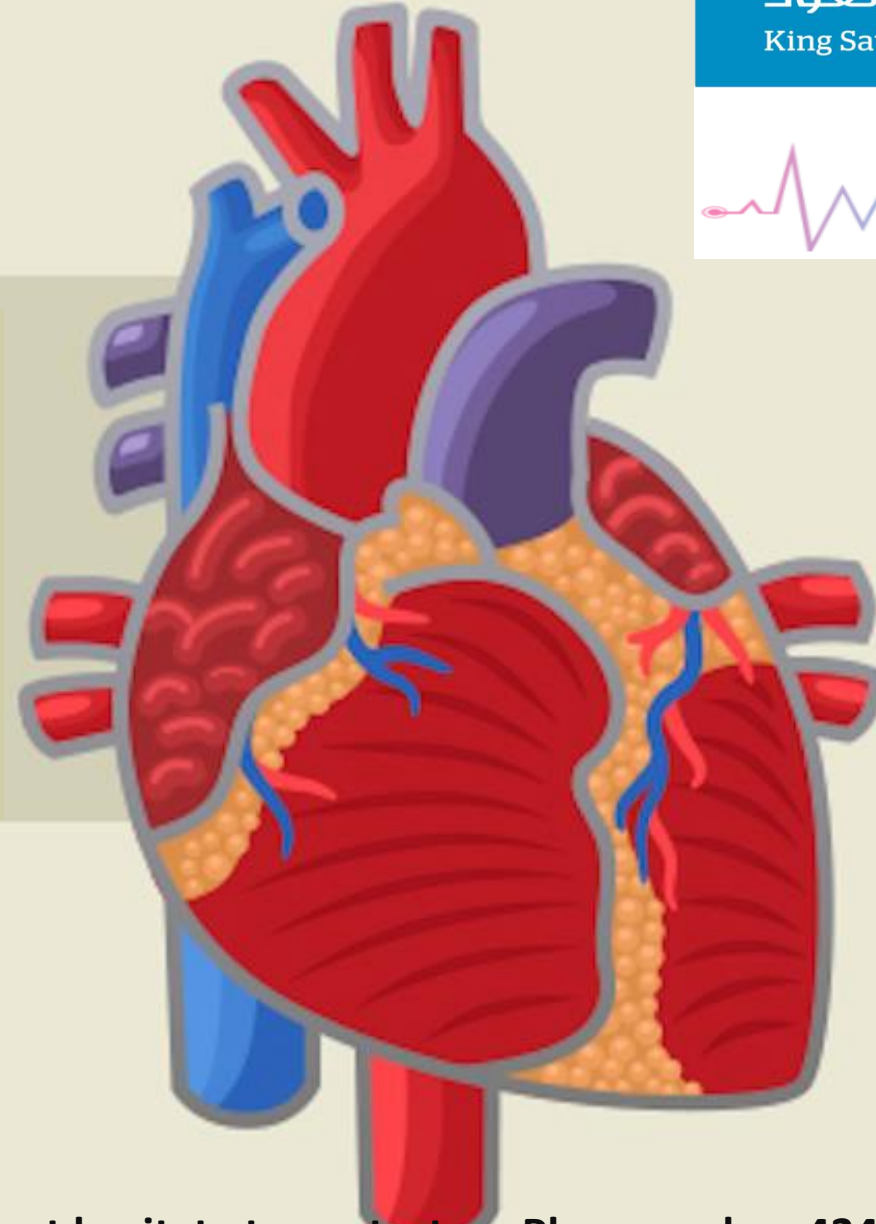


13

THROMBOLYTIC DRUGS (Fibrinolytic drugs)



Cardiovascular Block.

Additional note: Gray color

For any correction, suggestions or any useful information do not hesitate to contact as: Pharmacology434@gmail.com

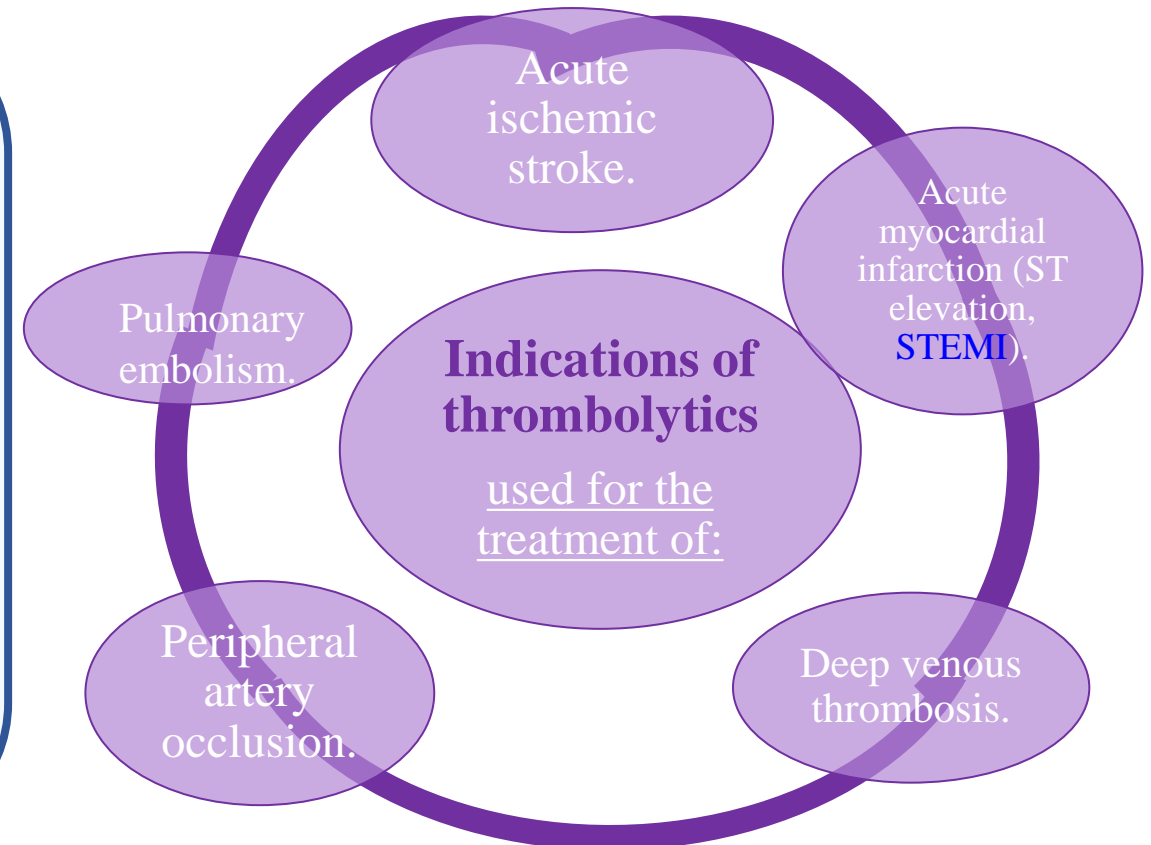
Definition of Thrombolytics:

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

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

Thrombolytic therapy

- The goal of **thrombolytic therapy** is rapid **restoration of blood flow** in an occluded vessel by accelerating proteolysis of the thrombus.
- **Thrombolytic therapy** is one part of an overall antithrombotic plan that frequently includes **anticoagulants, antiplatelet agents** and mechanical approaches to rapidly restore flow and prevent re-occlusion.



Rational for use of thrombolytic drugs in AMI

❖ improvement of ventricular function;

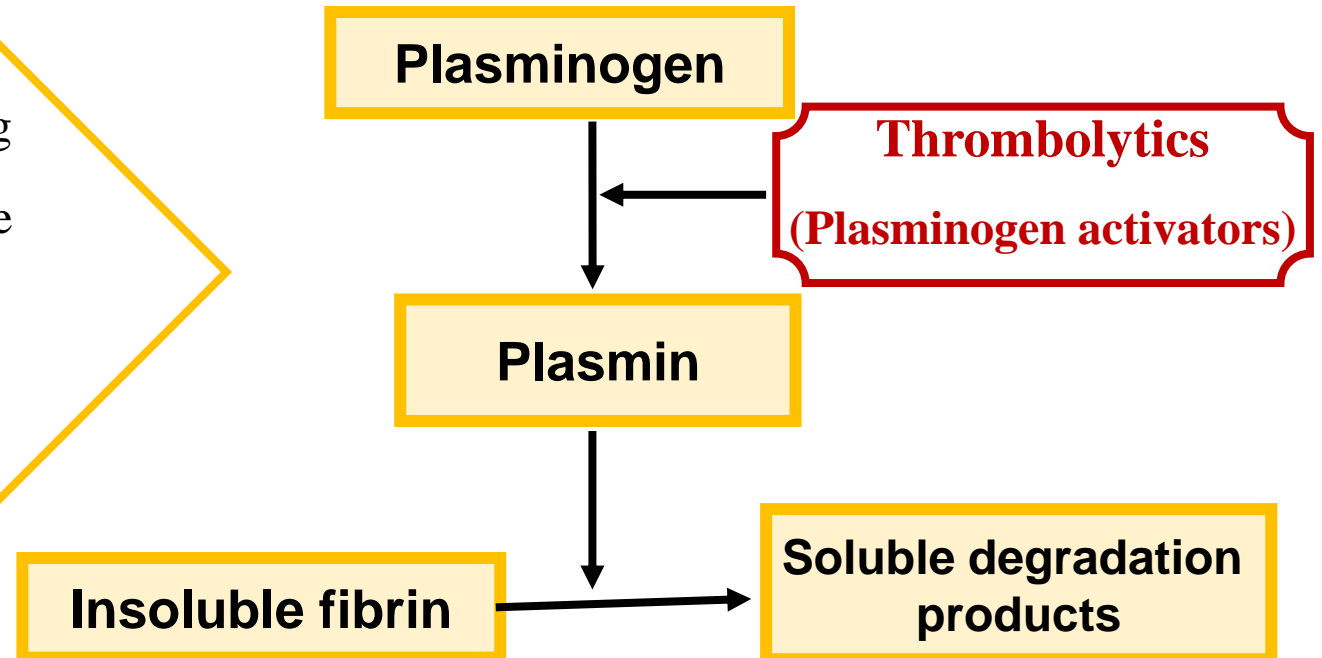
❖ reduction of the incidence of congestive heart failure

❖ reduction of mortality following AMI.

Mechanism of Action of thrombolytic drugs

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

Plasmin: is a nonspecific **protease** capable of breaking down **fibrin** as well as other circulating proteins, including **fibrinogen, factor V, and factor VIII.**



Types of thrombolytic drugs

Non-fibrin specific

- Streptokinase
- Anistreplase (USA)
- Urokinase

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

- ❖ binds **equally** to circulating and non-circulating plasminogen.
- ❖ produces breakdown of clot (local fibrinolysis) and circulating plasminogen and other plasma proteins thus cause an unwanted (systemic fibrinolysis) leading to **bleeding**.

Fibrin specific

Tissue plasminogen Activators (t-PA)

- Alteplase
- Reteplase (RAT)
- 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.

Streptokinase (SK)

Is a bacterial protein produced by B-hemolytic streptococci.

Action:

- It acts **indirectly** by forming plasminogen-streptokinase complex "**activator complex**" which converts other inactive plasminogen into active plasmin.
- Can degrade **fibrin clots** as well as **fibrinogen** and other plasma proteins (non-fibrin specific).

Uses

- Half life less than **20 minutes**
- given as intravenous infusion (250,000U then 100,000U/h for 24-72 h).
- used for venous or arterial thrombosis - Life threatening pulmonary embolism

Advantage

It is the least expensive.

Side effects

- Bleeding** due to activation of circulating plasminogen (systemic fibrinolysis)
- Antigenicity** and high-titer antibodies develop 1 to 2 weeks after use, retreatment until the titer declines
- Allergic reaction:** like rashes, fever, hypotension
- Prior exposure** to the streptokinase or **infection** can cause **sever allergic reaction**

Precautions “Not used in patients with”

Precautions

“Not used in patients with”

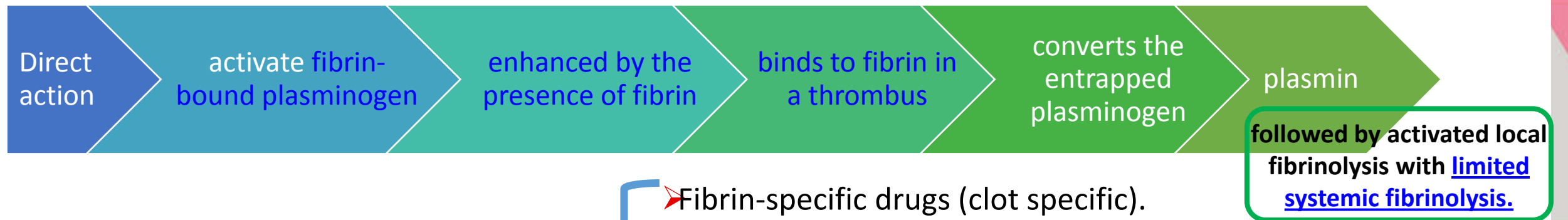
- Recent streptococcal infections or pharyngitis -Previous administration of the drug
- These patients may develop **fever, allergic reactions and resistance** upon treatment with streptokinase due to **antistreptococcal antibodies**

	Anistreplase (APSAC) (Anisoylated Plasminogen Streptokinase Activator Complex)	Urokinase (Human enzyme synthesized by the kidney)
Action	<p>-(APSAC) acylated plasminogen combined with streptokinase.</p> <p>-It is a prodrug, de-acylated in circulation into the active plasminogen-streptokinase complex. -Half life is 70-120 min</p>	<p>-obtained from either urine or cultures of human embryonic kidney cells. -acts directly to convert plasminogen to active plasmin.</p> <p>- Given by IV infusion.</p> <p>- Half life: 12-20 min.</p> <p>- Used for the lyses of acute massive pulmonary emboli</p>
Advantage	<p>- Given as a bolus I.V. injection - Longer duration of action than SK. - More thrombolytic activity than SK. - Greater clot selectivity than SK.</p>	<p>No anaphylaxis (not antigenic).</p>
Disadvantages	<p>Similar but but less than Streptokinase alone in:</p> <ul style="list-style-type: none"> -Antigenecity. -Allergic reactions -minimal fibrin specificity . -systemic lysis -but more expensive than SK 	<ul style="list-style-type: none"> -Minimal fibrin specificity. -systemic lysis (because it does not discriminate between fibrin-bound and circulating plasminogen) -Expensive.

Tissue Plasminogen Activators (t - PA)

- All are recombinant tissue plasminogen activators (t –PA).
- Prepared by recombinant DNA technology.
- Include drugs as
 - Alteplase
 - Reteplase
 - Tenecteplase

Mechanism of t-PA:



Advantages of t-PA:

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

A**R****T****Alteplase****Retepase****Tenecteplase (TNK- tPA)**

type	is a recombinant form of human tPA.	A variant of recombinant tPA	prepared by recombinant technology
Half life	has very short half life (~5 min)	It has longer duration than alteplase (15 min.)	It has half life of more than 30 min longer duration than alteplase.
Specificity		Has enhanced fibrin specificity	It is more fibrin-specific.
Administration	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.
ECG changes	In ST-elevation myocardial infarction (STEMI)	In ST-elevation myocardial infarction (STEMI); improvement of ventricular function; reduction of the incidence of CHF and the reduction of mortality following AMI.	
Uses		Pulmonary embolism.	It is only approved for use in acute myocardial infarction.

Contraindications to thrombolytics:

Active internal bleeding

Cerebral hemorrhagic stroke

Cerebrovascular disease

Major surgery within two weeks

Active peptic ulcer

Severe uncontrolled hypertension

Recent intracranial trauma or neoplasm

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.
- ✓ Given orally

□ Aprotinin

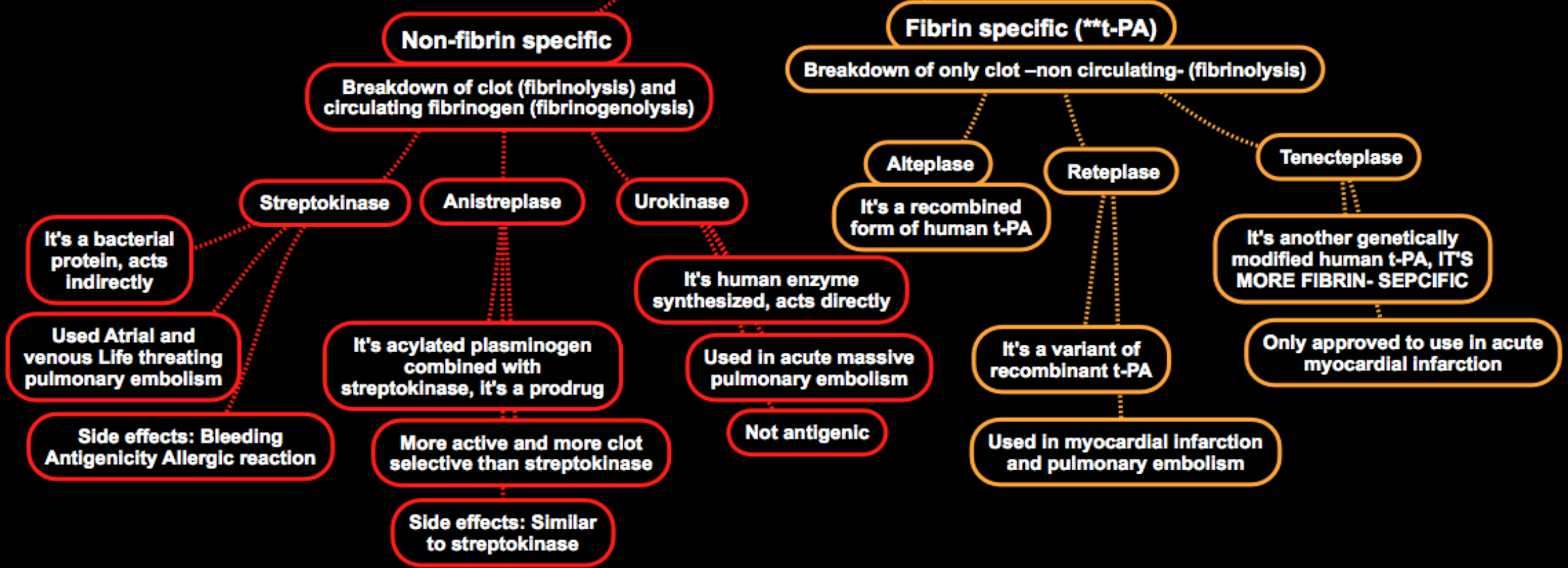
- ✓ It inhibits fibrinolysis by blocking the action of plasmin (**plasmin antagonist**)
- ✓ Given orally or i.v.

USES :

- ✓ **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).

Summary.

THROMBOLYTIC DRUGS (Fibrinolytic drugs)



These are drugs inhibit the plasminogen:

1. Aminocaproic acid (competitive inhibition, orally)
2. Tranexamic acid (competitive inhibition, orally)
3. Aprotinin (blocking plasmin, orally or I.V)

MCQs

1 - Patient has arterial thrombosis , and he has streptococcal infections , which one of these drugs we should not give him ?

- A. Urokinase
- B. Streptokinase
- C. Anistreplase
- D. Alteplase

2 - Which one of these drugs are produced by B-hemolytic streptococcus ?

- A. Alteplase
- B. Urokinase
- C. Streptokinase
- D. Anistreplase

3 - Which one of the following enzymes synthase by kidney ?

- A. Urokinase
- B. Streptokinase
- C. Anistreplase
- D. Alteplase

4 - A patient came to KKUH with acute massive pulmonary emboli , which one of the following the doctor should give him ?

- A. Urokinase
- B. Streptokinase
- C. Anistreplase
- D. Tenecteplase

5 - A patient came to the emergency , after examination , the doctor diagnose him with acute myocardial infraction , which one of the following drugs should he takes ?

- A. Tenecteplase
- B. Streptokinase
- C. Anistreplase
- D. Reteplase

6 - Which one of these are used in Pulmonary embolism ?

- A. Alteplase -Tenecteplase
- B. Alteplase – Reteplase
- C. Reteplase – Tenecteplase
- D. Tenecteplase – urokinase

7 –which one of the following is plasmin antagonist ?

- A. Tenecteplase
- B. Aprotinin
- C. Anistreplase
- D. Reteplase

Answers :

- 1) B
- 2) C
- 3) A
- 4) A
- 5)A
- 6)B
- 7)B

Thrombolytics

Heart and Vascular Plumbing Depot

If you've got a clogged artery, just run these IV and watch them ↑ perfusion, ↓ viscosity & aggregation of RBC's.

Our Clot Busters Work!

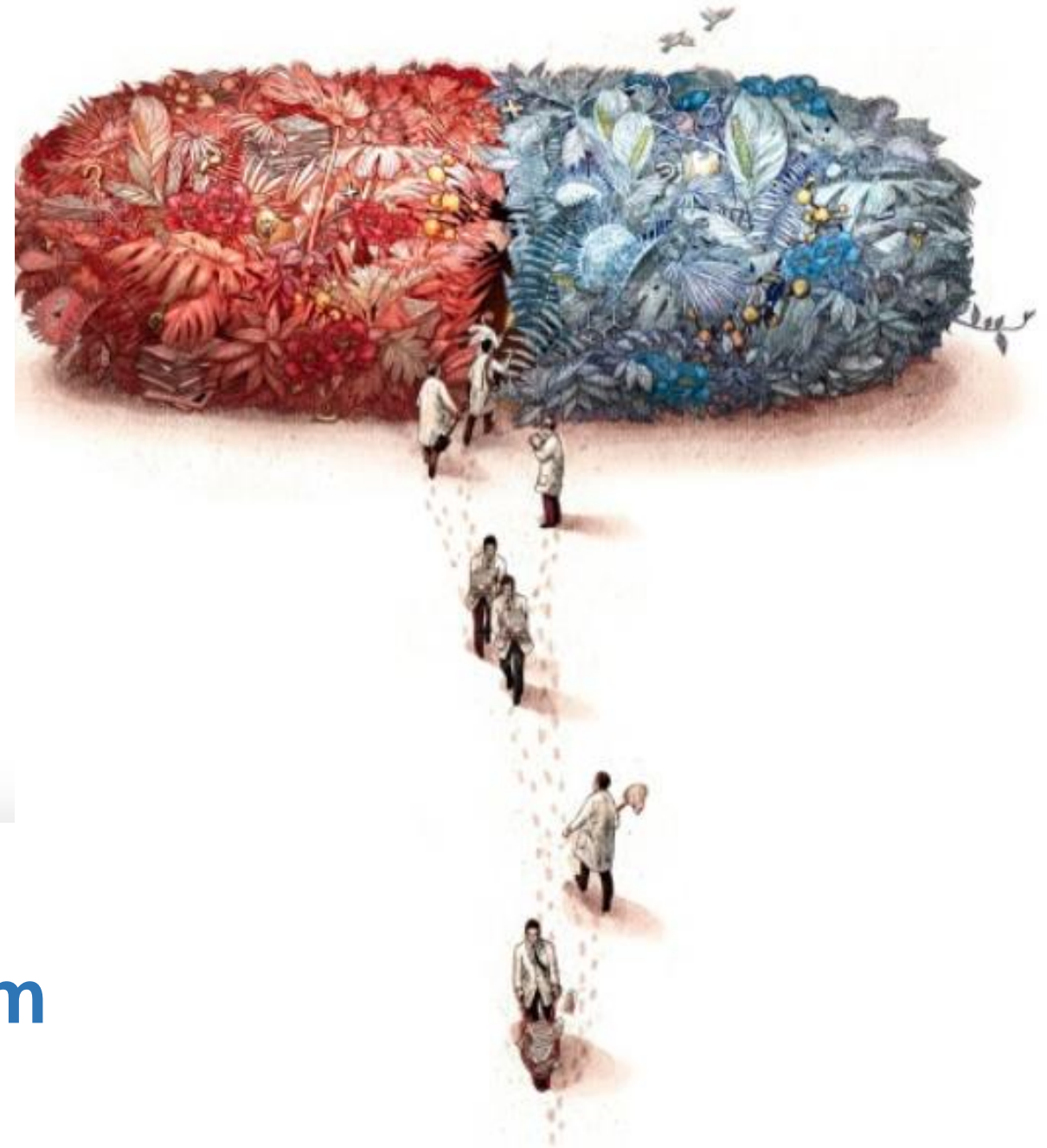
Activase t-PA

Streptokinase

Administer via an infusion pump immediately after the event

Watch for:
allergic reactions,
spontaneous bleeding,
& oozing from any
fresh wound site.

• Streptokinase & Activase (tPA):
Used for MI, ischemic stroke and PE.
May be used to open arteriovenous cannulas.



GOOD LUCK!

Done By Pharmacology Team

Fetoon Alnemari.