Overview of Anticoagulants

Lec 3 Pt 1

1. Traditional Anticoagulants

- Warfarin
  - Associated with numerous complications.
  - Common cause of hospitalization due to adverse effects.
- Heparin
  - Unfractionated heparin (UFH) is administered IV.
  - Used in DVT, pulmonary embolism (PE), and post-hip/knee replacement surgery

2. New Oral Anticoagulants (NOACs)

- Introduced after 2004.
- Classified into:
  1. Direct thrombin (factor IIa) inhibitors → Dabigatran.
  2. Factor Xa inhibitors → Rivaroxaban, Apixaban.

Dabigatran

Mechanism of Action (MOA)

- Direct thrombin inhibitor.
- Blocks:
  - Free and fibrin-bound thrombin.
  - Conversion of fibrinogen to fibrin.
  - Thrombin-induced platelet aggregation.

Pharmacokinetics & Monitoring

- Administered orally in a homogeneous formulation.
- Predictable anticoagulant effect → routine monitoring usually unnecessary.
- aPTT can be checked if bleeding occurs.
- Onset of action: ~1 hour.
- No need for bridging therapy.
- Less risk of transient thrombosis during initiation (unlike warfarin).
- Bleeding incidence: comparable to warfarin; higher risk of GI bleeding and dyspepsia.

Drug–Drug Interactions

- Fewer interactions than warfarin.
- P-glycoprotein (P-Gp) substrate:
  - P-Gp inducers → decrease dabigatran absorption → risk of thrombosis.
  - P-Gp inhibitors → increase absorption → risk of bleeding.
- Narrow therapeutic index → careful monitoring required when combined with P-Gp modulators.

Gastrointestinal Effects

- Dabigatran contains tartaric acid → ensures acidic environment for absorption.
- Can cause GI discomfort, esophagitis (~20%), and contribute to GI bleeding.

Reversal

- Specific antidote: Idarucizumab (monoclonal antibody fragment).

Contraindications

- Mechanical heart valves:
  - Dabigatran associated with increased thromboembolic events and major bleeding.
  - Warfarin or heparin preferred.

Factor Xa Inhibitors

(Rivaroxaban, Apixaban)

Uses

- Atrial fibrillation.
- DVT treatment and prevention.
- Post-stroke prevention.
- Prophylaxis after hip/knee replacement.

Bleeding & Safety

- Bleeding risk comparable to warfarin.
- Contraindicated in mechanical heart valves.
- Surgical considerations:
  - Avoid spinal anesthesia even after stopping drug → risk of spinal hematoma → potential permanent paralysis.

Drug Interactions

- Rivaroxaban: contraindicated with CYP3A4 and P-Gp inhibitors (metabolized by CYP3A4, expelled by P-Gp).
- Antidote: Andexanet

Heparin-Induced Thrombocytopenia (HIT)

- Acute HIT → widespread thrombosis → urgent anticoagulation required.
- Do NOT use:
  - Warfarin (first 2 days can worsen clotting).
    - Low-molecular-weight heparin (LMWH) if on UFH.
- Preferred anticoagulants:
  - IV, non-heparin options (e.g., fondaparinux – note: actually inhibits factor Xa).
  - Oral NOACs (dabigatran, rivaroxaban, apixaban) can be used but delayed onset may be insufficient in life-threatening cases.

Lec 3 Pt-2

Thrombolytics (Fibrinolytics)

1. Definition and General Concept

- Thrombolytic (fibrinolytic) agents are drugs that rapidly dissolve blood clots (thrombi).
- They act by converting plasminogen → plasmin, an active enzyme that breaks down fibrin, the main structural component of a clot.
- This process, known as fibrinolysis, dissolves the clot and restores normal blood flow.

2. Administration and Timing

- Thrombolytic therapy must be given early, depending on the condition:
  - In ischemic stroke, must be given within 6 hours of symptom onset.
  - In myocardial infarction (MI), the therapeutic window is longer.
- The earlier the drug is administered, the better the outcome.

3. Classification

There are three main classes of thrombolytic agents:

1. Streptokinase
2. Urokinase
3. tPA (tissue plasminogen activators) → includes
   - Alteplase, Tenecteplase, and Reteplase

Intravenous (IV) use:

Used to **dissolve serious blood clots** in major conditions such as:

1. **Multiple pulmonary emboli**
   → Clots blocking arteries in the lungs.
2. **Central deep vein thrombosis (DVT)**
   → e.g., **superior vena cava syndrome** or **ascending thrombophlebitis** of large leg veins (iliofemoral).
3. **Acute myocardial infarction (MI)**
   → To restore blood flow to the heart.
4. **Acute ischemic stroke**
   → Use **tPA within 3 hours** of symptom onset to reopen blocked brain arteries.

- Intra-arterially for:

-Peripheral vascular disease

4. Overview of Each Class

(1) Streptokinase

- An older drug.
- Produced by streptococcal bacteria → foreign protein (antigenic).
- Forms a complex with plasminogen → this complex converts another plasminogen molecule to plasmin.
- Because it's antigenic:
  - It can cause hypersensitivity reactions (fever, allergy).
  - It may be neutralized by antibodies in people previously infected with streptococci → ineffective.
- Causes systemic fibrinolysis (non–fibrin-selective) → high bleeding risk.

(2) Anistreplase (APSAC)

- A combination of streptokinase + plasminogen, acetylated to protect it temporarily.
- When injected, it becomes active and converts plasminogen → plasmin.
- Also antigenic (contains streptokinase).
- Non–fibrin-specific → higher risk of systemic bleeding.

(3) Urokinase

- A human enzyme, synthesized by the kidney, originally obtained from human urine.
- Directly converts plasminogen → plasmin (does not form a complex like streptokinase).
- Non-antigenic (safe in patients allergic to streptokinase).
- Non–fibrin-specific, so it also increases the risk of systemic fibrinolysis and bleeding.

(4) tPA (Tissue Plasminogen Activator) Family

tPA is a natural enzyme produced in the human body.

4-t-PA: an endogenous direct activator of plasminogen. It preferentially activates plasminogen that is bound to fibrin. This, in theory, confines fibrinolysis to formed thrombi

It can be manufactured using recombinant DNA technology and modified to improve its properties.

Members of this group:

1. Alteplase → recombinant (synthetic) tPA
2. Reteplase → genetically modified tPA (less fibrin-specific, cheaper, longer half-life)
3. Tenecteplase → genetically modified tPA with longest half-life and highest fibrin selectivity

5. Mechanism of Action (Step-by-Step)

1. Normal clot formation:
   - Fibrinogen (soluble) → converted to fibrin (insoluble) → forms a mesh (structure: D–E–D regions).
   - Factor XIIIa cross-links fibrin molecules → stable clot.
1. Drug action:
   - Thrombolytics convert plasminogen → plasmin.
   - Plasmin breaks down fibrin into fibrin degradation products and D-dimers.
1. Clinical marker:
   - D-dimer = a fragment containing two cross-linked D domains.
   - Used as a biomarker for clot formation and breakdown (e.g., in COVID-19).

9. Adverse Effects

1 Bleeding (Main Side Effect):

- Because thrombolytics break down both pathologic clots and normal hemostatic plugs.
- Degradation of circulating fibrinogen also contribute
- Risk ↑ with non–fibrin-specific drugs.

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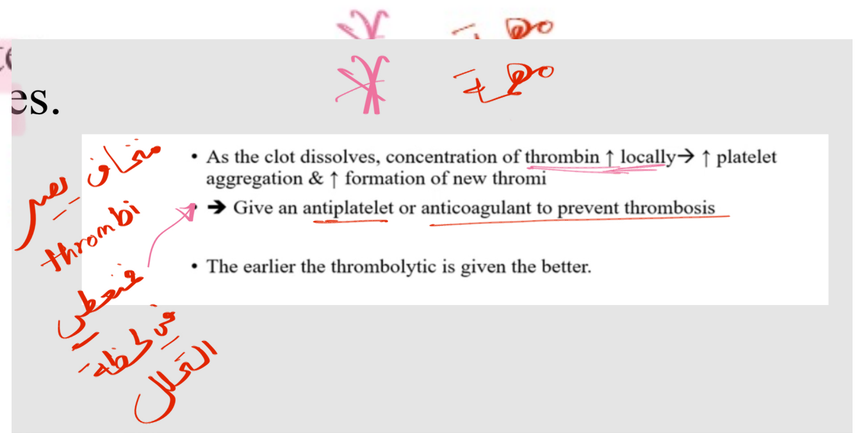

1 Reperfusion Arrhythmia:

- Occurs after coronary thrombus dissolution (MI treatment).
- Sudden restoration of blood flow → oxygen surge → disrupts ion balance → arrhythmias.

1 Hypotension:

- Monitor blood pressure during therapy.

1 Hypersensitivity (especially with Streptokinase & Anistreplase):

- Streptokinase is antigenic because it's a bacterial protein.
- People previously infected with streptococci may have antibodies that:
  - Cause fever, allergic reactions, or
  - Neutralize the drug (failure of therapy).
- Urokinase is non-antigenic → safe alternative for these patients.