432

# Pharmacology Team

## Lecture Thrombolytic Drugs

*Revised by: Shroog Al-harbi*

## 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.

# Thrombolytic Drugs

Drugs that are used to lyse already formed blood clots **(Not to prevent their formation)**

**Indications of thrombolytics**

1-Acute myocardial infarction (ST elevation, STEMI).

2-Acute ischemic stroke.

3-Peripheral artery occlusion.

4-Deep venous thrombosis.

5-Pulmonary embolism.

These agents are given immediately after a **MI.**

**Goal of treatment :** To restore the flow of blood in an already occluded vessel.

**Mechanism of Action (MoA):**

These agents have a common MoA Which is Activating **Plasminogen( a Zymogen)**
**( proenzyme)** Into **Plasmin (Active form of the Enzyme)**

**Plasmin :** a nonspecific serine protease that is capable of breaking the fibrin clot as well as other circulating proteins such as : Fibrinogen( inactive for of fibrin) Factor V and Factor V11 .

**1)Fibrin-Specific Agents(Tissue Plasminogin Activators)(t-PA): Remmember (ART):**

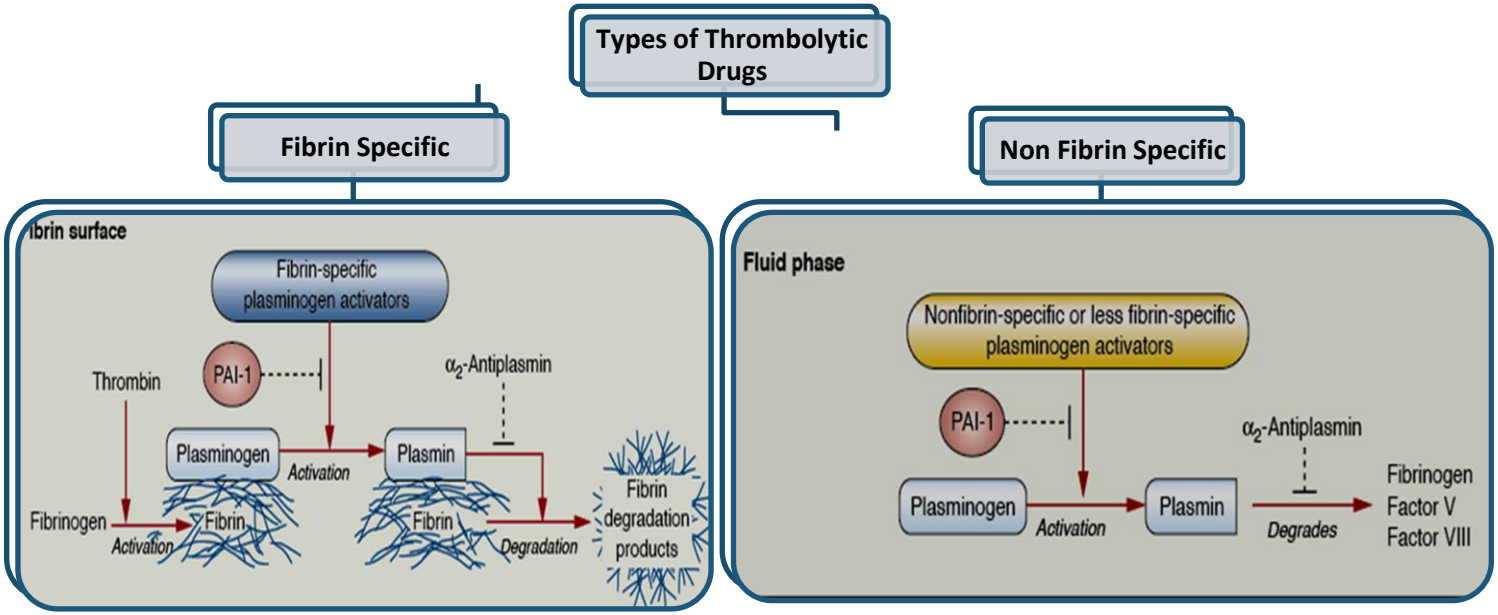
Alteplase, Reteplase, Tenecteplase

- **Selective** in nature(Fibrin Specific)
- Bind to Plasminogen at the fibrin surface (**Non circulating**) rather than the circulating
- Activity is enhanced upon **binding to fibrin**
- Risk of **bleeding is LESS**.

## 2)NON Fibrin Specific Agents: Remmeber (USA):

Urokinase, Streptokinase, Anistreplase

- Bind equally to circulating **and non-circulating**
- Breaks the fibrin**(Fibrinolysis)** through surface Plasminogen as well as circulating Fibrinogen**(Fibrinogenolysis)**
- Risk of **bleeding is INCREASE**




**Contraindications to Thrombolytics**

- Active internal bleeding
- Recent intracranial trauma or neoplasm
- Cerebral hemorrhagic stroke
- Cerebrovascular disease
- Major surgery within two weeks
- Active peptic ulcer
- Severe uncontrolled hypertension

**Fibrinolytic Inhibitors (Antiplasmin)** =>inhibit plasminogen activation and thus inhibit fibrinolysis and promote clot stabilization.
Aminocaproic Acid & tranexamic acid: acts by competitive inhibition of **plasminogen** activation (ORAL)

Aprotinin: It inhibits fibrinolysis by blocking **plasmin**(ORAL or IV)

**Protamine (Antidote of heparin) , Vit K (Antidote of Warfarin)**

Non-Fibrin Specific Agents

| Drug | Pharmacodynamics | Pharmacokinetics | uses | S/E | NOTES |
|---|---|---|---|---|---|
| **Streptokinase (SK)** | Binds to plasminogen forming the "Activator Complex" that functions to activate other Plasminogin (INDIRECT ACTION) | Half-life less than 20 minutes<br>Given as IV infusion | Arterial and venous thrombosis<br><br>Life thretaning Thrombosis | Bleeding<br>Antigenicity | A product of beta Hemolytic Streptococci<br><br>Not used with Pts who had a recent srep infection and who already received the drug |
| **Anistreplase (APSAC)** | **Acylated** Plasminogin-Streptokinase complex<br>A Prodrug de-acylated in the circulation into active complex | Given as bolus injection<br>Longer duration than SK(The main fiffrence)<br>More thrombolytic activity Grater Selectivity | | Has the S/E of SK but less Antigenicity<br>Systemic Lysis | More expensive than SK |
| **Urokinase** | Act DIRECTLY to convert Plasminogin into Plasmin | IV infusion<br>Half life 12 -20 minutes | Lyses of acute massive pulmonary emboli | Minimal fibrin specificity<br>Systimic Lysys<br>Expensive | Human Enzyme Synthesized by the kidney( obtained from Urine or cultures of Embryonic Kidney cells)<br>**NOT ANTIGENIC(Human Source)** |

Fibrin-Specifc Agents(t-PA) **Produced by recombinant DNA technology**

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| **Alteplase** | Direct action: They activate fibrin-bound plasminogen rather than free plasminogen in blood. Their action is enhanced by the presence of fibrin.<br>It binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin followed by activated local fibrinolysis with limited systemic fibrinolysis. | VERY Short Half Life<br>IV bolus followed by Infusion | | | **NOT Antigenic (Human Source)** |
| **Reteplase** | | Longer half life than alteplase<br>Two IV bolus injection | ST Eleavation MI<br>Pulmonary Embolism | | |
| **Tenecteplase** | | The longest half life<br>Single IV bolus | ONLY for Acute MI | | |