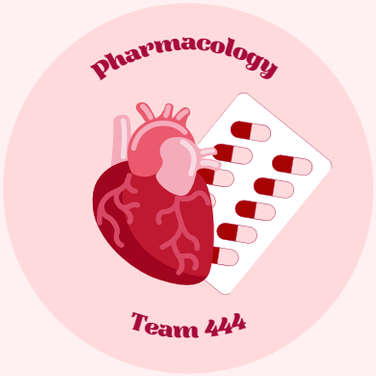
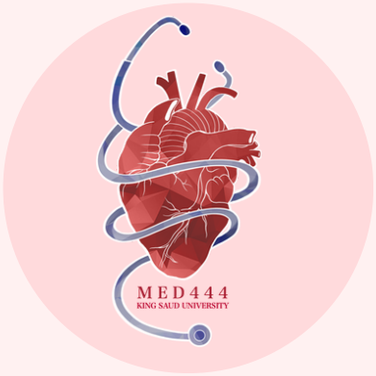


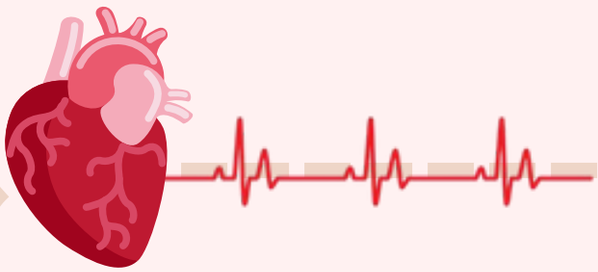


L8.
Thrombolytic therapy

special thanks for Mohammed Aldkhyyal from team 444

EDITING FILE

COLOR INDEX :
- MAIN TEXT
- IMPORTANT
- GIRL'S SLIDES
- BOY'S SLIDES
- NOTES
- EXTRA



والجلطات لو تبغاها تهجع
كَسْر الفيبرن واوزن قصيدك

علي العبدالعظيم ✍🏻

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.

EXTRA

Myocardial Infarction
Heart Attack

Definition:

An acute myocardial infarction, also called a heart attack, happens when a blood vessel in the heart suddenly becomes blocked.

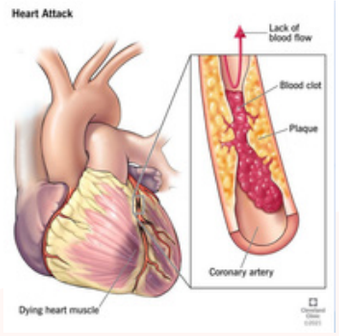
Ischemia ⟷ When a **blood vessel** in the heart gets **blocked**, blood cannot get to part of the heart. This part of the heart **does not get enough oxygen**.

Angina Pectoris ⟷ When the **heart muscle** becomes **ischemic** (does not get enough blood and oxygen), the ischemia often causes chest pain.

Infarction ⟷ If the **ischemia** lasts **long** enough, the heart muscle that is not getting enough oxygen dies.

Treatment:

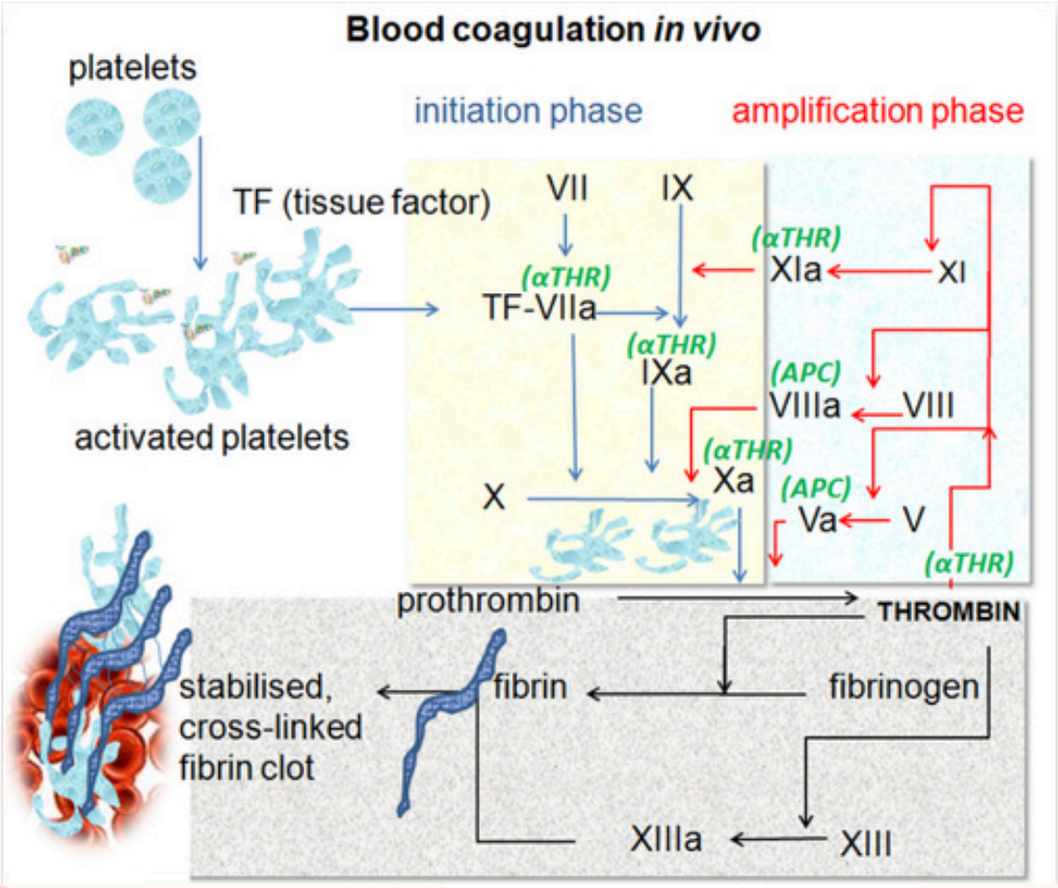
(Thrombolytics) and percutaneous coronary intervention (coronary angioplasty).



EXTRA

Thrombus Formation

Fibrin is a white insoluble fibrous protein formed by the action of thrombin on fibrinogen when blood clots. It forms a network that traps red cells and platelets.



Thrombolytic Drugs

Plasminogen Activators

Definition:

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

Mechanism Of Action:

They have a common MOA by stimulating plasminogen activation via converting plasminogen (proenzyme) to plasmin (active enzyme) → **lysis** of the insoluble fibrin clot into soluble derivatives.

Thrombolytics (Plasminogen Activators)

Plasminogen —(Activates)→ Plasmin

Plasmin —(Activates)→ Insoluble Fibrin → Soluble Degradation Products

What Is Plasmin?

Plasmin: is a nonspecific protease capable of breaking down:

- **Fibrin**
- **Other circulating proteins** including Fibrinogen, clotting factor V and factor VIII.

Thrombolytic Drugs

Plasminogen Activators

Indications Of thrombolytics:

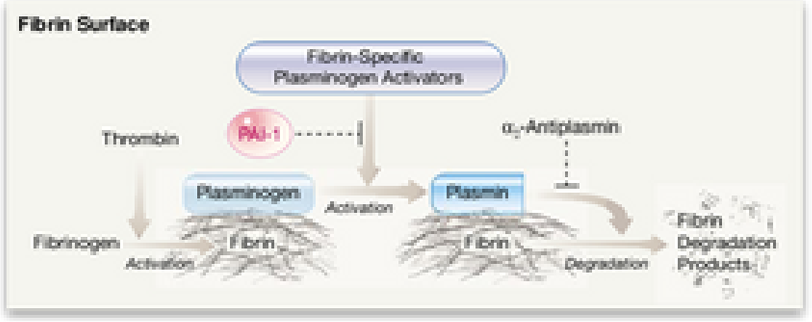
Used for the treatment of thromboembolic disorders as:

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

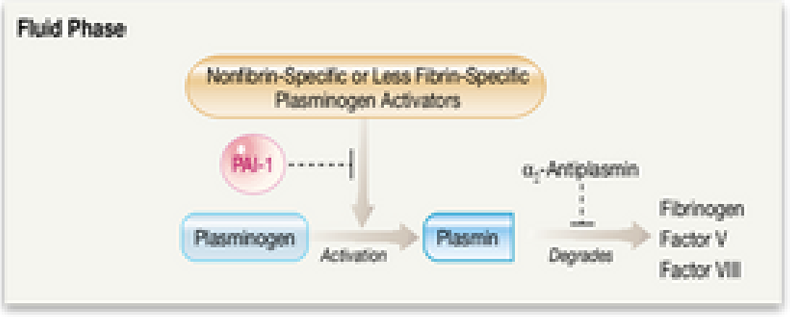
Rational for Use of Thrombolytic Drugs in AMI:

- Improvement of ventricular function; reduction of the incidence of congestive heart failure and the 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.

Fibrin specific plasminogen activators:



Non-fibrin specific plasminogen activators:



Types of Thrombolytic Drug

Classification and one example for each are important	Non-Fibrin Specific Agent	Fibrin Specific Agent Tissue Plasminogen Activators (t-PAs)
MOA	**Activate plasminogen bound to clot surface (local fibrinolysis) and circulating plasminogen in blood. (bound and unbound) with degradation of several plasma proteins including fibrinogen, factor V, and factor VIII, thus producing clot lysis & systemic fibrinolysis**	**Activate mainly plasminogen bound to clot surface (fibrin specific). Degrade mainly fibrin clots.**
Selectivity	**Less selective in action.**	**More selective in action.(clot or fibrin specific)**
Systemic Plasminogen Activation	**Extensive**	**Less**
Risk of Bleeding	**More**	**Less**
Drugs	**Streptokinase Anistreplase Urokinase (USA)**	**Alteplase Reteplase Tenecteplase (ART)**

Non-Fibrin Specific Thrombolytic Drugs-USA

	Streptokinase (SK) very important SAQ and MCQ	**Anistreplase (APSAC)**	**Urokinase**
MOA	**Is a bacterial protein produced by B-hemolytic streptococci. It acts indirectly "it has to be combined first" by forming plasminogen-streptokinase complex "activator complex" which converts inactive plasminogen into active plasmin. Can degrade fibrin clots as well as fibrinogen and other plasma proteins "Streptokinase is the only indirect acting throm bolytic".**	**Anisoylated Plasminogen Streptokinase Activator Complex (APSAC) is an acylated plasminogen combined with streptokinase. It is a prodrug, de-acylated in circulation into the active plasminogen-streptokinase complex. (direct) Instead of giving streptokinase, we could directly give the active complex: plasminogen+streptokinase. The difference is that APSAC is a prodrug with an anisoyl group to block it's active site & prevent nonspecific degradation & hemorrhage. Although it's still not considered a selective drug,it is more selective than streptokinase & causes less side effects.**	**Human enzyme synthesized by the kidney Obtained from either urine or cultures of human embryonic kidney cells. Is a direct plasminogen activator. "No formed complex"**
T 1/2	**Less than 20 minutes**	**70-120 minutes**	**12-20 minutes.**
Administration	given as **intravenous infusion** (250,000 U then 100,000 U/h for 24-72 h).	**Given as a bolus I.V. injection (30 U over 3 - 5 min.).**	**Given by intravenous infusion (300,000U over 10 min then 300,000U/h for 12h).**

Advantages	**- Least expensive.** **- Used for venous and arterial thrombosis.**	**- Longer duration of action than streptokinase.** **- More thrombolytic activity.** **- Greater clot selectivity.** **"Compared to streptokinase"**	**- Used for the lyses of acute massive pulmonary emboli. - No anaphylaxis (not antigenic). "Because it is a human protein"**
Disadvantages & Side effects	**- Antigenicity: high-titer antibodies develop 1 to 2 weeks after use, precluding retreatment until the titer declines. "because of its bacterial proteins, the body will develop antibodies against the drug"** **- Allergic reaction: like rashes, fever, hypotension"due to antigenicity"** **- Bleeding due to activation of circulating plasminogen (systemic fibrinolysis).** **- Not fibrin specific.**	**Similar but less than streptokinase alone in:** **- Antigenicity.** **- Allergic reactions.** **- Minimal fibrin specificity - Systemic lysis** **-But more expensive than streptokinase.**	**- Minimal fibrin specificity** **- Systemic lysis (acts upon fibrin-bound and circulating plasminogen).** **- Expensive (its use is now limited).**
Precautions	**Not used in patients with:** **- Recent streptococcal infections.** **- Previous administration of the drug "because the antibodies against streptokinase are still in the circulation->patient won't respond to the drug (resistance)"** **- These patients may develop fever, allergic reactions and resistance upon treatment with streptokinase due to antistreptococcal antibodies.**		

Fibrin Specific Thrombolytic Drugs-ART

	Alteplase (recombinant form of human tPA)	Reteplase (variant of recombinant tPA)	Tenecteplase (variant of recombinant tPA)
Overview	• End with the suffix "plase" • All are recombinant human tissue plasminogen activators (t–PA). (specific) • Prepared by recombinant DNA technology		
MOA	Directly act by: • 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.		
Advantges	• 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). • very safe		
T 1/2	has very short half life (5 min)	it has longer duration than Alteplase (15 min)	It has half life of more than 30 min
Administration (Dr talked briefly about it)	is usually administered as an intravenous bolus followed by an infusion. (60 mg i.v. bolus + 40 mg infusion over 2 h).	Given as two I.V. bolus injections of 10 U each	It can be administered as a single IV bolus.
Specificity		Has enhanced fibrin specificity	It is more fibrin-specific & longer duration than alteplase.
Uses	• In ST-elevation myocardial infarction (STEMI) • Pulmonary embolism.		It is only approved for use in acute Myocardial infarction.

Contraindications to thrombolytics

Absolute contraindications	Relative contraindications
1. Active internal bleeding 2. Previous intracranial/cerebral hemorrhage or stroke of unknown origin at any time 3. Ischaemic stroke in the preceding 6 months 4. CNS damage or neoplasms or AV malformation 5. Recent major (intracranial) trauma/surgery/head injury (within the preceding 2-3 weeks) 6. GI bleeding within the past month 7. Known bleeding disorder (excluding menses) 8. Aortic dissection 9. Non-compressible punctures in the past 24 hrs (e.g., liver biopsy, lumbar puncture)	1. Active peptic ulcer 2. Refractory (severe, uncontrolled) hypertension (systolic pressure >180 mmHg and/or diastolic pressure >110 mmHg) 3. Pregnancy or within one week postpartum 4. Oral anticoagulant therapy 5. Advanced liver disease 6. Infective endocarditis 7. Transient ischaemic attack in the preceding 6 months 8. Prolonged or traumatic resuscitation

Fibrinolytic Inhibitors
Used mainly in cases of thrombolytic overdose to prevent hemorrhage
female slide

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

Drugs	Aminocaproic Acid & Tranexamic acid	Aprotinin
Administration	Orally	Orally or I.V
MOA	Acts by competitive inhibition of plasminogen activation	It inhibits fibrinolysis by blocking the action of plasmin (plasmin antagonist). It is used as antidote if bleeding occurs "vomiting blood for example"
Uses	• Fibrinolytic therapy induced bleeding (antidote). "Vomiting blood for example". • Post surgical bleeding. • Post delivery. • 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)	

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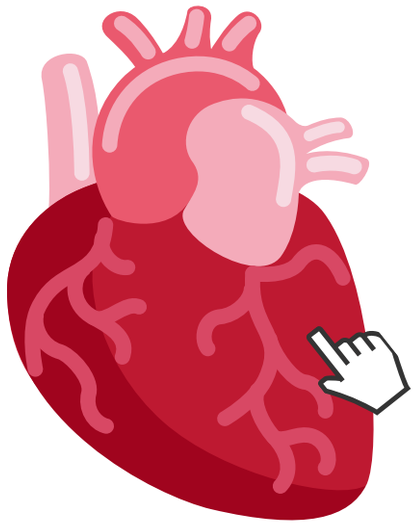


MCQs

1 A 73-year-old man develops crushing chest pain while walking in a shopping mall. He is brought to the emergency department for evaluation and treatment. He is thought to be having a myocardial infarction. He has immediately begun on streptokinase therapy. After the administration he developed fever, what is the reason?

A. antistreptococcal antibodies.
B. Recent viral infections.
C. Previous administration of Alteplase
D. None of the above

2 What is the mechanism of action of thrombolytics

A. Inhibiting plasmin
B. inhibiting plasminogen activation
C. stimulating plasminogen activation
D. none of the above

3 A 50 year old patient came to the hospital because he have headache and nausea. Further questions from the doctor and tests, showed that he have pulmonary embolism. patient's records say that he had streptococcal infection one week ago, which of the following drugs should not be used?

A. Streptokinase
B. urokinase
C. Aprotinin
D. Tenecteplase

1-A 2-C 3- A

MCQs

4 A 32 year old woman diagnosed with Deep Vein Thrombosis (DVT), before she starts to develop pulmonary embolism, the doctor want to give her a drug that have long half life instead of streptokinase, so what drug he can use?

A Urokinase
B Alteplase
C Anistreplase
D Aprotinin

5 A 40 year old man diagnosed with acute myocardial infarction, the doctor starts to give him a drug that treat his condition. After days the patient came with skin rash, fever, and bleeding. Which drug is the cause of his symptoms?

A Reteplase
B Streptokinase
C Alteplase
D Aprotinin

6 A 53-year-old man presents to the emergency department vomiting blood. Later it was found that the bleeding is due to fibrinolytic therapy, what drug should be administered in this case?

A Urokinase
B Aprotinin
C Anistreplase
D Alteplase

7 A doctor prescribed streptokinase to a patient with Pulmonary embolism. after days, the patient came with bleeding and the doctor gave him antidote. Now the doctor wants to give him a drug that more selective, so the bleeding less likely to occur. Which of the following he can use?

A Urokinase
B Aprotinin
C Anistreplase
D Reteplase

4-C 5-B 6-B 7-D

SAQs

1 **What is the mechanism of action of thrombolytic drugs?**

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

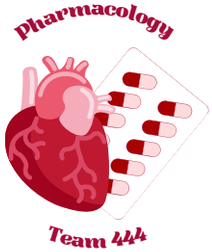
2 **List the precautions of streptokinase**

Not used in patients with:
1- Recent streptococcal infections. 2- Previous administration of the drug 3- These patients may develop fever, allergic reactions and resistance upon treatment with streptokinase due to antistreptococcal antibodies.

3 **Mention the classification of drugs used in thrombolytic therapy and give an example for each.**

Non-fibrin specific drugs: streptokinase.
Fibrin specific drugs: Reteplase.

4 **What is the mechanism of action of streptokinase**



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