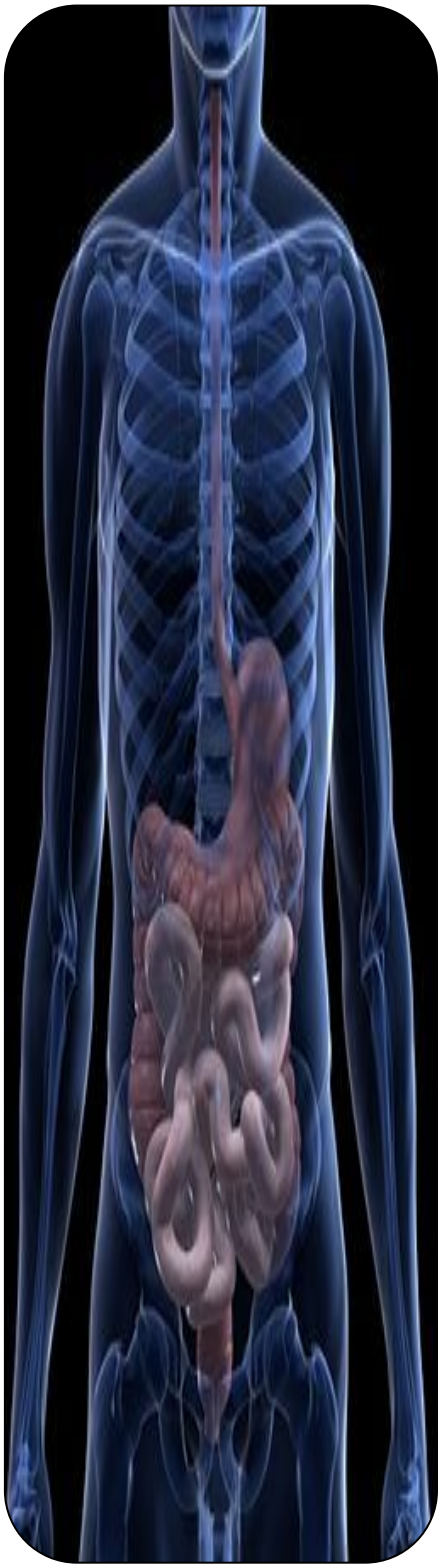

Pharmacology Team

Anti-Coagulants

Done by:
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Introduction:

The introduction is just for your information. Thanks to Pharmacology Team 430

Hemostasis refers to the finely regulated dynamic process of maintaining fluidity of blood, repairing vascular injury, and limiting blood loss while avoiding vessel occlusion (thrombosis) and inadequate perfusion of vital organs. Either extreme—excessive bleeding or thrombosis—represents breakdown of the hemostatic mechanism.

Blood vessel injury triggers the following sequence:

- The vessel constricts to reduce blood flow
- Circulating platelets adhere to the vessel wall at the site of trauma
- Platelet activation and aggregation, coupled with an intricate series of enzymatic reactions involving coagulation proteins, produces fibrin to form a stable haemostatic plug.

Antithrombotic drugs are used for prevention and treatment of thrombosis. Targeting the components of thrombi, the agents include **(1) antiplatelet drugs, (2) anticoagulants, and (3) fibrinolytic agents.** With the **predominance of platele in arterial thrombi, strategies to inhibit or treat arterial thrombosis focus mainly on antiplatelet agents**, although, in the acute setting, they often include anticoagulants and fibrinolytic agents.

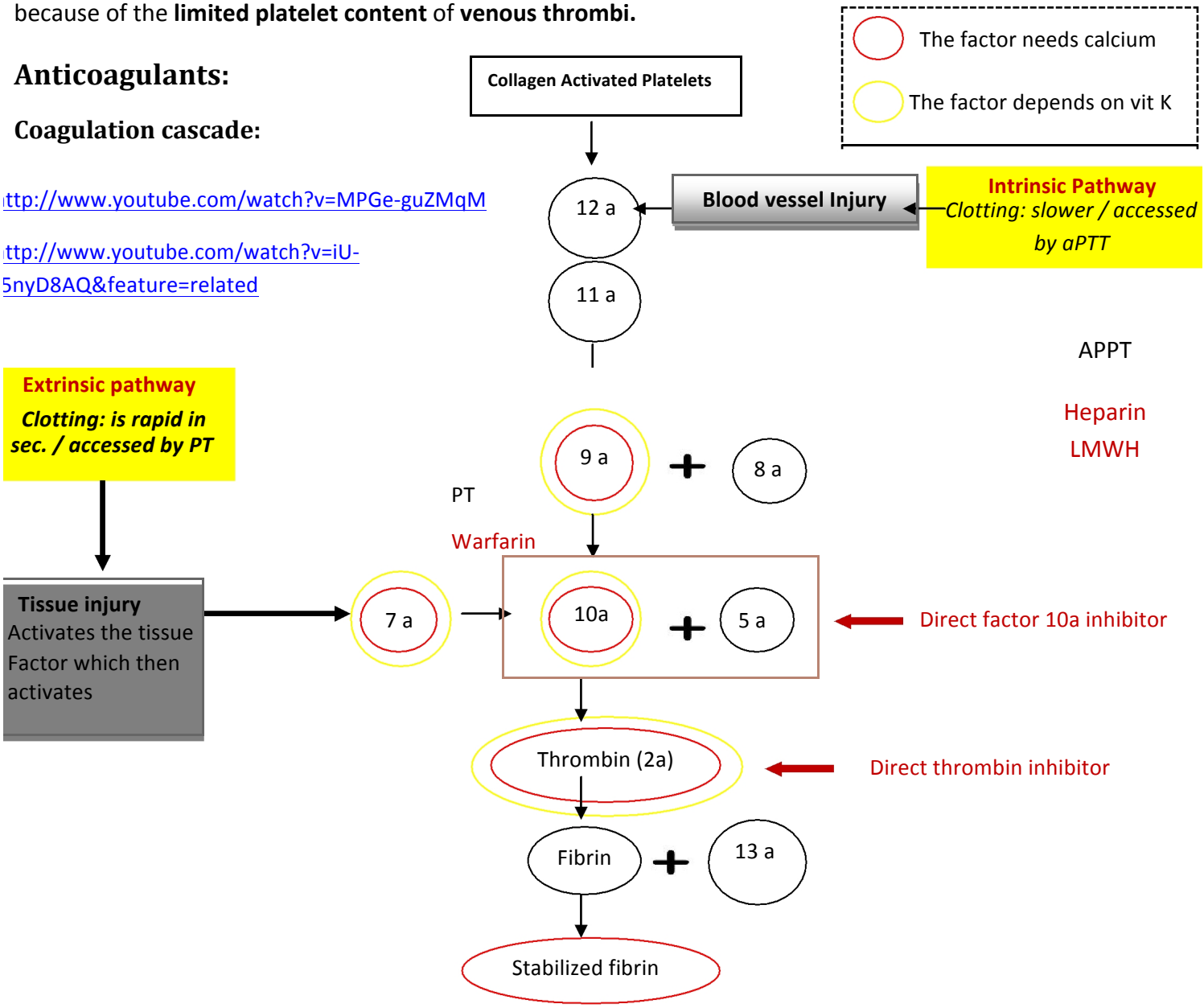
Anticoagulants are the mainstay of prevention and treatment of venous thromboembolism because fibrin is the predominant component of venous thrombi. Antiplatelet drugs are less effective than anticoagulants in this setti because of the **limited platelet content** of **venous thrombi.**

Anticoagulants:

Coagulation cascade:

ttp://www.youtube.com/watch?v=MPGe-guZMqM

ttp://www.youtube.com/watch?v=iU-5nyD8AQ&feature=related



Anticoagulant

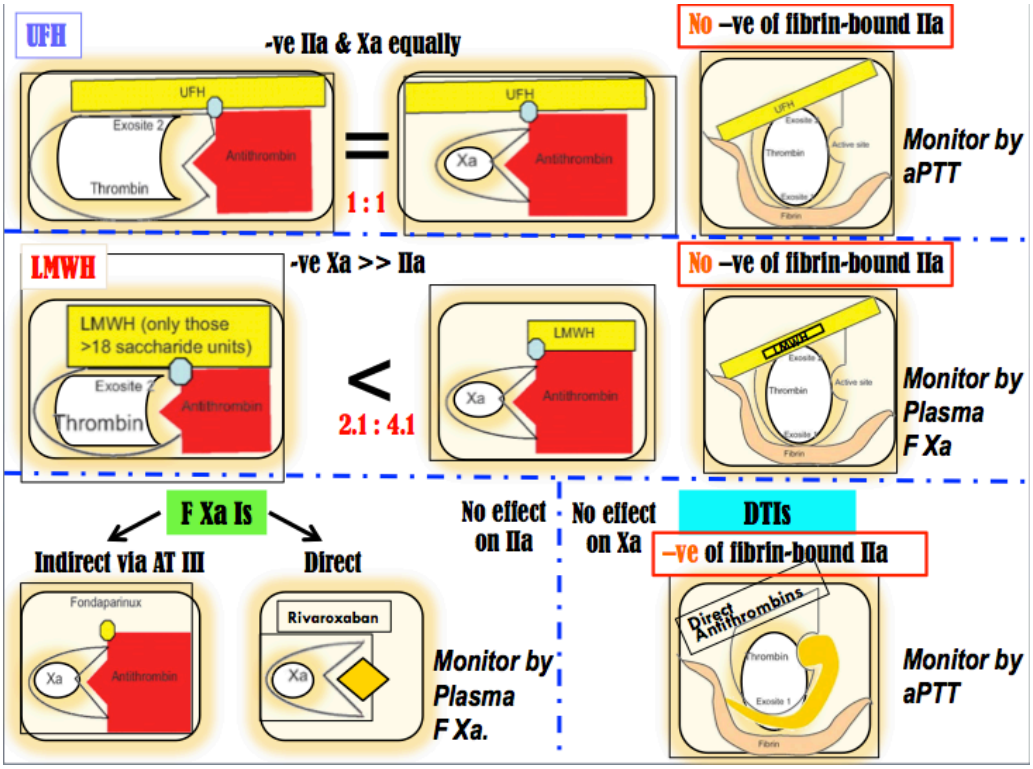
Works best on venous thrombosis than arterial thrombosis *(can be used as 2nd line after anti-platelet)*

	Parenteral Anticoagulant *(Used in acute 'emergency' Cases)*				Oral Anticoagulant
	Unfractionated heparin	**LMW Heparin**	**Direct Thrombin inhibitors**	**Factor Xa Inhibitor**	**Vitamin K antagonist**
Molecule weight	3000-30000	< 8000		Pentasaccharide	
Acts on	XIIa, XIa, IXa, Xa, IIa And thrombin *(1000 more potent than Anti thrombin3)*	**Works more on Xa**	Thrombin 2a	Factor Xa	Factors II, VII, IX & X
Drugs	Heparin	Enoxaparin Lovenox Dalteparin	**Reversible:** • Bivaluridin • Argatroban • Dabigatran **Irreversible:** • Lepirudin ➢ Irreversible is more dangerous It's not important to know which is reversible/irreversible	**Indirect:** Fondaparinux **Direct:** Rivaroxaban **Which is taken Orally** It's not important to know which is Direct/Indirect	**Coumarins:** ➢ **Warfarin** > 40 times potency than ➢ Dicumarol
MOA	**Inactivation of Coagulation Factors by Anti-thrombin III**				**Decrease Synthesis**
Pharmacokinetics	• **Rapid** • **Variable** *(unpredictable)*				• **Slow** • **Latency** • **Variable**
Monitor	• **aPTT** (1.5 - 2.5 times normal [30sec]) • **CT** (2-3 times normal [5-7 min])				• **PT** (2 times) • **INR** (2.5)
Antidote	• **Protamine Sulphate IV** ➔ 1mg for each 100 units UFH • **Fresh blood**				• **Vitamin K_1 infusion** • **Fresh blood** • Needs de novo synthesis

APTT: Activated partial thromboplastin time test is a laboratory test used to monitor the anticoagulant effect of unfractionated heparin and direct thrombin inhibitors; prolonged when drug effect is adequate.

Prothrombin time (PT) test: Laboratory test used to monitor the anticoagulant effect of warfarin; prolonged when drug effect is adequate

INR: It is a laboratory test that measure the time it takes for blood to clot and compares it to an average.

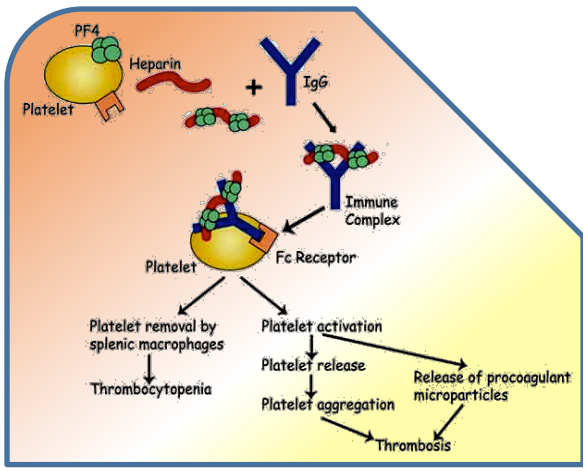


Notes:

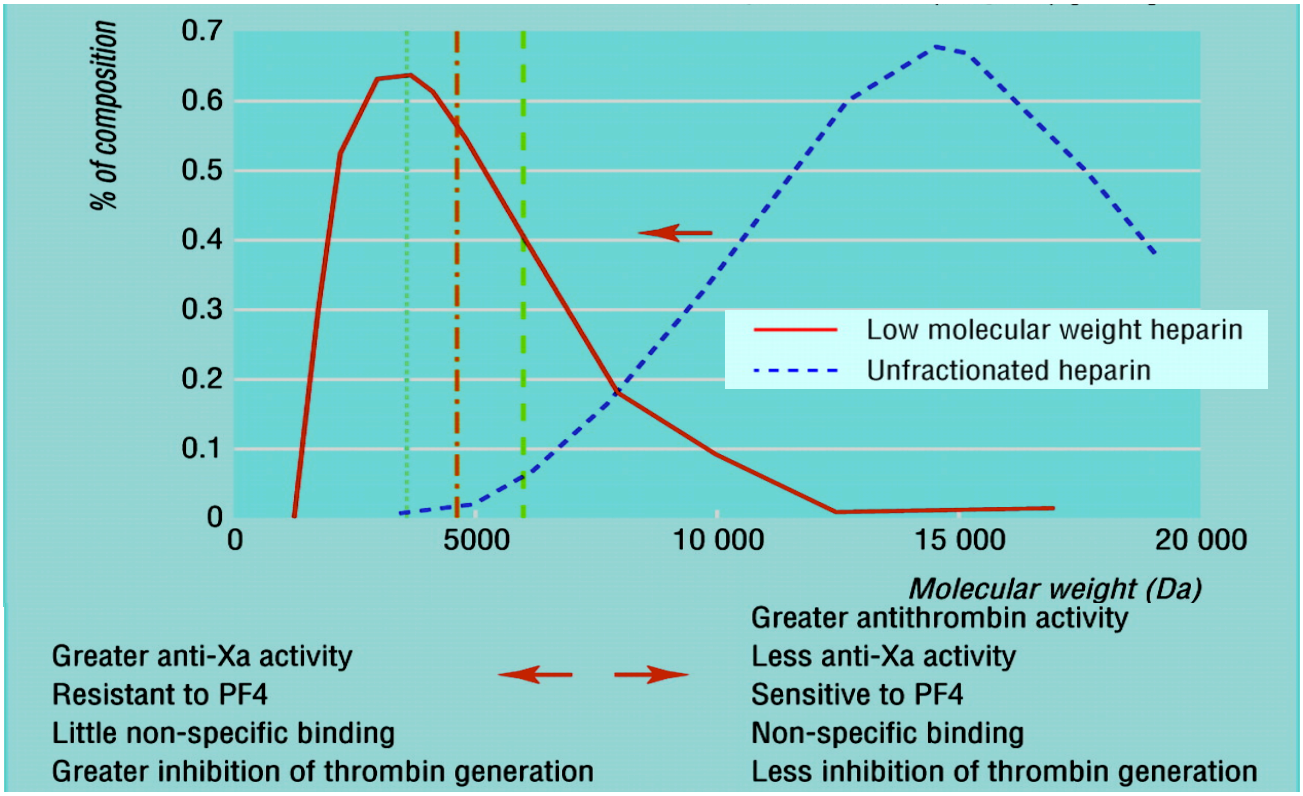
- **Unfractionated heparin** inhibits both antithrombin 2a and Factor Xa **equally.**
- **Low Molecular Weight heparin** inhibits Factor Xa **more** (double) than Antithrombin 2a
  - ❖ Both can cause recurrence of thrombosis *(does not inhibit the fibrin bound thrombin)*
- **Direct thrombin inhibitors** works only on the **fibrin bound thrombin** *(no re-thrombosis)*

Unfractionated Heparin 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 & it does not neutralize fibrin-bound II a *(usually occurs after 1 day or less)*
- **Heparin Induced Thrombocytopenia (HIT)**: In 4% pts. On heparin Venous > Arterial thrombosis
  - Latency:
    - 5-10 days after 1st exposure
    - Or 2-3 days after re-exposures
  - Signs:
    - Thrombocytopenia AND Thrombosis
  - Treatment
    - Heparin Disconnection
    - No Packed Platelets → will cause more thrombosis
    - No Warfarin → will cause venous gangrene
    - **GIVE Direct Thrombin Inhibitors**



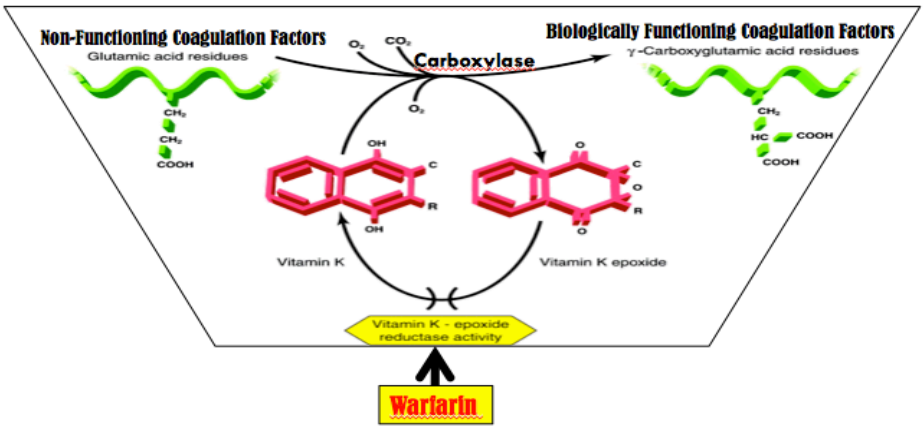
Comparison between Unfractionated Heparin and Low Molecular Weight Heparin



Low Molecular Weight Heparin Benefits:

- ↑ **Predictability of anticoagulant response** 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 subcutaneous
  - ↓ Frequency of administration due to longer duration of action
  - ↓ Need for regular monitoring
  - Outside hospital settings

Vitamin K Antagonists:



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

Vitamin K Antagonists Limitations:

- Wide **variation in drug response** ➔ a necessity for continuous monitoring (PT) and INR & dose adjustment
- Has **narrow therapeutic window**; high Plasma Protein Bound & 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 polymorphism 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 ➔ give heparin or LMWH instead

Factors Altering Response To VKAs:

Not Important

Increasing Factors:

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

Decreasing Factors:

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:

VERY IMPORTANT You should know the drugs and how they modulate VKAs

Drugs that increase INR:

1. **Inhibition of Vitamin K synthesis** by intestinal flora: **oral antibiotics**
2. Inhibition of **Vitamin 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**

Drugs that decrease INR:

1. **Inhibition of drug absorption** from GIT: **cholystyramine, colestipol**
2. **Increase in synthesis** of clotting factors: **Vitamin K, oral contraceptives**
3. **Increase in drug metabolism** by microsomal enzyme inducers: **carbamazepine, rifampicin**

Cases:

Case 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?

VKAs toxicity due to interaction with cimetidine which is an enzyme inhibitor

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)?

No need for an antidote or blood transfusion because it is minor bleeding

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

Gum bleeding is considered as a mild bleeding, so Dose adjustment is enough.

Case 2: A young rheumatic artheritic patient has undergone 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?

Since the patient is taking oral contraceptive there will be an increase in synthesis of clotting factors reducing the efficacy of the warfarin

What will the treating physician consider doing?

a) Giving heparin on top
b) Adjusting warfarin dose
c) Stopping the OC
d) Stopping warfarin

Answer is b

Case 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.

Which one of the following best explains the haematuria?

a) Inhibition of Vitamin K synthesis by chloramphenicol
b) Displacement of warfarin from protein binding site by rehydration
c) Decrease in warfarin metabolism induced by chloramphenicol
d) Inhibition of Vitamin K absorption caused by the diarrhea

Answer is c

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

a) Give a urinary antiseptic for fear of infection
b) Stop administering the regular intake of warfarin
c) Adjust the dose of warfarin after monitoring the situation.
d) Stop the course of chloramphenicol intended for typhoid therapy

Answer is c

Summary

Anticoagulants are mainly used in treatment of venous thromboembolism while antiplatelets used mainly in treatment of **arterial thrombosis.**

- **Heparin :** inactivate factors **12a ,11a ,9a, 10a , thrombin**, and has a variable response monitored by PTT or APPT.
- - If there is toxicity → Antidote; **Protamine Sulphate** IV➔ 1mg / 100 units UFH + Fresh blood
- - It does not inhibit the fibrin bound thrombin that's why it has an incidence of causing re thrombosis.
  - It also causes Heparin Induced Thrombocytopenia (HIT); latency 5-10 dys. after 1st exposure or 2-3 dys After re-exposures **if** this occurs: Heparin withdrawn and **give DTIs** .No packed platelets or warfarin.

- **Lower molecular weight heparin** works more on inhibiting activated **factor 10**.It has ↑ Predictability of anticoagulant response , ↑ Bioavailability , ↓Incidence of thrombocytopenia ,↓Incidence of bleeding tendency and better tolerability than UFH

- **Direct factor 10a inhibitors** affects factor10a , monitored by APTT or PPT (they are the same)

- ·**Direct thrombin inhibitors** affect fibrin bound thrombin , monitored by PTT. It is the only drug that doesn't cause re thrombosis.

- **Vitamin K Antagonists (warfarin)** affects on the factors that depend on vit k which are **7a , 9 a , 10 a , thrombin** by inhibiting **Vit K epoxide reductase**. Monitored by PT due to its variable response.
- Contraindicated in pregnancy ➔ give heparin or LMWH instead

- Slow onset of action, so not in given in emergency conditions

- Metabolize in the liver by CYT P450 → Numerous food- & drug-drug interactions.

Thanks to Pharmacology Team 430 For the introduction & summar

Question:

1- which one of the following is considered an advantage of low molecular weight heparin (LMWH)over unfractionated heparin?

a) has no sepecific antidote if bleeding occurs

b) is only given in a hospital setting.

c) has a predictable anticoagulant.

d) increase similar activation to antithrombine-111and Xa.

Answer : C

2- five years ago, a 53 year old patient had an aortic valve replacement and was sustained on warfarin. Two weeks ago, his lipid profile showed hypertriglyceridemia for which he received clofibrate. Today he began to develop bleeding from the gums.Which one of the following decisions should his treating physician consider?

a) stop the regular warfarin intake that he has been receiving for years.

b) Administer protamine sulphate intravenously as antidote.

c) stopthelipidloweringagentthatwasgivenrecently.

d) Ask for an INR and adjust the dose of warfarin accordingly.

Answer : D

3- A patient on oral anticoagulant therapy for treatment of deep vein thrombosis, developed severe gastroenteritis and was put on rehydration therapy and a course of oral cephalosporin. Today, on lab checkup, the INR is high.Which one of the following reasons is the likely cause of this lab finding?

a) inhibition of vitamin K synthesis by the suppressed intestinal flora.

b) displacemint of the anticoagulant from its protein binding site by the current treatment.

c) inhibition of absorption of vitamin K by cephalosporin.

d) increased bleeding tendency by activating the platelets by cephalosporin.

Answer : A

4- A patient previously on heparin developed thrombocytopenia and thrombosis on second exposure to the drug. He was diagnosed as heparin induced thrombocytopenia. Which one of the following drugs can best treat such condition?

a) vitamin K antagonists.

b) directthrombininhibitors.

c) low molecular weight heparin.

d) anti-factor X inhibitors.

Answer : B