Drugs used in Thromboembolic Disease I

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Risk Factors for Thromboembolism

- **Abnormalities of Blood Flow:**
  - Atrial fibrillation.
  - Left ventricular dysfunction.
  - Bed rest/immobilization/paralysis.
  - 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

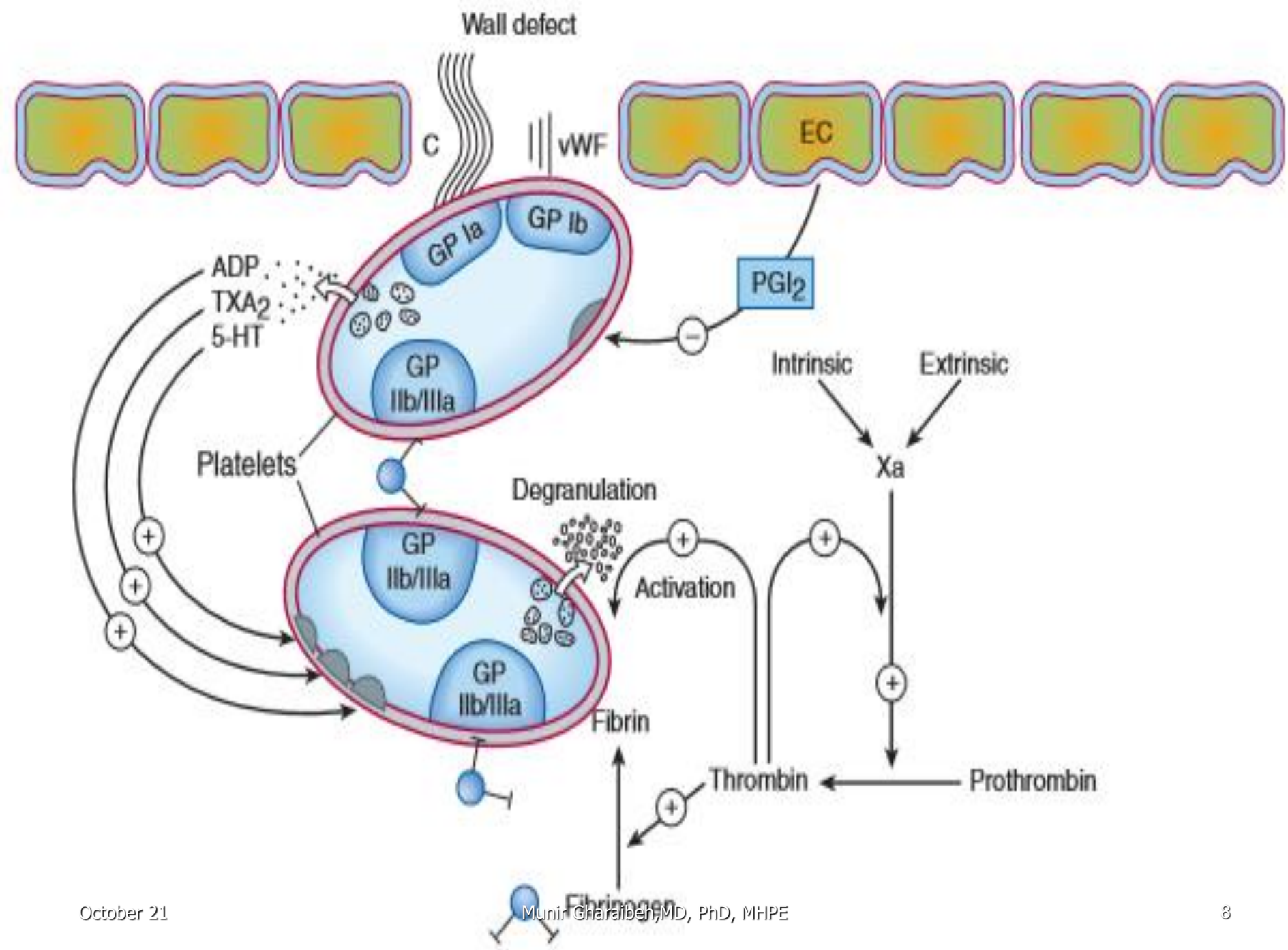
- Transmural negative electrical charges.
- Plasminogen activation.
- Protein C activation.
- Production of heparin-like proteoglyans.
- Release of PGI_2.

Physiological Inhibitors of Clotting Mechanisms

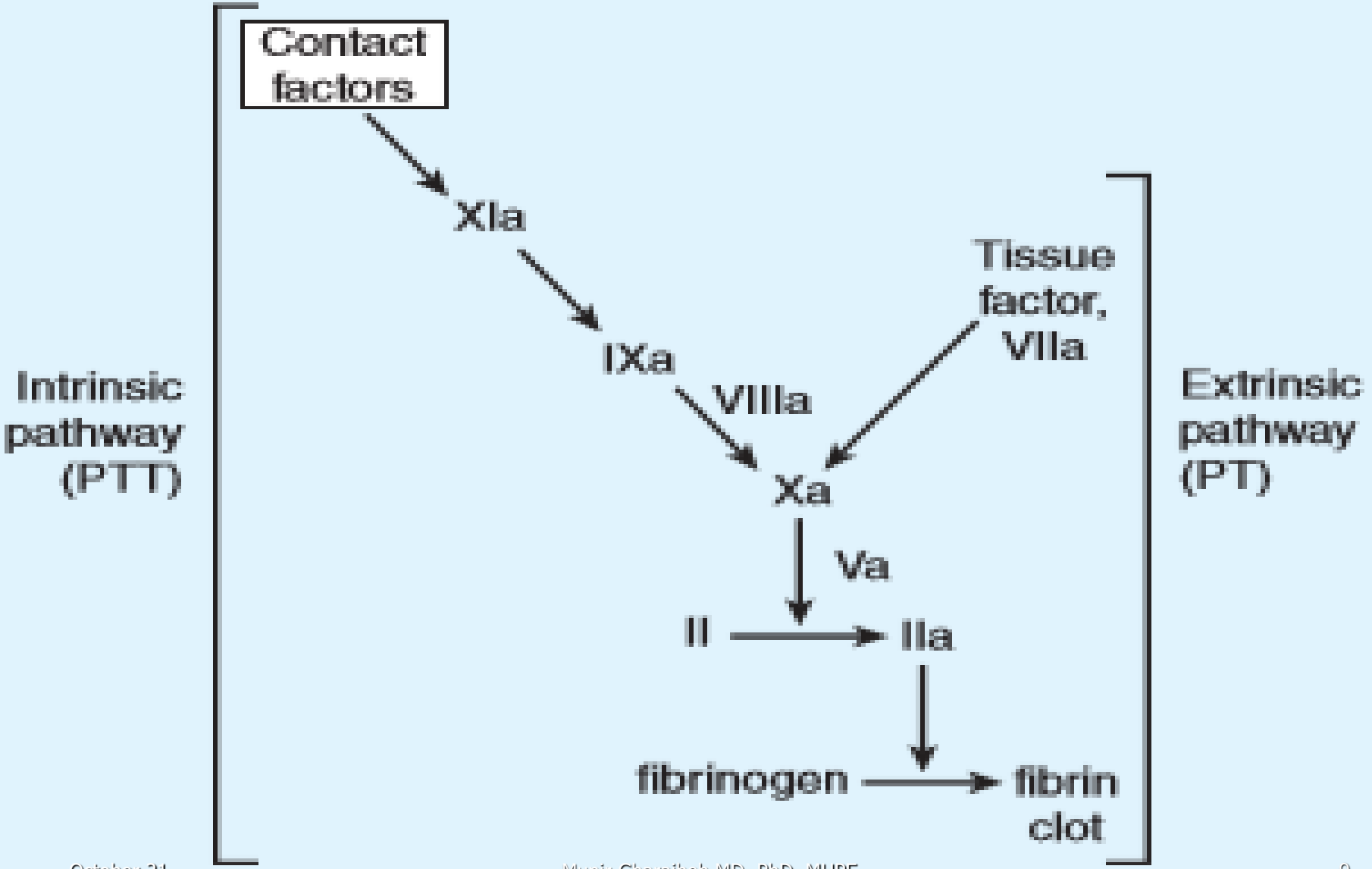
Inhibitor	*Target*
Antithrombin	Inhibits factor IIa, IXa and Xa.
Protein C	Inactivates factor Va and VIIIa
Protein S	Cofactor for activation of factor C
Tissue factor pathway inhibitor (TFPI)	Inhibits activity of factor VIIa.
Plasmin	Lyses fibrin into fibrin degradation products.

Risk of Thromboembolism in Hospital Patients

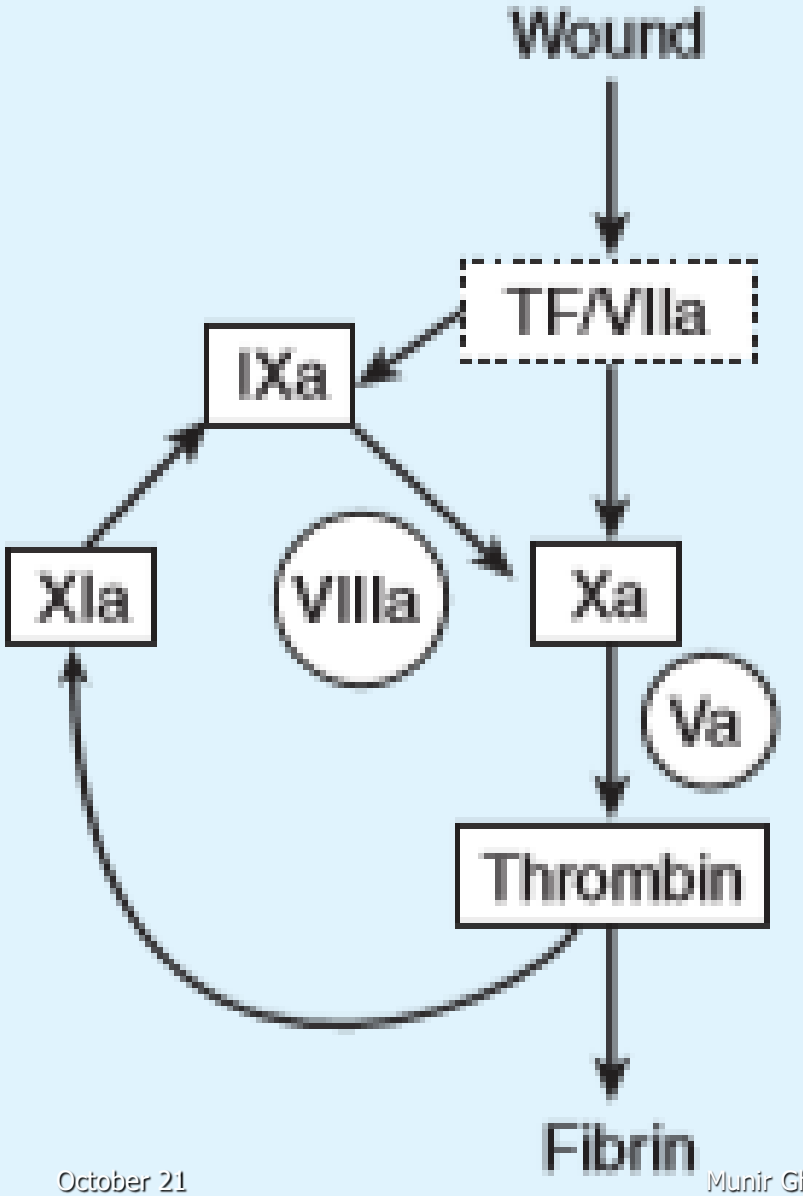
Risk	Procedure
Low	Minor surgery, no other risk factor Major surgery, age < 40 years, no other risk factors Minor trauma or illness
Moderate	Major surgery; age ≥ 40 years or other risk factor Heart failure, recent myocardial infarction, malignancy, inflammatory bowel disease. Major trauma or burns Minor 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.


Wall defect
C
vWF
EC
GP Ia
GP Ib
ADP
TXA2
5-HT
PGI2
GP IIb/IIIa
Intrinsic
Extrinsic
Xa
Platelets
Degranulation
GP IIb/IIIa
Activation
GP IIb/IIIa
Fibrin
Thrombin
Prothrombin
Fibrinogen

Clotting in the Lab



Clotting in Vivo



Natural Anticoagulant Systems

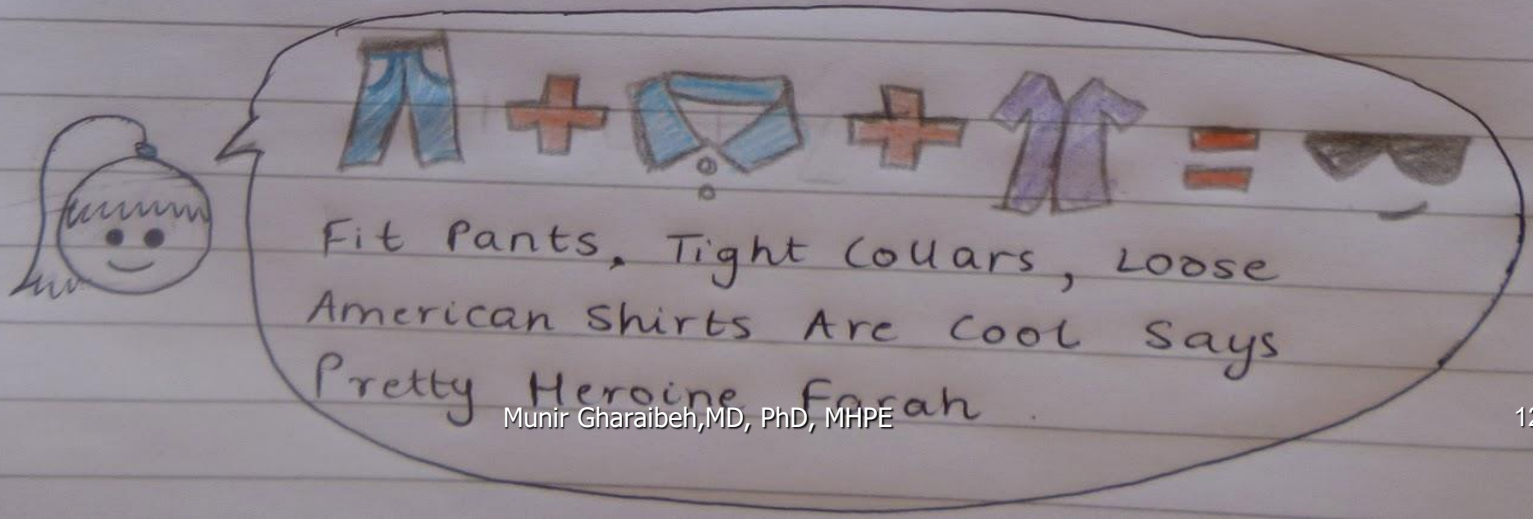
Antithrombin III/heparin

Protein C/Protein S

Tissue factor pathway inhibitor

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

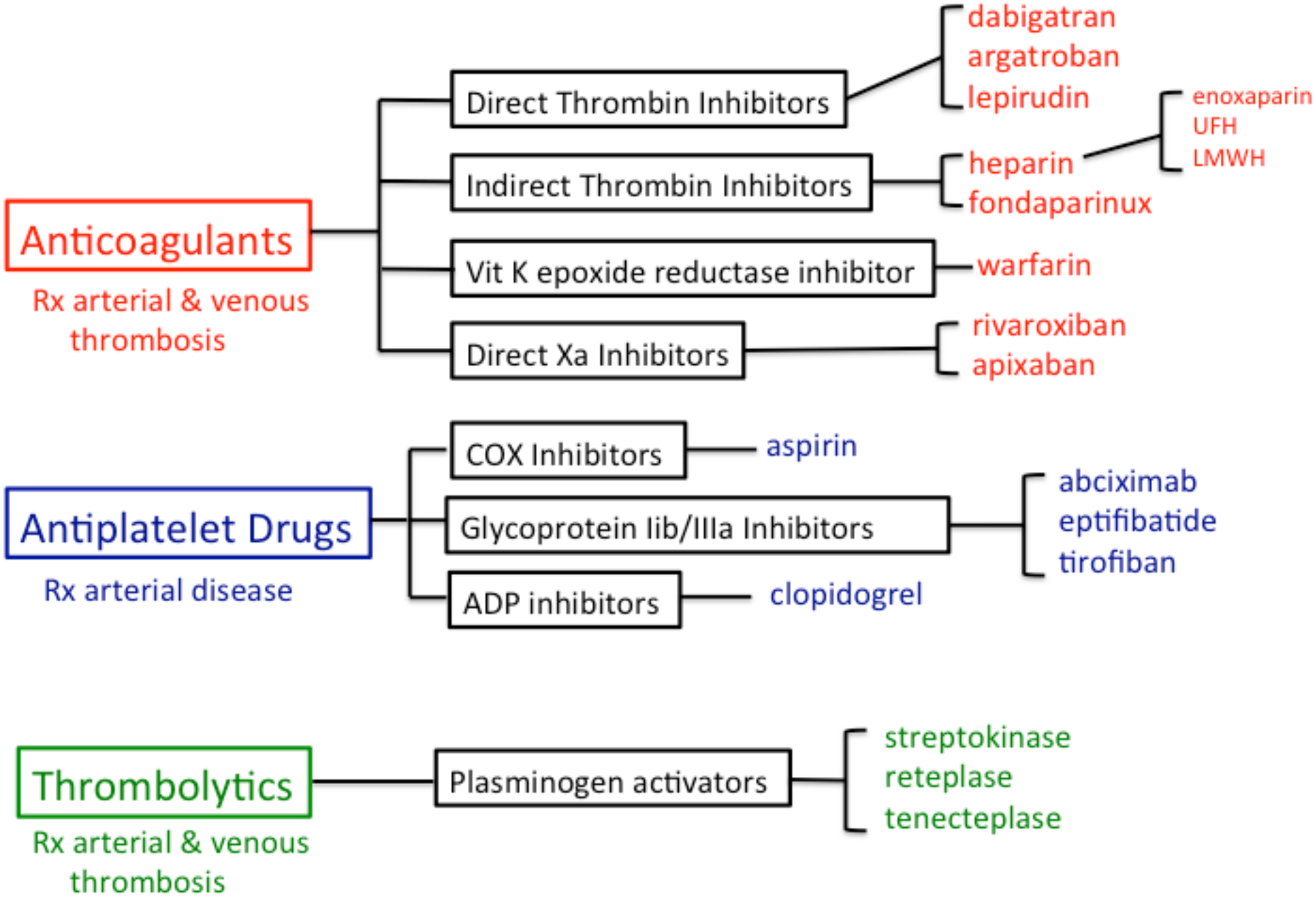
I	Fibrinogen	Freshers	Foolish
II	Prothrombin	Party	People
III	Tissue Thromboplastin	Tonights	Try
IV	Calcium ions	come	climbing
V	Labile factor	lets	long
VII	Stable factor	Sing	slopes
VIII	Antihemophilic factor	And	After
IX	Christmas factor	Call	Christmas
X	Stuart Prawer factor	Seniors	Some
XI	PTA	Please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



Drugs used in Thromboembolic Disease

- **Anticoagulants:**
  - Factor inhibitors: e.g. Heparin, Rivaroxaban.
  - Factor synthesis inhibitors: e. g. Oral anticoagulants.
- **Fbrinolytic Drugs:**
  - Streptokinase.
  - Urokinase.
  - ASPAC.
  - Tissue-type Plasminogen Activators (t-PA):
    Ateplase.
- **Antiplatelet Drugs:**
  - Aspirin.
  - Dipyridamole.
  - Sulphinpyrazone.

Drugs Used to Treat Clotting Disorders

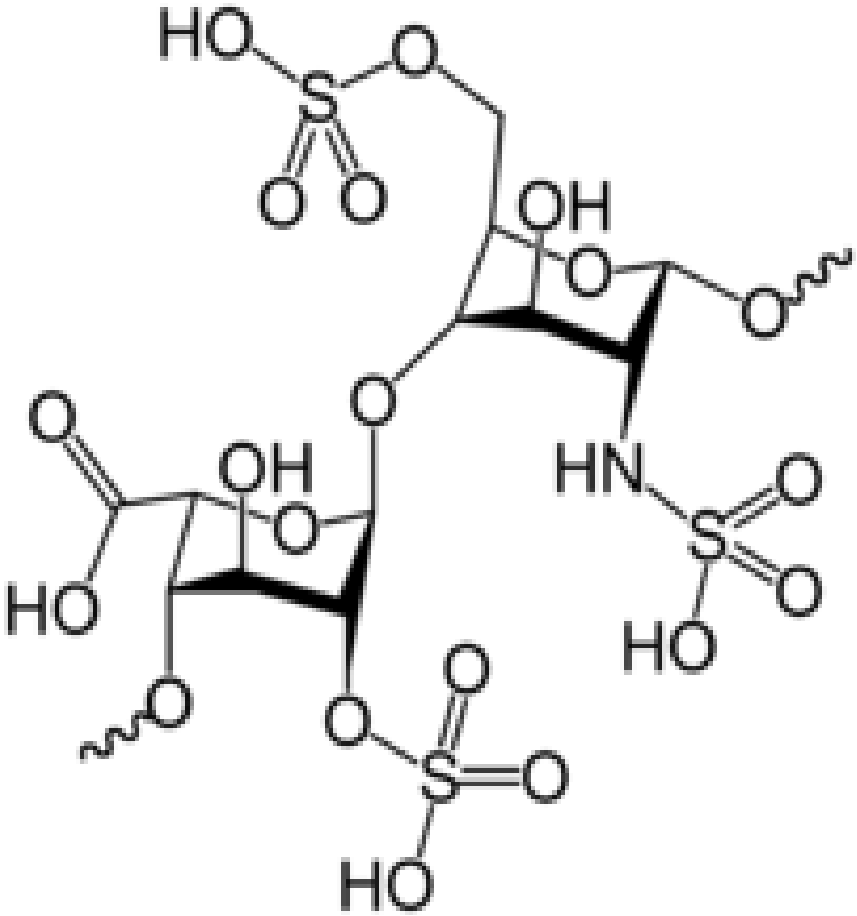


Indirect Thrombin Inhibitors

- **HEPARIN:**
  - **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 heart, liver, intestine, and lungs), in an inactive form, but has an obscure function.
- Released with anaphylaxis.
- Obtained from cow lung and pig intestinal mucosa.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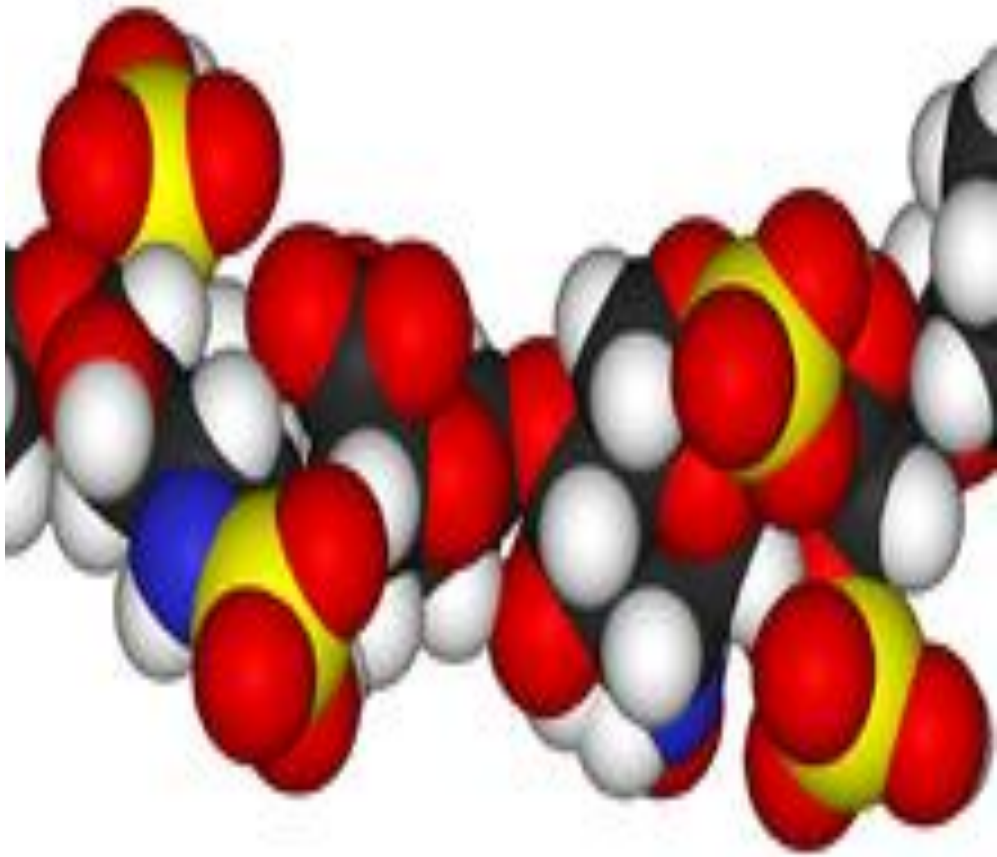


HEPARIN

- Molecular weight varies:
  - 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.
- Does not cross the placenta, and not excreted in breast milk.
- Eliminated by rapid metabolism by heparinase enzyme in the liver, renal excretion, and uptake by the RES .

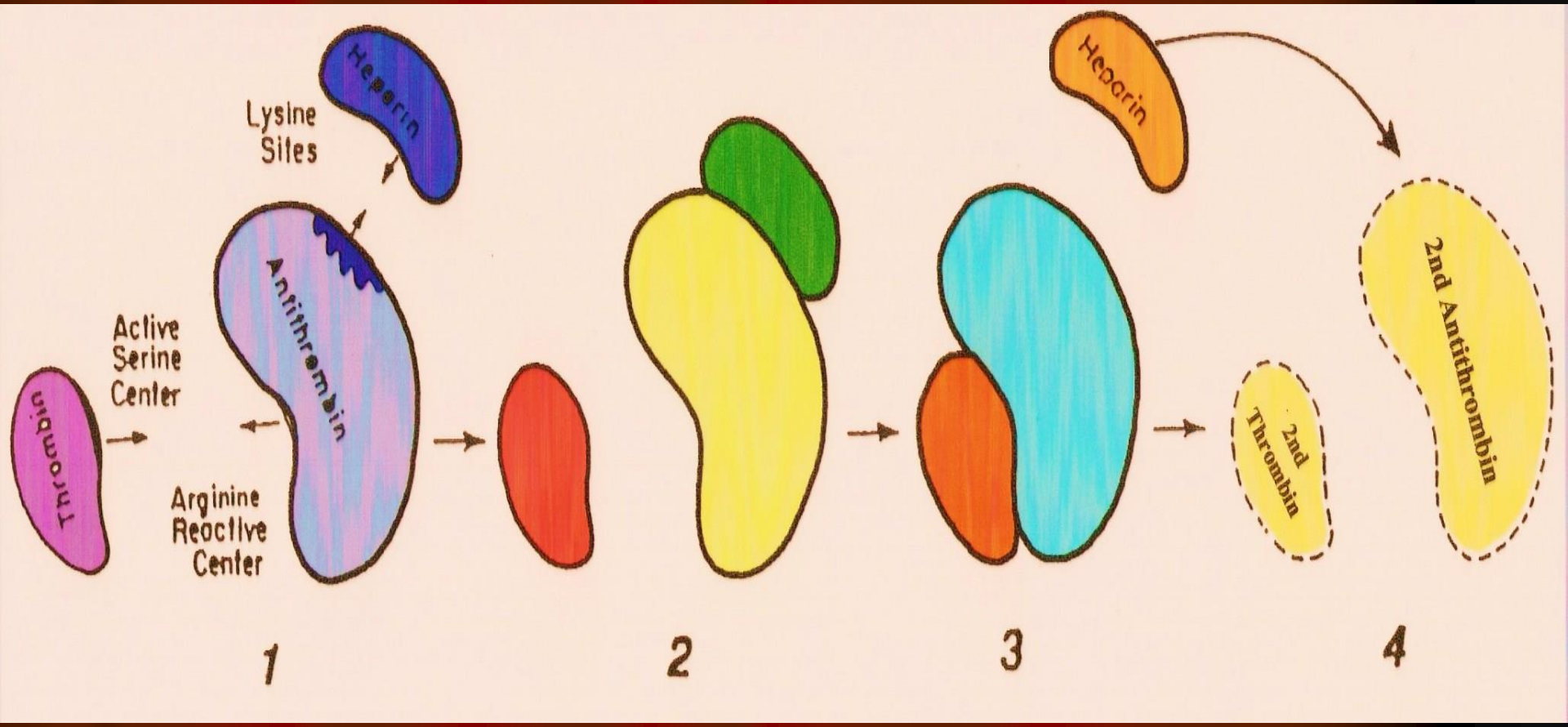
HEPARIN

- 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.

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.
- Heparin accelerates this complexing by 1000 folds.
- Heparin functions as a cofactor, it is not consumed.

HEPARIN


Heparin
Lysine Sites
Antithrombin
Active Serine Center
Thrombin
Arginine Reactive Center
1
2
Heparin
3
2nd Thrombin
2nd Antithrombin
4

HEPARIN

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

LMWHs

- 15 Polysaccharide units.
- LMWHs inhibit factor Xa, but have less effect on thrombin or endothelial cell-heparin receptors and plasma protein binding sites.
- Compared to UFH, LMWHs have:
  - Equal efficacy.
  - More predictable effects.
  - More bioavailability from s.c. site of injection.
  - Less frequent dosing requirements.
  - Treatment is not generally monitored (except in renal failure, pregnancy and obesity).

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.
- Allergic reactions: fever, 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).
- Hypersensitivity.
- Active bleeding.
- Severe hypertension.
- Hemophilia, purpura.
- Infective endocarditis, active TB.
- Ulcerative lesions of GIT.
- 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.
  - Not by intramuscular injection.

- Low dose prophylaxis:

  Subcutaneously 5000 units every 8-12 hrs.

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

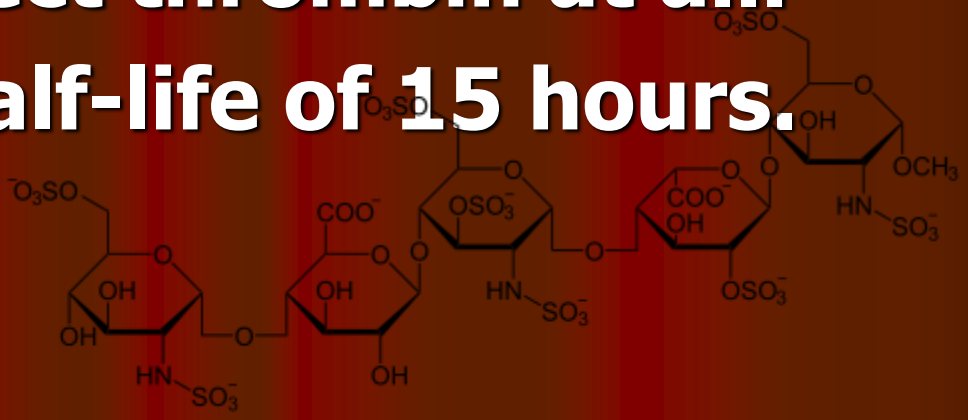
Administration of LMWHs

- 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.

- **Antidote:**
  - 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.



IV Direct Thrombin Inhibitors

- **Hirudine** (**from leeches, *Hirudo medicinalis*),**
- **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
  - 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.