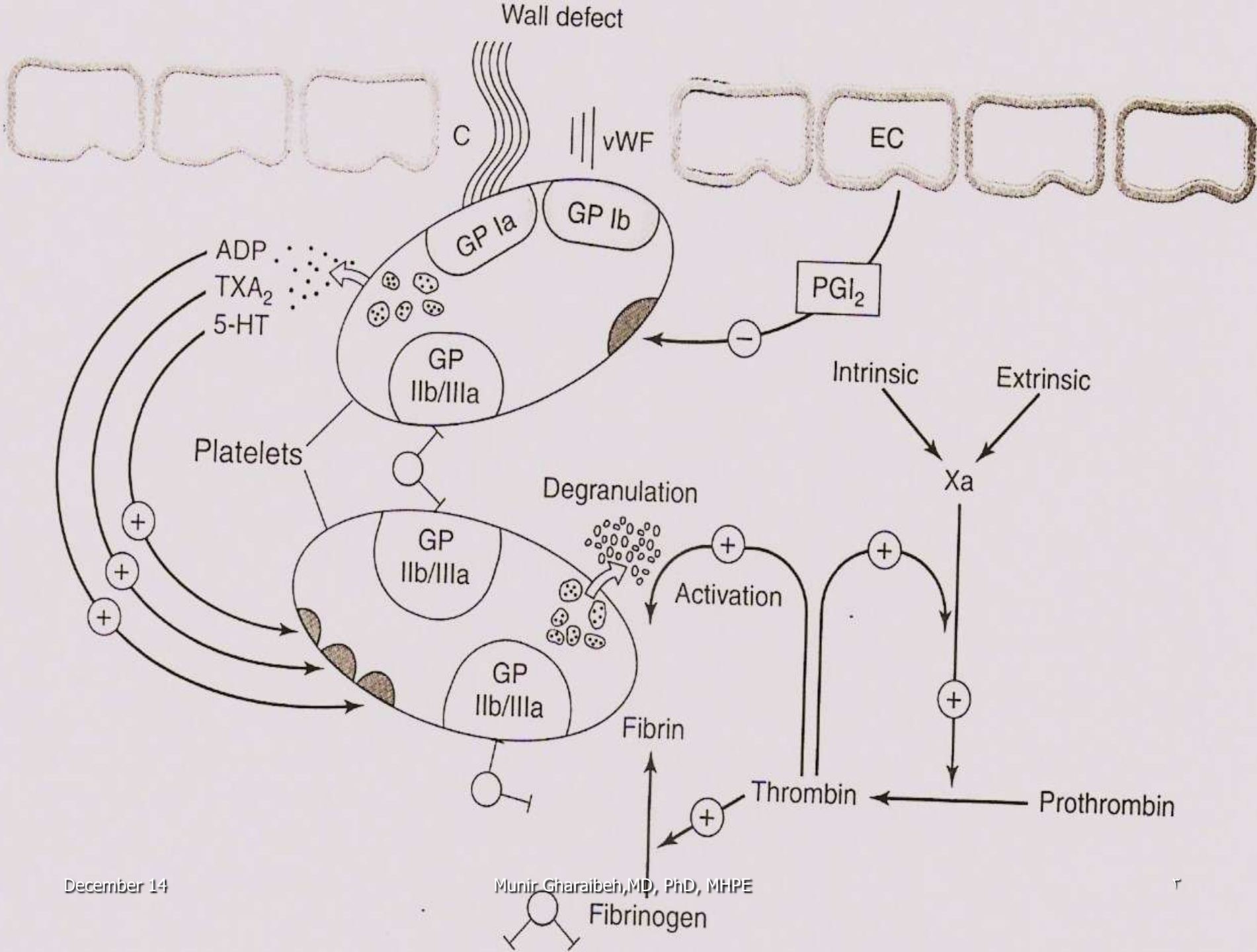
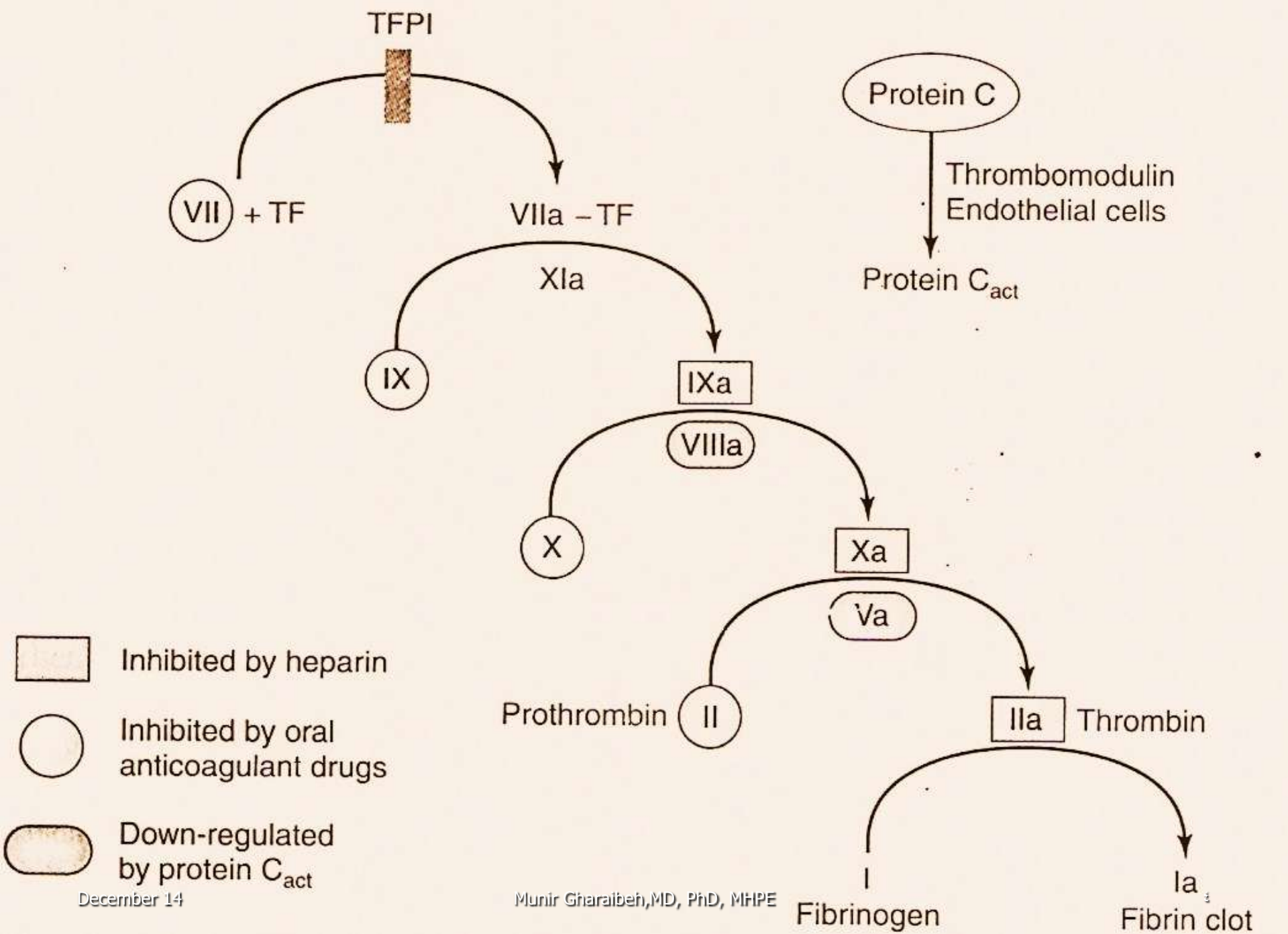
Drugs used in Thromboembolic Disease

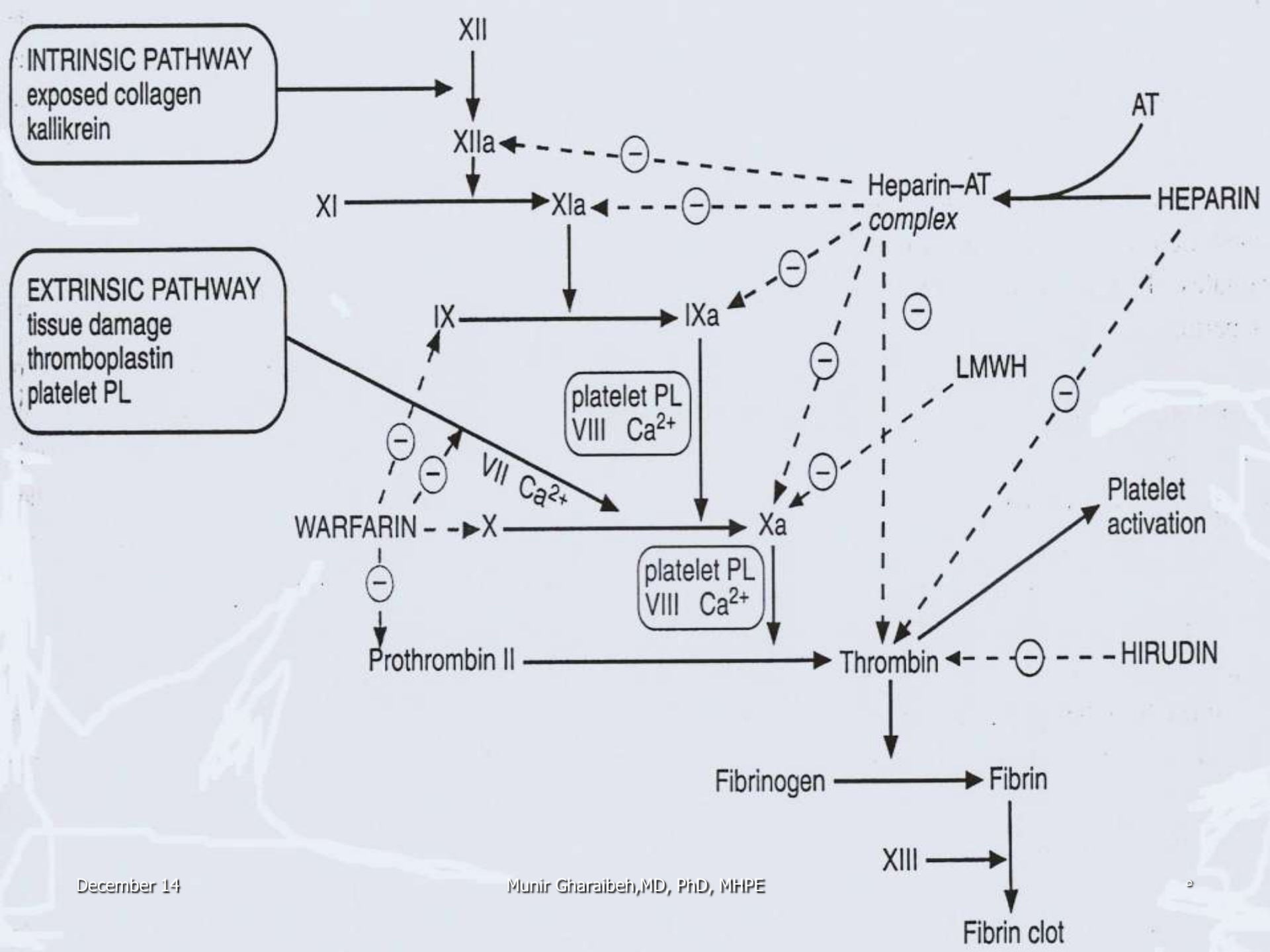
Munir Gharaibeh, MD, PhD, MHPE
Department of Pharmacology
Faculty of Medicine
October 2014

Drugs used in Thromboembolic Disease

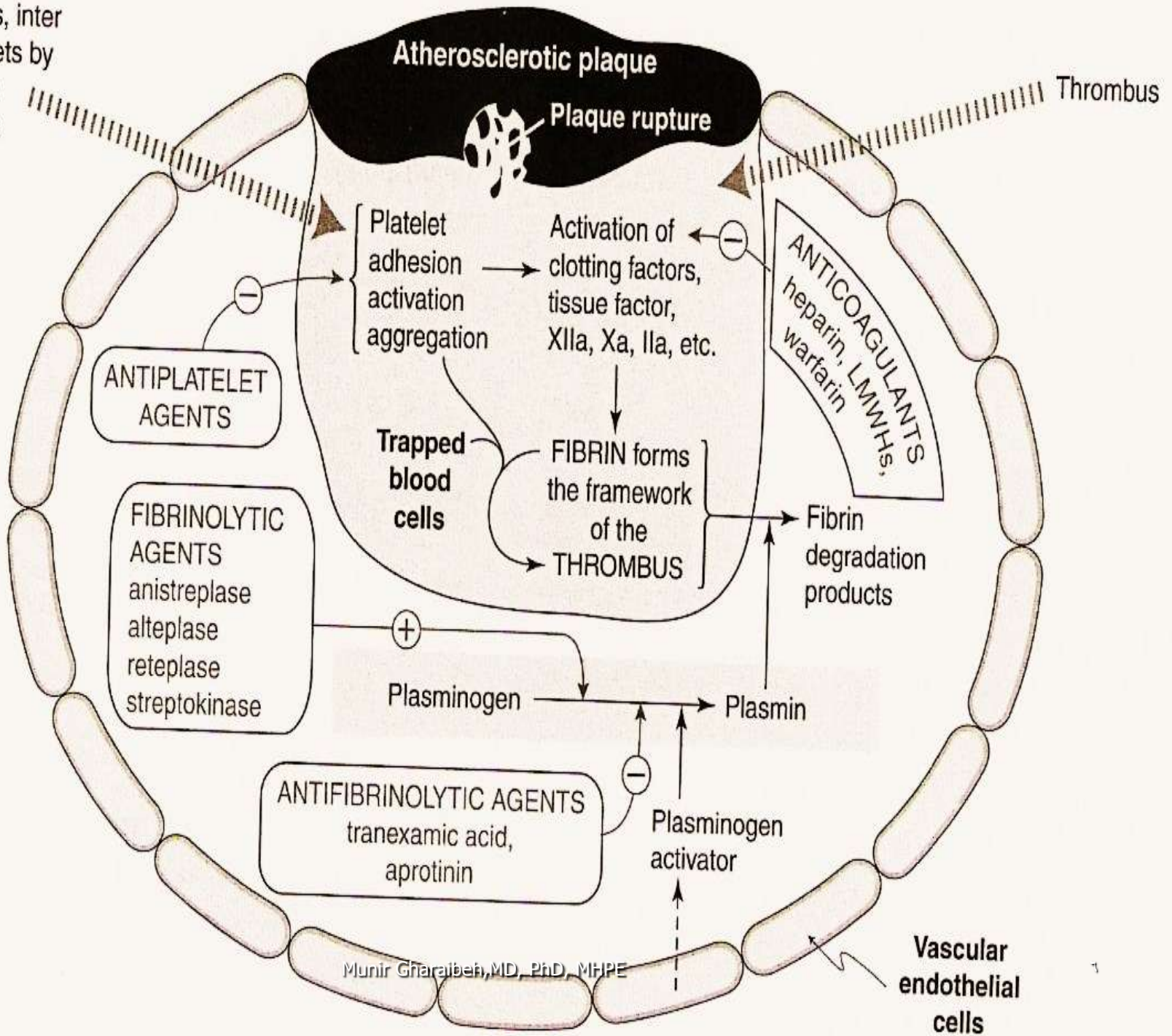
- **Anticoagulants:**
  - Heparin.
  - Oral anticoagulants.
- **Fbrinolytic Drugs:**
  - Streptokinase.
  - ASPAC
  - Rt-PA.
  - Urokinase.
  - Scu-PA.
- **Antiplatelet Drugs:**
  - Aspirin.
  - Dipyridamole.
  - Sulphinpyrazone.

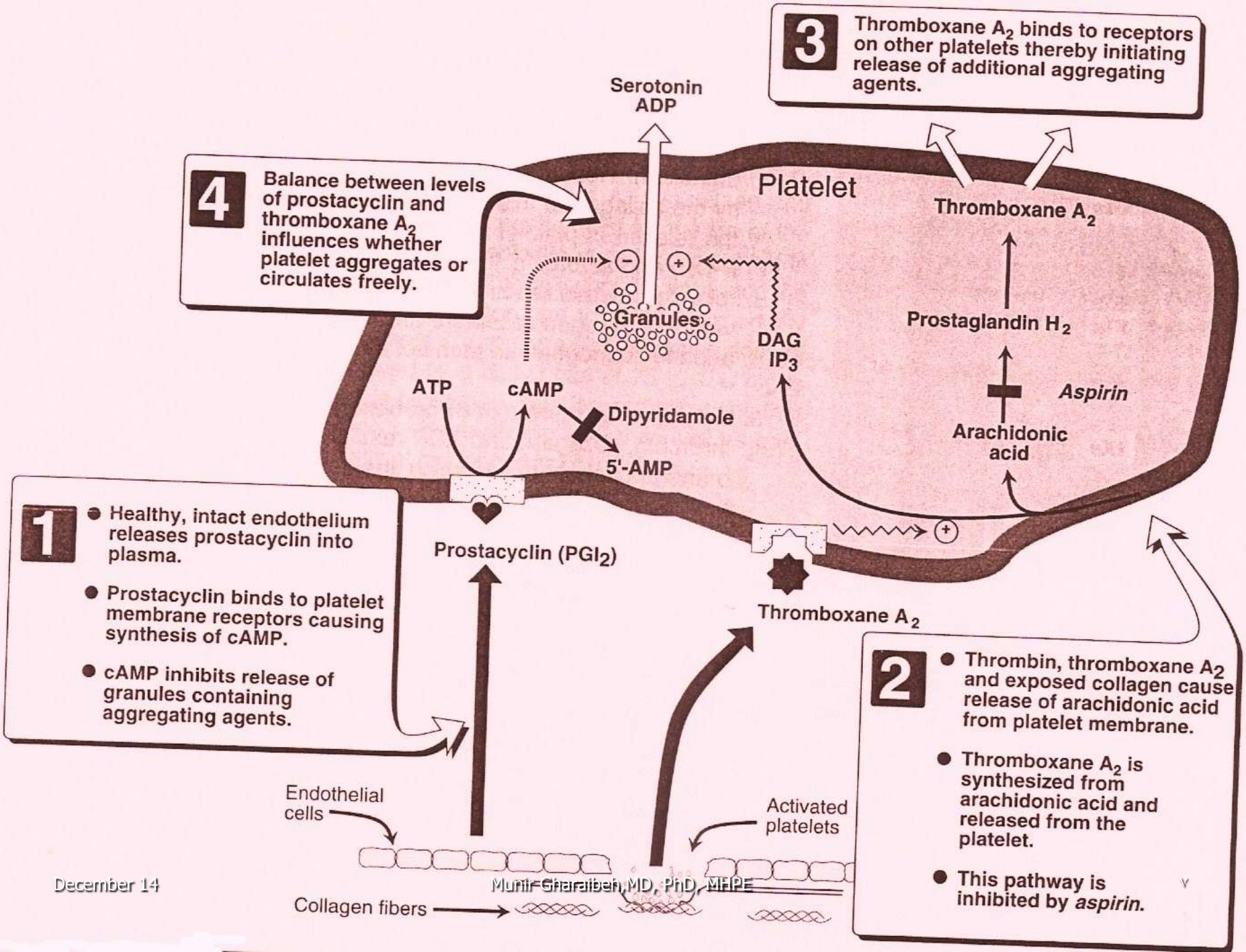

Wall defect
C
vWF
EC
GP Ia
GP Ib
ADP
TXA_2
5-HT
PGI_2
GP IIb/IIIa
Intrinsic
Extrinsic
Platelets
Xa
Degranulation
GP IIb/IIIa
Activation
GP IIb/IIIa
Fibrin
Thrombin
Prothrombin
Fibrinogen


TFPI
VII + TF
VIIa – TF
Protein C
Thrombomodulin
Endothelial cells
Protein C_{act}
XIa
IX
IXa
VIIIa
X
Xa
Va
Prothrombin
II
IIa
Thrombin
I
Fibrinogen
Ia
Fibrin clot
Inhibited by heparin
Inhibited by oral anticoagulant drugs
Down-regulated by protein C_{act}


INTRINSIC PATHWAY
exposed collagen
kallikrein
XII
XIIa
XI
XIa
AT
Heparin–AT
complex
HEPARIN
EXTRINSIC PATHWAY
tissue damage
thromboplastin
platelet PL
IX
IXa
LMWH
platelet PL
VIII Ca2+
VII Ca2+
WARFARIN
X
Xa
platelet PL
VIII Ca2+
Platelet
activation
Prothrombin II
Thrombin
HIRUDIN
Fibrinogen
Fibrin
XIII
Fibrin clot

Aggregation involves, inter alia, linking of platelets by fibrinogen binding to platelet GPIIb/GPIIIa receptors (GP, glycoprotein)




3
Thromboxane A_2 binds to receptors on other platelets thereby initiating release of additional aggregating agents.
Serotonin
ADP
4
Balance between levels of prostacyclin and thromboxane A_2 influences whether platelet aggregates or circulates freely.
Platelet
Thromboxane A_2
Granules
DAG
IP_3
Prostaglandin H_2
ATP
cAMP
Dipyridamole
5'-AMP
Aspirin
Arachidonic acid
1
Healthy, intact endothelium releases prostacyclin into plasma.
Prostacyclin binds to platelet membrane receptors causing synthesis of cAMP.
cAMP inhibits release of granules containing aggregating agents.
Prostacyclin (PGI_2)
Thromboxane A_2
2
Thrombin, thromboxane A_2 and exposed collagen cause release of arachidonic acid from platelet membrane.
Thromboxane A_2 is synthesized from arachidonic acid and released from the platelet.
This pathway is inhibited by *aspirin*.
Endothelial cells
Activated platelets
Collagen fibers

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, aminocaproic 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

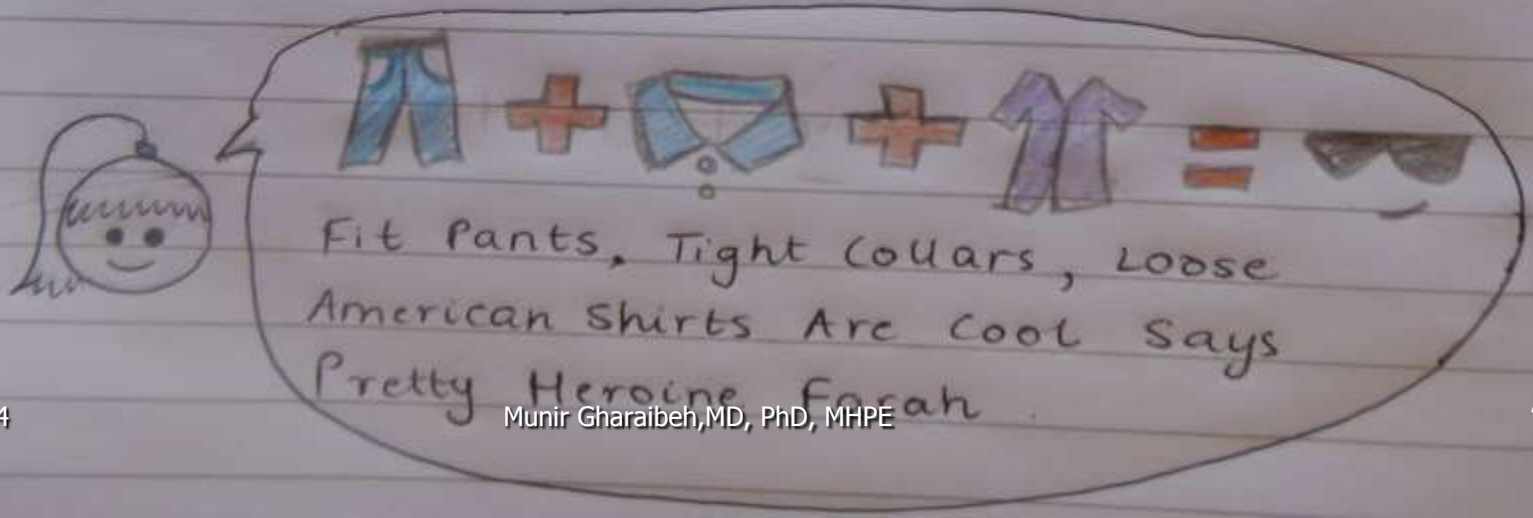
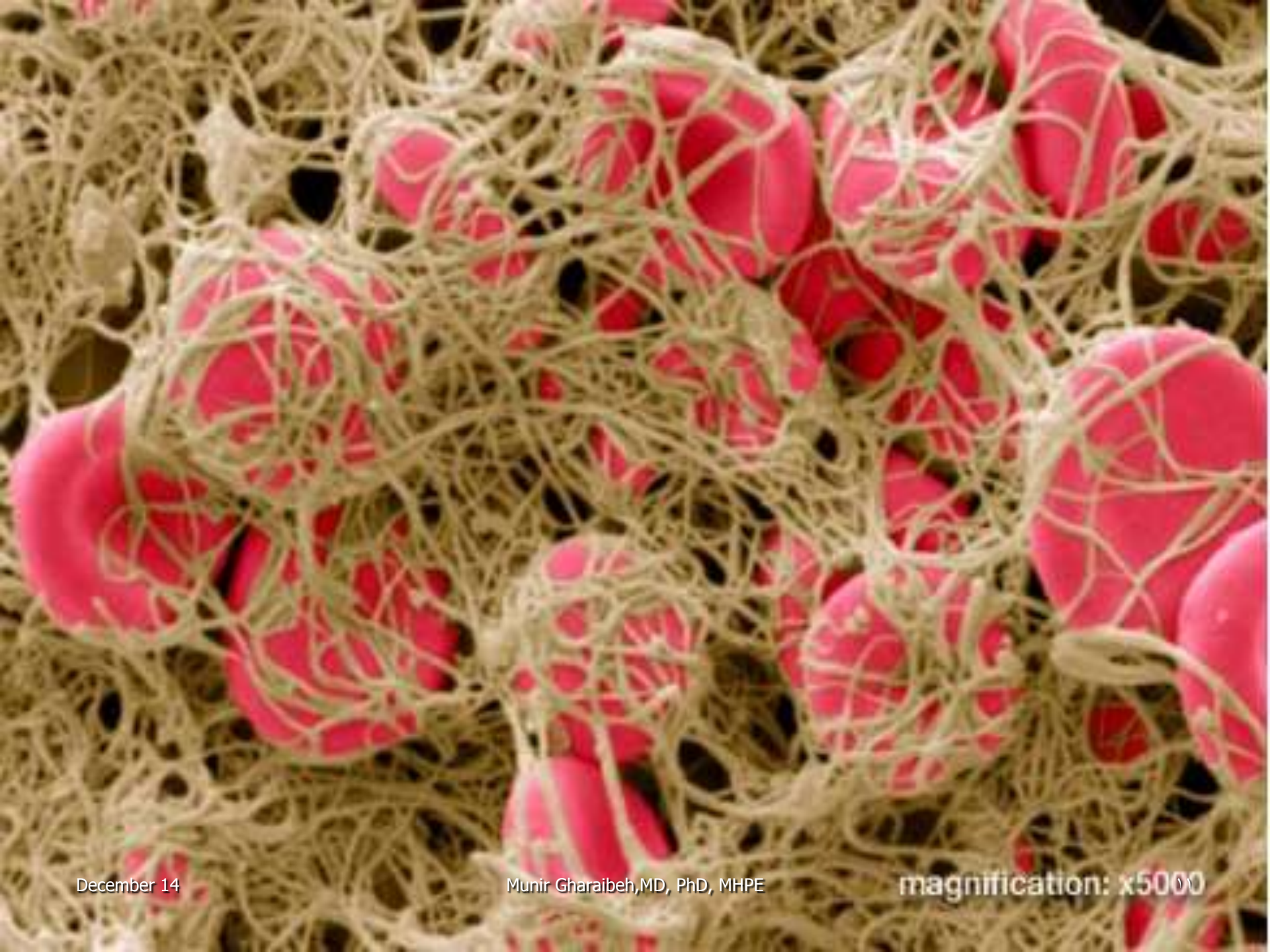


Table 28-1. Blood Coagulation Factors

Factor*	Synonyms	Synthesis	In vivo half-life
I	Fibrinogen	Liver	4–5 days
II	Prothrombin	Liver; K-dependent	3–5 days
III	Thromboplastin, tissue factor	—	—
IV	Ca^{2+}	—	—
V	Accelerator globulin, labile factor	Liver	12–36 hr
VII	Serum prothrombin conversion accelerator (SPCA), proconvertin	Liver; K-dependent	4–6 hr
VIII:C	Antihemophilic globulin (AHG), antihemophilic factor (AHF)	Liver; endothelium	10–18 hr
IX	Plasma thromboplastin component (PTC), Christmas factor	Liver; K-dependent	15–30 hr
X	Stuart factor, Stuart-Prower factor	Liver; K-dependent	20–80 hr
XI	Plasma thromboplastin antecedent (PTA)	?	60–70 hr
XII	Hageman factor	Liver?	60–70 hr
XIII	Fibrin-stabilizing factor	?	3–4 days
Protein C	Autoprothrombin II-A	Liver; K-dependent	—

*Roman numerals are international designations. There is no factor VI.


magnification: x5000

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.

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.

Non Thrombogenic Mechanisms in Blood Vessels

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

Inhibitors of Clotting Mechanisms

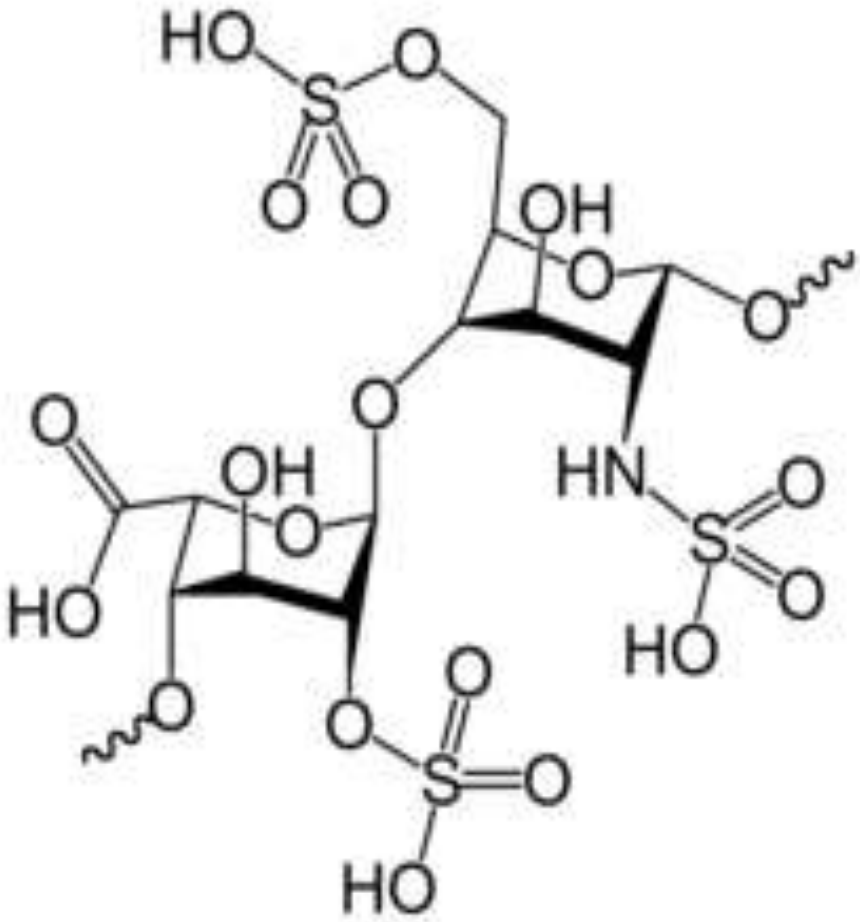
Inhibitor	*Target*
Antithrombin	Inhibits factor IIa, IXa and Xa.
Protein C	Inactivates factor Va and VIIIa
Protein S	Cofactor for activation of factor C
Tissue factor pathway inhibitor (TFPI)	Inhibits activity of factor VIIa.
Plasmin	Lyses fibrin into fibrin degradation products.

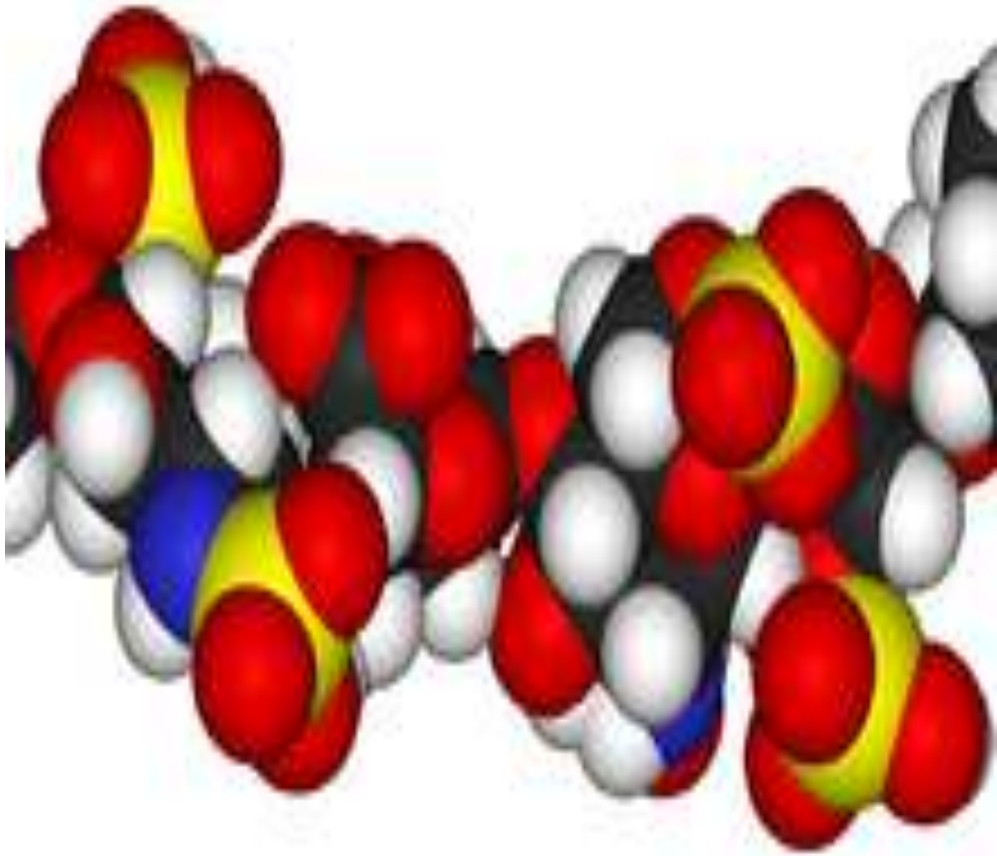
Indirect Thrombin Inhibitors

- **HEPARIN:**
  - Unfractionated heparin (UFH).
  - Low Molecular Weight Heparins (LMWHs):
    - Enoxaparin.
    - Dalteparin.
    - Tinzaparin(Innohep).
    - Danaparoid.
- **FONDAPARINUX**

HEPARIN(1922)

- Heterogenous mixture of sulfated mucopolysacharides.
- Composed of sulfated glucosamine and D-glucoronic acid connected by sulfaminic bridges.
- It is a normal physiological anticoagulant.
- Normally found in mast cells in an inactive form but has an obscure function. Released with anaphylaxis.
- Found in heart, liver, intestine and lungs.
- Obtained from cow lung and pig intestinal mucosa.


HO
S
O
O
O
OH
O
O
O
O
OH
O
HO
HN
S
O
O
HO
O
O
S
O
O
HO



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.
- 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 .

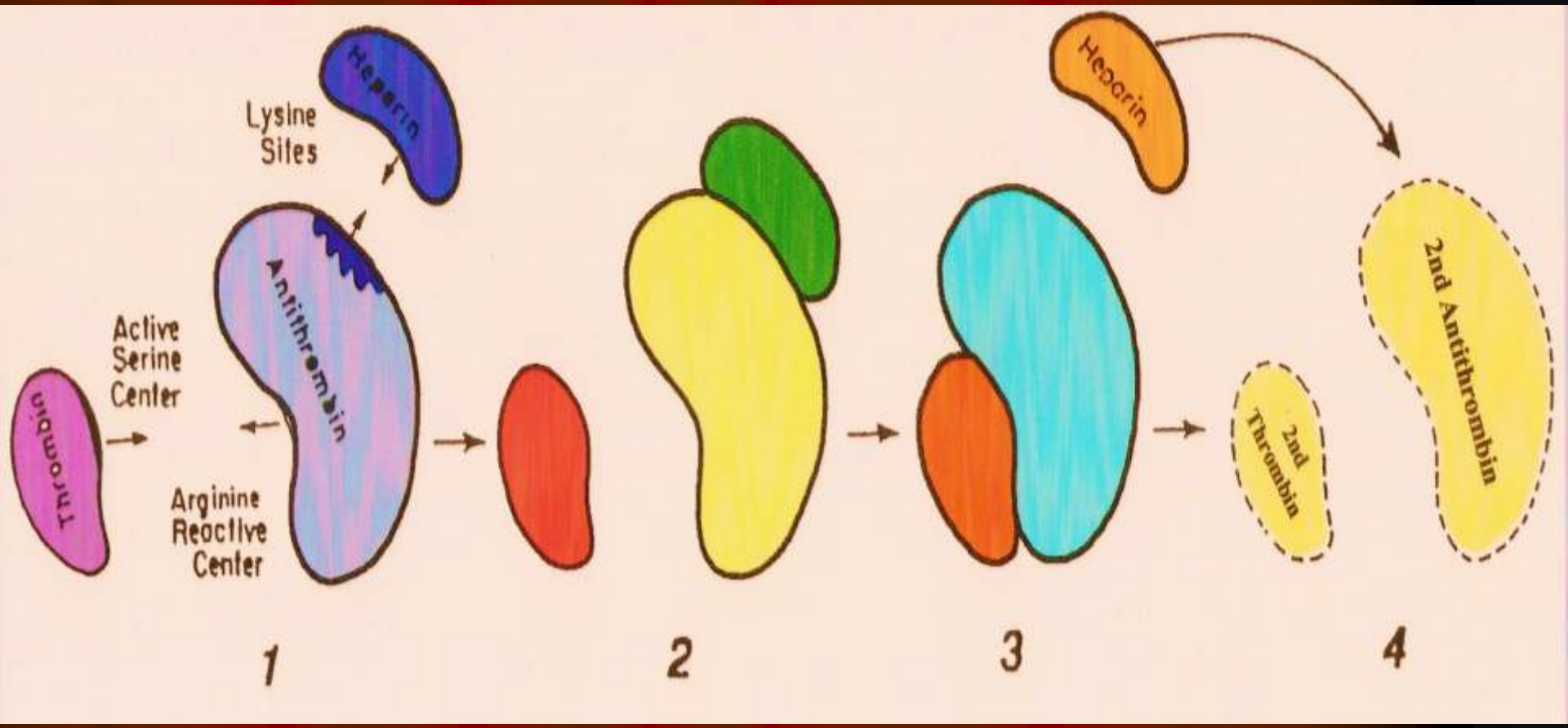
HEPARIN

- 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 Xa, platelets and endothelium.
- UFH inhibits platelets aggregation.
- Activates Lipoprotein Lipase which reduces platelets adhesiveness.

HEPARIN

- Antithrombin 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 proteases.
- Heparin accelerates this comlexing 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 and inhibit coagulation by inhibiting all three factors, especially thrombin and factor Xa.

LMWHs

- 15 Polysaccharide units.
- LMWHs inhibit factor Xa but have less effect on thrombin or endothelial cell-heparin receptors and plasma protein binding sites.
- LMWHs have:
  - Equal efficacy.
  - More predictable effects.
  - More bioavailability from s.c site of injection.
  - Less frequent dosing requirements.
  - Doses specified in milligrams rather than in units.
  - 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.**

HEPARIN

- **TOXICITY:**
- Bleeding.
- Allergic reactions: fever, anaphylaxis.
- Loss of hair, alopecia.
- 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.

HEPARIN

- **Contraindications:**
  - 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.

HEPARIN

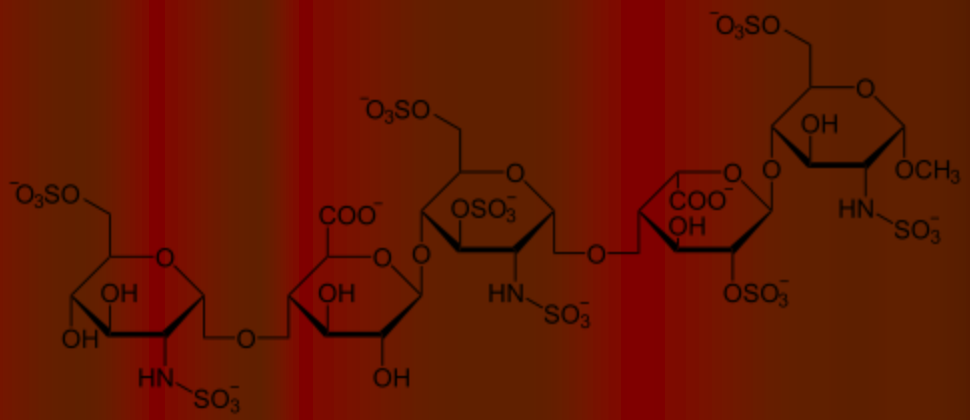
- **Administration of UFH:**
- **Initial bolus injection:80-100units/kg.**
- **Continuous infusion through a pump:**
  - **15-22 unit/kg/hr.**
  - **This usually maintains aPTT at 2-2.5 times control.**
  - **Not by intramuscular injection.**
  - **Low dose prophylaxis:**
    - **Subcutaneously 5000 units every 8-12 hrs.**
- **Antidote:**
  - **Protamine sulfate: is a highly basic low mol.wt compound.**

HEPARIN

- **Administration of LMWHs:**
  - Almost completely absorbed after s.c. injection.
  - Usually 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.
- Binds antithrombin with high specific activity, resulting in inactivation of factor Xa.
- Has a long half-life of 15 hours.



Direct Thrombin Inhibitors

- **Hirudine** (from leeches, *Hirudo medicinalis)*
- **Lepirudin**, *recombinant form.*
- **Bivalirudin.**
  - Are bivalent compounds, i.e. they bind at both the catalytic site and the substrate recognition site of thrombin.
  - Eliminated by the kidneys.
  - Can cause allergy and anaphylaxis.

Direct Thrombin Inhibitors

- Argatroban.
- Ximelagatran.
- Melagatran.
  - Are small molecules that bind only at the active site of thrombin.
  - Eliminated by the liver.