بسم الله الرحمن الرحيم

Pharmacology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

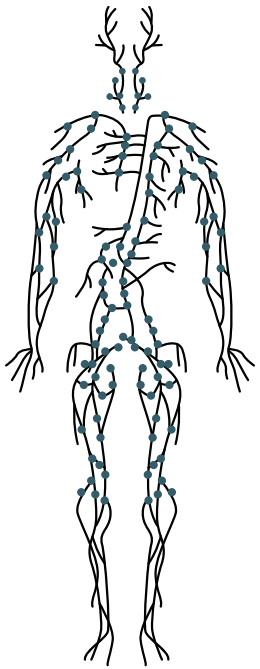
ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

FINAL | Lecture 2

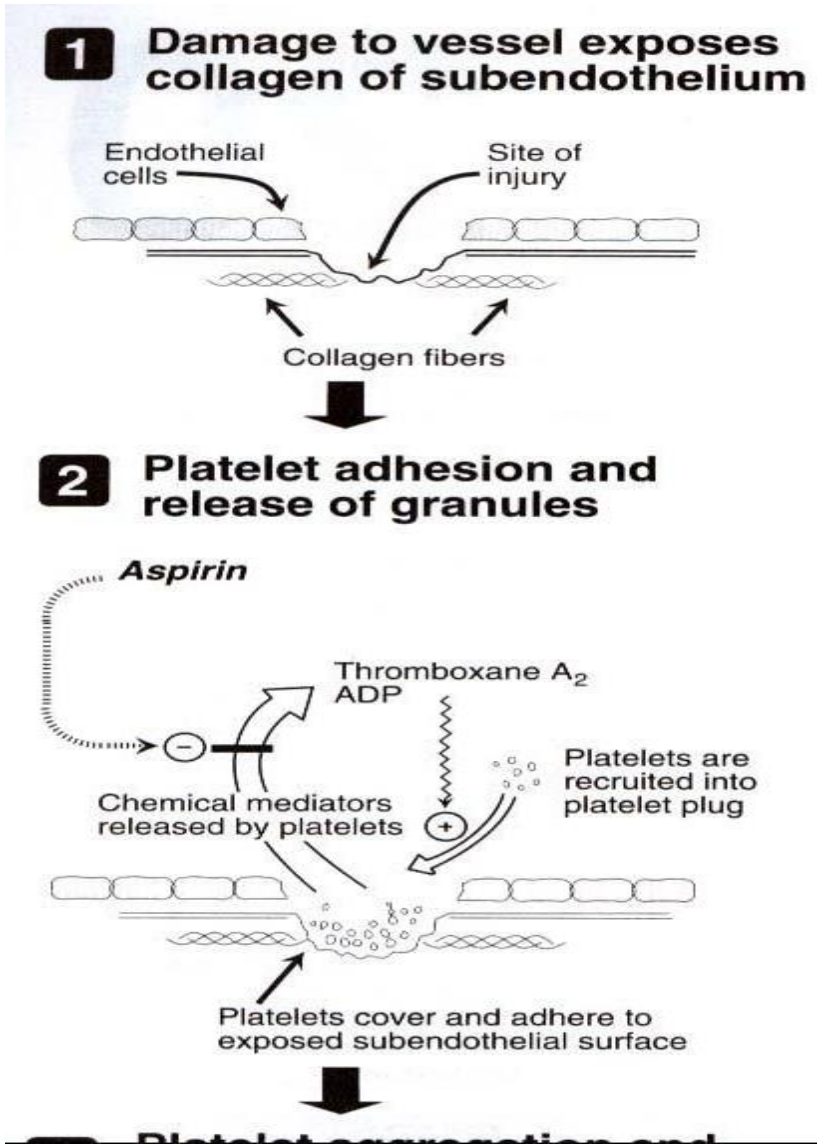
Anticoagulants

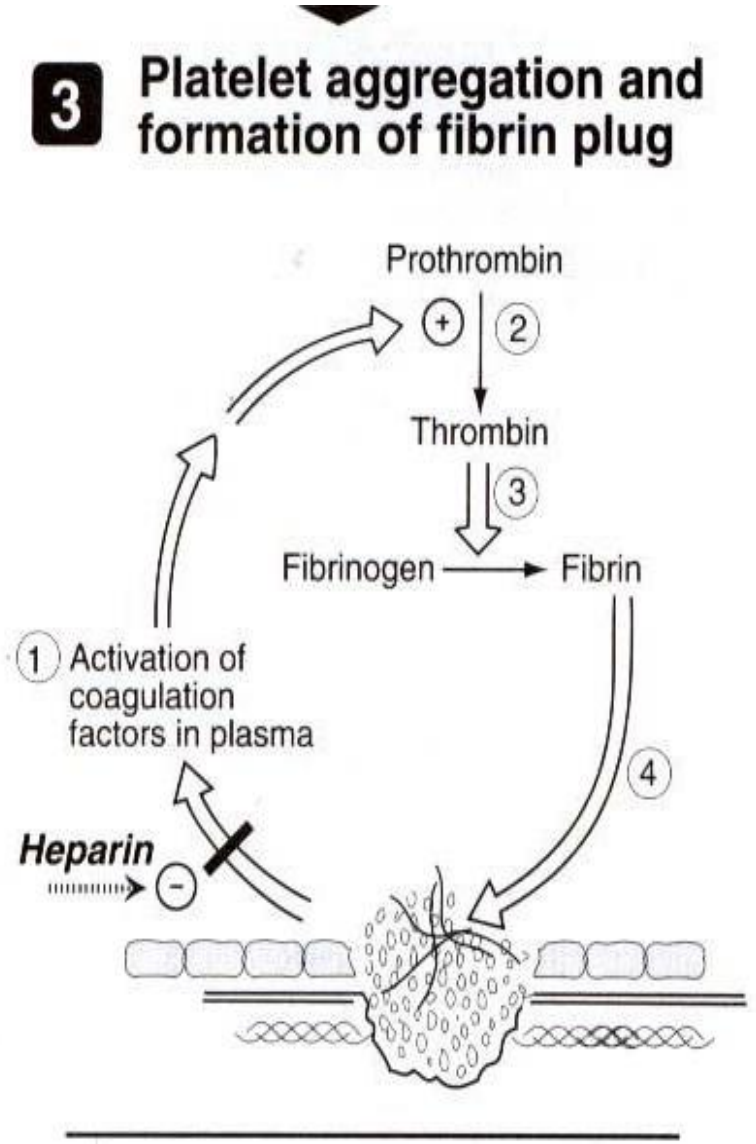
Written by:
Sadeel Al-hawawsheh

Reviewed by:
Layan Fawarseh



Antiplatelet vs. Anticoagulant





Antiplatelets vs. Anticoagulants

Antiplatelet drugs are mainly directed toward the prophylaxis of coagulation. After coagulation occurs, treatment involves either **anticoagulants** or **thrombolytics**, which differ in their mechanisms of action. Thrombolytics act as fibrin cutters and are used in specific cases, such as when a patient develops a myocardial infarction with complete blockage and is in a very critical condition. In such cases, an injection is given to dissolve all thrombi in the body.

Anticoagulants are widely used and are important but complex drugs, as they have a **narrow therapeutic index**. This means that both critical bleeding and thrombosis may occur. They are used in hemodynamically unstable patients with disturbed homeostasis presenting to the emergency room with conditions such as deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, or unstable angina. The use of these drugs interferes with normal hemostasis and can be life-threatening, even leading to death in some cases.

Anticoagulants

سبحان الله وبحمده

Most will be discussed separately in this lecture.

A) Heparin

B) Low-Molecular-Weight Heparins:

Enoxaparin, dalteparin, tenzaparin

C) Heparinoids: Danaparoid.

D) Direct & specific thrombin inhibitors: Hirudin (leech protein), lepiridun, bivalirudin, argatroban, melagatran.

E) Oral direct & specific thrombin inhibitors: Ximelagatran and Dabigatran

F) Pentasacharide specific Xa inhibitors: Fondaparinux, Rivaroxaban

G) Warfarin

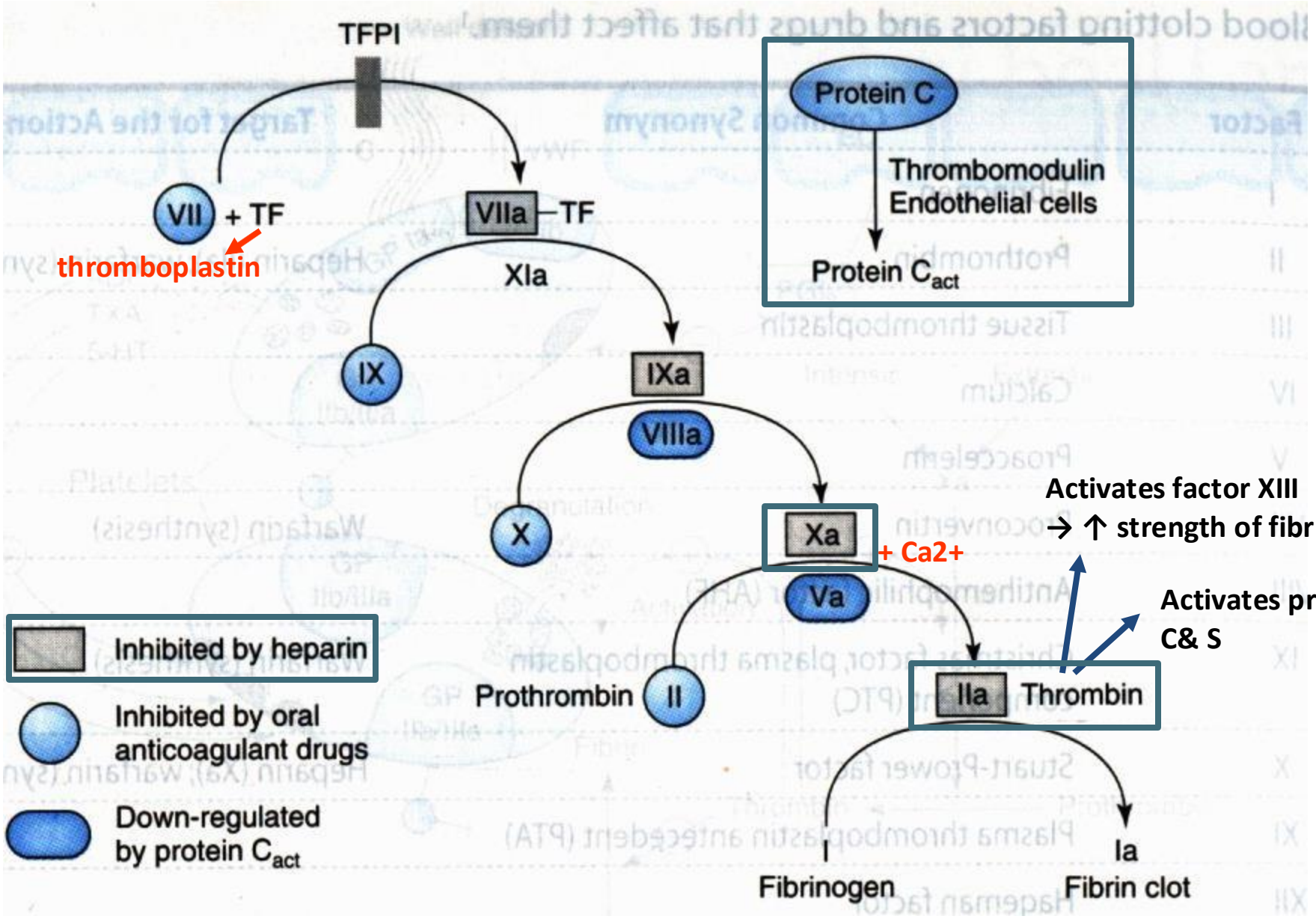
Anticoagulants

Coagulation Cascade

- Series of steps
- Precursor proteins in plasma are activated by proteolysis
- Activated proteins activate other proteins
- Plasma contains protease inhibitors like Antithrombin III (ATIII), protein C, and S that rapidly inactivate coagulation proteins as they escape from side of vessel injury

Anticoagulants (Take a deep look to the figure then see the next slide)

سبحان الله العظيم



Anticoagulants

The main idea behind anticoagulant therapy is to shift the body's balance toward an anticoagulated state, preventing further clot formation. To understand how anticoagulants work, we must first review the coagulation cascade, which includes two main pathways – the intrinsic and extrinsic pathways.

- **Intrinsic pathway:** originates within the blood and is mainly related to platelet activation and blood vessel injury.
- **Extrinsic pathway:** is triggered by tissue factor released from injured tissues outside the blood vessels.

Both pathways eventually converge into the **common pathway**, which activates Factor Xa , Factor IIa (prothrombin) and Factor V. Activated Factor II (thrombin) then converts fibrinogen into fibrin, forming the fibrin mesh that stabilizes the clot
– a process we aim to prevent when using anticoagulants.

Natural (Endogenous) Anticoagulant Mechanisms

Our bodies naturally maintain a delicate balance between coagulation and anticoagulation to ensure normal hemostasis. To counteract excessive clotting, the body produces **endogenous anticoagulants**, which enhance the anticoagulant state, these natural inhibitors include:

- **Antithrombin III**
- **Protein C and Protein S**

By using anticoagulants, we inhibit thrombin formation at the final stage of the coagulation cascade, thereby preventing fibrin clot formation. These drugs either preserve or may even enhance the action of endogenous anticoagulants. As a result, the existing clot gradually dissolves because it is no longer being maintained. Over the long term, this dissolution process can take months or even years, as seen in cases of deep vein thrombosis, where warfarin may be used for up to a year.

Anticoagulants

استغفر الله العظيم
وأتوب إليه

A) Heparin

B) Low-Molecular-Weight Heparins: Enoxaparin, dalteparin, tenzaparin

C) Heparinoids: Danaparoid**.**

D) Direct & specific thrombin inhibitors: Hirudin (leech protein), lepiridun, bivalirudin, argatroban, melagatran.

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F) Pentasacharide specific Xa inhibitors: Fondaparinux, Rivaroxaban

F) Warfarin (affects Vitamin K)

Heparin

Mechanism of unfractionated heparin UFH action

- Prevents further thrombus growth, allowing the body's own thrombolytic system to dissolve clot.
- Activates plasma protease inhibitor **antithrombin III (AT III).**
- The complex inactivates factors: XIIa, XIa, IXa, **Xa,**

& IIa (thrombin)

- For DVT & PE, heparin is given **for 5–7 days**.

Mechanism of unfractionated heparin UFH action

Heparin is an endogenous substance found in humans as well as in animals such as pigs, cows, and sheep. The heparin used for medical purposes, today is extracted from pigs (since 2008), whereas before 2008 it was taken from cows.

There is no other drug like heparin, as it is a naturally occurring compound. It binds to the endogenous anticoagulant **Antithrombin III** (a **protease** that deactivates Factor Xa and Factor IIa) , and this interaction greatly enhances its activity – from a working value of about 1 to a value of thousand.

By doing so, heparin causes a complete inhibition of several coagulation factors, most importantly Factor Xa and Factor IIa (thrombin) --> complete inhibition of coagulation in the body.

Heparin is therefore a very strong and highly effective drug with a unique mechanism of action, but it is also associated with many side effects. The main problem with heparin is that it is a very large macromolecule, composed of **pentasaccharide** units and **glucosamine** forming a long chain, which gives it a high molecular weight. Heparin also differs among animal sources such as cows and pigs, and when it is extracted and prepared in solution, the solution is **heterogeneous** – meaning that the length of the **glucosamine** chains varies, sometimes measuring 60, 50, or 40 ... kDa.

Because of this heterogeneity, when a patient receives a heparin injection, the amount of active drug entering the body is not always identical, since we are dealing with a non-uniform (heterogeneous) solution. For this reason, when administering heparin, we must **monitor** the patient carefully to ensure that the drug is working optimally – neither causing bleeding nor allowing coagulation.

This monitoring is especially important in patients with conditions like myocardial infarction or unstable angina, who are already hemodynamically unstable. Since heparin is a heterogeneous material, continuous monitoring is necessary to maintain the correct therapeutic balance. (note that Heparin is ONLY given in severe cases and in the hospital)

Laboratory Monitoring for UFH

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- Activated partial thromboplastin time **(aPTT)**:
- Normal aPTT is 24-36 sec.
- An aPTT ratio (patient aPTT/control aPTT) of 2–2.5 should be achieved throughout infusion or 6 hours after intermittent administration.

To monitor heparin, we use a test called **Activated Partial Thromboplastin Time (aPTT)**. This test measures how the **intrinsic pathway** of coagulation is functioning, which reflects how well heparin is working. Heparin is usually given to the patient either by **continuous intravenous drip** or as a **bolus injection**, and then a blood sample is taken to perform the aPTT test.

In this test, the blood sample is placed in a tube containing specific factors. Under normal conditions, blood clots within **24–36 seconds**. When we administer heparin, the goal is to increase this clotting time, typically to **48–72 seconds or more**, meaning we aim for about **2 to 2.5** times the normal value.

However, this increase is not always consistent, so repeated testing is necessary. The aPTT should be checked after 1 hour, 6 hours, and 12 hours to ensure that the patient remains within the safe therapeutic range.

- If the aPTT is **less** than twice the normal value, it indicates that heparin is not effective, and the dose should be **increased**.
- If the aPTT is **more** than 2.5 times the normal value, it means the effect is too strong, and the dose should be **decreased**.

UFH Toxicity

1. The major adverse effect is **bleeding.** If bleeding occurs, the antidote for heparin is **Protamine Sulfate**, which binds to heparin and neutralizes its effect.
2. Heparin is of animal origin & should be used cautiously in patients with **allergy**
3. Increased loss of hair (reversible **alopecia**)
4. **Long-term** heparin therapy: **osteoporosis.** However, it is typically used for just one week.
5. **Hyperkalemia (decreases aldosterone).** So K+ also should be monitored
6. **Heparin-induced thrombocytopenia (HIT).** Please see next slide

To sum up: when giving a patient Heparin, the following should be monitored: aPTT, Potassium, Platelets count.

Heparin-Induced Thrombocytopenia

One important side effect is Heparin-Induced Thrombocytopenia (HIT), which is a decrease in platelet count. This occurs because heparin not only binds to Antithrombin III, but part of it also binds to a factor called Platelet Factor 4 (PF4). When these bind, they form a complex called a hapten, which is recognized as a foreign substance (immunogenic) by the immune system. A hapten is defined as a small-molecule drug that are not capable of invoking an immune response when injected directly into animals but can covalently link to proteins, forming complexes that lead to the production of antibodies and subsequent immune responses, such as platelet destruction and thrombocytopenia.

The body then produces IgG antibodies against this complex. These antibodies attach to platelets to activate them everywhere in the circulation. As a result, widespread clot formation occurs in both arteries and veins, and the number of circulating platelets decreases, as they are being consumed in thrombus formation.

Another theory suggests that the immune system attacks and destroys platelets. During their destruction, the platelets release all the coagulation factors they contain, leading to widespread coagulopathy throughout the body.

This condition occurs in about 2-3% of patients. Therefore, it is essential to monitor platelet count frequently:

- **Perform a baseline platelet count (Day 0) before giving heparin.**
- **Then repeat the count on Day 3 and Day 5 as the previous reaction usually occurs on day 3 (early immunogenic reaction) or day 5 (late immunogenic reaction).**
- **If a decrease in platelet count is observed, heparin must be stopped immediately, as this indicates the development of HIT.**

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Low-Molecular Weight Heparins

Heparin is usually given either by continuous intravenous drip or frequent doses, because it has a short half-life. However, standard heparin therapy is complex, requiring careful monitoring and hospitalization. To overcome these challenges, **Low Molecular Weight Heparins (LMWHs)** were developed.

LMWHs are chemically modified to **cutting glucosamine while retaining the pentasaccharide structure (that's why it is called fractionated heparin)**, producing a **homogeneous** solution. This modification:

- Eliminates the need for routine monitoring
- Maintains the drug's anticoagulant activity, since binding occurs mainly through the pentasaccharide
- Reduces the risk of Heparin-Induced Thrombocytopenia (HIT) – hapten formation

Low-Molecular Weight Heparins (LMWHs)

- **Enoxaparin**, **dalteparin, tenzaparin & ardeparin** are fragments of heparin.
- Similar to heparin, they possess a unique pentasaccharide sequence in order to bind to & catalyze ATIII.
- As opposed to heparin, this complex preferentially inactivates factor Xa & **minimally affects thrombin (factor IIa)**. That's why they are sometimes considered factor Xa inhibitors.
- Since LMWHs minimally affect thrombin, they have minimal impact on the aPTT (which is most sensitive to thrombin).

Heparin is still used in ~10% of cases, when inhibition of (both II and X factors) is required; e.g; during surgical operations, a wound is created, which activates the coagulation process. Therefore, it is necessary to prevent excessive coagulation activation:

- **In the hospital, immediately after surgery, patients are given heparin, since their coagulation system is highly active, and we need a strong and fast-acting drug.**
- **After discharge, patients are given low molecular weight heparin (LMWH) as subcutaneous injections for weeks, which are safer and suitable for use at home, then oral type will be prescribed.**

Low-Molecular Weight Heparins (LMWHs)

- **Enoxaparin:** from same sources as regular heparin; doses are specified in milligrams. (Used in Jordan)

- **Eliminated renally.**

- Higher costs for these agents may be outweighed by earlier discharge from hospital due to dosing convenience.

- Neutralization by protamine is incomplete.

Advantages of LMWHs over Heparin

- ↓ laboratory monitoring: Blood conc determined only in renal failure, pregnancy, & obesity. These conditions affect both the volume of distribution and the clearance of the drug, so monitoring is always required to maintain safe and effective levels.
- ↑ predictability of response
- Once-twice daily injections (half life ↑)
- Ease of dosing and administration (SQ),
- ↓ requirement of hospitalization
- ↓ risk of thrombocytopenia. **Thrombocytopenia can still occur**, but with a very low incidence (less than 0.3–0.6%) – counting required
- ↓ risk of osteoporisis
- **Hyperkalemia still can occur**

ADR of LMWHs

- Reactions at the injection site: irritation, pain, hematoma, bruising & redness
- bleeding.
- HIT: platelets should be measured at baseline & between days 3 and 5 of therapy.

Heparinoids: Danaparoid

It is originally derived from heparin, but it has been chemically modified so that all glucosamine parts are removed, while the pentasaccharide structure is retained. By removing glucosamine, **Danaparoid** loses the activity on Factor II (thrombin).

Its specific pentasaccharide sequences bind antithrombin (ATIII) → selectively inhibit Factor Xa > Factor IIa (thrombin)

Warfarin

Warfarin & Coumarin Anticoagulants

- is generally used as sodium salt & has 100% bioavailability.

- > 99% is bound to plasma albumin → small Vd, long half life.

Warfarin is a coumarin compound, originally discovered from a plant eaten by cows that caused internal bleeding, which led to the recognition of its anticoagulant properties.

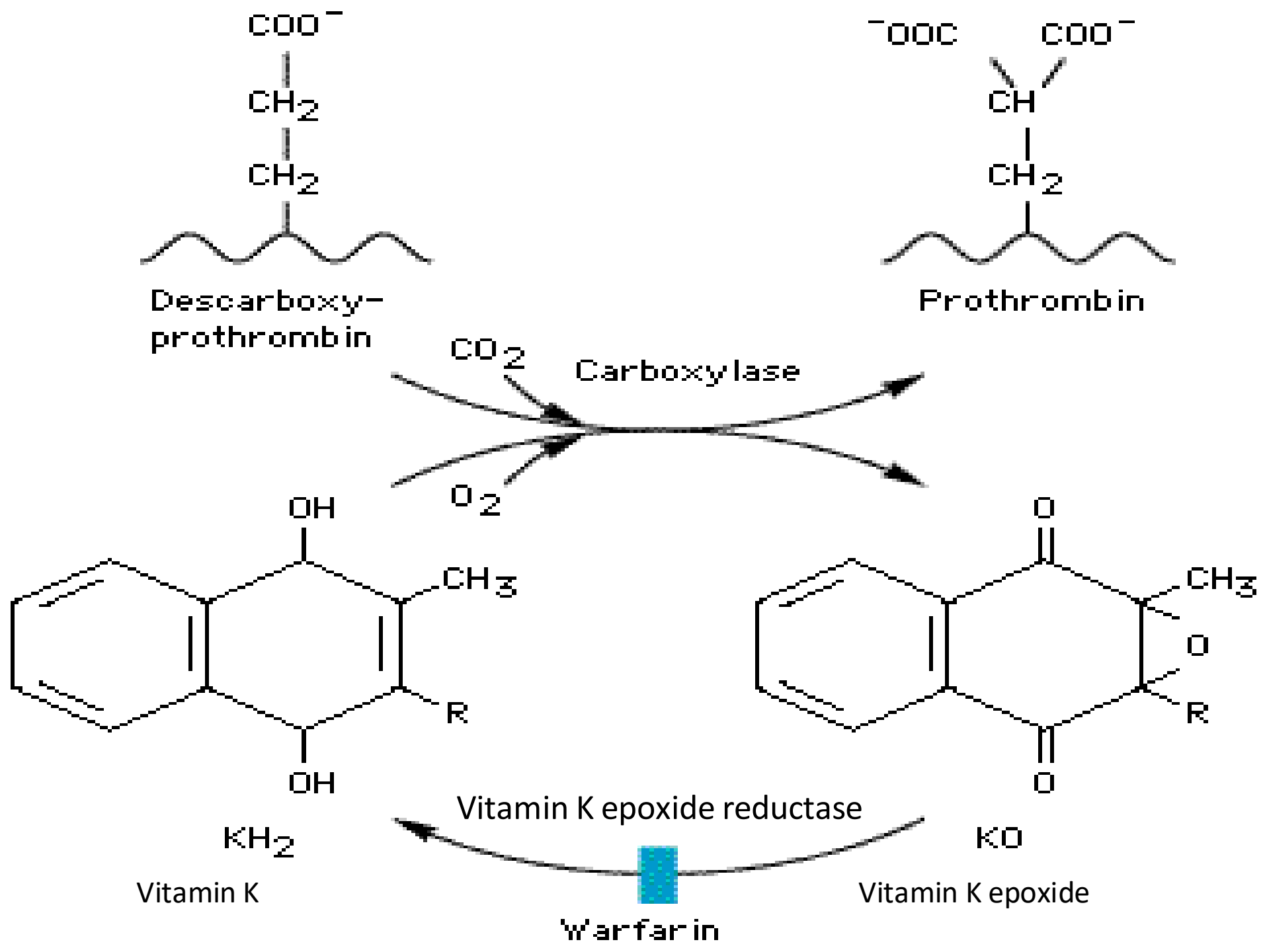
It is not practical to continue giving patients subcutaneous injections after they leave the hospital, so Warfarin is used instead as **an oral anticoagulant**. Before the development of newer oral agents (which will be discussed in the next lecture), Warfarin was the main drug used for long-term anticoagulation. For example, a patient with deep vein thrombosis (DVT) is treated in the hospital with Heparin, and then switched to Warfarin upon discharge, continuing the medication for one to three years.

Warfarin is **inexpensive** compared to other anticoagulants and has an additional advantage – it is **not excreted by the kidneys**. Therefore, it is the drug of choice for patients with kidney failure, since most other oral anticoagulants should not be used in renal impairment.

Although Warfarin has many adverse effects, it remains widely used. It is considered the most common drug responsible for hospital admissions due to its side effects, yet it continues to be prescribed because of its **low cost and safety in kidney-compromised patients.**

Mechanism of Warfarin Action

- Blocks carboxylation of factors VII, IX, & X, & II as well as the proteins C and S.
- The blockade results in incomplete molecules that are biologically inactive in coagulation.
- This carboxylation is physiologically coupled with the oxidative deactivation of vitamin K.
- Warfarin prevents reductive metabolism of inactive vitamin K epoxide back to vitamin K.


COO⁻
CH2
CH2
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CH
CH2
Prothrombin
CO2
Carboxylase
O2
OH
CH3
R
OH
KH2
Vitamin K
O
CH3
O
R
O
KO
Vitamin K epoxide
Vitamin K epoxide reductase
Warfarin

Mechanism of Warfarin Action

There are two forms of prothrombin in the body: **decarboxylated prothrombin** and **prothrombin**. Coagulation factors are produced in the liver in an **inactive** form, and to become active, they require **Vitamin K-dependent carboxylation reactions**. This process involves coupled reactions, where Vitamin K epoxide must be reduced back to active Vitamin K by the enzyme **Vitamin K epoxide reductase.**

Warfarin **inhibits** this enzyme – not the carboxylase enzyme – which prevents the regeneration of active Vitamin K and thus blocks the activation of coagulation factors.

Vitamin K opposes warfarin's mechanism **(antidote)**, since warfarin blocks vitamin K epoxide reductase → Vitamin K intake (from diet or supplements) → ↓ warfarin's effect.

The Vitamin K epoxide reductase enzyme shows **single nucleotide polymorphisms (SNPs)** in about 25% of Jordanians, affecting the gene responsible for this protein. This variation is related to differences in food metabolism, since Vitamin K is found in foods such as tomatoes and parsley البقدونس . Because of this, the enzyme is under constant pressure, leading to genetic variation (SNPs) among individuals (inter-individual variation).

This genetic heterogeneity means that patients respond **differently** to Warfarin, making **monitoring** essential to ensure the correct dosage and avoid complications.

Furthermore, Warfarin is metabolized by the enzyme **CYP2C9**, which also **varies** between individuals, adding another reason why continuous monitoring of Warfarin therapy is necessary.

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Warfarin Toxicity

1. **Bleeding** – the most dangerous.

2. Warfarin crosses the placenta readily & can cause hemorrhagic disorders & abnormal bone formation **in the fetus**. Thus, warfarin should never be administered during pregnancy**.** Warfarin is teratogenic and classified as a Category X drug in pregnancy, meaning it can cause serious fetal malformations and should never be used during pregnancy.

3. **Venous thrombosis** (due to ↓activity of protein C) – Warfarin is contraindicated in patients with (HIT). See slide 26

4. Purple toe syndrome (cholesterol microembolization → arterial obstruction)

One of the rare but serious complications of warfarin therapy is **Purple Toe Syndrome**. This condition occurs when small cholesterol emboli (microemboli) are released from atherosclerotic plaques during anticoagulation. These emboli travel through the bloodstream and may **lodge in small arteries** —such as those supplying the toes— leading to ischemia, tissue necrosis, and a characteristic purple discoloration of the affected area. It is most likely to occur in patients with **hypercholesterolemia** or high lipid levels, although its incidence is relatively low (about 3–4% of patients).

- **heparin or enoxaparin must be overlapped** with warfarin & continued for 4–5 days until an **INR** (extrinsic pathway) **between 2.0 and 3.0** is reached.

The International Normalized Ratio (INR) represents the ratio of the patient's prothrombin (PT) value to a standardized normal PT value, allowing results to be compared internationally. The therapeutic target range for INR is between 2 and 3, meaning the patient's clotting time should be about 2–3 times longer than normal. The aPTT test is not used for Warfarin monitoring because it is not sensitive to the drug's effects.

- Full therapeutic effect is not achieved until existing factor II is cleared ($t_{1/2}$ of factor II is 60 hours).

The main issue with warfarin therapy is that it acts in the liver to inhibit the synthesis of several vitamin K-dependent coagulation factors, most importantly factors II (prothrombin) and X, **as well as the natural anticoagulants** protein C (which binds factor V). Because of this, warfarin is not a specific inhibitor—it reduces both procoagulant and anticoagulant proteins.

Among these, **protein C has a much shorter half-life than factor II (prothrombin)**—about one-third of it. This means that after starting warfarin, the level of the existing protein C drops rapidly, while existing prothrombin persists longer in the blood. As a result, during the first 2–3 days of therapy, the patient temporarily enters a prothrombotic (clot-forming) state, because the anticoagulant effect of protein C disappears before the anticoagulant effect of warfarin on prothrombin fully develops.

This imbalance usually lasts about **60 hours** (2.5 days), until the remaining prothrombin is cleared from circulation. To prevent this early thrombotic risk, **bridging therapy** is used—similar in principle to how corticosteroids are "bridged" in rheumatoid arthritis treatment (DMART). Here, heparin - or mostly (LMWH) - is given together with warfarin at the beginning of therapy.

Heparin provides immediate anticoagulation and is monitored by aPTT, while warfarin requires PT/INR monitoring. Once warfarin reaches its full effect —usually by day 3 to 5— heparin is discontinued, and warfarin therapy continues alone.

Warfarin Drug Interactions

1. **Pharmacokinetic mechanisms**

- **Enzyme (mainly CYP2C9) induction.** **Result: ↑metabolism → ↓ Warfarin effect → blood clots more easily.**
- **Enzyme inhibition.** **Result: ↓ metabolism → ↑ Warfarin effect → ↑ bleeding risk.**
- **↓ plasma protein binding (About 99.9% of warfarin is bound to plasma albumin).**

2. **Pharmacodynamic mechanisms**

- **synergism** (impaired hemostasis). **Some drugs can inhibit platelet function or damage gastric mucosa can add to warfarin's bleeding tendency.**
- **competitive antagonism** (vitamin K). **Vitamin K opposes warfarin's mechanism, since warfarin blocks vitamin K epoxide reductase → Vitamin K intake (from diet or supplements) → ↓ warfarin's effect → ↑ risk of clotting.**

- Among the most dangerous are pharmacokinetic interactions with **azapropazone**:

Azapropazone displaces warfarin from plasma protein & inhibits its metabolism

- The use of a drug that interacts with warfarin is not absolute contraindication to addition of warfarin.

Prof.Malek said that these drugs are important but you are not required to memorize them

I. Drugs that ↑prothrombin time		
↓ ***warfarin metabolism***		
Allopurinol Cimetidine Omeprazole Phenytoin (sometimes) Phenylbutazone Azapropazone Amiodarone	Ethanol (acute) Disulfiram Metronidazole Ketoconazole Fluconazole Miconazole	Erythromycin Azithromycin Ciprofloxacin Norfloxacin Sulfonamides
↑ ***catabolism of clotting factors***		
	Thyroid hormones	
↓ ***synth. of clotting factors (↓ bacteria & direct inh. of epoxide reductase)***		
Cefamandole Cefotetan	Cefmetazole Cefoperazone	
Unestablished mechanisms		
Acetaminophen?	Fibrates Statins	Corticosteroids Androgens

II. Drugs that ↓ prothrombin time		
↑ synthesis of clotting factors		
Estrogens	Vitamin K	
↓ catabolism of clotting factors		
Methimazole	Propylthiouracil	
Induction of warfarin metabolism		
Carbamazepine Phenytoin (usually)	Barbiturates Ethanol (chronic)	Griseofulvin Rifampin
↓ absorption of warfarin		
Cholestyramine	Colestipol	Sucralfate
Unestablished mechanism		
Azathioprine	Cyclosporine	Cy clophosphamide
↑ risk of bleeding without effect on PT		
Aspirin NSAIDs	Ticlopidine Clopidogrel	SSRIs

Contraindications to warfarin

Absolute:

- pregnancy
- others – see heparin

Relative:

- severe hepatic or renal disease
- vitamin K deficiency
- chronic alcoholism
- NSAIDs therapy

Pharmacology Quiz 2

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For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			