ANTI COAGULANTS

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DEFINITION

- **Coagulants** : substances causing hemostasis
- **Haemostasis** Arrest of blood loss from a damaged blood vessel . This is done by

  1) Vasoconstriction 2) Adhesion & activation of platelets 3) Fibrin formation
- **Thrombosis** : Pathological formation of hemostatic plug within the blood vessels in the absence of bleeding.
- **Thrombolytics/Fibrinolytics** : Breakdown or dissolution of Thrombus or Fibrin

BLOOD COAGULATION

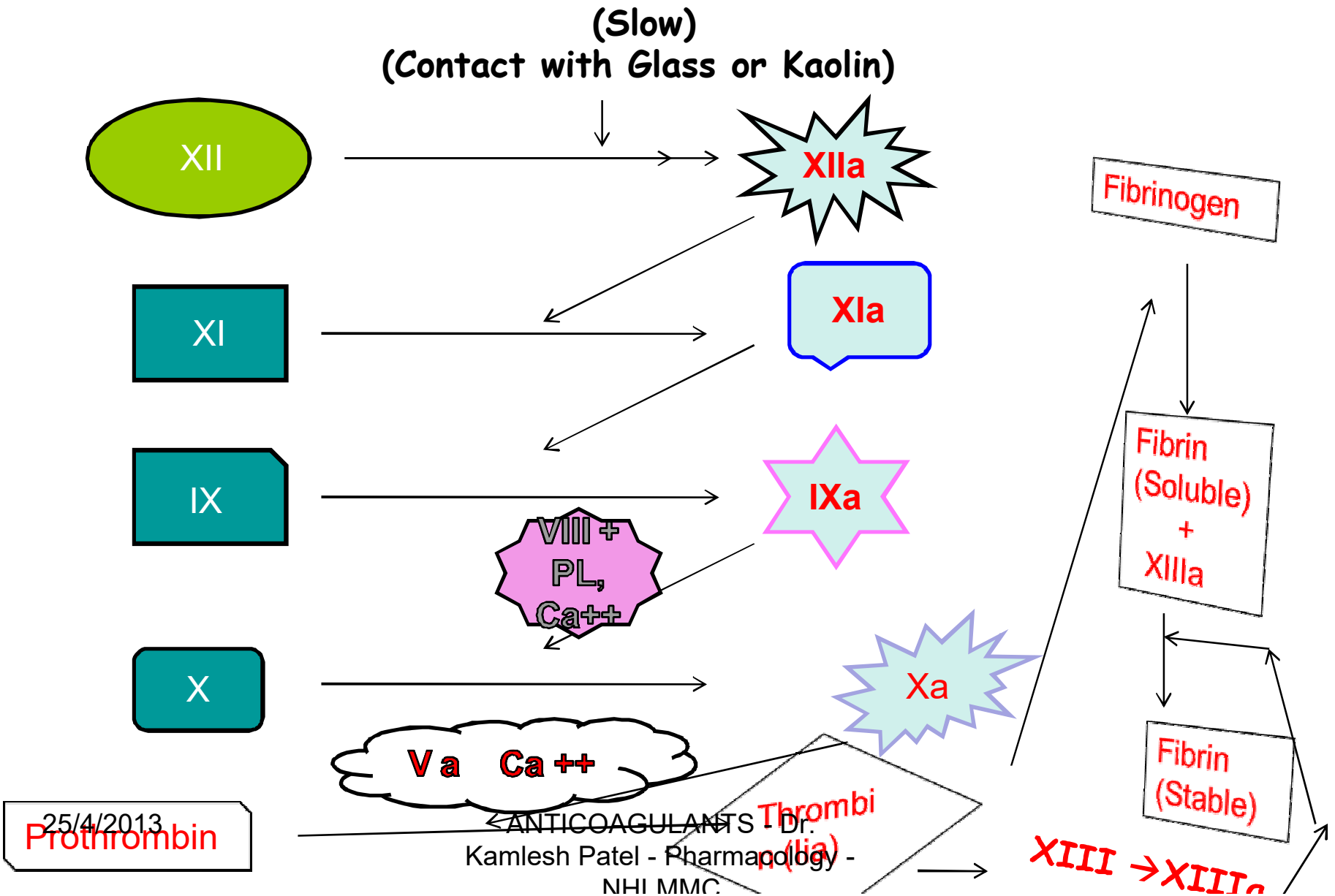
- Blood coagulation means conversion of
  Fluid blood ⟶ solid gel / clot

FIBRINOGEN ⟶ INSOLUBLE FIBRIN STRANDS

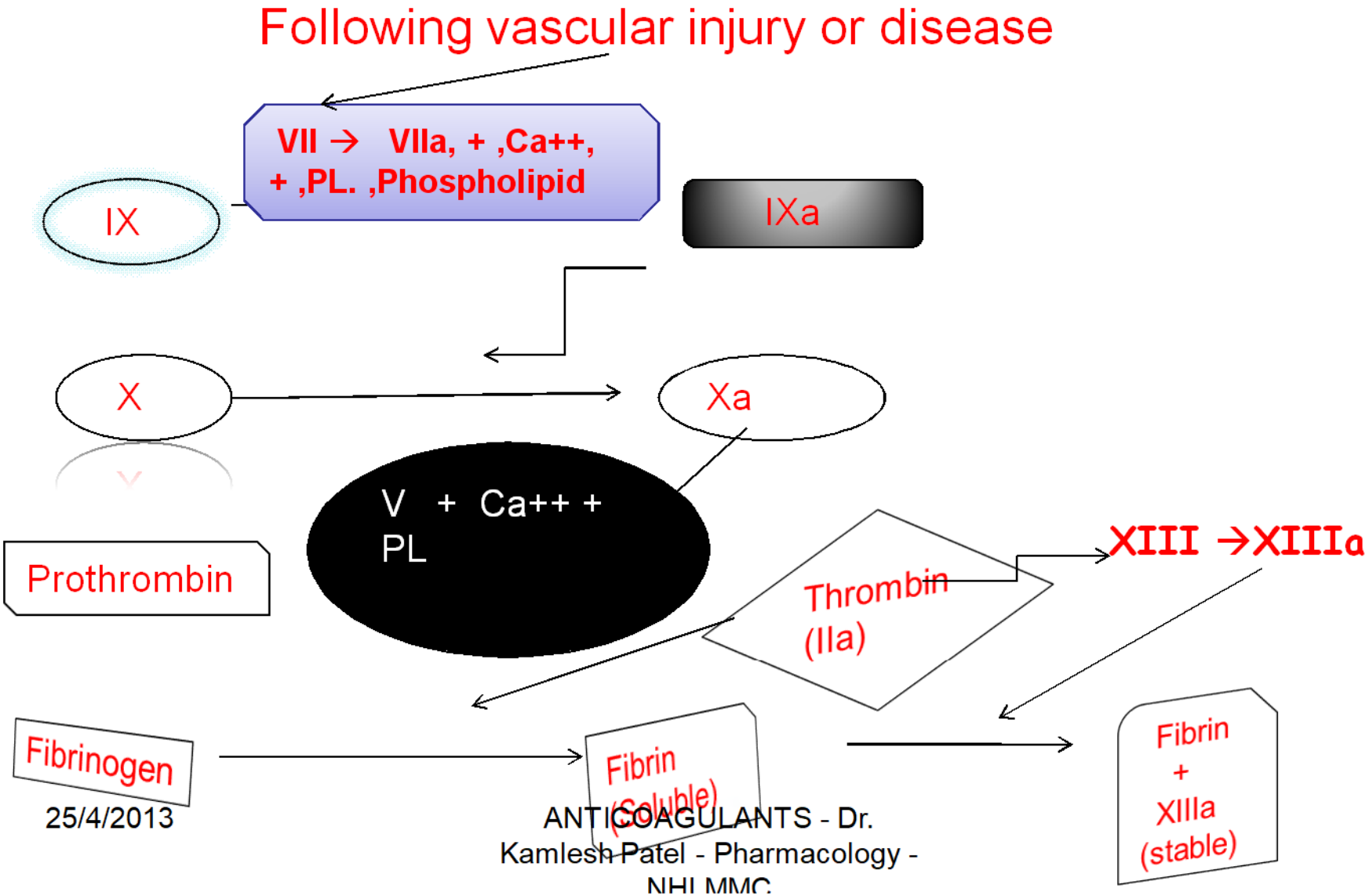
The two main pathways are

- **Intrinsic (in vitro or contact pathway)**
- **Deficit → Prolongs aPTT / KCCT [Activated partial thromboplastin time / Kaolin cephalin clotting time]**
- **Extrinsic (in vivo or physiological)**
- **Deficit → Prolongs Prothrombin Time (PT)**

Intrinsic pathway (in vitro)



Extrinsic Pathway (In vivo)



COAGULANTS

- 1) Acting Locally :-
- A) Clotting Factors :- Thrombin (Bovine Plasma), Human Fibrin
- B) Gelatin Foam with fibrin, Oxidized cellulose (surgical gauze with nitrogen dioxide), Thromboplastin, Adrenaline
- 2) Acing Systemically :-

  Fresh whole blood, Whole plasma, Vitamin K, Desmopressin, Fibrinolytic inhibitors (Rutin, Epsilon Aminocaproic acid, Tranaxemic acid, Ethamsylate), Carboprost

Vitamin K

- Vit K1(Phytonadione –alfa alfa grass), Vit K2 (Menaquinone - & sea fish)), Vit K3 (Menadione – water soluble – bile salts not required for absorption)
- Dietary sources:- green leafy vegetables, cabbage,spinach, liver, cheese, butter, milk
- Cofactor- In hepatic synthesis of clotting factors (II,VII,IX,X)
- Vit K1 & K2 Requires bile salt for absorption.
- Vit K is transported with LDL – stored in liver
- Daily Vit. K Reqd = 50-100 mcg

Deficiency of Vit. K

- Deficiency occurs :-
- Inadequate absorption(Lack of bile salt)
- Chronic diarrhoea
- Broad spectrum antibiotics-suppresses bacterial flora of gut)
- Consequences of Vit. K Deficiency :-
- Increased bleeding tendency – Epistaxis, Hematuria, GI & PO bleeding,

Uses of vitamin K

1. Dietary deficiency
2. Prolonged antimicrobial therapy
3. Obstructive jaundice (Vit K1) or malabsorption syndrome
4. Liver disease
5. Neonates (Vit K1 Phytonadione -1mg i.m.) routinely given to prevent bleeding
6. Overdose of anticoagulant (Warfarin)
7. Prevent bleeding due to Vit.K deficiency
8. Vit.K1 in Salicylate poisoning with bleeding

ANTICOAGULANTS

1. Used in vitro
   a) Heparin
   b) Sodium citrate – Used in Blood bank to store blood
   c) Sodium oxalate
   d) Sodium edetate (Both – used in Laboratory as an anti-coagulant)

ANTICOAGULANTS

2. Used in vivo

(a) Parenteral Anti-Coagulants :-

(i) Heparin

(ii) Low molecular weight heparins (LMWHs) :- Enoxaparin, Dalteparin

(iii) Heparinoids :- Heparan sulphate Lepirudin, Danaparoid

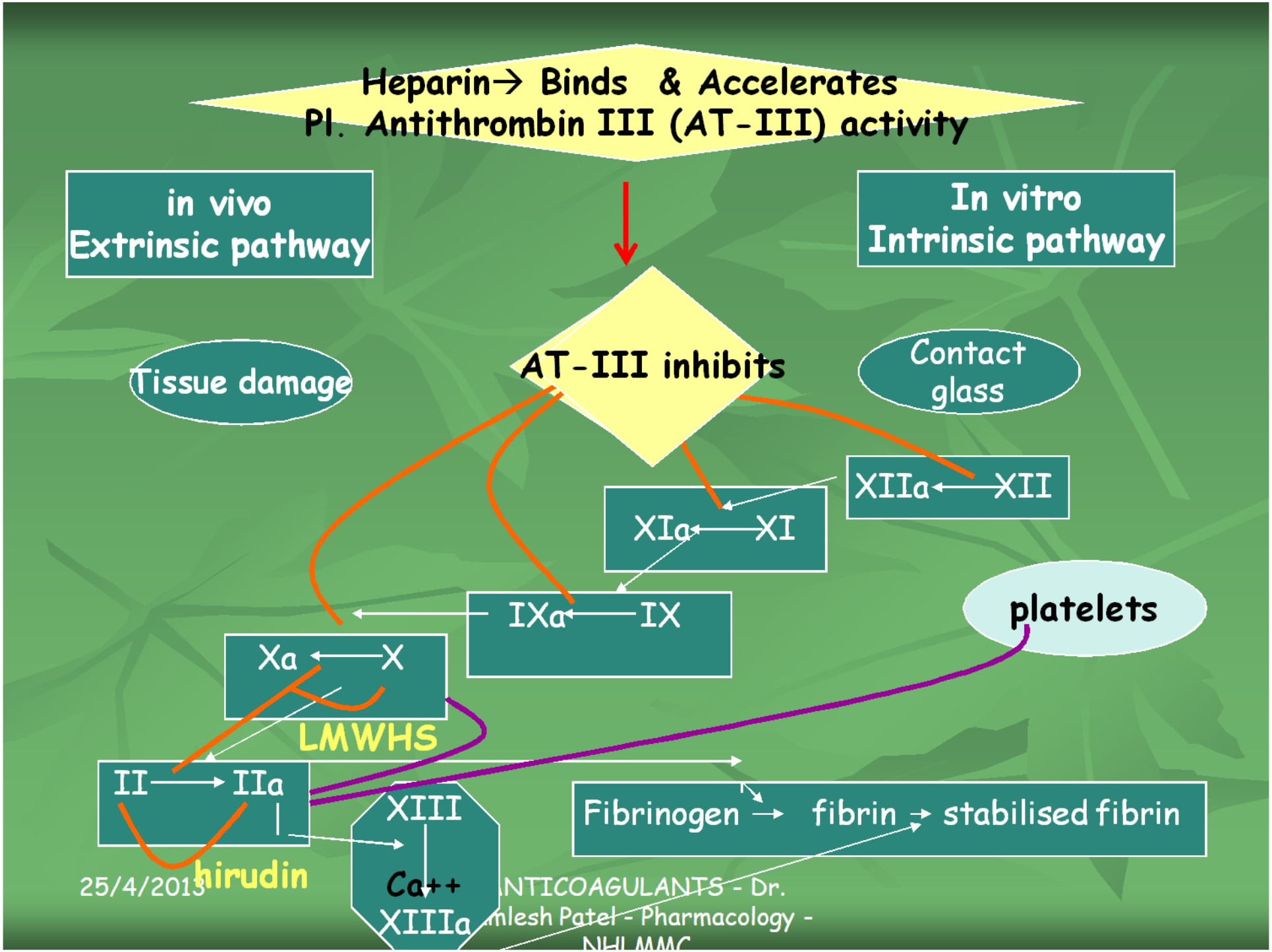
(b) Oral – Warfarin sodium, Dicumarol

Heparin

- McLean (1916) - medical student discovered
- Howell & Holt (1928) identified it
- Highest conc. in Liver (hence, Heparin)
- Strongly electronegative organic acid in body - M.W. -10,000 - 20,000.
- Richest source - lungs, liver, intestinal mucosa
- Commercially - ox lung, pig intestine

ACTION - Heparin

1. Anticoagulant
2. Antiplatelet
3. Lipemia clearing


Heparin→ Binds & Accelerates
Pl. Antithrombin III (AT-III) activity
in vivo
Extrinsic pathway
In vitro
Intrinsic pathway
Tissue damage
AT-III inhibits
Contact
glass
XIIa ← XII
XIa ← XI
IXa ← IX
platelets
Xa ← X
LMWHS
II → IIa
hirudin
XIII
Ca++
XIIIa
Fibrinogen → fibrin → stabilised fibrin

HEPARIN - ANTI-COAGULANT EFFECT

Heparin

↓

Binds and Accelerates Plasma Antithrombin - III (AT-III) activity

↓

Forms Heparin – AT-III complex

↓

Then, inhibits activated factors

Xa, IIa, IXa, XIa, XIIa & XIIIa

HEPARIN - ANTI-Coagulant EFFECT

- At Low Concentration,

Heparin

↓

Selectively inhibits

↓

Conversion of Prothrombin into Thrombin

↓

Thus, Prevents Thrombus Formation

HEPARIN - ANTI-PLATELET EFFECT

- In High Doses,

Heparin

↓

Has Anti-platelet activity

↓

Prolongs Bleeding Time

Heparin – Lipemia Clearing Effect

Heparin

↓

Releases Lipoprotein lipase (LL)from vessel wall & tissues in to the circulation

↓

Clears lipemia

TGs (LL)→ FFAs & glycerol

Pharmacokinetics - Heparin

- Highly ionized, Highly Protein Bound
- Not absorbed orally-Large MW & Electro-negativity
- Administered i.v (immediate effect) or s.c (1-2 hrs). i.m route cause Hematomas.
- Does not cross BBB or placenta (Safe during Pregnancy)
- Metabolized rapidly in liver by Heparinase
- Excreted in urine
- T1/2: 100,400,800U/kg (1,2.5,5hrs)

HEPARIN

- Low concentration prolong only aPTT (Activated Partial Thromboplastin Time)
- Higher concentration prolongs both - aPTT + PT (Prothrombin Time).
- **During Heparin Therapy, aPTT monitoring is necessary → Maintained at 1.5 – 2.5 times the control.**

PREPARATIONS

1. Heparin sod. : 1000, 5000 IU/ml in 5 ml, S.C /I.V
2. Heparin cal. : 25000IU / ml S.C / I.M

Dosage :

5000-10,000 U I.V bolus every 4-6 hrs

(Or) I.V infusion : 750-1000 U/ hr

Deep S.C.inj: 10,000-20000 U/12-24 hrs

ADR - Heparin

1. **BLEEDING:-** overdose

- Haematuria – first sign
- Common on intermittent I.V therapy
- GI or GU tract lesions
- Controlled by Heparin Antagonist – Protamine sulphate (PS) – 50mg i.v.
- 1mg PS neutralizes 100 U Heparin (Chemical antagonism)
- PS (Strong Basic Protein) * Heparin (Strong Acid)

ADR - Heparin

2) Heparin – Induced Thrombocytopenia (HIT) :-

- More common in bovine prep.
- 2.5 % incidence
- After 2-5 days of treatment
- Antibodies to heparin – platelet complex
- Stop H / LMWH

ADR - Heparin

3. **Osteoporosis** – on long term (6 mths)
4. **Alopecia** – transient
5. **Allergic reaction:** Chills, fever, urticaria, anaphylaxis
6. **Local :** pain, haematoma, burning sensation
7. **Hypoaldosteronism – Hyperkalaemia**
8. **Abnormal Liver function tests**

Contraindications - Heparin

- Bleeding disorders
- Severe hypertension : **Cerebral H, Piles, GIT ulcers, abortion (ecbolics)**
- Subacute bacterial endocarditis- embolism
- T.B.- hemoptysis
- Ocular, neurosurgery
- Aspirin & other antiplatelet- caution

Low molecular weight heparins (LMWHs)

- LMWHs -- Produced by partial chemical or enzymatic depolarization of natural heparin followed by fractionization (by Gel – Filtration Chromatography)
- MW 3000 -7000
- Eg. Enoxaparin, Dalteparin etc…

LMWHs

- LMWHs inhibit Factors Xa but not on thrombin → Produces anti-coagulant effect
- Does not require aPTT monitoring
- But, Pts with CRF require monitoring by measuring Factor Xa activity.

LMWHs- Advantages

1. Minimal effect on PTT& BT
2. Thrombocytopenia – less common
3. Bleeding – less common
4. Better S.C Bioavailability (70-90%) (heparin 20 – 30%)
5. O.D/B.D.- S.C adm. (longer acting)
6. Lab. monitoring not required
7. Less local reactions
8. No aPTT monitoring – Better Pt. compliance

HEPARINOIDS

- **1) Lepirudin :-**
- Recombinant Hirudin
- Directly inhibits Thrombin
- Used as an anticoagulant in HIT
- Administered I.V. → Requires aPTT monitoring.
- No antidote available

HEPARINOIDS

2) Danaparoid :-

- Derived from Pig intestinal mucosa
- Has anti-factor Xa activity
- Administered S.C for prophylaxis
- I.V. for treatment of DVT & HIT
- No antidote available

3) Bivalirudin :-

- Synthetic Heparanoid
- Used As Alternative to Heparin in Coronary Angioplasty