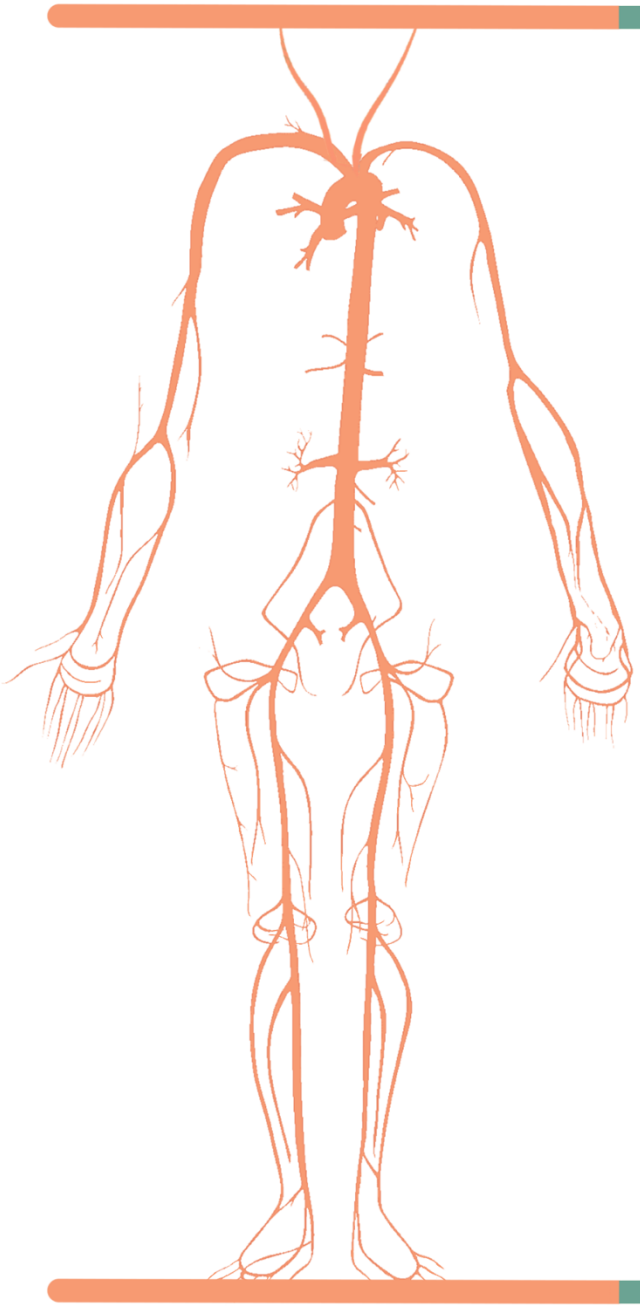
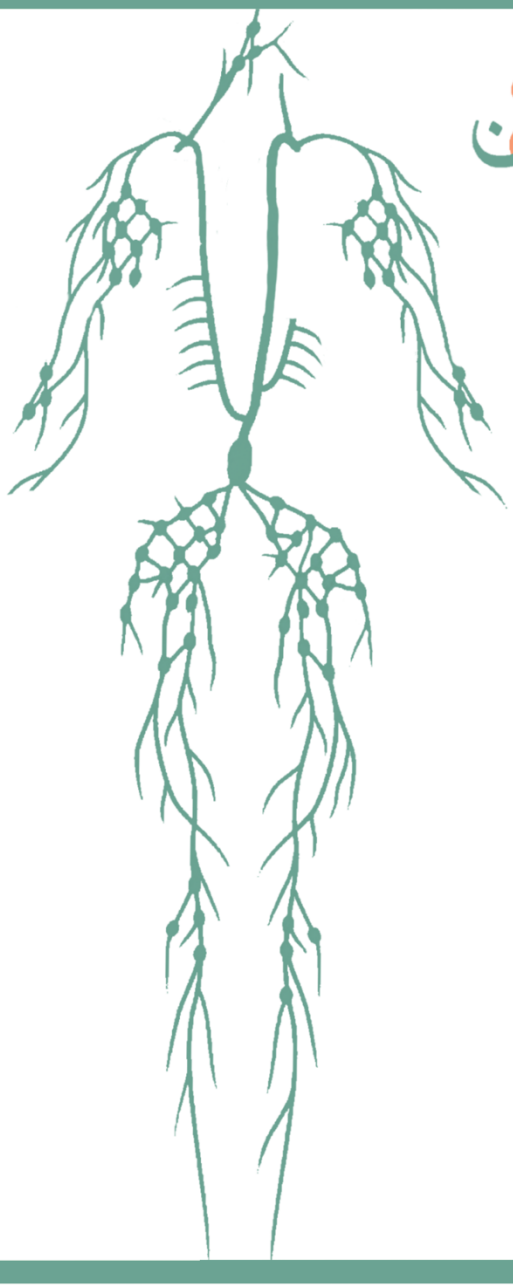
Pharmacology

HematoLymphatic





Title: Sheet 3 – Drugs used in thromboembolic disease part 1

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In this sheet, we'll be talking about some drugs that are used in thromboembolic disease in which blood clots (thrombi) form in blood vessels.

But before that, we need to go over some general information regarding blood clotting.

❖ Risk factors for thromboembolism can be divided into 3 categories

Don't get overwhelmed by the amount of information below! The professor went over them very quickly and the brief explanation next to each of them is added by us just to help you understand. 00:00

Abnormalities of blood flow, which include:

- **Atrial fibrillation**: irregular beating in the **atria** → blood doesn't flow as well as it should from the **atria** to ventricles → can lead to blood clots, stroke, and heart failure.
- **Left ventricular dysfunction**: occurs when the **left ventricle** is either defective or damaged.
- **Bed rest/immobilization/paralysis**: causes accumulation of **clotting** factors and fibrin, resulting in **blood clot** formation.
- **Venous obstruction**: partial or complete **occlusion** of the lumen of a blood vessel.

Abnormalities of Surface Contact with blood:

- **Vascular injury/trauma**: injury to blood vessels.
- **Heart valve disease and replacement**
- **Atherosclerosis**: buildup of substances like fats in artery walls (plaque), which can restrict blood flow. Also, the plaque can burst, triggering a blood clot formation.
- **Acute myocardial infarction**.
- **Indwelling catheters:** may trigger clot formation.
- **Previous deep venous thrombosis (DVT)/pulmonary embolism(PE).**
- **Fractures.**
- **Chemical irritation (K+, hypertonic solutions, chemotherapy)**.
- **Tumor invasion**.

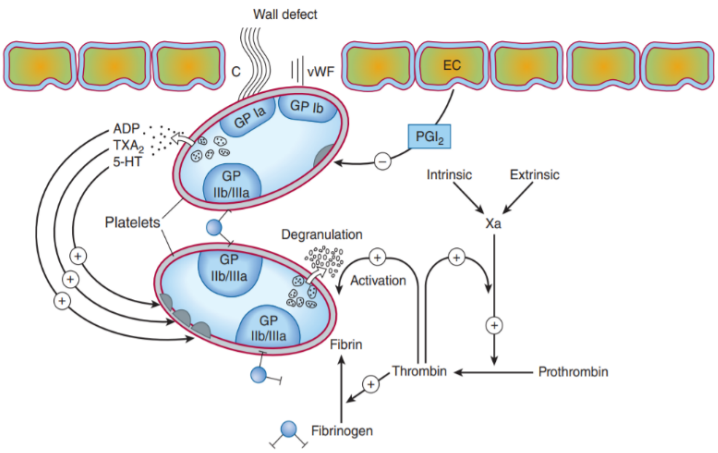
Abnormalities of Clotting Components:

- **Protein C, Protein S, Antithrombin deficiency** (these components have anti-thrombotic effects).
- **Prothrombin G20210A mutation**.
- **Antiphospholipd antibody syndrome** → the body creates antibodies that make the blood more likely to clot.
- **Estrogen therapy, pregnancy, malignancy**.
- **Homocysteinemia:** Elevated homocysteine levels may lead to thrombosis.
- **Dysfibrinogenemia**: coagulation disorder due to an abnormal form of fibrinogen.
- **Polycythemia, thrombocytosis**.
- **Myeloproliferative disorders**.

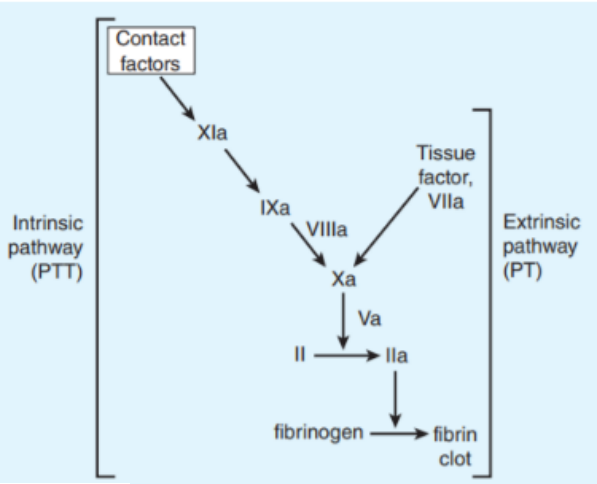
- Hospitalized patients are at risk of developing thromboembolism, but this risk varies depending on many factors. Patients with different levels of risk are prescribed different types of anti-thrombotic drugs. *(the ones in bold were mentioned by the prof)*

Risk	Procedure
Low	**1) Minor surgery; no other risk factor** **2) Major surgery, age is <40 years, no other risk factors.** **3) Minor trauma or illness.**
Moderate	**1) Major surgery; age ≥40 years or other risk factors.** 2) **Heart failure, recent myocardial infraction, malignancy, inflammatory bowel disease**. 3) Major trauma or burns. 4) Minor surgery, trauma, or illness in patient with previous DVT or PE.
High	1) Fracture or major orthopedic surgery of pelvis, hips, or lower limbs. 2) Major pelvic or abdominal surgery for cancer. 3) Major surgery, trauma, or illness in patient with previous DVT or PE. 4) Lower limb paralysis. 5) Major lower limb amputation.

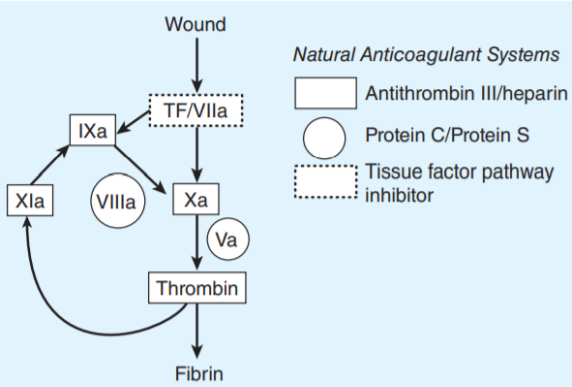
- Blood coagulation occurs due to the transformation of fibrinogen into fibrin by the enzyme thrombin, and for this process to occur, many molecules and proteins, shown in the table in the next page, are required. *(the professor didn't talk in details about the pathways)*



Clotting in the Lab



Clotting in Vivo



- *The professor said that memorizing the names of the clotting factors is not required, but he added mnemonics to help in memorization for those interested, choose one or come up with a new one ☺*

Component or Factor	Common Synonym	Target for the Action of:
I	Fibrinogen	
II	Prothrombin	Heparin, dabigatran (IIa); warfarin (synthesis)
III	Tissue thromboplastin	
IV	Calcium	
V	Proaccelerin (Labile factor)	
VII	Proconvertin (Stable factor)	Warfarin (synthesis)
VIII	Antihemophilic factor (AHF)	
IX	Christmas factor, plasma thromboplastin component (PTC)	Warfarin (synthesis)
X	Stuart-Prower factor	Heparin, rivaroxiban, apixaban, edoxaban (Xa); warfarin (synthesis)
XI	Plasma thromboplastin antecedent (PTA)	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
Proteins C and S		Warfarin (synthesis)
Plasminogen		Thrombolytic enzymes, aminocaproic acid

The mnemonics:

each word has the factor number next to it

Foolish$_{1}$ **p**eople$_{2}$ **t**ry$_{3}$ **c**limbing$_{4}$ **l**ong$_{5}$ **s**lopes$_{7}$ **a**fter$_{8}$ **c**hristmas$_{9}$ **s**ome$_{10}$ **p**eople$_{11}$ **h**ave$_{12}$ **f**allen$_{13}$

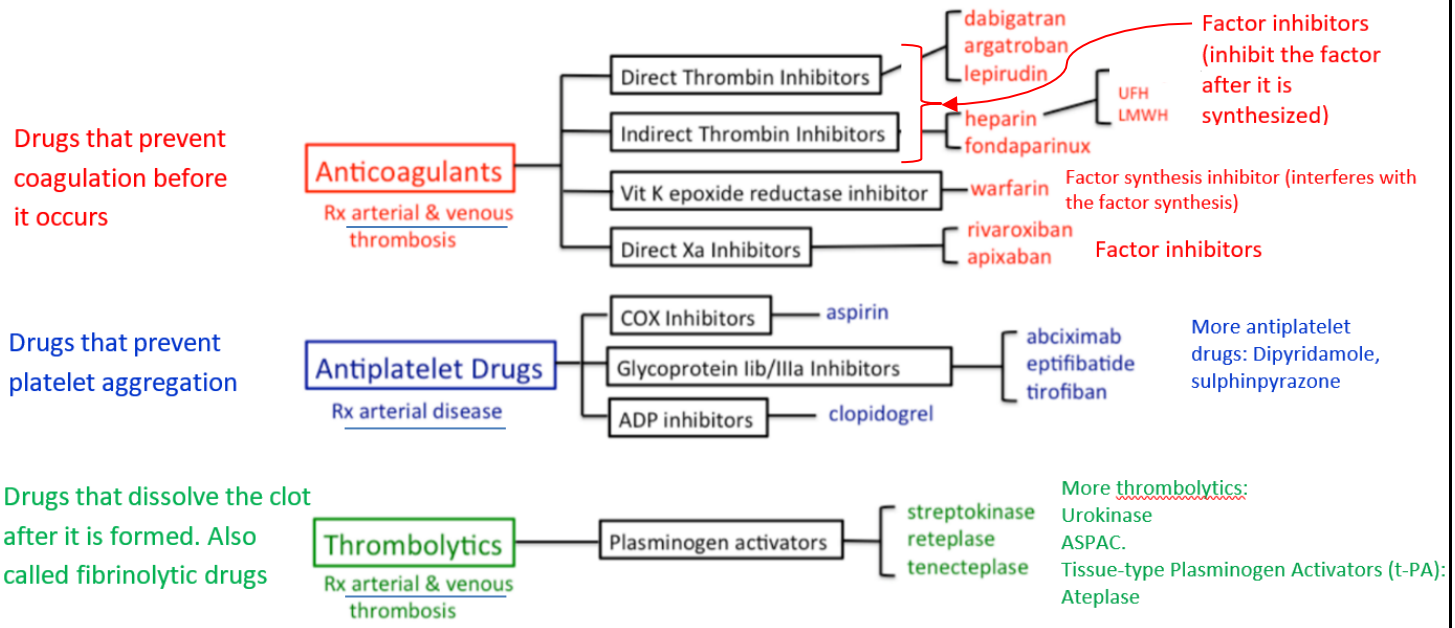
"Fit$_{1}$ pants$_{2}$ tight$_{3}$ colars$_{4}$ loose$_{5}$ shirts$_{7}$ are$_{8}$ cool$_{9}$" says$_{10}$ pretty$_{11}$ heroine$_{12}$ farah$_{13}$

Freshers$_{1}$ party$_{2}$ tonight$_{3}$ come$_{4}$ lets$_{5}$ sing$_{7}$ and$_{8}$ call$_{9}$ seniors$_{10}$ please$_{11}$ have$_{12}$ fun$_{13}$

- On the other hand, there are some natural **non thrombogenic** mechanisms in blood vessels that inhibit/remove the clots: (*we learn more about some of those in biochemistry lecture 7*)

  - Plasminogen activation → into plasmin → Lyses fibrin into fibrin degradation products (*remember fibrin has an important role in coagulation*)
  - Protein C → Inactivates factor Va and VIIIa.
  - Protein S Cofactor → for activation of protein C.
  - Tissue factor pathway inhibitor (TFPI)→ Inhibits activity of factor VIIa.
  - Anti-thrombin → Inhibits factor IIa, IXa and Xa.
  - Release of PGI2. PGI2 is an autacoid i.e. it performs its action locally.
  - Production of heparin-like proteoglycans. (heparin is an anticoagulant; it facilitates the action of Antithrombin III)
  - Transmural negative electrical charges: has anticoagulative effect.

- Now, let's start with the main topic of this lecture **"drugs used in thromboembolic disease"**. *They can be classified into 3 categories*. *(of course don't memorize the diagram now! We'll be talking about some of the drugs in detail later in this lecture and the next one)* 8:07



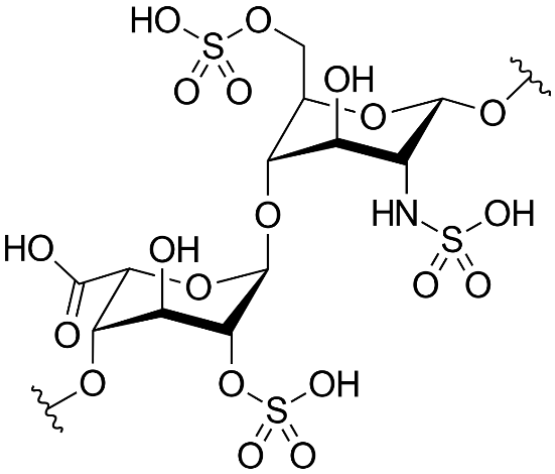
➢ CATEGORY 1: ANTICOAGULANTS. *Specifically factor inhibitors*.

A) Indirect thrombin inhibitors

Remember that thrombin converts fibrinogen to fibrin, which, in combination with platelets, forms a clot. Indirect thrombin inhibitors act on anti-thrombin, thus affecting the activity of thrombin indirectly.

1) Heparin 13:29

- An old drug (1922).
- It is a heterogeneous mixture of sulfated mucopolysacharides; it is composed of sulfated glucosamine and D-glucuronic acid connected by sulfaminic bridges.
- It is found naturally in mast cells (in heart, liver, intestine, and lungs), in an inactive form, but has an unknown function.
- Released with anaphylaxis.
- From outside our bodies, it's obtained from cow lung and pig intestinal mucosa.

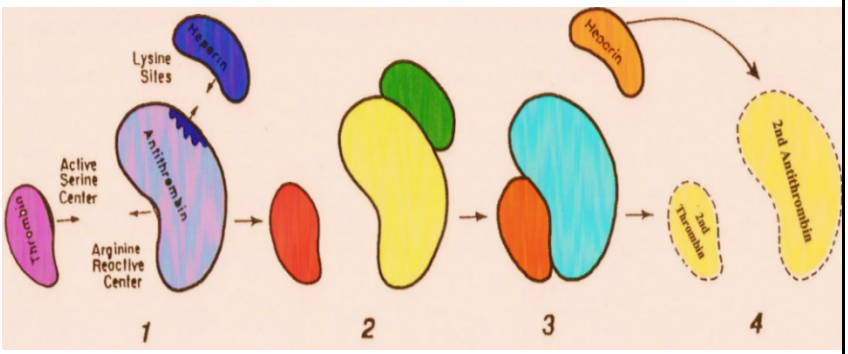


- Heparin's molecular weight varies depending on the source; the Commercial Unfractionated heparin (UFH) weighs around 5,000-30,000 Daltons:
  High Molecular Weight Heparin (HMWH) makes up 2/3rds of UFH
  Low Molecular Weight Heparin (LMWH) [composed of just 15 polysaccharides]
  ⇨ *Now, LMWH can be used separately as a treatment and UFH is referred to as HMWH.*

- Its T1/2 is relatively short = 1 hr.
- Its distribution is limited to the intravascular compartment (just in the circulation).
- Heparin **doesn't** cross the placenta and isn't excreted in breast milk, so it could be used by pregnant and lactating woman without affecting the fetus/the nursing baby.
- Heparin is **eliminated** by rapid metabolism by heparinase enzyme in the liver, renal excretion, and clearance by the reticuloendothelial system.
- Acts directly in peripheral blood and **does not affect the biosynthesis** or plasma levels of any coagulation factor. Remember that this group of drugs inhibits the coagulation factors after they're synthesized.
- Heparin acts as an anticoagulant in many ways:
  ⇨ The major and most important one is by binding to a variety of **plasma proteins, mainly antithrombin**.
  ⇨ When heparin is taken up by the endothelium, it increases the **electronegative potential** of the vessel wall, which has an anticoagulative effect. *(electrical effect)*
  ⇨ It causes the release of **Tissue Factor Pathway Inhibitor** (TFPI), which acts on factor Xa, platelets and endothelium.
  ⇨ UFH inhibits **platelets aggregation.**
  ⇨ Activates **lipoprotein lipase** which reduces platelets adhesiveness.

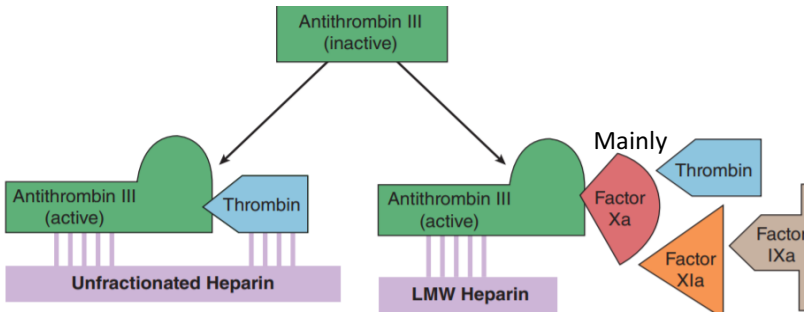
Let's get into details about this mechanism of action.

Antithrombin (ATIII) **inhibits** clotting factor proteases, especially thrombin (factor IIa), factors IXa and factor Xa → Heparin binds tightly to antithrombin and causes a conformational change exposing its active site for more rapid interaction with the factors → thus accelerating the complexing between antithrombin and the clotting factors by 1000 folds.



- Note: Heparin functions as a cofactor, **it is not consumed**. Notice how it aids in the interaction between the first antithrombin and the first factor by exposing the active site and then dissociates to repeat the same process between other antithrombin and factor molecules.

- ✓ A comparison between high molecular weight heparin (HMWH/UFH) and low molecular weight heparin (LMWH) 23:25



	UFH/HMWH	LMWH
Examples	-	**T**inza**parin**. **E**noxa**parin** **D**alte**parin**.
Factors it indirectly inhibits	Has high affinity for antithrombin, which will inhibit coagulation by inhibiting **all three factors (IIa,Xa,IXa)**	- Mainly inhibits factor **Xa** - Has less effect on thrombin or endothelial cell-heparin receptors and plasma protein binding sites.
Efficacy	**Equal efficacy**	
Administration 32:10	- Initial bolus injection: 80-100units/kg. - Then continuous infusion through a pump: 15-22 unit/kg/hr. This usually maintains aPTT at 2-2.5 times of the control. ** if it's above 2.5: bleeding risk. Below 2: thrombosis risk. - Low dose prophylaxis: **Subcutaneously** 5000 units every 8-12 hrs ** NOTE: it must not be given by **intramuscular** injection due to risk of muscle bleeding and formation of hematoma.	Usually given once or twice daily by subcutaneous injection. [and no pump]
Bioavailability from subcutaneous site of injection	Less	More (It is almost completely absorbed after subcutaneous injection)
Dosing requirements	More frequent	Less frequent
Effects	Less predictable (doses and molecular weights are variable + the duration of action and half-life are unpredictable)	More predictable
Monitoring	Constant monitoring is required	Usually, treatment is not routinely monitored (except in renal failure, pregnancy, obesity). Monitoring is done by Xa inhibition assay.
Antidote (when there is excess of the drug and a risk of bleeding) 34:45	Protamine sulfate, which is a highly basic, low molecular weight compound that is capable of neutralizing heparin.	- Protamine binds poorly and ineffective. - No antidote is available nor needed because if there is a bleeding risk→ stop the dose.

✓ **Methods of heparin monitoring**:

1- Activated Partial Thromboplastin Time (aPTT): measures the time taken to form a clot.
2- Protamine Titration
3- Anti-Xa assay.

✓ **Toxicity of heparin:**

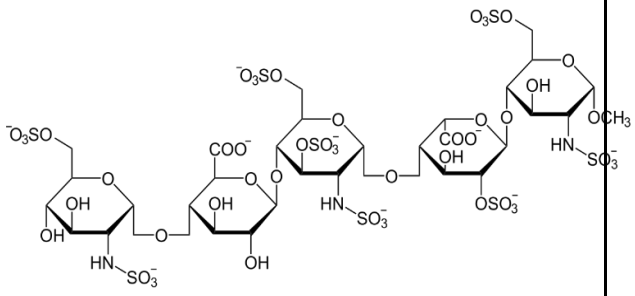
- Bleeding.
- Allergic reactions: fever, anaphylaxis. *Why? Because heparin is taken from animals and might contain foreign allergic molecules.*
- Alopecia, or loss of hair.
- Osteoporosis and ostealgia (bone pain).
- Mineralocorticoid deficiency.
- Thrombocytopenia:
  - Occurs in 1- 4% of patients *(high percentage)* taking UFH for 7 days.
  - More with UFH from bovine sources, less with LMWH.

✓ **Contraindications of heparin:**

- Hypersensitivity
- Infective endocarditis, active TB. (because it increases the chance of detachment of inflamed or infected regions)
- Active bleeding (*bleeding is already occurring so giving heparin would exaggerate the bleeding. Also, if trauma occurs **while** the patient is on heparin treatment, **administration should be stopped**).*
- In situations where there is an ***increased risk*** of bleeding:
  - Thrombocytopenia especially when platelet count is below 75,000.
  - Severe hypertension. *(risk of hemorrhage especially intracranial)*
  - Hemophilia, purpura.
  - Ulcerative lesions of GIT.
  - Threatened abortion.
  - Visceral carcinoma.
  - Advanced liver or renal disease.

2) Fondaparinux; *An indirect thrombin inhibitor.*

- **Synthetic** penta-saccharide fragment of heparin.
- Binds antithrombin with high specific activity, resulting in **more selective inactivation of factor Xa**.
- Does not affect thrombin at all.
- Has a **long half-life** of 15 hours.



Despite all of that, heparin is more commonly used while fondaparinux is rarely used.

B) Direct thrombin inhibitors 37:50

{*Those that directly act on thrombin and are divided into IV and oral inhibitors*}

1) IV direct thrombin inhibitors. They include:

- **Hirudine** (natural); taken from a **leech (علق) called** Hirudo Medicinalis.
- **Lepirudin**: it is the **recombinant** form of hirudine.
- **Bivalirudin**: is a **bival**ent compound, i.e. it binds at both the catalytic site and the substrate recognition site of thrombin → so it affects the catalytic activity of thrombin and its binding to a substrate.
  - ⇨ Note: bivalirudin can cause allergy and anaphylaxis.
- **Argatroban**

2) Oral Direct Thrombin Inhibitors

- **Dabigatran:**

Small molecule which binds only at the active **(catalytic)** site of thrombin.

C) Factor Xa inhibitors

• Edoxaban	• Apixaban	• Rivaroxaban (Xarelto)

- Expensive, but widely used nowadays.
- They inhibit **factor Xa**, in the final common pathway of clotting.
- Given **orally** at fixed doses and **do not require** monitoring → *Again, if there is a bleeding risk, drug administration should be stopped.*
- Administration can be stopped before a surgery.
- Used to prevent stroke in atrial fibrillation. Atrial fibrillation is relatively benign; it doesn't affect the heart or the cardiac output but it affect the blood flow (e.g. it becomes slower) → clots may form in atrium → clots could be displaced from the heart to the brain blocking blood flow causing a **stroke** → ***so anticoagulants should be given.***
- Eliminated **by the kidneys. (Elimination may be impaired in renal failure)**

Good luck