Content

- Oral Anticoagulants – Coumarin derivatives
  - Warfarin
  - Drug interactions
- Therapeutic uses of anticoagulants
- Fibrinolytic drugs

Objectives

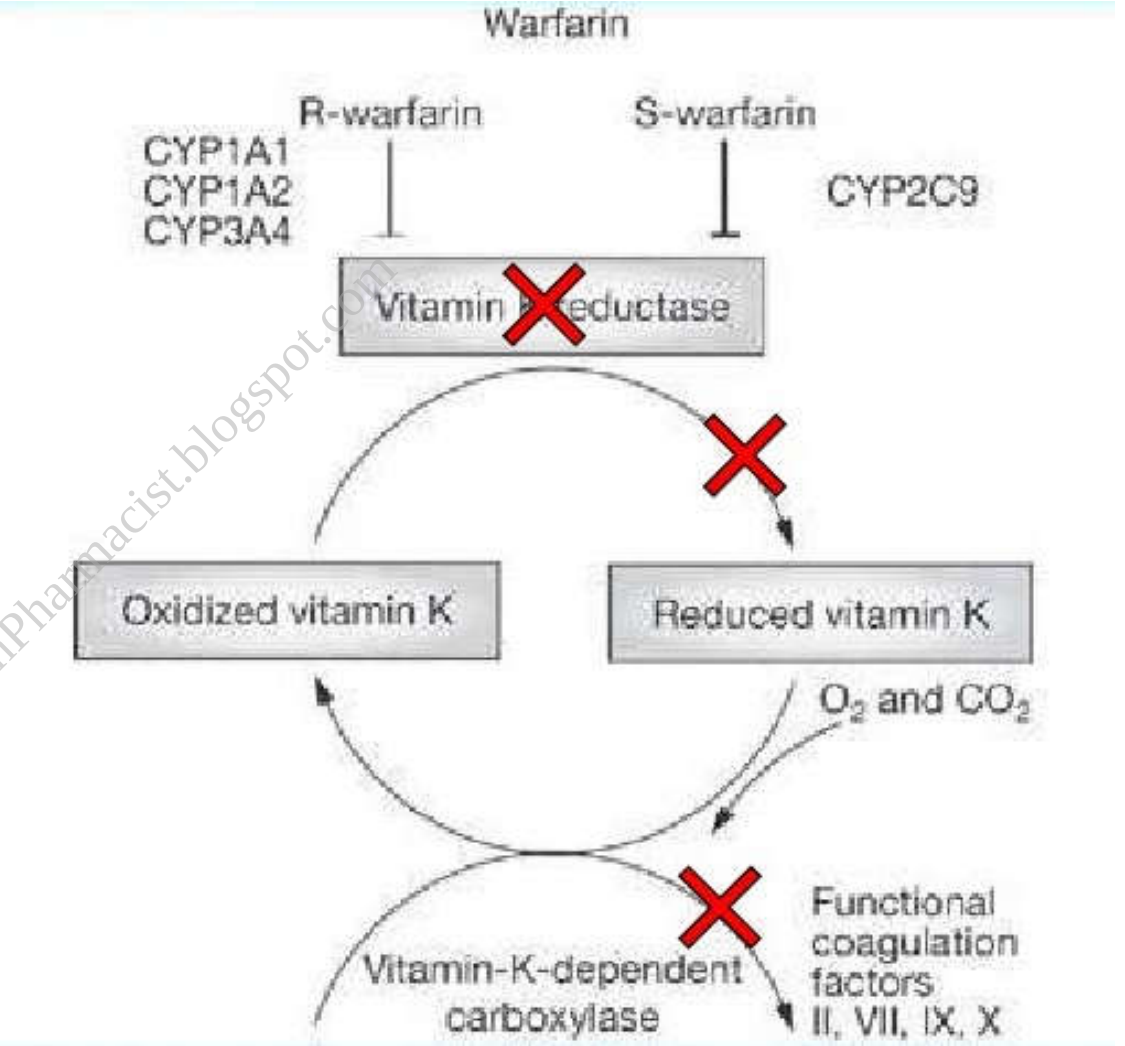
At the end of this lecture, student will be able to

- Explain the mechanism of action of warfarin
- Describe the drug interactions of warfarin
- Discuss the therapeutic uses of anticoagulants
- Classify fibrinolytic drugs
- Discuss the pharmacology of fibrinolytic drugs

Oral anticoagulants – Coumarin derivatives

Warfarin

- Competitively inhibits Vit K reductase
- Limits the synthesis of clotting factors II, VII, IX & X by liver



Warfarin

- Anticoagulant effect takes 1-3 days to develop
- Prothrombin (Factor II) is diminished last

Pharmacokinetics

- Oral bioavailability – 100%
- 99% - plasma protein bound
- Metabolised in liver
- Undergoes enterohepatic circulation
- Partly conjugated with glucuronic acid, excreted in urine

Drug interactions of Warfarin (Potentiating warfarin activity)

- Enzyme inhibitors – metronidazole, chloramphenicol, disulfiram, erythromycin, cimetidine
- Drugs displacing warfarin from protein binding site – Cotrimoxazole, indomethacin, phenytoin, probenecid
- Liquid paraffin
- Inhibitor of platelet aggregation – Aspirin
- Drugs reducing Vit K synthesis – broad spectrum antibiotics

Drug interactions of Warfarin (Reduction in warfarin activity)

- Enzyme inducer – Barbiturates, rifampicin, griseofulvin, carbamazepine
- Inhibition of absorption of warfarin – Cholestyramine & sucralfate
- Increase the synthesis of clotting factor – oral contraceptives with estrogen

Contraindication - pregnancy – abortion or birth defects

Therapeutic uses of anticoagulants

- Prevent thrombus extension, recurrence & embolic complications

* Prevention and treatment of deep vein thrombosis and pulmonary embolism – fibrin thrombi
* Myocardial infarction – to reduce secondary thrombo embolic complications
* Unstable angina – reduce MI
* Rheumatic heart disease
* Cerebrovascular diseases

Therapeutic uses of anticoagulants

Adverse effect of anticoagulants

- Haemorrhage – parenteral or oral anticoagulant

Heparin

- Thrombocytopenia
- Osteoporosis
- Transient alopecia
- Hypersensitivity

Warfarin

- Teratogenic
- Transient alopecia
- Dermatitis
- Diarrhoea

Contraindications of Anticoagulants

Heparin

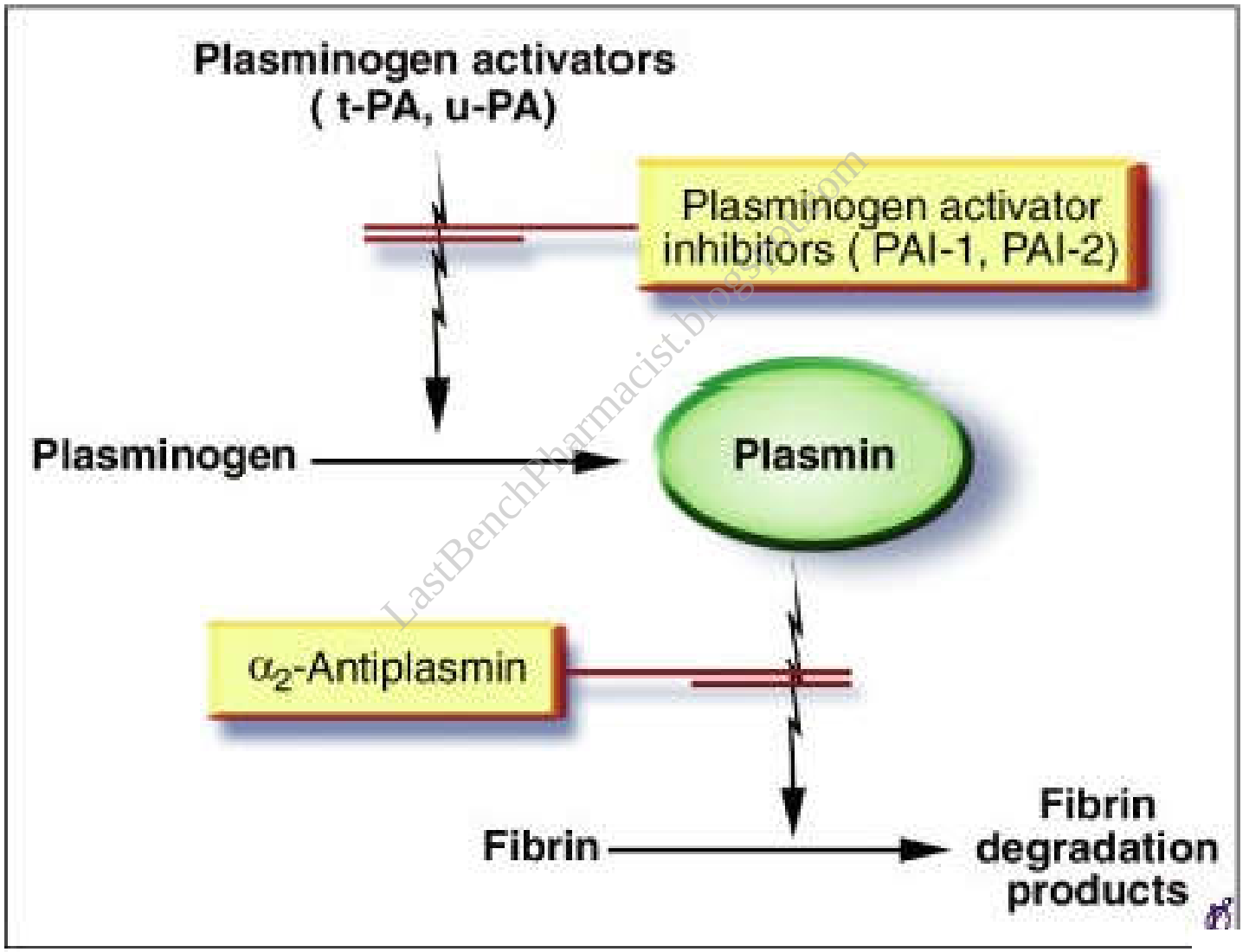
- Bleeding disorder
- Thrombocytopenia
- Severe hypertension
- Bleeding piles
- Subacute bacterial endocarditis
- Tuberculosis
- Concurrent use of aspirin or other platelet drugs

Contraindications of Anticoagulants

Warfarin

- Same as heparin
- Pregnancy – increased chances of birth defects (Skeletal muscles)
- Necrosis of soft tissues

Fibrinolytic system



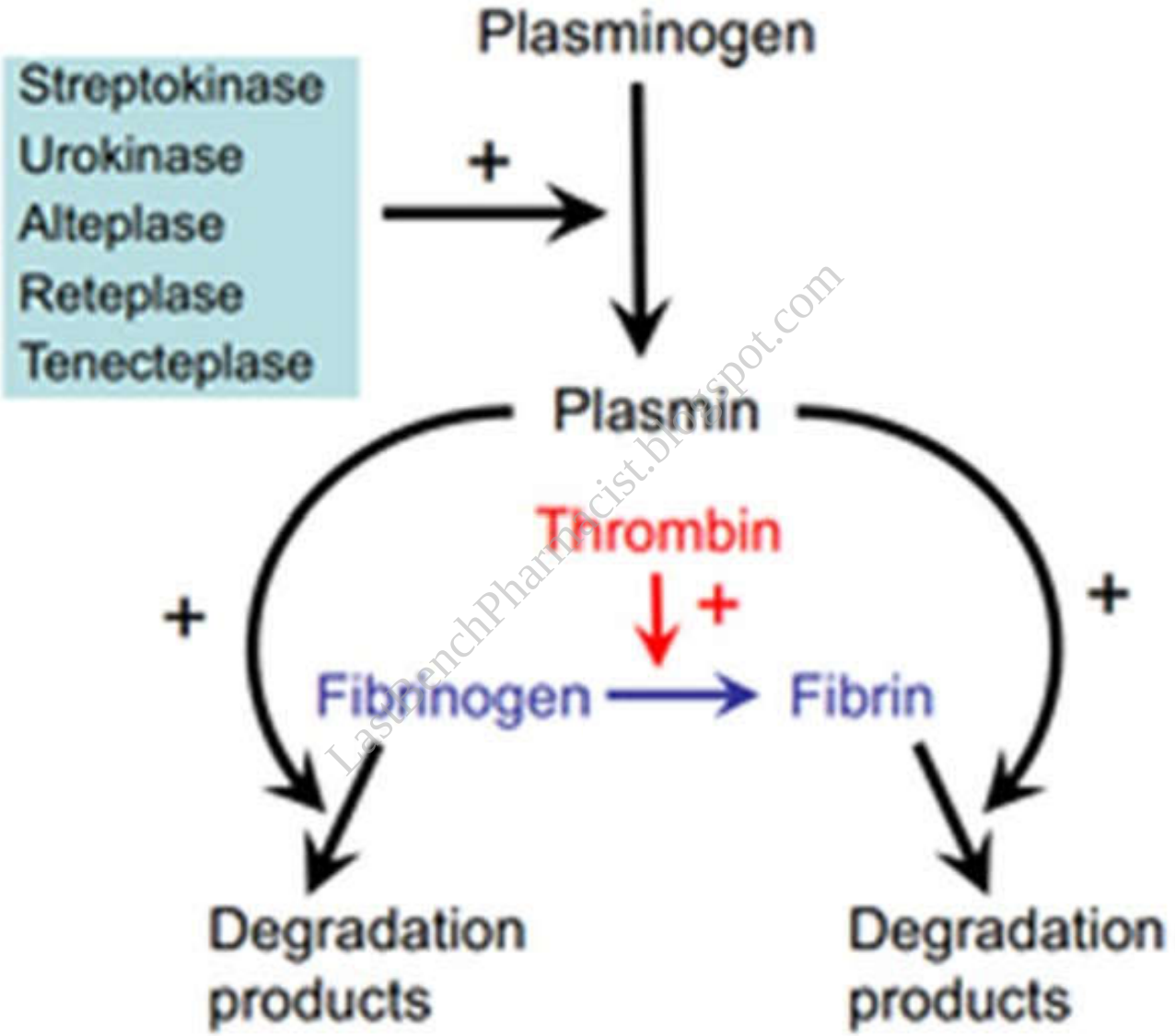
Fibrinolytic drugs

- To lyse (dissolve) thrombi (clot) in blood vessels (coronary artery)
- Activates fibrinolytic system

Drugs include

- Streptokinase
- Antistreplase
- Alteplase
- Reteplase
- Tenecteplase
- Urokinase

Mechanism of action of Fibrinolytics



Streptokinase

- Protease enzyme obtained from β– haemolytic streptococci
- Forms 1:1 complex with proactivator plasminogen
- Catalyses the conversion of inactive plasminogen to active plasmin
- Lysis of fibrin plug
- Breaks down fibrin plug
- Fibrin specificity is less

Alteplase

- Tissue type plasminogen activator (tPA)
- Prepared by recombinant DNA technology using human tissue culture
- Low affinity to circulating free plasminogen
- Rapidly activates plasminogen bound to fibrin in thrombus
- High fibrin specific

Other fibrinolytic drugs

Reteplase

- Recombinant tissue plasminogen activator
- Long half life (15-20 min)

Tenecteplase

- Genetically engineered mutant form of alteplase
- Half life 2 hours

Urokinase

- Protease enzyme
- Direct plasminogen activator
- Degrade fibrin & fibrinogen

Summary

- Oral anticoagulant – warfarin inhibits vit K reductase
- Activity of warfarin is increased with enzyme inhibitors while it is decreased with enzyme inducers
- Anticoagulants are used in cardiac diseases, cerebrovascular diseases, pulmonary embolism
- Fibrinolytic drugs lyse (dissolve) thrombi (clot) in blood vessels (coronary artery)
- Drugs include – streptokinase, urokinase, alteplase, reteplase, tenecteplase