DRUGS FOR DISORDERS OF HEMOSTASIS

HEMOSTASIS

Trauma to the vascular system initiates a complex series of interactions between platelets, endothelial cells, and the coagulation cascade.

- ✓ **Vasospasm of the damaged blood vessel**
- ✓ **Platelet adhesion and aggregation**
- ✓ **Formation of a clot**
- ✓ **Fibrinolysis**

- A clot that adheres to a vessel wall is called a “thrombus”
- Arterial thrombosis usually consists of a platelet-rich clot.
- Venous thrombosis is triggered by blood stasis. Venous thrombosis typically involves a clot that is rich in fibrin, with fewer platelets.

DRUGS FOR THROMBOSIS

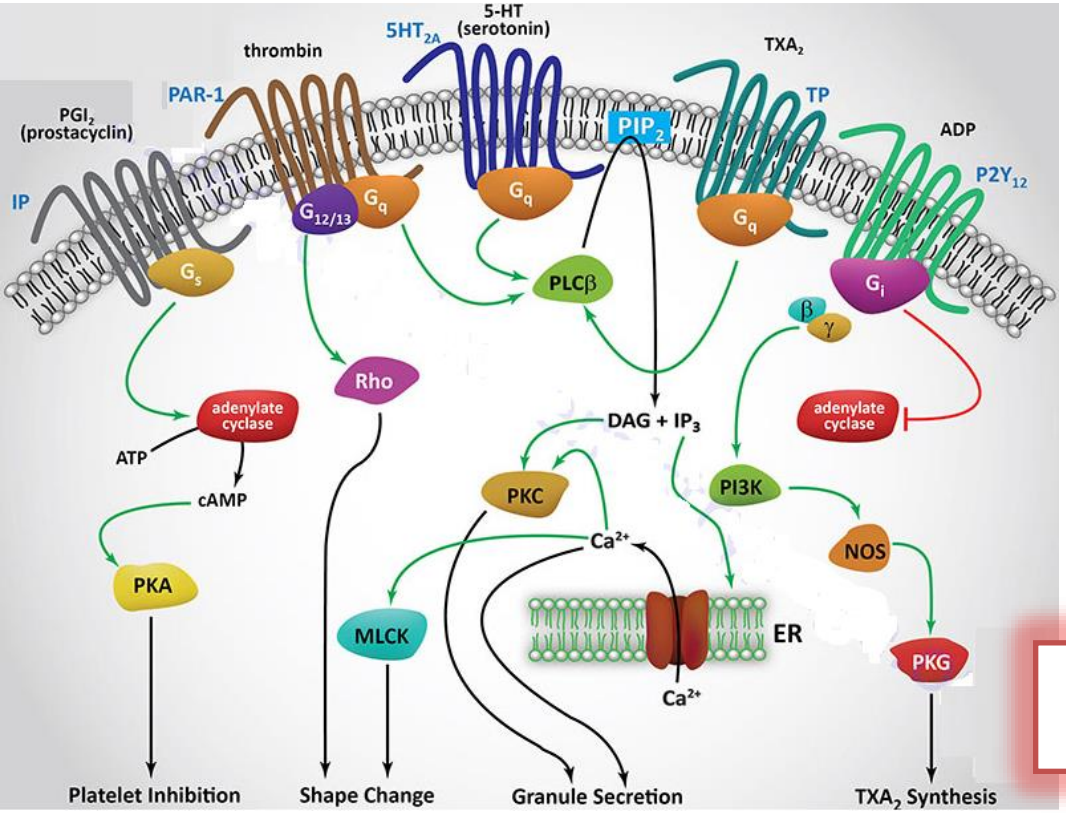
- **PLATELET INHIBITORS (Antiplatelet agents**) – drugs that disrupt Tr aggregation and adhesion
- **ANTICOAGULANTS** – anti-clotting drugs
- **THROMBOLYTICS (Fibrinolytic agents)** – drugs that dissolve the fibrin network

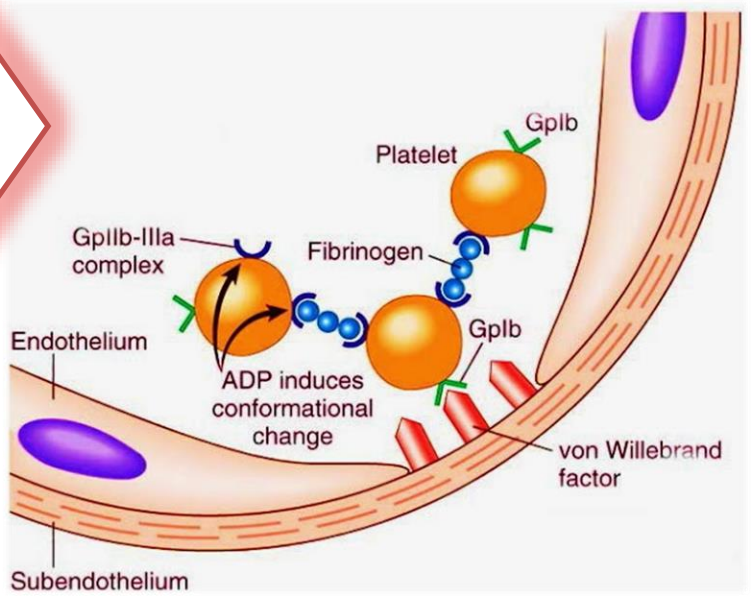
DRUGS FOR BLEEDING

- **Inhibitors of Fibrinolysis**
- Protamine sulfate (Heparin antidote)
- Vitamin K1 (Warfarine antidote)

Antiplatelet agents

Thrombocyte Receptors





Antiplatelet agent: Classification

❑ COX Inhibitors

- ***Acetylsalicylic acid*** **(T 0,05; 0,1; 0,3)**

❑ P2Y12 ADP receptor blockers

- ***Clopidogrel*** **(T 0,075)**
- ***Prasugrel***
- ***Ticagrelor***
- *Ticlopidine*

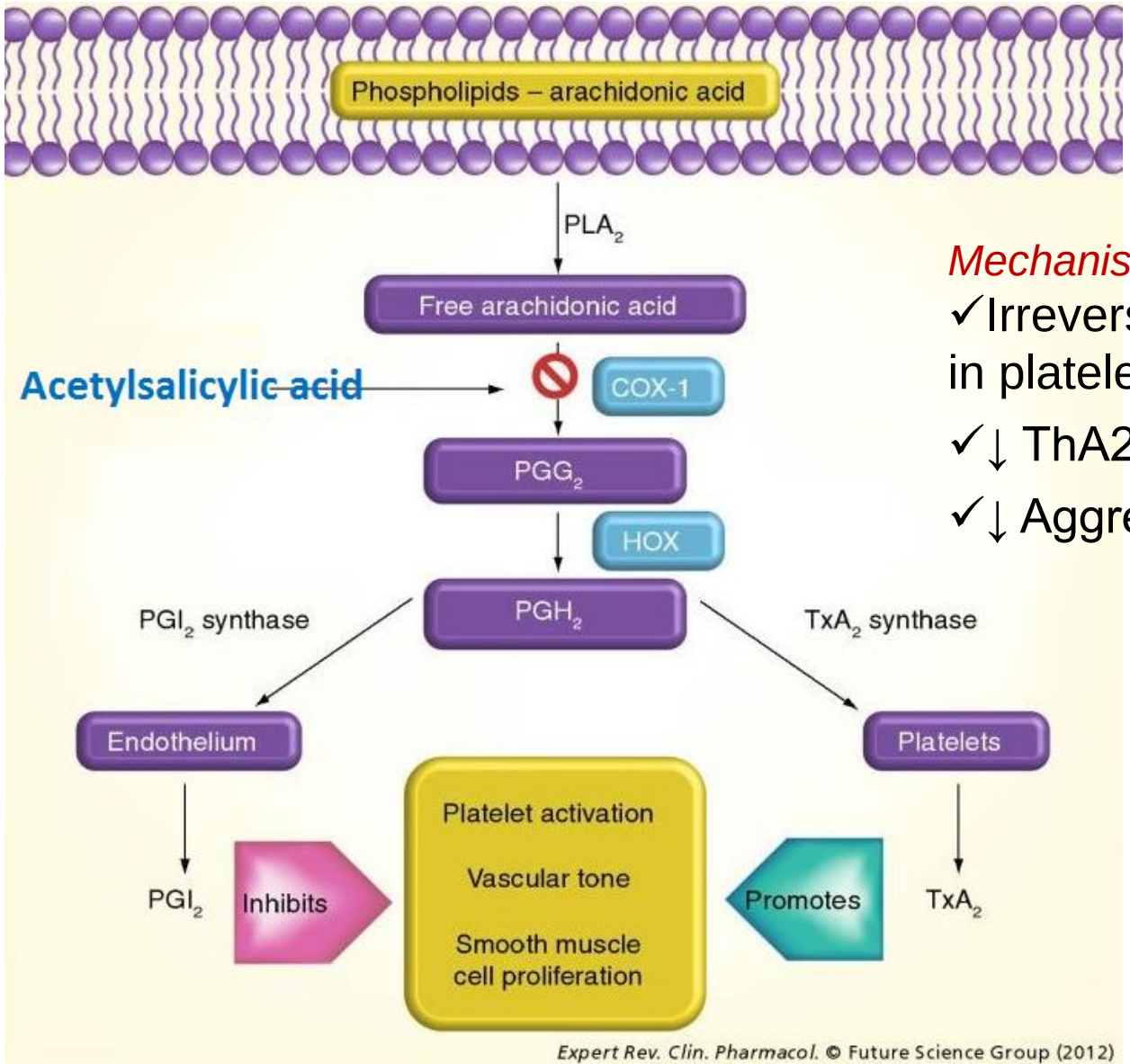
❑ Phosphodiesterase Inhibitors

- ***Dipyridamole***
- *Cilostazol*

❑ GP IIb/IIIa receptor blockers

- ***Abciximab*** **(A 0,2%-5,0 for i.v.)**

Acetylsalicylic acid



Mechanism of action

✓Irreversible inhibits of COX-1 in platelets

✓↓ ThA2

✓↓ Aggregation of platelets

Acetylsalicylic acid

Pharmacological Effects

In low doses

- ✓ *Antiaggregant*

In greater doses

- ✓ *Analgesic-Antipyretic*
- ✓ *Anti-inflammatory*

Side Effects

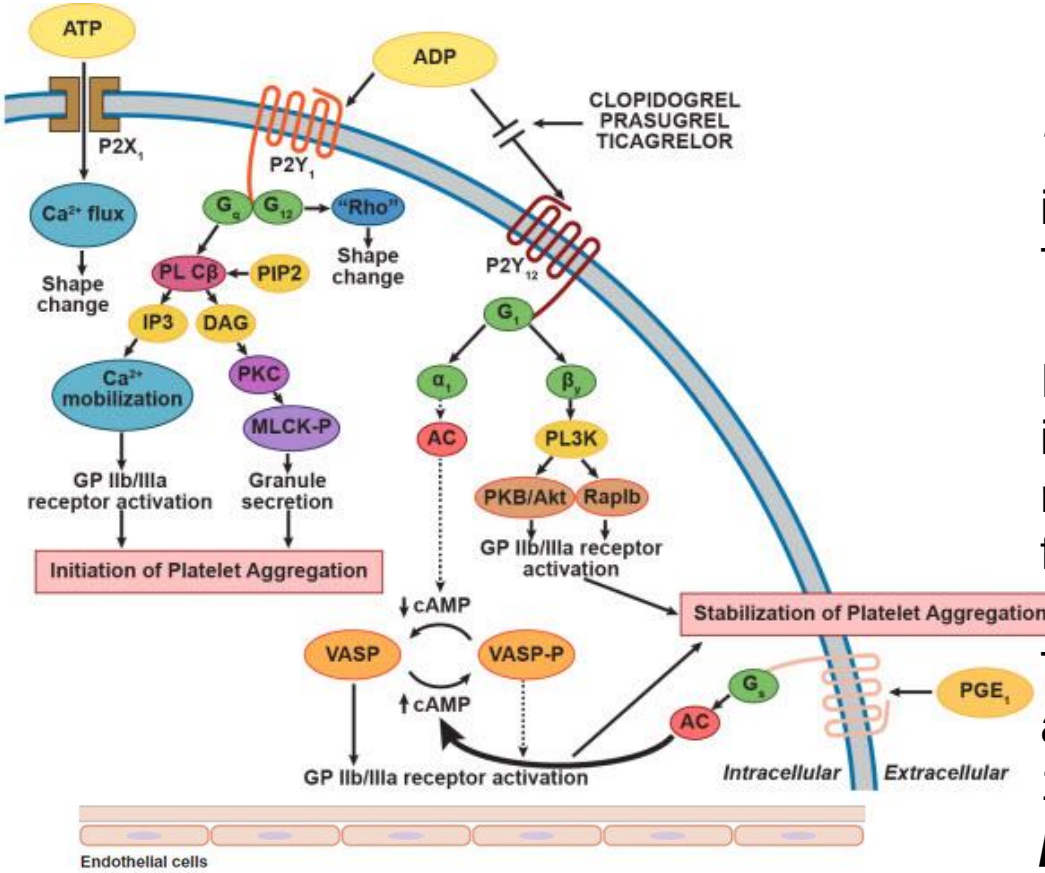
- ✓ Gastrointestinal ulceration
- ✓ Risk of bleeding
- ✓ Bronchospasm…

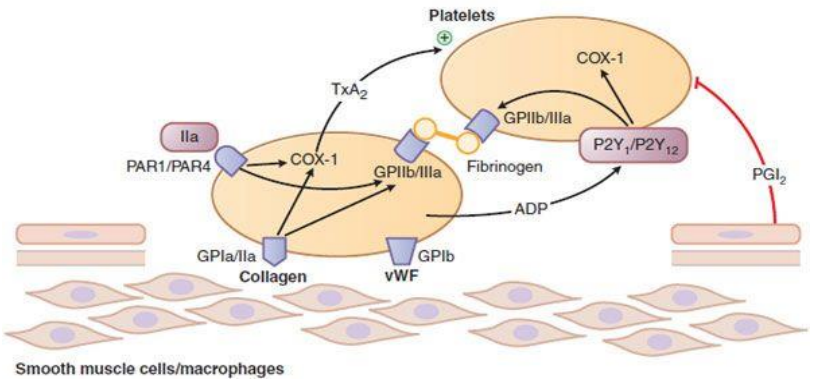
Therapeutic use:

prophylaxis of thrombosis (50-325 mg daily)

- transient cerebral ischemia
- to reduce the incidence of recurrent MI

Clopidogrel, Prasugrel, Ticagrelor





Ticagrelor binds to P2Y12 ADP Rp in a reversible manner.
The other agents bind irreversibly.

Inhibit the binding of ADP to its Rps, inhibit the activation of the GP IIb/IIIa required for platelets to bind to fibrinogen and to each other

The maximum inhibition of platelet aggregation is achieved in 1-3 h with ***ticagrelor***, *2-4 h with* ***prasugrel,*** *3-5 days with* ***clopidogrel****.*

When treatment is suspended, the platelet system requires time to recover.

Clopidogrel, Prasugrel, Ticagrelor

- They undergo hepatic metabolism by CYP P450 to active metabolites.
- ***Clopidogrel is a prodrug*** *(therapeutic efficacy* relies on its active metabolite), which is produced via metabolism by CYP 2C19.
- Genetic polymorphism of CYP 2C19 leads to a reduced clinical response in patients who are "poor metabolizers" of *clopidogrel.*
- It is recommended ***prasugrel* or *ticagrelor*** *for poor metabolizers*
- *The* drugs that inhibit CYP 2C19, such as *omeprazole and esomeprazole,* should not be administered concurrently with *clopidogrel.*

Side Effects

✓Bleeding

✓Hematologic reactions – agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia. (High risk with *ticlopidine – limited use)*

✓T*icagrelor can diminishe* effectiveness with concomitant use of *aspirin (above 100 mg)*

Dipyridamole

Mechanism of action

✓Inhibits cyclic nucleotide phosphodiesterase,
✓*Increases* intracellular levels of cAMP
✓Decreaseds thromboxane A2 synthesis.
✓Potentiates the effect of PgI_2 and decrease platelet adhesion

Pharmakokinetics

Has variable bioavailability following oral administration.
It is highly protein bound.
Undergoes hepatic metabolism, and is excreted mainly in the feces.

Therapeutic application

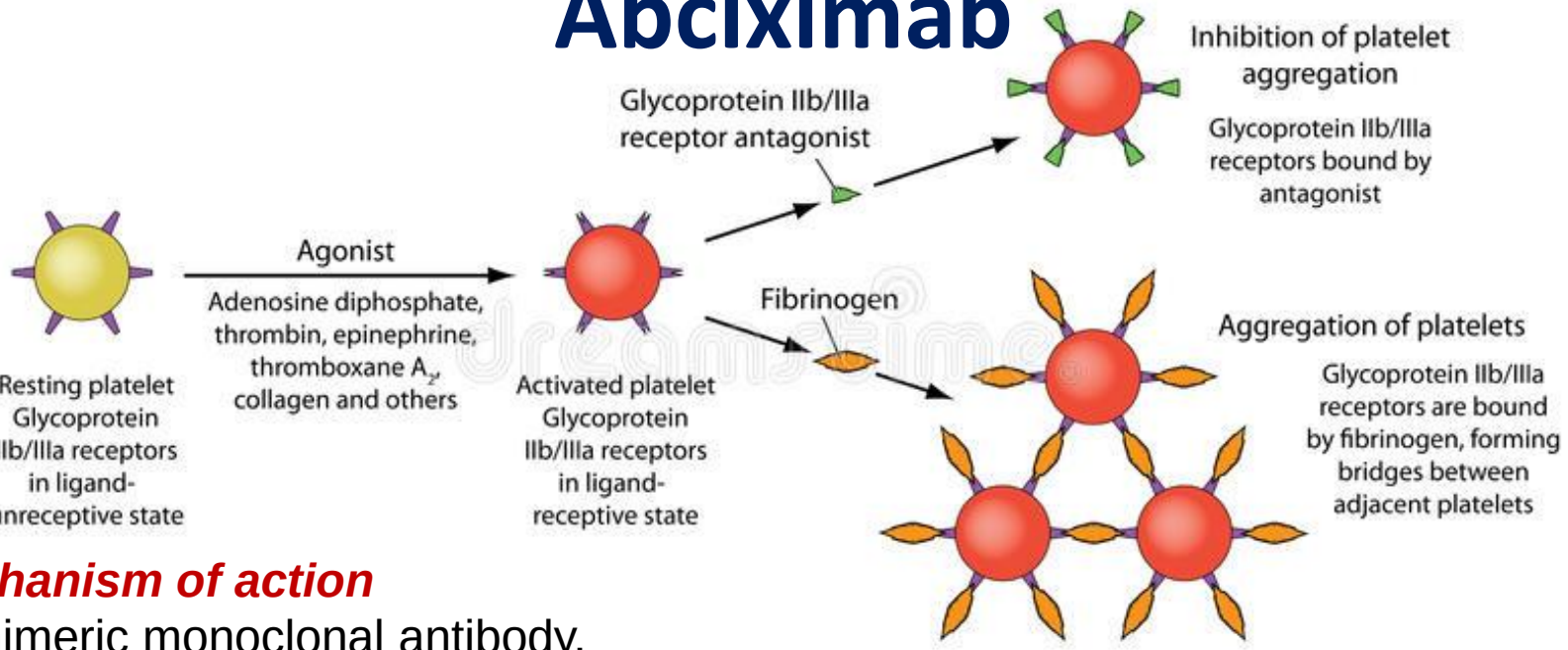
It is used for stroke prevention and is usually given in combination with ASA.

Patients with unstable angina should not use *dipyridamole because of its vasodilating properties, which* may worsen ischemia (coronary steal phenomenon).

Side Effects

Headache
Hypotension (especially if administered i.v.).

Abciximab



Mechanism of action

✓Chimeric monoclonal antibody,

✓ Binds to GP IIb/IIIa, *blocks the binding of* fibrinogen and von Willebrand factor

✓ Aggregation does not occur

Pharmakokinetiks

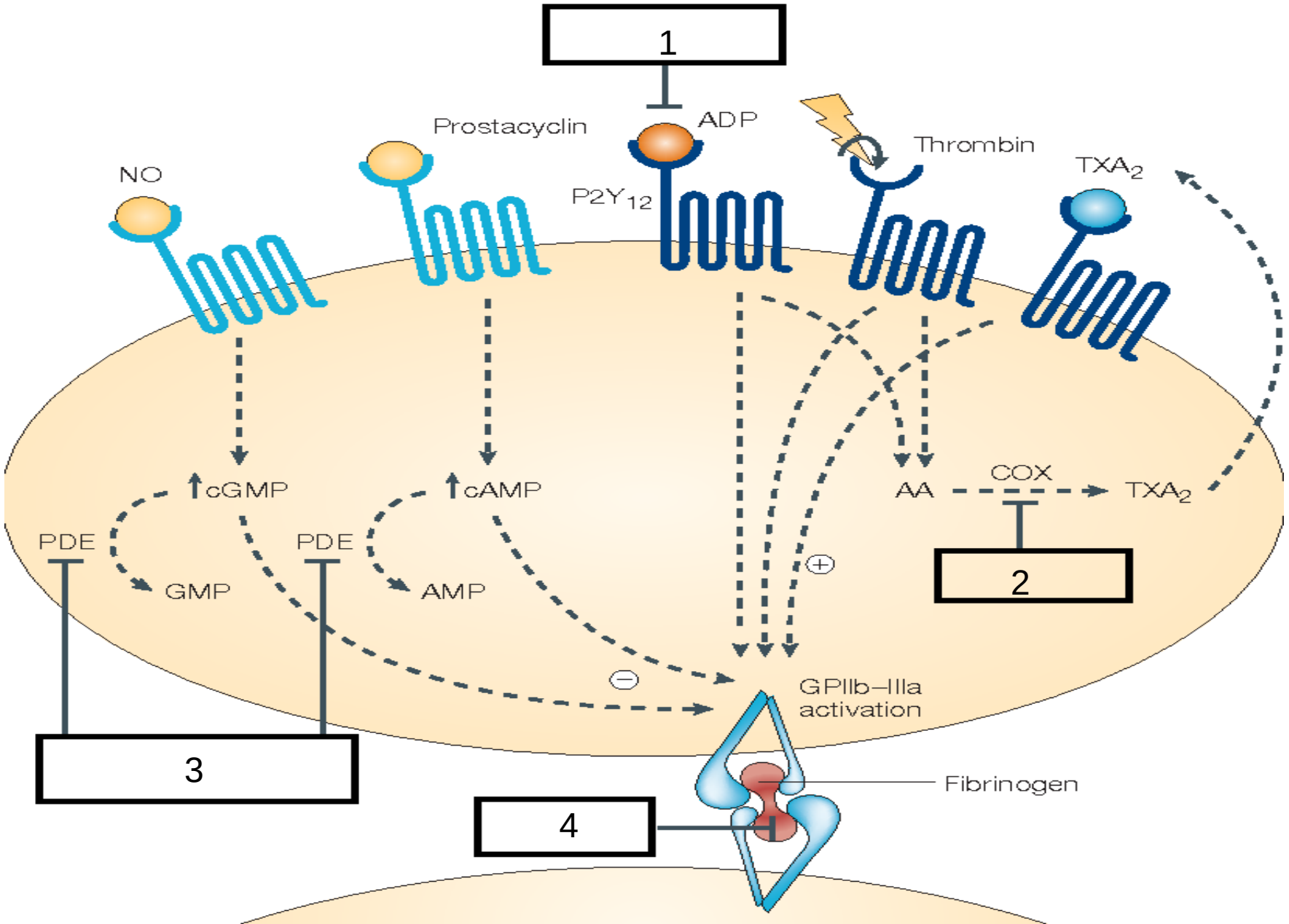
✓*Followed* ***by i.v.*** **infusion** – platelet inhibition within 30 min.

✓*After cessation of* infusion, platelet function gradually returns to normal

✓Pharmacological effect persists for 24-48 h.

Uses: with *heparin and aspirin, as an adjunct to* ***percutaneous coronary intervention*** *for the prevention* of cardiac ischemic complications.

Antiplatelet agent site of action



ANTICOAGULANTS

Anticoagulants: Classification

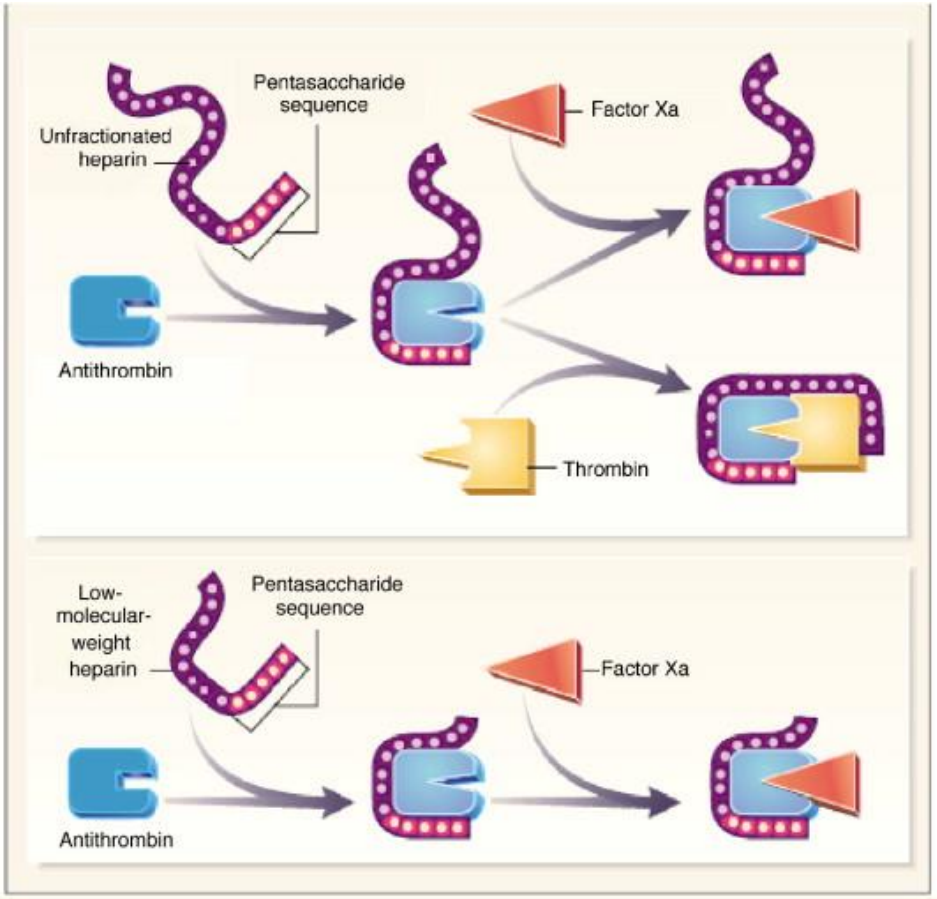
Directly acting

- **Antithrombin III enhancers**
  - **Heparin (A 5 ml for *s.c., i.v.*, 5000 IU/ml)**
  - **Low molecular weight heparins (LMWH)**
    - *Dalteparin*
    - *Enoxaparin* **(A 0,2 – 1,0 ml for s.c., i.v., 10000 IU/ml)**
  - **Synthetic pentasaccharide**
    - *Fondaparinux*
- **Direct clotting factor inhibitors**
  - *Rivaroxaban (inhibits Xa)* **(T 0,01; 0,02)**
  - *Dabigatran (inhibits IIa)* **(T 0,075; 0,15)**

Indirectly acting

- *Warfarin* **(T 0,0025)**

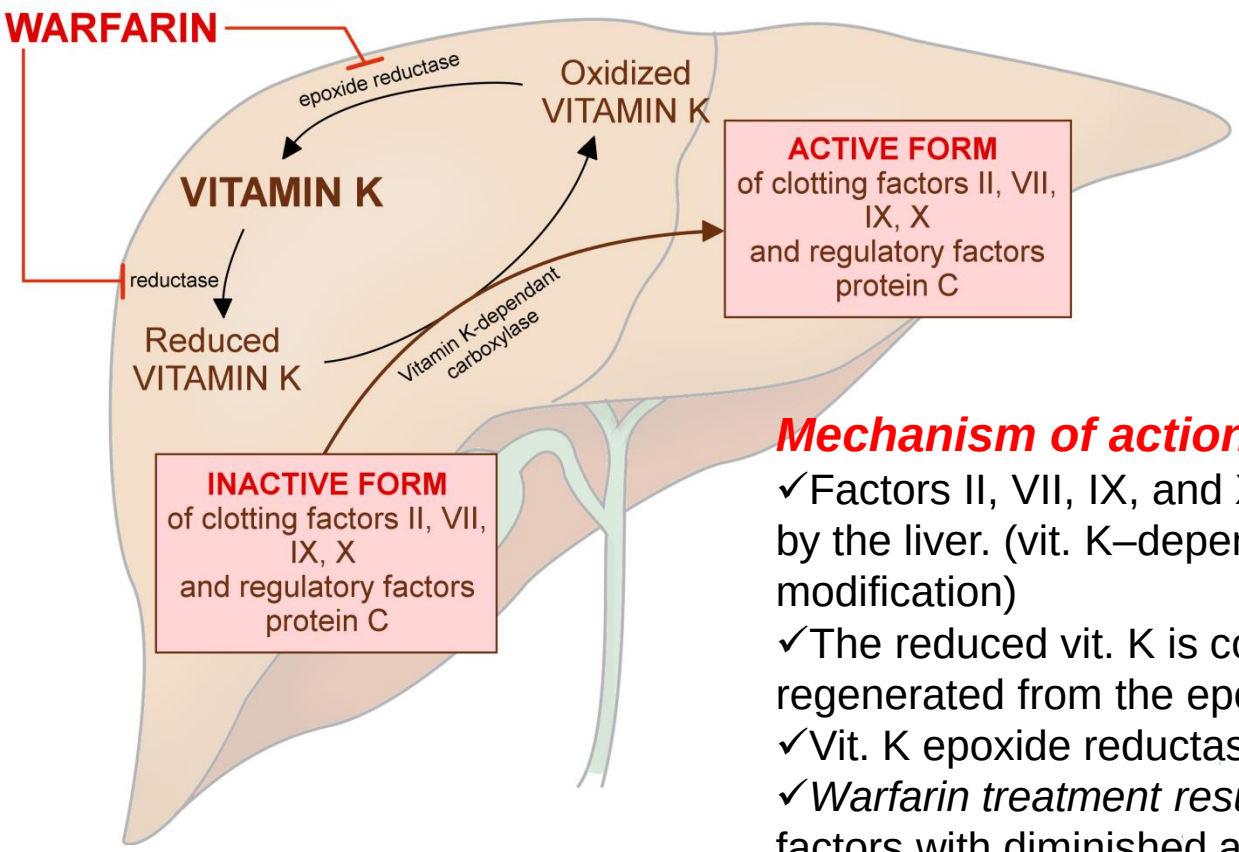
Heparin, LMWH, Fondaparinux



- **Binding to AT III** (unique pentasaccharide sequence *permits their binding)*.
- Conformational change occurs that catalyzes the **inactivation of coagulation factors** (serine proteases – thrombin (factor IIa) and factor Xa…).

LMWHs and Fondaparinux complex with ATIII and inactivate factor Xa but do not bind as avidly to IIa.

Warfarin



Mechanism of action:

✓Factors II, VII, IX, and X require vit.K for their synthesis by the liver. (vit. K–dependent posttranslational modification)

✓The reduced vit. K is converted to vit. K epoxide. Vit. K is regenerated from the epoxide by vit. K epoxide reductase,

✓Vit. K epoxide reductase is inhibited by *warfarin.*

✓*Warfarin treatment results in the production* of clotting factors with diminished activity (10% to 40% of normal)

✓*Anticoagulant effects of warfarin are not observed* immediately after drug administration. Peak effects may be delayed for 72 to 96 h.

✓The anticoagulant effects of *warfarin* can be overcome by the administration of *vitamin K.*

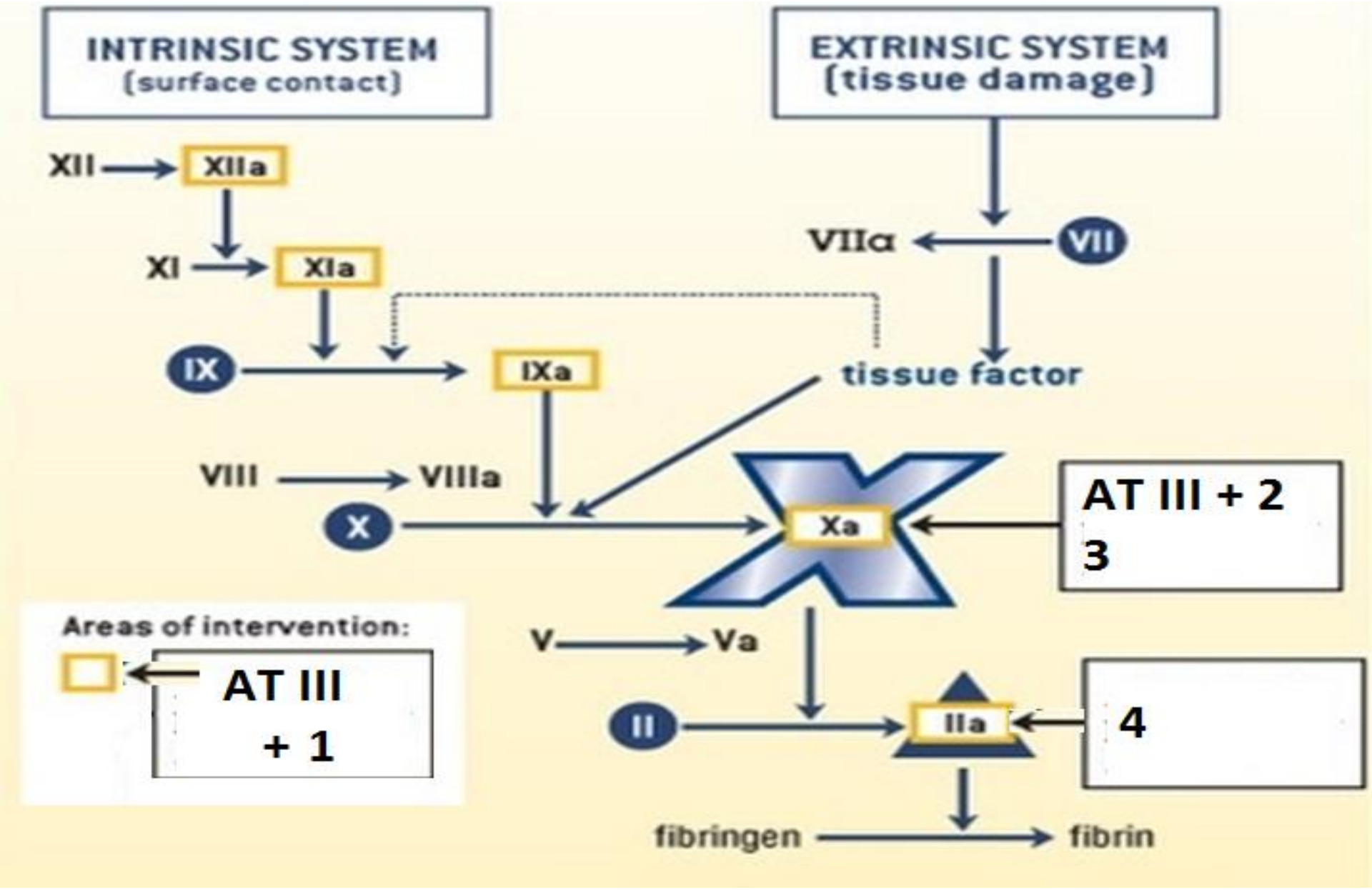
Antithrombin (AT) Enhancers: Heparin, LMWH, Fondaparinux

	Heparin	LMWH (enoxaparin)	Fondaparinux
Source	Endogenous Polysaccharide (bovine and porcine lung/intestine)	Derived from UFH	Synthetic (small molecule)
Chain Length	~45 saccharide units	~15 saccharide units	5 saccharide units
Route	IV, Subcutaneous	Subcutaneous, IV	Subcutaneous, IV
Time to Cmax	SC: 20-30 min (erratic absorption)	SC: 3-4.5 hours (predictable absorption)	SC: 2-3 hours (predictable absorption)
Half Life	0.5 to 2 hours	~4 to 7 hours (Daily to BID dosing)	15-17 hours (Daily SC dosing)
Dosing in Renal Impairment	No adjustment needed; Preferred agent for ESRD/dialysis patients	Adjust doses; Not recommended for dialysis patients	Adjust doses; Contraindicated when CrCl<30 mL/min
Laboratory monitoring	aPTT, ACT, anti-factor Xa Platelet monitoring	Not routinely recommended; optional anti-factor Xa assay Platelet monitoring	Not routinely recommended; optional anti-factor Xa assay

Warfarine *vs.* Heparin

	Warfarin	Heparin
Mechanism	Inhibits Vit K epoxide reductase	Potentiates ATIII
Route of Admin	Oral	Subcutaneous, IV
Time Course	Slow onset, long duration	Rapid onset, short duration
Placenta	Crosses	Does NOT Cross
Reversal	Vit K, fresh frozen plasma (FFP); prothrombin complex concentrate (PCC)	protamine

Anticoagulants: Site of Action



THROMBOLYTICS
AND
INHIBITORS OF FIBRINOLYSIS

Alteplase (A 0,05 for i.v.)
Tenecteplase
Urokinase
Streptokinase

Tranexamic acid (T 0,5; A 10% - 5 ml for i.v.)
Aminocaproic acid

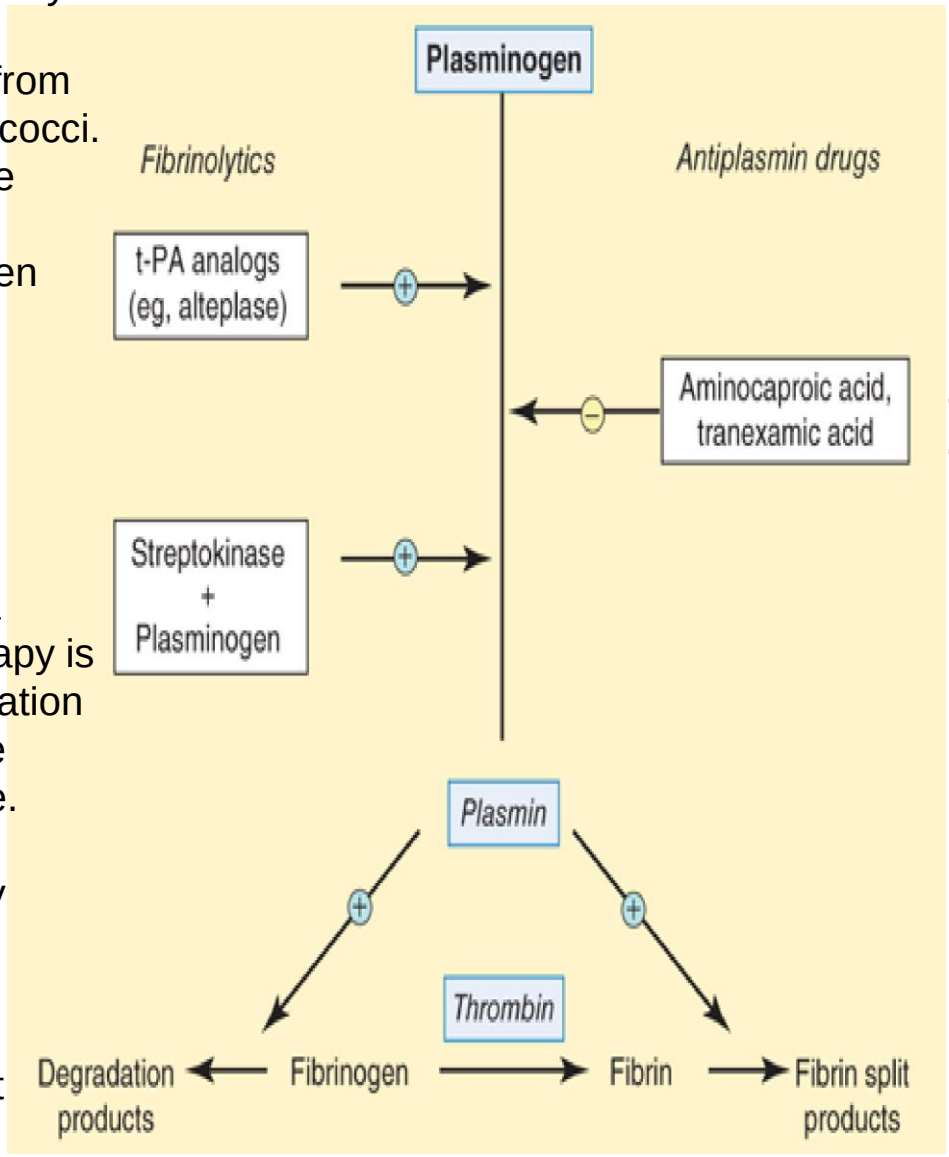
Mechanism of Action

Urokinase is produced naturally by the kidneys.
Streptokinase is an protein from group C β-hemolytic streptococci. It forms an active one-to-one complex with plasminogen.
Alteplase (tissue plasminogen activator or tPA) is a serine protease of human cells.

Convert plasminogen to plasmin

Clot dissolution occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age.

Increased local thrombi may occur as the clot dissolves, leading to thrombosis.
To prevent this include administration of antiplatelet drugs, *or heparin.*



Aminocaproic acid
Tranexamic acid

- synthetic agents
- orally active

Inhibit plasminogen activation

Tranexamic acid is 10 times more potent than aminocaproic acid.

Potential side effect is intravascular thrombosis.

Thanks for Attention!