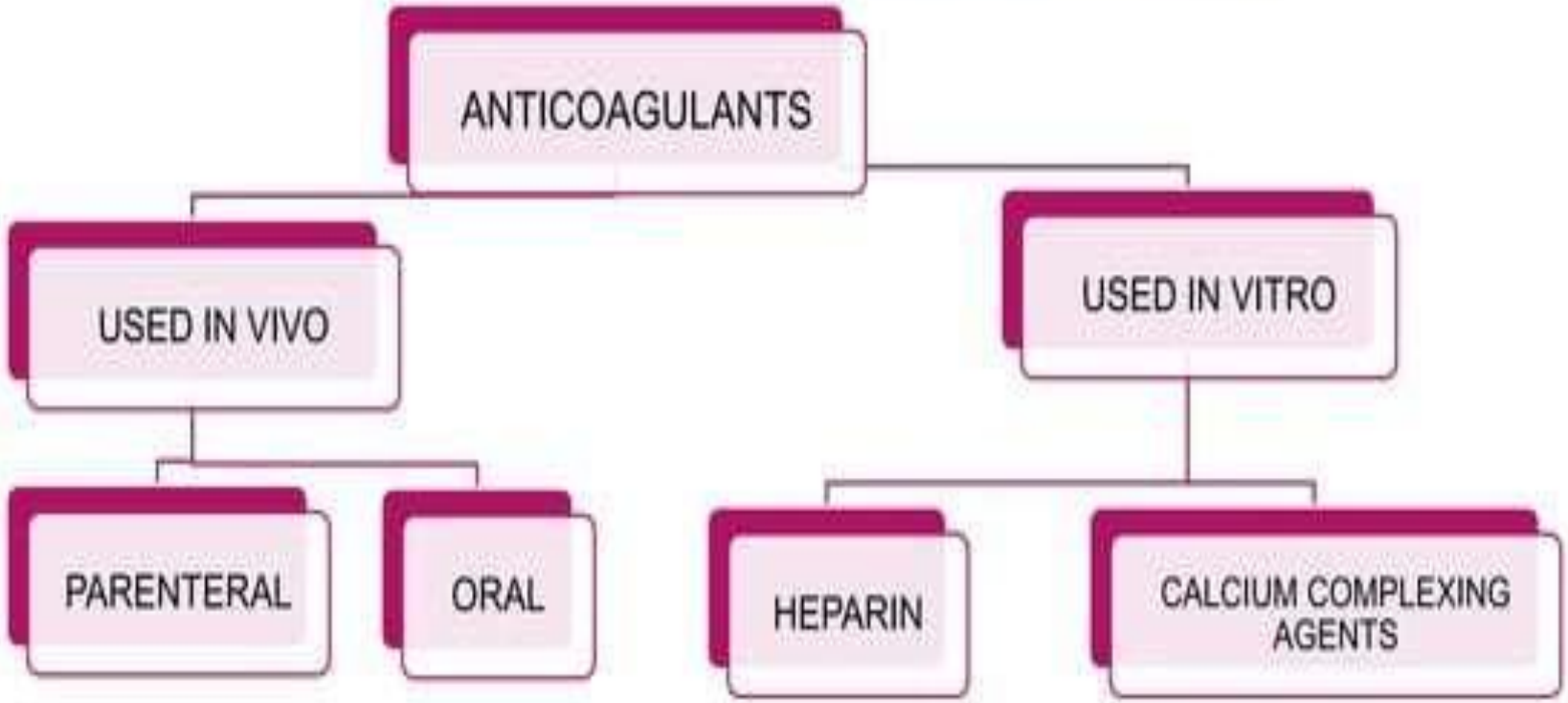
ANTICOAGULANTS

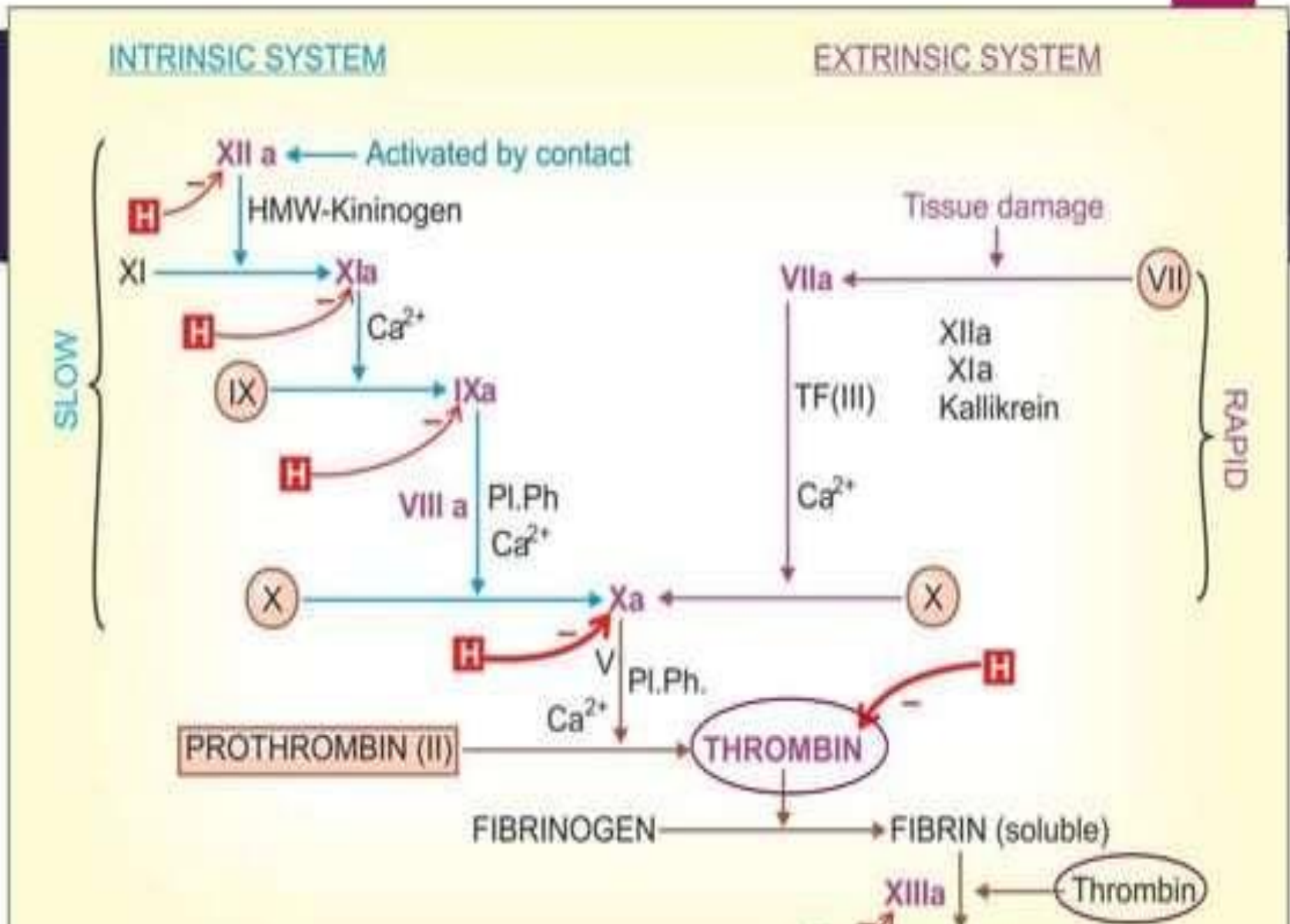
PRESENTER – DR.SOWMYA.S.M

ANTICOAGULANTS

- Drugs that help prevent the clotting (coagulation) of blood
- Coagulation will occur instantaneously once a blood vessel has been severed
- Blood begins to solidify to prevent excessive blood loss and to prevent invasive substances from entering the bloodstream.

CLASSIFICATION




INTRINSIC SYSTEM
EXTRINSIC SYSTEM
XII a
Activated by contact
H
HMW-Kininogen
XI
XIa
Ca2+
IX
IXa
VIII a
Pl.Ph
Ca2+
SLOW
Tissue damage
VIIa
VII
XIIa
XIa
Kallikrein
TF(III)
Ca2+
RAPID
X
Xa
X
V
Pl.Ph.
Ca2+
PROTHROMBIN (II)
THROMBIN
FIBRINOGEN
FIBRIN (soluble)
XIIIa
Thrombin

1) **USED IN VIVO:**

A) PARENTERAL ANTICOAGULANTS:

- INDIRECT THROMBIN INHIBITORS:	**- DIRECT THROMBIN INHIBITORS:**
Heparin	Lepirudin
Low molecular weight heparins	Bivalirudin
Fondaparinux	Argatroban
Danaparoid	

B) ORAL ANTICOAGULANTS:

- **COUMARIN DERIVATIVES:**
  - Bishydroxcoumarin (dicumarol)
  - Warfarin sodium
  - Acenocoumarol
  - Ethylbiscoumacetate
- **-INDANDIONE DERIVATIVE:**
  - Phenindione
- **-DIRECT FACTOR Xa INHIBITORS:**
  - Rivaroxaban
- **-ORAL DIRECT THROMBIN INHIBITOR:**
  - Dabigatran etexilate

2) USED IN VITRO:

A) HEPARIN:

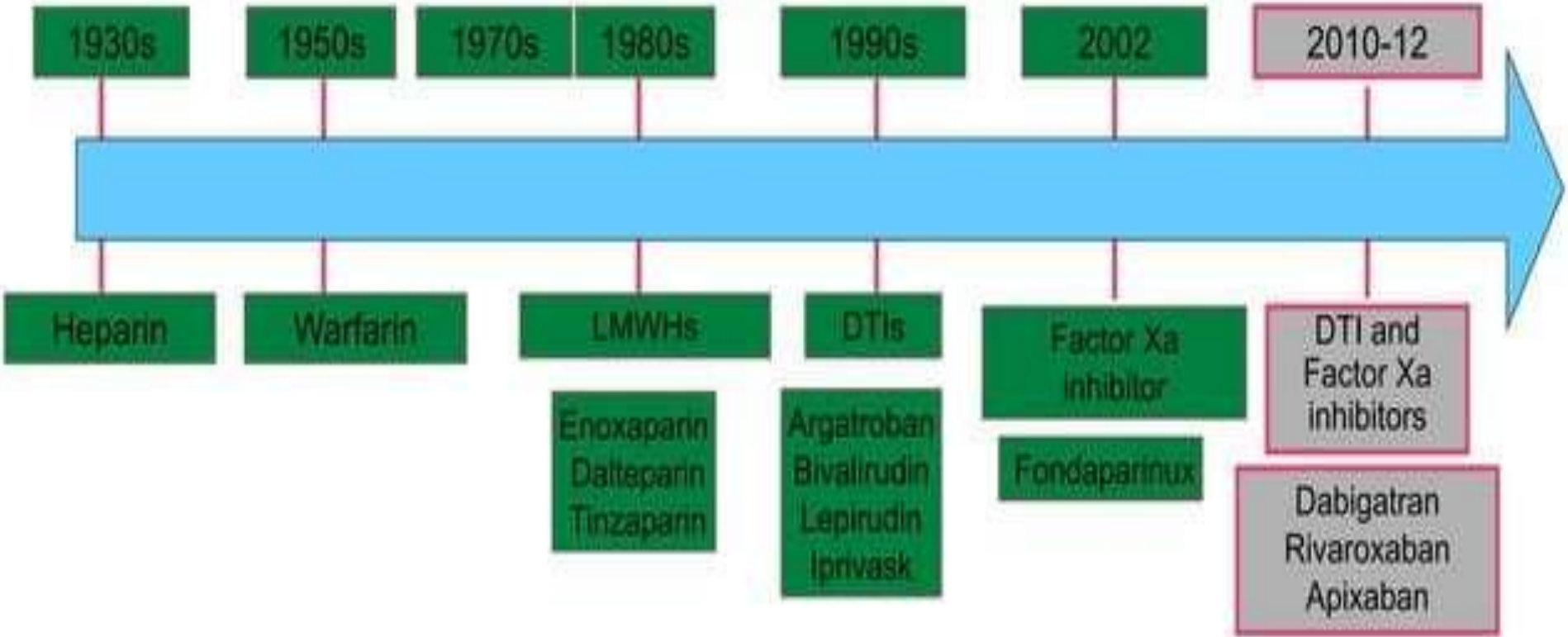
B) CALCIUM COMPLEXING AGENTS:

Sodium citrate

Sodium oxalate

Sodium edetate

Developmental History –
Current FDA Approved Anticoagulants



HEPARIN

- Heparin is a non-uniform mixture of straight chain mucopolysaccharides with MW 10,000 to 20,000.
- It contains polymers of two sulfated disaccharide units:

  D-glucosamine-L-iduronic acid

  D-glucosamine-D-glucuronic acid
- It is present in all tissues containing mast cells; richest sources are lung, liver and intestinal mucosa.

ANTICOAGULANT ACTION OF HEPARIN

HEPARIN

↓

Activates plasma AT III

↓

Heparin-AT III complex

↓

Binds to clotting factors of intrinsic and common pathways

(Xa, IIa, IXa, XIa, XIIa and XIIIa) and inactivates them

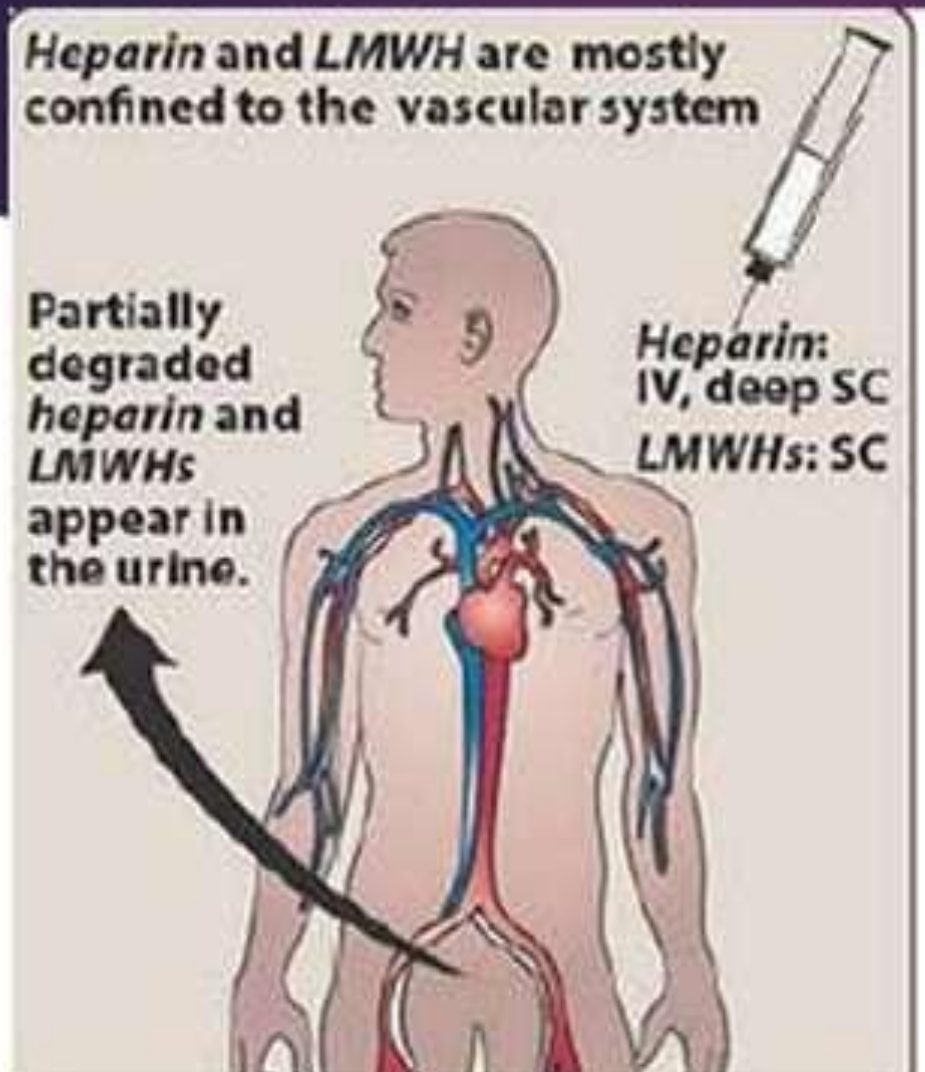
OTHER ACTIONS OF HEPARIN

- Heparin in higher doses inhibits platelet aggregation and prolongs bleeding time.
- Heparin in lower doses helps in lipaemia clearing.

PHARMACOKINETICS

- Heparin is not absorbed orally.
- If Injected i.v. - acts instantaneously.
- After s.c. injection anticoagulant effect develops after ~60 min.
- Bioavailability of s.c. heparin is inconsistent.
- Heparin does not cross blood-brain barrier or placenta (it is the anticoagulant of choice during pregnancy).
- It is metabolized in liver by heparinase.
- Fragments are excreted in urine.

- Heparin should not be mixed with penicillin, tetracyclines, hydrocortisone or NA in the same syringe or infusion bottle.
- Heparinized blood is not suitable for blood counts (alters the shape of RBCs and WBCs), fragility testing and complement fixation tests.


Heparin and *LMWH* are mostly confined to the vascular system
Partially degraded *heparin* and *LMWHs* appear in the urine.
Heparin: IV, deep SC
LMWHs: SC

ADVERSE EFFECTS

- Bleeding due to overdose - most serious complication.
- Thrombocytopenia - mild and transient.
- Transient and reversible alopecia is infrequent. Serum transaminase levels may rise.
- Osteoporosis - long-term use of relatively high doses.
- Hypersensitivity reactions – rare.

CONTRAINDICATIONS

- Bleeding disorders, history of heparin induced thrombocytopenia.
- Severe hypertension, threatened abortion, piles, g.i. ulcers.
- Subacute bacterial endocarditis, large malignancies, tuberculosis.
- Ocular and neurosurgery, lumbar puncture.
- Chronic alcoholics, cirrhosis, renal failure.

Low molecular weight (LMW) heparins

- Heparin has been fractionated into LMW forms (MW 3000–7000) by different techniques.
- LMWHs are defined as heparin salts having an average molecular weight of less than 8000 Da.
- These are obtained by various methods of fractionation or depolymerisation of polymeric heparin.

MECHANISM OF ACTION

- Selectively inhibit factor Xa with little effect on IIa.
- Act only by inducing conformational change in AT III
- Hence LMW heparins have smaller effect on aPTT and whole blood clotting time than unfractionated heparin (UFH)
- Also, they have lesser antiplatelet action—less interference with haemostasis.
- Lower incidence of haemorrhagic complications compared to UFH
- Elimination - primarily by renal excretion.

ADVANTAGES OF LMW HEPARIN

- Better subcutaneous bioavailability (70–90%) compared to UFH (20–30%)
- Longer and more consistent monoexponential t½(4–6 hours)
- Since aPTT/clotting times are not prolonged, laboratory monitoring is not needed.
- Risk of osteoporosis after long term use is much less.

INDICATIONS

- Prophylaxis of deep vein thrombosis and pulmonary embolism in high-risk patients undergoing surgery.
- Treatment of established deep vein thrombosis.
- Unstable angina and MI: they have largely replaced continuous infusion of UFH.
- To maintain patency of cannulae and shunts in dialysis patients.

A number of LMW heparins have been marketed-

- Enoxaparin
- Reviparin
- Nadroparin
- Dalteparin
- Parnaparin
- Ardeparin

FONDAPARINUX

- The pentasaccharide with specific sequence that binds to AT III with high affinity to selectively inactivate factor Xa without binding thrombin (factor IIa), has been recently produced synthetically.
- Bioavailability - If injected s.c. is 100%
- Excreted unchanged by the kidney.

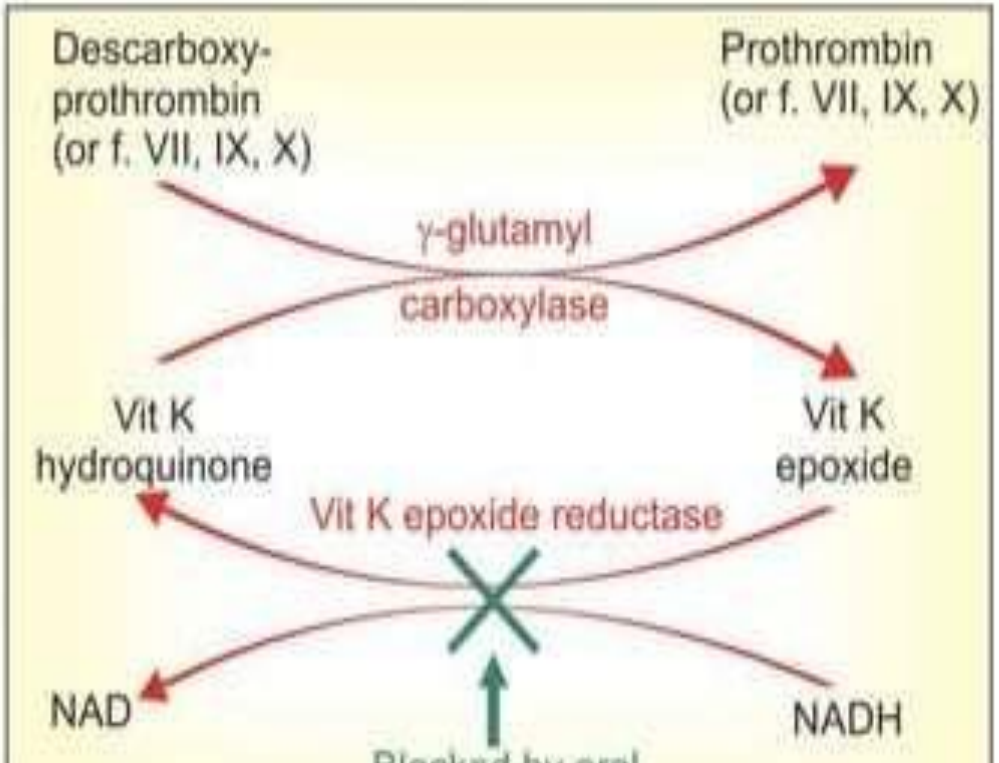
DIRECT THROMBIN INHIBITORS

- Unlike heparin, these recently developed anticoagulants bind directly to thrombin and inactivate it without the need to combine with and activate AT III.
- **Lepirudin**
- **Bivalirudin**
- **Argatroban**

ORAL ANTICOAGULANTS

- Act indirectly by interfering with the synthesis of vit K dependent clotting factors in liver.
- Apparently behave as competitive antagonists of vit K and lower the plasma levels of functional clotting factors in a dose-dependent manner.
- they inhibit the enzyme vit K epoxide reductase (VKOR) and interfere with regeneration of the active hydroquinone form of vit K which acts as a cofactor for the enzyme γ-glutamyl carboxylase.

MECHANISM OF ACTION OF ORAL ANTICOAGULANTS



DIRECT FACTOR XA INHIBITORS

- Act rapidly without a lag time
- Have short-lasting action.
- **Rivaroxaban**

ORAL DIRECT THROMBIN INHIBITOR

Dabigatran etexilate

- Reversibly blocks the catalytic site of thrombin and produces a rapid (within 2 hours) anticoagulant action.
- Oral bioavailability is low.
- No laboratory monitoring is required.
- The plasma t½ is 12–14 hours.
- Duration of action 24 hours.

USES OF ANTICOAGULANTS

- Deep vein thrombosis (DVT) and pulmonary embolism (PE)
- Myocardial infarction (MI)
- Unstable angina
- Rheumatic heart disease; Atrial fibrillation(AF)
- Cerebrovascular disease
- Vascular surgery, prosthetic heart valves, retinal vessel thrombosis, extracorporeal circulation, haemodialysis
- Defibrination syndrome or 'disseminated intravascular coagulation'

-THANK YOU