Haematinics, Coagulants and Anti-coagulants

Disclaimer

All the content material provided here is only made for teaching purpose.

ANAEMIA:

It is a condition in which the balance between production and destruction of RBCs is disturbed by:-

1. Blood Loss
2. Impaired red cell formation
3. Increased destruction of RBCs

HAEMATINICS

These are also called as anti-anaemics. They are the agents which are required for the formation of blood and are used for the treatment of Anaemics.These are mainly IRON, FOLIC ACID & VIT B_{12}

IRON

Distribution in the Body:

Total body iron in an adult is 2.5-5g. It is more in men than in women.

It is distributed into:--

Hemoglobin – 66%

Iron stores as ferritin & hemoglobin – 25%

Myoglobin - 3%

Parenchymal Iron – 6%

HAEMOGLOBIN

It is a protoparphyrin,each molecule having 4 iron containing haeme residues. It has 33% iron.

Daily Requirement :-

To make good average daily loss, requirement are:

Adult male	-	0.5 – 1 mg
Adult Female	-	1 – 2
Infants	-	60 μg / kg
Children	-	25 μg / kg
Pregnancy	-	3 – 5 mg

IRON ABSORPTION

The average daily diet contain 10-20 mg of iron. It absorption occurs all over the intestine, but magnify in the upper part.

Iron Transport

Iron is transmitted in blood in combination with a glycoprotien transferin it binds ferric iron.The total plasma content of iron is ~3 mg.

Iron Storage

Iron is stored in RE cells in liver , Spleen ,bone in narrow in hepotocytes and myocytes as ferritin & haemosiderin.

Iron Excertion

Iron is tenaciosly conserved by the body daily excretion in adult male is 0.5 – 1mg mainly as exploiated g.I mucosal cell, some RBC & in bile.

In menstruating women, monthly menstrual loss may be averaged to 0.5 – 1 mg/day

Ferrous Fumerate – 200 – 400 mg is divided daily dose.

Colloidal iron – 200 – 400 mg daily

Parental Iron Therapy

It is indicated when oral iron therapy fails

1. Iron dextran injection : Dose 1 ml

2.Iron sorbitol injection : Dose 1.5 mg of iron / kg

Adverse Effect:-

Local - * Pain at site of in injection.

* Pigmentation of skin

* Sterile abscess

Systemic - * Fever, headache, joint pains, flushing, palpitation, chest pain, dyspnoea, lymph node enlargement

* A metallic taste in mouth lasting for few hrs.

* An anaphylactoid reaction resulting in vascular collapse & death.

* Iron sorbital causes more imidiate reaction than iron dextran, should be avoided in patients with kidney disease

Uses:-

1. Iron Deficiency Anaemia :-

If is the most important indication for medicinal iron.Iron deficiency is the commonest cause of anaemia.Iron defciancy also accompanies repeated attacks of malaria & chronic inflammatory disease.The cause of iron-deficiency should be identified & treated with normal administration.

2. Megaloblastic Anamia:-

when brisk haemopoiesis is induced by Vit B12 or folate therapy,iron deficiency may be unmasked.The iron status of this patient should be evaluated & iron given accordingly.

3. AS AN ASTRINGENT:-

Ferric chloride is used in throat paint.

ACUTE IRON POISIONING:

It occurs when body is unable to excrete an excess of iron , which is deposited in heart,liver,pancreas & other organ leading to organ failure & death. It occurs mostly in infants& children. It is very rare in adults.
Manifestation are vomiting,abdominalpain,haematemesis,diarrhoea,lethargy,cyanosis,dehydration, acidosis,convulsions & finally shock , cardiovascular collapse & death.

TREATMENT:

Prevent further absorption of iron from gut.
Induce vomiting or perform gastric lavage with sodium bicarbonate solution to render iron insoluble.
Give egg yolk & milk orally complete iron.

Maturation Factors:-

Vitamin B_{12} & folic acid deficiency,results in megaloblastic anaemia.They are, therefore,called maturation factors

VITAMIN B_{12}

Cyanocobalamin & hydroxycobalamin are complex cobalt containing compounds in diet & refered to as vitamin $B_{12.}$

Dietary Sources:- Liver, kidney, sea fish, egg yolk, meat, cheese are the main vitamin B_{12} containing constituents of diet. Legumes is only vegetable source.

METABOLIC FUNCTIONS:-

Vitamin B_{12} is intricately linked with folate metabolism in many ways like megaloblastic anaemia occuring due to deficiency of either is indistinguishable.In addition vitamin B_{12} has some independent functions as well –

1-It is essential for the conversion of homocysteine to metionine.

2-Vitamin B_{12} is essential for cell growth & multiplication.

3-Vitamin B_{12} is also essential for degeneration of spinal cord.

DEFICIENCY:-

1-Addisonian pernicious anaemia
2-Malabsorption bowel resection
3-Other causes of mucosal damage eg; Chronic gastritis, gastric carcinoma, gastrectomy
4-Nutritional deficiency: less common cause
5-Increased demand- pregnancy,infancy

USES:

1-Used in treatment of B_{12} deficiency.
2-Mega doses of B_{12} have been used in neuropathies, psyciatric disorders , cutaneous sarcoid & as a general folic to allay fatigue, improved growth

Adverse effects:

Even large doses of B_{12} are quite safe. Allergic reaction have occurred on injection, probably due to contaminants. Anaphylactoid reactions have occurred on injection, this route should not be applied.

FOLIC ACID

It occurs yellow crystals which are insoluble in water, but its sodium salt is freely soluble water.

Dietary Sources:-

Liver,green leafy vegetables, egg,meat,milk

DEFICIENCY:-

1-Megaloblastic anaemia
2-Epithelial damage
3-General deability,weight loss,sterility.

Metabolic Functions:-

1-Conversion of homoysteine into methionine

2-Generation of thymidylate , an important constituent of DNA

3-Conversion of serine into glycine

4-Purine synthesis

5-Histidine metabolism

USES

1-In megaloblastic anaemia

2-In methotrexate toxicity

3-Citrovorum factor rescue

4-Antiepileptic therapy

ADVERSE EFFECT-

Oral folic acid is entirely nontoxic. Infection rarely causes sensitivity reaction.

Coagulant and Anti-coagulant Classes of Drugs

- **Prevent coagulation**
- **Dissolve clot**
- **Prevent bleeding and hemorrhage**
- **Overcome clotting deficiencies**

Phases of Blood Clotting

- **Vascular Phase**
- **Platelet Phase**
- **Coagulation Phase**
- **Fibrinolytic Phase**

Coagulation Phase

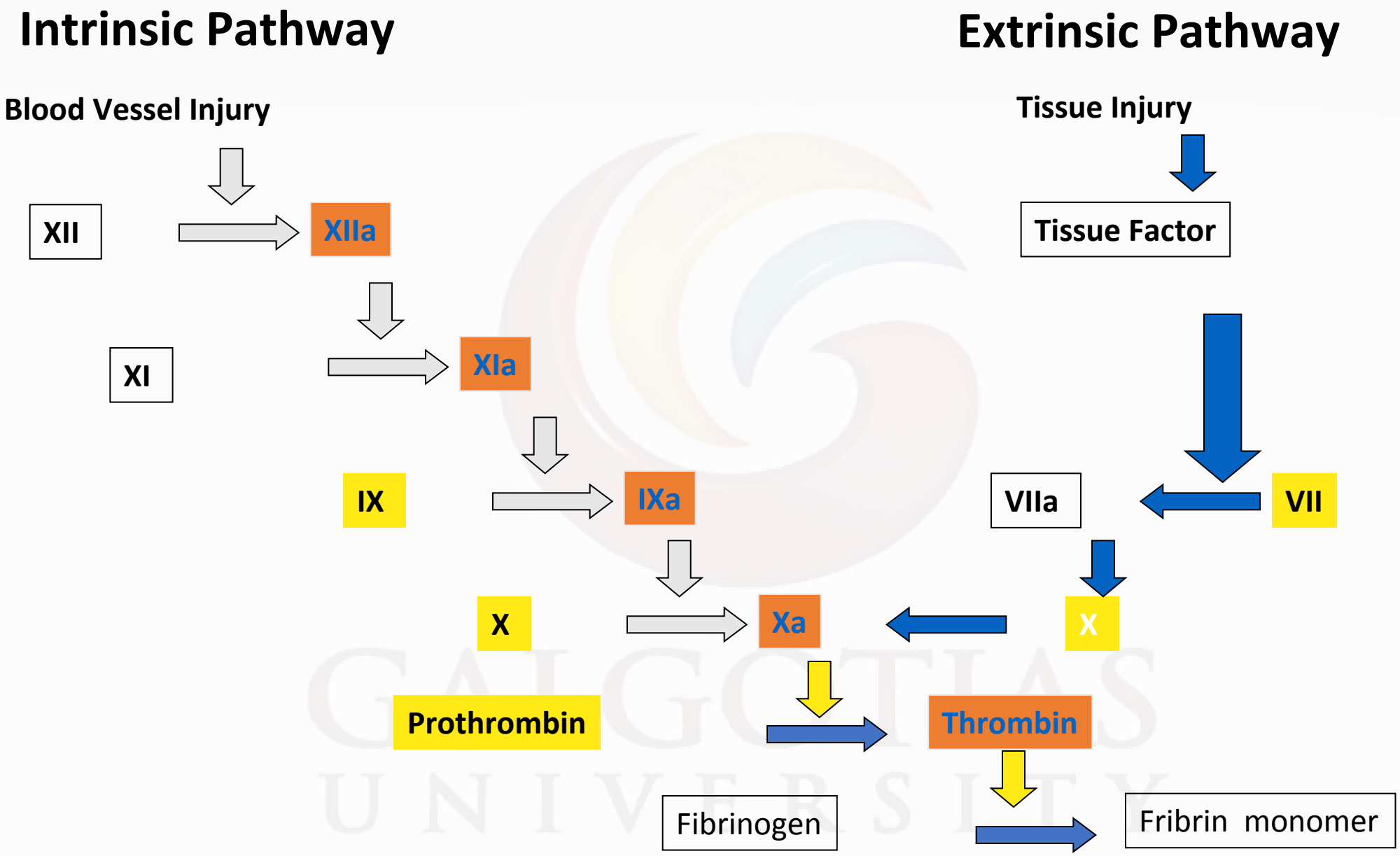
> Two major pathways

- Intrinsic pathway
- Extrinsic pathway

> Both converge at a common point

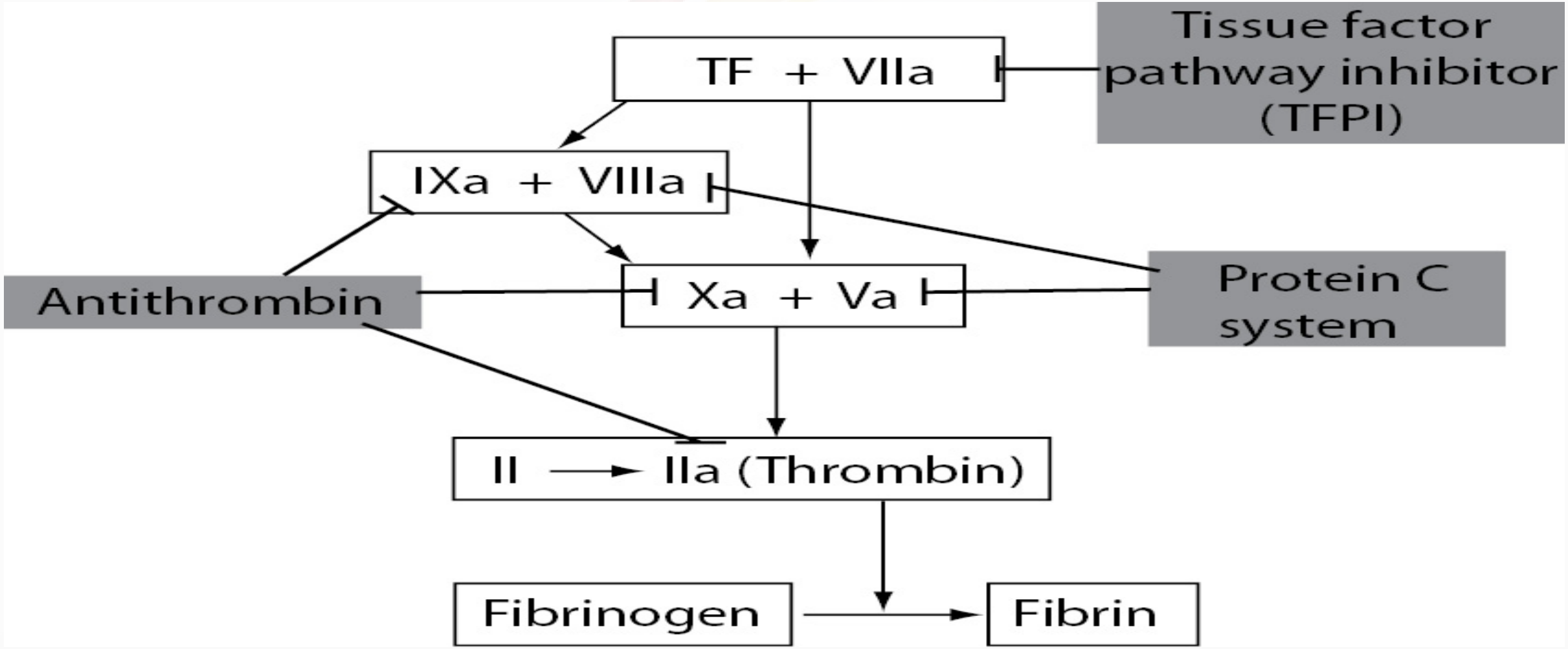
> 13 soluble factors are involved in clotting

> Normally inactive and sequentially activated


Intrinsic Pathway
Extrinsic Pathway
Blood Vessel Injury
Tissue Injury
XII
XIIa
Tissue Factor
XI
XIa
IX
IXa
VIIa
VII
X
Xa
X
Prothrombin
Thrombin
Fibrinogen
Fribrin monomer

Vitamin K-Dependent Clotting Factors

Natural anti-coagulant



Drugs influencing coagulation

- fibrin formation → Anticoagulants
- Platelet function → Antiplatelet drugs
- Fibrinolysis → Thrombolytic drugs

Anticoagulants

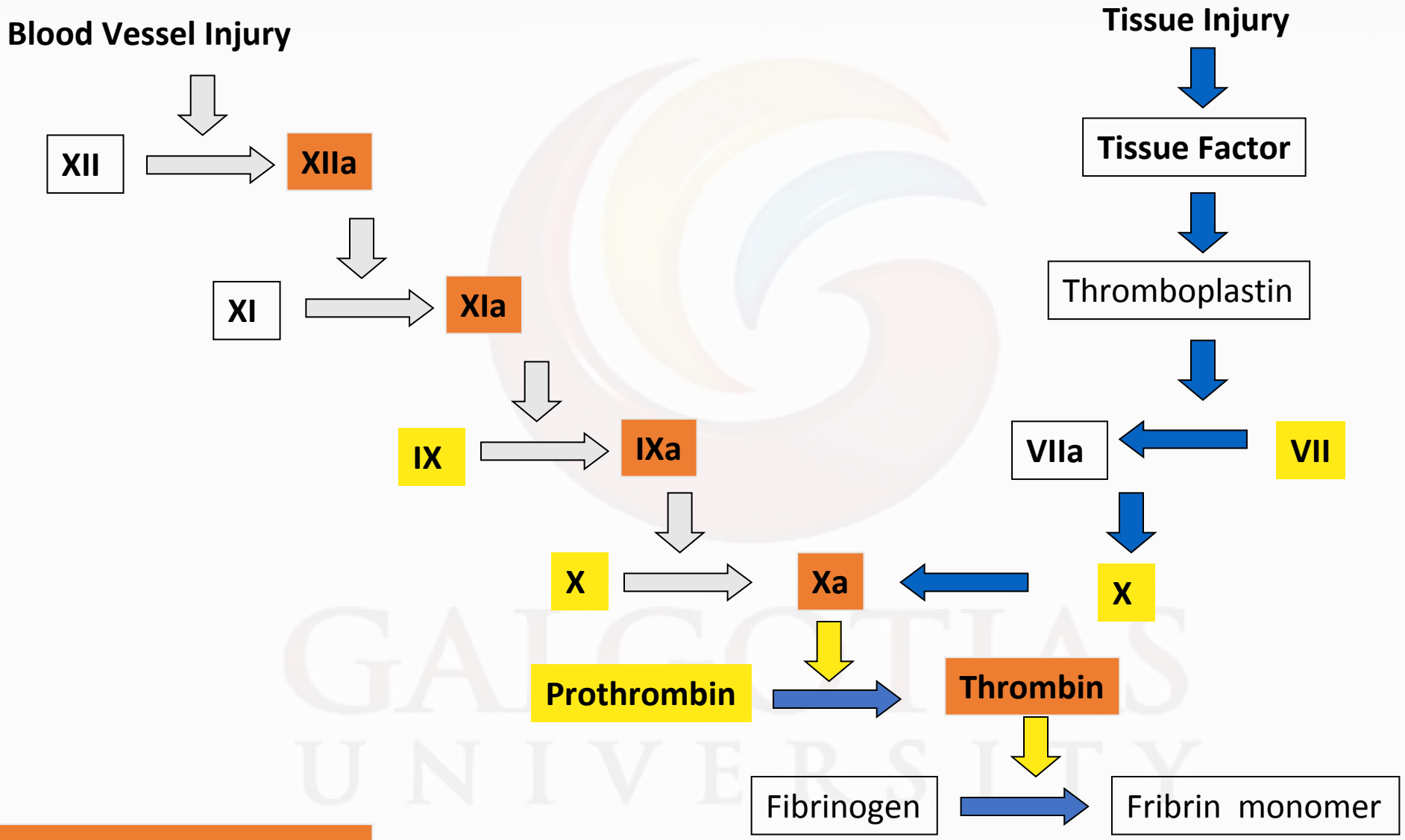
- Anti-thrombin activators
- Direct thrombin inhibitors
- Direct Factor Xa inhibitors
- Drugs that oppose action of Vitamin K

Heparin

- Heterogeneous mixture of branched glycosaminoglycans
- Potentiates the inhibition of IIa, IXa, Xa, XIa, XIIa by AT
- Binds to AT through a unique pentasaccharide sequence leading to a conformational change

Intrinsic Pathway

Extrinsic Pathway



Factors affected By Heparin

Heparin

- Given s.c. or i.v.
- Binds to plasma proteins, endothelial cells & macrophages
- Elimination
  - Depolymerisation in endothelial cells & macrophages (rapid, saturable)
  - Renal (slow, non-saturable) and RES

Heparin: variable anticoagulant effect

- Variable protein binding
- Clearance varies with chain length

- Therefore, anticoagulant response monitored by **activated partial thromboplastin time** (APTT)
- Target 1.5 – 2.5 times control

Clinical uses of Heparin

- Venous thrombosis ± embolism
- Acute coronary syndromes
- Arterial thrombosis
- Extracorporeal devices (e.g. haemodialysis)

Heparin: adverse effects

- Bleeding
- Heparin-induced thrombocytopenia (HIT)
  - Immune-mediated
- Osteoporosis

Low-molecular-weight heparins (LMWHs)

- Derived from UFH by chemical or enzymatic depolymerization
- Molecular weight 2000 – 9000
- About 15 monosaccharide units per molecule

Differences in Mechanism of Action

- Any size of heparin chain can inhibit the action of factor Xa by binding to antithrombin (AT)
- In contrast, in order to inactivate thrombin (IIa), the heparin molecule must be long enough to bind both antithrombin and thrombin
- Less than half of the chains of LMWH are long enough

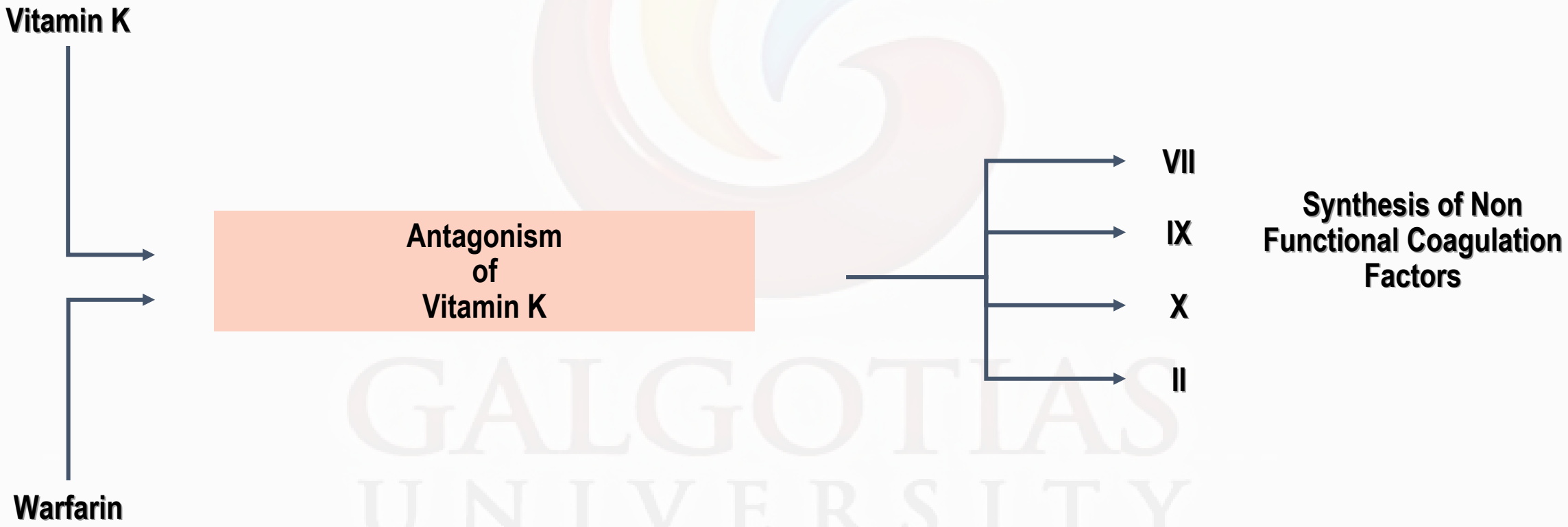
LMWHs

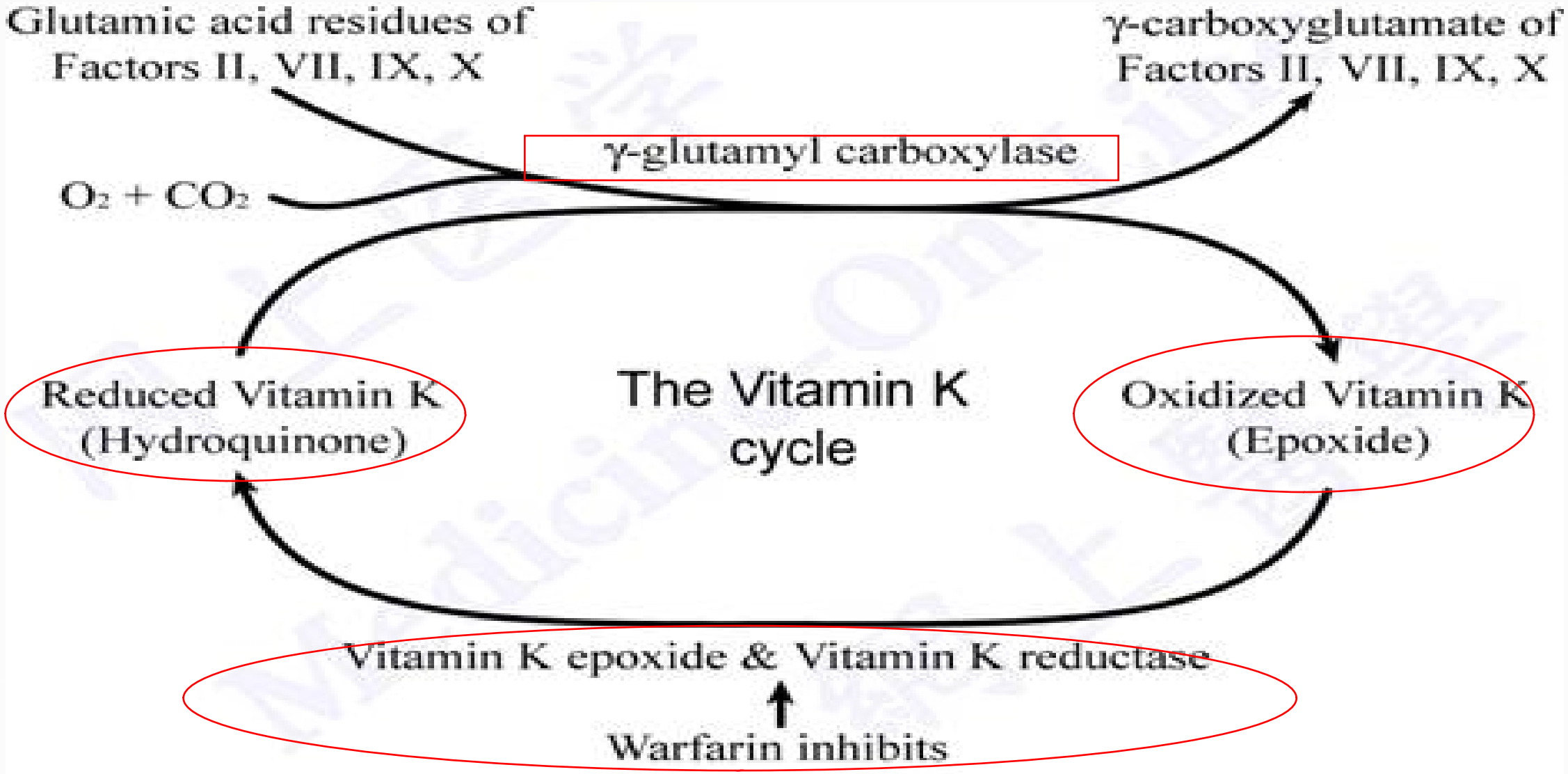
- Dalteparin
- Enoxaparin
- Tinzaparin

Direct thrombin inhibitors

- Recombinant hirudins
- Bivalirudin
- Ximelagatran / Melagatran
- Dabigatran

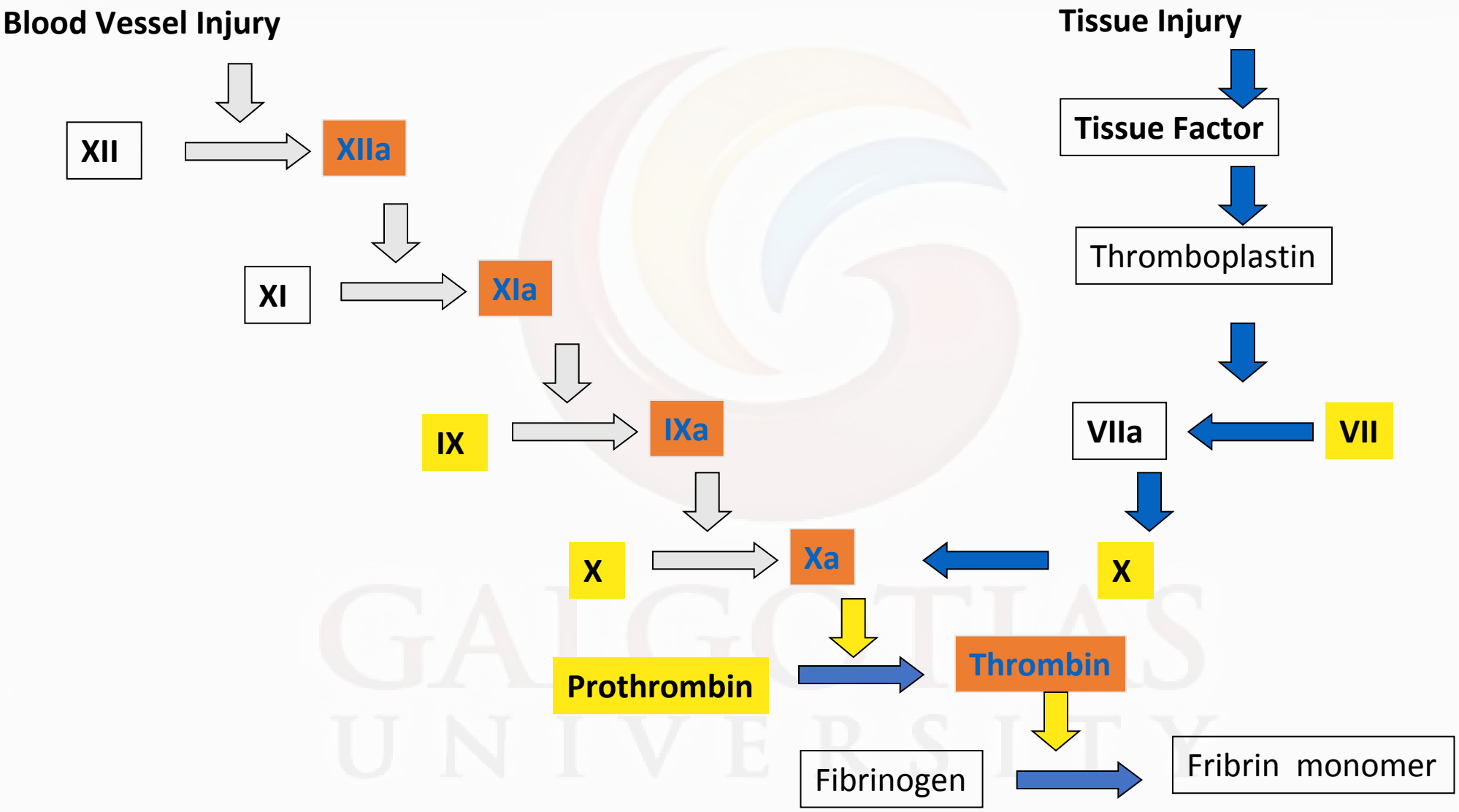
Warfarin Mechanism of Action




Glutamic acid residues of
Factors II, VII, IX, X
γ-carboxyglutamate of
Factors II, VII, IX, X
γ-glutamyl carboxylase
O2 + CO2
Reduced Vitamin K
(Hydroquinone)
The Vitamin K
cycle
Oxidized Vitamin K
(Epoxide)
Vitamin K epoxide & Vitamin K reductase
Warfarin inhibits

Intrinsic Pathway

Extrinsic Pathway



Vit. K dependent Factors Affected by Oral Anticoagulants

Warfarin

- Anticoagulant effect seen after 2-3 days
- Monitored by international normalized ratio (INR)
- Well absorbed form GIT
- Highly protein bound
- Metabolised by CYP-450

Adverse effects of Warfarin

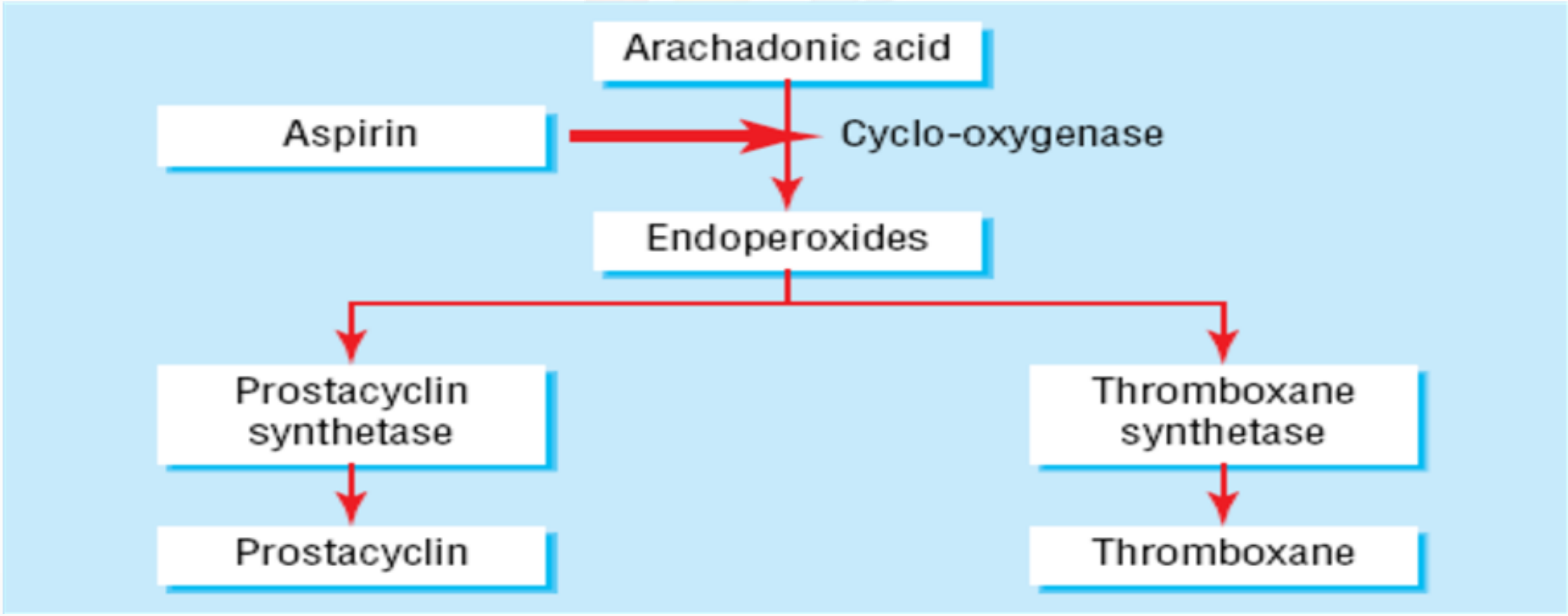
- Bleeding
- Rashes
- Alopecia
- Teratogenicity

Antiplatelet drugs

- COX inhibitors
- Adenosine diphosphate $P2Y_{12}$ receptor antagonists (thienopyridines)
- Phosphodiesterase inhibitors
- Glycoprotein IIb/IIIa receptor antagonists

Aspirin

- Irreversible acetylation of cyclo-oxygenase-1 in platelets



Thienopyridines

- Ticlopidine
- Clopidogrel

Clopidogrel

- Slightly more effective than aspirin
- Additive effect to aspirin

Use

- MI
- Stroke

Ticlopidine

- Slow onset of action: 3-7 days
- Idiosyncratic neutropenia

Antiplatelet drugs

- COX inhibitors
- Adenosine diphosphate $P2Y_{12}$ receptor antagonists (thienopyridines)
- Phosphodiesterase inhibitors
  - Dipyridamole
- Glycoprotein IIb/IIIa receptor antagonists

Dipyridamole

- Phosphodiesterase inhibitor

Glycoprotein IIb/IIIa receptor antagonists

Abciximab, Eptifibatide

- More complete inbibition of platlet function

- inceased risk of bleeding

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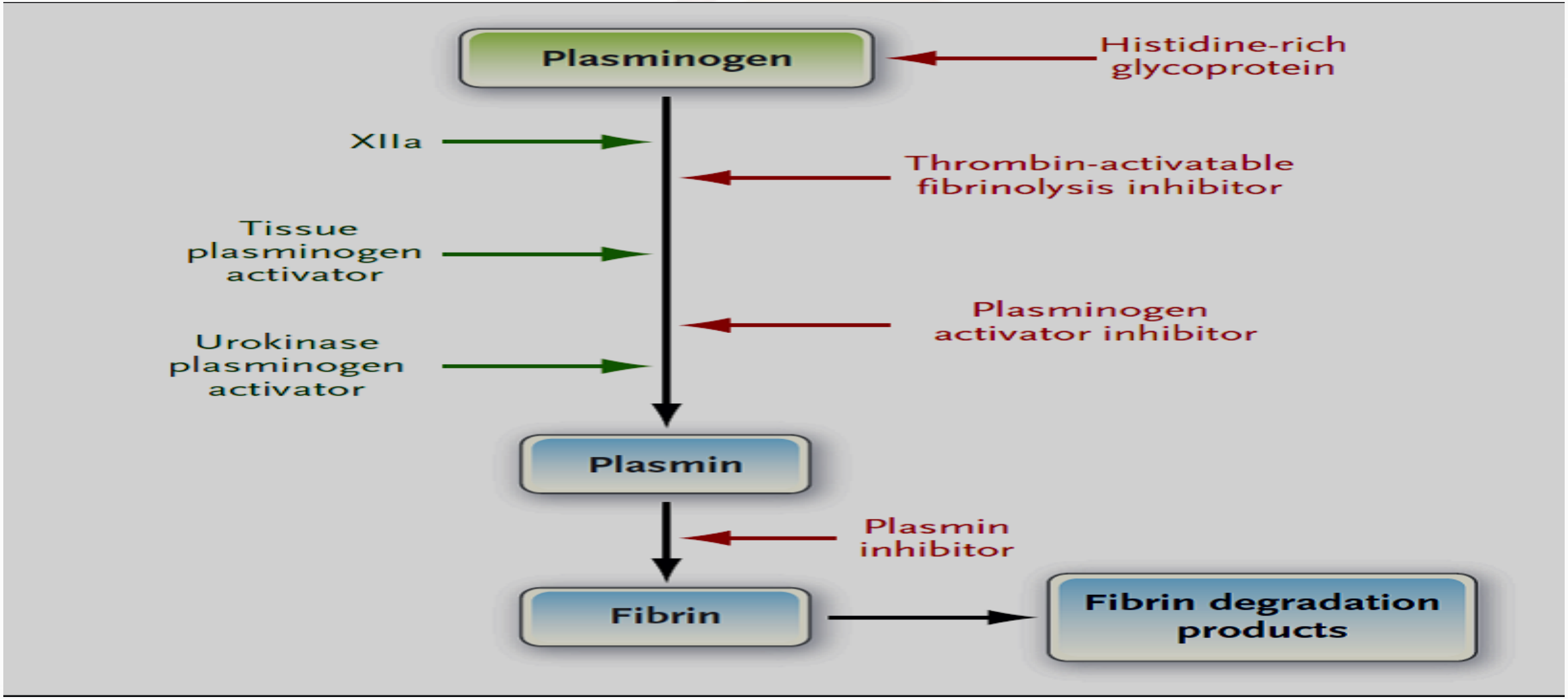
Fibrinolysis



Fibrinolysis

- Exogenously administered drugs
  - Streptokinase
  - Urokinase
  - Tissue plasminogen activator (tPA)

Streptokinase:

- Binds to plasminogen & activates it
- Source: β haemolytic streptococci
- Immunogenic (not repeated within one years of administration)
- T 1/2 - 20 min
- IV

Clinical uses

- STEMI
- Massive pulmonary embolism
- Ischaemic stroke
- Better if give within first 3 hr

Side effects

- Bleeding
- Multiple microemboli
- Cardic arrhythmias
- Allergy

Urokinase

- Human fetal kdney tisssue
- Activate plaminogen
- T1/2 – 15 min

tPA

- Produced by recombinant DNA technology
- Not immunogenic
- More clot-specific than SK – fibrin selective
- Less coagulation disturbance in plasma

- Short half life – iv infusion

References

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