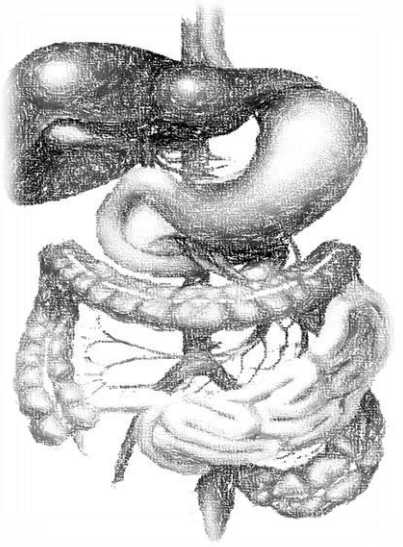
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



المحاضرة فيها اختلافات كبيرة بين البنات والأولاد بعد الرجوع إلى الدكاترة قالوا لنا نركز على **المشترك** (اللي مكتوب بالأسود)

تمت المراجعة
فوق الأحمري & عبدالعزيز العنقري

8: Anticoagulants

objectives

- Introduction about 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.

Color index

- Extra information and further explanation
- **Important**
- **Doctors notes**
- **Drugs names**
- **Mnemonics**
- **Only male's slides**
- **Only female's slides**

We highly recommend you to study physiology lecture "coagulation" before studying this lecture

Kindly check the editing file before studying this document

Introduction

Drugs and Coagulation

Anticoagulants

Molecules that prevent thrombus formation and extension by inhibiting clotting factors.
They inhibit the chemical process of formation of the fibrin polymer.
e.g. heparin, low molecular weight heparin, coumarins/ warfarin.

Antiplatelet drugs

Reduce risk of clot formation by inhibiting platelet functions
Molecules that **do not allow platelets to aggregate** and thus prevent clotting, especially in the arteries

e.g. aspirin and ticlopidine.

Fibrinolytic agents

Molecules that dissolve (**disintegrate**) thrombi already formed, that's why we don't need to use it if there is no thrombus (as prophylaxes)

e.g. streptokinase

Coagulation Pathways

Intrinsic pathway

All clotting factors are **within** the blood

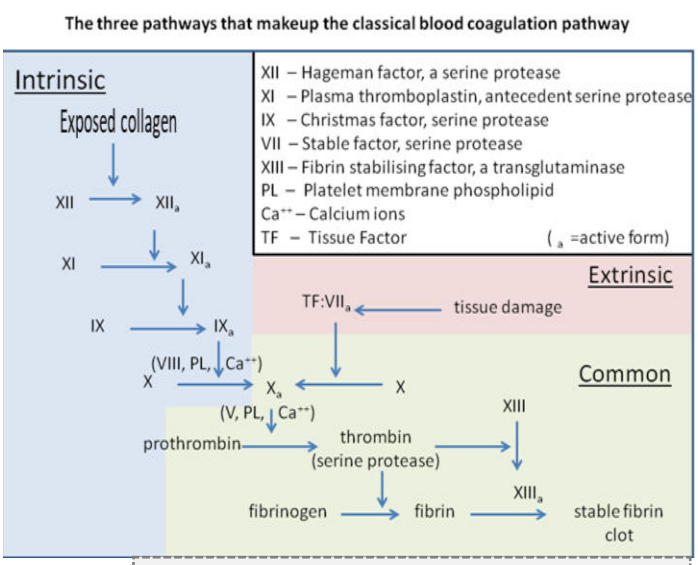
Extrinsic pathway

Initiating (triggering) factor is **outside** the blood
(tissue factor = thromboplastin)

Both converge to a **common** pathway

13 soluble factors are involved in clotting which normally circulate in an inactive state and must be activated to form a **fibrin clot**.

* Ca^{2+} are? required for promotion and acceleration of almost all blood clotting reactions
* Removal of Ca^{2+} with calcium chelators such as EDTA ethylenediamine tetra-acetic acid or citrate is used to prevent clotting in test tube



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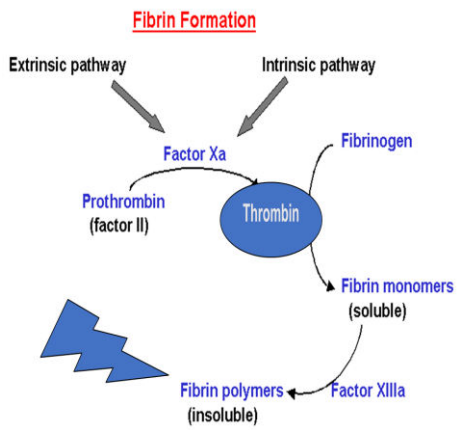


Thrombin plays a key role in coagulation as it is responsible for generation of fibrin mesh?

To understand !

Endogenous Inhibitors of Coagulation

Antithrombin III

- It is a plasma protein that inhibits **activated** thrombin (**factor IIa**) and **Xa** (10), IXa (9), XIa (11), XIIa (12) by forming complex with these factors
- It is the site of action of heparin.

Prostacyclin (PGI2)

synthesized by endothelial cells and inhibits platelet aggregation

Protein C and Protein S

these are vitamin K dependent proteins that slow the coagulation cascade by inactivating factor Va and VIIIa.

Anticoagulants

Parenteral Anticoagulants

Thrombin inhibitors:

- Indirect activate Antithrombin III:
  - Heparin (molecular weight: 3000-30000)
  - LMWH: (molecular weight: < 8000) e.g. Enoxaparin, Dalteparin

  They act on: XIIa, XIa, IXa, Xa, IIa
- Direct inhibit thrombin (IIa):
  - * Bivaluridin : R Is
  - * Argatroban : R Is
  - * Lepirudin : IR Is
  - * Dabigatran oral : R Is
- Factor Xa: is Pentasaccharide
  - * Indirect : Fondaparinux
  - * Direct : Rivaroxaban (oral)

Oral Anticoagulants

Vitamin K antagonists:

Warfarin > 40 times potency than Dicumarol

It acts on II, VII, IX & X

Indications:

- ✓ Myocardial infarction (MI)
- ✓ Deep venous thrombosis (DVT)
- ✓ Peripheral arterial emboli, pulmonary embolism (PE) and many other conditions
- ✓ Anticoagulants are also used in blood transfusions, and dialysis procedures

Heparin and heparin-related agents

- Heparin is an injectable rapidly acting anticoagulant
- Active in vitro and in vivo
- Low–molecular–weight forms (LMWHs), 1/3 the size of UFH are used as well and have many advantages over UFH (UnFractionated Heparin)

Indirect Thrombin Inhibitors

المحاضرة شرحتها لنا بروف. يلدز، اللي ركزت عليه حطيناه لكم **بالعنابي**

Drug

Unfractionated Heparin

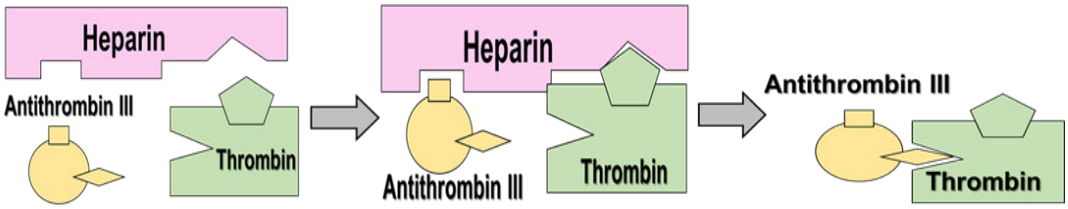
Notes

- Normally occurs as macromolecule in mast cells with histamine (its physiological role is unknown)
- Commercial preparations are extracted from **beef** lung or **pig** intestine (can cause **hypersensitivity** reaction)
- Heparin **stops the expansion** of a thrombus and **prevents the formation** of new thrombi but it **DOES NOT dissolve** an existing thrombus

Mechanism of action

- **Indirect Thrombin Inhibitor** (both UFH and LMWH)
- It acts indirectly by increasing the activity of the endogenous anticoagulant "**Antithrombin III**" (1000 folds) which inhibits activated (inactivate) clotting factors mainly thrombin (**factor IIa** and **Xa** 10 and VIIa 7) , In the absence of heparin this incativation (of anithrombin) is slow
- When Heparin binds to Antithrombin III, it causes conformational changes that accelerates its rate of action 1000 fold

Heparin has high MW, so it can bind antithrombin III with thrombin and antithrombin III will inhibit thrombin



Heparin binds to both antithrombin III and thrombin to form a ternary complex

Heparin dissociates leaving the thrombin bound to its inhibition.

Once dissociated, Heparin is free to bind to another antithrombin molecule and subsequently inhibits more thrombin

Pharmacokinetic

- Heparin is not absorbed from the GIT
- It should be administered by IV or SC injection. **Not injected IM as it causes haematomas at injection site**
- Once in the blood stream, UFH (UnFractionated Heparin) binds to plasma proteins, endothelial cells and macrophages (so it has low bioavailability)
- Heparin does not cross the placenta; therefore it is the **drug of choice as anticoagulant during pregnancy**

If we have a case: pregnant lady has DVT, what is the drug of choice? Heparin بليز ركزوا على هالمعلومة مره مهمه

- No predictable anticoagulant effects; inter-patient & intra-patient variability in response to a given dosage → in hospital setting, repeated monitoring Close monitoring of the activated partial thromboplastin time (**aPTT**) is necessary in patients receiving UFH.مهم تحفظون اسم الفاكتور اللي نستخدمه في المراقبة

Indirect Thrombin Inhibitors (con.)

Drug

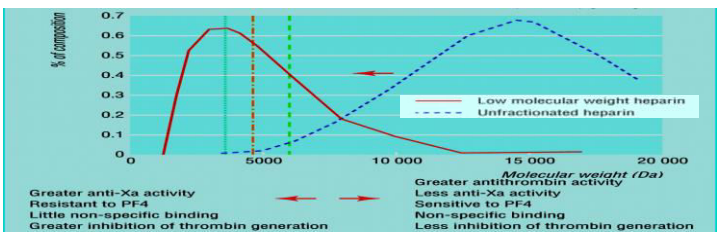
Unfractionated **Heparin**

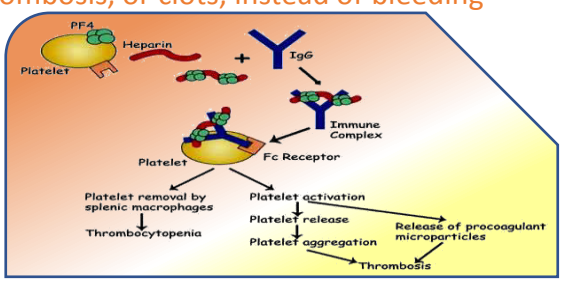
Indications

- Due to its rapid onset of action, it is used to **initiate immediate anticoagulation** in thromboembolic disease (PE, DVT, MI) in emergency conditions, mainly as induction for oral vitamin K antagonists (VKAs)
- **Prevention of postoperative DVT** (in patient undergoing hip replacement)
- Prevention of coagulation during renal dialysis or cardiac surgery

Disadvantage

- The inconvenience of administration by injection
- Re-thrombosis: activates platelets as it does not neutralize fibrin-bound IIa
- Heparin discontinuation, No packed platelets → More thrombosis, No warfarin → ppt .venous gangrene. Give → DTIs (Direct Thrombin Inhibitors) ☺ هم معقدين السالفة هنا
  باختصار ميزة الهيبارين إن أول ما نوقفه عادي نعطيه أي دوا ثاني (مثلًا المريض صار عنده سايتوبينيا بسبب الهيبارين على طول أوقف هيبارين وأعالجه بهيرودين) عكس الوارفرين لازم أراقب وقت البروثرومبن عشان أتأكد إنه طلع من الجسم وماراح يأثر بشكل عكسي بعدين أعطي هيرودين
- The need for regular monitoring (aPTT)
- UFH carries a risk of **heparin-induced thrombocytopenia (HIT)**, a fall in the platelet count and increased risk of thrombosis due to binding to platelets. In 4% pts. on heparin, latency 5-10 days. after 1st exposure or 2-3 days. after re-exposures → Venous > Arterial thrombosis.
- **Heparin-induced thrombocytopenia (HIT):**
  - Generally, if the number of platelets is too low, excessive bleeding can occur
  - If the number of platelets is too high, blood clots can form thrombosis
  - However, There are disorders that reduce the number of platelets, such as heparin-induced thrombocytopenia (HIT) that typically cause thrombosis, or clots, instead of bleeding





ADRs

- Heparin-induced thrombocytopenia (HIT)
- The major adverse effect of heparin is **bleeding**
- **Allergic reactions** (chills, fever, urticaria) as heparin is of animal origin and should be used cautiously in patients with allergy
- Long-term heparin therapy is associated with **osteoporosis**

C.I.

- Bleeding disorders, hemophilia اي دواء يزود سيولة الدم مانقدر نعطيه لاحد عنده هيموفيليا او يكون مسوي من قريب عملية عشان مايصير عنده نزيف
- Patients with hypersensitivity to the drug
- Recent surgery of the brain, eye or spinal cord, threatened abortion

Reversal of action (antidote of heparin)

- Discontinuation of the drug
- Heparin is strongly acidic and is neutralized by IV protamine sulfate (a strongly basic protein) It combines with heparin to form a stable complex devoid of anticoagulant activity

Only in female's slides

Indirect Thrombin Inhibitors (con.)

Low-Molecular-Weight Heparins (LMWH)

Drug	Heparin fragments (e.g. **enoxaparin, dalteparin**)	Synthetic pentasaccharide (**fondaparinux**)
Advantages	❁ LMWHs are derived from the chemical or enzymatic degradation of UFH into fragments approximately one-third the size of heparin. ❁ Have equal efficacy, **without frequent laboratory monitoring** (suitable for outpatient therapy) ❁ Have a more predictable anticoagulant response ❁ (better bioavailability, longer t ½) ❁ Binding to platelets and osteoblasts is **reduced** with LMWH compared with UFH, so it will not cause osteoporosis or HIT	
M.O.A	LMWHs increase the action of antithrombin III on factor Xa 10 but not its action on thrombin, because the molecules are too small to bind to both enzyme and inhibitor	
Use	Are used increasingly in place of unfractionated heparin	

Synthetic Heparin Derivatives

Drug	**Fondaparinux**
M.O.A	A synthetic compound that inhibits factor Xa 10 by antithrombin but **does not inhibit thrombin**
Advantages	• Fondaparinux can be given once a day at a fixed dose without coagulation monitoring • Less likely than UFH or LMWHs to trigger HIT it will not cause HIT

Differences between UFH and LMW Heparins تجميعه جميله جدا

Drug characteristics	**Heparin (UFH)**	**LMWH**
IV ½ life	2 hours	4 hours longer
Bioavailability after SC injection	20%	90% As it hardly binds to plasma proteins, endothelium & macrophages
Anticoagulant response	Variable (Unpredictable) We need to monitor the blood to see if the dose in the therapeutic level or not	Predictable i.e. little inter-patient and intra-patient variability in response to a given dosage.
Major adverse effect	Frequent bleeding, HIT, osteoporosis	Less frequent bleeding because it has less effect on AT III , less HIT and osteoporosis as it seldom sensitive to PF4
Specific antagonist	Protamine sulphate	Incomplete
Setting for therapy	Hospital	Hospital and OPC (outpatient)
Laboratory monitoring	Needed aPTT	Not needed

Advantages of LMWHs over UFH

- ★ The theoretical pharmacologic advantages of LMWH over UFH arise from the preferential binding ratio to **factor Xa** (10) over thrombin
- ★ The convenience of once- or twice- daily subcutaneous injections **without regular coagulation monitoring** due to:
  - ✓ More predictable response
  - ✓ Long plasma half-life and improved bioavailability (Good bioavailability)
  - ✓ Less plasma protein binding
  - ✓ Less platelet activation and lower risk of re-thrombosis and thrombocytopenia
  - ✓ Much better tolerability
- ★ Given subcoutanous

Only in female's slides

Direct Thrombin Inhibitors (DTIs)

Drug	Hirudin	Lepirudin
Notes	The first DTI to be developed, which was isolated from the saliva of the leech (علقة)	A polypeptide that binds **directly** to the active site of thrombin
M.O.A	▸ DTIs exert their anticoagulant effect by direct binding to thrombin ▸ This direct effect is **rapid and potent** ▸ DTIs are not associated with the development of thrombocytopenia	
Uses	**Recombinant** hirudin "Lepirudin" is used as IV anticoagulant in patients with heparin-induced thrombocytopenia (HIT).	

Only in female's slides

Oral Anticoagulants "Vitamin K Antagonists"

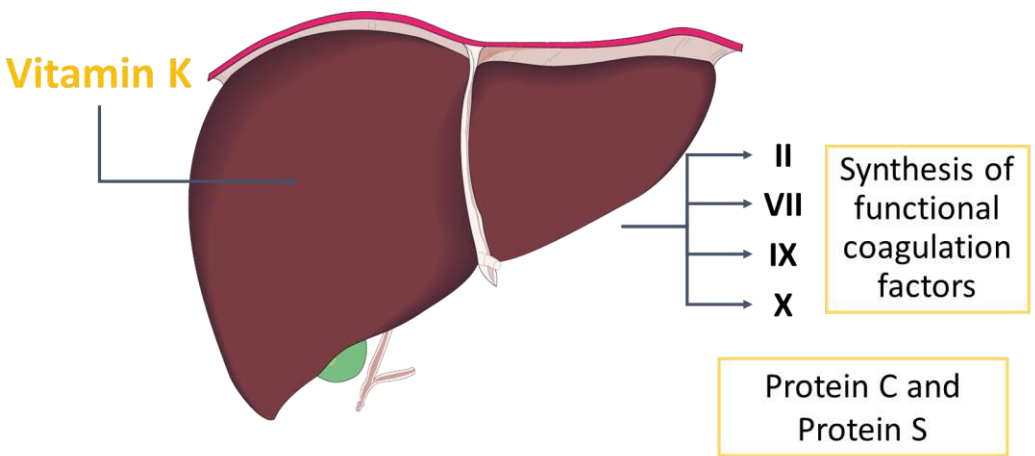
Vitamin K (Fat soluble vitamin)

Source of vitamin K
- Green vegetables.
- Synthesized by intestinal flora

excessive use of antibiotic will kill this bacteria and may lead to vitamin K deficiency

Required for synthesis of:
- Active form of Factors **II**, **VII** 7, **IX** 9, **X** 10
- Protein **C** and **S** (endogenous anticoagulants)

Causes of deficiency
- Malnutrition
- Malabsorption
- Antibiotic therapy



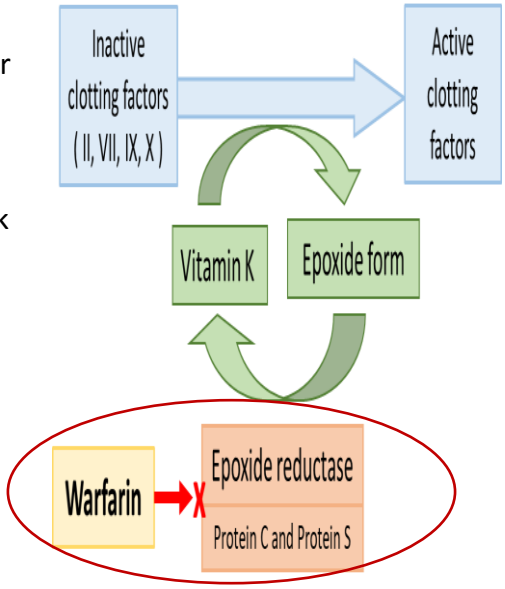
Oral Anticoagulants

Drug

Coumarins: Warfarin

Mechanism of action

- Inhibits synthesis of biologically active forms of Vitamin K-dependent coagulation factors II, VII (7), IX (9) , & X (10), these factors 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 (like warfarin) losing the coagulation factors the ability to function, so The anticoagulant effect of vitamin K antagonists, such as warfarin, is due to the synthesis of non-functional clotting factors. Prothrombin, factors VII, IX and X as well as anticoagulant protein C and protein S are all inactivated by vitamin K antagonists
- Does not have any 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



Pharmacokinetic

- Monitoring anticoagulant effect of warfarin by measuring PT, which is expressed as an International Normalized Ratio (INR) مهم مره تعرفون هذا الفاكتور
- Warfarin has a slow offset of action (slow elemination) due to the time required for synthesis of new, functional coagulation factors
- Act only in vivo (in human)
- Bioavailability 100%
- 98% bound to plasma proteins (albumin)
- Their effect takes several days (3-4) to develop because of the time taken for degradation of circulating functional clotting factors
- Therefore the onset of action starts when these factors have been eliminated
- Wide variation in drug response

Disadvantages

- Variable, unpredictable effect necessitating regular INR monitoring and dose adjustment
- Narrow therapeutic window leading to **increased risk of severe bleeding** we have to monitor the drug's level in the blood
- Slow onset and offset of action يعني يأخذ وقت عشان يبدا مفعوله ويأخذ وقت عشان يطلع من الجسم
- Polymorphisms in CYT P450 isoforms that metabolizes warfarin → adds to its non predictable response → liability to toxicities or under use.
- Numerous interactions with foods containing vitamin K and drugs

C.I.

Warfarin is contraindicated during pregnancy as it can cross the placental barrier and cause abortion, hemorrhagic disorder in the fetus and birth defects → **Teratogenicity**

Oral Anticoagulants (con.)

Drug

Coumarins: **Warfarin**

Drug Interaction

الدكتورة ركزت كثير على النقاط اللي بالأسود وحرصت عليهم

Increase the effect of warfarin

1. Vitamin K deficiency: Inadequate diet: malnutrition, dieting, decreased GI absorption…etc
2. Impaired synthesis of clotting factors: In hepatocellular disorders; (hepatitis; infective or chronic alcoholism ... etc.)
3. Increased catabolism of clotting factors: In hypermetabolic states: as in fever, thyrotoxicosis
4. Inhibition of Vit. K synthesis by intestinal flora: oral antibiotics
5. Inhibition of Vit K absorption: liquid paraffin
6. Decrease in drug metabolism by microsomal enzyme inhibitors: chloramphenicol, & cimetidine
7. Displacement of the drug from protein binding sites: phenylbutazone & salicylates
8. Co-administration of drugs that increase bleeding tendency by: (inhibiting platelet function: NSAIDs like aspirin,) or (inhibiting coagulation factors: heparin "Be carful when give warfarin together with heparin because the bleeding tendency will increase and we should keep monitoring both drugs")

Decrease the effect of warfarin

1. Decreased plasma protein binding: ↑ elimination of free drug & shortening of its t ½. as pts with nephrotic syndrome (proteinuria)
2. Decreased catabolism of clotting factors: Hypothyroidism
3. Hereditary resistance to oral anticoagulants
4. Inhibition of drug absorption from GIT: cholystyramine, colestipol
5. Increase in synthesis of clotting factors: Vit K, oral contraceptives
6. Increase in drug metabolism by microsomal enzyme inducers: Carbamazepine, barbiturates, rifampicin

Reversal of action (antidote)

If the patient develop **Bleeding due to Warfarin:**

- Stop the drug
- IV injection of vitamin K

Both warfarin and heparin need antidote but LMWH doesn't need

- Fresh frozen blood because it contain active clotting factors

Summary

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 (Drug of choice for pregnant women)	Given orally, 98% protein bound, PO, liver metabolism, half-life = 30+ h, placental access
Mechanism (مهم — بس ركزوا على clotting factors أو البروتينات اللي راح يشتغل عليها الدوا)	↑ Activity of antithrombin III (Indirect effect), 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)

Summary

Indirect thrombin inhibitors (parenteral)	Unfractionated Heparin (IV,SC)	▪**stops the expansion** of a thrombus by increasing the activity of "**Antithrombin III**" which inhibits activated clotting factors mainly thrombin (**factor IIa** "2a") and **Xa** 10 (which means at M.O.A is indirect) ▪ **prevents the formation** of new thrombi ▪**DOES NOT dissolve** an existing thrombus ▪Drug of choice as anticoagulant during pregnancy ▪**initiate immediate anticoagulation** in thromboembolic disease ▪**Prevention of postoperative DVT** ▪Need close monitoring of the activated partial thromboplastin time (**aPTT**) ▪**Can cause heparin induces thrombocytopenia** (HIT) ▪Prevention of coagulation during renal dialysis of cardiac surgery ▪Threatened abortion ▪Antidote: protamine sulfate
	low molecular weight heparin (enoxaparin, dalteparin Fondoparinux)	•**without frequent laboratory monitoring (no need for monitoring aPTT)** •Binding to platelets and osteoblasts is **reduced** with LMWH compared with UFH, so it will not cause osteoporosis or HIT •no action on thrombin •Outpatient therapy
		Fondoparinux: inhibits factor Xa 10 by antithrombin but **does not inhibit thrombin**
Direct thrombin inhibitors (parenteral)	Hirudin, lepirudin	• direct affect on thrombin • Not associated with thrombocytopenia • Used as IV anticoagulant in heparin induced thrombocytopenia
Vitamin k anticoagulants (oral)	warfarin	* The effect take days * Slow offset of action * Narrow therapeutic window * Monitoring anticoagulant effect of warfarin by measuring International Normalized Ratio (INR) * Warfarin has a slow offset of action due to the time required for synthesis of new, functional coagulation factors * Numerous interaction (بليز أرجعوا لسلايد ١٠ موجودة فيها تعارضات الأدوية) * Teratogenic (contraindicated in pregnancy) * Antidote: IV injection of vitamin K

Cases – From Dr.Ishfaq's slides.

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.

Q1: What is the expected explanation of his finding?
Warfarin toxicity, because Cimetidine inhibits its metabolism.
Q2: 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)?
we can stop the warfarin and give him Vitamin K as antidote or actually bleeding of gums not emergency situation, so we have time to do lab investigations.
Q3: Once lab findings are there, is the physician expected first to withdraw or to adjust the existing therapy?
Give him another anti-peptic ulcer drug. Or change Warfarin to heparin.

A young rheumatic arthritic 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.

Q1: What is the expected explanation of her lab result?
Contraceptive pills induces the coagulation factors → ↓ INR → increase tendency of thrombus.
Q2: What will the treating physician consider doing?
A. Giving heparin on top >> the best choice (given instead of).
B. Adjusting warfarin dose >> 1st step, and we can decrease the dose to the half.
C. Stopping the OC >> it is Better, but maybe she want to continue on this medication.
D. Stopping warfarin

MCQs

Q1: Which must heparin bind to in order to exert its anticoagulant effect?

A. GP IIb/IIIa receptor. *B. Thrombin.* *C. Antithrombin III.*

Q2: Which is most appropriate for reversing the anticoagulant effects of heparin?

A. Aminocaproic acid. B. Protamine sulfate. C. Vitamin K .

Q3: A 32-year-old female is diagnosed with as deep vein thrombosis. Her past medical history shows that she was stable on Warfarin for DVT, and now she want to be pregnant. What the doctor should do in this case ?

A. Stop Warfarin and start Heparin. B. Adjust the dose of Warfarin. C. Give her Vitamin K supplement

Q4: A62-year-old male taking warfarin for stroke prevention in atrial fibrillation presents to his primary care physician with an elevated INR of 10.5 without bleeding. He is instructed to hold his warfarin dose and given 2.5 mg of oral vitamin K1. When would the effects of vitamin K on the INR most likely be noted in this patient?

A. 1 hours. B. 6 hours. C. 24 hours.

Q5: Which of the following anticoagulant is a proven to be associate with human teratogen?

A. Fondaparinux B. Warfarin C. Heparin

Q6: An 80-year-old male is taking warfarin indefinitely for the prevention of deep venous thrombosis. He is a compliant patient with a stable INR and has no issues with bleeding or bruising. He is diagnosed with a urinary tract infection and is prescribed sulfamethoxazole/ trimethoprim. What effect will this have on his warfarin therapy?

A. Sulfamethoxazole/trimethoprim will decrease the anticoagulant effect of warfarin.
B. Sulfamethoxazole/trimethoprim will increase the anticoagulant effect of warfarin.
C. Sulfamethoxazole/trimethoprim will not change anticoagulation status.

Q7: A patient with pulmonary embolism and he was on heparin for that later he developed thrombocytopenia. Now he need immediately Anticoagulation for parenteral administration. Which one of the following Anticoagulation can be used and has no risk to develop drug-induced thrombocytopenia?

A. Lepirudin B. Enoxaparin C- Both of them

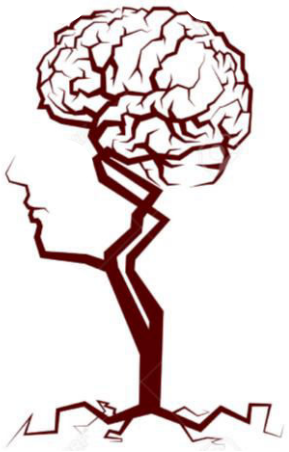
Q8: Which of the following is a major adverse effect of Heparin?

A. Allergic reactions B. Osteoporosis C. Bleeding

Q9: **Which of the following is a major adverse effect of Heparin in long-term use ?**

A. Allergic reactions B. Osteoporosis C. Bleeding

1) C
2) B
3) A
4) C
5) B
6) B
7) A
8) C
9) B



إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

قادة فريق علم الأدوية :

- جومانا القحطاني - اللولو الصليهم
- فارس النفيسة

الشكر موصول لأعضاء الفريق المتميزين :

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دعاء وليد

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ابراهيم فتياني

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* الشعار و القالب الأساسي من تصميم لين التميمي