Anticoagulant Drugs

Dr. Vafa Baradaran Rahimi

Pharm.D., Ph.D. of Clinical Pharmacology

Assistant Professor; Department of Cardiovascular Diseases, Faculty of Medicine, Mashhad University of Medical Sciences

ANTICOAGULANT DRUGS

1- Parenteral Anticoagulants

Heparin (Unfractionated Heparin)

Low molecular weight Heparin

(LMWH)

Fondaparinux

2- Other Parenteral Anticoagulants

Desirudin, Lepirudin

Bivalirudin, Argatroban

3- Vitamin K Antagonist

Warfarin

4- Direct Oral Anticoagulants

4-1- Direct Oral Thrombin Inhibitor

Dabigatran

4-2- Direct Oral Factor Xa Inhibitors

Rivaroxaban, Apixaban, and Edoxban

Parenteral Anticoagulants

1- Heparin (Unfractionated Heparin)

2- Low molecular weight Heparin (LMWH)

3- Fondaparinux

Mechanism of action:

Bind to anti-thrombin (AT)

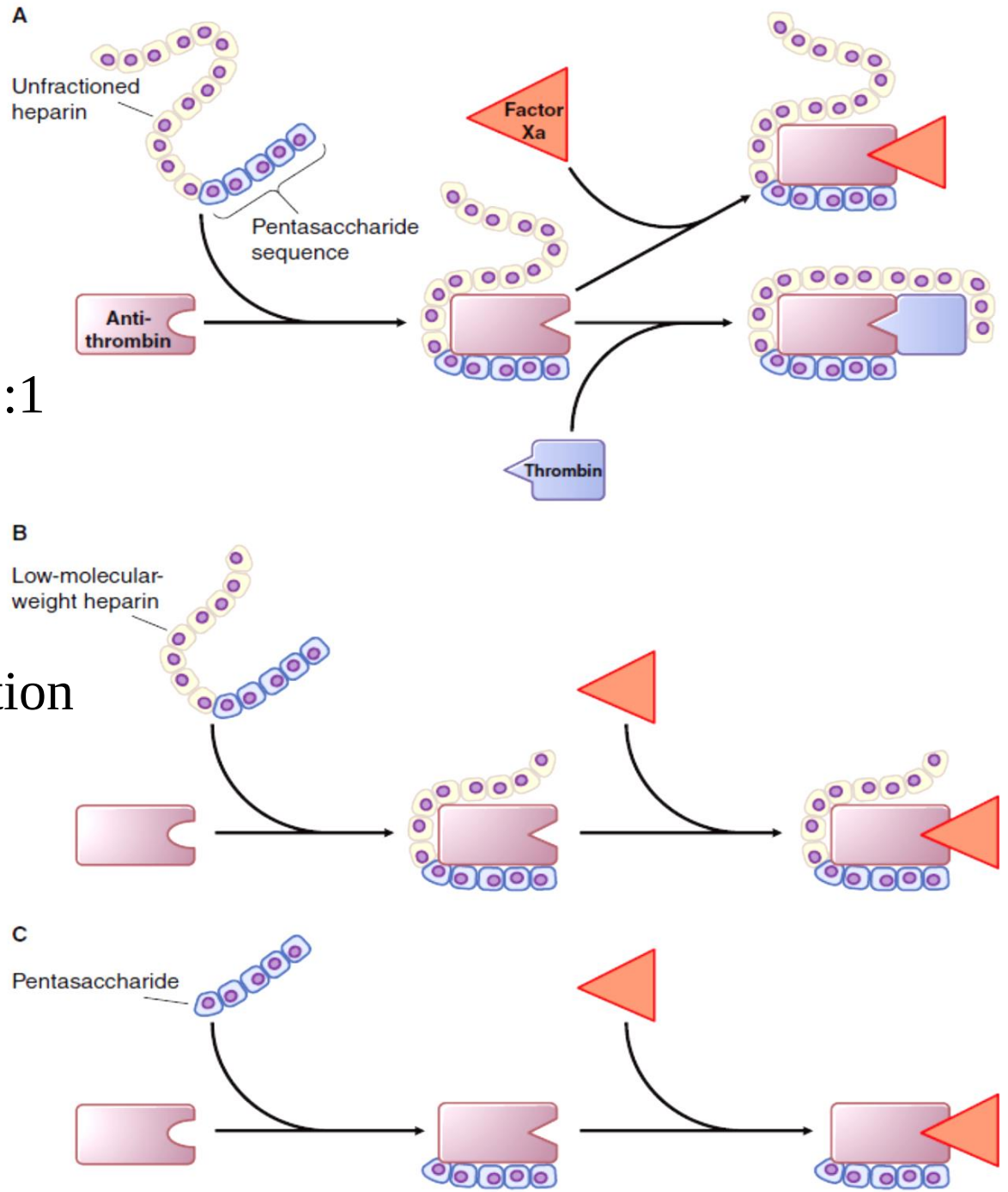
Inhibits activated coagulation factors, particularly **thrombin and factor Xa**

Parenteral Anticoagulants

Heparin: anti-factor Xa to thrombin ratio of 1:1

LMWH: 3:1 to 2:1 depending on the preparation

Fondaparinux: only factor Xa inhibition



UNFRACTIONATED HEPARIN

- **Rapid-acting** anticoagulant
- administered intravenously (IV) by continuous infusion, or subcutaneously (SC)
- Bioavailability reduced by SC administration (30%)
- IM administration should be avoided → Potential for **hematoma formation**
- **Unpredictable** dose response
- Monitoring: activated partial thromboplastin time (**aPTT**)
- Ampule 5000/ml and 10000/ml

LOW MOLECULAR WEIGHT HEPARIN (LMWH)

- **Enoxaparin, dalteparin and tinzaparin**
- Improved bioavailability after SC injection (90%)
- **Predictable dose response**
- Monitoring is not done routinely
- Longer pharmacodynamic effect compared with UFH
- Administered SC every 12 to 24 hours at fixed doses
- Prefilled syringes:
  - 2, 4, 6, 8, and 10000 Unit
  - 20, 40, 60, 80, and 100 mg

FONDAPARINUX

- Binds to AT to inactivate factor Xa with no direct impact on factor IIa
- Long elimination half-life (17 h)
- Once-daily SC administration at a fixed dose without routine coagulation monitoring

- **Should not be used in creatinine clearance < 30 mL/min**
  - ✓ Risk of accumulation and subsequent bleeding

- Fondaparinux is much less likely than heparin or LMWH to trigger HIT
  - ✓ Used to treat patients with this condition

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

Heparin, LMWH, and Fondaparinux

- Not absorbed through the GI mucosa → Must be given parenterally

- **Heparin**:
  - ❖ Continuous IV infusion, intermittent infusion every 4–6 h, or SC every 8–12 h
  - ❖ **Immediate onset of action** when given IV
  - ❖ Considerable variation in bioavailability given SC, onset of action is **delayed 1–2 h**

- t1/2 depends on the dose administered:
  - ❑ doses of 100, 400, or 800 units/kg IV, half-lives are about 1, 2.5, and 5 h

- Heparin cleared and degraded primarily by the reticuloendothelial system
  - Small amount of intact heparin appears in the urine

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

Heparin, LMWH, and Fondaparinux

- **LMWH and fondaparinux**

  - ❖ Absorbed more uniformly after SC injection (90 and 100%)
  - ❖ Longer biological half-lives than heparin
  - ❖ Cleared by the kidneys
  - ❖ The drugs can accumulate in patients with renal impairment and lead to bleeding
  - ❖ **Contraindicated** in creatinine clearance **below 30 mL/min**

ADMINISTRATION AND MONITORING

Heparin, LMWH, and Fondaparinux

- **Heparin**

  - ✓ Therapy is monitored by measuring aPTT
  - ✓ The therapeutic range for heparin:
    - ➢ Determined with an aPTT **2 or 3 times the normal**

  - ✓ aPTT should be measured **initially**
  - ✓ The infusion rate is adjusted **every 6 h**
  - ✓ **Daily monitoring** in steady dosage schedule

ADMINISTRATION AND MONITORING

Heparin, LMWH, and Fondaparinux

- Do not cross the placenta
- Have not been associated with fetal malformations
- **Choice for anticoagulation during pregnancy**

Heparin, LMWH, and Fondaparinux

BLEEDING

- The major untoward effect is **Bleeding**
- Anticoagulant effect of heparin disappears within hours of discontinuation
- Mild bleeding due to heparin usually controlled without administration of antagonist

- If life-threatening hemorrhage occurs:
  - Heparin can rapidly be reversed by the IV infusion of **protamine sulfate**
  - A mixture of basic polypeptides
  - Binds tightly to heparin and neutralizes its anticoagulant effect
  - 1 mg of protamine for every 100 units of heparin remaining
  - Given IV at a slow rate (up to a maximum of 50 mg over 10 min)
- Protamine binds only long heparin molecules
  - **Partially** reverses the anticoagulant activity of LMWH
  - **No effect** on fondaparinux

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

- Platelet count < 150,000/mL or 50% decrease from the pretreatment value
- Occurs in about 0.5%, 5–10 days after initiation of heparin
- Occurs with LMWH with a lower incidence and rarely with fondaparinux
- Women are twice as likely as men to develop HIT

- Heparin or LMWH **should be discontinued immediately**
- Thrombotic complications may occur after cessation of therapy
  - Alternative anticoagulant should be administered
    - **Bivalirudin or argatroban or fondaparinux**
- LMWH should be avoided because cross-reacts with heparin antibodies
- Warfarin may precipitate venous limb gangrene or skin necrosis in patients with HIT
  - Should not be used until the platelet count returns to normal

OTHER TOXICITIES

- **Abnormalities of hepatic function tests**
  - Frequently by heparin or LMWH
- **Osteoporosis**
  - In therapeutic doses of heparin for extended periods (e.g., 3–6 months)
    - The risk of osteoporosis is lower with LMWH or fondaparinux than heparin
- Heparin can inhibit the synthesis of aldosterone by the adrenal glands
  - **Hyperkalemia**

Parenteral Anticoagulants

FEATURES	HEPARIN	LMWH	FONDAPARINUX
Source	Biological	Biological	Synthetic
Mean molecular weight (Da)	15,000	5000	1500
Target	Xa and IIa	Xa and IIa	Xa
Subcutaneous			
Bioavailability (%)	30 (at low doses)	90	100
$t_{1/2}$ (h)	1–8[a]	4	17
Renal excretion	No	Yes	Yes
Antidote effect	Complete	Partial	None
Thrombocytopenia	<5%	<1%	<0.1%

[a]Half-life $t_{1/2}$ is dose dependent; half-life is 1 h with 5000 units given subcutaneously and can extend to 8 h with higher doses.

OTHER PARENTERAL ANTICOAGULANTS
DESIRUDIN, LEPIRUDIN, BIVALIRUDIN, ARGATROBAN

- Recombinant or synthetic forms of hirudin
- **Mechanism of action**: Directly inhibits thrombin
- Administered IV
- Used as an alternative to heparin
  - Used for treating thrombosis in the setting of HIT

- **Desirudin, Lepirudin and Bivalirudin**
- Eliminated by kidneys
- Used cautiously in:
  - Decreased renal function
  - Serum creatinine and aPTT monitored daily

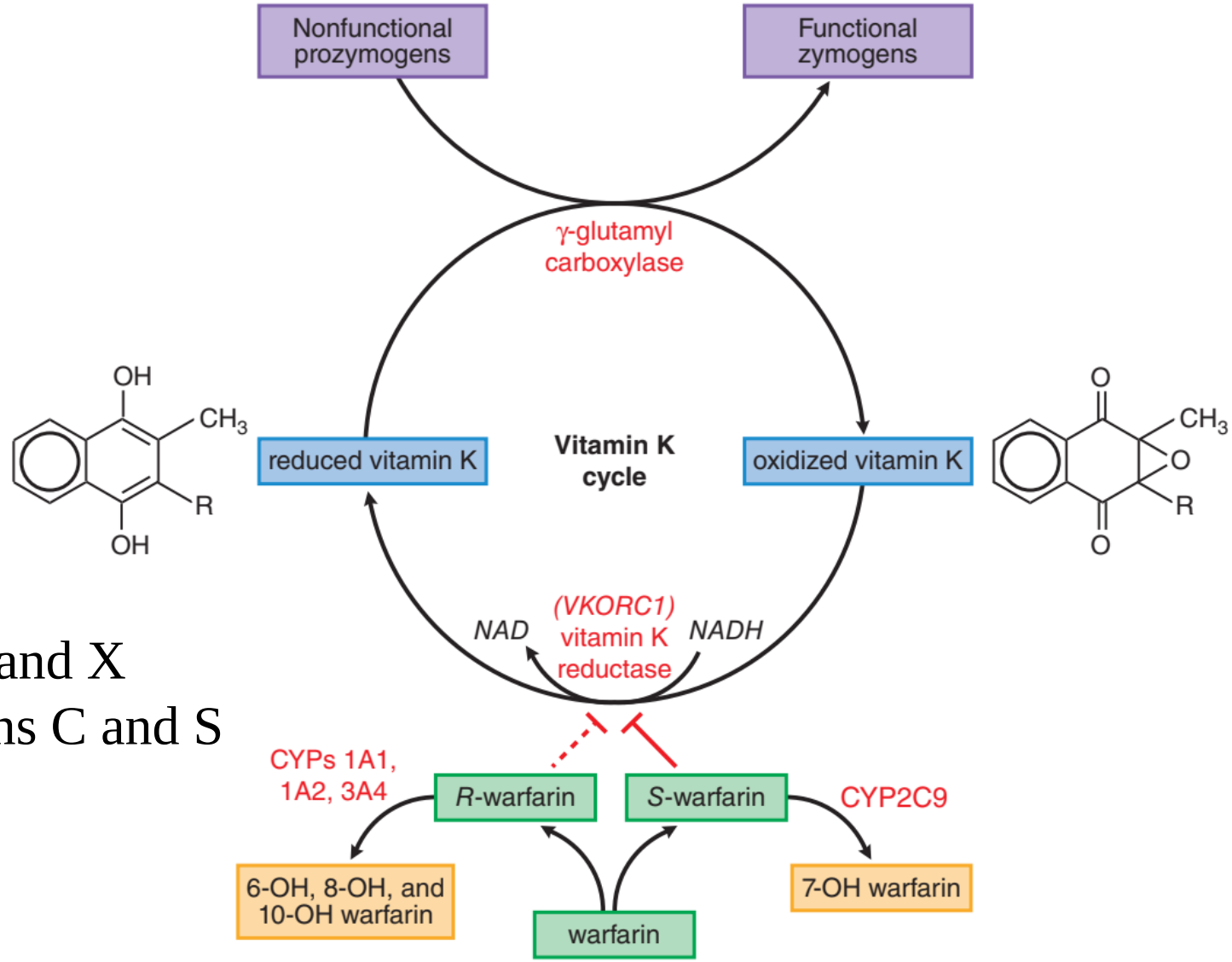
- **Argatroban**
- Metabolized in liver and excreted in the bile
- Can be used in renal impairment
- Dose reduction is required in hepatic insufficiency

VITAMIN K ANTAGONIST
WARFARIN

✓ Mechanism of Action

✓ Inhibition of Vitamin K epoxide reductase (VKOR)

✓ Inhibition of synthesis in the liver:
- ✓ Coagulation factors II, VII, IX, and X
- ✓ Anti-coagulation factors: proteins C and S



VITAMIN K ANTAGONIST
WARFARIN

- ✓ **No effect** on the activity of coagulation factors in the circulation
- ✓ t1/2 of factors VII, IX, X, and II are 6, 24, 36, and 50 h
- ✓ t1/2 of protein C and S are 8 and 24 h
- ✓ Because of the long t1/2 of coagulation factors, the full antithrombotic effect of warfarin is not achieved for **4 to 5 days**
- ✓ **Warfarin must be overlapped with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux, in patients with thrombosis or at high risk for thrombosis**

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION
WARFARIN

- ✓ Oral bioavailability is nearly complete
- ✓ Generic warfarin tablets may vary in their rate of dissolution
  - ✓ May cause some variation in rate and extent of absorption
- ✓ Food in the GI tract can **decrease absorption**
- ✓ Inactive metabolites of warfarin are excreted in urine and stool
- ✓ The *t*1/2 varies (25–60 h), but the duration of action of warfarin is 2–5 days

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION
WARFARIN

- ✓ Polymorphisms in two genes, CYP2C9 and VKORC1 account for most of the genetic contribution to variability in warfarin response
- ✓ **Hepatic impairment: Dosage modification**
  - ✓ May increase warfarin response because of decreased metabolism
  - ✓ Impaired synthesis of clotting factors
- ✓ Monitoring: **INR**
- ✓ For most indications, an **INR range of 2–3**

INTERACTIONS
WARFARIN

- ✓ **Reduced warfarin efficacy:**
  - ✓ reduced absorption (e.g., binding to cholestyramine in the GI tract) or
  - ✓ increased hepatic clearance from induction of hepatic enzymes:
    - ✓ CYP2C9 induction by barbiturates, carbamazepine, or rifampin

- ✓ **Increased warfarin efficacy** and risk of hemorrhage:
  - ✓ decreased metabolism due to CYP2C9 inhibition:
    - ✓ amiodarone, azole antifungals, cimetidine, clopidogrel, cotrimoxazole, disulfiram, fluoxetine, isoniazid, metronidazole, sulfinpyrazone, or zafirlukast

INTERACTIONS
WARFARIN

- ✓ Relative warfarin resistance:
  - ✓ Ingestion of large amounts of vitamin K–rich foods or supplements or
  - ✓ Increased levels of coagulation factors during pregnancy

- ✓ Gut bacteria synthesize vitamin K and are important source of this vitamin
  - ✓ Antibiotics can cause an **increase in the INR** in patients on warfarin

- ✓ Low concentrations of coagulation factors:
  - ✓ Result from impaired hepatic function, congestive heart failure, or hyper-metabolic states, such as hyperthyroidism
  - ✓ **Enhance the effect of warfarin on the INR**

HYPERSENSITIVITY TO WARFARIN

- ✓ About 10% of patients require less than 1.5 mg/d of warfarin to achieve an INR of 2–3
- ✓ Often possess variants of CYP2C9 or VKORC1

- ✓ Supplementation with **low daily doses of vitamin K**
  - ✓ renders these patients less sensitive to warfarin
  - ✓ may result in more stable dosing

ADVERSE EFFECTS
WARFARIN

1. **Bleeding:** The most common side effect

- INR above the therapeutic range and no bleeding:
  - warfarin can be held temporarily
  - restarted at a lower dose once the INR is within the therapeutic range

- INR ≥ 10: **vitamin K1 can be given orally (2.5 to 5 mg)**
  - These doses of oral vitamin K1 decrease INR within 24–48 h without rendering the patient resistant to further warfarin therapy

- Higher doses or parenteral administration may be required if more rapid correction of the INR is necessary
- The effect of vitamin K1 is delayed for at least several hours
  - Synthesis of coagulation factors

ADVERSE EFFECTS
WARFARIN

1. Bleeding

- If **immediate** hemostatic competence is necessary because of serious bleeding
  - PCC (Prothrombin Complex Concentrate) (25–50 units/kg)
  - **Supplemented with 10 mg vitamin K1** slow IV infusion

- Vitamin K1 administered IV carries the risk of anaphylactoid reactions

- Patients who receive high doses of vitamin K1
  - Become unresponsive to warfarin for several days

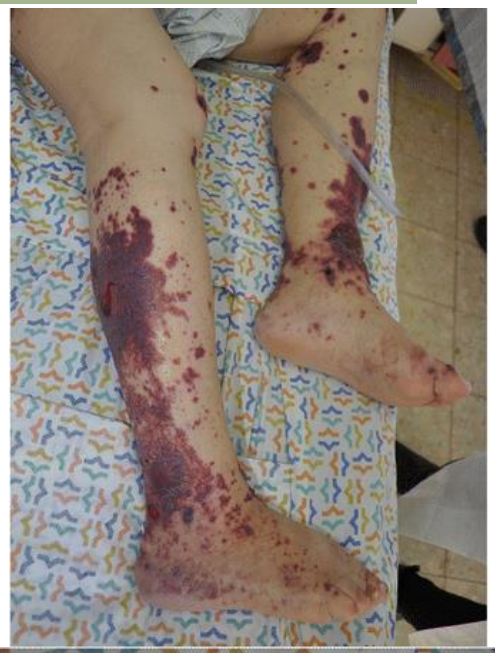
ADVERSE EFFECTS
WARFARIN

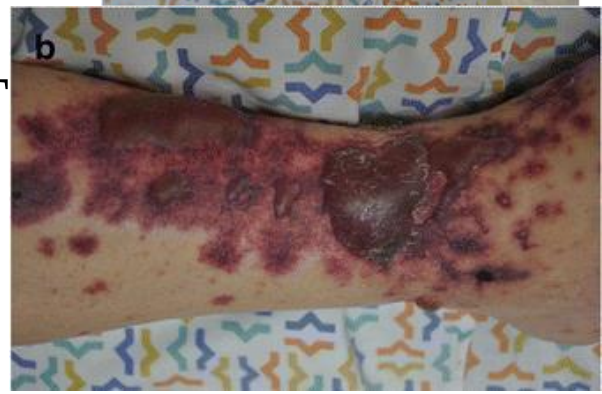
2- Birth Defects

- Administration during pregnancy causes birth defects and abortion
- Hemorrhage and intrauterine death may occur, even when maternal INR are within the therapeutic range
- **Warfarin should not be used during pregnancy, but heparin or LMWH can be used safely**

ADVERSE EFFECTS
WARFARIN

3- Skin Necrosis



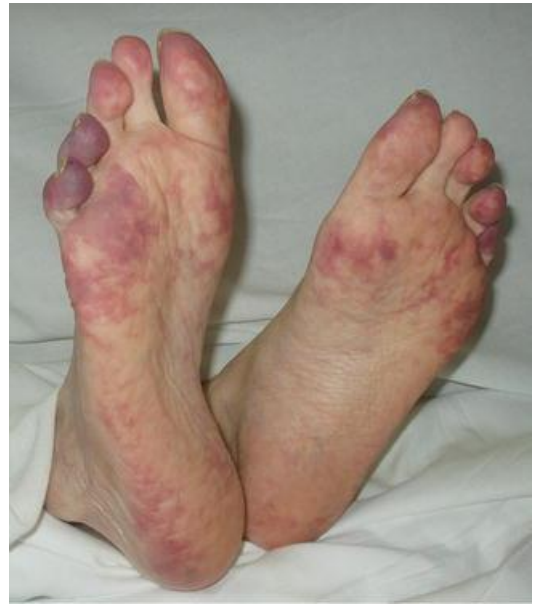


- ❖ Rare complication
- ❖ Characterized by the appearance of skin lesions
- ❖ 3–10 days after treatment is initiated
- ❖ Typically on the extremities, but adipose tissue, the penis, and the female breast may be involved
- ❖ Occurs in patients with protein C or S deficiency or in those with HIT

ADVERSE EFFECTS
WARFARIN

4- Purple toe syndrome

- A reversible, sometimes painful, blue-tinged discoloration of the plantar surfaces and sides of the toes
- Develop 3–8 weeks after initiation of therapy
- Cause: Cholesterol emboli released from atheromatous plaques



5- Other toxicities

Other infrequent reactions include

- alopecia, urticaria, dermatitis, fever
- nausea, diarrhea, abdominal cramps, and anorexia

DIRECT ORAL ANTICOAGULANTS

- **Direct Oral Thrombin Inhibitor**
  Dabigatran

- **Direct Oral Factor Xa Inhibitors**
  Rivaroxaban, Apixaban, and Edoxban

DIRECT ORAL THROMBIN INHIBITOR

DABIGATRAN

Mechanism of Action

- Competitively and reversibly blocks the active site of free and clot-bound **thrombin**

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION
DABIGATRAN

- t1/2 of 12–14h ⇒ twice a day
- Bioavailability is altered if capsules are chewed or broken prior to ingestion
- Capsules **should be swallowed whole**
- 80% is excreted unchanged by the kidneys
- Patients with severe renal impairment (creatinine clearance 15 to 30 mL/min)
  - Dosage reduction is required
- Patients with a **creatinine clearance <15 mL/min**
  - Dosage recommendations are not available
- Produces a **predictable** anticoagulant response
  - Routine coagulation monitoring is unnecessary

ADVERSE EFFECTS
DABIGATRAN

- ✓ Major side effect: **Bleeding**
- ✓ Risk of intracranial bleeding is reduced by 70% with dabigatran compared with warfarin
- ✓ Risk of GI bleeding is higher with dabigatran, particularly in age>75 years

- ✓ Additional risks for bleeding with dabigatran include:
  - ✓ renal impairment
  - ✓ concurrent use of antiplatelet agents or nonsteroidal anti-inflammatory drugs

DRUG INTERACTIONS
DABIGATRAN

- ✓ Dabigatran is a substrate for P-glycoprotein

- ✓ Inhibit P-glycoprotein:
  - ✓ Verapamil, dronedarone, quinidine, ketoconazole, and clarithromycin
    - ✓ **Increase dabigatran concentrations**

- ✓ Induce P-glycoprotein:
  - ✓ Barbiturates, carbamazepine, or rifampin
    - ✓ **Decrease the concentration**

DIRECT ORAL FACTOR XA INHIBITORS
RIVAROXABAN, APIXABAN, AND EDOXBAN

- **Mechanism of Action**

- Inhibit free and clot-associated factor Xa
  - Reduced thrombin generation
    - Suppressed platelet aggregation and fibrin formation

- **Rivaroxaban:** Tablet 2.5, 5, 10, 15, and 20 mg
- **Apixaban:** Tablet 2.5 and 5 mg

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION
RIVAROXABAN

- t1/2 of 7–11 h
- Should be administered **with a meal** to enhance absorption
- The tablet can be crushed and delivered via nasogastric tube
- About one-third is excreted unchanged in the urine
  - The remainder is metabolized by the **hepatic CYP3A4** system
  - Inactive metabolites are excreted equally in the urine and feces

- Rivaroxaban exposure is increased in renal impairment or severe hepatic dysfunction
- Creatinine clearance 15–50 mL/min
  - **Dose is reduced** from 20 mg once daily to 15 mg once daily
- Creatinine clearance < 15 mL/min **Should not be used**

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION
APIXABAN

- Food **does not affect** absorption
- Can be administered as a whole tablet or crushed and delivered via nasogastric tube
- About 27% of the drug is cleared unchanged via the kidneys
- Apixaban is metabolized by the **hepatic CYP3A4** system
  - Metabolites are excreted in the bile, intestines, and urine

- Patients who have two of the following three characteristics:
  - Age over 80 years
  - Body weight of 60 kg or less
  - Serum creatinine 1.5 mg/dL or higher

→ **The dose is reduced**

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION
RIVAROXABAN, APIXABAN, AND EDOXBAN

- Rivaroxaban, apixaban, and edoxaban are given in fixed doses
- **Do not require routine coagulation monitoring**
- Renal function should be assessed at least **yearly**
  - More frequently in patients with renal dysfunction

ADVERSE EFFECTS
RIVAROXABAN, APIXABAN, AND EDOXBAN

- The major adverse effect is **bleeding**
- Rates of intracranial bleeding: at least 50% lower than warfarin
- Rates of GI bleeding with rivaroxaban, but not Apixaban: higher than warfarin
- Rates of life-threatening bleeding: lower with all than with warfarin

- **Drug Interactions**
- All of the oral factor Xa inhibitors are substrates for P-glycoprotein
  - Potent inhibitors or inducers of P-glycoprotein will increase or decrease drug concentrations

REVERSAL AGENTS FOR DIRECT ORAL ANTICOAGULANTS

- **Idarucizumab**
- A specific and rapid reversal agent for **dabigatran**

- **Andexanet Alfa**
- A recombinant analogue of factor Xa designed for **oral factor Xa inhibitors**
- Higher doses of andexanet are needed to reverse rivaroxaban or edoxaban than apixaban
- An ongoing phase 3 study is evaluating the effect of andexanet in patients taking these agents who present with serious bleeding

- **Ciraparantag**
- Reported to bind **dabigatran, rivaroxaban, apixaban, edoxaban, heparin, LMWH**
- Has yet to be evaluated in patients