HLS

MODIFIED NO. 2

PHARMACOLOGY

كتابة: فاعل خير

تدقيق: فاعل خير

الدكتور: مالك زحلف

Abciximab, eptifibatide, & tirofiban.

Glycoprotein IIb/IIIa inhibitors:

- **Abciximab** is a humanized monoclonal antibody directed against IIb/IIIa complex.
  Binds to these two receptors (IIb/IIa) to inhibit the fibrinogen from cross linking between platelets.
- **Eptifibatide** & **Tirofiban** inhibit ligand binding to IIb/IIIa receptor by their occupancy of the receptor.

➔ All Inhibit bridging of platelet by fibrinogen.

Abciximab is injectable. The strongest mechanism , that is why we don't use it much

- Approved for use in percutaneous coronary intervention (PCTA) & in ACSs.

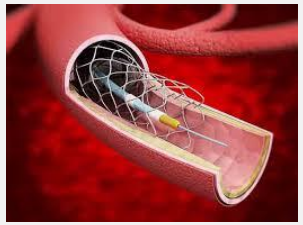
Only used in emergency situation.

- The three agents are administered parenterally

ACS: acute care surgery

PCTA: percutaneous transluminal coronary angioplasty

- When preparing a patient for surgery, we administer 300 mg of clopidogrel. If the patient is at risk of reduced CYP2C19 activity, we consider using ticagrelor or prasugrel instead.
- In emergency situations where rapid preparation is needed, cangrelor is given because it is injectable, works quickly, and wears off fast. However, if cangrelor is not available, abciximab is used as an alternative.
- Abciximab is given one hour before the angioplasty to prevent the accumulation of platelets around the stent.
- A stent is a small mesh tube typically used to hold open passages in the body, such as weak or narrowed blood vessels. Stents are often used to treat narrowing in the coronary arteries, which provide the heart with oxygen-rich blood.



- Major side effect: Bleeding, because abciximab is IV monoclonal antibody.
- A monoclonal antibody (mAb) is a laboratory-produced molecule designed to bind to a specific target, usually a protein. These antibodies are called "monoclonal" because they are made by identical immune cells that are all clones of a unique parent cell, meaning they recognize and attach to the same specific epitope (part of the target).

Dipyridamole:

We are making inhibition toward the degranulation

It decreases the Ca+2 concentration in platelets by increasing cAMP by inhibition of phosphodiesterase and preventing degranulation of aggregating agents.

- **MOA: -inhibits phosphodiesterase→ ↑ cAMP→ potentiates effects of prostacyclin→ platelet inhibition.**

It produce headache .

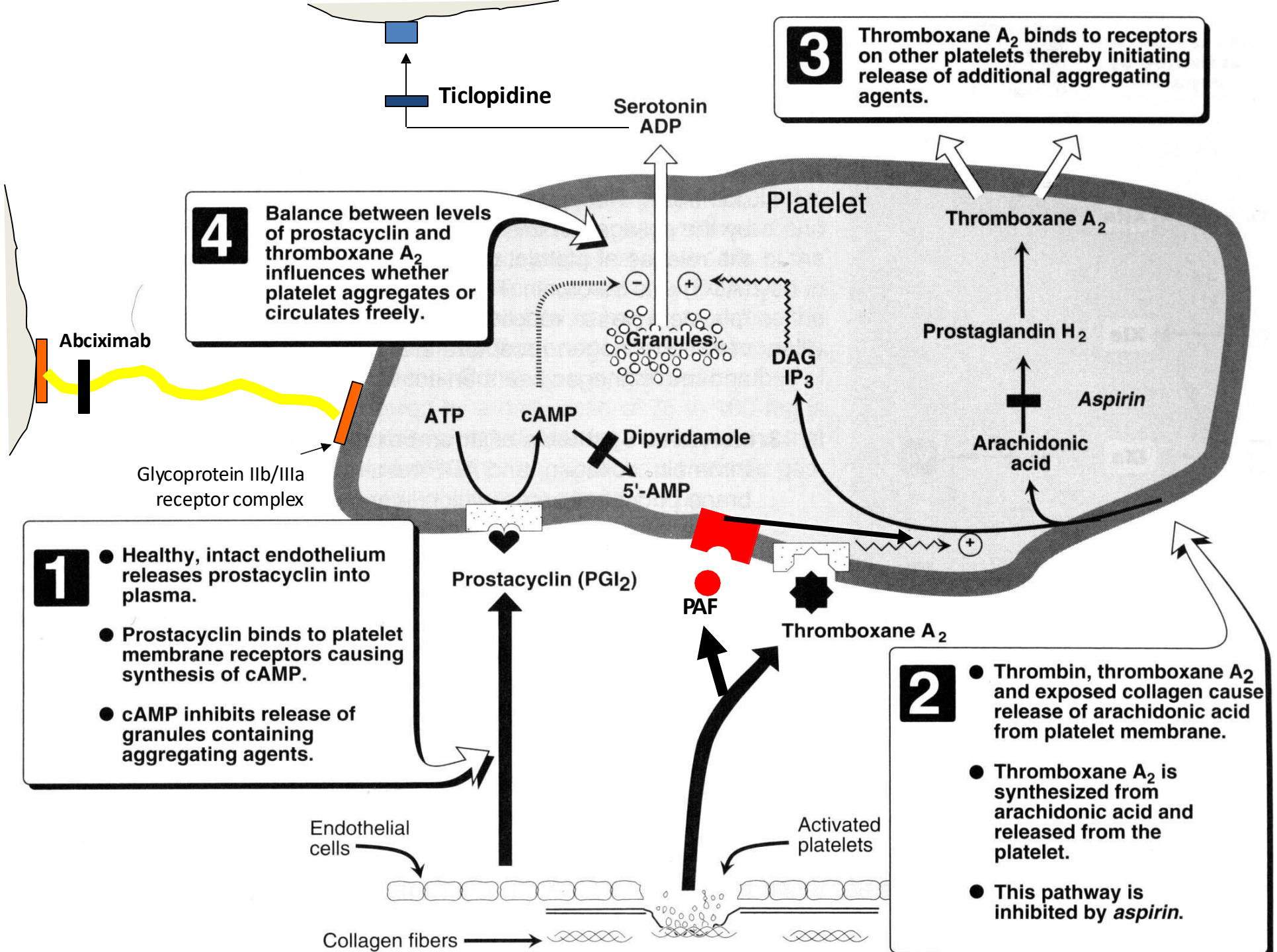
-dipyridamole is also a coronary vasodilator.

Increasing cAMP in smooth muscles leads to vasodilation, which is useful in cases of coronary artery spasms or coronary artery clots. It helps prevent the buildup of platelets over the clot.

- **Indications:-with aspirin for prophylaxis in angina.**

  -with warfarin to inhibit embolization from prosthetic heart valves.

It has a weak effect, so it is used only as an adjunct therapy, added to other medications such as aspirin and warfarin.


Ticlopidine
Serotonin
ADP
3
Thromboxane A_2 binds to receptors on other platelets thereby initiating release of additional aggregating agents.
Platelet
Thromboxane A_2
4
Balance between levels of prostacyclin and thromboxane A_2 influences whether platelet aggregates or circulates freely.
Granules
DAG
IP_3
Prostaglandin H_2
Abciximab
ATP
cAMP
Dipyridamole
5'-AMP
Aspirin
Arachidonic acid
Glycoprotein IIb/IIIa receptor complex
1
Healthy, intact endothelium releases prostacyclin into plasma.
Prostacyclin binds to platelet membrane receptors causing synthesis of cAMP.
cAMP inhibits release of granules containing aggregating agents.
Prostacyclin (PGI_2)
PAF
Thromboxane A_2
2
Thrombin, thromboxane A_2 and exposed collagen cause release of arachidonic acid from platelet membrane.
Thromboxane A_2 is synthesized from arachidonic acid and released from the platelet.
This pathway is inhibited by *aspirin*.
Endothelial cells
Activated platelets
Collagen fibers

- In previous slide, we focused on platelet aggregation and prophylaxis towards either starting of the clot or building on the clot.

- Now we are dealing with the coagulation itself, we have already a clot, so will try to dissolve it.

- RECALL: we have balance between coagulation and anticoagulation within the body.

- To dissolve the clot quickly:

- Use thrombolytic (ابرة الحياة) which degrade fibrin meshwork, it breaks the cross linkages between (IIb/IIa) glycoproteins and fibrinogen, so it releases the fibrinogen.
- Side effects: serious bleeding problem as it dissolves all the thrombi in the body (affecting thrombosis process)

- Slow dissolving:

- Avoiding the serious bleeding problems when using thrombolytics.
- Advantage towards anticoagulants
- This process is done within hospital after surgeries, e.g. prosthetic valves stimulation coagulation process.
- atrial fibrillation(يرفرف): Rapid and irregular beating of the atrial chambers of the heart it can create blood clots in the heart that may cause stroke, it is a chronic situation in which anticoagulants can manage it.

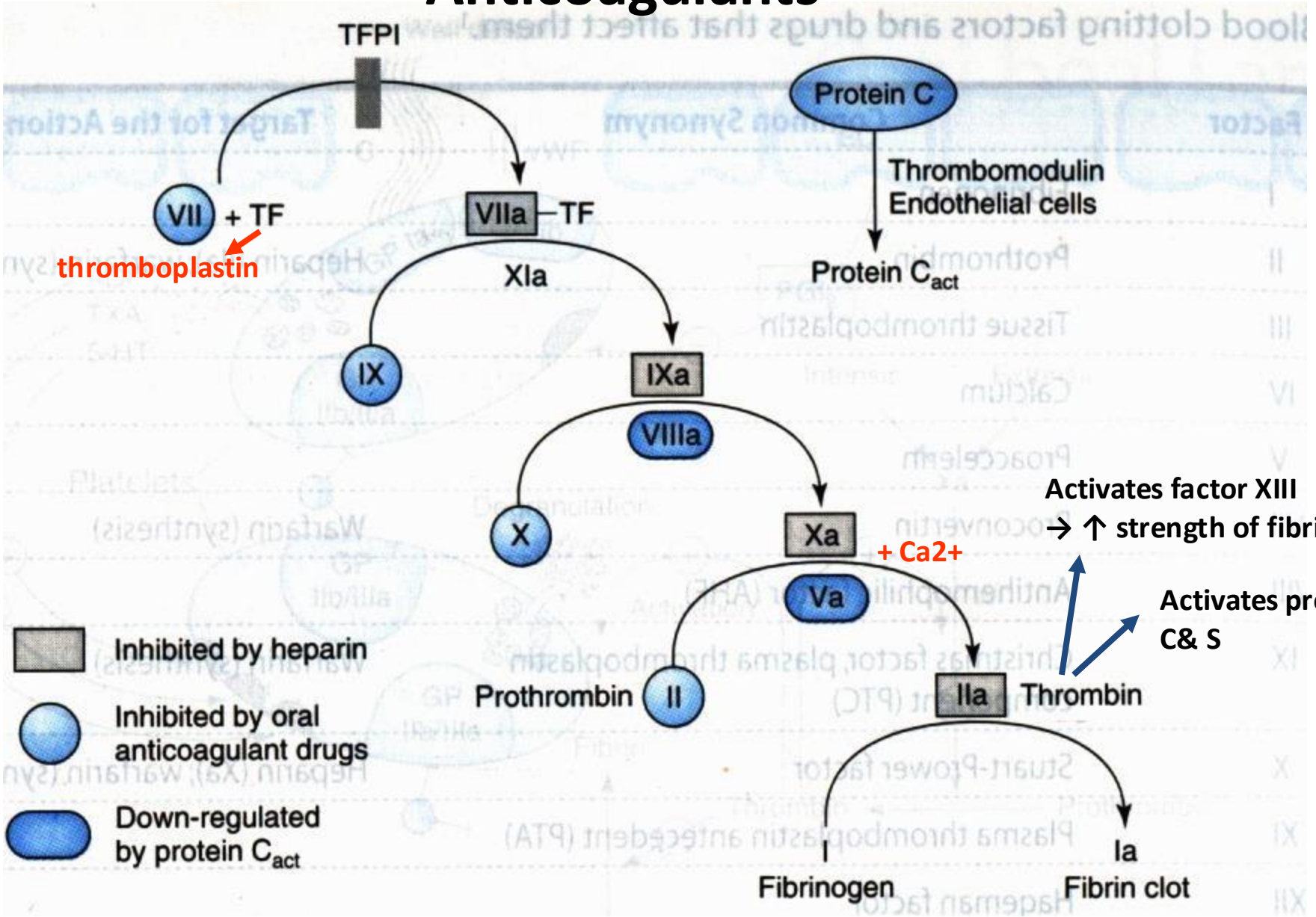
Anticoagulants

Coagulation Cascade

before they where prophylactic now we are removeing the coagulation (treatment)

- 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 site of vessel injury.

Anticoagulants



Anticoagulants

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) Pentasaccharide specific Xa inhibitors:

Fondaparinux, Rivaroxaban

F) Warfarin. (vitamin k inhibitor)

old , the most drug lets the patients enter the hospitals in term of bleeding till now

Mechanism of unfractionated heparin UFH action

Structure: long chain of Pentasaccharides with glycan glucosamine chain

- Prevents further thrombus growth, allowing the body's own thrombolytic system to dissolve clot.

Stimulates the system towards anticoagulation, by the time the clot dissolves.

Activates plasma protease inhibitor **antithrombin III (AT III).**

when heparin binds to antithrombin lll, it causes the activity of it *100000 folds

- The complex(heparin + anti..III) inactivates factors:

XIIa, XIa, IXa, **Xa, & IIa** (thrombin) Direct Xa and IIa inhibitor

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

DVT: deep vein thrombosis
PE: pulmonary embolism

Routes of administration: injectable/infusion, since it has low half life

UFH Toxicity

1. The major adverse effect is **bleeding** since it stimulates the anticoagulation in all the body
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**
5. Hyperkalemia (decreases aldosterone)
6. **Heparin-induced thrombocytopenia (HIT**).

Unfractionated Heparin (UFH) is a fast-acting blood thinner that works together with antithrombin

Chronic use of heparin

When your immune is stimulated to release antibodies that bind to complexes of heparin (UFH) and platelet factor 4 (PF4) within the platelets, activating the platelets to clot everywhere in the body, so all the platelets have been used resulting in your platelets levels dropping (antigenic reaction) so you should do platelets count.

Heparin is a naturally occurring anticoagulant, often extracted from animal tissues like pigs or cows. The extraction process typically leads to the production of a heterogeneous solution
(تكسر خلال عملية الاستخلاص، في منه تكسر ومنه بقي حبة كاملة)
due to variations in molecular weight and chemical structure.

- كل سحبة من المستخلص رح يعطيني تركيز مختلف، على سبيل المثال مرة 3 حبات مكسرة و 5 كاملات، السحبة الثانية 8 مكسرات ووحدة كاملة.

- Heterogenous solution are those that have non-uniform compositions and prosperities throughout the solution.

- Note: the effect of the inhibitory activity of heparin-antithrombin III should be intact, however, the heterogeneity of the extraction will not give us this intact activity, so we should do what's knonw as lab monitoring.

- Summary:
- Heterogeneity of Heparin:

The extracted crude of heparin consists of mixture of heparin molecules with varying molecular weights, leading to the categorization into two types:

- Unfractionated Heparin (UFH): this is the mixture of heparin molecules with wide range of molecular weights. UFH has complex pharmacokinetics, interacting with various proteins in the blood.
- Fractionated Heparin (Low Molecular Weight Heparin, LMWH): through further processing (such as gel filtration or chromatography), a subset of lower molecular weight heparin molecules is isolated. LMWH typically ranges between 1 to 10 kDa. This fraction is more predictable in its anticoagulant effects, with less binding to proteins, longer half-life, and reduced risk of certain side effects.

Laboratory Monitoring for UFH

we don't use heparin except we have Monitoring value ,
almost every day

- Activated partial thromboplastin time **(aPTT)**:

It measures the number of seconds it takes for a clot to form in a sample of blood after substances (reagents) are added

- Normal aPTT is 24-36 sec.

In EP patients and DVT patients:

- An aPTT ratio (patient aPTT/control aPTT) of 2–2.5 should be achieved throughout infusion or 6 hours after intermittent administration.

Lab monitoring ensures that the dose give the required efficacy/affect (2-2.5)

Shorter Pentasaccharides Chain OR Fractionated Heparin

B) Low-Molecular Weight Heparins (LMWHs)

The natural extracted heparin goes fractionation/separation, so we get a homogenous solution.

- **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 so it has lower efficacy than (UFH), it has moderate activity which is good, therefore, the side effects are reduced – (↓ bleeding risk)

  More efficacious → UFH
  Less efficacious → LMWH/ fractionated heparin

- Since LMWHs minimally affect thrombin, they have minimal impact on the aPTT (which is most sensitive to thrombin). LMWH doesn't need to lab monitoring.

B) Low-Molecular Weight Heparins (LMWHs)

- **Enoxaparin:** from same sources as regular heparin; doses are specified in milligrams.
- Eliminated renally.

UFH can be eliminated in urine and feces
LMWH is contraindicated in patient with compromised renal function, however high molecular heparin can be given, because (LMWH) would affect renal function and accumulate in the body increasing the risk of bleeding.

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

- Neutralization by protamine is incomplete. (Antidote)

Thus, it decrease the bleeding effect of heparin in patients after surgery.

Advantages of LMWHs over Heparin

- ↓ laboratory monitoring: Because the solution is homogeneous

Blood conc determined only in renal failure, pregnancy, & obesity (also renal failure patients)

- ↑ predictability of response
- Once-twice daily injections
- Ease of dosing and administration (SQ), Subcutaneous
- ↓ requirement of hospitalization
- ↓ risk of thrombocytopenia
- ↓ risk of osteoporisis
- ↓ risk of (HIT)

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.

Warfarin & Coumarin Anticoagulants

- is generally used as sodium salt & has 100% bioavailability.
- > 99% is bound to plasma albumin → small Vd, long half life.

Mechanism of Warfarin Action

Inhibits the activation of factors which are synthesized in the liver, the activation process is K-dependent.

- Blocks carboxylation of factors (VII, IX, & X, & II) as well as the (proteins C and S)

The activation of protein C and S balance the coagulation effect of (VII,XI,X and II) protect the body from clots.

Coagulants

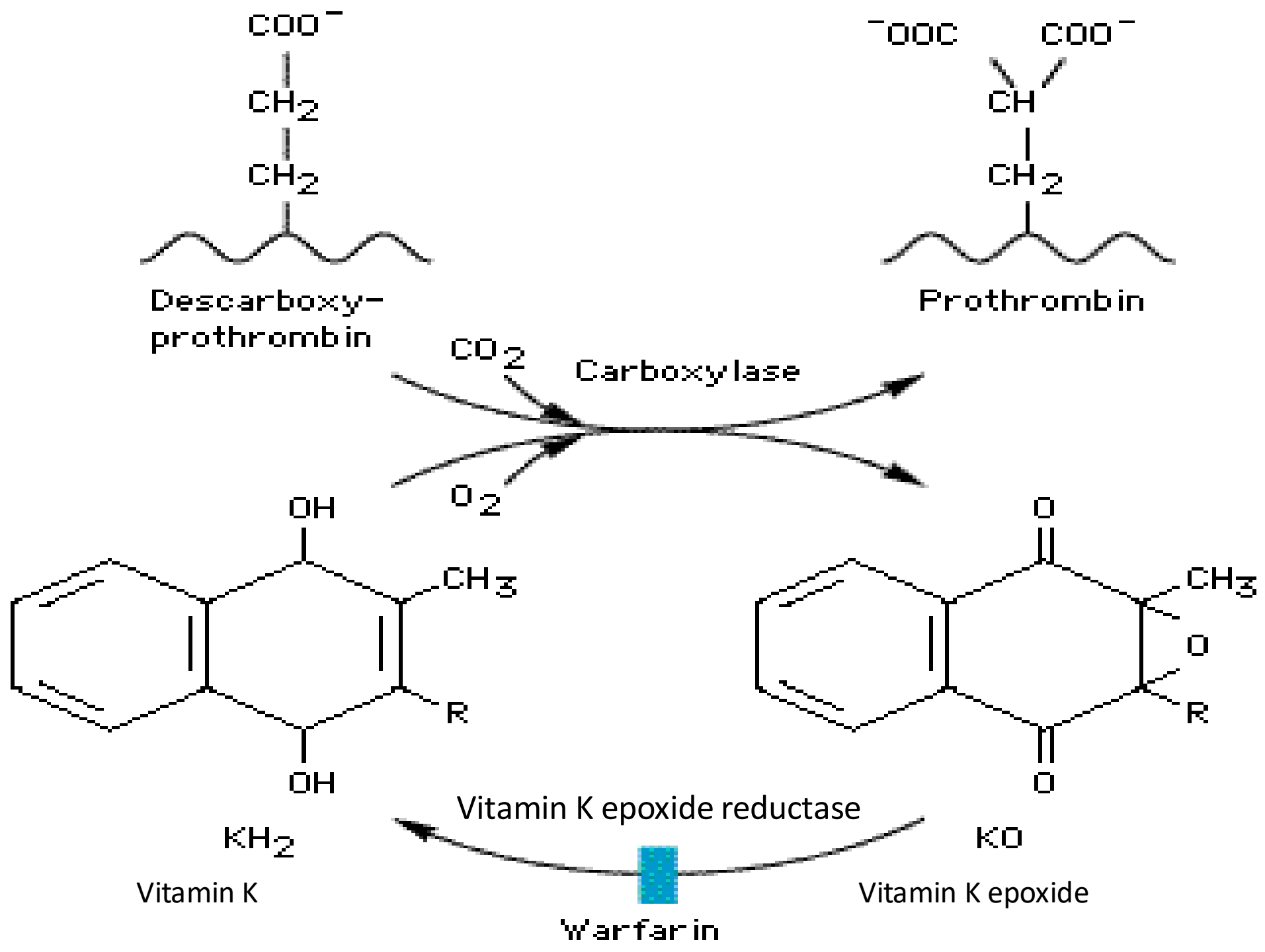
Anti-Coagulants

Binds to thrombomodulin to inactivate factor Va and VIIIa

- 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.

It inhibits Vitamin K epoxide reductase which reduces vitamin K

The antidot of warfarin is Vitamin K


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

Warfarin Drug Interactions

Food drug interaction, Tomatoes and parsley (بقدونس) are rich in Vit.K

1. Pharmacokinetic mechanisms

- **enzyme induction,**
- **enzyme inhibition,**
- **↓ plasma protein binding.**

Warfarin is metabolized by CYP2C9 in liver, so any drug induces or inhibits CYP2C9 would affect warfarin kinetics which is serious since warfarin has narrow therapeutic index.

2. Pharmacodynamic mechanisms

- **synergism** (impaired hemostasis),
- **competitive antagonism** (vitamin K).

CYP2C9 polymorphism: the activation of the enzyme varies between population, thus drug monitoring is needed, when CYP2C9 is very active, this results in synergism effect.

- 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.

I. Drugs that ↑ prothrombin time

مش حفظ

↓ *warfarin metabolism*

Allopurinol	Ethanol (acute)	Erythromycin
Cimetidine	Disulfiram	Azithromycin
Omeprazole	Metronidazole	Ciprofloxacin
Phenytoin (sometimes)	Ketoconazole	Norfloxacin
Phenylbutazone	Fluconazole	Sulfonamides
Azapropazone	Miconazole	
حفظ Amiodarone		

↑ *catabolism of clotting factors*

	Thyroid hormones	

↓ *synth. of clotting factors (↓ bacteria & direct inh. of epoxide reductase)*

Cefamandole	Cefmetazole	
Cefotetan	Cefoperazone	

Unestablished mechanisms حفظ

Acetaminophen?	Fibrates	Corticosteroids
Paracetamol because it affects liver function, and many cause liver toxicity	Statins	Androgens

II. Drugs that ↓ prothrombin time		مش حفظ
↑ 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	Cyclophosphamide
↑ risk of bleeding without effect on PT		
Aspirin NSAIDs	Ticlopidine Clopidogrel حفظ	SSRIs

Warfarin Toxicity

1. **Bleeding** – the most dangerous.

   Contraindication: teratogenic category (X)

2. Warfarin crosses the placenta readily & can cause hemorrhagic disorders & abnormal bone formation **in the fetus.** Thus, warfarin should never be administered during pregnancy**.**

3. **Venous thrombosis** (due to ↓activity of protein C) and S

   Might lead to

4. Purple toe syndrome (cholesterol microembolization → arterial obstruction) clots might close the small arteries.

It is all about the half lives of protein, the coagulant factor specially factor II has higher half lives than protein C and S (anti coagulants). This means that during initial days of warfarin therapy, the body loses its natural anticoagulants more quickly than the pro-coagulants, creating a temporary pro-thrombotic state

Half lives (t1/2) is the time it takes for the plasma concentration of a substance to reduce by 50%.

To protect the patient from this, we do what is known as Bridging, so in the first 2 days of taking warfarin, heparin is also given until an INR between 2 and 3 is reached.

Heparin → lab monitoring: aPTT

Warfarin → lab monitoring: INR or PT

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

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

PT is a blood test that measures how long it takes for blood to clot.

INR (international Normalized Ratio) is a standardized measures used to assess the clotting tendency of blood, primarily for patients on anticoagulant therapy like warfarin. It allows for consistent ad reliable monitoring of blood clotting times across different laboratories, ensuring that warfarin dosage can be adjusted appropriately to prevent excessive clotting or bleeding.

Contraindications to warfarin:

Absolute:

- pregnancy
- others – see heparin

Relative:

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

Additional sources

1. Book pages
2. Youtube videos
3. Webpages…etc

آية أو حديث شريف دعاء أو نصيحة .....
اترك أثر جميل للقارئ

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	22 19	--------- …….	**Amiodarone** decreases the metabolism of warfarin احفظ المحددين باللون الأصفر Switch between anticoagulant and coagulants
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!