# ANTICOAGULANTS

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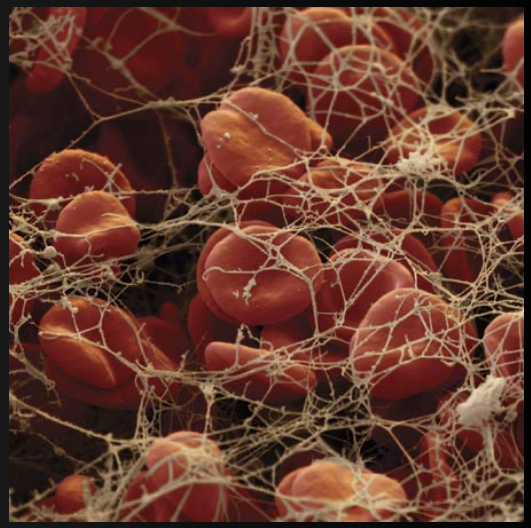


## ILOs

- Re-visit the 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.
- Apply such variability in a clinical scenario.

# Drugs and coagulation

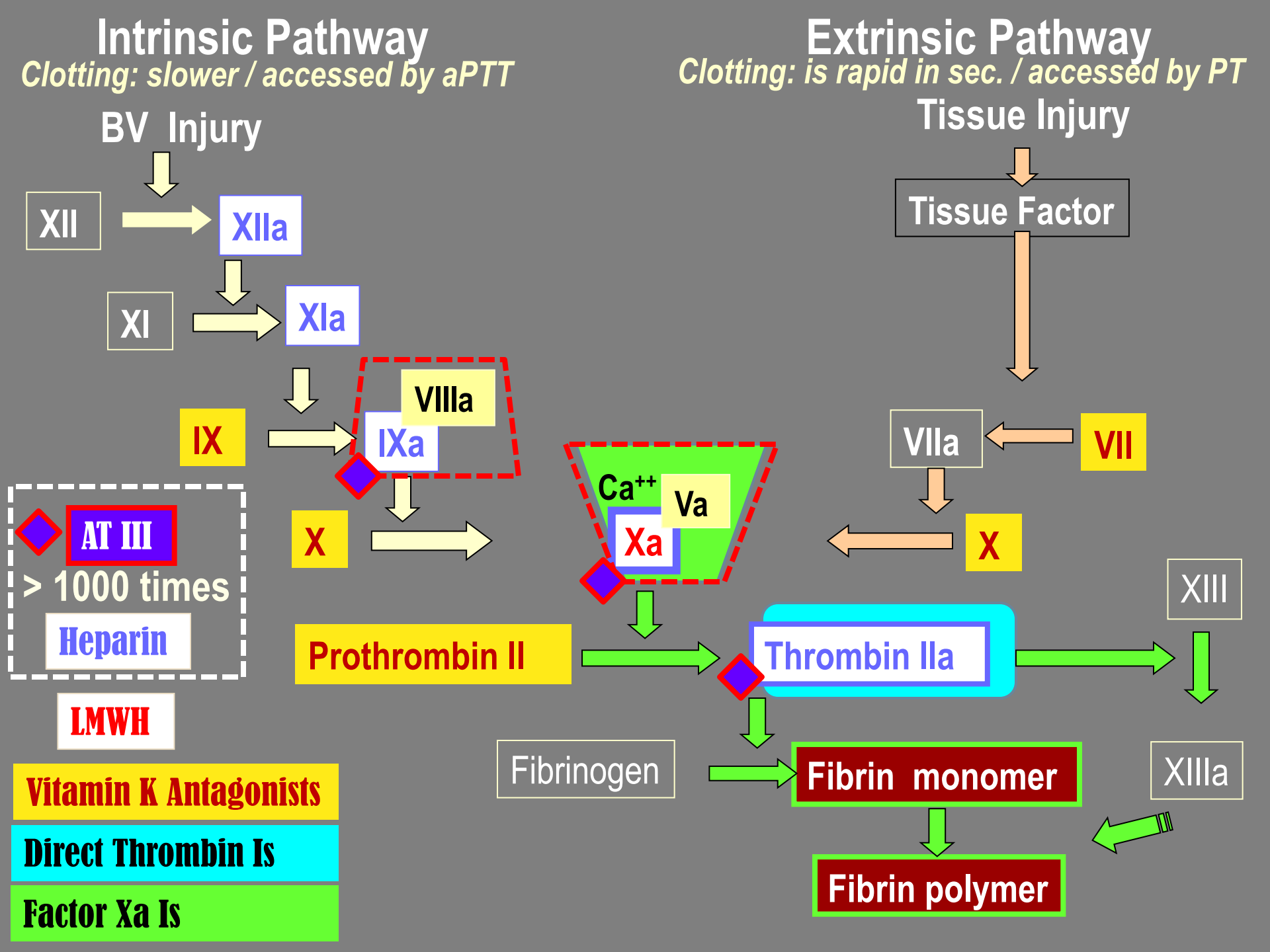
- **Anti-coagulants** are molecules that prevent blood from clotting. They inhibit the chemical process of formation of the fibrin polymer.
- These include heparin, low molecular weight heparin, coumarins/ warfarin.
- Molecules that **do not allow platelets to aggregrate** and thus prevent clotting, especially in the arteries, are called anti-platelet agents e.g aspirin and ticlopidine.
- Molecules that **disintegrate a pre-formed clot** are called fibrinolytic agents. A typical example in this category is the enzyme, streptokinase.

# Indication of anti-coagulant

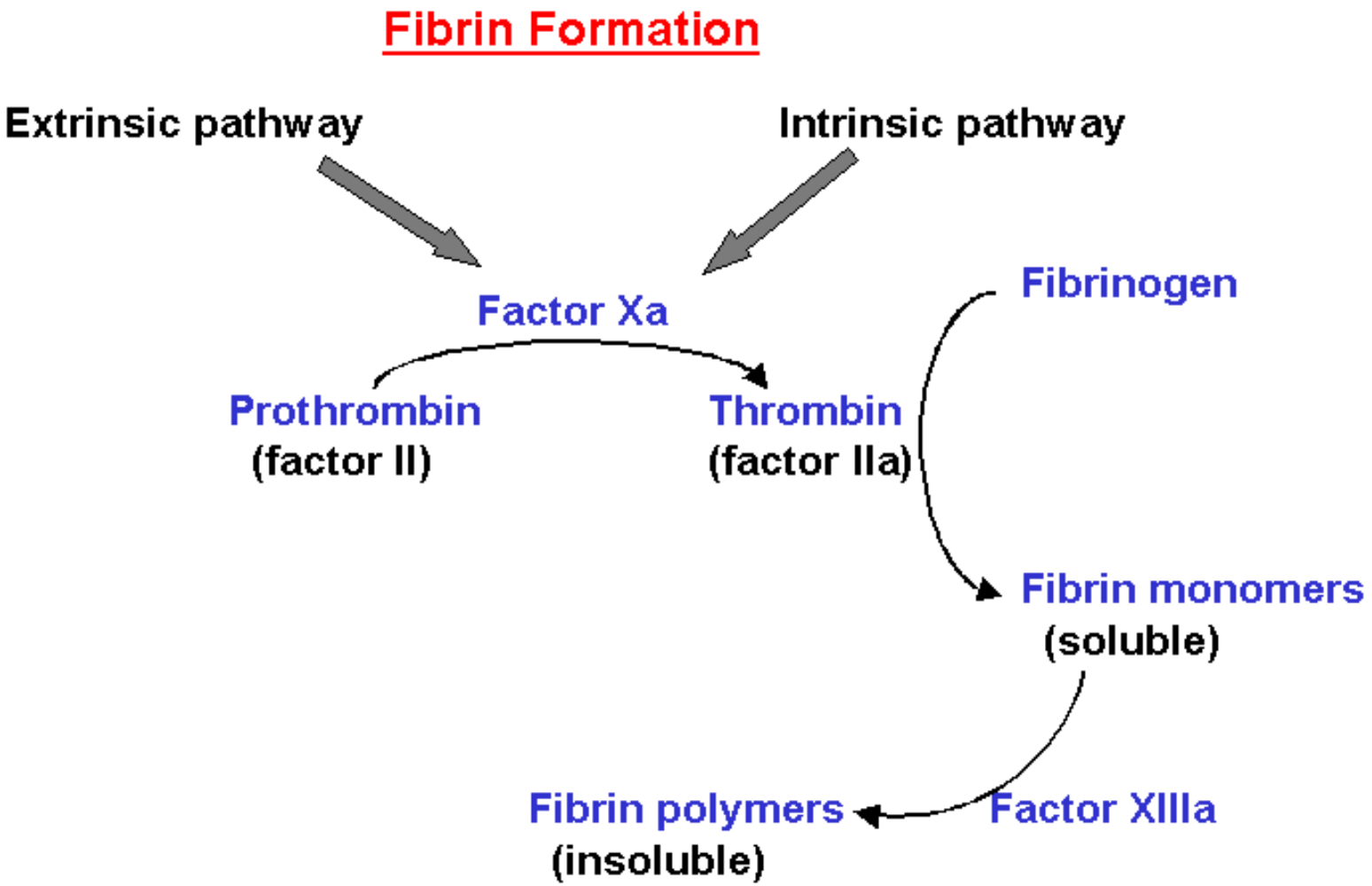
Anticoagulants are indicated:

- In myocardial infarction,
- Deep venous thrombosis,
- peripheral arterial emboli, pulmonary embolism and many other conditions.
- Anticoagulants are also used in blood transfusions, and dialysis procedures.

# Coagulation pathways and anticoagulants


Intrinsic Pathway
Clotting: slower / accessed by aPTT
BV Injury
XII
XIIa
XI
XIa
IX
VIIIa
IXa
X
AT III
> 1000 times
Heparin
LMWH
Vitamin K Antagonists
Direct Thrombin Is
Factor Xa Is
Extrinsic Pathway
Clotting: is rapid in sec. / accessed by PT
Tissue Injury
Tissue Factor
VIIa
VII
X
Ca++
Va
Xa
Prothrombin II
Thrombin IIa
XIII
XIIIa
Fibrinogen
Fibrin monomer
Fibrin polymer

# Chemical Process of Clotting



# ANTICOAGULANTS

## VENOUS THROMBOSIS

## Parenteral Anticoagulants

## Oral Anticoagulants

| UFH | LMWH | Direct Thrombin Is | Factor Xa Is | Vitamin K Antagonists |
|---|---|---|---|---|
| 3000-30000 | < 8000<br>> Xa | II a | Pentasaccharide<br>X a | Coumarins;<br>Warfarin<br>> 40 times potency than Dicumarol |
| | Enoxaparin<br>Dalteparin | Bivaluridin *R Is*<br>Lepirudin *IR Is* | *Indirect Is*<br>Fondaparinux | |
| | | Argatroban *R Is*<br>Dabigatran *R Is* | Rivaroxaban<br>*Direct Is* | |
| XIIa, XIa, IXa, Xa, IIa | | | | II, VII, IX & X |
| **Inactivation** Of Coagulation Factors | | | | **Decrease Synthesis** |
| *Rapid / Variable*<br>*Monitor by aPTT (1.5 - 2.5 times normal [30sec])*<br>*Or CT (2-3 times normal [5-7 min)*<br>*Antidote; Protamine Sulphate IV → 1mg / 100 units UFH*<br>*+/ Fresh blood* | | | | *Slow / Latency / Variable*<br>*Monitor by PT ( 2 times)*<br>*INR (2.5)*<br>*Antidote; Vit. $K_1$ infusion*<br>*+/ Fresh blood*<br>+ Needs de novo synthesis |

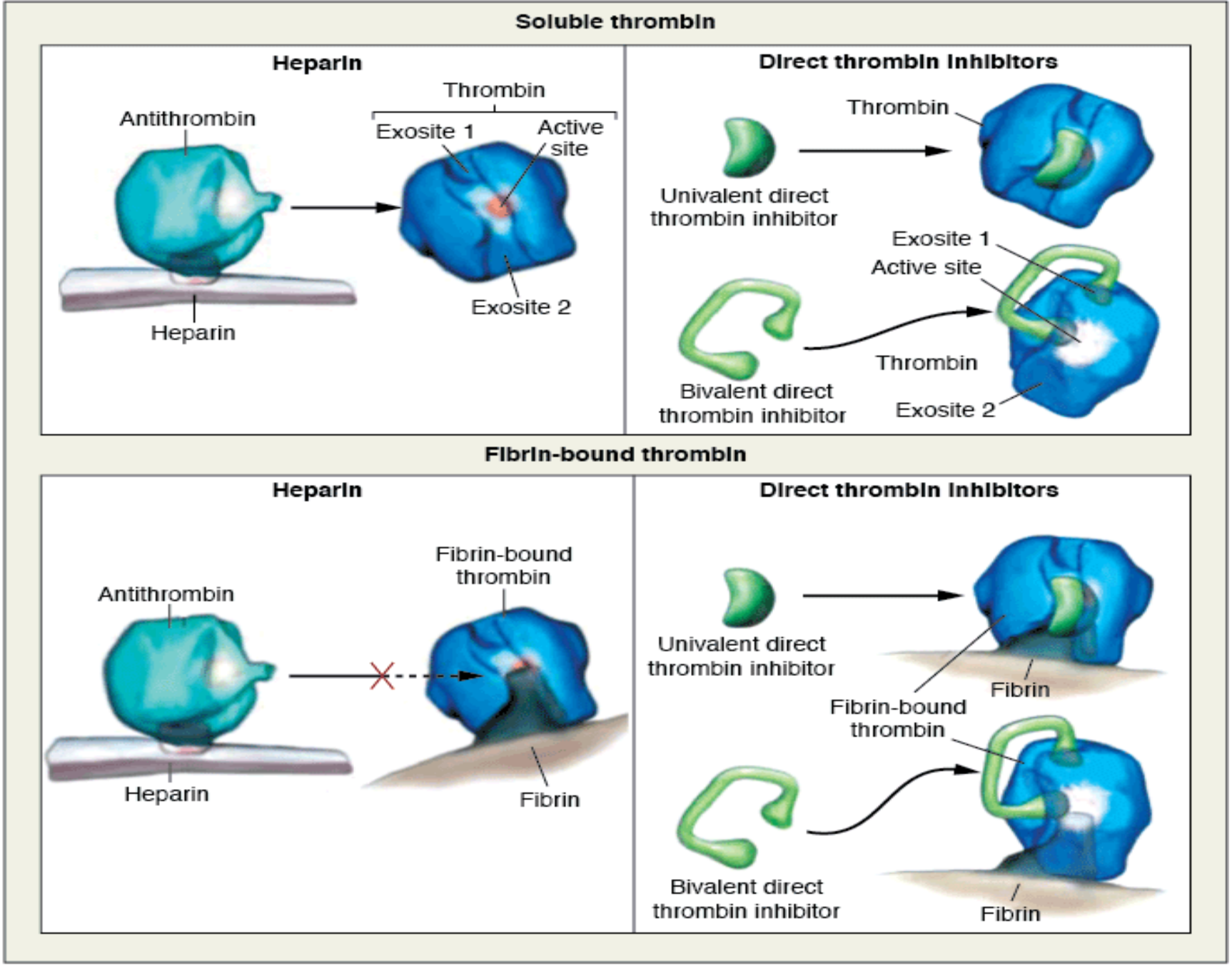
# Anti-thrombin III

- Anti-thrombin III: It inactivates thrombin and other coagulation factors (IXa, Xa, XIa and XIIa) by forming complex with these factors. Heparin like molecules enhances these interactions.
- Protein C and S: these are vitamin K dependent proteins that slow the coagulation cascade by inactivating factor Va and VIIIa.

# Heparin mechanism of action

- The anti-coagulant effect of heparin is mediated via anti-thrombin III.
- Anti-thrombin III inactivate thrombin (essential for clot formation) and other serine proteases (clotting factors) e.g VIIa, IXa and particularly Xa.
- In the absence of heparin this incativation is slow, heparine acting is a co-factor accelerate the reaction by 1000-fold.

(B)

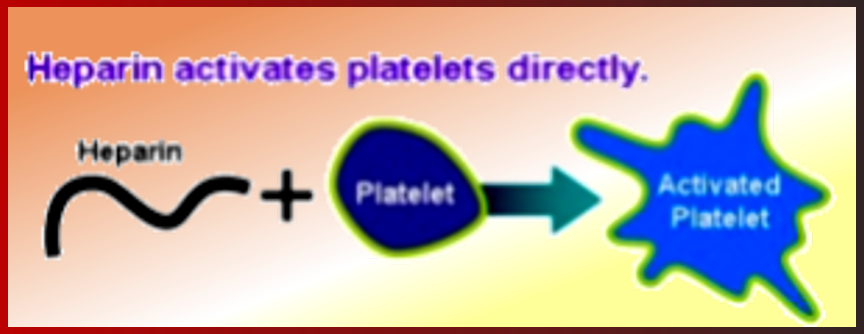


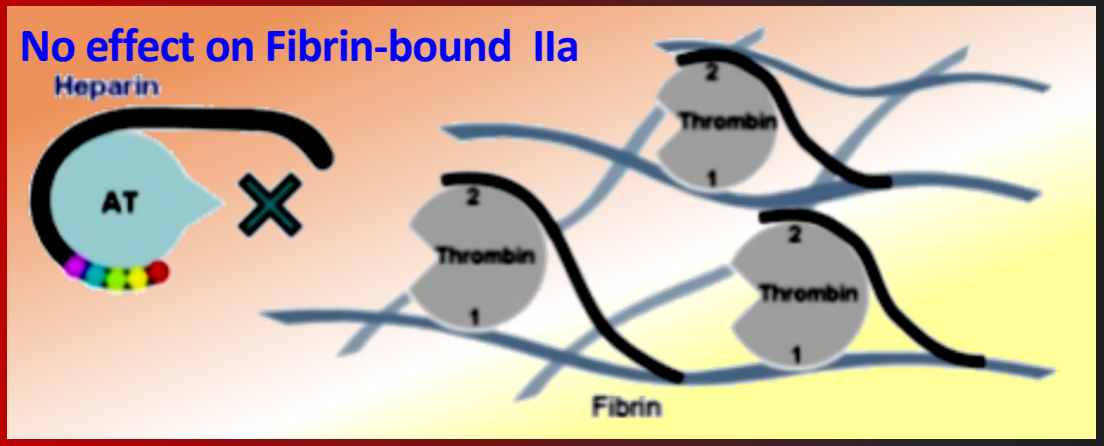
# ANTICOAGULANTS

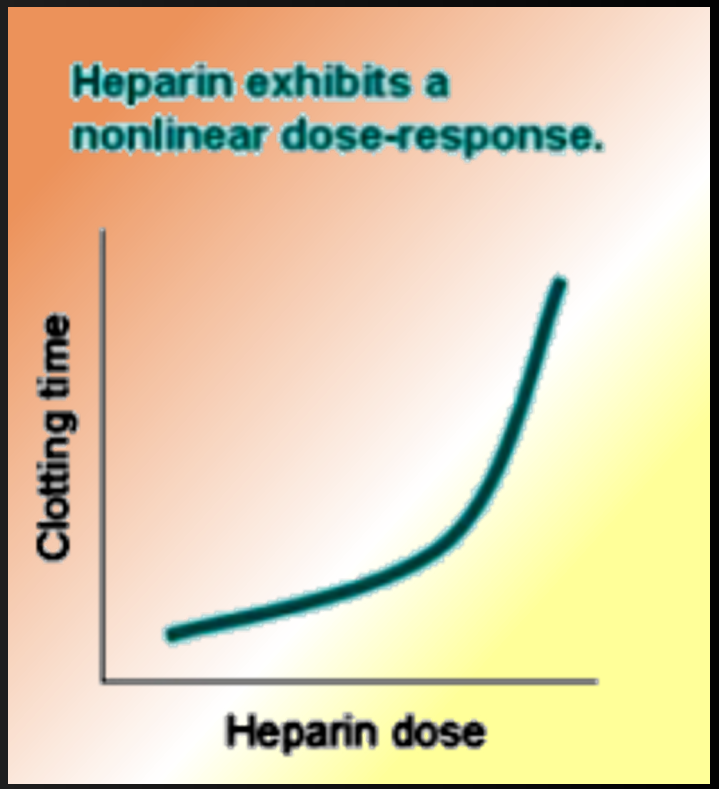
## unfractionated heparin (UFH

### LIMITATIONS

- No predictable anticoagulant effects: inter-patient & intra-patient variability in response to a given dosage ➔ *in hospital setting, repeated monitoring*
- Low bioavailability ➔ *binds to* plasma proteins, endothelium & macrophages
- Re-thrombosis ➔ *activates platelets as it does not neutralize fibrin-bound II a*



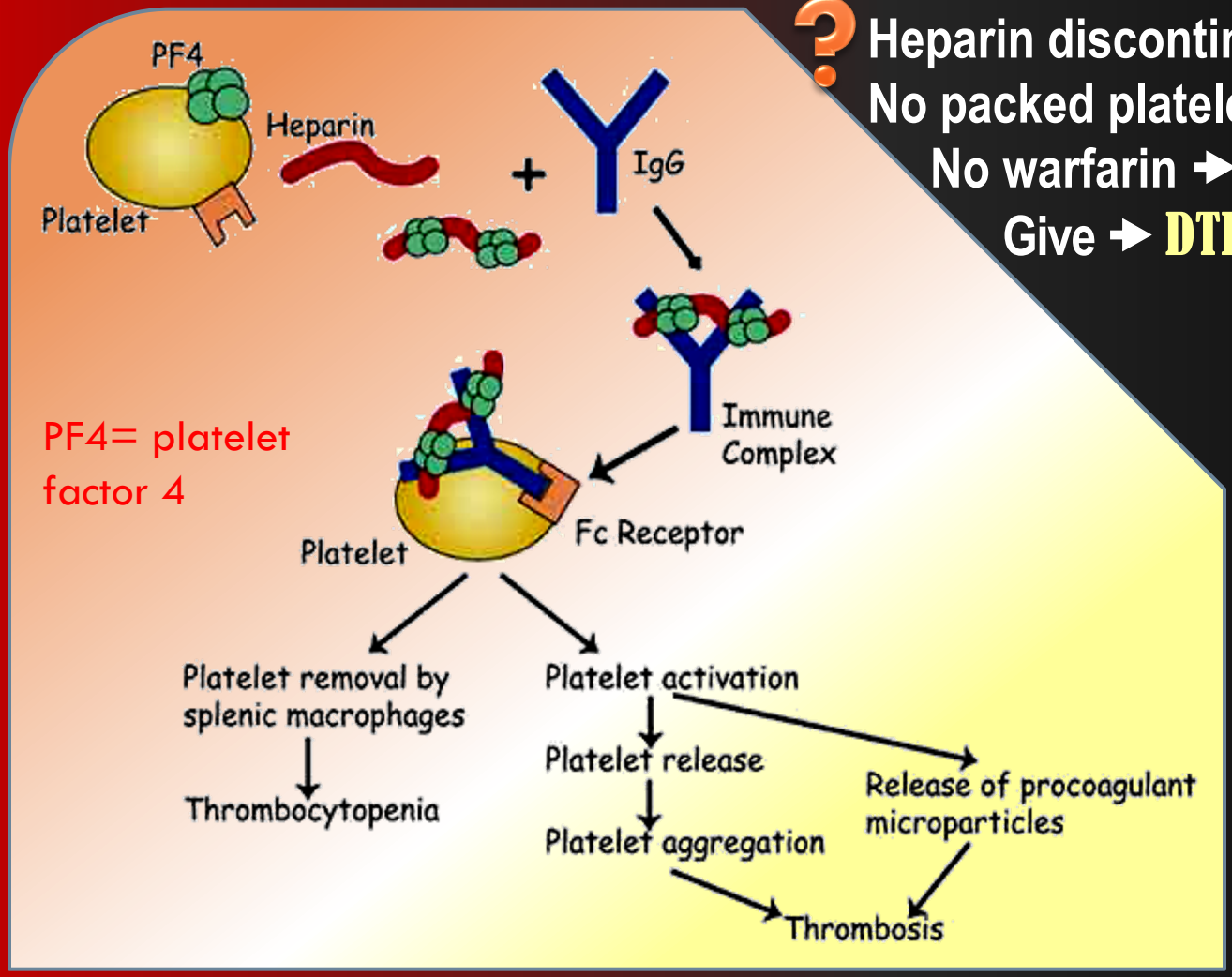



# ANTICOAGULANTS

## UFH LIMITATIONS

- **Heparin Induced Thrombocytopenia (HIT):** in 4% pts. on heparin, latency 5-10 dys. after 1st exposure or 2-3 dys. after re-exposures ➔V enous > Arterial thombosis




PF4= platelet factor 4

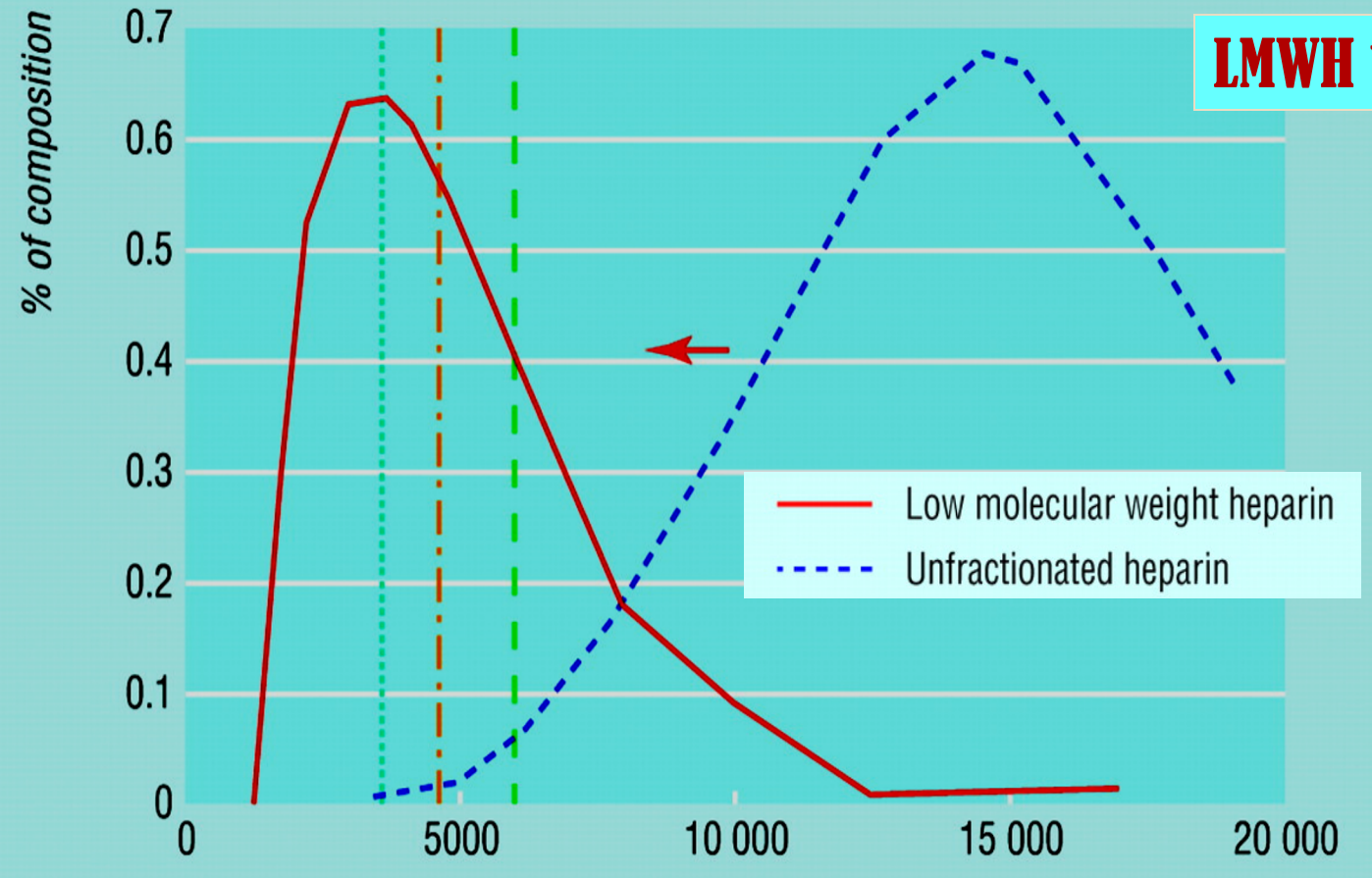
? Heparin discontinuation

No packed platelets ➔ More thrombosis

No warfarin ➔ ppt .venous gangrene

Give ➔ DTIs

# LMWH versus UFH




| LMWH | UFH |
| --- | --- |
| Greater anti-Xa activity | Greater antithrombin activity |
| Resistant to PF4 | Less anti-Xa activity |
| Little non-specific binding | Sensitive to PF4 |
| Greater inhibition of thrombin generation | Non-specific binding |
| | Less inhibition of thrombin generation |

# UF heparin and LMW Heparin

The theoretical pharmacologic advantages of LMWH over UFH arise from the preferential binding ratio to factor Xa over thrombin.

LMWH (**Enoxaparin , Dalteparin) have**:

less plasma protein binding,
less platelet activation and lower risk of re-thrombosis and thrombocytopenia.,
Good bioavaialibility
More predictable response

# ANTICOAGULANTS

## LMWH BENIFITS

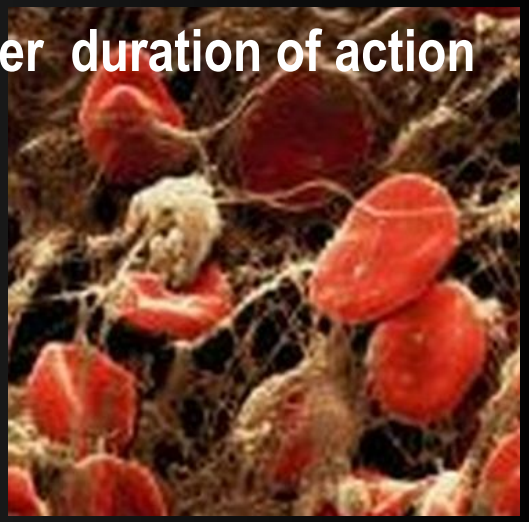
- ↑ Predictability of anticoagulant response i.e. little inter-patient and intra-patient variability in response to a given dosage. without the need for laboratory monitoring
- ↑ Bioavailability; as it hardly binds to plasma proteins, endothelium & macrophages
- ↓Incidence of thrombocytopenia; as it seldom sensitive to PF4
- ↓Incidence of bleeding tendency; ↓ effect AT III & ↓ platelet interactions
- Much better tolerability;

  given sub. cut.

  ↓ frequency of administration due to longer duration of action

  ↓ need for regular monitoring

  Outside hospital settings



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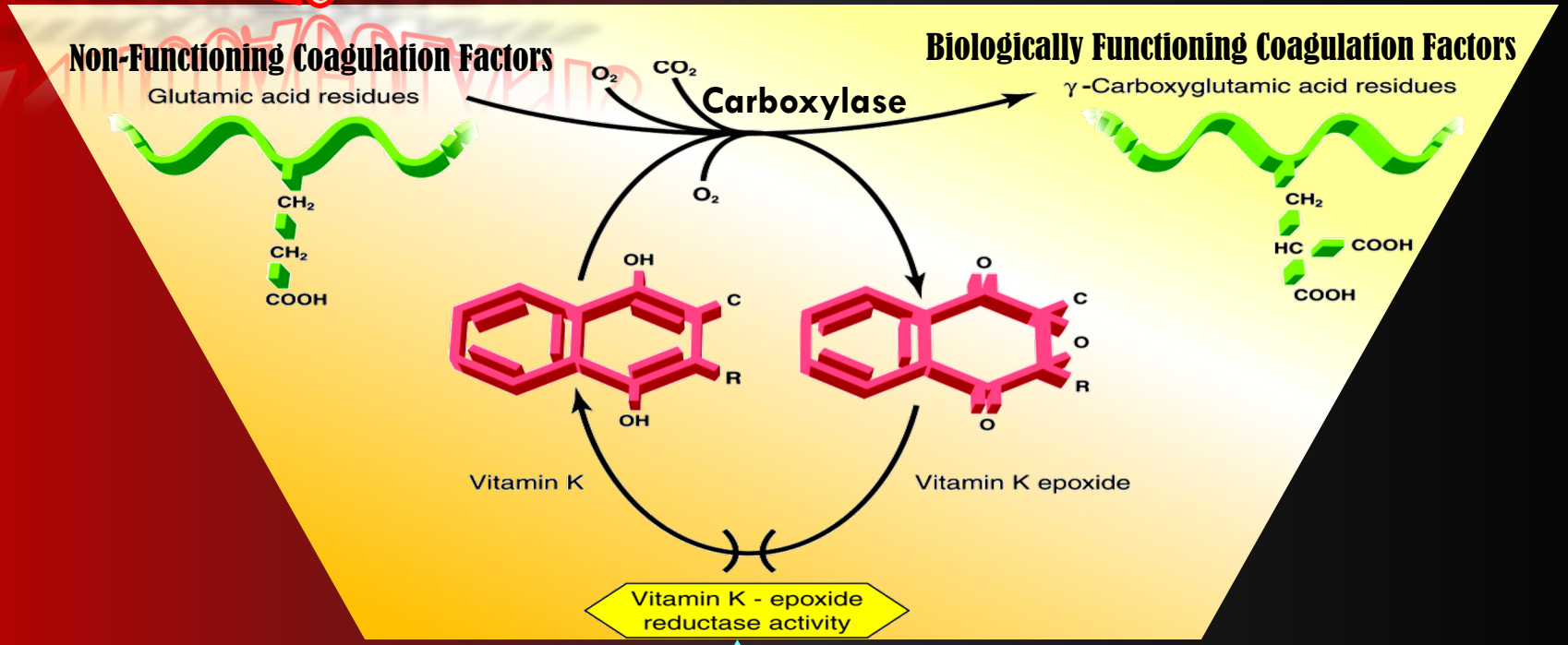
VKAs



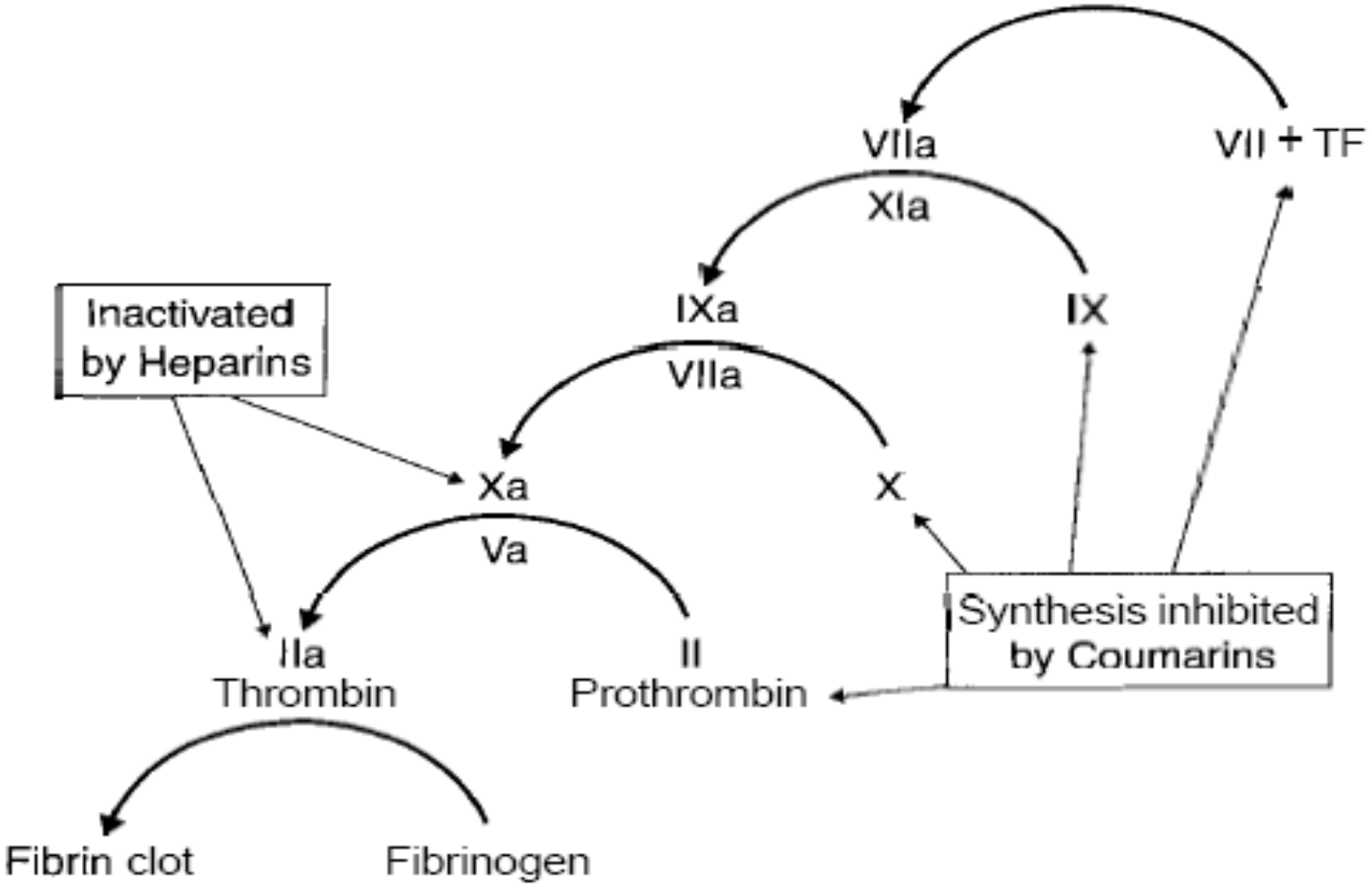

Warfarin

Precursors of factors II, VII, IX & X require carboxylation of their glutamic a. residues to allow them to bind to phospholipid surfaces. This is provided by Vit. K as it changes from its oxidized to its reduced form. Instantaneously , the reduced Vit K has to recycle back to oxidized form by Vit K epoxide reductase. This enzyme is blocked by VKAs ➔ losing the coagulation factors the ability to function.

# Mechanism of Action of Warfarin

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

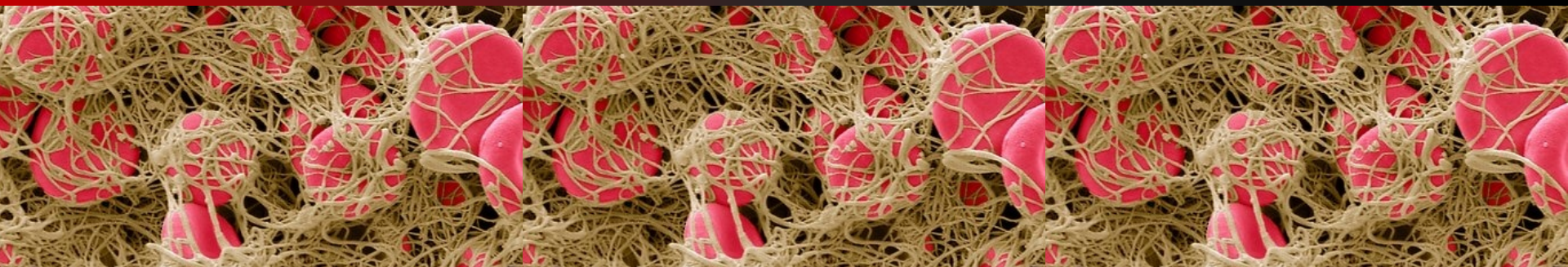
# Heparin and warfarin actions



# ANTICOAGULANTS

## VKAs LIMITATIONS

- Wide variation in drug response
- Has narrow therapeutic window, So any change in that level can be hazardous.
- Slow onset of action, so not in given in emergency conditions
- Polymorphisms in CYT P450 isoforms that metabolizes warfarin ➔ adds to its non predictable response ➔ liability to toxicities or under use.
- Numerous food- & drug-drug interactions ➔ liability to toxicities or under use.
- Contraindicated in pregnancy ➔ give heparin or LMWH instead



# FACTORS ALTERING RESPONSE TO VKAs

1. Vitamin K deficiency;
   a- Inadequate diet; malnutrition, dieting, decreased GI absorption….

2. Impaired synthesis of clotting factors;
   a. In hepatocellular disorders; ( hepatitis;infective or chronic alcoholism ... etc.)

3. Increased catabolism of clotting factors;
   In hypermetabolic states; as in fever, thyrotoxicosis

1. Decreased plasma protein binding;
   ↑ elimination of free drug & shortening of its t1/2. as pts with nephrotic syndrome (proteinuria)
2. Decreased catabolism of clotting factors; Hypothyroidism
3. Hereditary resistance to oral anticoagulants

# DRUGS MODULATING RESPONSE TO VKAs

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
   inhibiting coagulation factors; 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

# Summary of Heparin and wrafarin

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) |

# ANTICOAGULANTS

GOOD LUCK