Pharmacology - HLS

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Drugs used in Thromboembolic Disease I

Thromboembolic diseases are Group of diseases which are very important in medicine , can affect all specialities of medicine like (internal medicine, surgical medicine, obstetrics and gynecology)

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Risk Factors for Thromboembolism

- **Abnormalities of Blood Flow:**

  - **Atrial fibrillation.**
  - **Left ventricular dysfunction.**
  - **Bed rest/immobilization/paralysis**. (Paraplegia, hemiplegia, old people who are immobilized in bed for a long period of time)
  - **Venous obstruction.**

Risk Factors for Thromboembolism

- **Abnormalities of Surface Contact with blood:**

  - **Vascular injury/trauma.**
  - **Heart valve disease and replacement.**
  - **Atherosclerosis.**
  - **Acute myocardial infarction.**
  - **Indwelling catheters.**
  - **Previous DVT/PE.**
  - **Fractures.**
  - **Chemical irritation (K+, hypertonic solutions, chemotherapy).**
  - **Tumor invasion.**

Risk Factors for Thromboembolism

- **Abnormalities of Clotting Components:**

  - **Protein C, Protein S, Antithrombin deficiency.**
  - **Prothrombin G20210A mutation.**
  - **Antiphospholipd antibody syndrome.**
  - **Estrogen therapy.**
  - **Pregnancy, malignancy.**
  - **Homocystenemia, dysfibrinogenemia,**
  - **Polycythemia, thrombocytosis.**
  - **Myeloproliferative disorders.**

Non Thrombogenic Mechanisms in Blood Vessels

Fortunately there are a few mechanisms in blood vessels which guard against thrombosis and embolism)

- **Transmural negative electrical charges.**
- **Plasminogen activation.**
- **Protein C activation.**
- **Production of heparin-like proteoglyans.**
- **Release of PGI_2. (very important autacoid released to prevent thrombosis)**

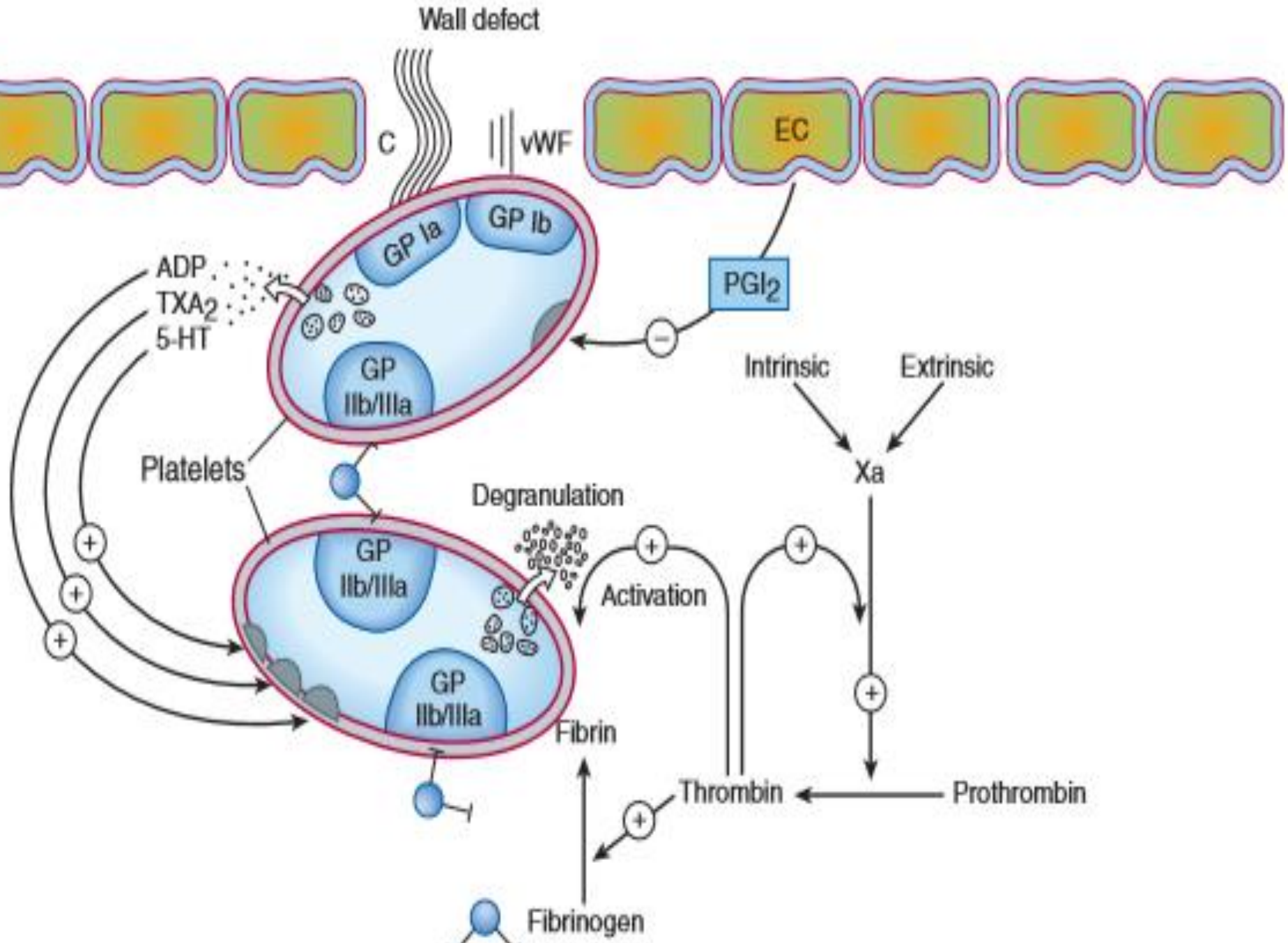
Physiological Inhibitors of Clotting Mechanisms

Inhibitor	*Target*
Antithrombin	**Inhibits factor IIa, IXa and Xa.**
Protein C	**Inactivates factor Va and VIIIa**
Protein S	**Cofactor for activation of factor C**
Tissue factor pathway inhibitor (TFPI)	**Inhibits activity of factor VIIa.**
Plasmin	**Lyses fibrin into fibrin degradation products.**

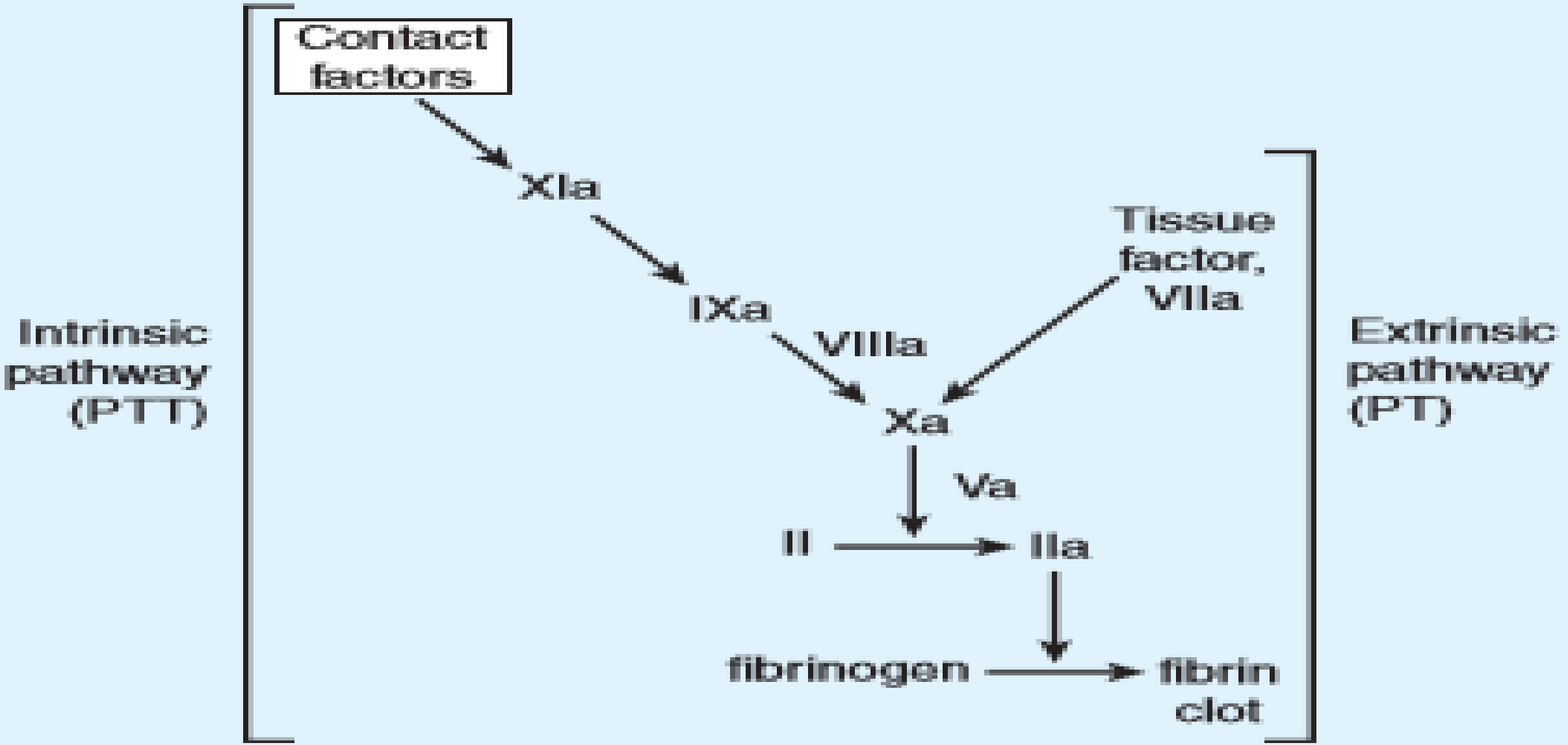
Risk of Thromboembolism in Hospital Patients

Risk	Procedure
Low	Minor surgery, no other risk factor Major surgery, age < 40 years, no other risk factors Minor trauma or illness
Moderate	Major surgery; age ≥ 40 years or other risk factor Heart failure, recent myocardial infarction, malignancy, inflammatory bowel disease. Major trauma or burns Minor surgery, trauma or illness in patient with previous deep vein thrombosis or pulmonary embolism.
High	Fracture or major orthopaedic surgery of pelvis, hips or lower limb Major pelvic or abdominal surgery for cancer Major surgery, trauma or illness in patient with previous deep vein thrombosis or pulmonary embolism. Lower limb paralysis. Major lower limb amputation.

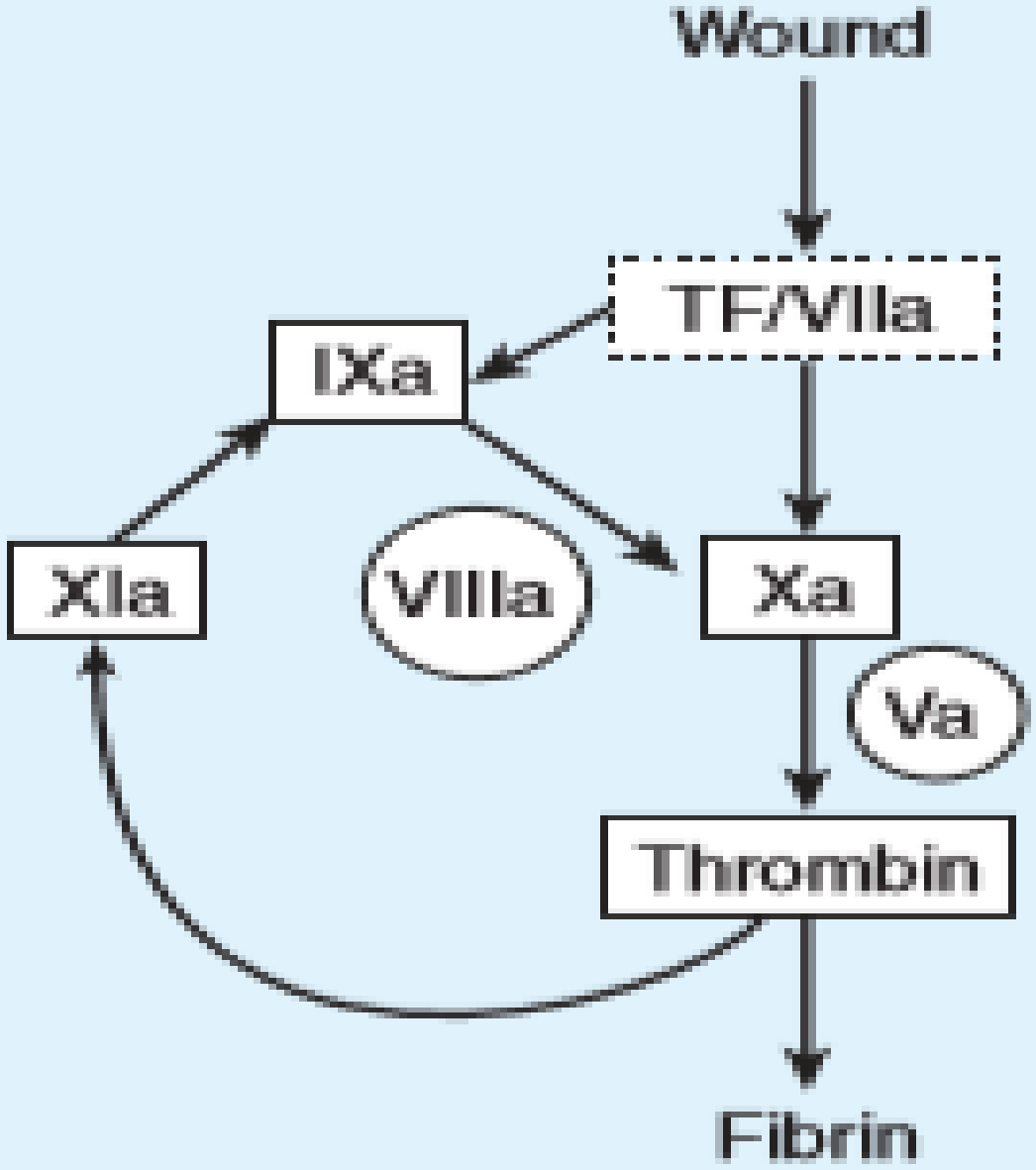
The process of normal clotting involves blood vessel wall activation (after a defect) and release of PGI2 and other factor which will react and end in formation of fibrin from fibrinogen



Clotting in the Lab



Clotting in Vivo



Natural Anticoagulant Systems

Antithrombin III/heparin

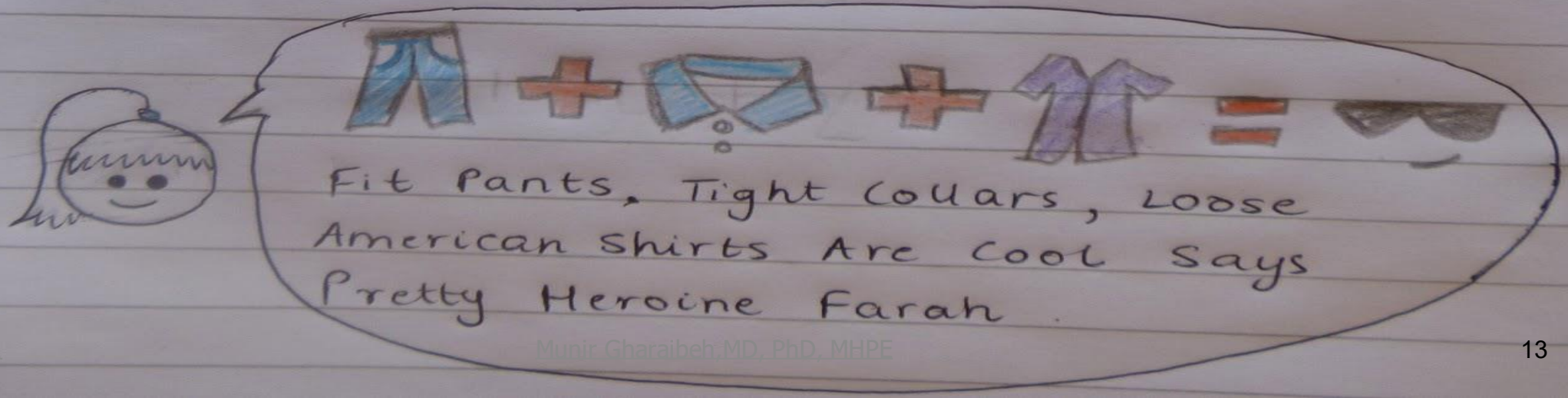
Protein C/Protein S

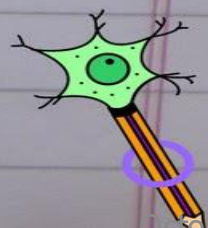
Tissue factor pathway inhibitor

It's not our subject but you can memorize it if you're interested and the next slide will help you

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

I	Fibrinogen	Freshers	Foolish
II	Prothrombin	Party	People
III	Tissue Thromboplastin	Tonights	Try
IV	Calcium ions	come	Climbing
V	Labile factor	Lets	Long
VII	Stable factor	Sing	Slopes
VIII	Antihemophilic factor	And	After
IX	Christmas factor	Call	Christmas
X	Stuart Prower factor	Seniors	Some
XI	PTA	Please	People
XII	Hageman factor	Have	Have
XIII	Fibrin stabilizing factor	Fun	Fallen





Drugs used in Thromboembolic Disease

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- **Anticoagulants:** These drugs Prevent coagulation before it occurs
  - **Factor inhibitors: e.g. Heparin, Rivaroxaban.**

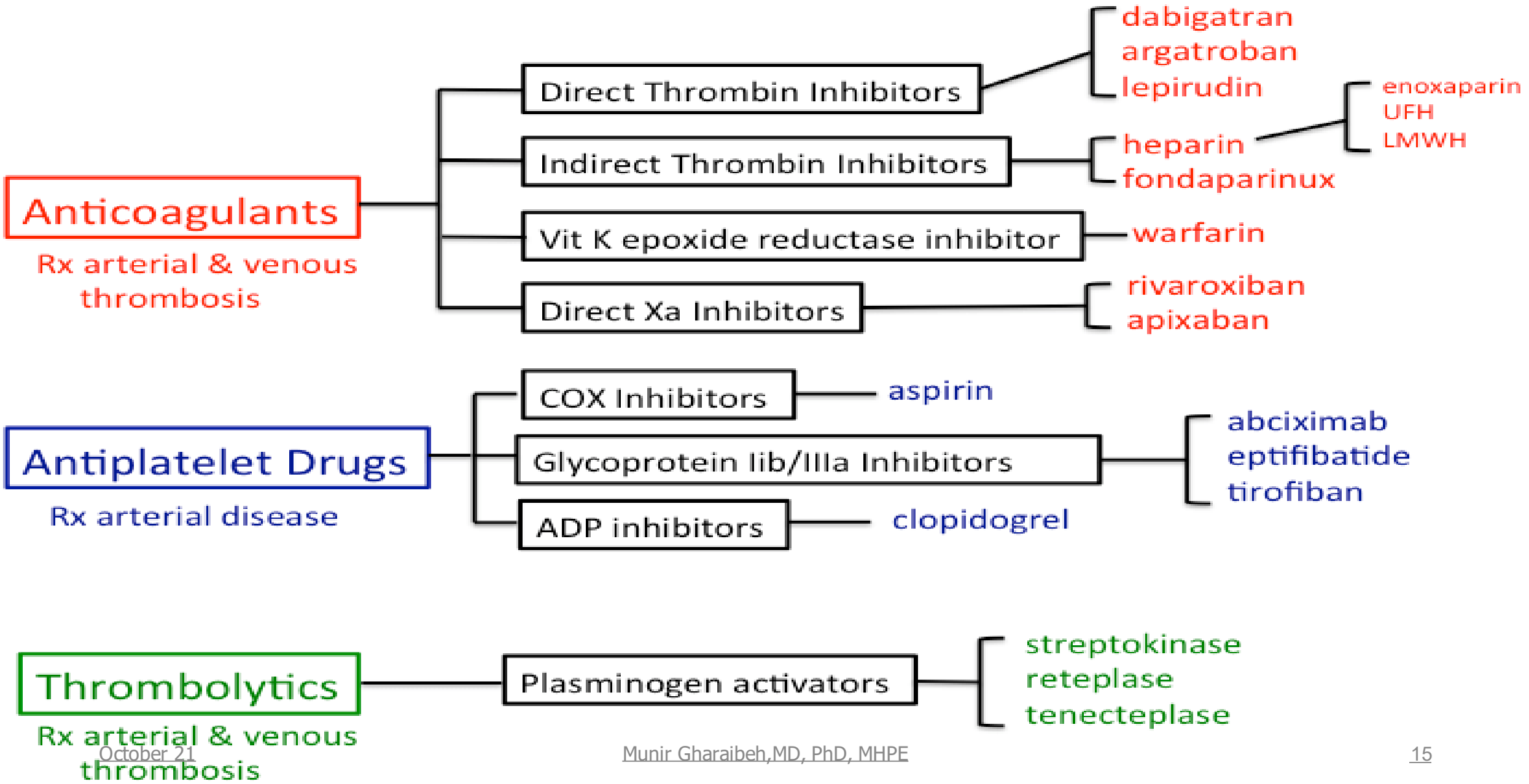
    Inhibit clotting factors either directly or indirectly
  - **Factor synthesis inhibitors: e. g. Oral anticoagulants.**

Mainly clotting factors are synthesized in the liver so these drugs work on the liver to prevent the synthesis of coagulation factors

- **Fbrinolytic Drugs:** These drugs Lyse fibrin and dissolve clots after formation
  - **Streptokinase.**
  - **Urokinase.**
  - **ASPAC.**
  - **Tissue-type Plasminogen Activators (t-PA):**

    Ateplase.
- **Antiplatelet Drugs:** Plateletes aggregation will make the first initial step in the stimulation of the coagulation process, these drugs prevent Plateletes aggregation
  - **Aspirin.**
  - **Dipyridamole.**
  - **Sulphinpyrazone.**

Drugs Used to Treat Clotting Disorders



Indirect Thrombin Inhibitors

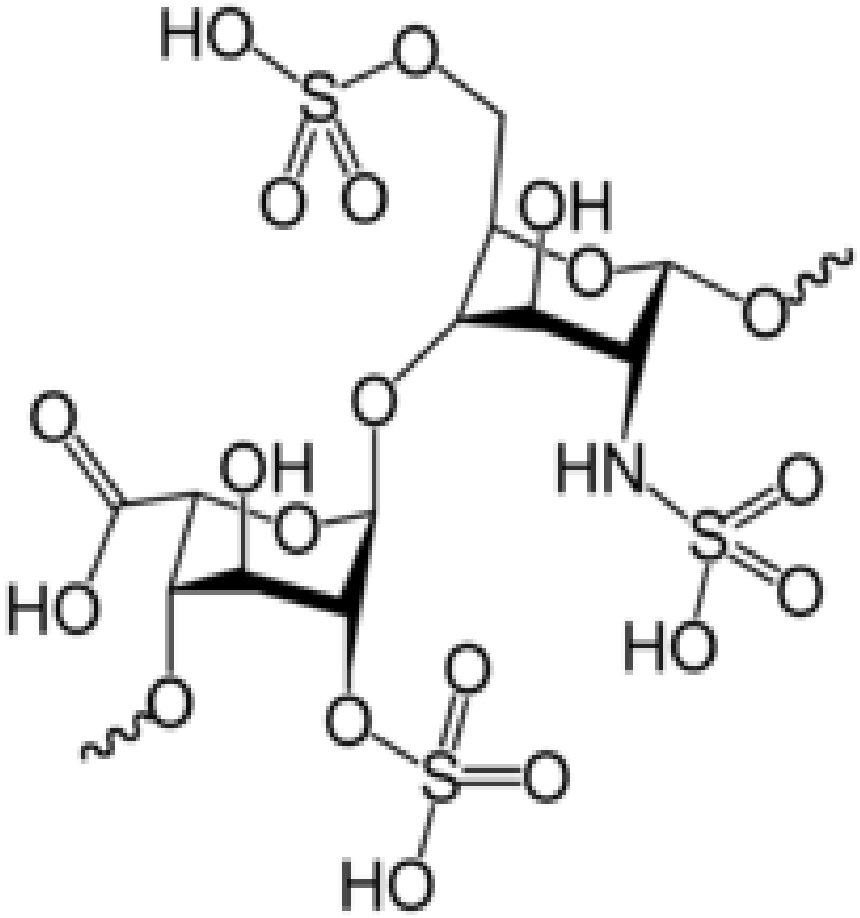
- **HEPARIN:** The oldest
  - **Unfractionated heparin (UFH), *old fashioned.***
  - **Low Molecular Weight Heparins (LMWHs):**
    - **Enoxaparin.**
    - **Dalteparin.**
    - **Tinzaparin.**

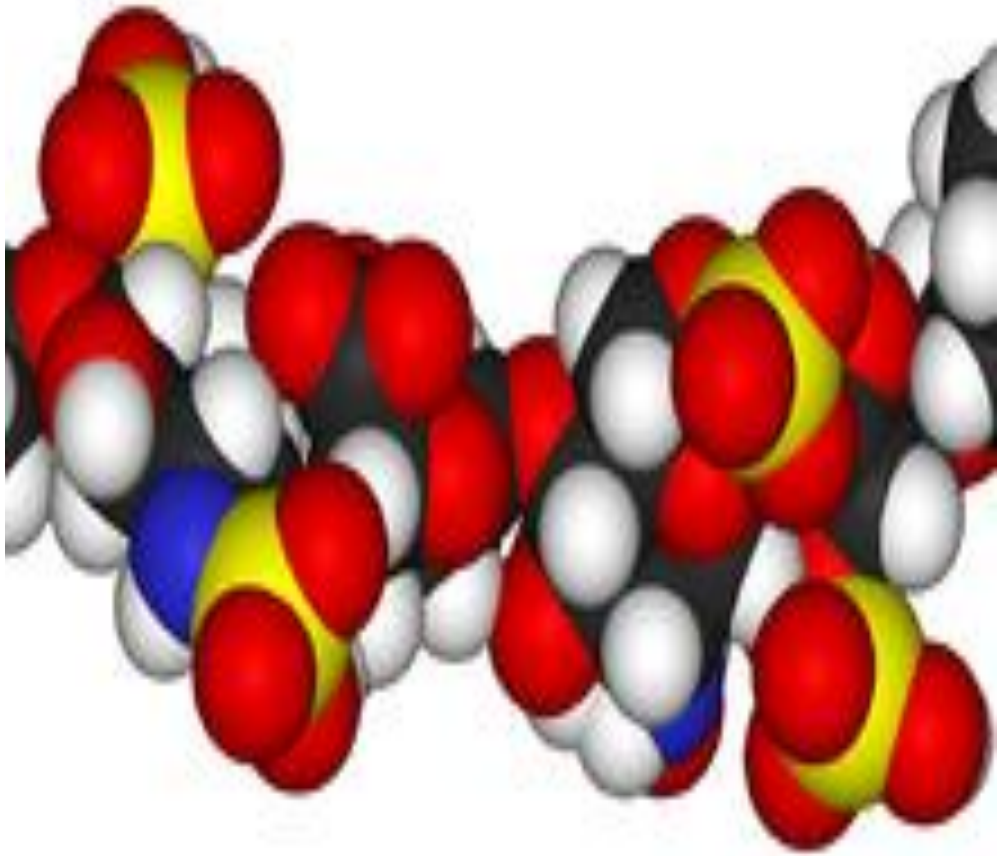
- **FONDAPARINUX**

HEPARIN(1922)

- **Heterogenous mixture of sulfated mucopolysacharides.**
- **Composed of sulfated glucosamine and D-glucoronic acid connected by sulfaminic bridges.**
- **Naturally found in mast cells(in an inactive form, but has an obscure function.**
- **Released with anaphylaxis.**
- **Obtained from cow lung and pig intestinal mucosa.**

The original heparin is from animal sources





The structure of heparin

HEPARIN

- **Molecular weight varies:**

  Depending on the source and and the animal from which the heparin is isolated

  - **Commercial Unfractionated(UFH):5,000-30,000.**
    - **High Molecular Weight Heparin (HMWH):2/3rds of UFH**
    - **Low Molecular Weight Heparin (LMWH)**
- **$T_{1/2}$ = 1 hr.**
- **Given parenterally, distribution limited to the intravascular compartment.**

  Has no action outside the blood , does not go to tissues
- **Does not cross the placenta, and not excreted in breast milk.**

  Possible to use in pregnancy and for lactating women
- **Eliminated by rapid metabolism by heparinase enzyme in the liver, renal excretion, and uptake by the RES .**

HEPARIN

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- **Acts directly in peripheral blood.**
- **Does not affect the biosynthesis or plasma levels of any coagulation factor.**
- **Taken up by the endothelium where it increases the electronegative potential of the vessel wall.**
- **Binds to a variety of plasma proteins, mainly antithrombin.**
- **Causes the release of Tissue Factor Pathway Inhibitor (TFPI), which works on factor Xa, platelets and endothelium.**
- **UFH inhibits platelets aggregation.**
- **Activates Lipoprotein Lipase which reduces platelets adhesiveness.(which is a contributing factor for clotting)**

Physical (electrical activity)

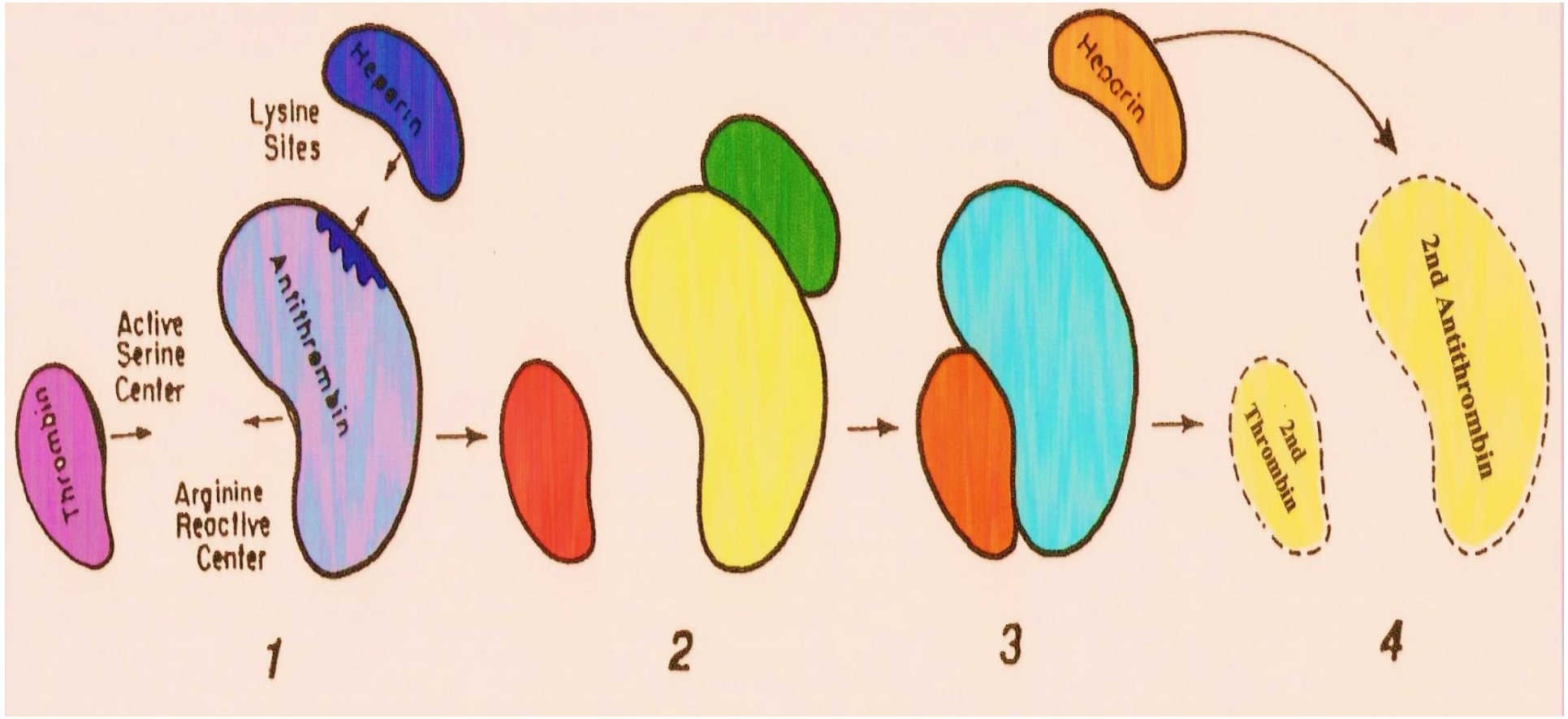
Not the major mechanism of action

HEPARIN

- **Antithrombin(ATIII) inhibits clotting factor proteases, especially thrombin (IIa), IXa and Xa.**
- **Heparin binds tightly to antithrombin and causes a conformational change to expose its active site for more rapid interaction with the factors.** (More effective)
- **Heparin accelerates this complexing by 1000 folds.**
- **Heparin functions as a cofactor, it is not consumed.**

Antithrombin is normally present in the plasma but has a weak activity

HEPARIN



Heparin binds to antithrombin exposing the arginine reactive center, so thrombin will be inactivated in accelerated way and this reaction is repeated many times until thrombin is inactivated

HEPARIN

- **HMWHs have high affinity for antithrombin which will inhibit coagulation by inhibiting all three factors.**

LMWHs

Less affinity

- 15 Polysaccharide units.
- LMWHs inhibit factor Xa, but have less effect on thrombin or endothelial cell-heparin receptors and plasma protein binding sites.

Factor ten inhibitors mainly

- Compared to UFH, LMWHs have:
  - Equal efficacy.
  - More predictable effects.
  - More bioavailability from s.c. site of injection.
  - Less frequent dosing requirements.

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Once daily, longer duration of action ,the dose Is fixed
But in unfractionated heparin, the dose may differ from one to another and from day to day , not all of the dose is absorbed and you may give the dose more frequently

- Treatment is not generally monitored (except in renal failure, pregnancy and obesity).

Unfractionated heparin needs constant monitoring , and might be difficult to monitor the patient

HEPARIN MONITORING

- **Activated Partial Thromboplastin Time (aPTT)**
- **Also, Protamine Titration and Anti-Xa units.**

- **Monitoring the response is needed only in patients receiving UFH, but not needed with LMWH.**

TOXICITY of HEPARIN

- **Bleeding.** Bleeding gums, peptic ulcers, renal stones,trauma, injury
- **Allergic reactions: fever, anaphylaxis.** Because heparin is obtained from animal sources and might contain foreign proteins that induce anaphylaxis
- **Alopecia, or loss of hair.**
- **Osteoporosis and ostealgia.**
- **Mineralocorticoid deficiency.**
- **Thrombocytopenia:**
  - **Occurs in 1- 4% of patients taking UFH for 7 days.**
  - **More with UFH from bovine sources.**
  - **Lower with LMWH.**

CONTRAINDICATIONS of HEPARIN

- **Thrombocytopenia (<75,000).** Because the patient is susceptible to bleeding and susceptibility to thrombosis is much lesser
- **Hypersensitivity.**
- **Active bleeding.**
- **Severe hypertension.** Because Patient is susceptible to hemorrhage specially intracrania hemorrhage
- **Hemophilia, purpura.**
- **Infective endocarditis, active TB.** Greater chance of embolism
- **Ulcerative lesions of GIT.** Will inhance bleeding
- **Threatened abortion.**
- **Visceral carcinoma.**
- **Advanced liver or renal disease.**

Administration of UFH

- **Initial bolus injection:80-100units/kg.**
- **Continuous infusion through a pump:**
  - **15-22 unit/kg/hr.**
  - **This usually maintains aPTT at 2-2.5 times of the control.**

More than this means increase bleeding tendency, and lesser than this means the patient is not anticogulated

  - **Not by intramuscular injection.**

Causes bleeding in the muscle and hematoma

- **Low dose prophylaxis:**

  Subcutaneously 5000 units every 8-12 hrs.

- **<u>Antidote:</u>**
  - **Protamine sulfate: is a highly basic, low mol.wt, compound.**

When there is increase in the dose or the patient is bleeding profusely

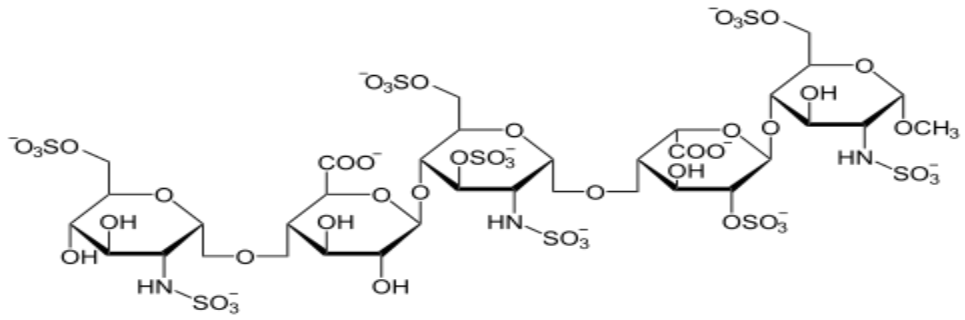
Administration of LMWHs

- **Almost completely absorbed after s.c. injection.**
- **Usually given once or twice daily by subcutaneous injection.**
- **Monitoring is by Xa inhibition assay which is not routinely carried.**

- **<u>Antidote:</u>**
  - **Protamine binds poorly and ineffective.**
  - **No antidote is available nor needed.**

Fondaparinux

- **Synthetic pentasaccharide 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.** **Good drug but rarely used**



IV Direct Thrombin Inhibitors

- **Hirudine (from leeches, *Hirudo medicinalis),*** حشرة العلق
- **Lepirudin, *recombinant form.***
  - ***Both can cause* allergy and anaphylaxis.**

- **Bivalirudin.**
- **Argatroban**
  - **Are bivalent compounds, i.e. they bind at both the catalytic site and the substrate recognition site of thrombin.**

Oral Direct Thrombin Inhibitors

- **Dabigatran:**
  - **Oral.**
  - **Small molecule which binds only at the active site of thrombin.**

Factor Xa Inhibitors

- **Rivaroxaban "Xarelto"**
- **Apixaban**
- **Edoxaban**

Widly used
Given orally
Very expensive

  - **These inhibit factor Xa, in the final common pathway of clotting.**
  - **Given orally at fixed doses and do not require monitoring.**
  - **Used to prevent stroke in atrial fibrillation.**
  - **Eliminated by the kidneys.**