THROMBOLYTIC DRUGS

(Fibrinolytic drugs)

By

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Learning objectives

- To know mechanism of action of thrombolytic therapy.
- To differentiate between different types of thrombolytic drugs.
- To describe indications, side effects and contraindications of thrombolytic drugs.
- To recognize the mechanisms, uses and side effects of antiplasmins.

Definition of Thrombolytics

Thrombolytic agents are drugs used to lyse **already** formed blood clots in clinical settings where ischemia may be fatal.

Mechanism of action of thrombolytic drugs

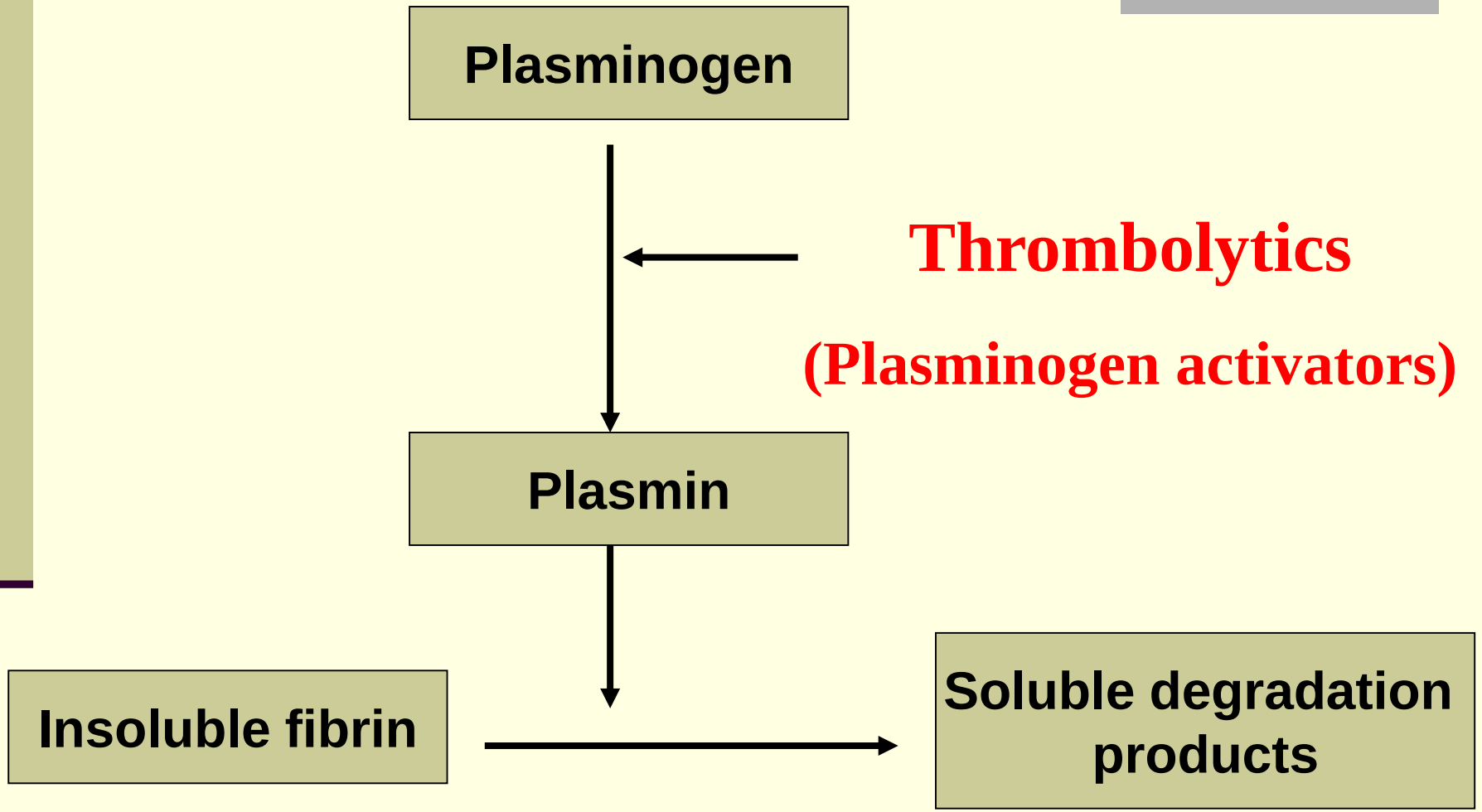
They have common mechanism of action by stimulating **activation of plasminogen** via converting **plasminogen** (pro-enzyme) to **plasmin** (active enzyme) → lysis of the insoluble fibrin clot into soluble derivatives.

What is plasmin?

Plasmin: is a nonspecific **protease** capable of breaking down:

- **Fibrin**
- **Other circulating proteins** including fibrinogen, clotting factor V & factor VIII.

Thrombolytic drugs
Plasminogen activators



Indications of thrombolytics

used for the treatment of thromboembolic disorders as:

- Acute myocardial infarction (ST elevation, STEMI).
- Acute ischemic stroke.
- Peripheral artery occlusion.
- Deep venous thrombosis.
- Pulmonary embolism.

Types of thrombolytic drugs

Non-fibrin specific

Streptokinase

Anistreplase

Urokinase

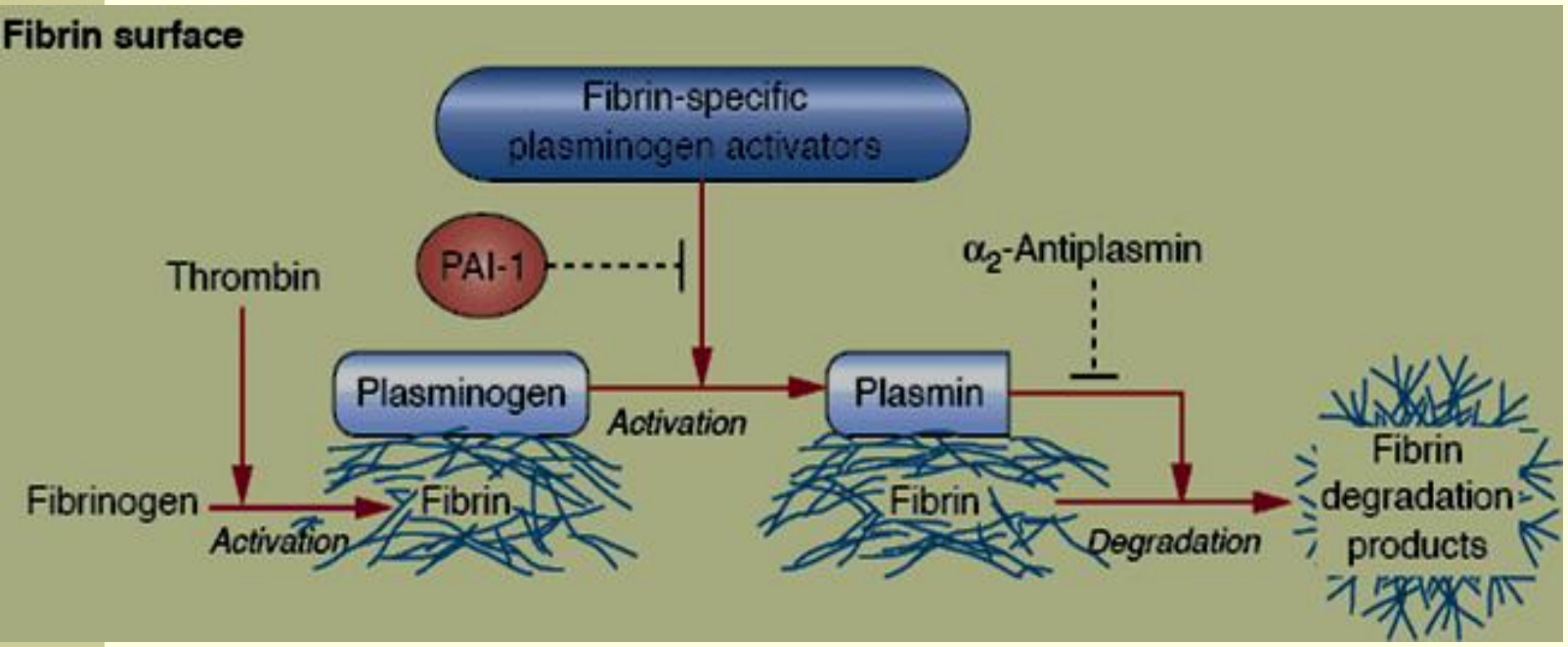
Fibrin specific

Tissue plasminogen

Activators (t-PA)

- Alteplase
- Reteplase
- Tenecteplase

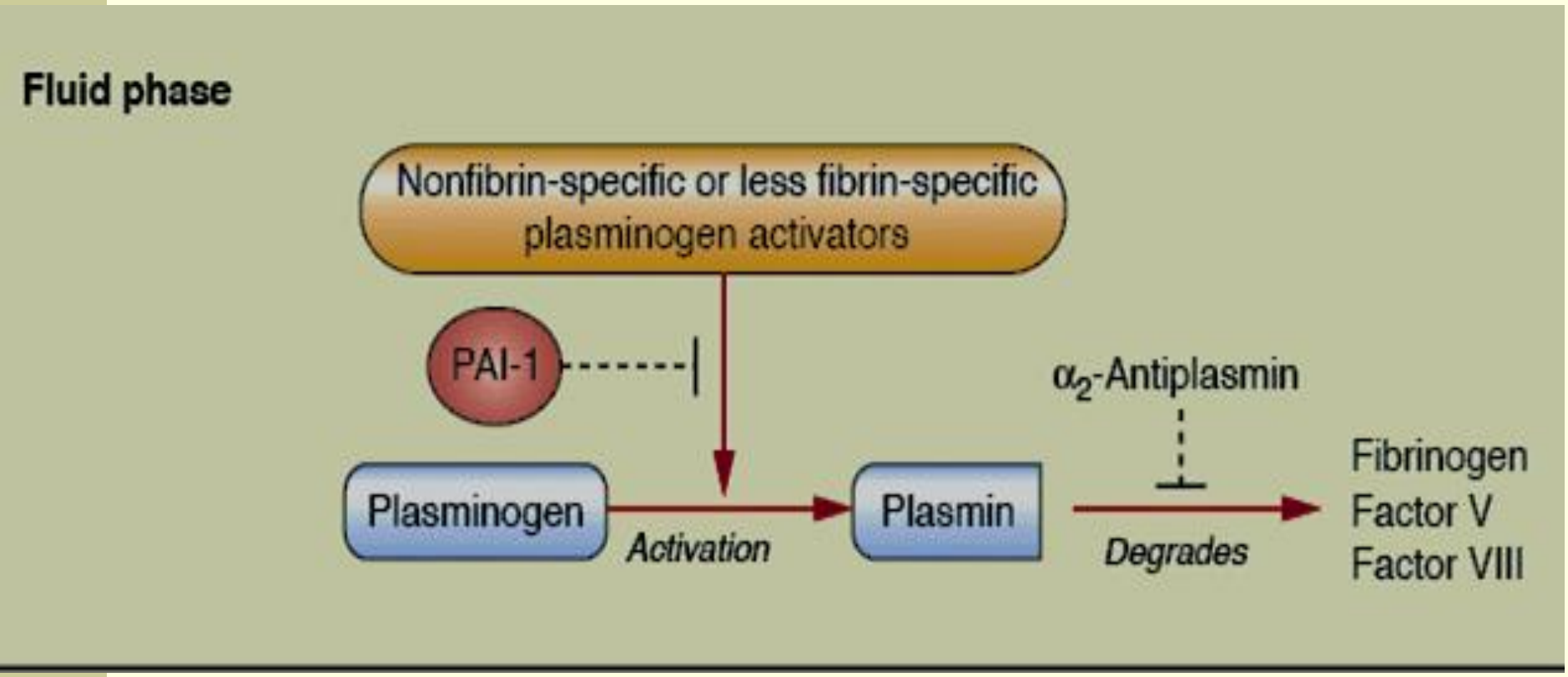
Fibrin specific plasminogen activators



Fibrin specific plasminogen activators activate **mainly plasminogen bound to clot surface** and have less effect on circulating plasminogen.

PAI= plasminogen activator inhibitor

Non-fibrin specific plasminogen activators



Activate both **plasminogen bound to clot surface and circulating plasminogen in blood** leading to extensive systemic plasminogen activation, with degradation of several plasma proteins including fibrinogen, factor V, and factor VIII.

Non fibrin-specific thrombolytic drugs	Fibrin-specific thrombolytic drugs
Activate plasminogen bound to clot surface and circulating plasminogen in blood	activate **mainly** plasminogen bound to clot surface **(fibrin specific)**
Degrade fibrin clots as well as fibrinogen and other plasma proteins.	Degrade mainly fibrin clots
Less selective in action	**More** selective in action (clot or fibrin specific)
Extensive systemic plasminogen activation	**Less** systemic plasminogen activation
More risk of bleeding	**Less** risk of bleeding
Streptokinase Anistreplase Urokinase	Alteplase Reteplase Tenecteplase

Non fibrin-specific thrombolytic drugs

e.g. Streptokinase – Anistreplase – Urokinase

- activates plasminogen both in blood and at the clot surface thus produces clot lysis and systemic fibrinolysis leading to **bleeding.**

Fibrin-specific thrombolytic drugs

- are tissue plaminogen activators
- e.g. Alteplase – Reteplase -Tenecteplase
- selective in action (clot or fibrin specific)
- binds preferentially to plasminogen at the fibrin surface (non-circulating) rather than circulating plasminogen in blood.
- Risk of bleeding is less than non specific agents.
- Activity is enhanced upon binding to fibrin.

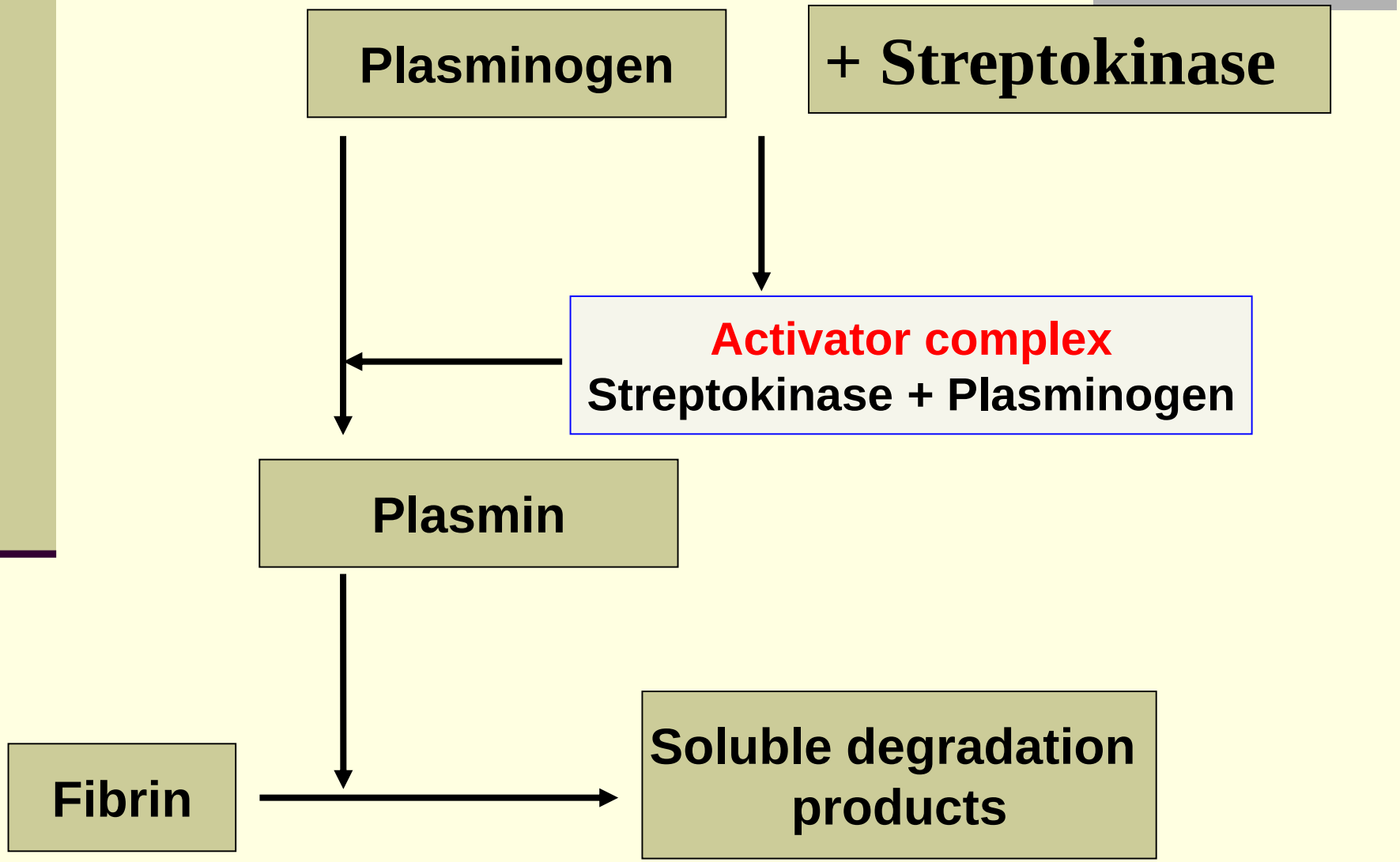
Non fibrin-specific thrombolytic drugs

- Streptokinase
- Anistreplase
- Urokinase

Streptokinase (SK)

- **Is** a bacterial protein produced by B-hemolytic streptococci.
- It acts indirectly by forming plasminogen-streptokinase complex "activator complex" which converts inactive plasminogen into active plasmin.
- Streptokinase is non-fibrin specific
- can degrade fibrin clots as well as fibrinogen and other plasma proteins.

Mechanism of action of streptokinase



Streptokinase

- T 1/2 = less than **20 minutes.**
- given as intravenous infusion (250,000 U then 100,000 U/h for 24-72 h).
- It is the least expensive among others.
- used for venous or arterial thrombosis.

Side effects of streptokinase

- Antigenicity: high-titer antibodies develop 1 to 2 weeks after use, precluding retreatment until the titer declines.
- Allergic reaction: like rashes, fever, hypotension
- Bleeding due to activation of circulating plasminogen (systemic fibrinolysis).
- Not fibrin specific.

Precautions

Not used in patients with:

- Recent streptococcal infections or
- Previous administration of the drug
- These patients may develop fever, allergic reactions and resistance upon treatment with streptokinase due to **antistreptococcal antibodies.**

Anistreplase (APSAC)

- **Anisoylated Plasminogen Streptokinase Activator Complex (APSAC) acylated** plasminogen combined with streptokinase.
- It is a **prodrug,** de-acylated in circulation into the active plasminogen-streptokinase complex.
- $T_{1/2}$ is **70-120 min**

Advantages

- Given as a bolus I.V. injection (30 U over 3 - 5 min.).
- Longer duration of action than streptokinase.
- More thrombolytic activity.
- Greater clot selectivity.

Disadvantages

Similar but less than streptokinase alone in:

- Antigenicity.
- Allergic reactions.
- Minimal fibrin specificity
- Systemic lysis.

But more expensive than streptokinase

Urokinase

- Human enzyme synthesized by the kidney
- obtained from either urine or cultures of human embryonic kidney cells.
- is a **direct** plasminogen activator.
- Given by intravenous infusion (300,000 U over 10 min then 300,000 U/h for 12h).

Urokinase

- Has an elimination half-life of 12-20 minutes.
- Used for the lyses of acute massive pulmonary emboli

Advantages No anaphylaxis (not antigenic).

Disadvantages

- Minimal fibrin specificity
- Systemic lysis (acts upon fibrin-bound and circulating plasminogen).
- Expensive (its use is now limited).

Tissue Plasminogen Activators (t-PAs)

- All are recombinant human tissue plasminogen activators (t–PA).
- Prepared by recombinant DNA technology.
- Include drugs that end with suffix "**plase**"
  - Alteplase
  - Reteplase
  - Tenecteplase

Mechanism of t-PAs

- They activate fibrin-bound plasminogen rather than free plasminogen in blood.
- Their action is enhanced by the presence of fibrin.
- They bind to fibrin in a thrombus and convert the entrapped plasminogen to plasmin followed by activated local fibrinolysis with limited systemic fibrinolysis.

Advantages of t-PAs

- Fibrin-specific drugs (clot specific).
- Limited systemic fibrinolysis.
- Reduced risk of bleeding
- Not-antigenic (can be used in patients with recent streptococcal infections or antistreptococcal antibodies).

Alteplase

- is a recombinant form of human tPA.
- has very short half life (~5 min)
- is usually administered as an intravenous bolus followed by an infusion.
- (60 mg i.v. bolus + 40 mg infusion over 2 h).

Uses

- In ST-elevation myocardial infarction (STEMI)
- Pulmonary embolism.

Reteplase

- A variant of recombinant tPA
- It has longer duration than alteplase (15 min.)
- Has enhanced fibrin specificity
- Given as two I.V. bolus injections of 10 U each

Uses

- In ST-elevation myocardial infarction (STEMI)
- Pulmonary embolism.

Tenecteplase

- Is another modified human t-PA.
- prepared by recombinant technology
- It has half life of more than 30 min.
- It can be administered as a single IV bolus.
- It is more fibrin-specific & longer duration than alteplase.
- It is only approved for use in acute myocardial infarction.

What is the role of thrombolytic therapy in antithrombotic plan ?

- The goal of **thrombolytic therapy** is rapid restoration of blood flow in an occluded blood vessel by accelerating proteolysis of the already formed thrombus.

Rational for use of thrombolytic drugs in AMI

- Improvement of ventricular function
- Reduction of the incidence of congestive heart failure
- Reduction of mortality following AMI.
- Thrombolytic drugs need to be given immediately to the patient after diagnosis of MI, delay in administration will be of no value.

What is the role of thrombolytic therapy in antithrombotic plan ?

- **Thrombolytic therapy** is one part of an overall antithrombotic plan that frequently includes anticoagulants, antiplatelet agents and mechanical approaches to rapidly restore blood flow and prevent re-occlusion.

Contraindications to thrombolytics

Absolute contraindications include:

- Active internal bleeding
- Cerebral hemorrhagic stroke
- Recent intracranial trauma or neoplasm
- Major surgery within two weeks

Relative contraindications include:

- Active peptic ulcer
- Severe uncontrolled hypertension

Contraindications to thrombolytics

Absolute	Relative
Previous intracranial haemorrhage or stroke of unknown origin at any time	Transient ischaemic attack in the preceding 6 months
Ischaemic stroke in the preceding 6 months	Oral anticoagulant therapy
CNS damage or neoplasms or AV malformation	Pregnancy or within one week postpartum
Recent major trauma/surgery/head injury (within the preceding 3 weeks)	Refractory hypertension (systolic pressure >180 mmHg and/or diastolic pressure >110 mmHg)
GI bleeding within the past month	Advanced liver disease
Known bleeding disorder (excluding menses)	Infective endocarditis
Aortic dissection	Active peptic ulcer
Non-compressible punctures in the past 24 hrs (e.g., liver biopsy, lumbar puncture)	Prolonged or traumatic resuscitation

Fibrinolytic Inhibitors

Fibrinolytic inhibitors (**Antiplasmins)** inhibit plasminogen activation and thus inhibit fibrinolysis and promote clot stabilization.

Fibrinolytic Inhibitors
Antiplasmins

- **Aminocaproic Acid & tranexamic cid**

✓ acts by competitive inhibition of plasminogen activation

✓ Given orally

- **Aprotinin**

✓ It inhibits fibrinolysis by blocking the action of plasmin **(plasmin antagonist)**

✓ Gien orally or i.v.

Uses of Fibrinolytic Inhibitors

- ✓ Adjuvant therapy in hemophilia
- ✓ Fibrinolytic therapy-induced bleeding (antidote).
- ✓ Post-surgical bleeding
- ✓ These drugs work like antidotes for fibrinolytic drugs. Similar to **Protamine** (Antidote of the anticoagulant, heparin) or **Vitamin K** (Antidote of the oral anticoagulant warfarin).