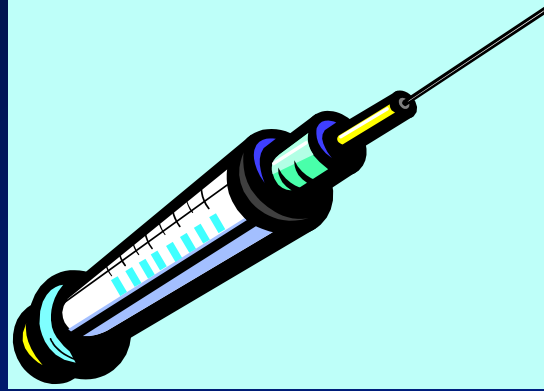


Anticoagulants



ILOs



- Introduction about coagulation cascade
- Classify drugs acting as anticoagulants
- Elaborate on their mechanism of action, correlating that with methods of monitoring
- Contrast the limitations & benefits of injectable anticoagulants in clinical settings
- Emphasis on the limitations of VKAs & on variables altering or modifying their response.

Drugs and coagulation

- **Anticoagulants:** prevent thrombus formation and extension by inhibiting clotting factors e.g. heparin, low molecular weight heparin, coumarins/ warfarin.
- **Antiplatelet drugs:** reduce risk of clot formation by inhibiting platelet functions e.g. aspirin and ticlopidine.
- **Fibrinolytic agents:** dissolve thrombi already formed e.g. streptokinase.

Coagulation Pathways

- Two major pathways

- ◆ Intrinsic pathway

- ◆ Extrinsic pathway

- Both converge to a common pathway

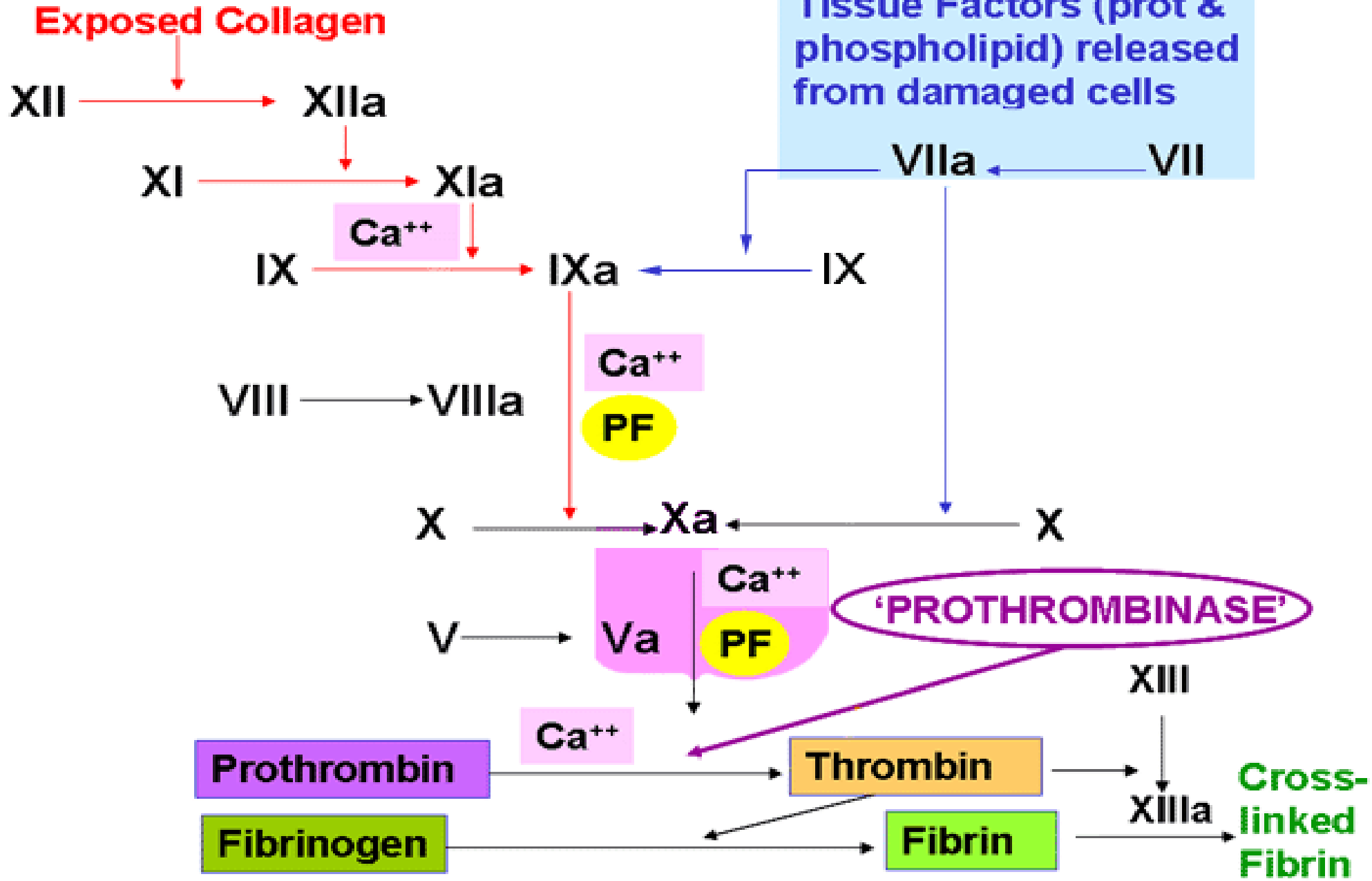
- 13 soluble factors are involved in clotting which normally circulate in an inactive state and must be **activated** to form a fibrin clot

All clotting factors are
within the blood
(tissue factor =
thromboplastin)

INTRINSIC PATHWAY

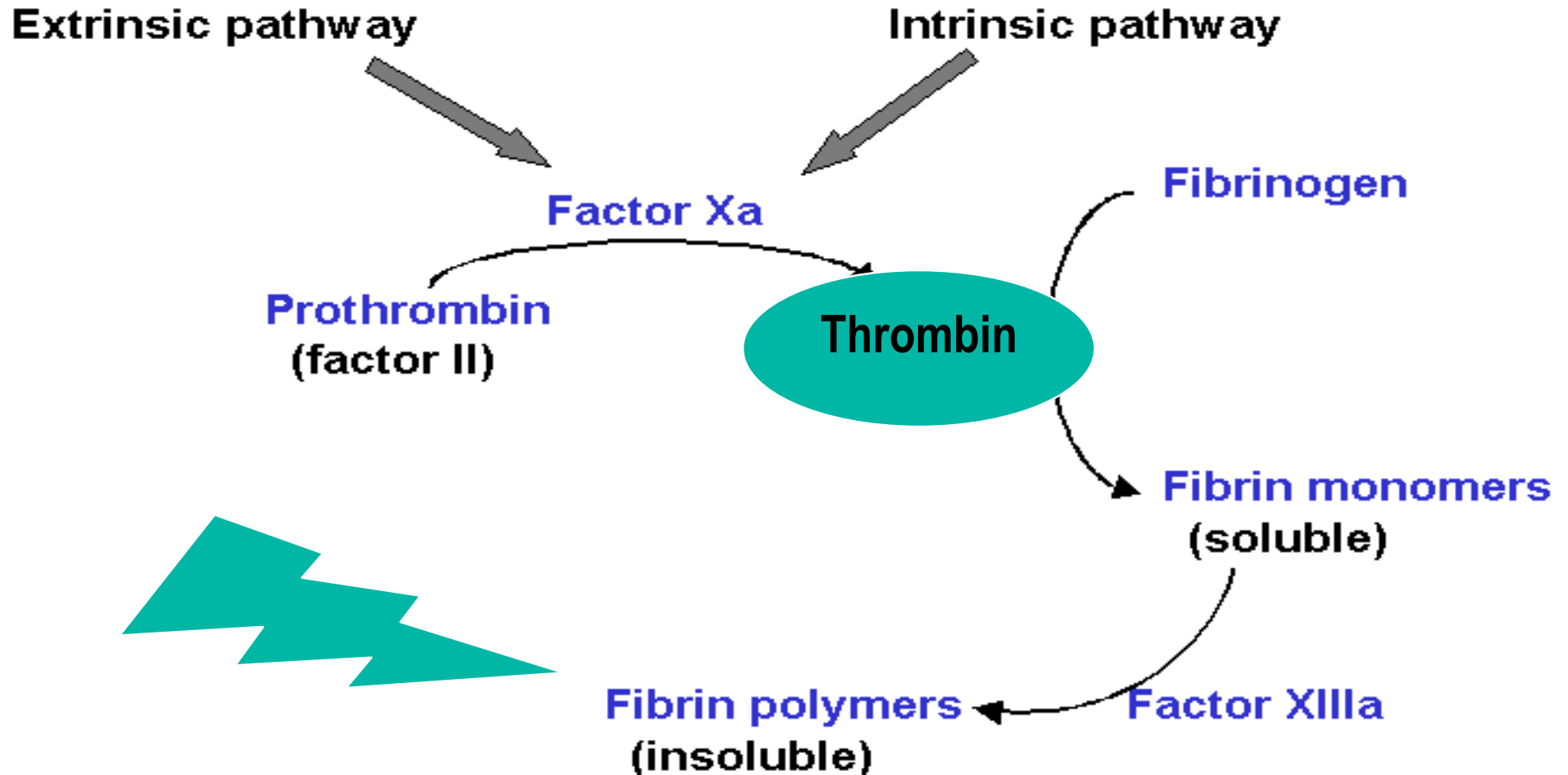
EXTRINSIC PATHWAY

Tissue Factors (prot & phospholipid) released from damaged cells



Common pathway & Fibrin clot formation

Fibrin Formation



Endogenous Inhibitors of Coagulation

- **Antithrombin III**, is a plasma protein that inhibits **activated thrombin (*factor IIa*) and Xa**, **it is the site of action of heparin**
- **Prostacyclin (PGI₂)**, is synthesized by endothelial cells and inhibits platelet aggregation
- **Protein C and Protein S**

ANTICOAGULANTS

**Parenteral
Anticoagulants**

**Oral
Anticoagulants**

Thrombin inhibitors

- **Indirect**
- **Direct**

Vitamin K antagonists

Warfarin

Indication of anti-coagulants

Anticoagulants are indicated in:

- Myocardial infarction (MI)
- Deep venous thrombosis (DVT)
- Peripheral arterial emboli, pulmonary embolism (PE) and many other conditions
- Anticoagulants are also used in blood transfusions, and dialysis procedures

Parenteral Anticoagulants

Indirect Thrombin inhibitors

Heparin and

heparin- related agents

Heparin (Unfractionated Heparin)

- Normally occurs as macromolecule in mast cells with histamine (its physiological role is unknown)
- Commercial preparations are extracted from **beef** lung or **pig** intestine (can cause hypersensitivity reaction)
- Heparin stops the expansion of a thrombus and prevents the formation of new thrombi but it does not dissolve an existing thrombus

Heparin and related H- agents

- Heparin is an injectable rapidly acting anticoagulant
- Active in vitro and in vivo
- Low-molecular-weight forms (LMWHs), 1/3 the size of UFH are used as well and have many advantages over UFH

Heparin: Mechanism of action

- **Indirect Thrombin Inhibitor**
- It acts indirectly by increasing the activity of the endogenous anticoagulant “antithrombin III” (1000 folds) which inhibits **activated clotting factors** mainly thrombin (*factor IIa*) and Xa
- When Heparin binds to antithrombin III, it causes conformational changes that accelerates its rate of action 1000 fold

Heparin: Mechanism of action

Heparin



The diagram illustrates the mechanism of action of Heparin. It shows a purple bar labeled 'Heparin' at the top. Below it, a teal circle labeled 'Antithrombin III' and a black shape labeled 'Thrombin' are shown. A teal arrow points downwards to a second purple bar labeled 'Heparin'. Below this second bar, the 'Antithrombin III' and 'Thrombin' are shown bound to the Heparin bar, forming a ternary complex.

Antithrombin III

Thrombin

Heparin

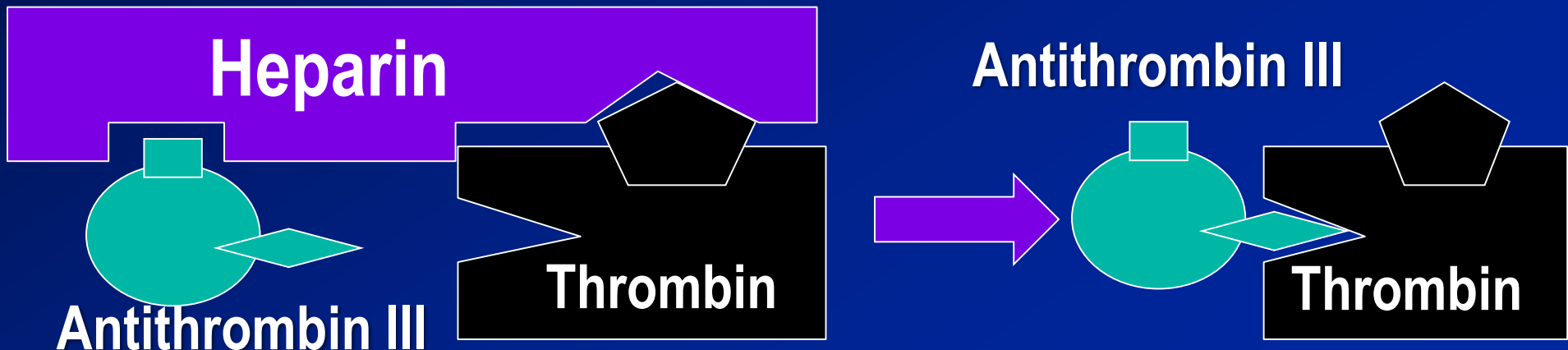
Antithrombin III

Thrombin

- Heparin binds to both antithrombin III and thrombin to form a ternary complex

Heparin: Mechanism of action

- ❑ Heparin dissociates leaving the thrombin bound to its inhibitor
- ❑ Once dissociated, Heparin is free to bind to another antithrombin molecule and subsequently inhibits more thrombin



UFH : Pharmacokinetics

- Heparin is not absorbed from the GIT
- It should be administered by IV or SC injection. Not injected IM as it causes haematomas at injection site
- Once in the blood stream, UFH binds to plasma proteins, endothelial cells and macrophages
- Heparin does not cross the placenta; therefore it is the drug of choice as anticoagulant during pregnancy
- Close monitoring of the activated partial thromboplastin time (aPTT) is necessary in patients receiving UFH.

Heparin: Therapeutic uses

- Due to its rapid onset of action, it is used to **initiate immediate anticoagulation** in thromboembolic disease (PE, DVT, MI) mainly as induction for oral vitamin K antagonists (VKAs)
- **Prevention of postoperative DVT (in patient undergoing hip replacement)**
- Prevention of coagulation during renal dialysis or cardiac surgery

Disadvantages of UFH

- The inconvenience of administration by injection
- The need for regular monitoring (aPTT)
- UFH carries a risk of **heparin-induced thrombocytopenia (HIT)**, a fall in the platelet count and increased risk of thrombosis due to binding to platelets

Heparin-induced thrombocytopenia (HIT)

- Generally, if the number of platelets is too low, excessive bleeding can occur
- If the number of platelets is too high, blood clots can form thrombosis
- However, There are disorders that reduce the number of platelets, such as **heparin-induced thrombocytopenia (HIT)** that typically cause thrombosis, or clots, instead of bleeding

UFH: Adverse effects

- The major adverse effect of heparin is **bleeding**
- **Allergic reactions (chills, fever, urticaria)** as heparin is of animal origin and should be used cautiously in patients with allergy
- Long-term heparin therapy is associated with **osteoporosis**
- ***Heparin-induced thrombocytopenia (HIT)***

Heparin: Contraindications

- Bleeding disorders, hemophilia
- Patients with hypersensitivity to the drug
- Recent surgery of the brain, eye or spinal cord, threatened abortion

Reversal of Heparin Action

- Discontinuation of the drug
- Heparin is strongly acidic and is neutralized by i.v. protamine sulfate (a strongly basic protein)
- It combines with heparin to form a stable complex devoid of anticoagulant activity

Low-Molecular-Weight Heparins

- LMWHs are derived from the chemical or enzymatic degradation of UFH into fragments approximately one-third the size of heparin.
- Have equal efficacy, **without frequent laboratory monitoring** (suitable for outpatient therapy)
- **Have a more predictable anticoagulant response**
(better bioavailability, longer $t_{1/2}$)
- **Binding to platelets and osteoblasts is reduced** with LMWH compared with UFH

Examples of LMWHs:

- Heparin fragments (e.g. **enoxaparin, dalteparin**)
- Synthetic pentasaccharide (**fondaparinux**)
- are used increasingly in place of unfractionated heparin
- LMWHs increase the action of antithrombin III on **factor Xa** but not its action on **thrombin**, because the molecules are too small to bind to both enzyme and inhibitor

Synthetic Heparin Derivatives

- Fondaparinux is a synthetic compound that inhibits factor Xa by antithrombin but does not inhibit thrombin

Advantages:

- Fondaparinux can be given once a day at a fixed dose without coagulation monitoring
- Less likely than UFH or LMWHs to trigger HIT

Differences between UFH and LMW Heparins

Drug characteristics	Heparin (UFH)	LMWH
IV $\frac{1}{2}$ life	2 hours	4 hours
Bioavailability after SC injection	20%	90%
Anticoagulant response	variable	Predictable

Major adverse effect	Frequent bleeding	Less frequent bleeding
	HIT, osteoporosis	Less
Specific antagonist	Protamine sulphate	-Incomplete-
Setting for therapy	Hospital	Hospital and OPC
Laboratory monitoring	Needed aPTT	Not needed

Advantages of LMWHs over UFH

- The theoretical pharmacologic advantages of LMWH over UFH arise from the preferential binding ratio to **factor Xa** over thrombin
- The convenience of once- or twice- daily subcutaneous injections **without regular coagulation monitoring** due to:
 - More predictable response
 - Long plasma half-life and improved bioavailability
 - Less plasma protein binding
 - Less platelet activation and lower risk of re-thrombosis and thrombocytopenia

Direct thrombin inhibitors (DTIs)

- DTIs exert their anticoagulant effect by **direct** binding to thrombin
- This direct effect is **rapid and potent**
- DTIs are **not associated** with the development of thrombocytopenia

Direct thrombin inhibitors (DTIs)

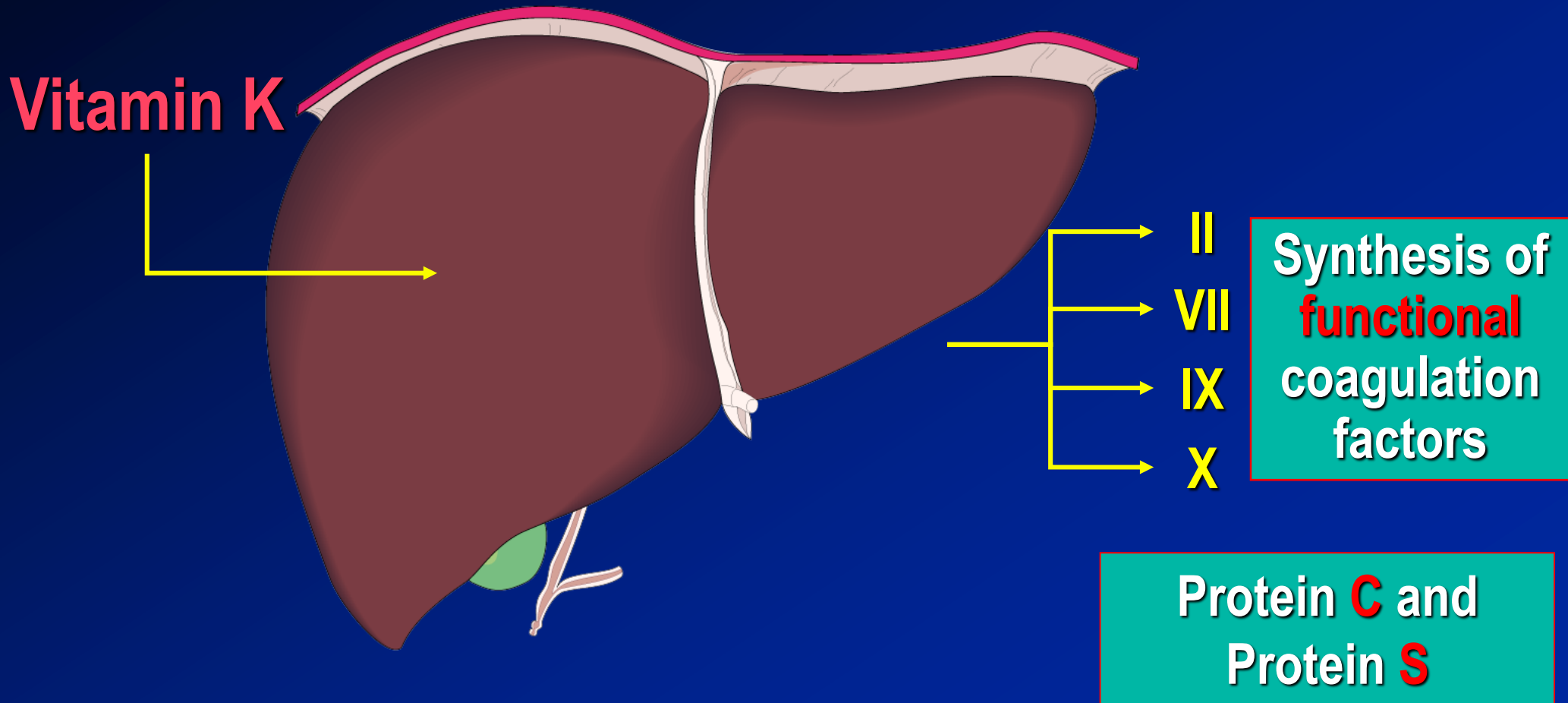
- The first DTI to be developed was **hirudin**, which was isolated from the saliva of the leech (علقة)
- **Lepirudin** is a polypeptide that binds **directly** to the active site of thrombin
- **Recombinant hirudin “Lepirudin”** is used as IV anticoagulant in patients with HIT

Oral Anticoagulants
“Vitamin K antagonists”

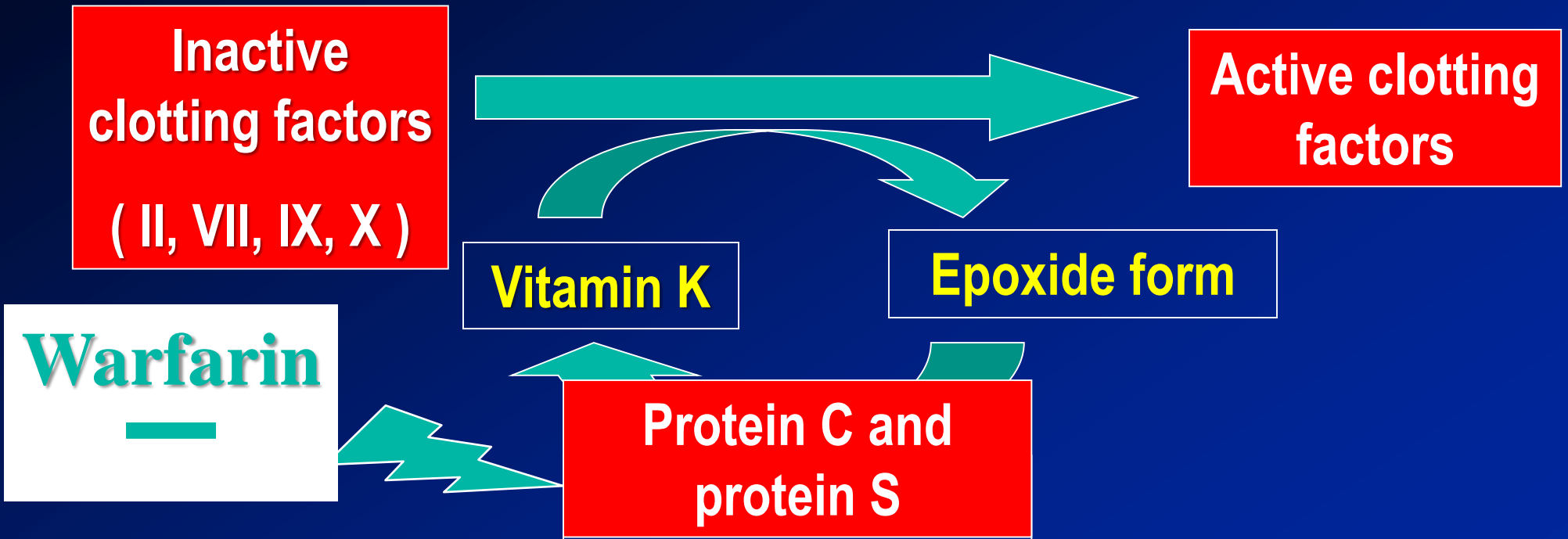
Vitamin K (Fat soluble vitamin)

- Source of vitamin K
Green vegetables
Synthesized by intestinal flora
- Required for synthesis
Factors II, VII, IX, X
Protein C and S (endogenous anticoagulants)
- Causes of deficiency
Malnutrition
Malabsorption
Antibiotic therapy

Vitamin K-Dependent Clotting Factors



Warfarin: Mechanism of action



Warfarin inhibits the synthesis of biologically active forms of vitamin K-dependent clotting factors II, VII, IX and X

Mechanism of Action of Warfarin

- Inhibits synthesis of Vitamin K-dependent coagulation factors II, VII, IX, & X as well as anticoagulant proteins C & S
- 3-4 days until effect is seen ??
- Does not have any effect on already-synthesized coagulation factors; therefore, the therapeutic effects are not seen until these factors are depleted

Coumarins: Warfarin

- Act only **in vivo**
- Bioavailability 100%
- 98% bound to plasma proteins (albumin)
- Monitoring anticoagulant effect of warfarin by measuring PT, which is expressed as an **International Normalized Ratio (INR)**

Coumarins: Warfarin

- Their effect takes several days (3-4) to develop because of the time taken for degradation of circulating **functional clotting factors**
- Therefore the onset of action starts when these factors have been eliminated
- Warfarin has a slow offset of action due to the time required for synthesis of new, **functional coagulation factors**

Disadvantages of Warfarin therapy

- Variable, unpredictable effect necessitating regular INR monitoring and dose adjustment
- Narrow therapeutic window leading to increased risk of severe bleeding
- Slow onset and offset of action
- Numerous interactions with foods containing vitamin K and drugs

Drug interactions with oral anticoagulants

1. Inhibition of Vit. K synthesis by intestinal flora; **oral antibiotics**
2. Inhibition of Vit K absorption; **liquid paraffin**
3. Decrease in drug metabolism by microsomal enzyme inhibitors;
chloramphenicol, & cimetidine
4. Displacement of the drug from protein binding sites;
phenylbutazone & salicylates
5. Co-administration of drugs that increase bleeding tendency by;
inhibiting platelet function; **NSAIDs**
heparin

1. Inhibition of drug absorption from GIT; **cholystyramine, colestipol**
2. Increase in synthesis of clotting factors; **Vit K, oral contraceptives**
3. Increase in drug metabolism by microsomal enzyme inducers;
Carbamazepine; barbiturates, rifampicin

Oral anticoagulants : Teratogenicity

Warfarin is contraindicated during pregnancy as it can cross the placental barrier and cause abortion, hemorrhagic disorder in the fetus and birth defects



Bleeding due to Warfarin

- Stop the drug
- IV injection of vitamin K
- Fresh frozen blood

Table VII-1-1. Properties of Heparin and Warfarin (Coumarins)

Feature	Heparin(s)	Warfarin (Coumarins)
Chemical Nature	Large polysaccharide, water-soluble	Small molecule, lipid-soluble derivatives of vitamin K
Kinetics	Given parenterally (IV, /SC), hepatic and reticuloendothelial elimination, half-life = 2 h, no placental access	Given orally, 98% protein bound, PO, liver metabolism, half-life = 30+ h, placental access
Mechanism	↑ Activity of antithrombin III, resulting in the inactivation of factors IIa and Xa. Actions <i>in vivo</i> and <i>in vitro</i> .	↓ Hepatic synthesis of vitamin K-dependent factors II, VII, IX, X — coumarins prevent γ -carboxylation; no effect on factors already present. <i>In vivo</i> effects only.
Monitoring	Partial thromboplastin time (PTT)	Prothrombin time (PT); INR

Table VII-1-1. Properties of Heparin and Warfarin (Coumarins) (continued)

Antagonist	Protamine sulfate—chemical antagonism, fast onset	Vitamin K—↑ cofactor synthesis, slow onset; fresh frozen plasma—fast
Uses	Rapid anticoagulation (intensive) for thromboses, emboli, unstable angina, disseminated intravascular coagulation (DIC), open-heart surgery, etc.	Longer-term anticoagulation (controlled) for thromboses, emboli, post-MI, heart valve damage, atrial arrhythmias, etc.
Toxicity	Bleeding, osteoporosis, heparin-induced thrombocytopenia (HIT), hypersensitivity	Bleeding, skin necrosis (if low protein C), drug interactions, teratogenic (bone dysmorphogenesis)



Thank
You