

# Thrombolytic drugs



## 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.



**Important**



In male and female slides



Only in male slides



Only in female slides



Extra information



helpful video

Editing file

# thrombolytic agents:

## Definition

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

## goal of use

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

## Indications of Thrombolytics

1

Acute myocardial infarction  
(ST elevation, STEMI)

3

Peripheral artery occlusion.

2

Acute ischemic stroke.

4

Deep venous thrombosis.

5

Pulmonary embolism.

## ❖ Rational for Use of Thrombolytic Drugs in AMI:

1

Improvement of ventricular function.

2

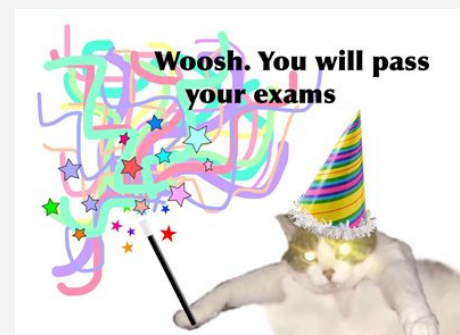
reduction of the incidence of congestive heart failure

3

the reduction of mortality following AMI.

4

Thrombolytic drugs need to be given **immediately** to the patient after diagnosis of MI, delay in administration will be of no value.



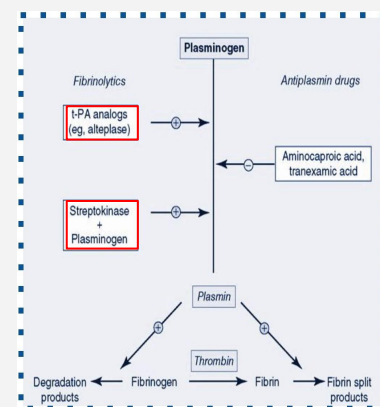
# Mechanism Of Action :

1

They have common MOA by stimulating plasminogen "gen means inactive"

2

activation via **converting plasminogen** (proenzyme) **to plasmin** (active enzyme) → lysis of the insoluble fibrin clot into soluble derivatives.



Plasminogen → plasmin → lysis of the fibrin



## What is plasmin?

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

- **fibrin**
- other circulating proteins, including **fibrinogen, factor V, and factor VIII.**

## Types of thrombolytic drugs

\*Fibrin surface  
clot surface  
fibrin bound to tissue  
All have same meaning.

### Non-Fibrin specific agent

- It binds equally to circulating and non-circulating plasminogen.
- Activates plasminogen bound to clot surface (local fibrinolysis) & **circulating** plasminogen & other plasma proteins thus causes an unwanted (systemic fibrinolysis) → leads to bleeding.

- E.g: (USA) :  
**Urokinase.**  
**Streptokinase.**  
**Anistreplase.**

Note:  
Non fibrin specific agents also degrade physiological clots. Physiological clots are formed when there is an injury. They are helpful clots formed to prevent hemorrhage.

### Fibrin specific agent

- They are tissue plasminogen activators they act as tPA (human factor).
- selective in action (clot or fibrin specific).
- they 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.

- E.g: (ART): (suffix "**plase**")
- **Alteplase.**
- **Retepase.**
- **Tenecteplase**

# Non fibrin specific thrombolytic drugs

	Streptokinase (SK)	Anistreplase (APSAC)	Urokinase
M.O.A	<ul style="list-style-type: none"> <li>- Is a bacterial protein produced by B-hemolytic streptococci.</li> <li>- It acts <b>indirectly</b> by forming plasminogen-streptokinase complex "<b>activator complex</b>" which converts inactive plasminogen into active plasmin.</li> <li>- Can degrade <b>fibrin clots</b> as well as <b>fibrinogen</b> and other plasma proteins.</li> </ul>	<ul style="list-style-type: none"> <li>- <b>(APSAC) : Anisoylated Plasminogen Streptokinase Activator Complex</b> is an acylated plasminogen combined with streptokinase.</li> <li>- It is a <b>prodrug</b>, de-acylated in circulation into the active plasminogen-streptokinase complex.</li> <li>- <b>direct</b></li> </ul> <p>Note: Prodrugs become active after administration.</p>	<ul style="list-style-type: none"> <li>- Human enzyme synthesized by the kidney</li> <li>- Obtained from either urine or cultures of human embryonic kidney cells.</li> <li>- Is a <b>direct</b> plasminogen activator.</li> </ul>
T 1/2	<b>Less than 20 minutes</b>	<b>70-120 minutes</b>	<b>12-20 minutes</b>
Administration	Given by <b>I.V.</b> infusion (infusion is given continuously)	Given as <b>bolus I.V.</b> injection (bolus is given repeatedly by single injection)	Given by <b>I.V.</b> Infusion
Advantages	<ul style="list-style-type: none"> <li>- Least expensive.</li> <li>- Used for <b>venous</b> and <b>arterial</b> thrombosis.</li> </ul> <p>Note: Streptokinase should not be given more than once yearly.</p>	<ul style="list-style-type: none"> <li>- Longer duration of action than streptokinase.</li> <li>- More thrombolytic activity.</li> <li>- Greater clot selectivity.</li> </ul>	<ul style="list-style-type: none"> <li>- Used for the lyses of acute massive pulmonary emboli</li> <li>- No anaphylaxis (not antigenic).</li> </ul>
Disadvantages & side effects	<ol style="list-style-type: none"> <li>1- <b>Antigenicity</b> (the property of being able to induce a specific immune response) : high-titer antibodies develop 1 to 2 weeks after use, precluding retreatment until the titer declines. <small>Titer: conc</small></li> <li>2- <b>Allergic reaction</b>: like rashes, fever, hypotension</li> <li>3- <b>Bleeding</b> due to activation of circulating plasminogen (systemic fibrinolysis).</li> <li>4- Not fibrin specific.</li> </ol>	<p><b>Similar but less than streptokinase alone in:</b></p> <p><small>"streptokinase يعني يحصل الضرر ولكن بدرجة أقل من"</small></p> <ul style="list-style-type: none"> <li>- Antigenicity.</li> <li>- Allergic reactions.</li> <li>- Minimal fibrin specificity</li> <li>- Systemic lysis/hemorrhage</li> </ul> <p><b>More expensive than streptokinase</b></p>	<ul style="list-style-type: none"> <li>- Minimal fibrin specificity (the chance of bleeding is higher than streptokinase)</li> <li>- Systemic lysis (acts upon fibrin-bound and circulating plasminogen).</li> <li>- Expensive (its use is now limited).</li> </ul>
Precautions	<p><b>Not used in patients with:</b></p> <ul style="list-style-type: none"> <li>- Recent streptococcal infections.</li> <li>- Previous administration of the drug</li> </ul> <p>* These patients may develop fever, allergic reactions and resistance upon treatment with streptokinase due to <b>antistreptococcal antibodies</b>.*</p>	<p><b>Note from 438</b></p> <div style="border: 1px solid black; padding: 5px;"> <p>**Patient with pharyngitis or streptococcal infection and Ab high in the body so when we give drug will be considered as antigen and will be destroyed by Ab and will not be effective -</p> <p>***Plasminogen is a human enzyme, and Streptokinase is a foreign protein, so when u give it as a complex the Antigenicity &amp; Allergic reaction would be less.</p> <p>****Urokinase is obtained from urine or human kidney cell, so there is NO allergic reaction or antigenicity.</p> </div>	

# Fibrin specific thrombolytic drugs

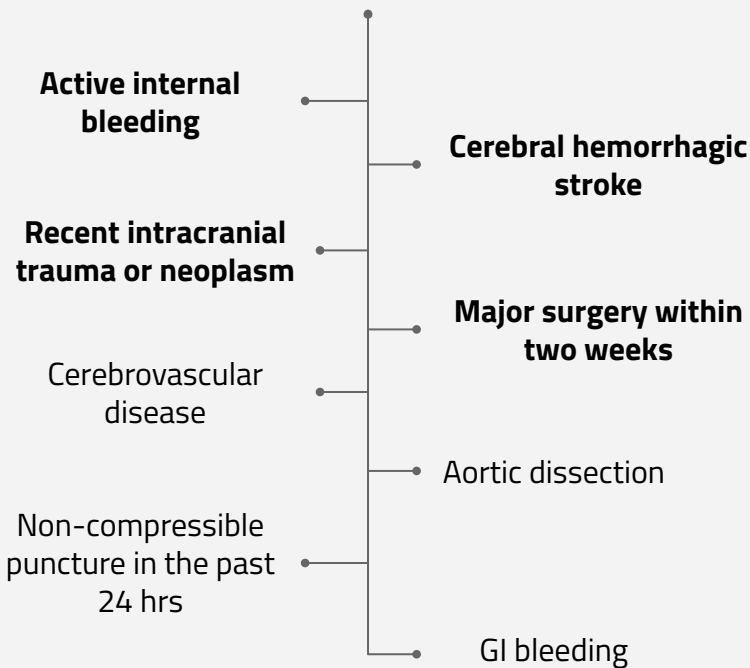
## Tissue Plasminogen Activators (t-PAs)

	Alteplase	Retepase	Tenecteplase
M.O.A	<ul style="list-style-type: none"> <li>- All are recombinant human tissue plasminogen activators (t-PA).</li> <li>- Prepared by recombinant DNA technology.</li> </ul> <p><small>DNA Technology: the joining together of DNA molecules from different organisms and inserting it into a host organism to produce new genetic combinations. This is carried out in scientific labs.</small></p> <p><b>Directly act by:</b></p> <ul style="list-style-type: none"> <li>- They activate <b>fibrin-bound plasminogen</b> rather than free plasminogen in blood.</li> <li>- Their action is <b>enhanced by the presence of fibrin</b>.</li> <li>- They bind to fibrin in a thrombus and convert the entrapped plasminogen to plasmin followed by activated local fibrinolysis with <b>limited systemic fibrinolysis</b>.</li> </ul>		
Advantages	<ol style="list-style-type: none"> <li>1. Fibrin-specific drugs (clot specific).</li> <li>2. Limited systemic fibrinolysis.</li> <li>3. Reduced risk of bleeding</li> <li>4. Not-antigenic (can be used in patients with recent streptococcal infections or antistreptococcal antibodies).</li> </ol>		
T 1/2	<b>5 minutes (short)</b>	<b>15 minutes (longer)</b>	<b>30 minutes (longest)</b>
Administration	Given as <b>bolus I.V. injection followed by infusion.</b>	Two <b>I.V. bolus</b> injections	Single <b>I.V. bolus</b> injection
Specificity	-	<b>Has Enhanced fibrin specificity</b>	<b>It is More fibrin specific</b>
Uses	<ul style="list-style-type: none"> <li>-In <b>ST-elevation myocardial infarction (STEMI)</b></li> <li>-<b>Pulmonary embolism.</b></li> </ul>		<b>It is only approved for use in acute myocardial infarction.</b>

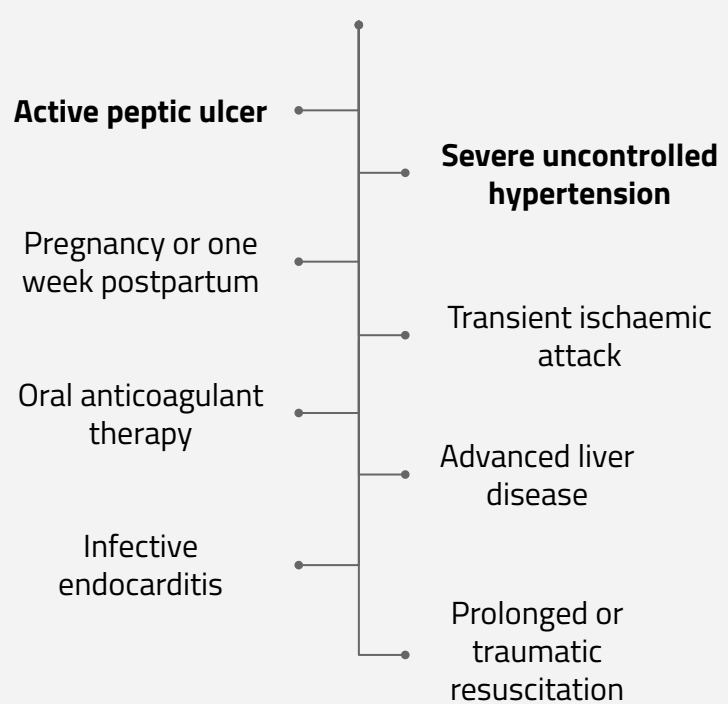
# What is the role of thrombolytic therapy in antithrombotic plan ?

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.

## Absolute contraindications to thrombolytics



## Relative contraindications to thrombolytics



## Fibrinolytic Inhibitors ( Antiplasmin )

Drugs that inhibit plasminogen activation and thus inhibit fibrinolysis and promote clot stabilization

Note:  
Fibrinolytic inhibitors are used when there is an overdose of fibrinolytic drugs & there is an increased risk of hemorrhage.

**Aminocaproic Acid & Tranexamic acid**

**Aprotinin**

**Administration**

**Orally**

**Orally or I.V.**

**Mechanism of action**

Acts by competitive inhibition of plasminogen activation

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

**Uses**

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

# MCQs

1- which one of the following Fibrin specific thrombolytic drugs has the longest duration of action

A- Antistreplase

B- Alteplase

C- Reteplase

D- Tenecteplase

2- which one of the following drugs is used for both Used for venous and arterial thrombosis?

A- Urokinase

B- Anistreplase

C- Reteplase

D- Streptokinase

3- which one of the following Fibrinolytic Inhibitors acts via competitive inhibition of plasminogen activation?

A- Reteplase

B- Tranexamic acid

C- Antistreplase

D- Aprotinin

4- A patient with a recent streptococcal infections comes to the ER suffering from thrombosis, it's best to **avoid** which drug ?

A- Streptokinase

B- Reteplase

C- Tenecteplase

D- Alteplase

5- which one of the following drugs Is a direct plasminogen activator ?

A- Antistreplase

B- Aprotinin

C- Urokinase

D- Tranexamic acid

6- which one of the following scenarios you should **not** be using any thrombolytic drug?

A- recent bone fracture

B-Active internal bleeding

C- diabetic patient

D- gouty arthritis



## Answers

1	2	3	4	5	6
D	D	B	A	C	B

# SAQ

Q1) What is the definition of a thrombolytic agent and state why its used.

Q2) List the non fibrin specific thrombolytic drugs and write the M.O.A of each.

Q3) What are the advantages of fibrin specific thrombolytic drugs?

Q4) What are fibrinolytic inhibitors?

Q5) What is the best mode of administration for Alteplase?

## Answers

A1) Thrombolytics are drugs used to lyse already formed blood clots in clinical settings where ischemia may be fatal. The goal of thrombolytic therapy is rapid restoration of blood flow in an occluded vessel by accelerating proteolysis of the thrombus.

A2) **Streptokinase**: acts indirectly by forming plasminogen- streptokinase complex "**activator complex**" which converts inactive plasminogen into active plasmin.

**Antistreplase**: is a prodrug, de-acylated in circulation into the active plasminogen-streptokinase complex

**Urokinase**: Is a direct plasminogen activator.

A3)

- 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).

A4) Drugs that inhibit plasminogen activation and thus inhibit fibrinolysis and promote clot stabilization(antiplasmin)

A5) Given as **bolus I.V.** injection **followed by infusion.**





# GOOD LUCK!

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