ANTICOAGULANTS

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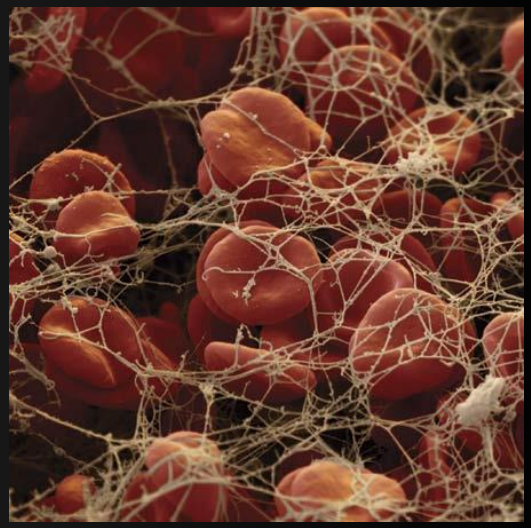
ANTICOAGULANTS



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.

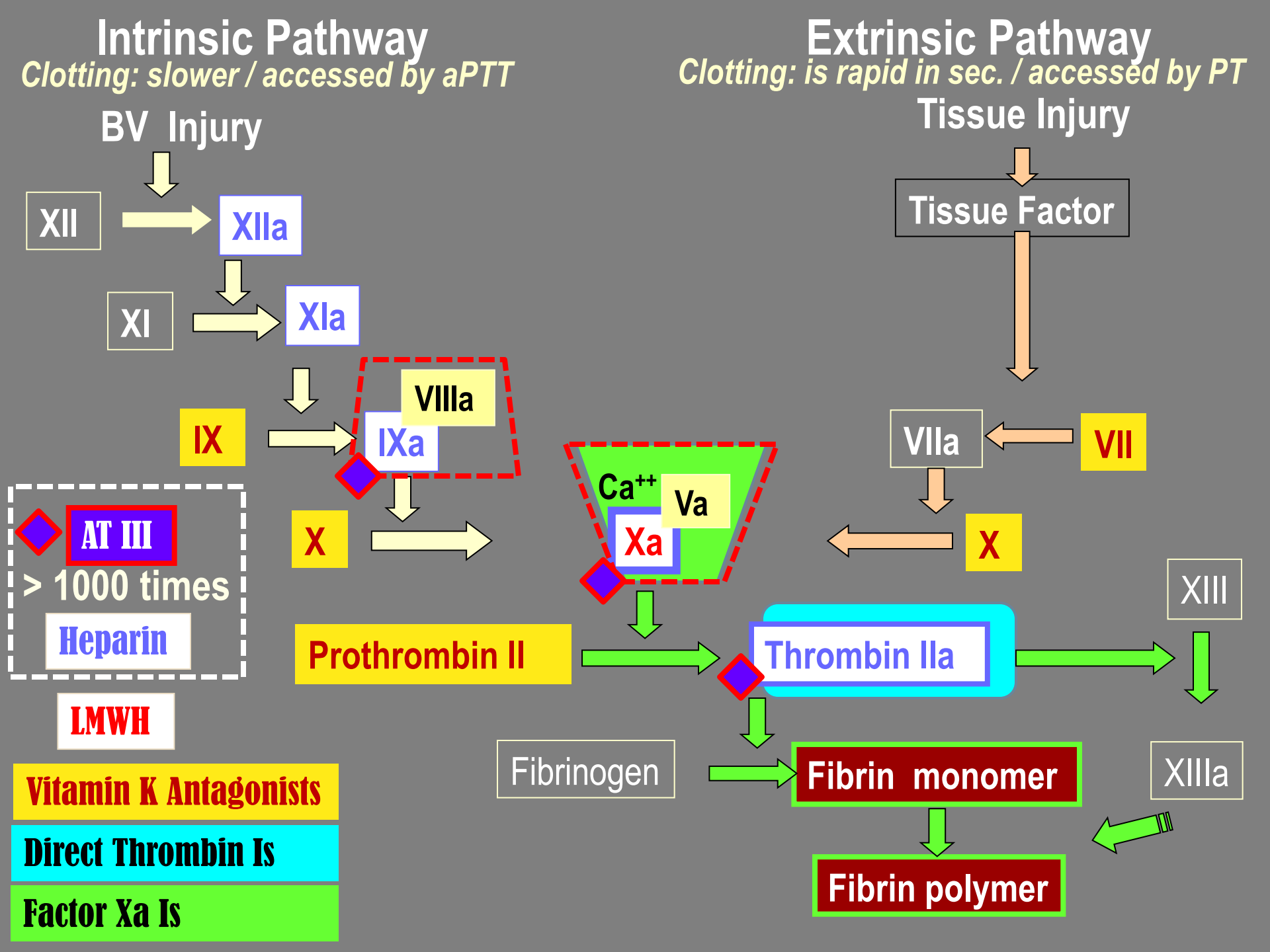
Drugs and coagulation

- **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.

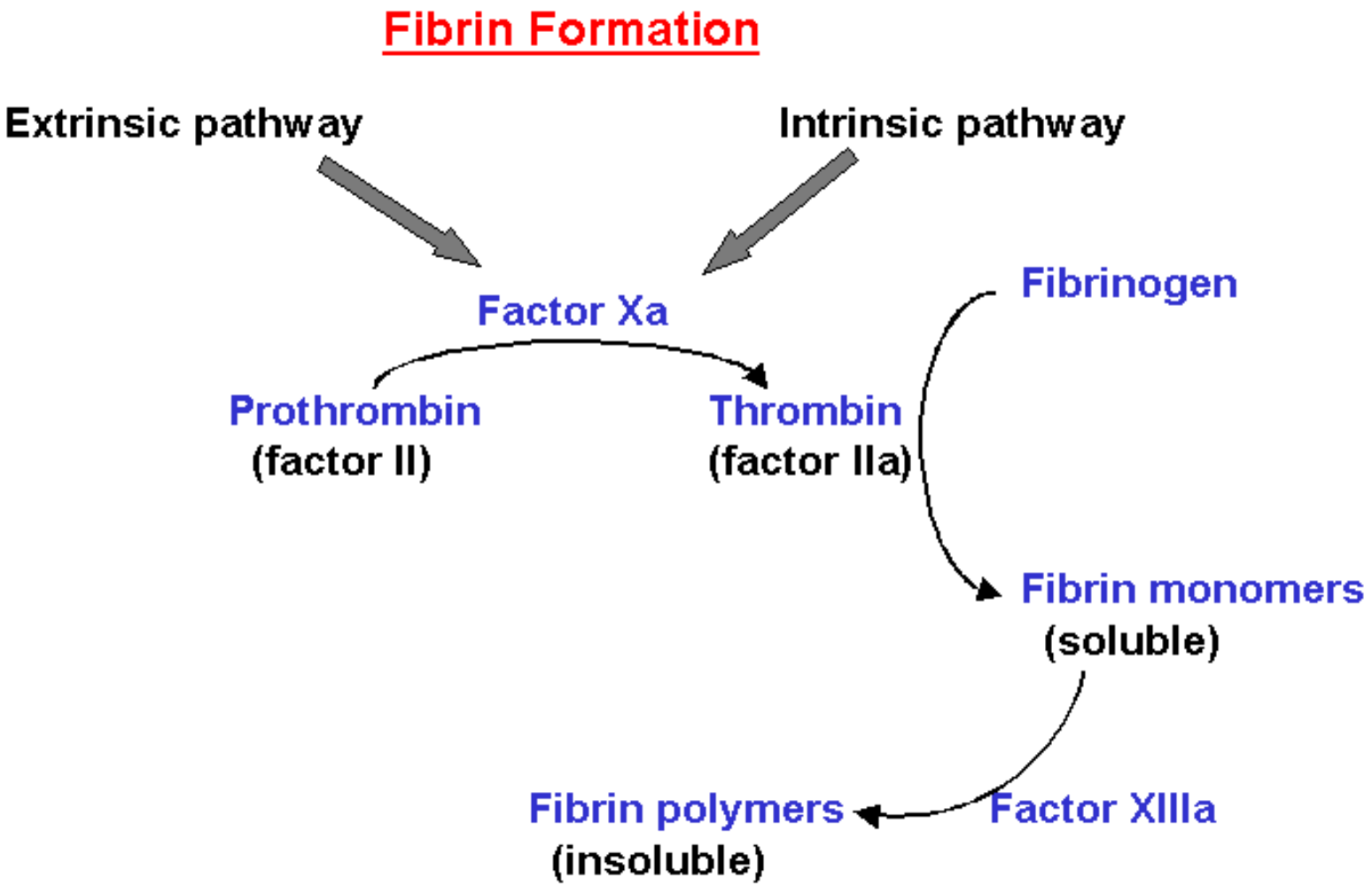
Indication of anti-coagulant

- 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



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VENOUS THROMBOSIS

Parenteral Anticoagulants

UFH

3000-30000

LMWH

< 8000

> Xa

Enoxaparin
Dalteparin

Direct Thrombin Is

II a

Bivaluridin *R Is*
Lepirudin *IR Is*

Argatroban *R Is*
Dabigatran *R Is*

Factor Xa Is

Pentasaccharide
X a

Indirect Is
Fondaparinux

Rivaroxaban
Direct Is

XIIa, XIa, IXa, Xa, IIa

Inactivation Of Coagulation Factors

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

Oral Anticoagulants

Vitamin K Antagonists

Coumarins;
Warfarin
> 40 times potency than
Dicumarol

II, VII, IX & X

Decrease Synthesis

Slow / Latency / Variable
Monitor by PT (2 times)
INR (2.5)
Antidote; Vit. K_1 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 incativation is slow, heparine acting is a co-factor accelerate the reaction by 1000-fold.

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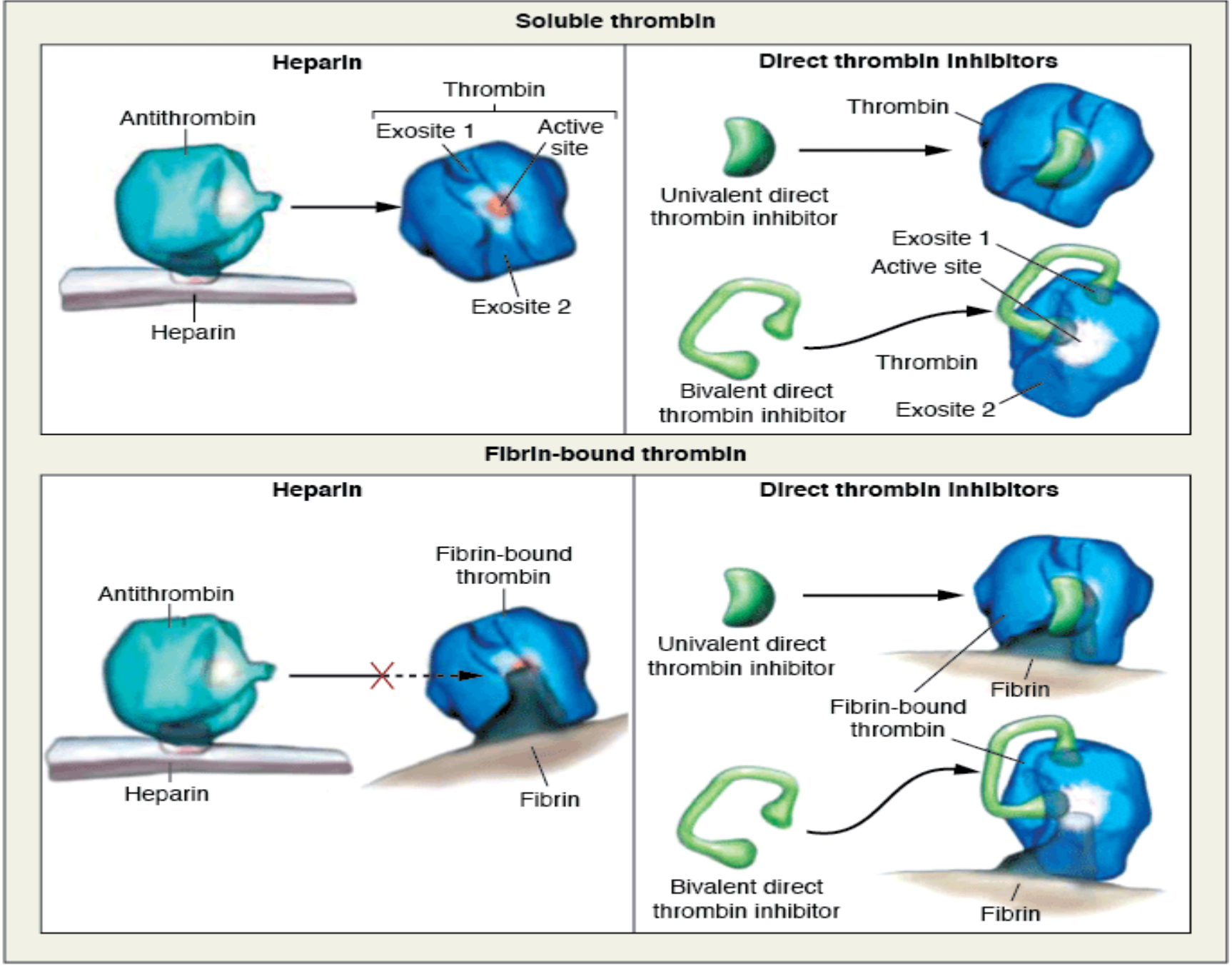

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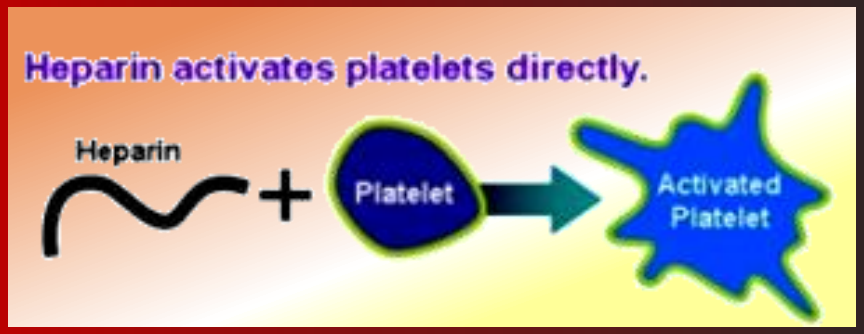
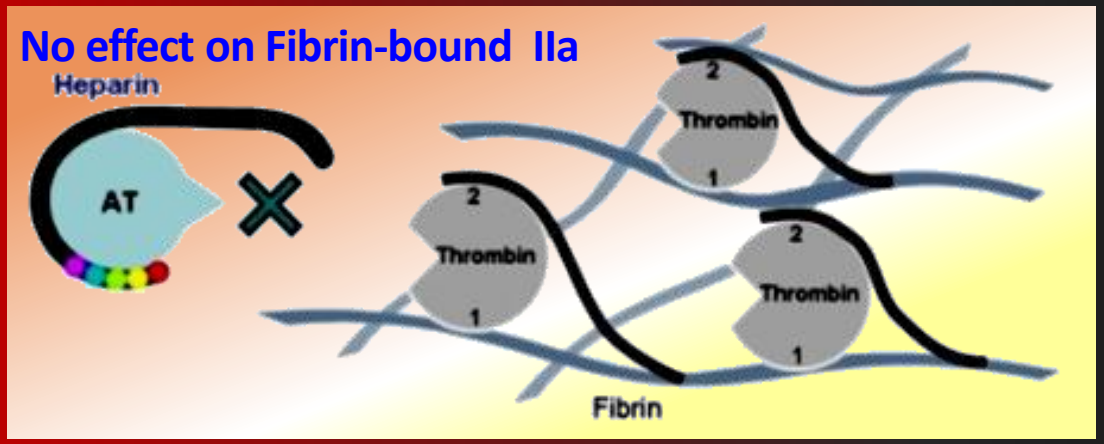
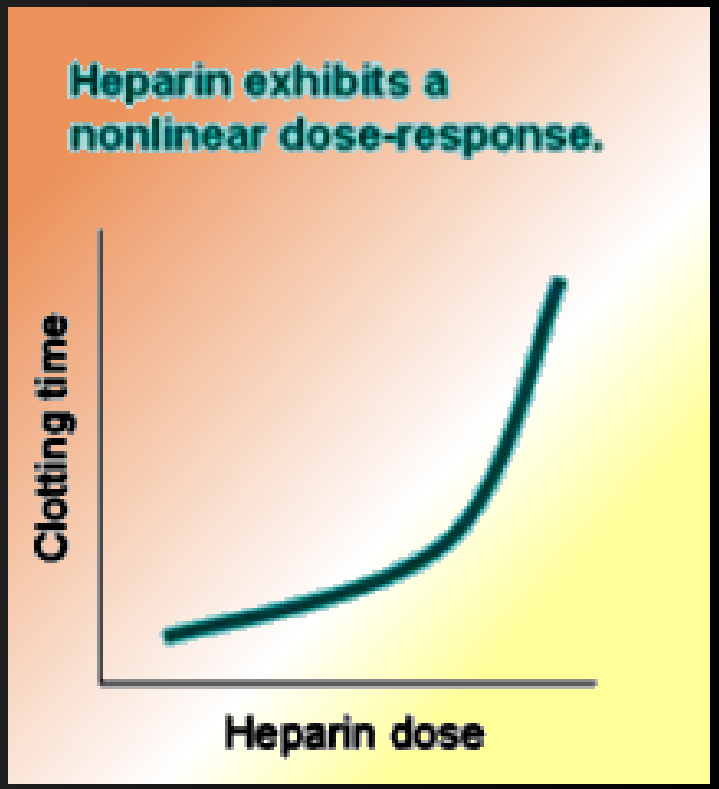
unfractionated heparin (UFH

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*







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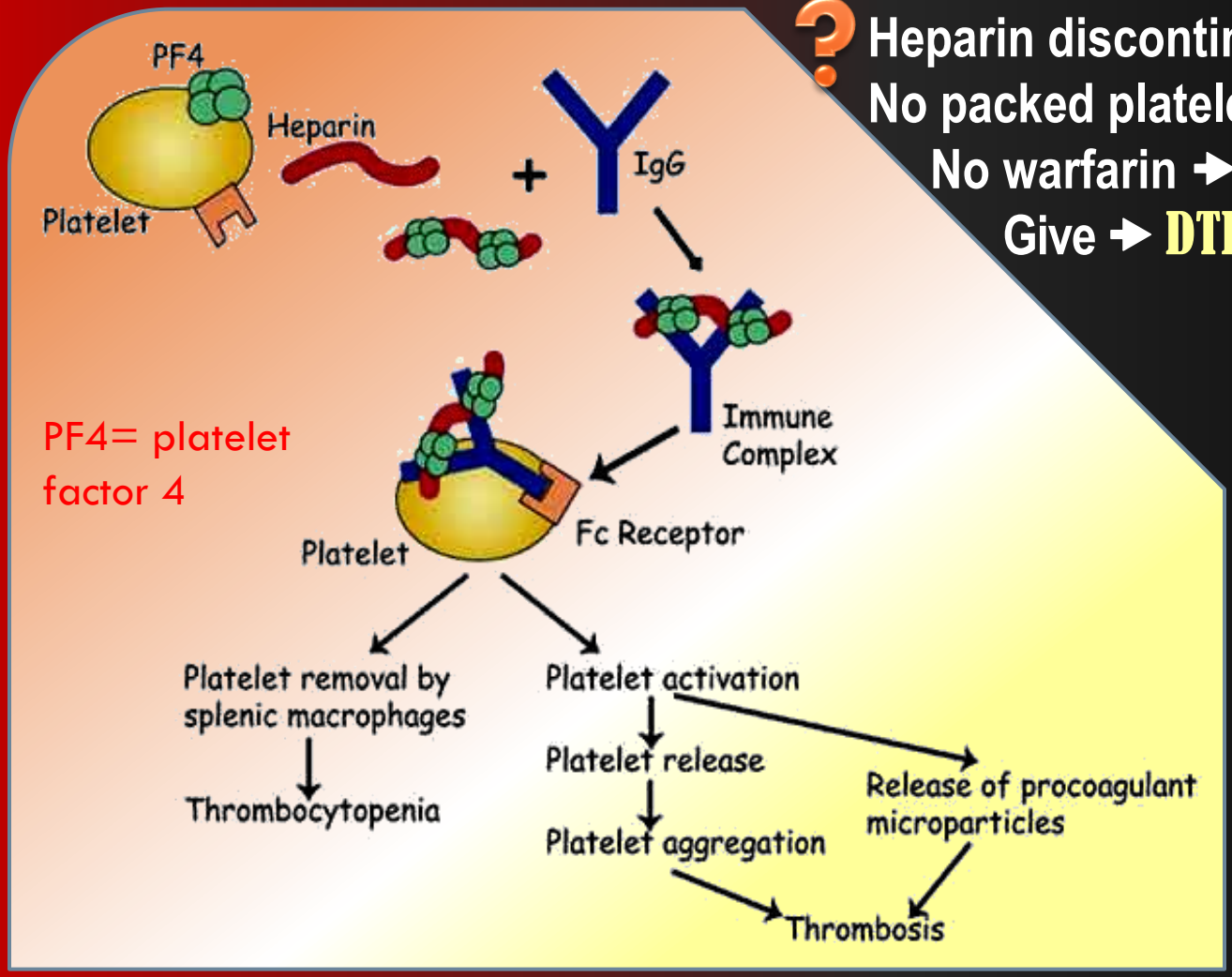
UFH LIMITATIONS

- 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 thombosis



PF4= platelet factor 4

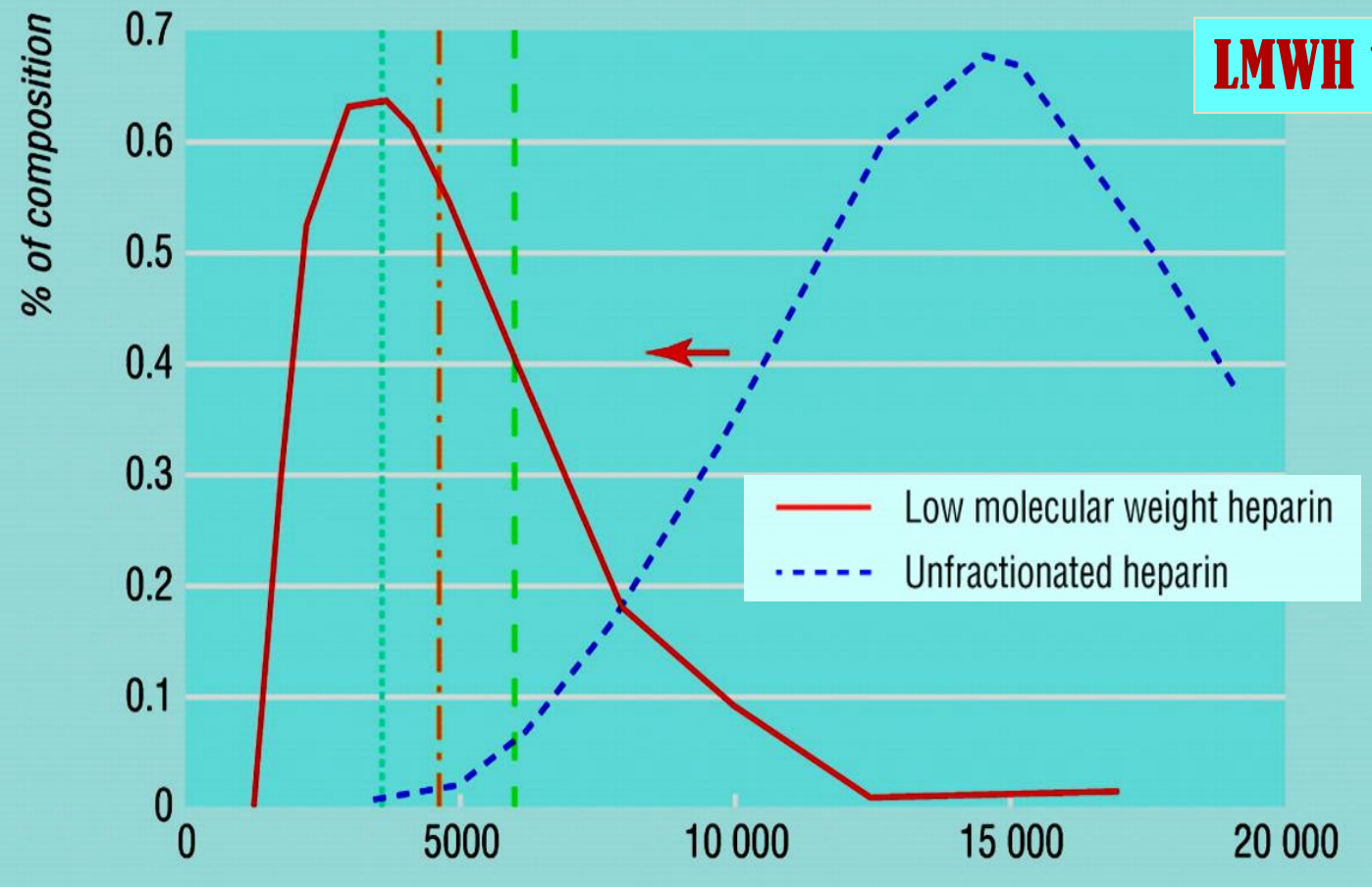
? Heparin discontinuation

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

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LMWH BENIFITS

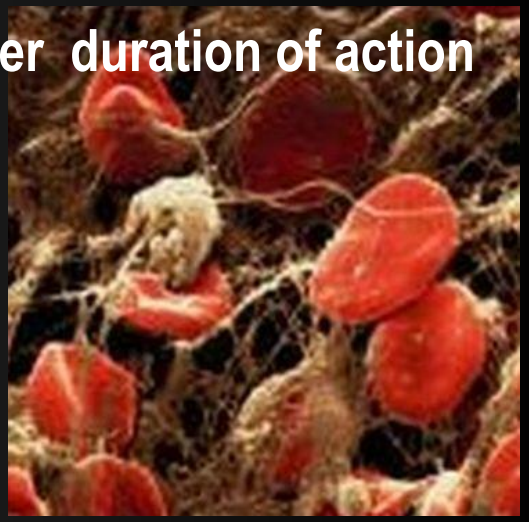
- ↑ Predictability of anticoagulant response i.e. little inter-patient and intra-patient variability in response to a given dosage. without the need for laboratory monitoring
- ↑ Bioavailability; as it hardly binds to plasma proteins, endothelium & macrophages
- ↓Incidence of thrombocytopenia; as it 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 monitoring

  Outside hospital settings



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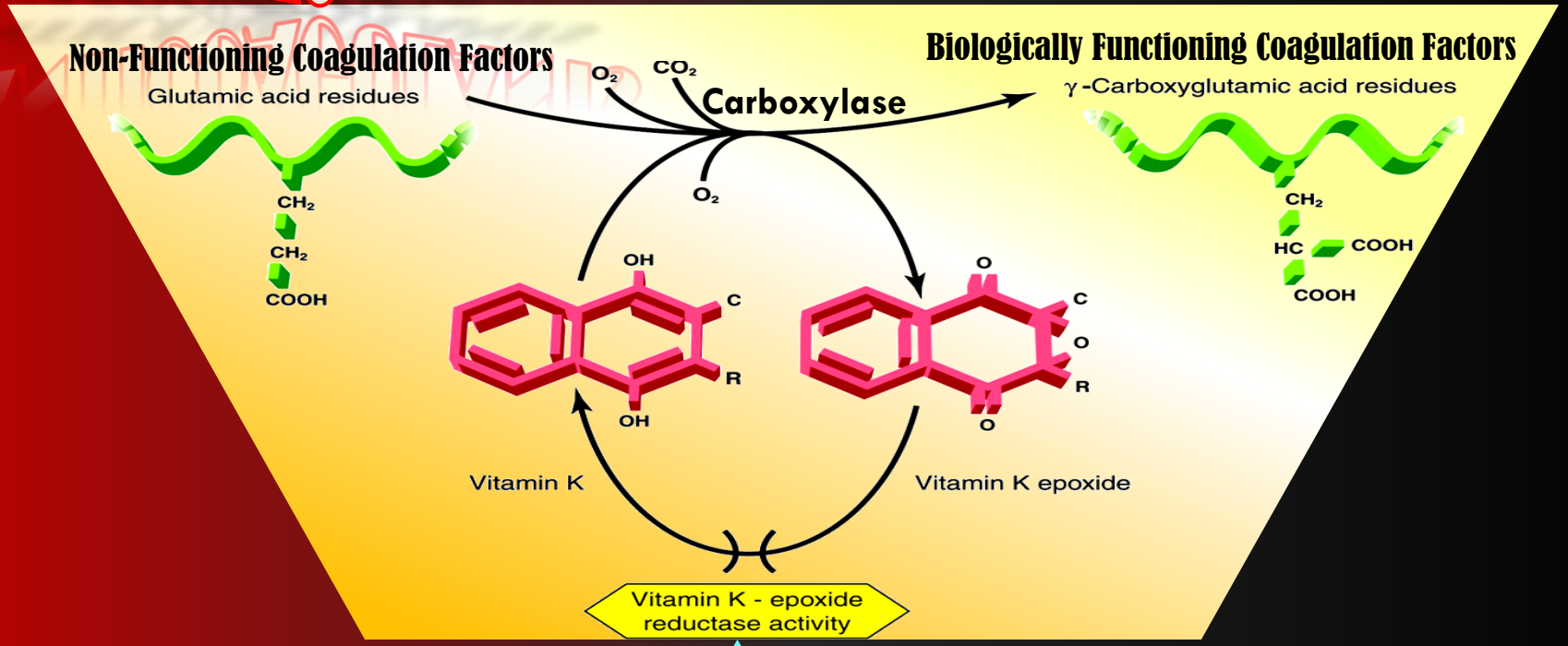
VKAs



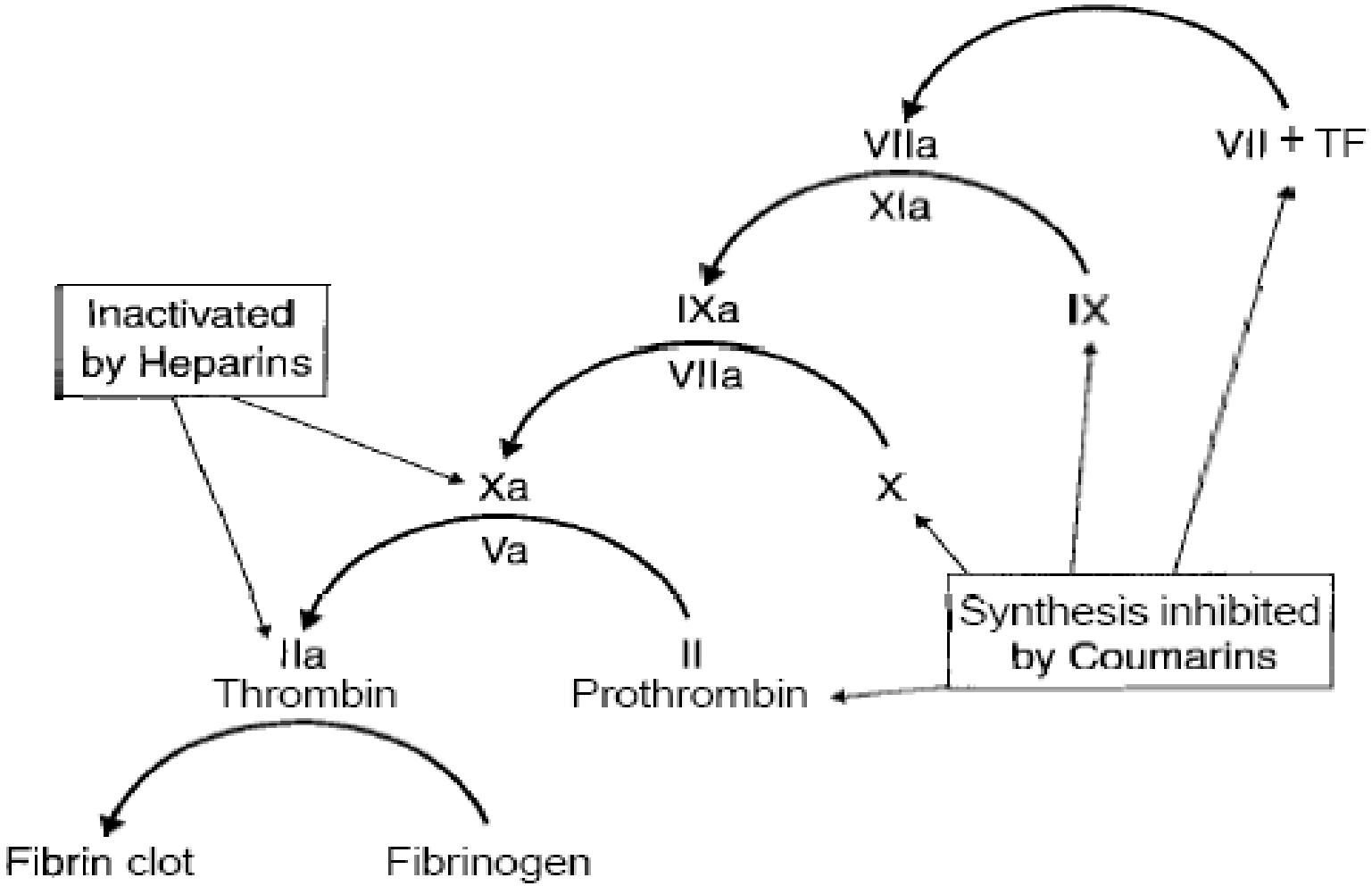
Warfarin

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



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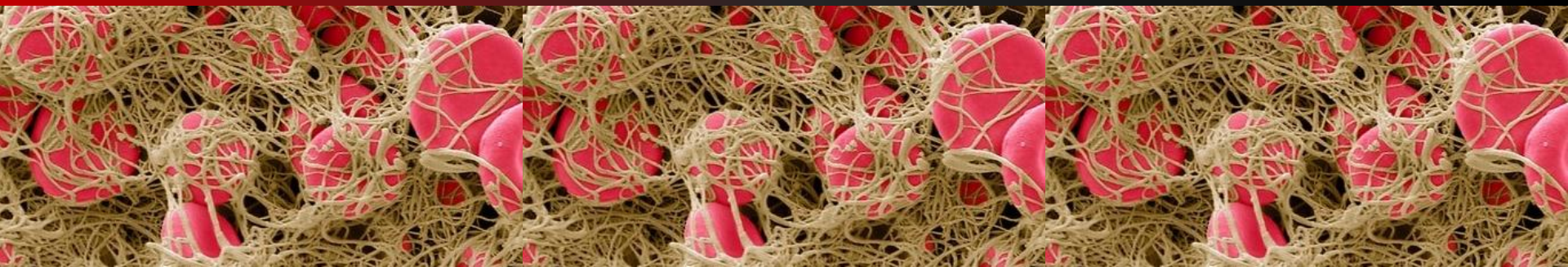
VKAs LIMITATIONS

- 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 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

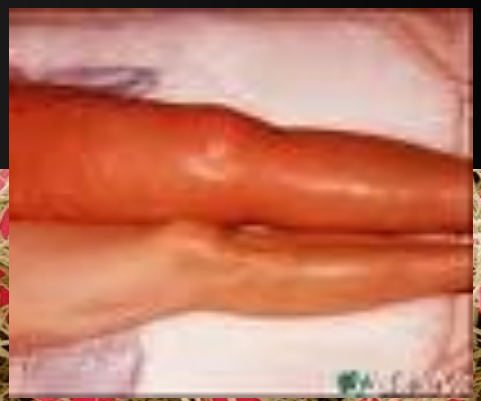
1. Inhibition of drug absorption from GIT; cholystyramine, colestipol
2. Increase in synthesis of clotting factors; Vit K, oral contraceptives
3. Increase in drug metabolism by microsomal enzyme inducers; Carbamazepine; barbiturates, rifampicin

An old, peptic ulcer patient, sustained on cimetidine, has been bed ridden since a month following a major orthopedic surgery for pelvic fracture. The last week he began to complain of pain, tenderness, warmth & swelling of his left leg. He was diagnosed as deep vein thrombosis. His treating physician put him first on heparin that was replaced after three days by VKAs. Today he began to show bleeding of gums.

What is the expected explanation of his finding?

Will the treating physician 1st of all, consider giving an antidote to stop bleeding (if so then state) or will he probably ask for lab investigation (if so then state)?

Once lab findings are there, is the physician expected first to withdraw or to adjust the existing therapy?



A young rheumatic artheritic patient has underwent valve replacement and is sustained on warfarin therapy for the last three years. When she married, last summer, she did not want to get pregnant, so she has taken since then, oral contraceptive pills. Her regular lab monitoring today showed a decrease in INR this time.

What is the expected explanation of her lab result?

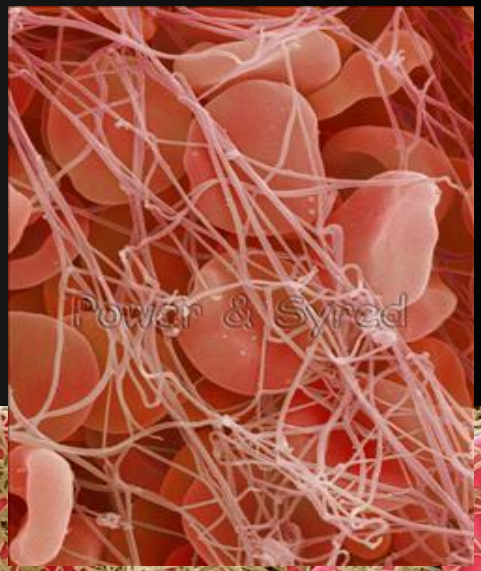
What will the treating physician consider doing?

-Giving heparin on top

-Adjusting warfarin dose

- Stopping the OC

- Stopping warfarin



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)

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GOOD LUCK