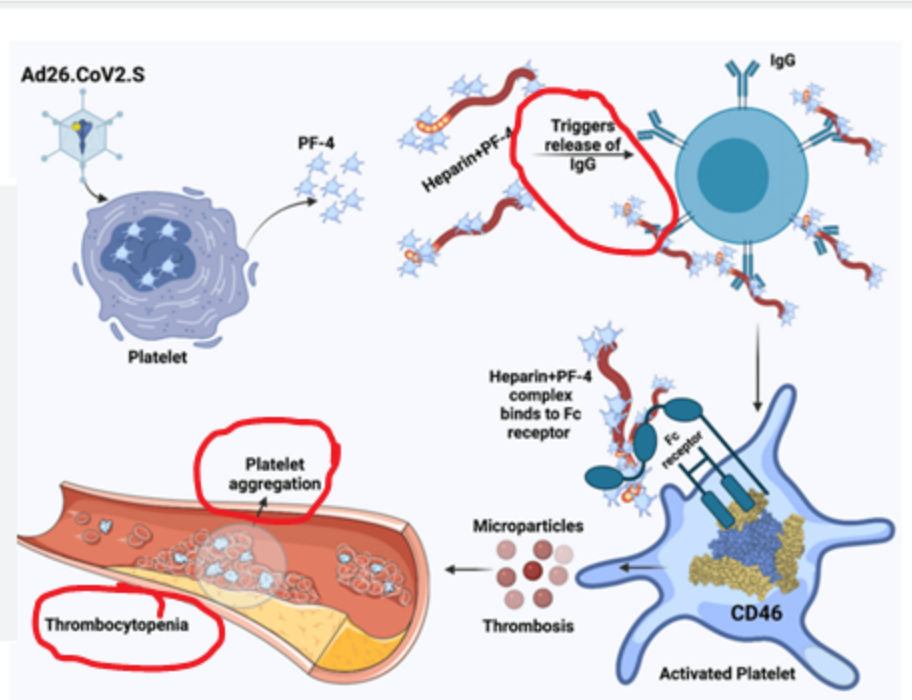
- **in about 0.5 % of patients after 5 days of starting drug therapy.**
- **<u>Management</u>: heparin must be stopped, and the patient must be given alternative anticoagulant.**

3. Osteoporosis

4. Alopecia

5. Hypersensitivity

6. Muscle hematoma if given IM



B) Low Molecular Weight Heparins (LMWH)

- **Enoxaparin (Clexane)**
- **Fragments of unfractionated heparin which composed of shorter polysaccharide chains with average MW about 5000 d.**
- **Affect only factor Xa: less risk for thrombocytopenia and less osteoporosis**
- **Longer duration of action: 24 H: single daily dose: at home**

Pharmacological properties of (LMWH)

Enoxaparin (Clexan; S.C.): they differ from heparin in:

1. They are **fragments** of unfractionated heparin with **low molecular weight**.
2. Promote inhibition of **factor Xa** by antithrombin with little effect on thrombin.
3. Have **longer t½** , so they are used S.C. once / day.
4. They have **high bioavailability and predictable anticoagulant effect**, so no need for routine lab monitoring or dose adjustment.
5. They have **lesser side effects** as thrombocytopenia, osteoporosis and bleeding.
6. Their effect is **incompletely** neutralized by protamine sulphate.
7. They are **monitored by antifactor Xa activity** but not by aPTT.

2- Oral anticoagulants
Warfarin sodium (Dendivan or marivan ®)

* **Prototype of cumarine anticoagulants (synthetic)** and **effective only in vivo**.

Mechanism of action:

* **Vit K antagonist** : **inhibits the enzyme Vit k epoxide reductase** which is responsible for the production and activation of vitamin k-dependent coagulation factors (II, VII, IX, and X) by the liver.
* Slow onset of action because its effect is dependent on the $t_{1/2}$ of these factors (from 5-100 hours).
* So,
* **(heparin + warfarin)** must be given for first 4-5 days followed by warfarin alone.

Pharmacokinetics of Warfarin:

* **Taken only orally:**
* No more benefits from parenteral administration. Its oral bioavailability is very high.
* **Plasma Protein Binding:** about 99%.
* **Metabolized into:** inactive metabolites by the liver.
* **$t_{1/2}$ = 40 hours & duration of action = 2-5 days.**
* **Enterohepatic circulation:** long half-life.
* **Inactive metabolites:** excreted by the kidneys.

Administration of warfarin:

- **It is given orally.**
- **Dosage adjustment based on prothrombin time (PT) (INR: International Normalized Ratio) monitoring: should be twice the control (2.0 to 3.0)**
- **Normal: (INR= 0.8 to 1.1).**

Factors affecting warfarin activity

* **Factors that decrease warfarin effectiveness:**
* **Cholestyramine** inhibits warfarin absorption.
* **Genetic resistance to vit K epoxide reductase**.
* **Factors that increase warfarin effectiveness:**
* ↓ **vit k** due to damage of intestinal flora by **broad spectrum antimicrobial agents.**
* ↑ **displacement of warfarin from plasma protein binding by NSAIDs**.
* ↓ metabolism of warfarin by **enzyme inhibitors** (metronidazole, cimetidine, allopurinol, amiodarone and acute alcohol intake

Adverse effects and toxicity of warfarin:

1. **Bleeding: antidote:** **by vitamin K1.: 3-5 mg IV**
2. **Warfarin-induced skin necrosis (WISN):** is a rare, serious complication (1 in 10,000) occurring 3–6 days after starting warfarin, characterized by painful, purpuric skin lesions, It is primarily caused by a rapid drop in protein C, creating a transient hypercoagulable
3. **Abortion, birth defects and intrauterine fetal death, CNS hemorrhage. Therefore, it must be avoided during pregnancy. (teratogenic): fetal warfarin syndrome**
4. **Osteoporosis.**
5. **Sudden withdrawal:** rebound synthesis vitamin K- dependent clotting factors: thrombosis

WISN

Fetal warfarin syndrome

3. Direct Oral Anticoagulants (DOACs) (NOACs)

- Newer anticoagulants that directly inhibit specific clotting factors (IIa or Xa)
- **Advantages:**
- No Routine Monitoring: Fixed daily doses remove the need for regular International Normalized Ratio (INR) testing.
- Rapid Onset/Offset: Action starts and stops quickly, improving management during surgery.
- Fewer Interactions: Fewer restrictions on diet and fewer drug interactions.
- **Classification:**
- **Factor Xa Inhibitors**: Apixaban , Rivaroxaban.
- **Direct Thrombin Inhibitor**: Dabigatran.

3. Direct Oral Anticoagulants (DOACs)

- **Disadvantages:**
- Bleeding: The most common side effect is bleeding, including easy bruising or nosebleeds.
- Adherence: Shorter half-lives make it crucial to take doses consistently to avoid clot risks.
- Renal Function: Dosing often requires adjustment based on kidney function.
- Cost: Generally more expensive than warfarin.

3. Direct Oral Anticoagulants (DOACs)

1. Dabigatran: Direct thrombin inhibitors

- It is **prodrug** and approved for **stroke prevention in patients with atrial fibrillation**.
- ***Direct thrombin inhibitor*** **with high affinity and specificity.**
- **Half-life: 12–14 hours**
- It produces **predictable anticoagulant** response and so routine coagulation monitoring is unnecessary.
- **It is more safe and more effective than warfarin.**
- **Dabigatran antidote is recently available (idarucizumab)**

2. Betrixaban:

*** Direct factor Xa inhibitor**

*** Safe and well tolerated.**

- **It is The only [anticoagulant] that is not cleared by the kidneys and so no dose adjustment in renal impairment.**

4- Newer Parenteral Anticoagulants (DTIs)

1. **Lepirudin:** is a **direct thrombin inhibitor** and approved **I.V. for treatment of patients with heparin-induced thrombocytopenia.** There is **no antidote** for lepirudin.
2. **Bivalirudin :** administered **I.V.** and is used as an **alternative to heparin in patients undergoing coronary angioplasty or cardiopulmonary bypass surgery**.
3. **Argatroban:** an intravenous direct thrombin inhibitor used as an anticoagulant to treat or prevent blood clots in patients with heparin-induced thrombocytopenia (HIT) or those at risk for HIT undergoing percutaneous coronary intervention (PCI)

- Its small molecular weight make it suitable for patients with renal impairment

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Thank you