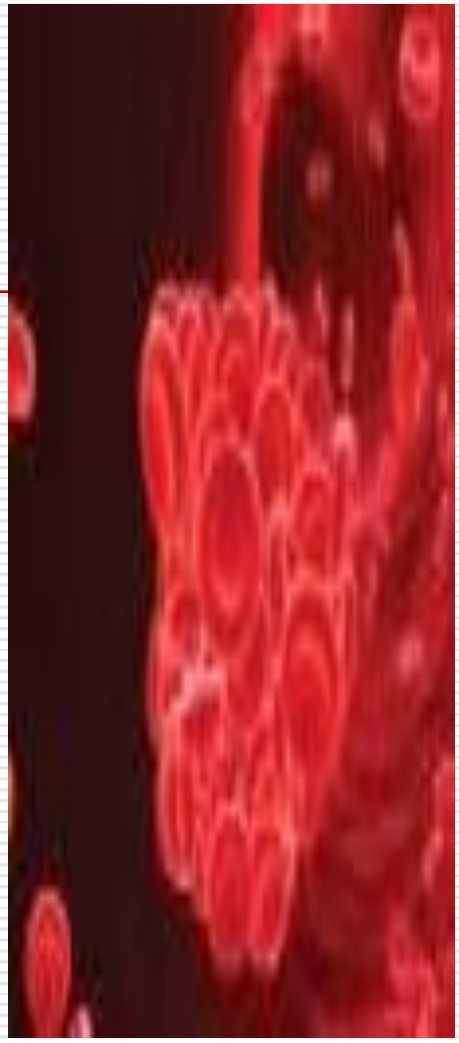
Blood Thinner Agent

Done by:

Meznah Al-mutairi

Pharm.D Candidate

PNU Collage of Pharmacy



Outline:

- Blood thinner agent definition .
- anticoagulants drugs.
- Thrombolytics.

Blood thinner agent

- Therapeutic interference with the clotting mechanism of the blood to prevent or treat thrombosis and embolism.
- reducing the formation of blood clots in arteries and veins.

Pathophysiology of Hemostasis

- **Hemostasis** is a process which causes bleeding to stop, meaning to keep blood within a damaged blood vessel.
- Thrombosis is the most common abnormality of hemostasis; that is the formation of unwanted clot within a blood vessel.
- **Thrombotic disorders include;**

  -Acute myocardial infarction (arterial)

  -Acute ischemic stroke (arterial)

  -Pulmonary embolism (arterial)

  -Deep venous thrombosis (venous)

These disorders are treated with anticoagulants and fibrinolytics.

Classes of Drugs affect Thrombotic disorders

- **Prevent coagulation:**

Drugs used to prevent unwanted blood clots developing and used as primary prevention or secondary prevention as Antiplatelet drugs .

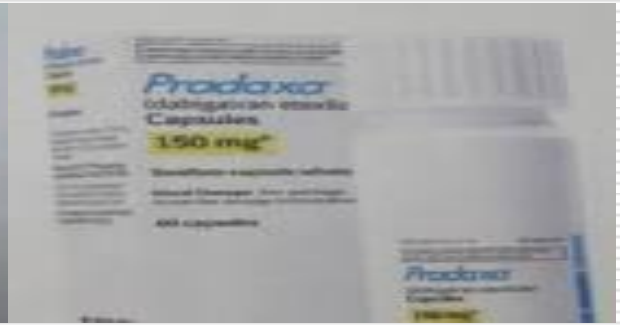
- **stabilize existing blood clots:**

Cause stabilize for clot and will not dissolve a formed clot but prevent its propagation and growth as anticoagulants drugs.

- **Dissolve existing blood clots:**

restore circulation patency more quickly by dissolving the existing clot as Thrombolytics drug.

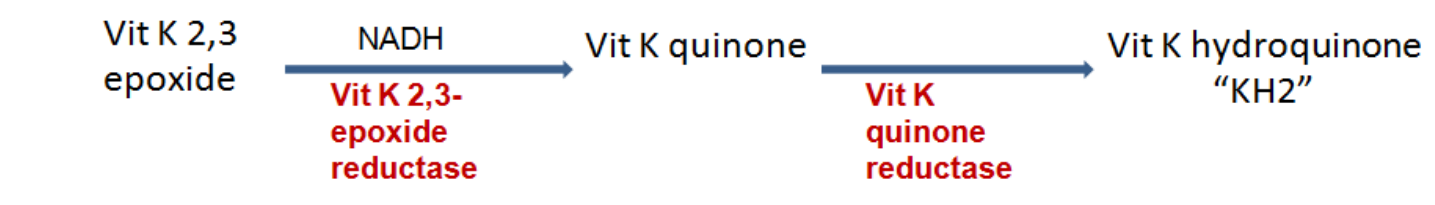
anticoagulants drugs



1- Warfarin (Coumarin)

- Warfarin have been the main oral anticoagulant for more than 50 years.
- Its anticoagulant effect is not immediate, until those circulating clotting factors are cleared (5 hr for factor V and 2-3 days for factor II; thrombin).
- **Mechanism of action:**

Warfarin inhibit Vit K 2,3 epoxide reductase and possibly Vit K quinone reductase,so prevent Vit K-dependent clotting factors to be activated (II, VII, IX, X and Prot C).



1- Warfarin (Coumarin)

- **Therapeutic Uses:**

It is used for chronic anticoagulation,

1. To prevent progression or recurrence of deep venous thrombosis "DVT" or pulmonary embolism after initial heparin therapy.
2. Prophylactic in patients with; prosthetic heart valve or atrial fibrillation "AF".

1- Warfarin (Coumarin)

❑ Adverse effects:

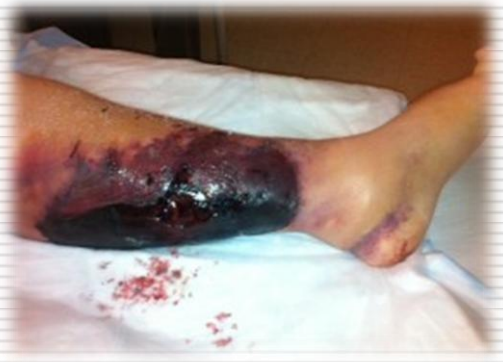
1. Bleeding disorders

   -Minor bleeding can be treated with stopping warfarin and giving oral Vit K(2.5-5 mg).

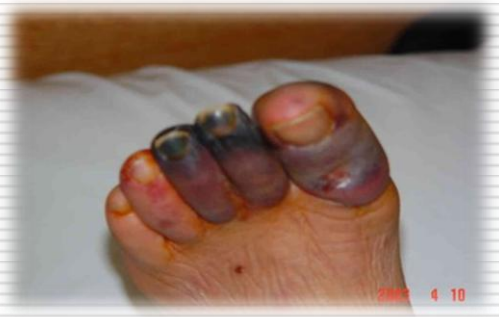
   -Major bleeding need larger doses of Vit K (IV 5-10 mg) along with whole blood/ fresh frozen plasma or plasma concentrates.

2. Skin necrosis is rare, 'women primarily'
3. Purple toe syndrome; painful blue discoloration of the toe.

It is contraindicated during pregnancy, since it is teratogenic/abortifacient.



Warfarin skin necrosis



Purple toe syndrome

1- Warfarin (Coumarin)

❑ Warfarin-related Drug Interactions :

Some Warfarin-related Drug Interactions

Potentiating Anticoagulant activity		**Antagonizing Anticoagulant activity**	
Drugs	Factors	Drugs	Factors
Alcohol (acute intoxication) Acetaminophen Aspirin Indomethacin Ibuprofen Mefenamic acid Napoxen Heparin Cephalosporin Erythromycin INH Ketoconazole Fluconazole Metronidazole Omeprazole Oral hypoglycemics	Fever Stress Congestive heart failure Diarrhea Cancer Hyperthyroidism Hepatic dysfunction Vit K deficiency	Alcohol (chronic abuse) Antacids Antihistamines Cholestyramine Colestipol Corticosteroids Aminoglycosides Penicillins Barbiturates Carbamazepine Phenytoin Rifampicin Vitamin K Oral contraceptive pills	High Vit K diet: spinach, cheddar cheese, cabbage Oedema Hypothyroidism Nephrotic syndrome

1- Warfarin (Coumarin)

- **Laboratory Monitoring:**

- **Prothrombin time (PT)** assess the activity of vit K dependent clotting factor. It is quiet sensitive to factor VII. Normal PT is 10-13 sec.
- **INR** is optimally maintained at 2-3 . Initially we check PT & INR daily after starting warfarin therapy. Once stable it can be checked monthly or bimonthly.

peak effect of warfarin is around 72-96 hr.

Warfarin Counseling

- The patient should know that:

-What is warfarin?

-Why was warfarin prescribed for you?

-Advise taking at the same time (6pm) each day .

-If forget a dose, take it as soon as remember, as long as it is the same day.

-Never skip a dose or take a double dose.

-Possible Side Effects of Warfarin as bleeding .

-should report any symptom as Red or brown urine, red or tarry stools and Blood in vomit or mucus .

Warfarin Counseling

Using Other Medications (OTC):

- **Pain medications**

Medications **may use :**

Acetaminophen no more than 2000 mg per day

Medications to **avoid**

Ibuprofen ,Naproxen and Aspirin unless prescribed by your doctor.

- **Herbal products to avoid**

Garlic ,Ginkgo ,Ginseng ,Fish oil , Omega-3 fatty acids and q enzyme 10.

Diet for Warfarin Users

To help warfarin work effectively, it is important to keep **vitamin K intake as consistent as possible**

- The highest amount of vitamin K is found in green, leafy vegetables .
- Alcohol should be limited to **1 drink per day .**
- Avoid eating **mangos and liver.**

2-Heparin

- This group include:

Unfractionated Heparin

Low molecular weight heparin “LMWHs”

Fondaparinux “synthetic pentasaccharide”

1-**Unfractionated Heparin**

It is the standard heparin / high molecular weight heparin and It has a very high affinity for antithrombin III with significant anticoagulant activity.

2-**Low molecular weight heparin**

They have more favorable pharmacokinetics and pharmakodynamics compared to heparin. Examples; Enoxaparin, Dalteparin and Tinzaparin.

2-Heparin

- Different in Pharmacokinetics between UH and LMWH:

- UH and LMWH are administered IV or SC but not orally "polysaccharide chains are broken down by gastric acid"

It is NOT recommended to give heparin via IM because it can cause hematoma.

- UH has very high affinity and non-specific binding to various protein receptors, such as; those on plasma proteins, endothelial cells, platelets, **platelet factor 4 (PF4)…..** heparin-induced thrombocytopenia.
- LMWHs has lower affinity to PF4 correlates with a reduced incidence of HIT.

2-Heparin

Mechanism of action:

- UH binds to circulating Antithrombin III and potentiates its action; inhibition of thrombin (factor IIa) and factor Xa.
- LMWHs is more selective with more targeted activity against Xa_and less activity against thrombin.

Factor Xa: thrombin activity is

1:1 for unfractionated heparin

2-4: 1 for LMWHs

2-Heparin

- **Therapeutic Uses:**

1- Prophylactically to prevent postoperative thromboembolic complications in patients undergoing abdominal and orthopaedic surgeries.

2-Treatment of acute deep venous thrombosis and pulmonary embolism and to reduce their recurrence.

3- In acute phase of myocardial infarction, and post thrombolytic therapy to prevent coronary artery re-thrombosis.

4- In dialysis machines to prevent thrombosis.

5- Treating pregnant patients with prosthetic heart valves or venous thromboembolism, since they don't cross the placenta.

2-Heparin

- **Adverse effects:**

1- Bleeding is the chief complication of heparin therapy.

- In case of haemorrhage; discontinuation of heparin and administering its antidote: Protamine sulfate is given slowly IV (1 mg/100 Units of heparin given).

2- Hypersensitivity reactions due to heparin antigenicity "due to animal source" and producing; fever, chills, urticaria or anaphylactic shock.

3- Heparin might produce abnormal liver function tests and osteoporosis (less likely to happen with LMWHs).

4- Heparin-induced thrombocytopenia (with UH).

2-Heparin

- **Laboratory Monitoring:**

- Heparin is monitored via **activated partial thromboplastin time (aPTT)** assay which monitors factor II, X along with others.
- Normal "non-heparinized" plasma has aPTT of 25-45 sec. This value rises to 70-140 sec in patients on heparin therapy.
- Unfractionated heparin dose is modified according to aPTT results.
- LMWHs have highly predicatble dose-response realtionships and does not require monitoring with aPTT.
- Enoxaparin dose is based on body weight (1 mg/Kg once or twice).
- Dalteparin and Tinzaparin dose is based on antifactor Xa units (a-Xa U) and given once daily.

3-Fondaparinux

- This is a purely synthetic administered via SC injection, once daily .
- It has predictable anticoagulant activity and does not require monitoring.
- NO significant drug interactions were reported.
- **Mechanism of action:**

it is indirect inhibitors of Xa. Unlike heparin and LMWHs, it has no effect on thrombin.

3-Fondaparinux

- **Therapeutic Uses:**

It is the first selective factor Xa inhibitor approved for prophylaxis against DVT in patients undergoing orthopaedic surgeries.

- **Adverse effects:**

Bleeding mainly. It does not cause thrombocytopenia.

In fact it can be used in patients with HIT.

- **Contraindication:**

Patients with severe renal impairment (crcl<30 ml/minute).

body weight < 50 kg.

4-Rivaroxaban

- Rivaroxaban is an orally active once daily in 10-mg doses.
- The initial dose should be taken 6–10 hours after surgery, provided that haemostasis has been established.
- **Mechanism of action:**

direct factor Xa inhibitor.

- There is currently no specific way to reverse the anticoagulant effect of rivaroxaban in the event of a major bleeding , unlike warfarin.

4-Rivaroxaban

- **Adverse effects:**
  - Bleeding (less than Warfarin).
  - Spinal/epidural hematoma.
- Laboratory Monitoring:
  - Periodically assess renal function as clinically indicated and adjust therapy accordingly.

Direct Thrombin Inhibitors

- **Hirudin** is a small protein isolated from the salivary glands of the medicinal leech, which has potent and specific inhibitory effects on thrombin through formation of 1:1 complex with it.

Direct Thrombin Inhibitors

- **Mechanism of action:**

DTIs bind and inactivate free thrombin as well as thrombin-bound to fibrin

This binding is direct and does not require antithrombin III as a cofactor for their anticoagulant activity.

- **Lepirudin** and **Desirudin**

- These are recombinant hirudin derivatives. Both approved for treatment of HIT and HIT patients with thrombotic syndromes.
- Lepirudin is administered via IV (bolus and then infusion). Desirudin is given SC twice daily
- Lepirudin has immunologic properties, and patients might develop antihirudin Abs. Hemorrhage might occur as complication.

Direct Thrombin Inhibitors

- **Bivalirudin**
- It has been approved for patients with unstable angina undergoing percutaneous coronary intervention (PTCA), HIT, ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.
- It has rapid-onset, short-acting, administered via IV bolus/infusion.
- Risk of bleeding is less than the other antithrombotics
- No reports of antibodies formation.
- **Argatroban**
- It has been approved for prophylaxis and treatment of HIT patients with thrombosis, during percutaneous coronary interventions in patients who have HIT or are at risk for developing it.
- Administered SC.

Direct Thrombin Inhibitors

❑ Dabigatran

- **Dabigatran** oral anticoagulant was developed as an alternative to warfarin, since it does not require maintenance of international normalized ratio or monitoring by frequent blood tests.
- there is no way to reverse the anticoagulant effect of dabigatran in the event of clinically significant bleeding, unlike warfarin.
- They have a more predictable anticoagulant response, absence of food interactions, and limited drug interactions compared with warfarin.
- the issue of medication adherence can become problematic because The half-life periods of these agents are also shorter than that of warfarin.
- More expensive.

❑ Adverse effects:

Bleeding (lower than warfarin)

drugs	Time of take it
Rivaroxaban	The 15 mg and 20 mg tablets should be taken with food, while the 10 mg tablet can be taken with or without food.
Warfarin	Administer with or without food . take at the same time each day.
Dabigatran	May be taken without regard to meals.

Drugs	Pregnancy category
Warfarin	Category x
Heparin	Category c (use LMWH is preferred)
Fondaparinux	Category B (can be used only in women can not use LMWH)
Rivaroxaban	Category c.
Dabigatran	Category c.

Thrombolytics

Thrombolytics

- Thrombolytic drugs attack and dissolve the formed clot to restore circulation.

- Early application of reperfusion therapy with thrombolytic agents has significantly improved the outcomes of acute MI, pulmonary embolism, DVT, stroke and other arterial thrombosis.

Thrombolytics

Mechanism of action:

- It converts plasminogen to plasmin " following the cleavage of a peptide bond" by a protease called " **tissue plasminogen activator**" that is released from the vascular endothelium.
- **Plasmin** function to digest fibrin, however, it also digests some plasma proteins and coagulation factors

First generation thrombolytic agents

❑ Streptokinase

- *It is a protein purified from group C β-hemolytic* streptococcus.
- streptokinase is considered fibrin-nonspecific drug.
- It half life is short (30 min), infused over an hour and within 4 hours of MI.

Streptokinase

- **Streptokinase is approved for:**
- Acute massive pulmonary embolism.
- Acute myocardial infarction .
- DVT (proximal).
- Acute arterial occlusion.
- **Adverse effects:**

1. Significant hypersensitivity reactions could occur in 3% of patients; due to prior exposure to streptococcus. Circulating antibodies will be available and the response vary.
2. Bleeding by dissolving hemostatic plugs.

First generation thrombolytic agents

Anistreplase

- It is considered a pro-drug .
- It has a longer half life = 90 min and can be given over 3-5 hours.

Urokinase

- It is an enzyme isolated from human fetal kidney that directly degrade fibrin and fibrinogen.
- It lacks the antigenicity of streptokinase, so used in patients expected to show allergic reactions against streptokinase.
- It is much more expensive than streptokinase, half life is 15 min.
- approved for pulmonary embolism only.

Second generation thrombolytic agents

Alteplase (tissue plasminogen activator; tPA)

- it is fibrin-specific agent.
- It is produced via recombinant DNA technology.
- It has a short half life (5 min), so it is given via IV bolus, followed by IV infusion over 90 min.
- Approved for acute MI, acute ischemic stroke (within 3 hours) and massive pulmonary embolism.

Third generation thrombolytic agents

They are derived by structural modifications of the basic t-PA.

Reteplase

- It is highly fibrin-specific.
- It has a longer half life than alteplase (15 min), administered as 2 bolus doses 30 min apart.
- approved for STEMI.

Tenecteplase

- It is highly fibrin-specific.
- It has a half life is 17 min, given as single bolus.
- approved for STEMI.

Contraindications for thrombolytic therapy

1. Active internal bleeding (not including menses).
2. Previous history of intracranial hemorrhage, and ischemic stroke within 3 months.
3. Known intracranial neoplasm or vascular lesion (such as arteriovenous malformation).
4. Suspected aortic dissection.
5. Significant closed head/ facial trauma within 3 months.

Reference

- American heart association.
- Up to date.
- Lippincott pharmacology book.

Thank you