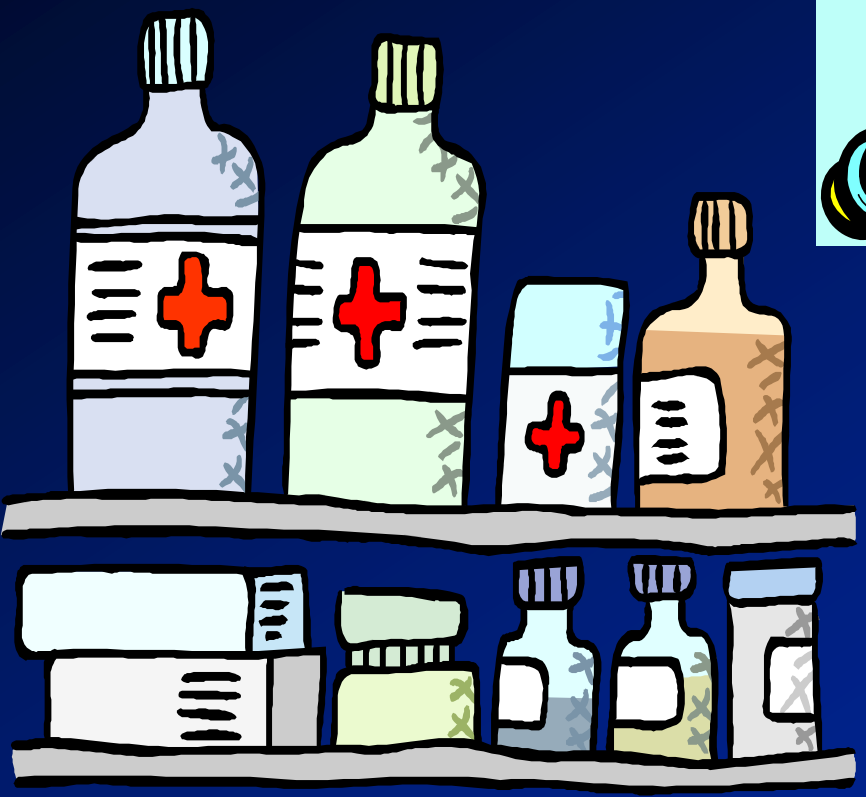
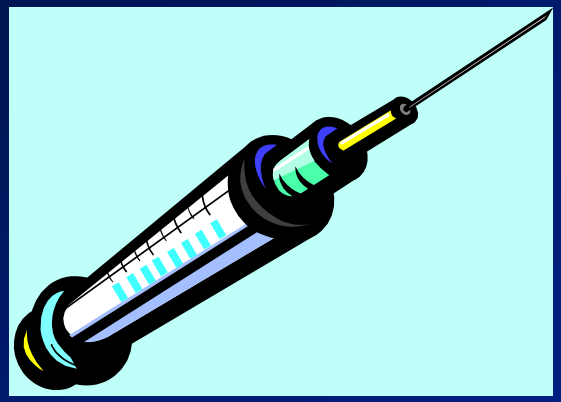
Anticoagulants





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.

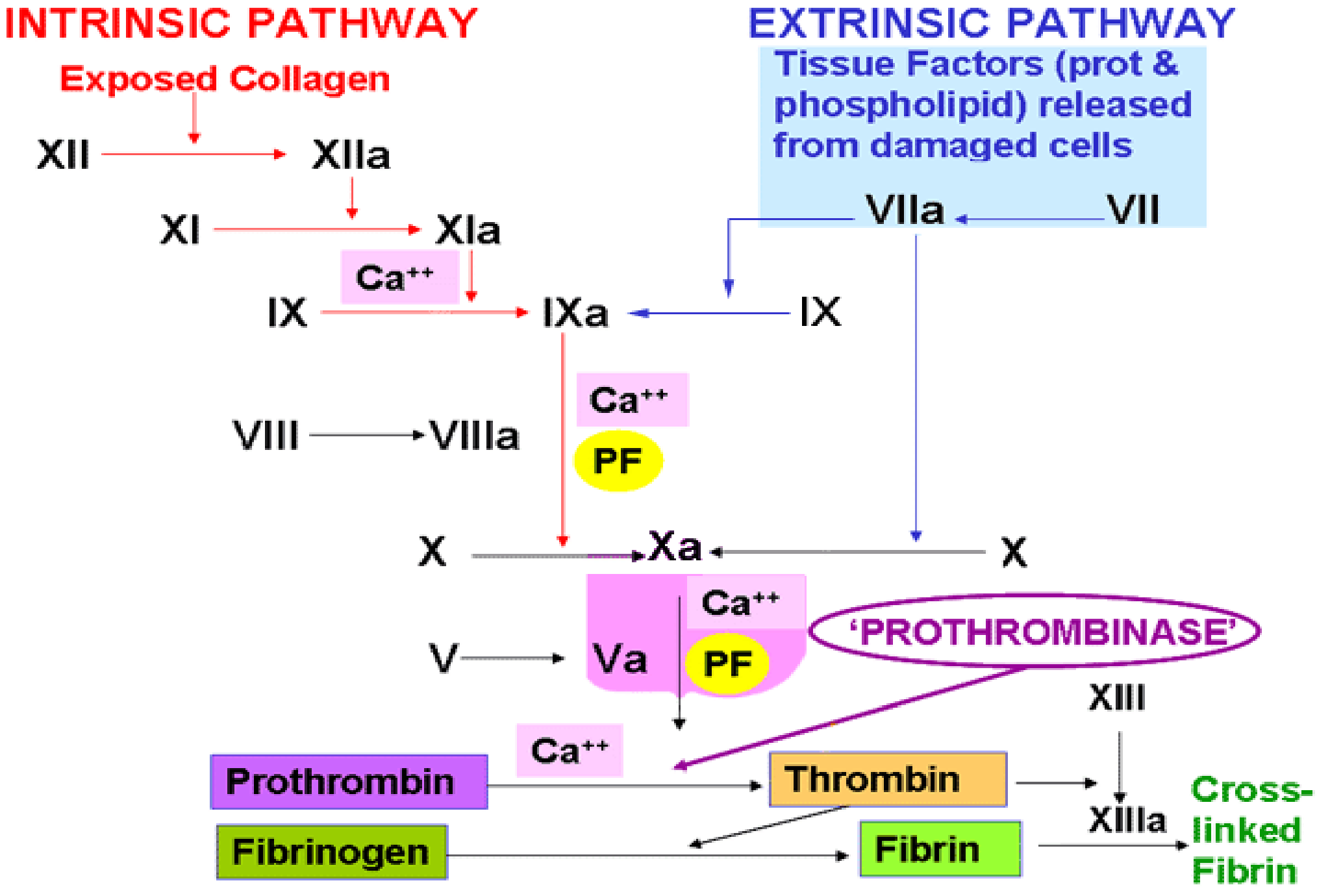
Coagulation Pathways

- Two major pathways
  - Intrinsic pathway
  - Extrinsic pathway

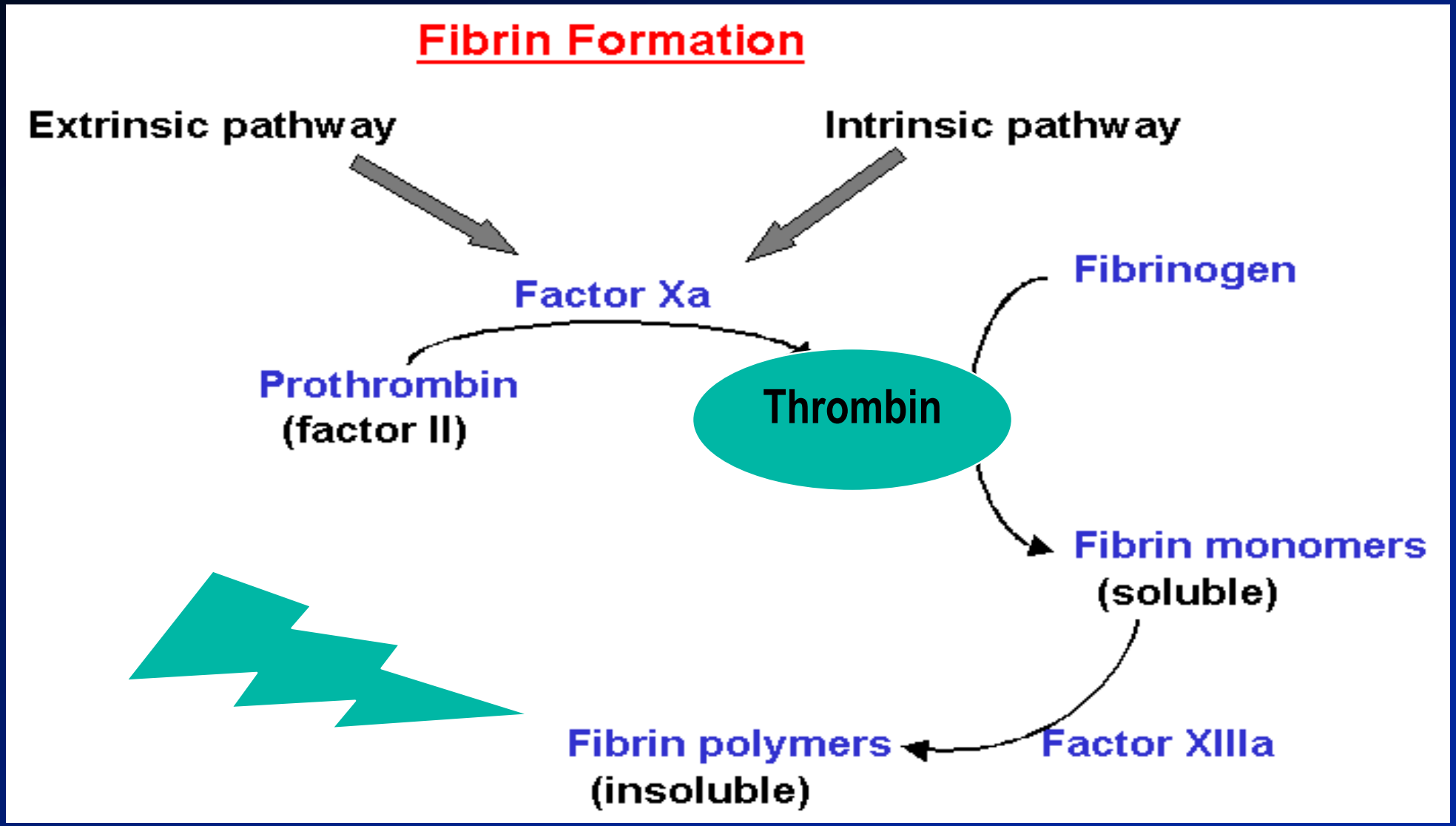
All clotting factors are within the blood

(tissue factor = thromboplastin)

- 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


INTRINSIC PATHWAY
Exposed Collagen
XII
XIIa
XI
XIa
Ca++
IX
IXa
VIII
VIIIa
EXTRINSIC PATHWAY
Tissue Factors (prot & phospholipid) released from damaged cells
VIIa
VII
IX
Ca++
PF
X
Xa
X
V
Va
Ca++
PF
'PROTHROMBINASE'
XIII
Ca++
Prothrombin
Thrombin
XIIIa
Cross-linked Fibrin
Fibrinogen
Fibrin

Common pathway & Fibrin clot 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** (PGI_2), is synthesized by endothelial cells and inhibits platelet aggregation
- **Protein C and Protein S**

ANTICOAGULANTS

Parenteral Anticoagulants

- Thrombin inhibitors
  - Indirect
  - Direct

Oral Anticoagulants

- 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

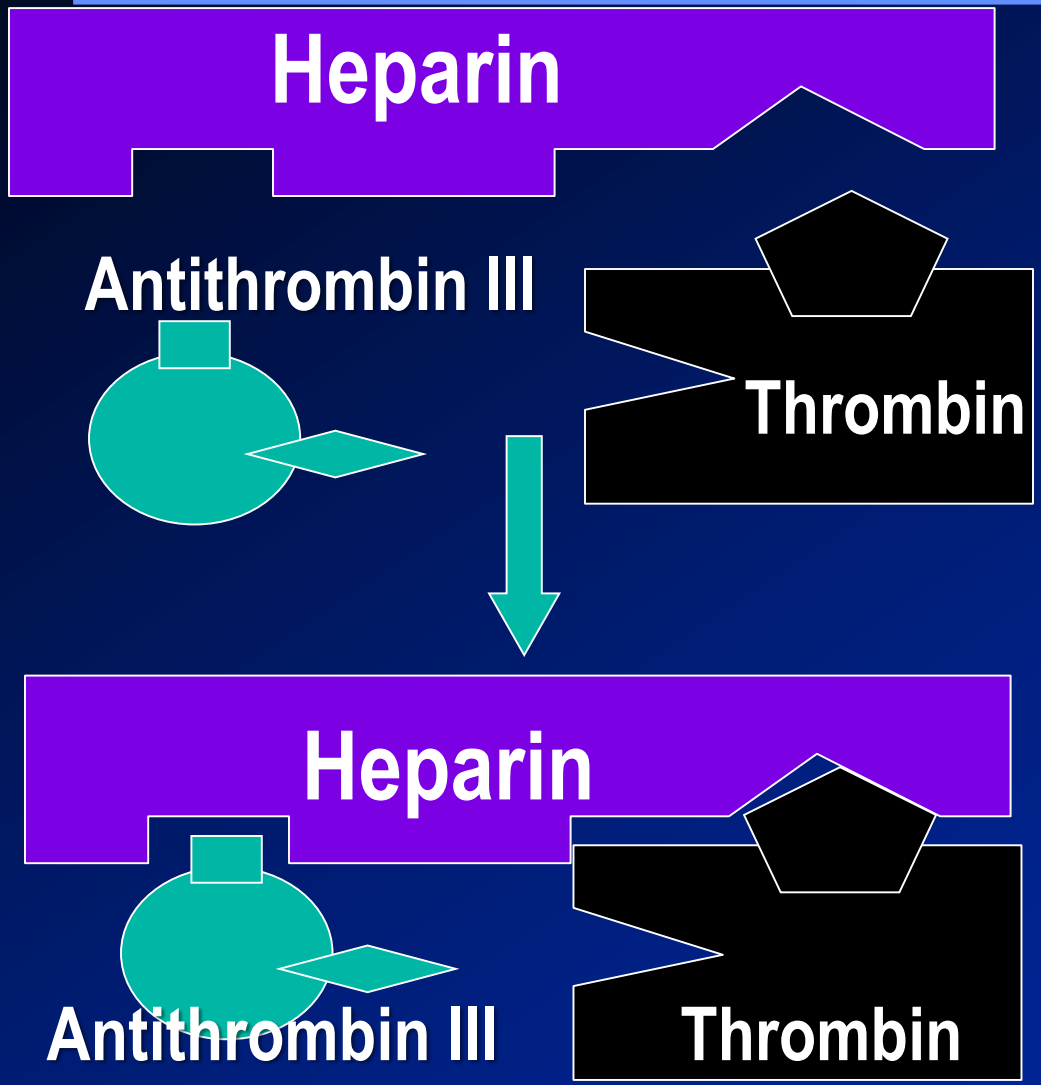
Heparin and related H- agents

- 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

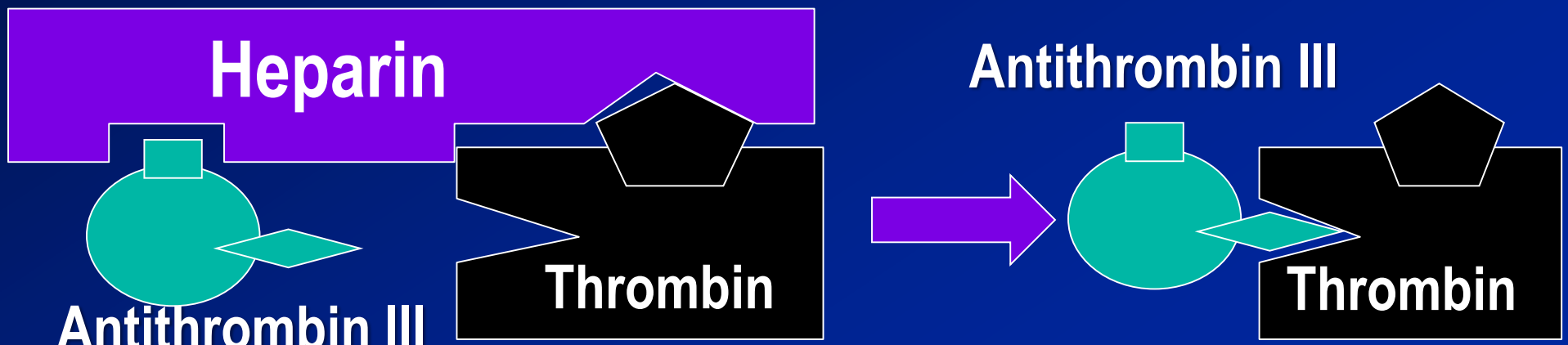
Heparin: Mechanism of action



- Heparin 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 anticoagulat 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 ½ 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)

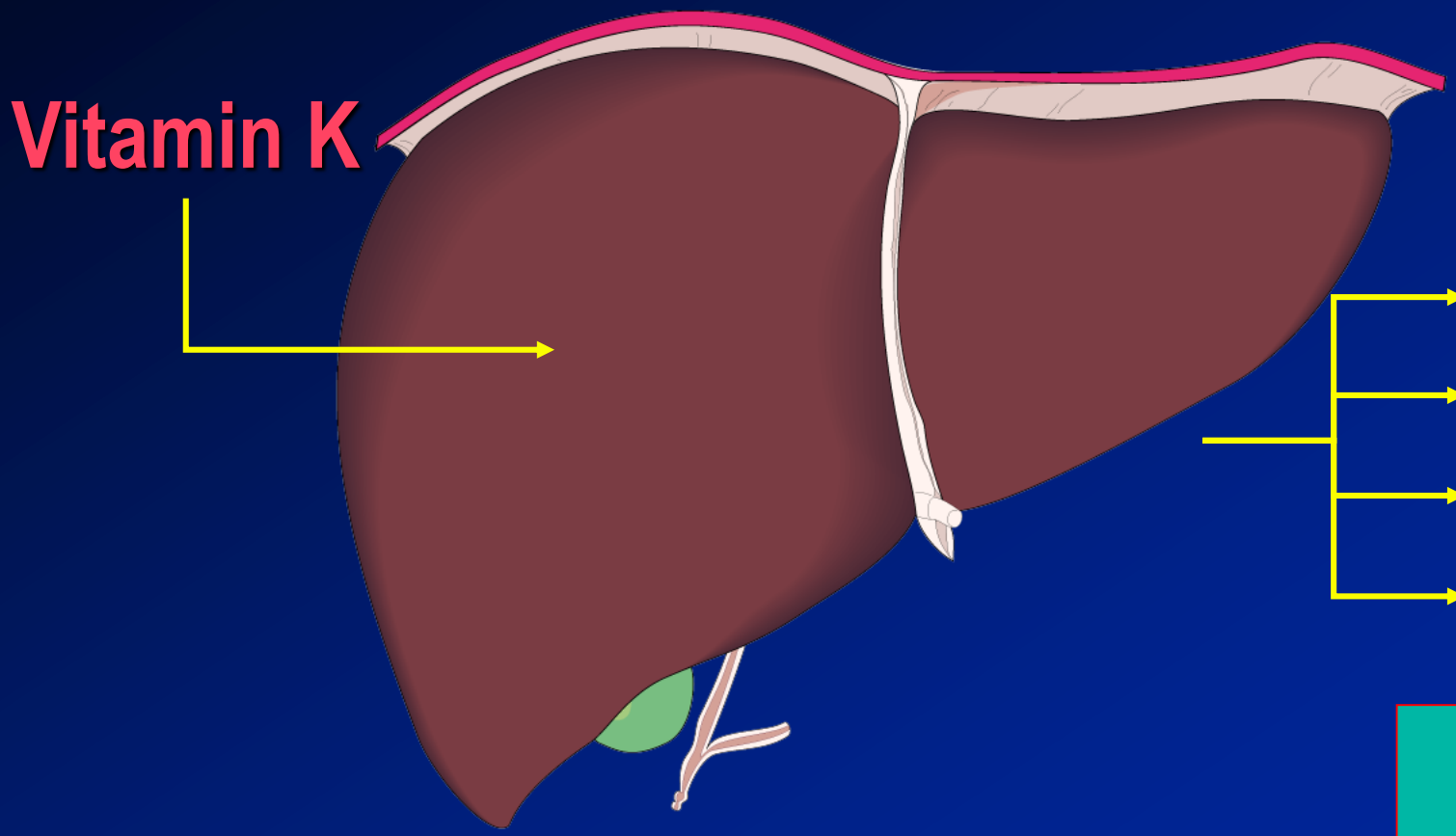
- The first DTI to be developed was hirudin, which was isolated from the saliva of the leech (علقة)
- Lepirudin is a polypeptide that binds directly to the active site of thrombin
- Recombinant hirudin "Lepirudin" is used as IV anticoagulant in patients with HIT

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

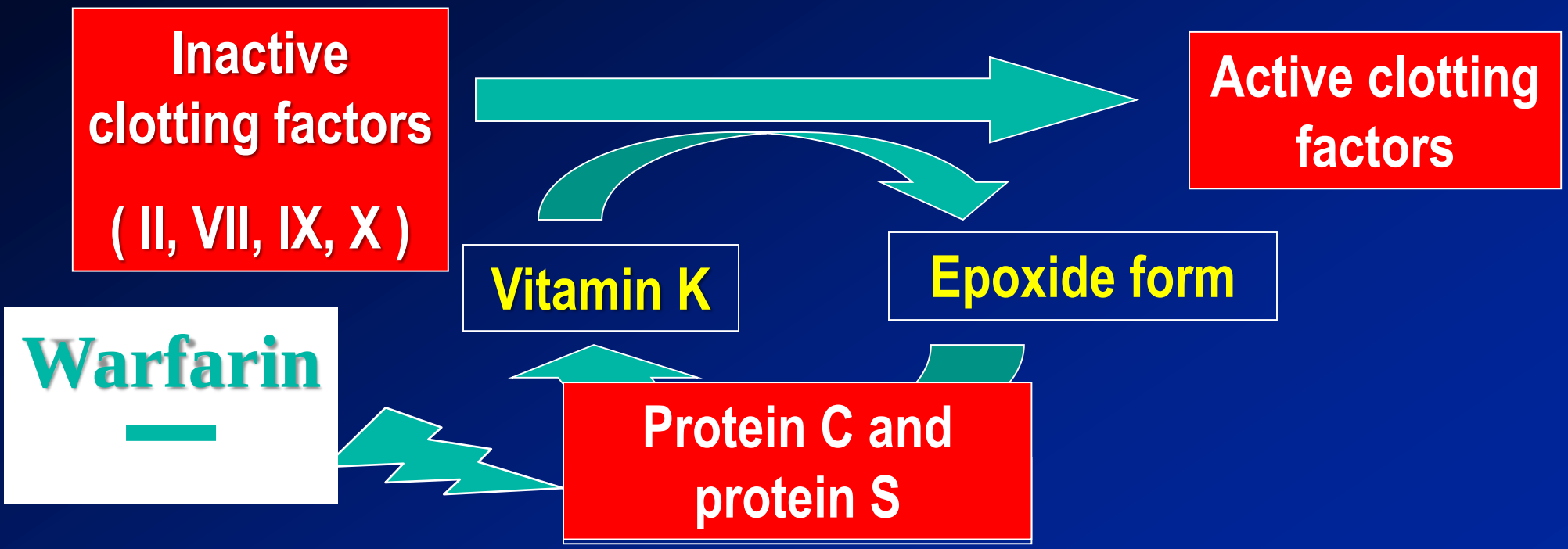


II
VII
IX
X

Synthesis of **functional** coagulation factors

Protein **C** and Protein **S**

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

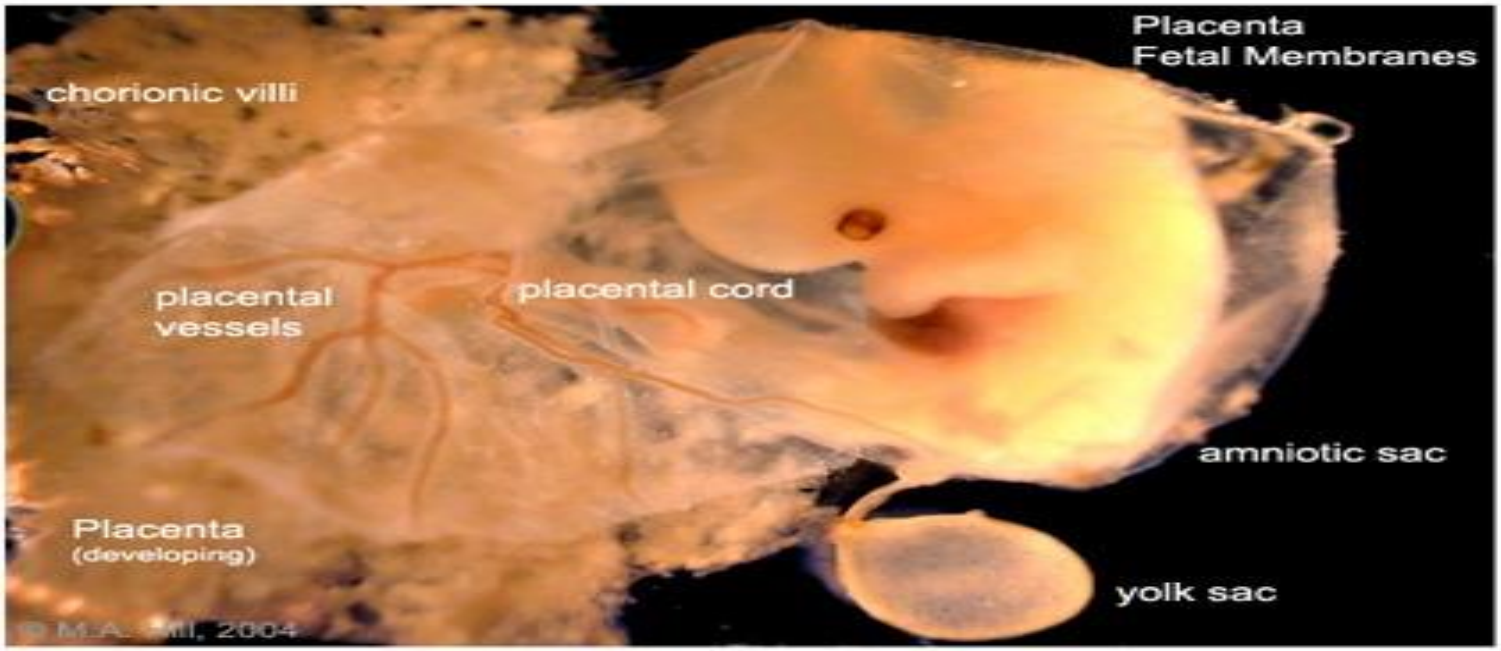
Drug interactions with oral anticoagulants

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. Displacment 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 *in vivo* and *in vitro*.	↓ Hepatic synthesis of vitamin K–dependent factors II, VII, IX, X — coumarins prevent γ–carboxylation; no effect on factors already present. In *vivo* 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