ANTICOAGULANTS

Notes.. By :

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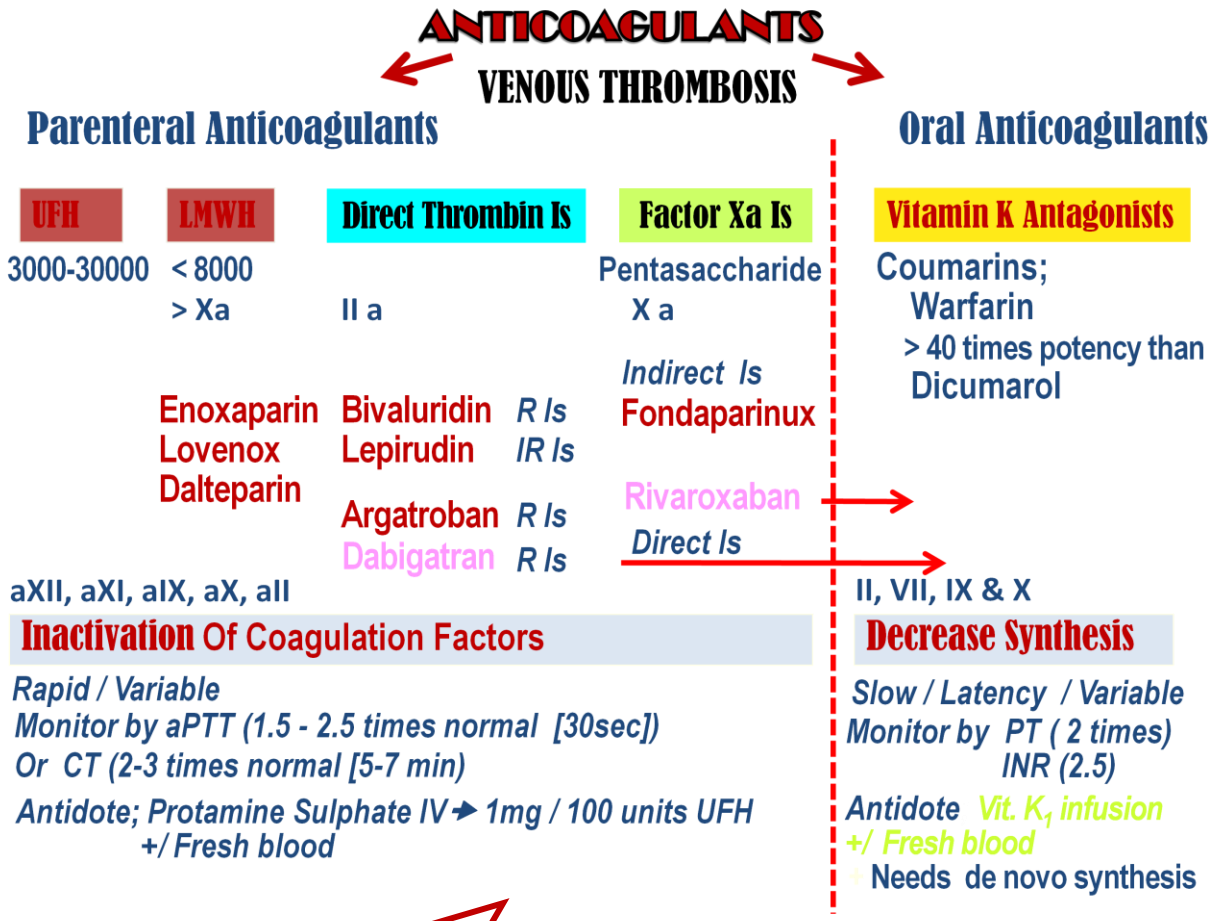


Note

What u need to know from previous slide :

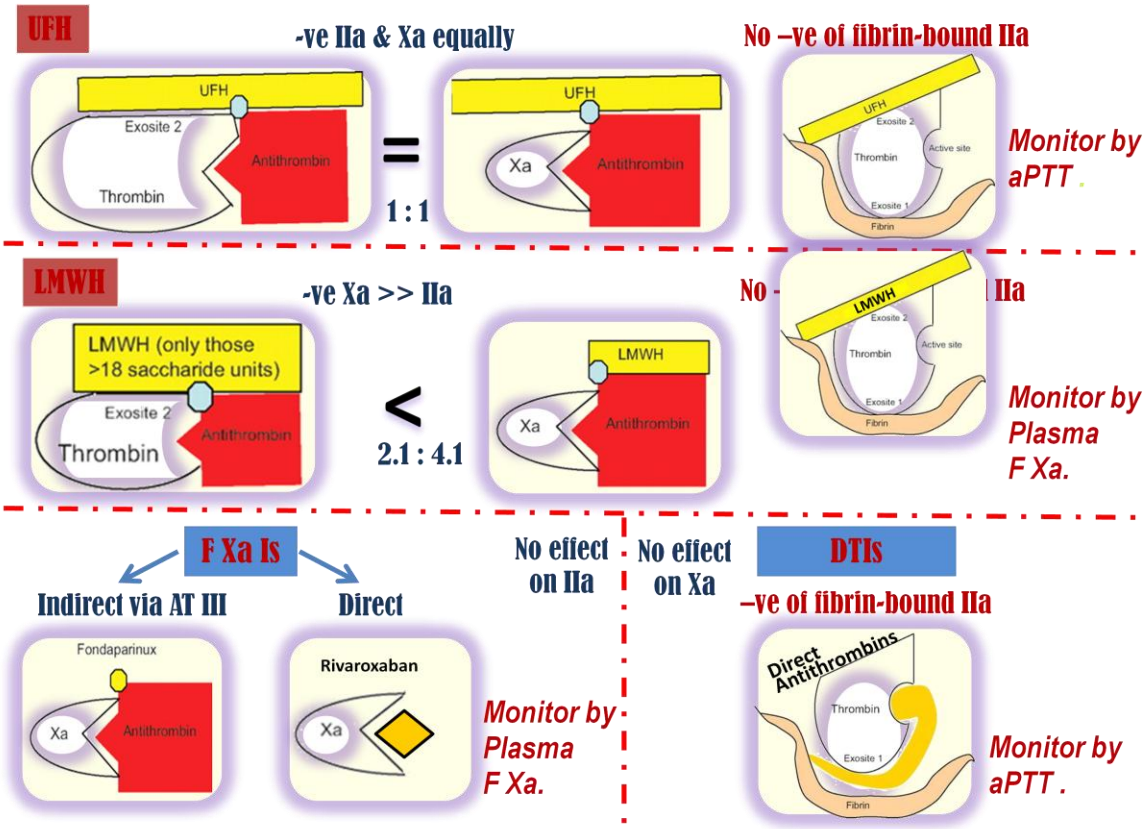
**** UFH (unfractionated heparin)= HMW (I.V) :**

- *Rapid / Variable*
- **Inactivation** Of Coagulation Factors aXII, aXI, aIX, aX, aII
- *Monitor by aPTT (1.5 - 2.5 times normal [30sec])*
- *Antidote (treat. ER cases develpe toxicity) >> Protamine Sulphate IV + Fresh blood*

**** Vitamin K Antagonists = warfarin (oral) :**

- **Decrease Synthesis of** II, VII, IX & X
- *Slow / Latency / Variable*
- *Monitor by PT (2 times) and INR (2.5) (with bad response to VKA , the INR will be low)*
- *Antidote >> Vit. K_1 infusion + Fresh blood*

**** LMWH <<< inactivate** Xa



Note

What u need to know from previous slide :

drugs can act on active thrombi -fibrin-bound IIa - (which already formed) is **DTI direct thrombin inhibitors** << Only ..imp

The other drugs use for inhibition of **new thrombus formation**

Anticoagulants

1- UFH LIMITATIONS (disadvantages) :

1- No predictable anticoagulant effects (*poor prognosis*); inter-patient & intra-patient variability in response to a given dosage ➔ *SO, need to : hospital setting, repeated monitoring*

2- Low bioavailability ➔ *binds to* plasma proteins, endothelium & macrophages

3- Re-thrombosis ➔ *activates platelets as it does not neutralize fibrin-bound IIa*

4- 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

Heparin discontinuation ?

No packed platelets ➔ More thrombosis

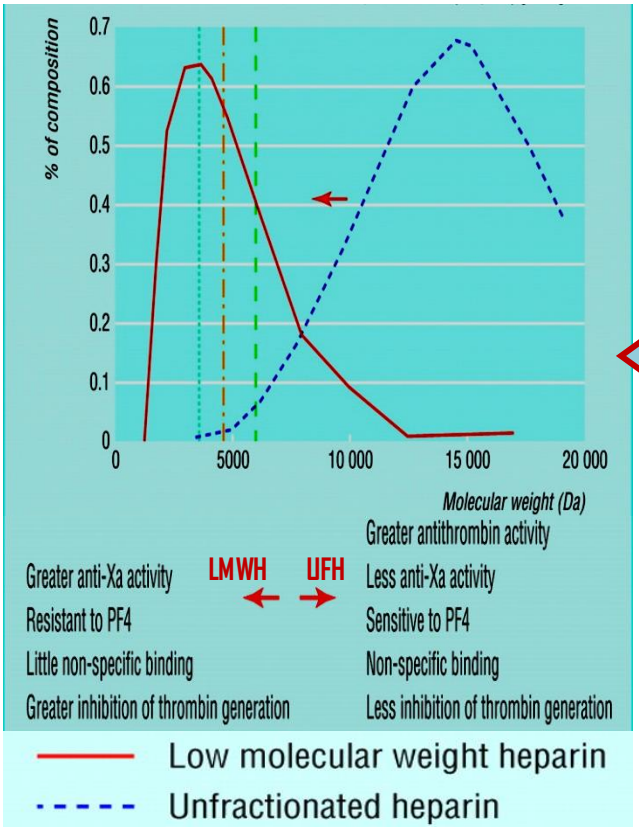
No warfarin ➔ ppt .venous gangrene

Give ➔ DTIs

Note

pt. with HIT <<< treated by DTI

LMWH versus UFH :



Note

What u have to get :

(LMWH better than UFH)

See next schedule ..

2-LMWH BENEFITS:

- ↑ Predictability of anticoagulant response (good prognosis) i.e. little inter-patient and intra-patient variability in response to a given dosage. So → effective anticoagulant activity can be achieved by calculating dosages based on body weight 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

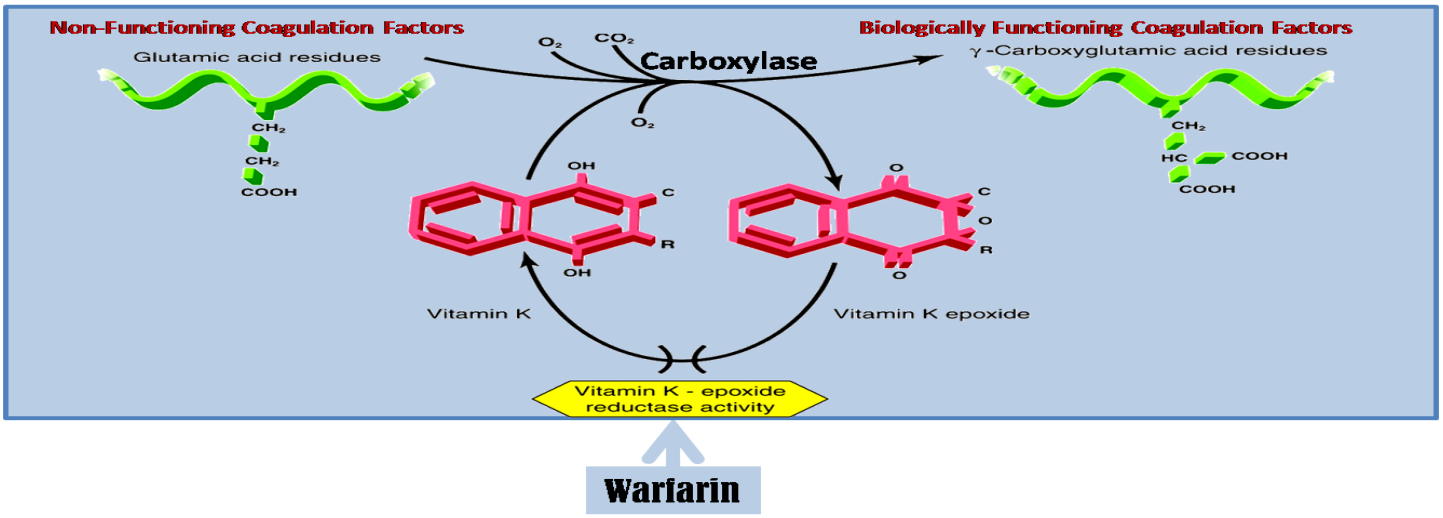
  Outside hospital settings

Note

(Conclusion of page 4, 5)

LMWH (*Low Molecular Weight Heparin*)	HMW (High Molecular Weight *)*
↑ Predictability of anticoagulant response (good prognosis about the drug response) so << no need for laboratory monitoring	Low Predictability of anticoagulant response (bad prognosis about the drug response) so << need for laboratory monitoring
↑ Bioavailability	Low Bioavailability
↓Incidence of thrombocytopenia (resistance to PF4)	High incidence of thrombocytopenia (sensitive to PF4) treated by DTI
↓Incidence of bleeding tendency	Re-thrombosis
↓ frequency of administration due to longer duration of action	Short duration of action
given sub. cut. Outside hospital settings	Hospitalization Given I.V

3- VKAs :



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.

VKAs LIMITATIONS (disadvantages) :

- **Wide variation in drug response ➔ a necessity for continuous monitoring (PT) & dose adjustment .**
- **Has narrow therapeutic window; high PPB & action depends on very small fraction of free drug. So any change in that level can be hazardous.**
- **Slow onset of action, so not in given in emergency conditions**
- **Has latency in its action➔ presents the time needed to launch new biologically inactive coagulation factors**
- **Common genetic 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 some conditions liable to develop thrombosis i.e as in pregnancy….**

FACTORS ALTERING RESPONSE TO VKAs :

Imp. !!!

Increase the VKAs action lead to toxicity << (bleeding)	decrease the VKAs action (low INR)
1. Vitamin K deficiency; a- Inadequate diet; malnutrition, dieting,…. b- Inadequate absorption; diseases of small intestine, diseases ↓biliary secretion 2. Impaired synthesis of clotting factors; a. In hepatocellular disorders; (hepatitis; viral, autoimmune, drug-induced, chronic alcoholism ... etc.) b. In hepatic congestion; in congestive HF,…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 :

Increase the VKAs action	decrease the VKAs action
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, disulfiram & cimetidine 4. Displacment of the drug from protein binding sites; phenylbutazone, sulphonamides, diazoxide , clofibrate & salicylates 5. Co-administration of drugs that increase bleeding tendency by; a- inhibiting platelet function; NSAIDs b- inhibiting coagulation factors; heparin & antimetabolite	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; barbiturates, rifampicin & griseofulvin

Cases :

1) 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?

Decrease in drug metabolism by cimetidine >> increase accumulation >> increase anticoagulation >> bleeding

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)?

Ask for lab investigation (no need for antidote cuz no sever bleeding)

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

Adjust the dose

2) 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?

oral contraceptive pills decrease warfarin action lead to decrease INR

What will the treating physician consider doing?

- Giving heparin on top
- Adjusting warfarin dose correct Answer
- Stopping the OC
- Stopping warfarin

3) A 53 years old patient had an aortic valve replacement since 5 years and he is sustained on warfarin. A week ago, he developed low grade fever, diarrhea and was diagnosed as having typhoid. He was given rehydration fluid and a course of chloramphenicol.
Today he is complaining from haematuria.<<< indicate presence of bleeding)

Which one of the following best explains the haematuria?

- Inhibition of Vit K synthesis by chloramphenicol
- Displacement of warfarin from protein binding site by rehydration
- Decrease in warfarin metabolism induced by chloramphenicol correct
- Inhibition of Vit K absorption caused by the diarrhea

Which is the right decision to do in such a case?

- Give a urinary antiseptic for fear of infection
- Stop administering the regular intake of warfarin
- Adjust the dose of warfarin after monitoring the situation correct
- Stop the course of chloramphenicol intended for typhoid therapy