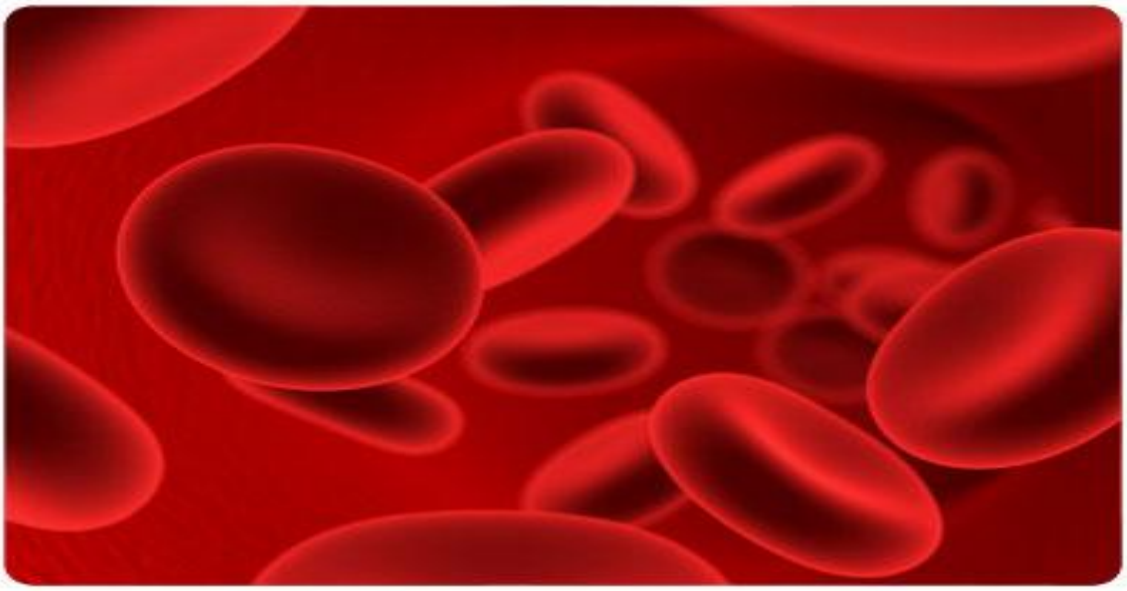
King Saud University
College Of Medicine
Pharmacology Team 430
Hematology Block

Anti-coagulants



Note: the first page is an introduction, and textboxes with **thick maroon** margins are additional info.

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Introduction:

Hemostasis refer 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 a 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.

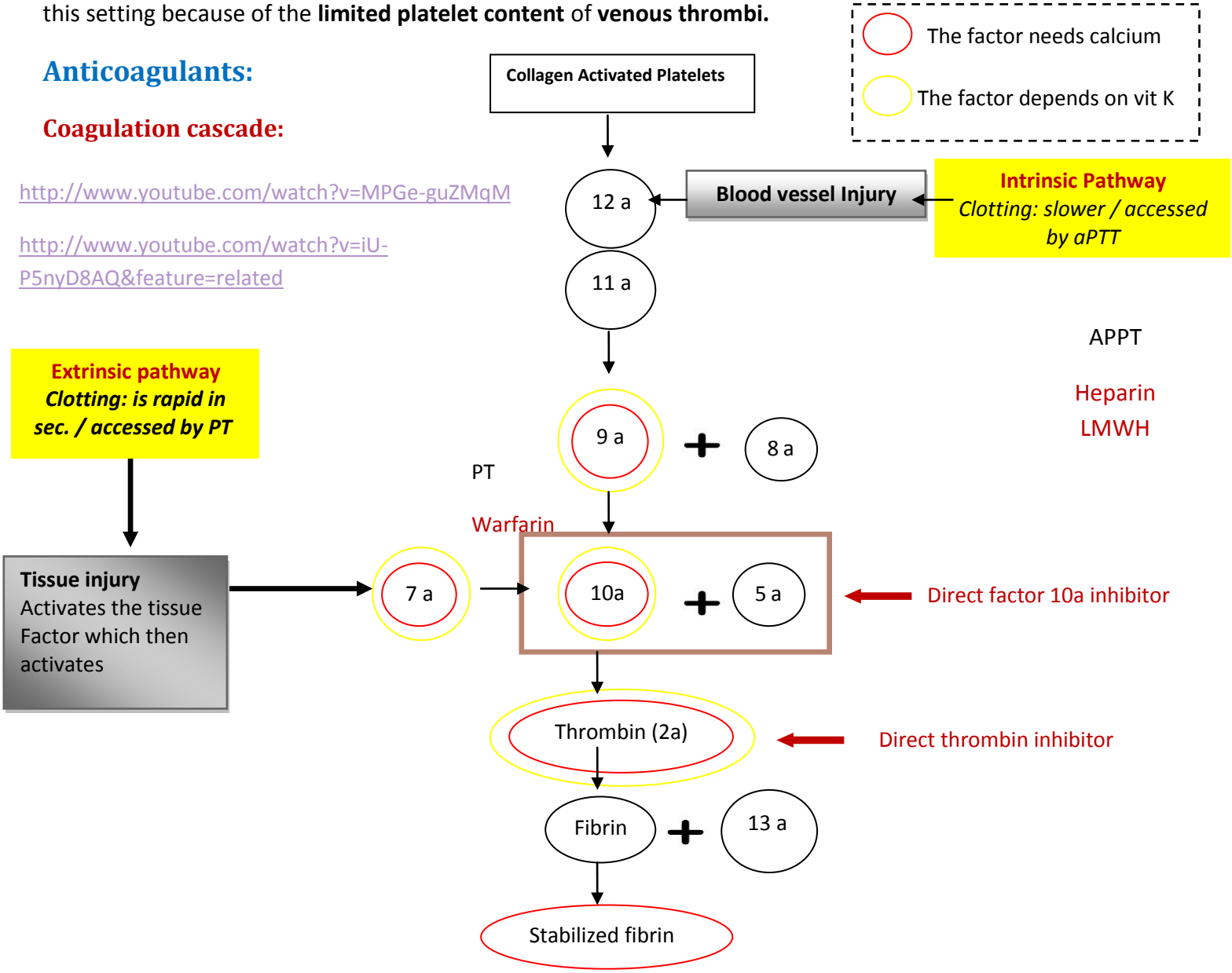
Antithrombotic drugs are used for prevention and treatment of thrombosis. Targeting the components of thrombi, these agents include **(1) antiplatelet drugs, (2) anticoagulants, and (3) fibrinolytic agents.** With the **predominance of platelets in arterial thrombi, strategies to inhibit or treat arterial 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 setting because of the **limited platelet content** of **venous thrombi.**

Anticoagulants:

Coagulation cascade:

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

http://www.youtube.com/watch?v=iU-P5nyD8AQ&feature=related



- **Heparin** and **LMWH**(low-molecular weight heparin) affect factor **12a ,11a ,9a, 10a , thrombin.** They are monitored by APTT
- factor **10a inhibitors** affects **factor10a** , monitored by PTT
- **Direct thrombin inhibitors** affect **fibrin bound thrombin** , monitored by APTT
- **Vitamin K Antagonists (warfarin)** affects on the factors that depend **on vit k** which are **7a , 9 a , 10 a , thrombin.** Monitored by PT
- **Anti thrombin 3** naturally produced from tissues inhibits activated factors **9, 10, and 2**. Heparin activates it up to 1000 times

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

Anticoagulants in "venous thrombosis"

Parenteral Anticoagulants :

Pharmacokinetics :

- Rapid
- Variable response. Monitor by aPTT (Activated partial thromboplastin time) (1.5 - 2.5 times normal [30sec]) Or CT(clotting time) (2-3 times normal [5-7 min) This 1.5-2,5 increase is due to administration of heparin and it is called therapeutic APPT or PPT.
- **Antidote; Protamine Sulphate IV** ➔ 1mg / 100 units UFH + Fresh blood

Note: Excessive anticoagulant action of heparin is treated by discontinuance of the drug. If bleeding occurs, administration of a protamine **sulfate** is indicated. **Protamine is** a highly basic peptide that combines with heparin as an ion pair to form a stable complex devoid of anticoagulant activity**. For every 100 units of heparin** remaining in the patient, **1 mg of protamine** sulfate is given intravenously. Excess protamine must be avoided; it also has an anticoagulant effect. & transfusing fresh blood that has unaffected factors would also help in improving the case.

UFH (unfractionated heparin) : high molecular weight :**3000-30000** .

MOA : Inactivation of coagulation factors : **XIIa, XIa, IXa, Xa, IIa**

Lower Molecular Weight Heparin < 8000 : works more on inhibiting **activated factor 10.**

Enoxaparin – Lovenox - Dalteparin

Direct Thrombin : it works specifically on **thrombin.**

Reversible : **Bivaluridin – Argatroban - Dabigatran**

irreversible : Lepirudin

Activated factor 10 inhibitors : only works on activated factor 10

Indirect Is :Fondaparinux

Direct Is: Rivaroxaban

N.B: Rivaroxaban and Dabigatran can be given orally

Oral Anticoagulants: Vit. K antagonists

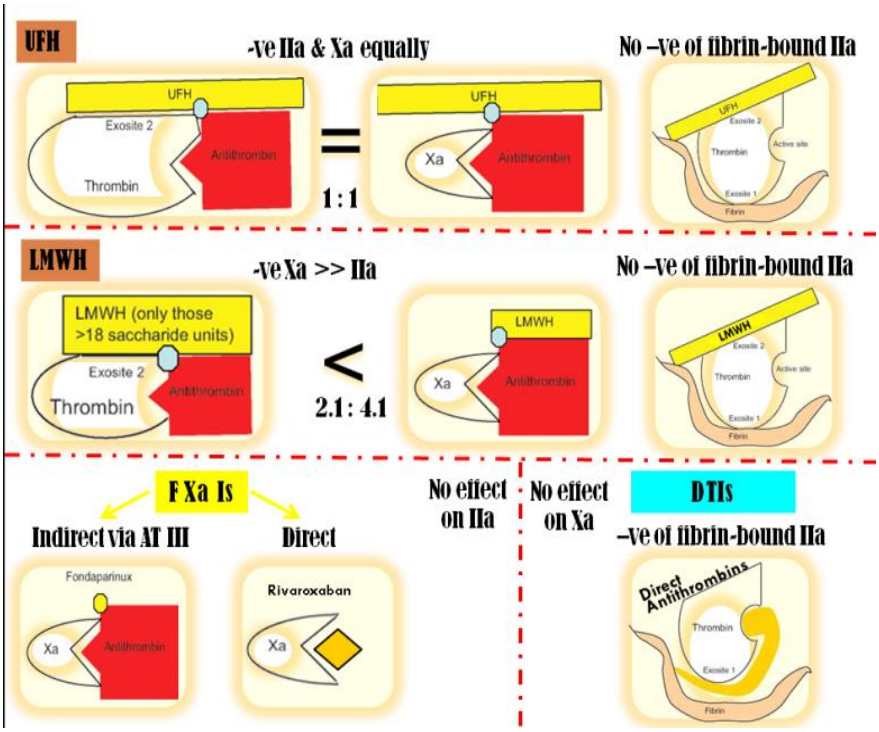
MOA : Decrease Synthesis of **II, VII, IX & X**

Pharmacokinetics :

- Slow / Latency . Because it works on **inhibiting** synthesis of **coagulation factors**; however, it doesn't not affect the already produced and activated coagulation factors.
- Variable . Monitor by PT (2 times) . INR (2.5)
- **Antidote; Vit. K1 infusion + Fresh blood + Needs de novo synthesis**

Coumarins; Warfarin – Dicumarol. (Warfarin > 40 times potency than Dicumarol)

Note: The therapeutic range for oral anticoagulant therapy is defined in terms of an international normalized ratio (INR).It Is a laboratory test that measure the time it takes for blood to clot and compares it to an average.



Heparin inhibit activated **factor 10 and thrombin equally,** however it **does not** inhibit the **fibrin bound thrombin** that's why it has an incidence of causing **re thrombosis.**

Low molecular weight heparin works more on inhibiting **activated factor 10 more than thrombin.**

Activated 10 inhibitors only works on **activated factor 10** either directly or indirectly.

Direct thrombin inhibitors works only on the **fibrin bound thrombin**. That's why it is the only drug that doesn't cause **re thrombosis.**

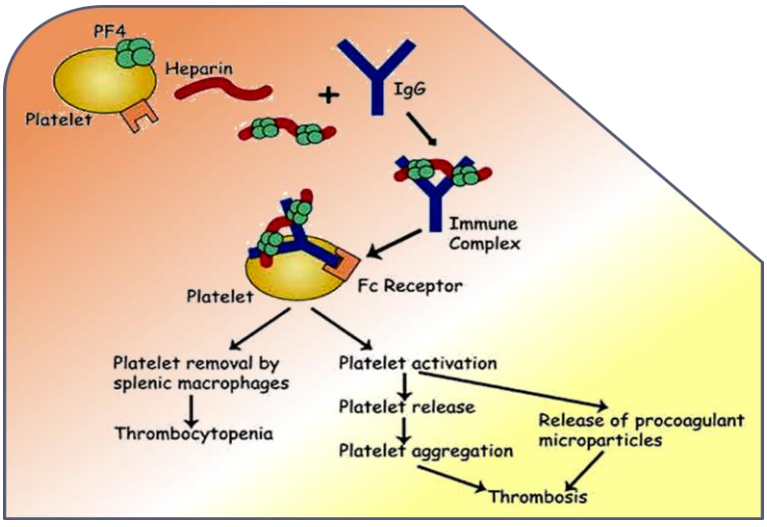
UFH limitations:

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

Managing this case :

- ✱ Heparin discontinuation
- ✱ No packed platelets ➔ More thrombosis
- ✱ No warfarin ➔ ppt .venous gangrene
- ✱ Give ➔ DTIs (Direct thrombin inhibitors)

In some patients heparin will bind to **platelet factor 4** → binds to IgG making an immuncomplex which will bind to the platelet. Most of these platelets will be destroyed causing **thrombocytopenia**. The small no. of platelets that are left will **become active** and may cause a **thrombosis .**

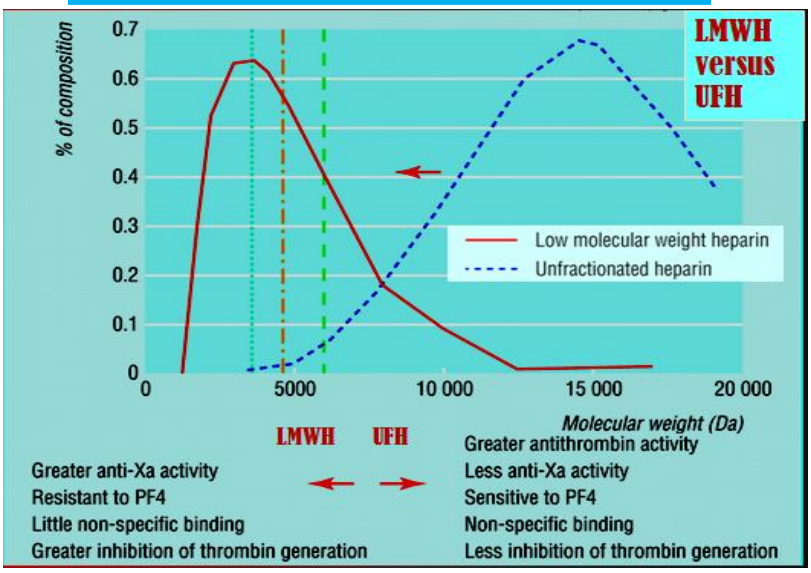


Note: Heparin-induced thrombocytopenia (HIT) is a systemic **hypercoagulable** state that occurs in 1–4% of individuals treated with UFH for a minimum of 7 days. **Surgical patients are at greatest risk.** The risk of HIT may be higher in individuals treated with **UFH of bovine origin** compared **with porcine heparin** and is lower in those treated exclusively with **LMWH. (meaning that it would cause thrombosis, and it usually venous thrombosis.**

LMWH benefits :

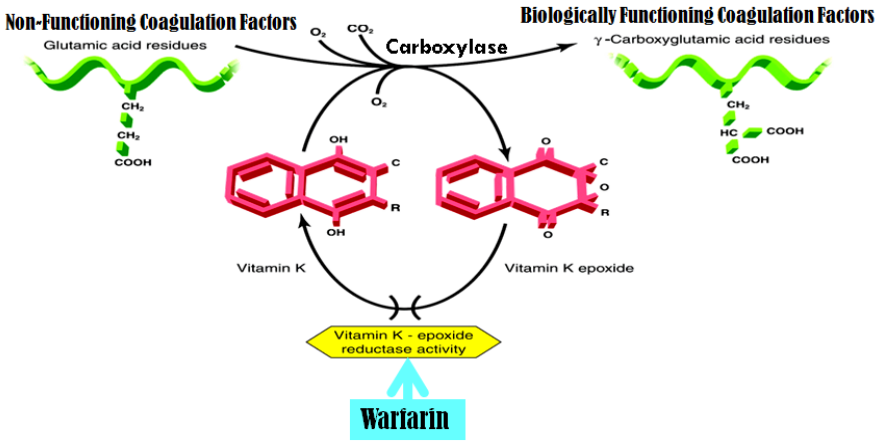
- ↑ Predictability of anticoagulant response i.e. little inter-patient and intra-patient variability in response to a given dosage. So → effective anticoagulant activity can be achieved by calculating dosages based on body weight without the need for laboratory monitoring
- ↑ Bioavailability; as it hardly binds to plasma proteins, endothelium & macrophages
- ↓Incidence of thrombocytopenia; as it seldom sensitive to PF4
- ↓Incidence of bleeding tendency; ↓ effect AT III (anti thrombin 3) & ↓ platelet interactions
- Much better tolerability;
    - Given subcutaneously.
    - ↓ frequency of administration due to **longer duration of action .**
    - ↓ need for regular monitoring. Outside hospital settings

Comparison between heparin and low molecular



Vitamin K antagonist:

Precursors of factors **II, VII, IX & X** require **carboxylation** of their **glutamic acid 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 :

- Wide variation in drug response → a necessity for continuous monitoring (PT) & dose adjustment.
- **Has narrow therapeutic window**; high PPB (plasma protein bounding) & 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 (Category X) ➔ give heparin or LMWH instead

Note: The FDA has a categorization of drug risks to the fetus that runs from:"CategoryA" (safest) to "Category X" (known danger—do not use!)

Drugs modulating response to VKAs: (imp)

Drugs that increase toxicity (bleeding):

- **Inhibition of Vit. K synthesis by intestinal flora; oral antibiotics**
- **Inhibition of Vit K absorption; liquid paraffin**
- **Decrease in drug metabolism by microsomal enzyme inhibitors; chloramphenicol, & cimetidine**
- **Displacment of the drug from protein binding sites; phenylbutazone,, clofibrate & salicylates**
- **Co-administration of drugs that increase bleeding tendency by; inhibiting platelet function; NSAID & inhibiting coagulation factors; heparin & antimetabolite**

Drugs that reduce efficacy (thrombosis)

- **Inhibition of drug absorption from GIT; cholystyramine, colestipol**
- **Increase in synthesis of clotting factors; Vit K, oral contraceptives**
- **Increase in drug metabolism by microsomal enzyme inducers; barbiturates, rifampicin & griseofulvin**

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 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?

This is due to the reduced efficacy of warfarin by oral contraceptive.

What will the treating physician consider doing?

a) Giving heparin on top

b) Adjusting warfarin dose

c) Stopping the OC

Replacing it with heparin would give the chance of having many side effects (As she is using it for a long term). Since there is no serious impairment of warfarin (Only a decrease in INR). Dose adjustment is the best option

d) **Stopping warfarin** Answer : 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 Vit 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 Vit K absorption caused by the diarrhea** Answer : 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 : c

The patient needs both drugs in his situation, so the best option is dose adjustment of warfarin

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.