Anti-coagulant drugs

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- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

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.

●◦→ full sentence male slide
●◦ → full sentence female slide
●◦ → full sentence extra
●◦ → full sentence doctor note

Dr. Fouda Video

Drugs and Coagulation

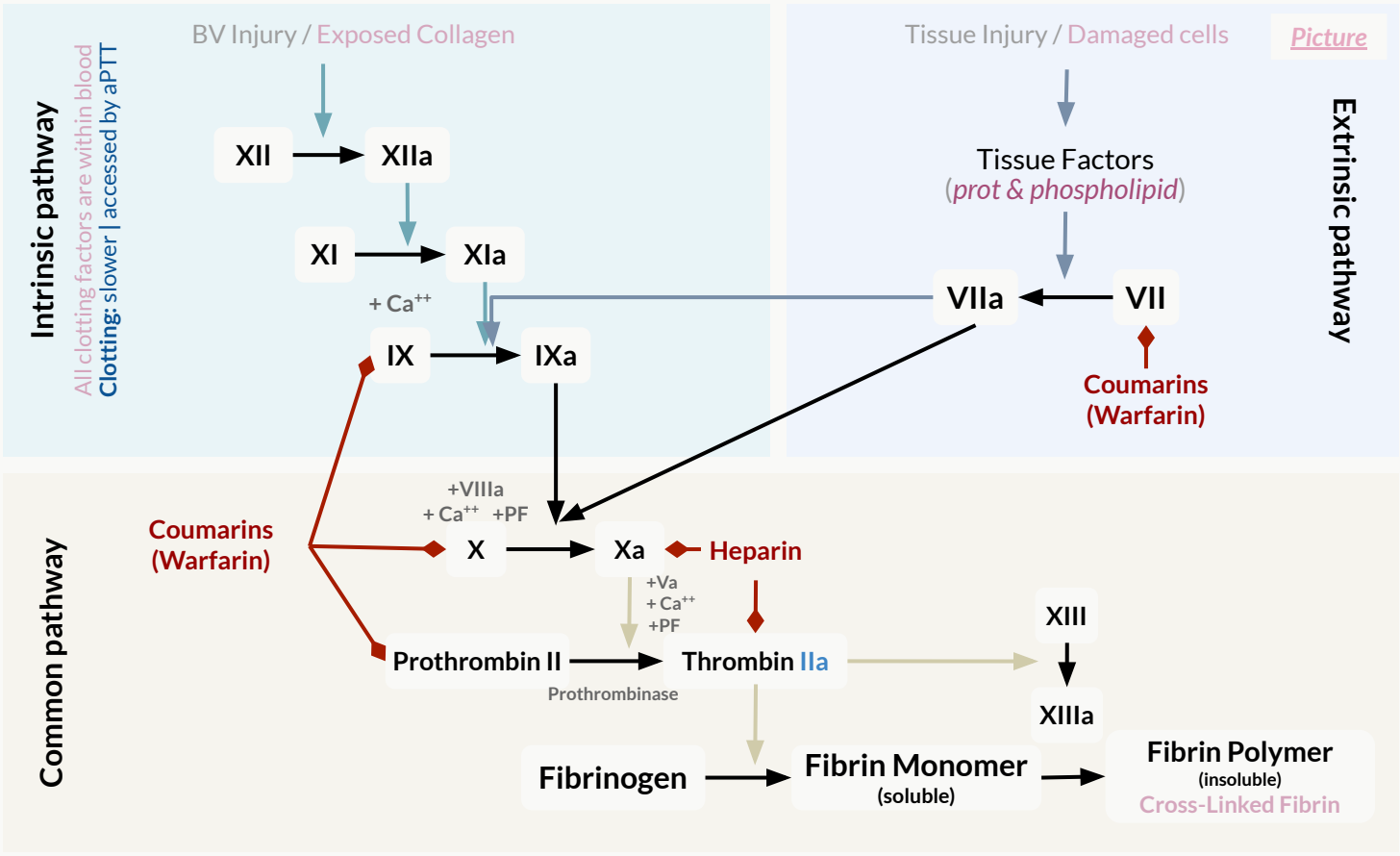
Drugs & Coagulation

Anticoagulants	Antiplatelet Drugs	Fibrinolytic Agents
Prevent thrombus formation & extension by **inhibiting clotting factors.**	Reduce risk of clot formation by inhibiting platelet functions.	**Dissolve** thrombin **already formed.**
○ Heparin ○ Low molecular weight heparin ○ Coumarins / Warfarin	○ Aspirin ○ Ticlopidine	○ Streptokinase

Coagulation Cascade

- **The coagulation process prevents blood loss after injury or damage to a blood vessel.**
- This process occurs as part of the normal hemostasis mechanism. which has three major steps: 1) vasoconstriction, 2) temporary blockage of a break by a platelet plug, and 3) blood coagulation, or formation of a fibrin clot. These processes seal the hole until tissues are repaired.
- Disorders of coagulation are disease states which can results in bleeding or obstructive clotting (thrombosis). A portion of a thrombus may break away, travel as an embolus and lodge downstream, causing ischemia and infarction.
- Thus, the inhibition of thrombin is essential in preventing and treating thromboembolic disorders.

- 13 soluble factors [*normally circulate in an inactive state*] are involved in clotting & must be activated to form a **Fibrin Clot**.



Anticoagulants

Classification

PLEASE BE AWARE THAT NOT ALL THE ANTIDOTES WORKS ON ALL THE ANTICOAGULANT DRUGS YOU HAVE TO BE SPECIFIC.

Parenteral

- Act as **thrombin inhibitors** either in a **direct** or an **indirect** way.
- Coagulation factors **inactivation** [XIIa - XIa - IXa - Xa - IIa].
- Rapid
- **Monitor by:**
  - **APTT**

Antidote:

- **Protamine Sulphate**

Oral

- Act as **Vitamin K antagonist (warfarin).**
- ↓ Coagulation factor **synthesis** [II - VII - IX - X].
- Slow
- **Monitor by:**
  - PT
  - INR

Antidote:

- **Vit. K1 infusion +/ Fresh blood**

Direct Thrombin inhibitors:

- IIa
- **Lepirudin**

Indirect thrombin inhibitors :

Unfractionated Heparin (UFH):

- **> AT III** *"more active on AntiThrombin III"*

Low Molecular Weight Heparin (LMWH)

- **Heparin fragments: Enoxaparin - Dalteparin**
- **Synthetic pentasaccharide: fondaparinux**

Female slide

Endogenous Coagulation Inhibitors

- Physiological coagulation inhibitors synthesised inside the body , 3 types:
- **Antithrombin III:** plasma protein, **inactivates thrombin** (factor IIa) & Xa
  - Site of action of **heparin** (heparin like molecules **enhances these interactions**).
- **Prostacyclin (PGI_2):** synthesized by endothelial cells , inhibits platelet aggregation.
- **Protein C & S:** vitamin K dependent proteins, slow coagulation cascade by inactivating factor Va & VIIIa.

Anticoagulants Indications

1. **Myocardial infarction (MI)**
2. **Deep venous thrombosis (DVT)**
3. **Pulmonary embolism (PE)**
4. **Blood transfusion & dialysis.**
5. **Peripheral arterial emboli.**
6. **Many other conditions.**

Female slide

1.A. Direct Thrombin Inhibitors (DTIs)

MOA	exert their anticoagulant effect by **direct binding to thrombin**.
Effect	rapid and potent.
Advantage	not associated with thrombocytopenia development.
Drug **hirudin/ Lepirudin**	• The first DTI to be developed was hirudin, which was isolated from the saliva of the leech (علقة) • Lepirudin is a polypeptide that binds directly to the active site of thrombin • Recombinant hirudin "Lepirudin" isused as IV anticoagulant in patients with HIT

Anticoagulant

1.B. Indirect Thrombin Inhibitors:

I. Unfractionated Heparin (UFHs)

Drug	Heparin (Unfractionated Heparin)
Origin of the drug	• one of the oldest drugs currently used. • Naturally/Normal macromolecule/anticoagulant in/produced by basophils and **mast cells** with **histamine** (unknown physiological role) in the body. • **Commercial preparations:** extracted from **beef lung** or **pig intestine** → can cause hypersensitivity reaction.
M.O.A ★	• Indirect Thrombin Inhibitor. ★ Heparin binds to antithrombin III and thrombin → conformational changes (ternary complex) → ↑ rate of action **1000x**. (no heparin → slow inactivation). ★ ↑ **Activity of** endogenous anticoagulant [**Antithrombin III**] → inhibits/inactivate activated clotting factors mainly thrombin (factor **IIa)** and **Xa**. • This is a physiological reaction but heparin accelerate it tp 1000 folds • Heparin dissociates → leaving thrombin bound to inhibitor • Once dissociated, heparin is free to bind to another antithrombin molecule and subsequently inhibit more thrombin • "You could simply say that it **increases the activity of Antithrombin III by 1000 folds**"
P.K.	• **Administration:** injectable (**IV** or **SC** | **Not IM** → **haematomas** at injection site), because it is degraded when taken orally • **Absorption:** not absorbed from GIT, **Onset of action:** rapid. • **In bloodstream:** binds to plasma proteins - endothelial cells - macrophages • close monitoring of the activated partial thromboplastin time (aPTT) is necessary in patients receiving UFH • Active in vitro (in test tubes) and in vivo (in the body).
Uses	★ **Drug of choice** anticoagulant during **pregnancy** (doesn't cross the placenta). • Stops the expansion of a thrombus + prevents formation of new thrombi • Does not dissolve an existing thrombus. • Initiates immediate (rapid onset of action) anticoagulation in thromboembolic disease (PE - DVT - MI) as induction for oral vitamin K antagonists. • **Prevents postoperative DVT** (hip replacement) • prevention of coagulation during renal dialysis or cardiac surgery.
Limitations	• The need for regular monitoring (aPTT) • Inconvenience of administration by injection. ★ **Risk of Heparin Induced Thrombocytopenia (HIT):** • due to binding to platelets → ↓ platelet count + ↑ thrombosis or clots risk (instead of bleeding). • heparin introduced platelets aggregation within blood vessels, and formation of antiplatelet and antibodies both results in thrombocytopenia. ○ **Generally:** ↓ platelets → excessive bleeding | ↑ platelets → blood clot → thrombosis.
ADRs	• Bleeding (major ADR). ★ HIT (serious ADR) • Allergic reactions (chills - fever - urticaria) →heparin is of animal origin, caution in allergic patients. • Long-term therapy associated with osteoporosis
Reversal of Action	• Discontinuation of drug. ★ Heparin is strongly acidic and is neutralized by i.v. **protamine sulfate** (a strongly basic protein) • It combines with heparin to form a stable complex devoid of anticoagulant activity
C.I.	• Bleeding disorders - hemophilia. • Recent surgery of the brain, eye or spinal cord. • Hypersensitivity to drug. • Threatened abortion.

II. Low Molecular-Weight Heparins (LMWHs)

Drug	Heparin fragments (Enoxaparin - Dalteparin)	Synthetic pentasaccharide (Fondaparinux)
M.O.A.	◦ Derived from the chemical or enzymatic degradation of UFH into fragments. ◦ Equal efficacy without frequent laboratory monitoring (suitable for outpatient therapy). ◦ Have a more predictable anticoagulant response ◦ Binding to platelets and osteoblasts is reduced with LMWH compared with UFH.	
	• ↑ Action of antithrombin III on factor Xa but not its action on thrombin (molecules are too small to bind to both enzyme and inhibitor).	
		• Inhibits factor Xa by antithrombin but **does not inhibit thrombin.**
P.K.	• **Size:** 1/3 the size of UFH, many advantages over UFH. • **Plasma half-life (t ½):** longer → better bioavailability. • **Duration of action:** longer → ↓ frequency of administration. • **Administration:** SC, once- or twice- daily.	
		• Given once a day at a fixed dose without coagulation monitoring.
Uses	• Used increasingly in place of unfractionated heparin.	
ADR's		• Less likely than UFH or LMWHs to trigger HIT.

Female slide

Advantages of LMWHs over UFH

- The theoretical pharmacologic advantages of LMWH over UFH arise from the preferential binding ratio to factor Xa over thrombin
- The convenience of once- or twice- daily subcutaneous injections without regular coagulation monitoring due to:
  - ↑ predictable response
  - ↑ plasma half-life and improved bioavailability
  - ↓ plasma protein binding
  - ↓ platelet activation
  - ↓ risk of re-thrombosis and thrombocytopenia

Drug	Heparin (UFH)	LMWH
P.K	• **IV ½ life:** 2 hours • **Bioavailability after SC:** 20% • **Non-Specific Binding:** more	• **IV ½ life:** 4 hours • **Bioavailability after SC:** 90% • **Non-Specific Binding:** little "↑*bioavailability*"
Response	Variable	Predictable *"used more often"*
ADRs	• Frequent bleeding • HIT • Osteoporosis	• Less frequent bleeding • Less HIT • Less osteoporosis.
Antagonist	Protamine sulphate	Incomplete
Therapy setting	Hospital	Hospital & OPC
Monitoring	Needed aPPT	Not needed

Vitamin K: Fat Soluble Vitamin

Vitamin K

Source	Required for	Deficiency Causes
• Green vegetables. • Synthesized by intestinal flora.	• Functional coagulation factors II, VII, IX ,X synthesis. • Protein C & S synthesis (*endogenous anticoagulants*).	• Malnutrition. • Malabsorption. • Antibiotic therapy.

Drugs In Modulating Response to VKAs (Oral Anticoagulants):

Female slide

01 Increase the actions of anticoagulants

- **Oral antibiotics:** inhibition of Vit K synthesis by intestinal flora
- **Liquid Paraffin:** inhibition of Vit K absorption
- **chloramphenicol, & cimetidine:** ↓ Drug Metabolism by Microsomal Enzyme Inhibitors
- **phenylbutazone & salicylates**: displacement of the drug from protein binding sites
- **NSAIDs & heparin**: Co-administration of drugs that increase bleeding tendency by inhibiting platelet function and coagulation factors ,respectively.

02 Decrease the actions of anticoagulants

- **cholestyramine, colestipol:** inhibition of drug absorption from GIT
- **Vit K, oral contraceptives:** increased synthesis of clotting factors
- **Carbamazepine; barbiturates, rifampicin:** Increase in drug metabolism by microsomal enzyme inducers

2. Vitamin K Antagonists: coumarin (warfarin)

Coumarin (Warfarin)

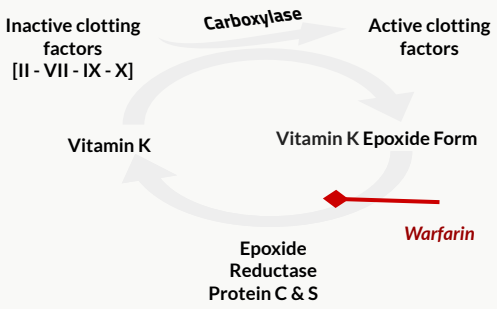
M.O.A

- Precursors of factors II, VII, IX & X require **carboxylation** of their glutamic acid residues to bind to phospholipid surfaces.
- Carboxylation of glutamic acid residues is provided by Vitamin K [changes from oxidized to reduced form].
- oxidized Vitamin K recycles back to Reduced form by Vitamin K by **epoxide reductase**.
- **Epoxide reductase is blocked by VKA → lost functioning ability of coagulation factors.**

i.e

★ Inhibits biologically active forms of vitamin K-dependent clotting factors **[II - VII - IX - X]** , and anticoagulant proteins C and S synthesis.

★ No effect on already-synthesized coagulation factors → therapeutic effects are not seen until these factors are depleted.



P.K

- Active only in vivo because it acts by interfering with the synthesis of vit. K dependant clotting factors and anticoagulant proteins in the liver
- **In bloodstream:** 98% bound to plasma proteins (albumin) "*when taken with Phenylbutazone & Salicylates (high protein binding) → displace Warfarin from binding sites → ↑ free Warfarin in blood → ↑ effect*".
- **Bioavailability:** 100%
- **Onset of action:** starts when already-synthesized factors are eliminated.
- Effect takes 3 - 4 days to develop because of the time taken for degradation of circulating functional clotting factors.
- Monitoring anticoagulant effect by measuring **PT** [*International Normalized Ratio (**INR**)*].
- **Offset of action:** slow due to time required for synthesis of new, functional factors.

Limitation

- Variable, unpredictable effect necessitating regular INR monitoring and dose adjustment
- Narrow therapeutic window leading to increased risk of severe bleeding
- Slow onset and offset of action
- Numerous interactions with foods containing vitamin K and drugs
- Oral anticoagulants: **Teratogenicity**
- Polymorphisms in CYT P450 isoforms that metabolize warfarin → ↑ non- predictable response → toxicities / under use.

ADRs ★

- The most common adverse effect of oral anticoagulants is **bleeding**, which may vary in severity from a mild nosebleed to life-threatening hemorrhage. Patients should report any signs of bleeding.
- Treatment of bleeding may include a decrease in dosage and the administration of phytonadione (vitamin K1)

Reversal of Action

- Stop the drug.

★ IV **Vitamin K** , administration of phytonadione (vitamin K1)

- Fresh frozen blood.

#

★ **Pregnancy [Cross placental barrier → abortion - hemorrhagic disorder in fetus - birth defects] , (category D)**

- replaced by heparin

Heparin Vs. Warfarin

Drug	Heparins	Coumarin (Warfarin)
Chemical Nature	• Large polysaccharide • Water soluble	• Small molecule • Lipid soluble derivative of Vit. K
★ M.O.A.	• ↑ activity of Antithrombin III → inactivation of coagulation factors IIa - IXa - Xa - XIa - XIIa. • Action in **vivo and vitro** • Rapid / variable	• ↓hepatic synthesis of Vitamin K- dependent factors II, VII, IX, X - cournarins prevent their γ-carboxylation. • Has no effect on factors already present. • Action in **vivo only.** • Slow / latency / variable.
P.K.	• **Administration:** parenterally (IV/SC). • **Half-life:** 2 h • **Elimination:** hepatic & reticuloendothelial. • No placental access.	• **Administration:** orally. • 98% protein bound. • PO • **Metabolism:** liver. • **Half-life:** 30+ h • Placental access.
Monitoring	• Partial thromboplastin time (PTT) 1.5-2.5 times normal (30 sec) • Clotting time 2-3 times normal (5-7 min)	• Prothrombin time (PT) • Expressed as International Normalized Ratio (INR)
Antagonist (Anti-dote)	★ Protamine sulfate I.V (1mg/100 units UFH) (chemical antagonism, fast onset) • + Fresh blood	★ ↑ Vit K cofactor synthesis (slow onset) ★ Fresh frozen plasma (fast onset) • Fresh blood + needs de novo synthesis – Has clotting factors → manage bleeding fast.
Uses	• **Rapid anticoagulation (intensive,** emergency**) for:** - Thromboses - Emboli - Unstable angina - Disseminated intravascular coagulation (DIC) - Open heart surgery	• **Long term anticoagulation (controlled,** prophylaxis**) for:** - Thromboses - Emboli - Post MI - Heart valve damage - Atrial arrhythmias
★ Toxicity	• Bleeding • Osteoporosis ★ Thrombocytopenia (HIT) • Hypersensitivity	★ Bleeding • Skin necrosis (if low protein C) • Drug interactions ★ Teratogenic (Bone dysmorphogenesis)

MCQ

1. Which drug increases the activity of Antithrombin III?			
A. Warfarin	B. Protamine sulfate	C. Fresh frozen plasma	D. Heparin
2. What is the main antagonist (antidote) for Coumarin (Warfarin) toxicity?			
A. Fresh frozen plasma	B. Protamine sulfate	C. Vit K	D. Heparin
3. A 67-year-old hospitalized patient with a deep venous thrombosis of the left calf and pulmonary embolism is currently on intravenous heparin on an hourly drip. Unfortunately, because of a calculation error, the heparin drip is running at 100 times the rate it should be running at. Protamine sulfate is immediately given intravenously. This agent works by which of the following mechanisms of action?			
A. Agonist	B. Chemical Antagonist	C. Partial Agonist	D. Partial antagonist
4. Warfarin prevents the y-carboxylation of which of the following clotting factors?			
A. Factor IX	B. Factor VIII	C. Factor I	D. Factor V
5. A 61-year-old man with hypertension develops atrial fibrillation. His medications include simvastatin and metoprolol. His physician prescribes an anticoagulant for clot prophylaxis, which directly inhibits thrombin. Which drug is this?			
A. Warfarin	B. Ticlopidine	C. Heparin	D.Lepirudin
6. Which of the following would represent a contraindication to heparin therapy?			
A. recent surgery to the spinal cord	B. immune deficiency state	C. drug abuse	D. Hypertension
7. A pregnant patients has recently been diagnosed with DVT, which drug is the most appropriate?			
A. Warfarin	B. Aspirin	C. Heparin	D. Streptokinase

1: D ,2: C ,3: B ,4: A ,5:D ,6: A ,7: C

★ MCQ

1. Which drug causes HIT?			
A. Warfarin	B. Protamine sulfate	C. Vitamin K	D. Heparin
2. What is the main antagonist (antidote) for Coumarin (Warfarin) toxicity?			
A. Warfarin	B. Protamine sulfate	C. Vitamin K	D. Heparin
3. What is the main antagonist (antidote) for heparin toxicity?			
A. Warfarin	B. Protamine sulfate	C. Vitamin K	D. Heparin
4. Which of the following is teratogenic?			
A. Warfarin	B. Protamine sulfate	C. Vitamin K	D. Heparin
5. in pregnants you should replace drug mentioned above with?			
A. Warfarin	B. Protamine sulfate	C. Vitamin K	D. Heparin
6. which of the following interferes with the synthesis of vit. k dependant clotting factors?			
A. Warfarin	B. Protamine sulfate	C. Vitamin K	D. Heparin
7. which of the following bind with antithrombin III and accelerates its activity?			
A. Warfarin	B. Protamine sulfate	C. Vitamin K	D. Heparin

1: D ,2: C ,3: B ,4: A ,5:D ,6: A ,7: D

SAQ

01

What are the potential adverse effects of warfarin on pregnancy, and what alternative treatment is recommended for pregnant women?

Warfarin can cross the placental barrier and lead to abortion, hemorrhagic disorder in the fetus, and birth defects. It is recommended to give heparin or LMWH instead of warfarin to pregnant women.

02

What are the main differences between Heparin and Warfarin ?

Slide 12

03

what are the advantages of LMWH over UFH?

Slide 7

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