Artery Academy

Done by Mariam

حكينا إنه بتعمل **inhibition** لتكوين ال **fibrin** أساسًا لهيك بقدر استعملها ك **prophylactic**

Anticoagulants

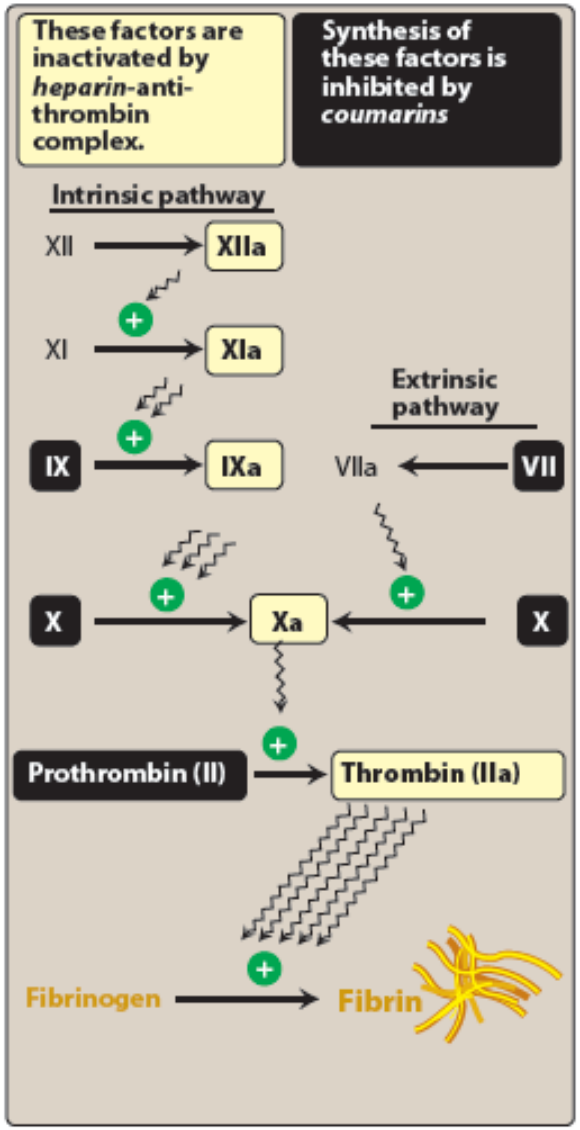
- Anticoagulants inhibit the formation of fibrin clots. ممكن نحكي بشتغل بطريقتين:
- The anticoagulant drugs inhibit either the action of the coagulation factors (such as heparin and heparin-related agents) or interfere with the synthesis of the coagulation factors (such as warfarin).
- Three major types of anticoagulants are available:: أنواعه

1. Heparin and related products, which must be used parenterally.
2. Direct thrombin and factor X inhibitors, which are used parenterally or orally.
3. The orally active coumarin derivatives (eg, warfarin).

كل واحد باختصار بعمل **activation** للتاني لهيك سمّيناه **cascade** وانتبهوا إنه في عندي **interinsic and extrinsic pathway**

TABLE 34– **Blood clotting factors and drugs that affect them.**[1]

Component or Factor	Common Synonym	Target for the Action of:
I	Fibrinogen	
II	Prothrombin	Heparin (IIa); warfarin (synthesis)
III	Tissue thromboplastin	
IV	Calcium	
V	Proaccelerin	
VII	Proconvertin	Warfarin (synthesis)
VIII	Antihemophilic factor (AHF)	
IX	Christmas factor, plasma thromboplastin component (PTC)	Warfarin (synthesis)
X	Stuart-Prower factor	Heparin (Xa); warfarin (synthesis)
XI	Plasma thromboplastin antecedent (PTA)	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
Proteins C and S		Warfarin (synthesis)
Plasminogen		Thrombolytic enzymes, amino-caproic acid

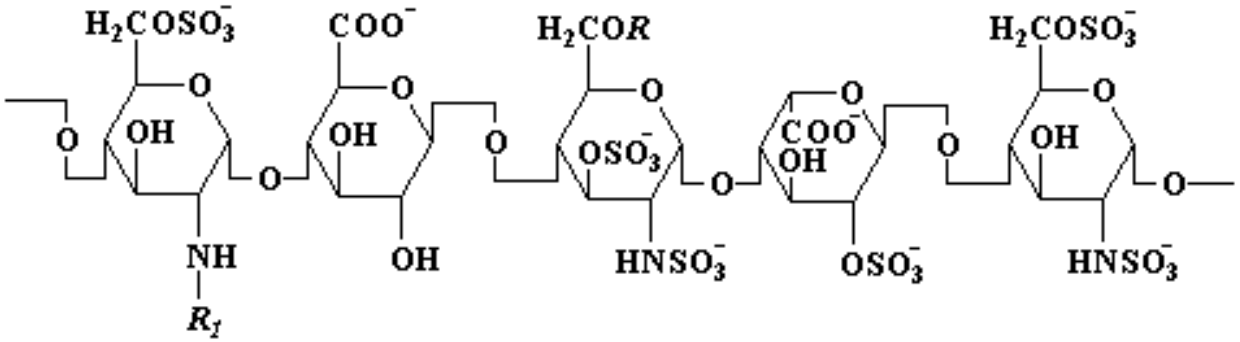


Heparin and related products

Chemistry خصائص ال **Heparin:**

- Heparin is a large sulfated polysaccharide polymer obtained from animal sources. Each batch contains molecules of varying size, with an average molecular weight of 15,000–20,000. حجمه كتير كبير
- Heparin is given intravenously or subcutaneously to avoid the risk of hematoma associated with intramuscular injection. ما بنعطيها **IM** لحتى نتجنب خطر ال **hematoma** (تجمع الخلايا)
  - A **hematoma** is a localized collection of blood outside the blood vessels,usually in liquid form within the tissue.

Heparin



مش حفظ

$R_1 = SO_3^-$ or $COCH_3$ $R = H$ or SO_3^-

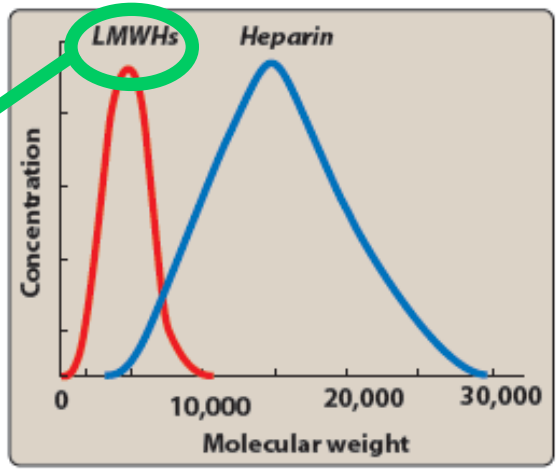
Heparin and related products

هون بنحكي عن ال **fractions of Heparin** وبنقارنها مع ال **unfractionated** إلّي حكينا عنهم بالسلايد الماضي

Chemistry

- Low-molecular-weight fractions of heparin (**LMWH**; eg, **enoxaparin)** have molecular weights of 2000–6000. LMW heparins have greater bioavailability and longer durations of action than unfractionated heparin; thus, doses can be given less frequently (eg, once or twice a day). They are given subcutaneously.
- **Fondaparinux** is a small synthetic drug that contains the biologically active pentasaccharide present in unfractionated and LMW heparins. It is administered subcutaneously once daily.

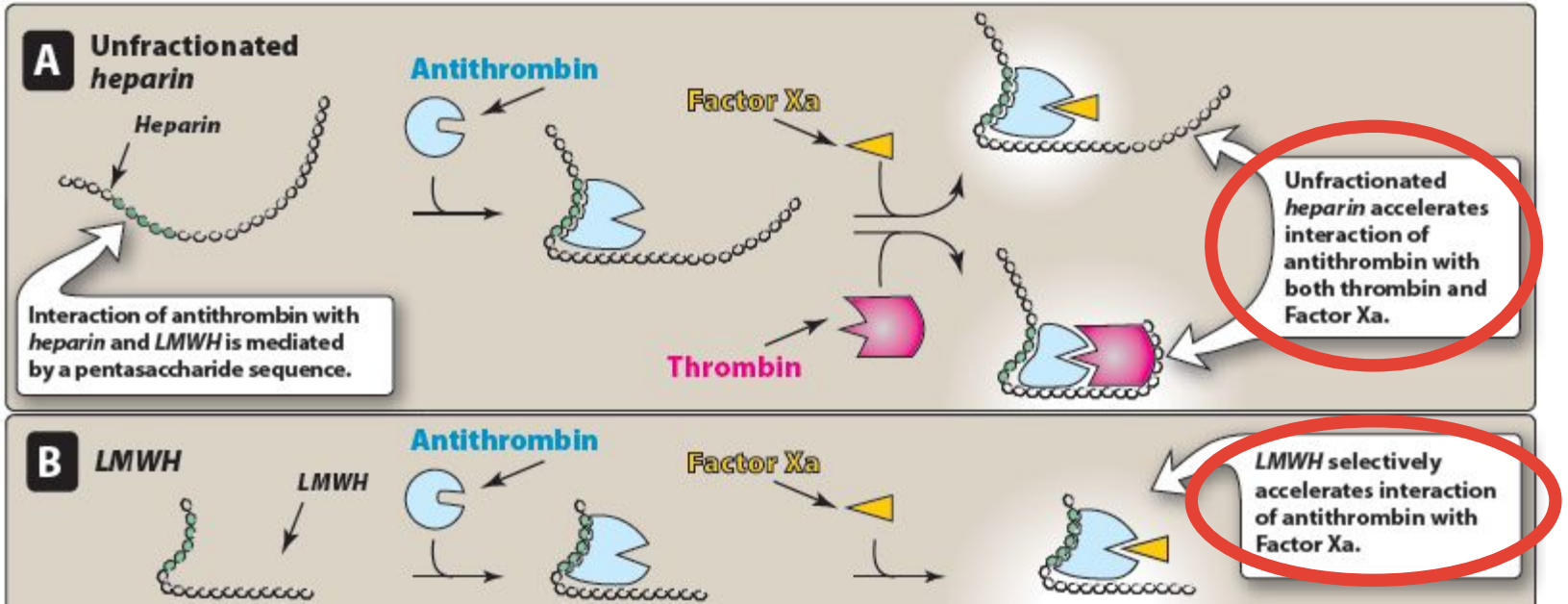
أعطونا نفس ال **effect** بس بوقت أسرع



Heparin and related products

Mechanism of action:

- Unfractionated heparin binds to endogenous **antithrombin III (ATIII)** via a key pentasaccharide sequence. The heparin–ATIII complex combines with and irreversibly inactivates thrombin and several other factors, particularly factor Xa. In the presence of heparin, ATIII proteolyzes thrombin and factor Xa approximately 1000-fold faster than in its absence.
- LMW heparins and fondaparinux, like unfractionated heparin, bind ATIII. These complexes have the same inhibitory effect on factor Xa as the unfractionated heparin–ATIII complex. However, they fail to affect thrombin.



عنا ال **unfractionated Heparin** برتبط بال **endogenous antithrombin III** ,
ف ال **complex** هاد إلّي نتج رح يعمل **combination with and irreversible**
inactivates thrombin يعني رح يعطل شغل ال **thrombin** بشكل نهائي وكمان
ح يرتبط **other factors** بالذات تحديدًا **factor XIa** ، ف هالشي رح يمنع ال
fibrinogen تشكّل **fibrin**
طبعًا ال **LMWH** برضو بترتبط بال **ATIII** وبتشكل نفس ال **complex** إلّي ح يعمل
نفس الشي بس الفرق إنه ما إلها أي **effect** على ال. **thrombin**

Heparin and related products

Clinical Uses:

- Because heparin acts on preformed blood components, it provides anticoagulation immediately after administration.
- Because of its rapid effect, heparin is used when anticoagulation is needed immediately (eg, when starting). Common uses include treatment of DVT, pulmonary embolism, and acute myocardial infarction.
- Because it does not cross the placental barrier, heparin is the drug of choice when an anticoagulant must be used in pregnancy.
- LMW heparins and fondaparinux have similar clinical applications.

Heparin and related products

Toxicity:

- **Increased bleeding** is the most common adverse effect of heparin and related molecules; the bleeding may result in hemorrhagic stroke.
- If bleeding occurs, administration of a specific antagonist such as **protamine sulfate** is indicated. **antidote of Heparin ال**
- Protamine only partially reverses the effects of LMW heparins and does not affect the action of fondaparinux.
- Unfractionated heparin causes moderate transient **thrombocytopenia** in many patients and severe thrombocytopenia (heparin-induced thrombocytopenia or HIT) in a small percentage of patients who produce an antibody that binds to a complex of heparin and platelet factor 4.
- LMW heparins and fondaparinux are less likely to cause this immune-mediated thrombocytopenia.
- Prolonged use of unfractionated heparin is associated with **osteoporosis**.

Heparin and related products

بقيسلي درجة التميّع عند هدول ال **patient's**

- Close monitoring of the **activated partial thromboplastin time** (**aPTT or PTT**) is necessary in patients receiving unfractionated heparin.
- Weight-based dosing of the LMW heparins results in predictable pharmacokinetics and plasma levels in patients with normal renal function. Therefore, LMW heparin levels are not generally measured except in the setting of renal insufficiency, obesity, and pregnancy.
- The aPTT test does not reliably measure the anticoagulant effect of the LMW heparins and fondaparinux.

هسا طالما أنه عم بنعطي ال **LMW** حسب الوزن ف نسبة إنه يتعدّى وجودها الحد الطبيعي بالدم ح تكون أقل من ال **unfractionated Heparin** ، مع إنه ما بقدر أقيسه برضو في حالات ال **renal insufficiency, obesity, pregnancy**

هاد ال **test** مش مفضّل استخدامه في قياس نسبة التخثر لل **LMW and fondaparinux** ، وإنما بس بستخدمه في حالة ال **unfractionated Heparin**

Direct Thrombin and Factor Xa Inhibitors

هون عم بتحكي عن أدوية بشتغل بشكل مباشر على ال **thrombin inhibitor**

Direct thrombin inhibitors

- **Lepirudin** (administered parentrally (I.V)) and **dabigatran** is an orally active direct thrombin inhibitor.
- Direct thrombin inhibitors are used as **alternatives to heparin primarily in patients with heparin-induced thrombocytopenia.**

بقدر استخدمله هاد التيست

- The action of these drugs is monitored with the aPTT laboratory test.
- Like other anticoagulants, the direct thrombin inhibitors can cause bleeding. No reversal agents exist. بعمل **bleeding** متل الباقي

Medicinal leech therapy (hirudotherapy)

يعني **complementary**

Hirudin is the prominent constituent of leech saliva.

نوع من انواع ال **parasite** موجودة بال **saliva** وبتعمل **lysing** لل **fibrin**

Direct Thrombin and Factor Xa Inhibitors

هون الأدوية إلّي بتشتغل على تثبيط ال **Factor Xa** بشكل مباشر

Direct oral Factor Xa inhibitors

- Oral Xa inhibitors, including **rivaroxaban** and **apixaban**, have a rapid onset of action and shorter half-lives than warfarin. من خصائصهم :
- Rivaroxaban is approved for:

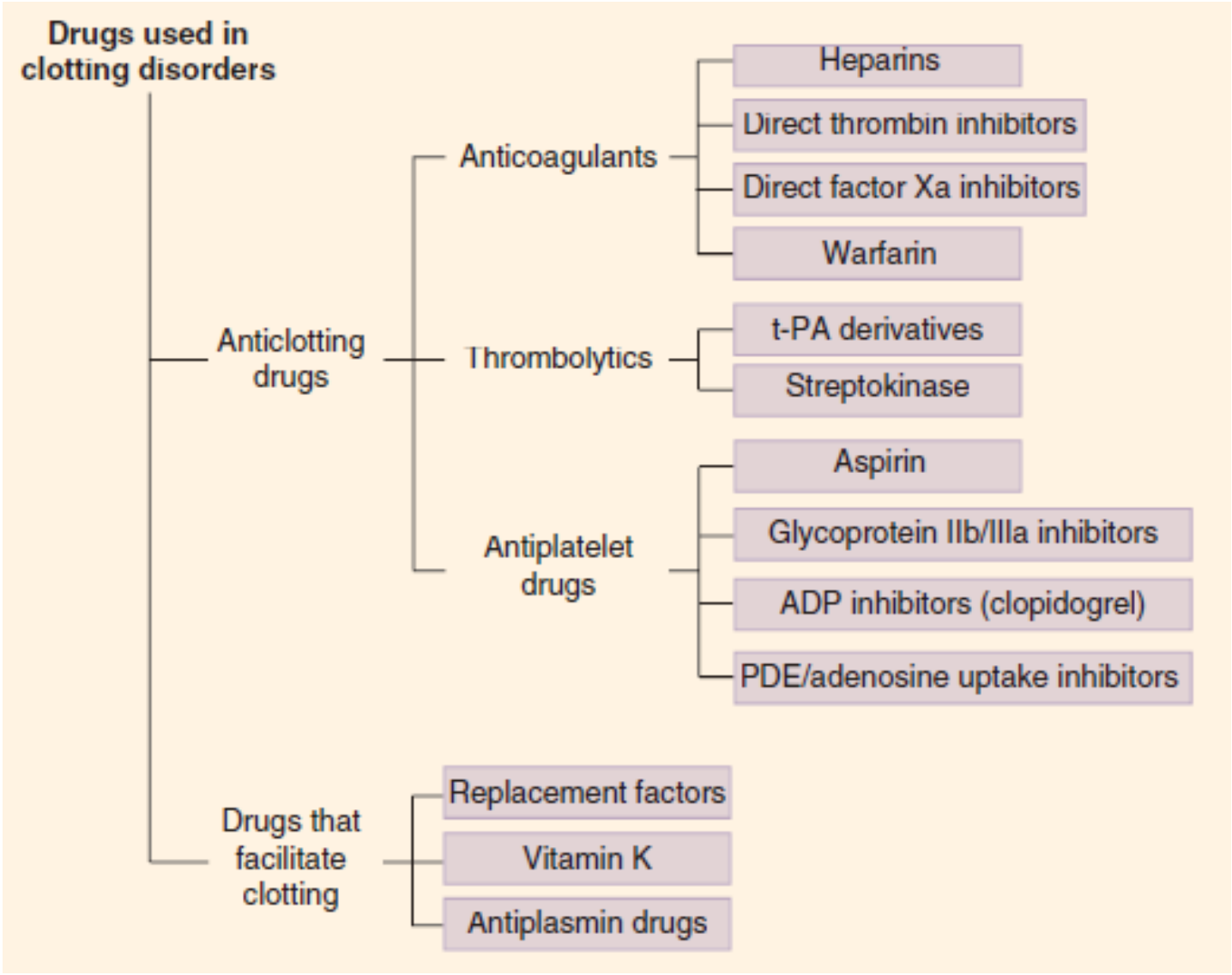
1. prevention of venous thromboembolism following hip or knee surgery
2. prevention of thromboembolic complications in patients with atrial fibrillation.

- Like other anticoagulants, the factor Xa inhibitors can cause bleeding. No reversal agents exist.

الناس إلّي بتعمل **knee surgery** بكونوا ممنوعين لفترة طويلة من الحركة ف هون بتكون عندهم احتمالية ال **clot** عالية ف بنستخدم الدوا هون ك **prevention**

كمان بشتغل ك **prevention** للمرضى إلّي عندهم **atrial fibrillation**

سلبيته باختصار شديد إنه ما إله **antidote**


Drugs used in clotting disorders
Anticlotting drugs
Anticoagulants
Heparins
Direct thrombin inhibitors
Direct factor Xa inhibitors
Warfarin
Thrombolytics
t-PA derivatives
Streptokinase
Antiplatelet drugs
Aspirin
Glycoprotein IIb/IIIa inhibitors
ADP inhibitors (clopidogrel)
PDE/adenosine uptake inhibitors
Drugs that facilitate clotting
Replacement factors
Vitamin K
Antiplasmin drugs

Warfarin

بعمل inhibition synthesis لل coagulant

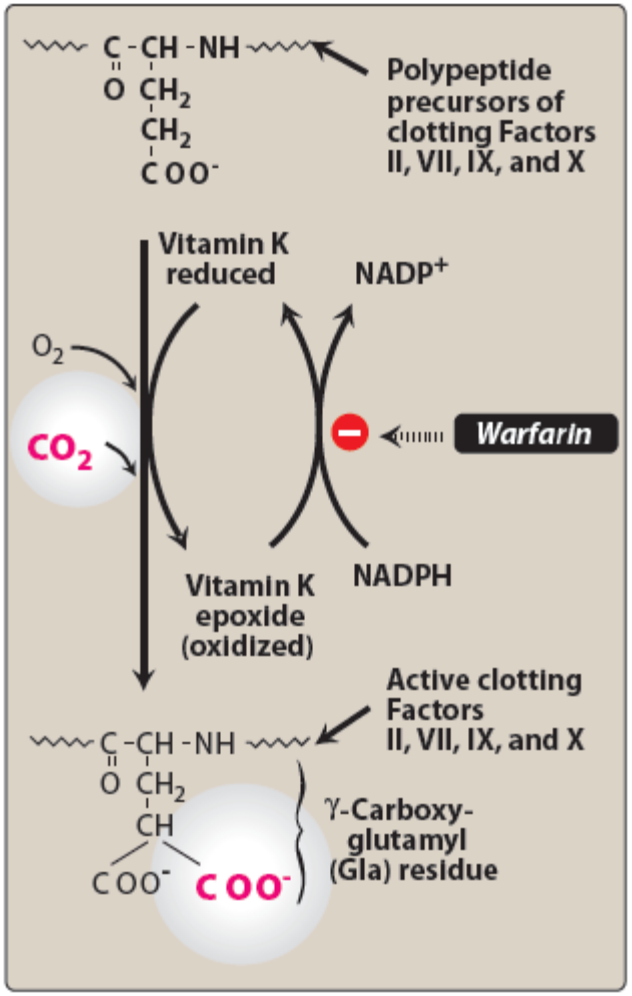
The clinical use of the coumarin anticoagulants began with the discovery of an anticoagulant substance formed in spoiled sweet clover silage which caused hemorrhagic disease in cattle. At the behest of local farmers, a chemist at the University of Wisconsin identified the toxic agent as bishydroxycoumarin. A synthesized derivative, dicumarol and its congeners, most notably warfarin (**W**isconsin **A**lumni **R**esearch **F**oundation, with "arin" from coumarin added; Figure 34–5), were initially used as rodenticides. In the 1950s warfarin (under the brand name Coumadin) was introduced as an antithrombotic agent in humans. Warfarin is one of the most commonly prescribed drugs, used by approximately 1.5 million individuals, and several studies have indicated that the drug is significantly underused in clinical situations where it has proven benefit.

هون بحكي كيف تم اكتشاف ال warfarin

ال warfarin بمنع ال vitamin K reduction ف بالتالي ما رح يكون في عندي coagulation factor
ف بالتالي ما رح يخلي ال fibrinogen يتحول ل fibrin

Warfarin

- **Chemistry and pharmacokinetics:**
- **Warfarin** and other coumarin anticoagulants are small, lipid-soluble molecules that are readily absorbed after oral administration.
- Warfarin is highly bound to plasma proteins (>99%), and its elimination depends on metabolism by cytochrome P450 enzymes.
- **Mechanism and effects:**
- Warfarin and other coumarins interfere with the normal post-translational modification of clotting factors in the liver, a process that depends on an adequate supply of reduced vitamin K.
- The drugs inhibit vitamin K epoxide reductase, which normally converts vitamin K epoxide to reduced vitamin K. The vitamin K-dependent factors include thrombin and factors VII, IX, and X.



عنده narrow therapeutic index لهيك لازم نعمل monitoring باستمرار
حتى جرعته بنغيرها حسب اكله لأنه مثلاً المرضى إلّي بياخدوا warfarin لازم كل فترة يعملوا فحص
وبنحدد للمريض كم نسبة معينة ممكن ياكلها من ال vitamin K لإنه إذا قلت ح يصير عندي extra dose of warfarin
والعكس صحيح
وهو high protein binding ف رح تأثر بالدوز برضو
وكمان ال metabolized إله بتأثر بال CYP450
إذا زاد نسبة ال warfarin رح تزيد نسبة ال bleeding
إذا قلت نسبته رح يصير coagulation

Warfarin oral

- Because the clotting factors have half-lives of 8–60 h in the plasma, an anticoagulant effect is observed only after sufficient time has passed for elimination of the normal preformed factors.
- The action of warfarin can be reversed with vitamin K, but recovery requires the synthesis of new normal clotting factors and is, therefore, slow (6–24 h). More rapid reversal can be achieved by transfusion with fresh or frozen plasma that contains normal clotting factors.
- The effect of warfarin is monitored by the **prothrombin time (PT) test.**

Clinical use:

- Warfarin is used for chronic anticoagulation in all of the clinical situations described previously for heparin after initial heparin treatment, except in pregnant women.
- Treatment with warfarin should be initiated with standard doses of 5–10 mg.

ضروري تعرفوا ال **maintenance dose**

- The initial adjustment of the prothrombin time takes about 1 week, which usually results in a maintenance dose of 5–7 mg/d.

بحالات ال **chronic** ح يعطوا **warfarin and Heparin** سوا لمدة ٤ ايام وبعدها بكملوا **warfarin** لحاله

Warfarin

Toxicity:

- **Bleeding** is the most important adverse effect of warfarin.كلهم بشتركوا فيها
- Warfarin can cause bone defects and hemorrhage in the developing fetus and, therefore, is **contraindicated in pregnancy**. بعمل تشوّه للطفل
- Because warfarin has a narrow therapeutic window, its involvement in drug interactions is of major concern.

  Drug -drug interaction with warfarin

  – Cytochrome P450-inducing drugs (eg, carbamazepine, phenytoin, barbiturates) increase warfarin's clearance and reduce the anticoagulant effect of a given dose. شرحها بالسلايد إلّي بعده

  – Cytochrome P450 inhibitors (eg, amiodarone, selective serotonin reuptake inhibitors, cimetidine) reduce warfarin's clearance and increase the anticoagulant effect of a given dose.

- Excessive anticoagulant effect and bleeding from warfarin can be reversed by stopping the drug and administering oral or parenteral **vitamin K 1 (phytonadione),** fresh-frozen plasma, prothrombin complex concentrates such as Bebulin and Proplex T, and recombinant factor VIIa (rFVIIa).

ليييه ما بيتّاخد مع أدوية ال CYP450 inducing drug? لأنه وجود ال CYP450 رح يزيد من ال metabolism لل warfarin ف بالتالي رح يزيد ال clearance إله وبقلل ال effect تبعه

على العكس في النقطة التانية وقت يكون عندي inhibition لهاد الإنزيم ، ف رح يقل ال metabolism of warfarin ف بتقل ال clearance إله ورح يزيد بالجسم ويوصل ل toxic dose

عشان اتخلص من ال bleeding إلّي بعمله ال warfarin ف بعمل إيقاف للأدوية هديك و بعطيه Vitamin K إما أورال أو IV

TABLE 34–2 Pharmacokinetic and pharmacodynamic drug and body interactions with oral anticoagulants.

Increased Prothrombin Time		Decreased Prothrombin Time	
Pharmacokinetic	***Pharmacodynamic***	***Pharmacokinetic***	***Pharmacodynamic***
Amiodarone	**Drugs**	Barbiturates	**Drugs**
Cimetidine	Aspirin (high doses)	Cholestyramine	Diuretics
Disulfiram	Cephalosporins, third-generation	Rifampin	Vitamin K
Metronidazole[1]	Heparin		**Body factors**
Fluconazole[1]	**Body factors**		Hereditary resistance
Phenylbutazone[1]	Hepatic disease		Hypothyroidism
Sulfinpyrazone[1]	Hyperthyroidism		
Trimethoprim-sulfamethoxazole			

TABLE 34–1 Properties of heparins and warfarin.

Property	Heparins	Warfarin
Structure	Large acidic polysaccharide polymers	Small lipid-soluble molecule
Route of administration	Parenteral	Oral
Site of action	Blood	Liver
Onset of action	Rapid (minutes)	Slow (days); limited by half-lives of preexisting normal factors
Mechanism of action	Activates antithrombin III, which proteolyzes coagulation factors including thrombin and factor Xa	Impairs post-translational modification of factors II, VII, IX and X
Monitoring	aPTT for unfractionated heparin but not LMW heparins	Prothrombin time
Antidote	Protamine for unfractionated heparin; protamine reversal of LMW heparins is incomplete	Vitamin K_1, plasma, prothrombin complex concentrates
Use	Mostly acute, over days	Chronic, over weeks to months
Use in pregnancy	Yes	No

aPTT, activated partial thromboplastin time; LMW, low molecular weight.