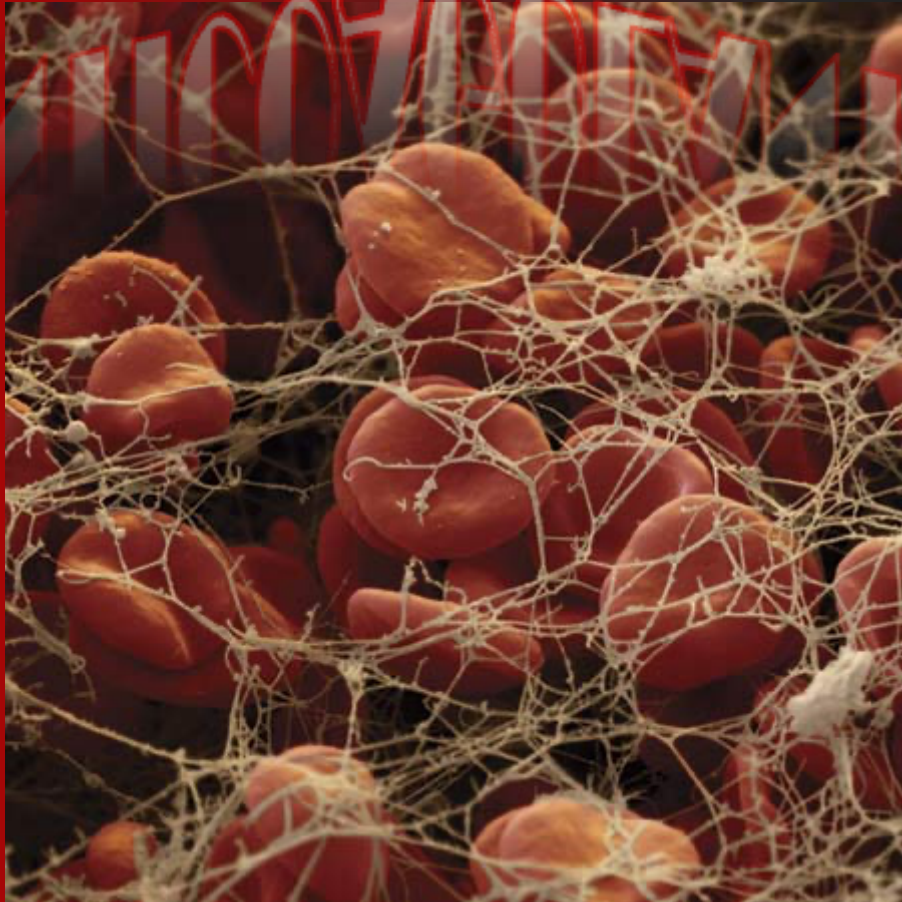
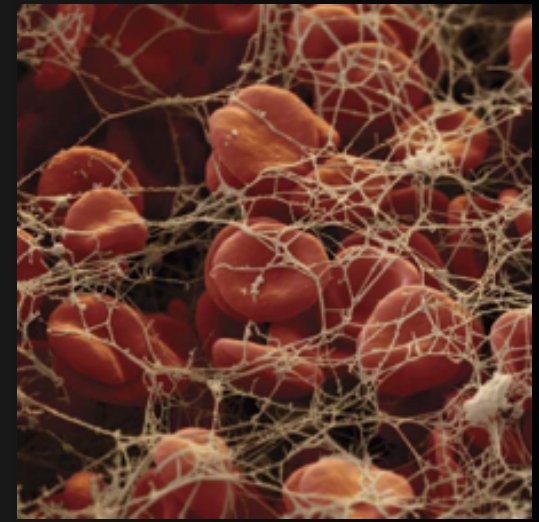


ANTICOAGULANTS



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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 aggregate** 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.

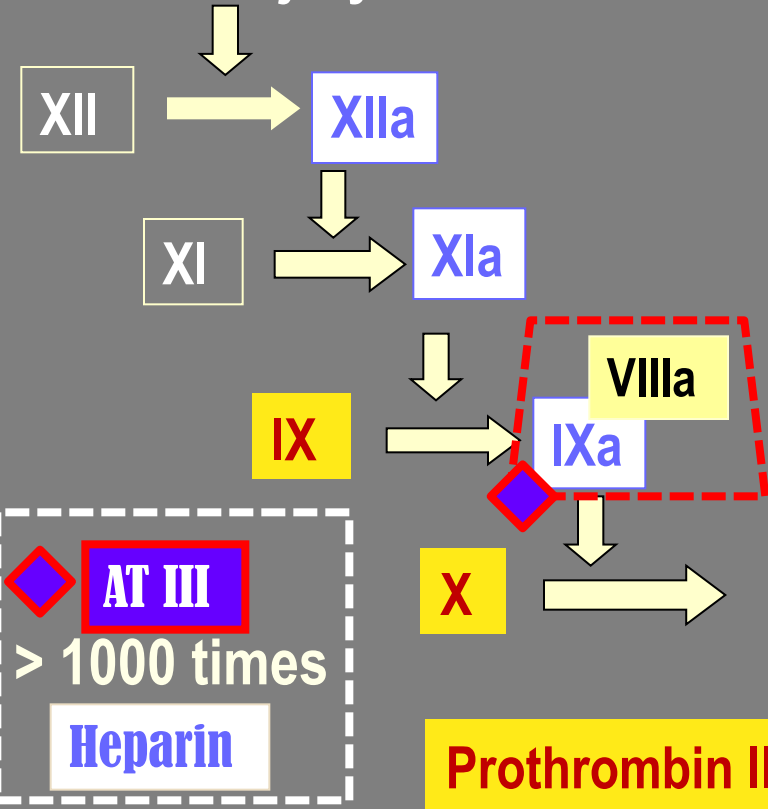


Coagulation pathways and anticoagulants

Intrinsic Pathway

Clotting: slower / accessed by aPTT

BV Injury



AT III
> 1000 times

Heparin

LMWH

Vitamin K Antagonists

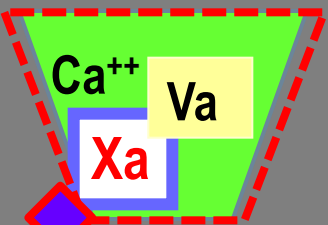
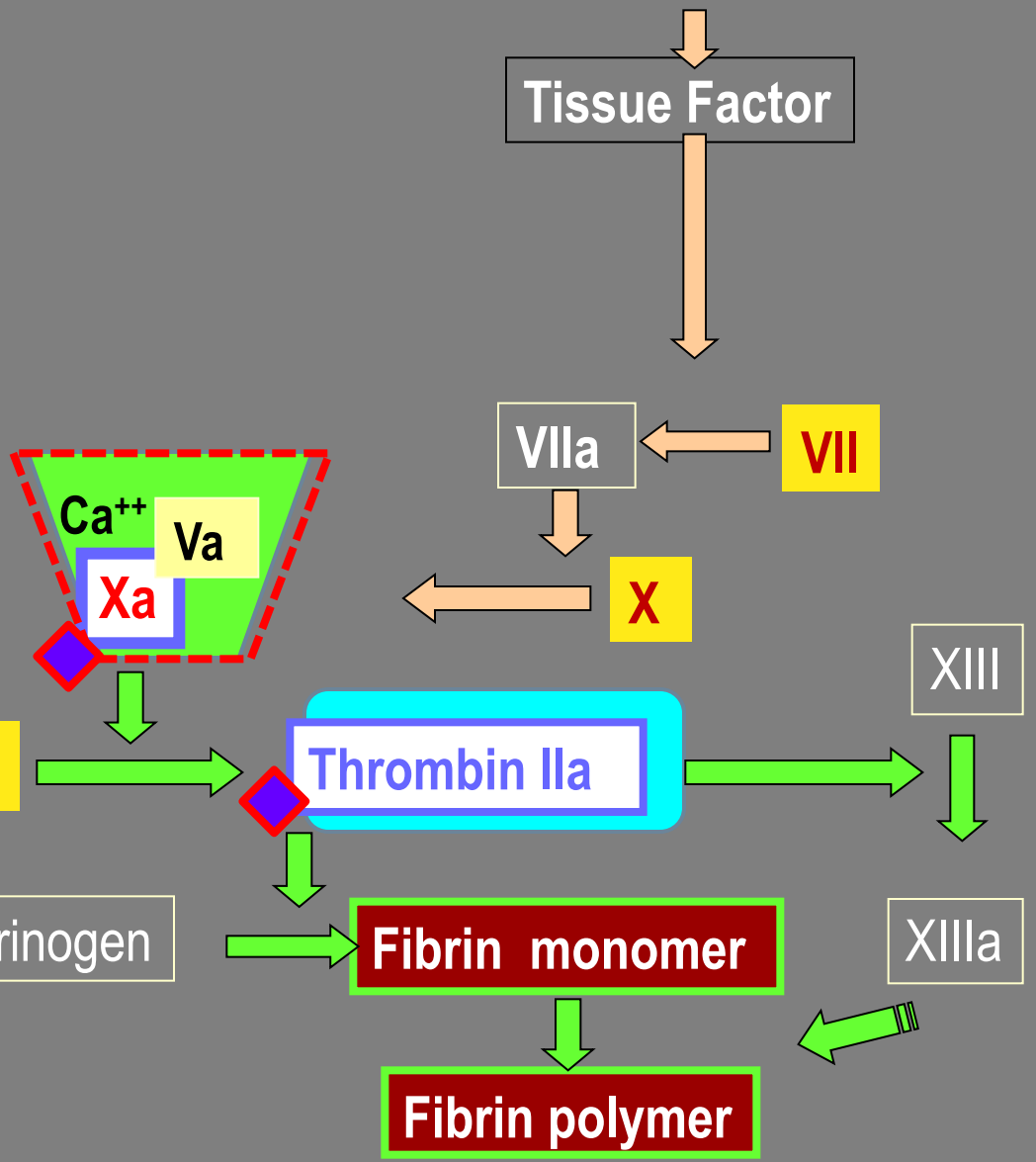
Direct Thrombin Is

Factor Xa Is

Extrinsic Pathway

Clotting: is rapid in sec. / accessed by PT

Tissue Injury



Fibrinogen

Fibrin monomer

Fibrin polymer

XIII

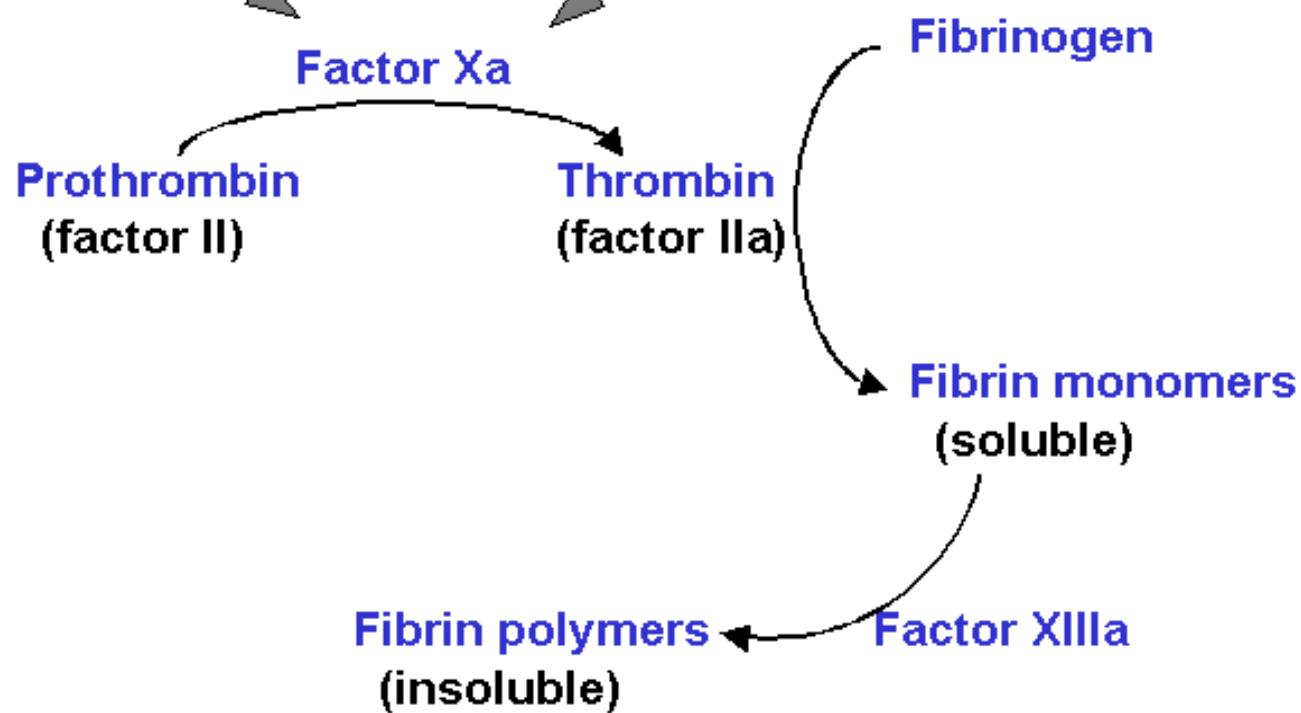
XIIIa

Chemical Process of Clotting

Fibrin Formation

Extrinsic pathway

Intrinsic pathway



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← VENOUS THROMBOSIS →



Parenteral Anticoagulants

Oral Anticoagulants

UFH

LMWH

Direct Thrombin Is

Factor Xa Is

Vitamin K Antagonists

3000-30000

< 8000

> Xa

II α

Pentasaccharide

X α

Coumarins;
Warfarin

> 40 times potency than
Dicumarol

Enoxaparin

Bivaluridin *R Is*

Indirect Is

Fondaparinux

Dalteparin

Lepirudin *IR Is*

Argatroban *R Is*

Rivaroxaban

Dabigatran *R Is*

Direct Is

XIIα, XIα, IXα, Xα, IIα

II, VII, IX & X

Inactivation Of Coagulation Factors

Decrease Synthesis

Rapid / Variable

Monitor by *aPTT* (1.5 - 2.5 times normal [30sec])

Or *CT* (2-3 times normal [5-7 min])

Antidote; *Protamine Sulphate IV* → 1mg / 100 units UFH
+ / *Fresh blood*

Slow / Latency / Variable

Monitor by *PT* (2 times)

INR (2.5)

Antidote; *Vit. K₁ infusion*

+ / *Fresh blood*

+ Needs de novo synthesis

Anti-thrombin III

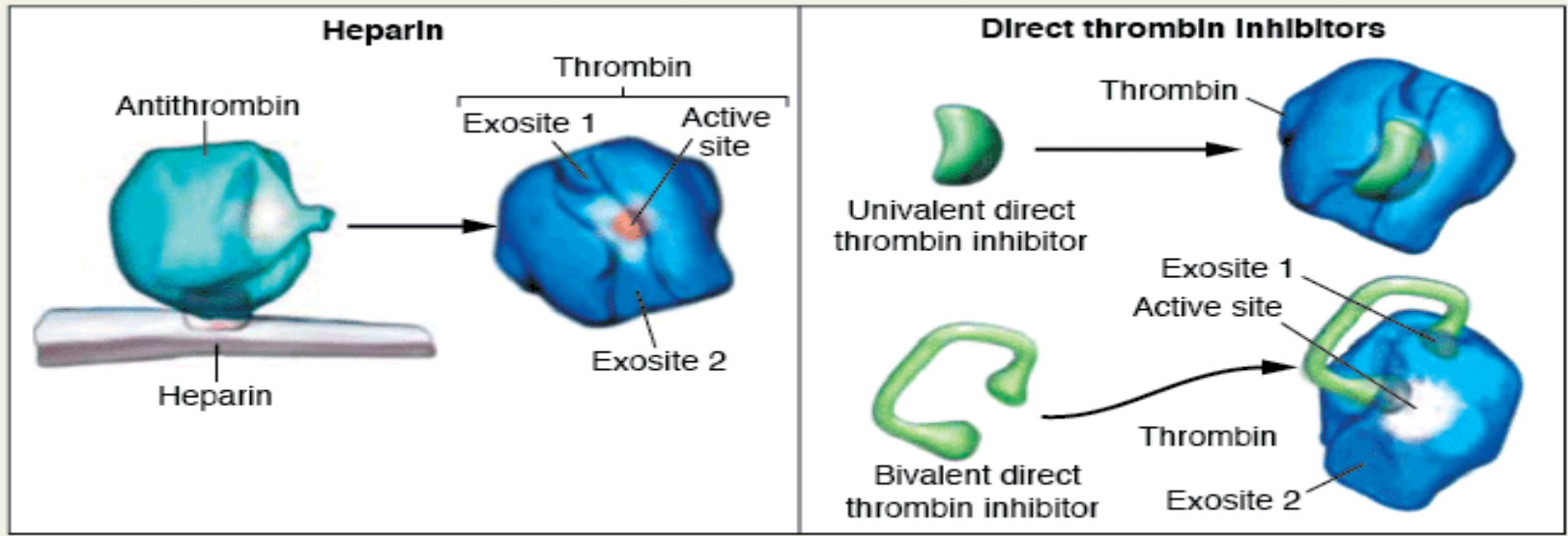
- Anti-thrombin III: It inactivates thrombin and other coagulation factors (IXa, Xa, XIa and XIIa) by forming complex with these factors. Heparin like molecules enhances these interactions.
- Protein C and S: these are vitamin K dependent proteins that slow the coagulation cascade by inactivating factor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

Heparin mechanism of action

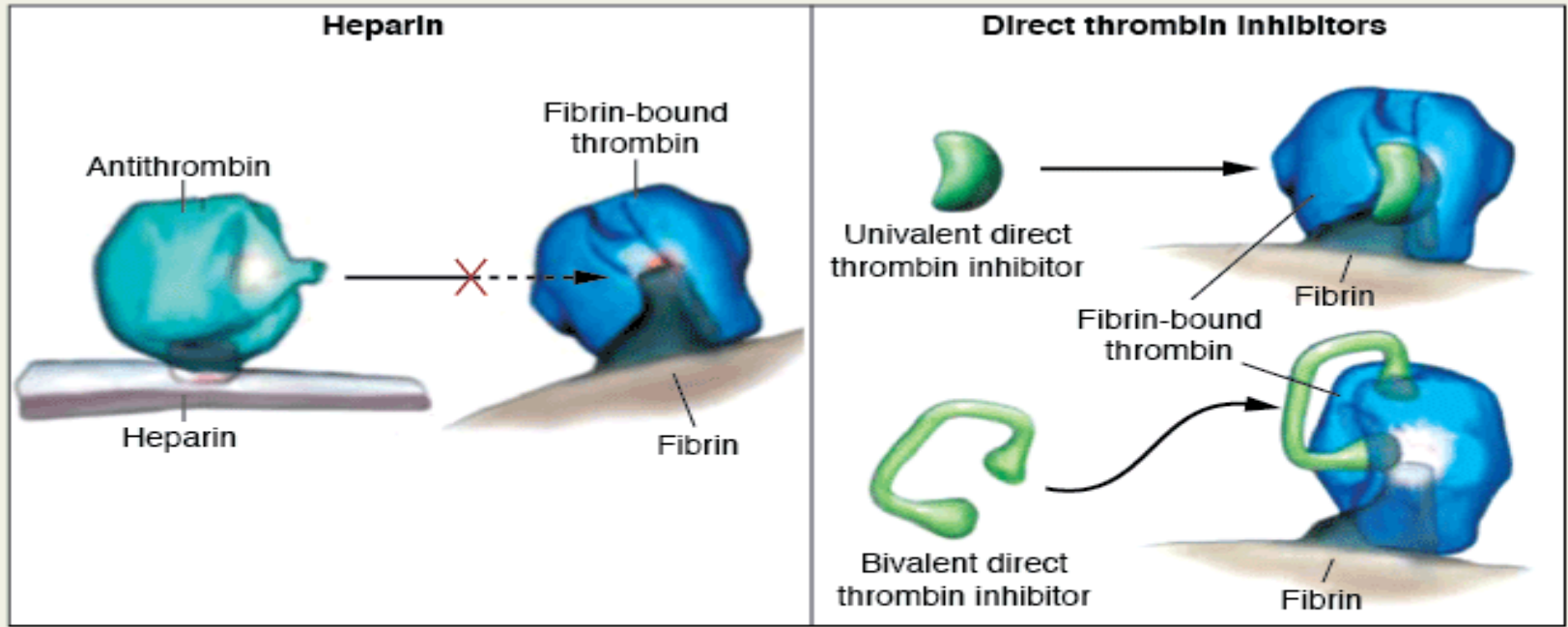
- The anti-coagulant effect of heparin is mediated via anti-thrombin III.
- Anti-thrombin III inactivate thrombin (essential for clot formation) and other serine proteases (clotting factors) e.g VIIa, IXa and particularly Xa.
- In the absence of heparin this inactivation is slow, heparin acting as a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

(B)

Soluble thrombin



Fibrin-bound thrombin



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unfractionated heparin (UFH)

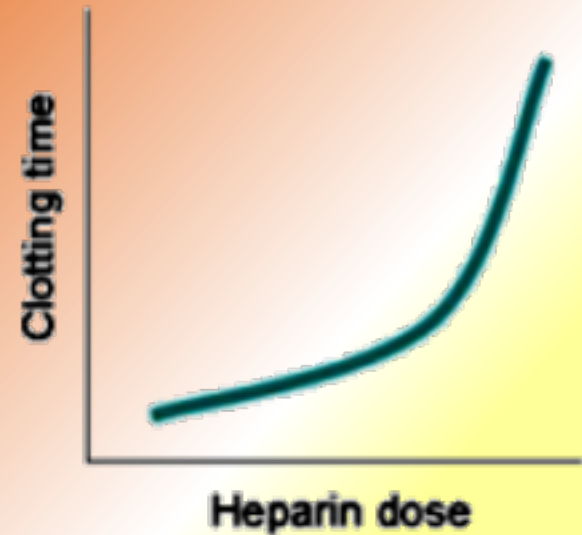
LIMITATIONS

- ✚ 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 IIa*

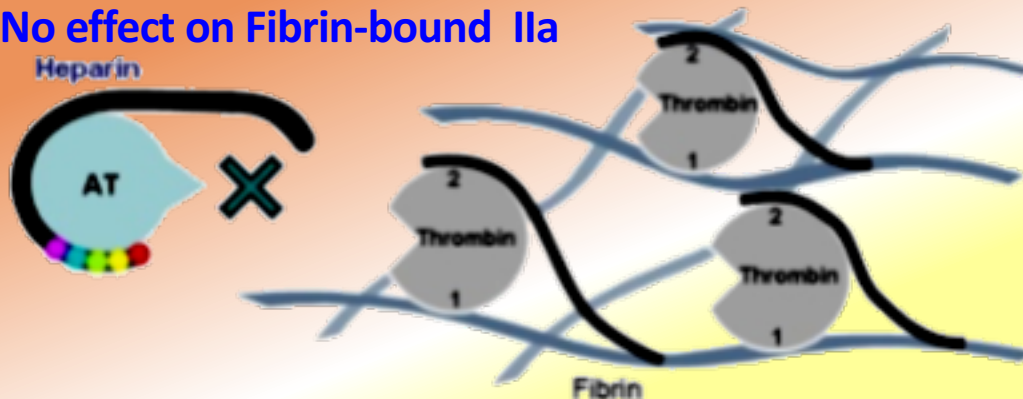
Heparin activates platelets directly.



Heparin exhibits a nonlinear dose-response.



No effect on Fibrin-bound IIa



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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 thrombosis

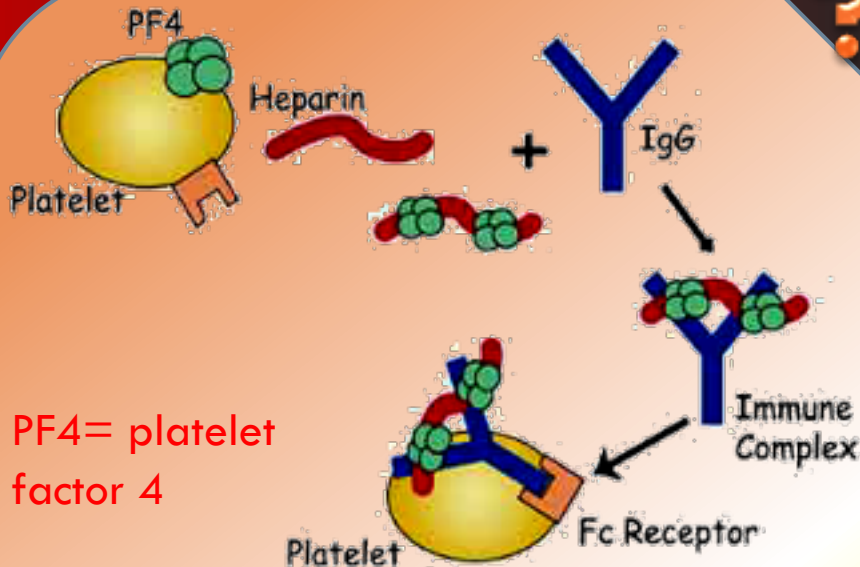


Heparin discontinuation

No packed platelets → More thrombosis

No warfarin → ppt .venous gangrene

Give → **DTIs**



PF4= platelet factor 4

Platelet removal by splenic macrophages

Thrombocytopenia

Platelet activation

Platelet release

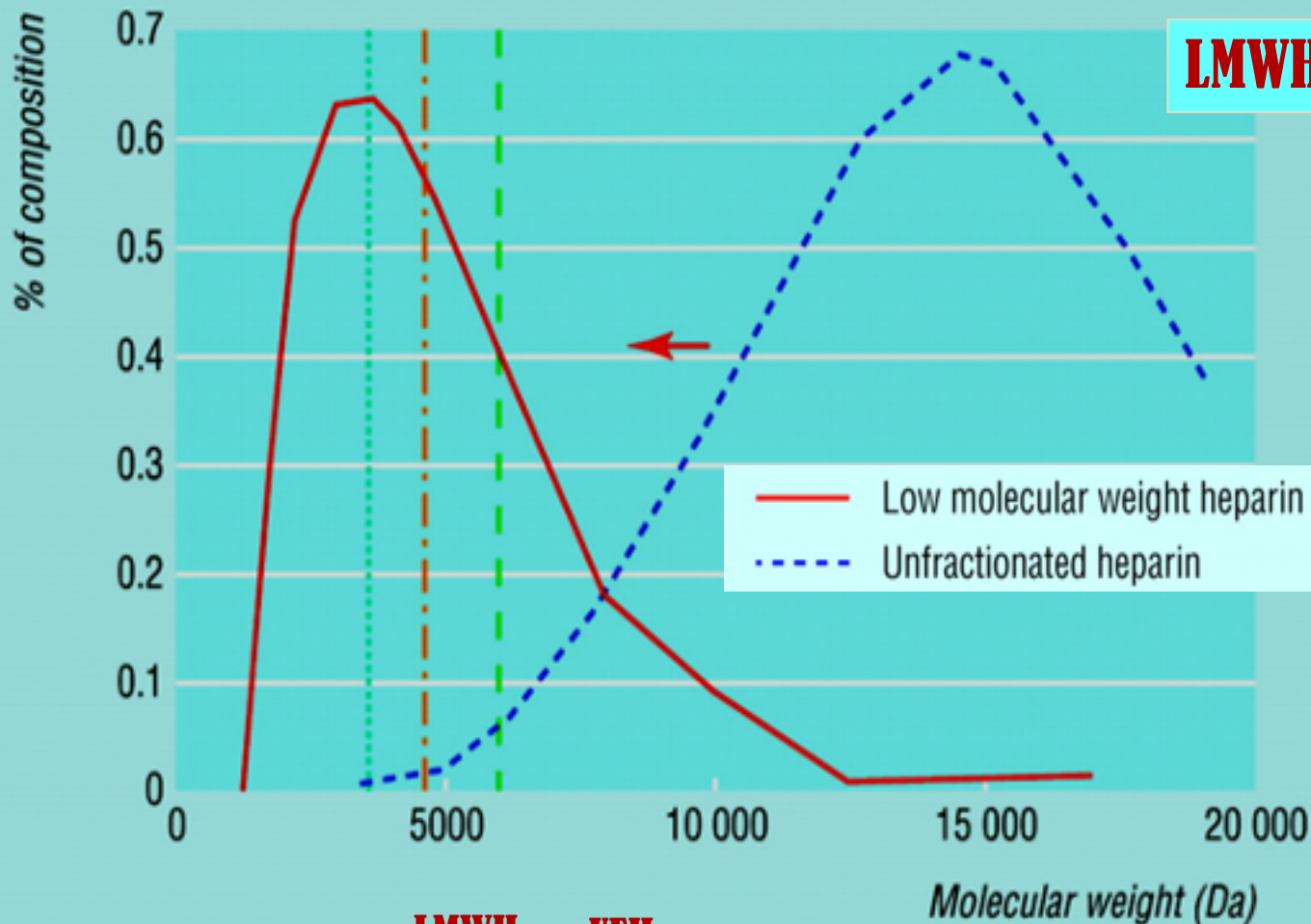
Platelet aggregation

Thrombosis

Release of procoagulant microparticles



LMWH versus UFH



LMWH
 Greater anti-Xa activity
 Resistant to PF4
 Little non-specific binding
 Greater inhibition of thrombin generation



UFH
 Greater antithrombin activity
 Less anti-Xa activity
 Sensitive to PF4
 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 bioavailability

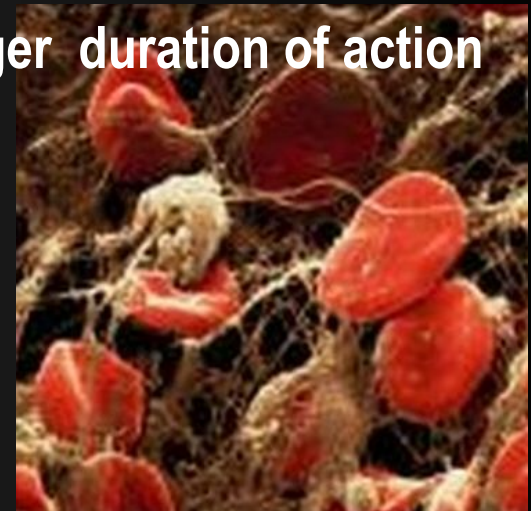
More predictable response

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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 monitoringOutside hospital settings

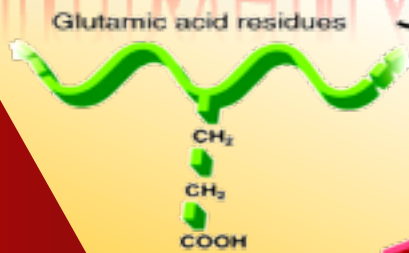


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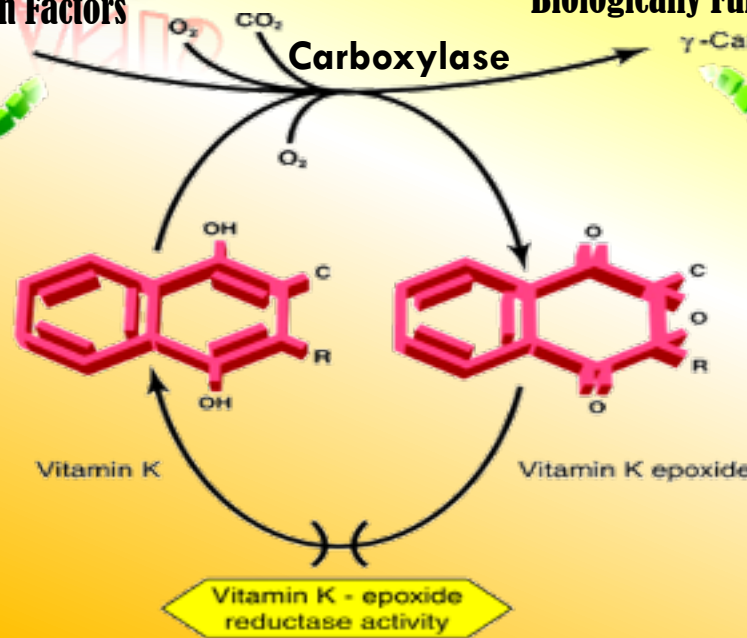
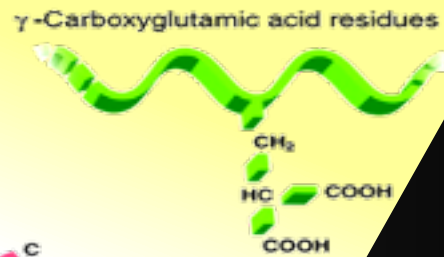
VKAs



Non-Functioning Coagulation Factors



Biologically Functioning Coagulation Factors



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

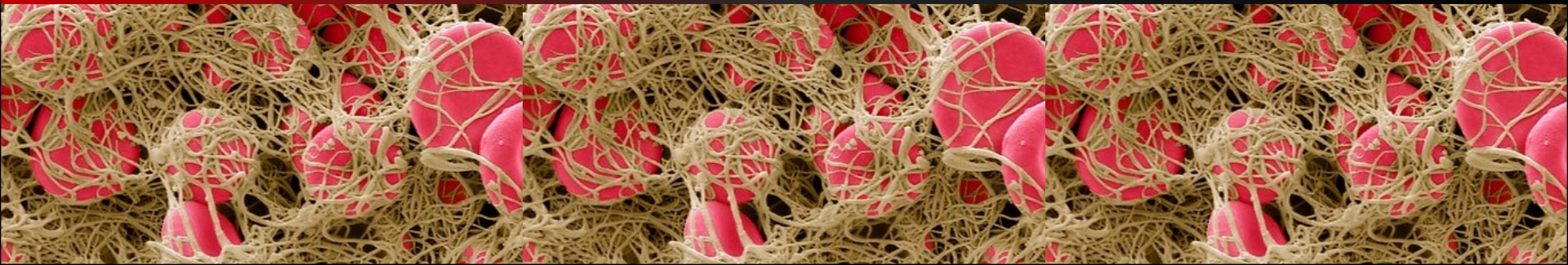
- **Inhibits synthesis of Vitamin K-dependent coagulation factors II, VII, IX, & X as well as anticoagulant proteins C & S**
- **Does not have an effect on already-synthesized coagulation factors; therefore, the therapeutic effects are not seen until these factors are depleted**
- **3-4 days until effect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

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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 $t_{1/2}$. 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. Displacement 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

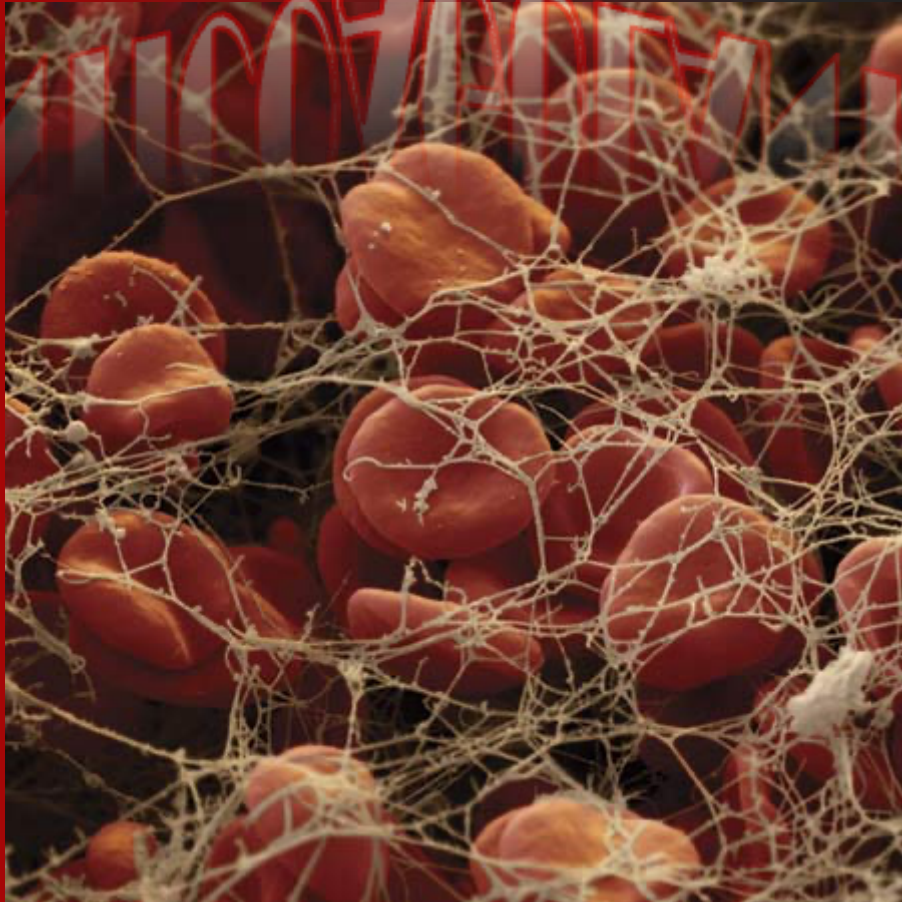
Table VII-1-1. Properties of Heparin and Warfarin (Coumarins)

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 <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)

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