HLS

MODIFIED NO. 3

PHARMACOLOGY

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Anticoagulants

Color code
Slides
Doctor
Additional info
Important

- In previous lectures we've discussed Warfarin and heparin , which are injectable drugs with many side effects , specifically warfarin which causes hospitalization of patients.

- Recently,new **Direct agents** have been found ،known as NO ACs : Novel **Oral**stnalugaoc-itna .
- oral drugs, subgrouped based on their mechanisms of action, they either block Factor 10 / factor X or block Factor II/ thrombin
- We're going to discuss 3 drugs

1. Dabigatran,
2. Apixaban
3. Rivaroxaban

Dabigatran (Pradaxa)

Dabigatran

- **MOA**: direct thrombin inhibitor which **inhibits**:
  - Both free and fibrin-bound thrombin
  - Cleavage of fibrinogen to fibrin
  - Thrombin-induced platelet aggregation

Mechanism of Action : MOA
Thrombin : factor II

Dabigatran

- Monitoring
  - aPPT

- Normally there is no need for monitoring because Dabigatran is,homogeneous solution with high protection , however, aPTT monitoring is needed when there is bleeding as a side effect.
- aPTT is a monitoring parameter toward thrombin related drugs like dabigatran which is an antithrombin .
- aPTT is used in monitoring the bleeding , but not the effect because it is a direct agent with obvious response

- Onset: **1 hour**, delayed by food

Fast

- Antidote: **idarucizumab**

- ADRs
  - **Bleeding** (8% to 33%; major ≤ 6%)
  - Dyspepsia (11%)

GI bleeding

Dyspepsia It is characterized by discomfort or pain in the upper abdomen and can often include various digestive symptoms.

Dabigatran

- **Drug-drug interactions**

  - **Category X: P-Gp inducers**
  - **Category D:** Amiodarone, **P-Gp inhibitors,** quinidine, St. john's Wort, verapamil

P-glycoprotein (P-gp) is an important protein in the **gastrointestinal (GI)** tract that plays a key role in drug absorption and resistance. It acts as an **efflux pump**, actively transporting various substances **out** of cells, including **many medications like dabigatran** and toxins, back into the intestinal lumen to be **excreted**.

- The Drug – drug interaction happens When giving inhibitor or inducer toward P-G p
  - Inducers→ increases the excretion of dabigatran → decreases [dabigatran] in blood → Thrombosis
  - inhibitor→ decrease the excretion(eg. Amiodarone)→ increases [dabigatran] in blood→ bleeding
- Increasing he dose leads to bleeding while decreasing the dose leads to thrombosis due to the **narrow therapeutic index**
- It has less drug-drug interaction than warfarin

Common side effect

- The most of dabigatran is **gastrointestinal upset.**

- **When compared with people anticoagulated with warfarin, patients taking dabigatran had fewer life-threatening bleeds, fewer minor and major bleeds, including intracranial bleeds, but the rate of gastrointestinal bleeding was significantly higher.**

- Dabigatran capsules contain **tartaric acid,** which lowers the gastric pH and is required for adequate absorption. The lower pH has previously been associated with [1] **dyspepsia**; some hypothesize that this plays a role in the[2] **increased risk of gastrointestinal bleeding.**
- Smoe patients also could suffer from [3]**oesophagitis** as a side effect of tartaric acid

- If a **small amount of GI bleeding** is diagnosed, the clinicians may consider adding H_2 receptor inhibitor (H_2RA), proton pump inhibitors (PPIs) to increase the PH

- in **serious** GI bleeding (**Antidote**) **idarucizumab** is given, which is a "mab" monoclonal antibodies that will neutralise the effect of dabigatran

Recall the antidote of : heparin → protamine sulfate, warfarin→ vitamin k, dabigatran → Idarocuzimab

Contraindication

1. active pathological bleeding

2. The use of dabigatran should also be avoided in patients with mechanical prosthetic heart valves due to the increased risk of thromboembolic events (e.g. valve thrombosis, stroke, and myocardial infarction) and major bleeding when compared with warfarin.

When using anticoagulants to prevent clots around the Prosthetic valves, **warfarin is preferred on dabigatran**

Current FDA guidelines states that patients with mechanical heart valves should not be using dabigatran.

Factor Xa inhibitor
(rivaroxaban, apixaban)

- same as dabigatran
  - When compared with people anticoagulated with warfarin, patients taking rivaroxaban, apixaban had fewer life-threatening bleeds,
  - **NOT approved for patients with Prosthetic valve**
  - approved in in arterial fibrillation, post- stroke Post-hip or knee replacement

- Dosing recommendations /drug – drug interaction :

do not recommend administering rivaroxaban with drugs known to be strong combined **CYP3A4/P-glycoprotein inhibitors** because this results in significantly higher plasma concentrations of rivaroxaban.

- rivaroxaban is metabolized by CY P 3A4 and P_Gp , thus, their inhibitors→ increase[riveroxaban] in blood→ increases the risk of bleeding ,Both rivaroxaban and dabigatran carry a somewhat higher risk of gastrointestinal (GI) bleeding compared to warfarin, with rivaroxaban sometimes having a slightly higher GI bleeding risk than dabigatran.

Factor Xa inhibitor
(rivaroxaban, apixaban)

- More common with apixabam

- **Spinal anesthesia or puncture**, people who are being treated with anti-thrombotic agents are at higher risk for developing a **hematoma**, **long-term or permanent paralysis**

- **Antidote Andexanet**

- If a patient has developed heparin-induced thrombocytopenia (HIT), what to do in this case ?

- Never ever give warfarin due to the risk of thrombosis in the initial days of treatment, which can occur due to decreased levels of C-protein and S-protein.
- Instead, options such as rivaroxaban, apixaban, or dabigatran can be considered; however, these medications are orally administered and have a slower onset compared to injectable options.

- **The drug of choice in this situation is fondaparinux**, an injectable drug that acts as a factor X inhibitor.

Thrombolytics (Fibrinolytics)

1. Streptokinase
2. Urokinase
3. t-PA (tissue plasminogen activator) like:

(Alteplase, Tenecteplase & Reteplase)

- Both protective hemostatic thrombi & target pathogenic thromboemboli are broken down.

- Circulating fibrinogen will be degraded

➔ Bleeding can occur.

- However, these drugs differ in their selectivity to plasminogen in clot & circulating plasminogen.

Thrombolytic agents, or fibrinolytics, are essential medications used to break down blood clots by activating plasminogen, which converts to plasmin, the enzyme that digests fibrin in clots. In this course, three main thrombolytics are emphasized: **streptokinase, urokinase, and tissue plasminogen activator (tPA).**

1. Mechanism and Bleeding Risk:

These agents work by targeting plasminogen. However, their specificity differs, influencing their safety profiles, particularly in terms of bleeding risk.

1. **Streptokinase and urokinase** activate both circulating and clot-bound plasminogen, leading to a broader systemic effect. This lack of specificity can result in a higher risk of bleeding, as plasminogen is activated throughout the bloodstream.
2. **tPA** is unique because it primarily targets plasminogen within the clot itself rather than circulating plasminogen. This specificity reduces systemic bleeding risk, making tPA more accurate and preferable in clinical settings where precise clot dissolution is necessary, such as in acute ischemic stroke.

2. The Drug Differences:

1. **Streptokinase:** Indirectly activates plasminogen with no clot specificity.
2. **Urokinase:** Directly activates plasminogen but still lacks clot specificity.
3. **tPA:** Specifically activates clot-bound plasminogen, minimizing systemic bleeding risk.

This targeted approach of tPA makes it the preferred choice in many clinical situations over streptokinase and urokinase due to its reduced bleeding risk and increased efficacy in dissolving clots directly.

Thrombolytics (Fibrinolytics)

- **<u>Indications</u>:**

- IV for:

-Multiple pulmonary emboli

We should make a quick intervention because he will in a critical situation

-Central deep venous thrombosis (eg, superior vena caval syndrome, ascending thrombophlebitis of iliofemoral vein).

Most important for IV

-Acute myocardial infarction

-Acute ischemic stroke: tPA should be used within 3 hours after onset of symptoms.

- Intra-arterially for:

Can be dangerous under certain conditions due to the bleeding

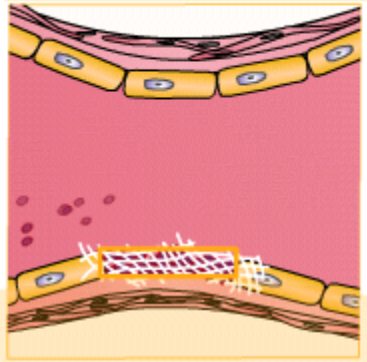
-Peripheral vascular disease

At the end: we want to dissolve the thrombi wherever it is

Thrombolytic drugs – mechanism of action

Thrombolytic/fibrinolytic drugs

Haemostasis

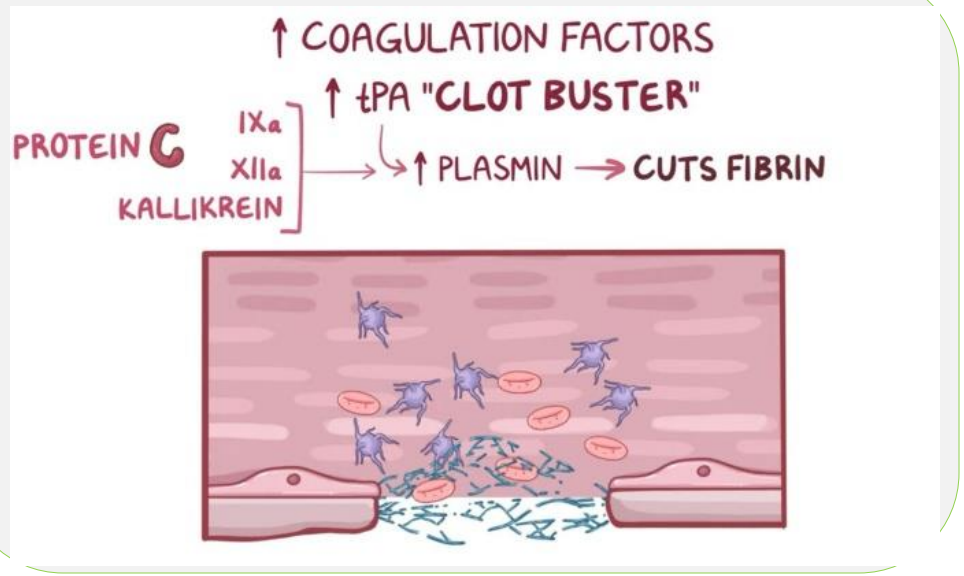


Thrombolytic drugs

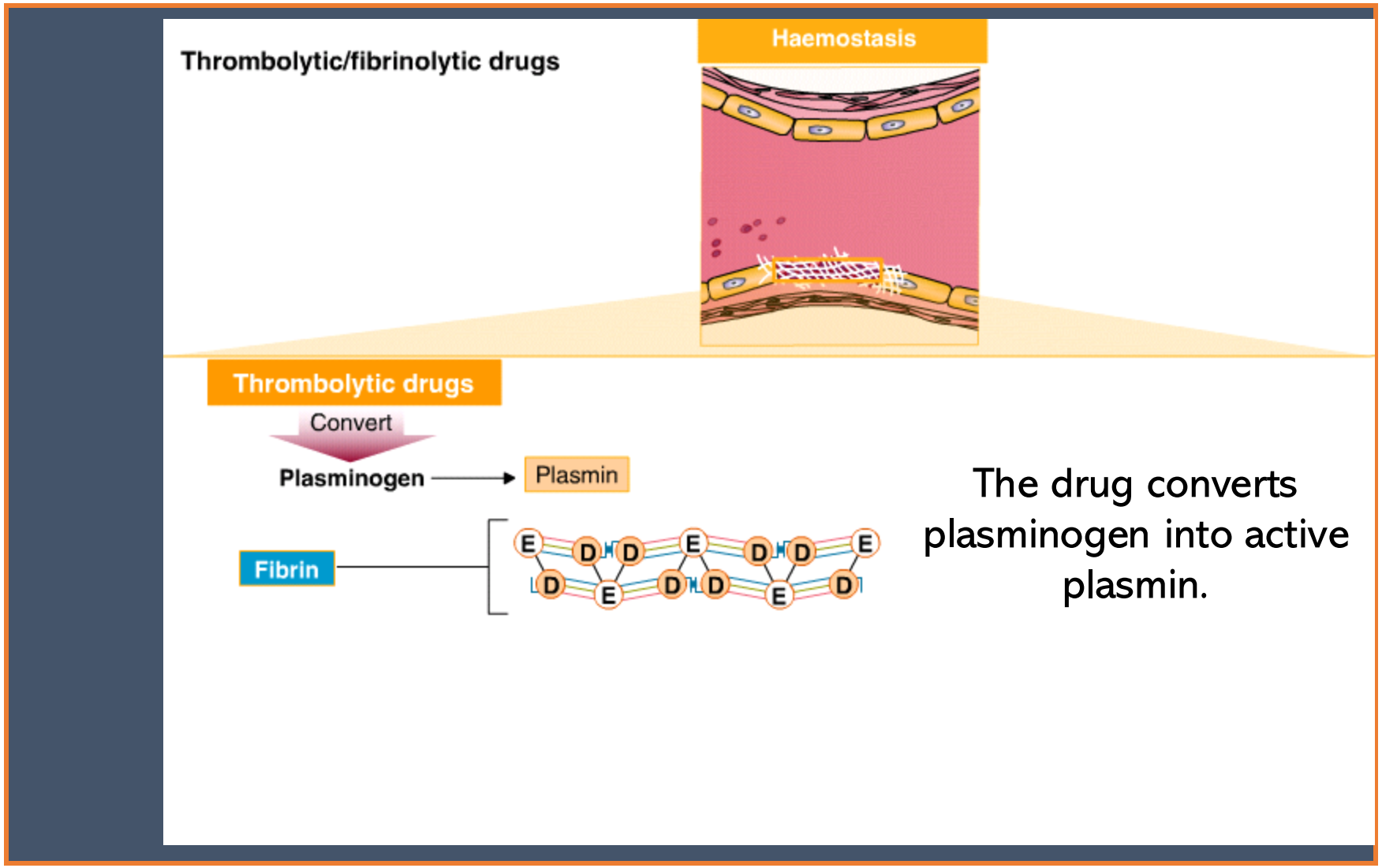
Fibrin

Blood clot forms with a fibrin mesh that holds blood clots

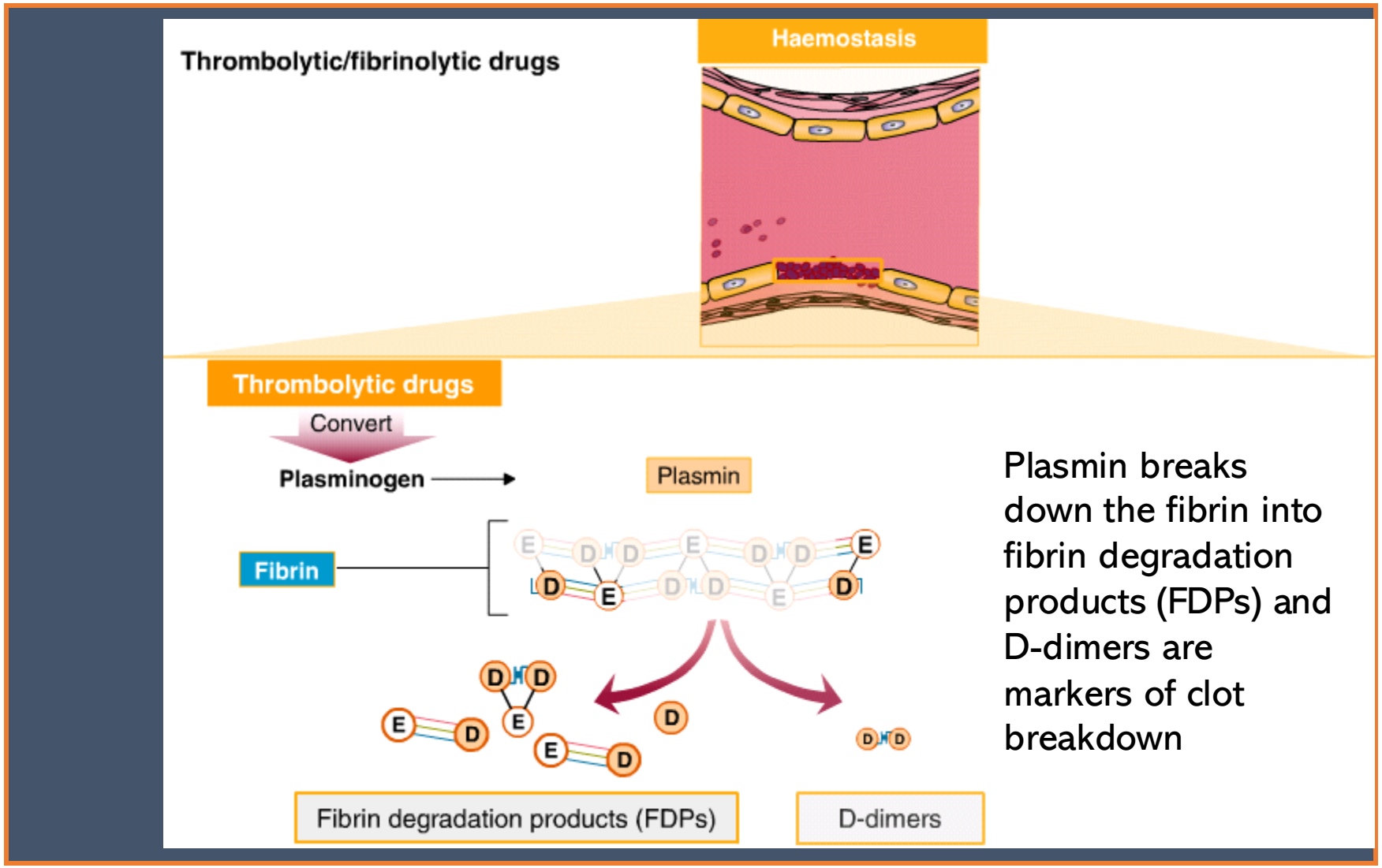
External image



Thrombolytic drugs – mechanism of action



Thrombolytic drugs – mechanism of action



Plasmin breaks down the fibrin into fibrin degradation products (FDPs) and D-dimers are markers of clot breakdown

MOA:

1-Streptokinase: combines with plasminogen. The complex cleaves another plasminogen molecule to plasmin

2-Anistreplase: an acetylated streptokinase-plasminogen complex that cleaves plasminogen to plasmin

3-Urokinase: directly cleaves plasminogen to plasmin

4-t-PA: an endogenous direct activator of plasminogen. It preferentially activates plasminogen that is bound to fibrin. This, in theory, confines fibrinolysis to formed thrombi

5-Alteplase: recombinant t-PA

6-Reteplase: genetically-modified recombinant.

-Less expensive than t-PA but less fibrin-selective

7-Tenecteplase: genetically-modified recombinant t-PA → long $t_{1/2}$

-Slightly more fibrin-selective than t-PA

In summary, the non preferential drugs like: Streptokinase, Anistreplase and Urokinase are very dangerous and can lead to severe bleeding because these are non-selective drugs, it target the plasminogen in the circulating blood and within the clot, so be careful!!!!

In the next 2 slides I arranged the information in a proper way so you can study it properly. Enjoy!!!!

- **Streptokinase** is formed by streptococci
- **Urokinase** is a human enzyme synthesized by kidney

- As the clot dissolves, concentration of thrombin ↑ locally→ ↑ platelet aggregation & ↑ formation of new thrombi

- → Give an antiplatelet or anticoagulant to prevent thrombosis

- The earlier the thrombolytic is given the better.

- **<u>Side effects</u>:**

1) Bleeding: happens because these agents do not distinguish between the fibrin in an unwanted thrombus & fibrin in a beneficial hemostatic plug, or fibrinogen in the circulation.
2) Reperfusion arrhythmia.
3) Hypotension.

Thrombolytic Agents

1.Streptokinase

Source: Derived from streptococci bacteria.

2. Urokinase:

Source: A human enzyme synthesized by the kidneys.

Effects of Thrombolysis

- **Local Increase in Thrombin**: As the clot dissolves, the concentration of thrombin increases locally, which can lead to:
  - ↑Increased platelet aggregation.
  - ↑Increased formation of new thrombi.
- **Preventing Re-Thrombosis**: when we dissolve the thrombi, it will stimulate rebuilding of new thrombi and that will result secrete multiple factors in the body like thrombin, so to prevent that we give antiplatelets and anti coagulant to prevent the thrombosis, but all of that will depend of the situation at least we give the patient one of them as prophylaxis to prevent the thrombosis happen again
- **Early Administration**: The Earlier the thrombolytic is given the better would be.

4) Hypersensitivity: with streptokinase & anistreplase (which includes streptokinase in its composition):

streptokinase is purified from culture broths of streptococci→ it is a foreign body & is, thus, antigenic.

Most people have had a streptococcal infection→ they may have circulating antibodies against streptokinase→ the streptokinase-antibody reaction can cause fever, hypersensitivity &/or failure of therapy (because the streptokinase molecules complexed with the antibody are pharmacologically inactive).

- Urokinase is nonantigenic because it exists normally in human urine→ it is used in patients hypersensitive to streptokinase.

Side Effects

1.Bleeding:

Thrombolytics do not distinguish between fibrin in unwanted thrombi and fibrin in beneficial hemostatic plugs or circulating fibrinogen, leading to an increased risk of bleeding.

2.Reperfusion Arrhythmia:

Reperfusion arrhythmia occurs because cardiac cells are rapidly reoxygenated and nourished following a period of ischemia. When a thrombus in the coronary artery is dissolved, a sudden influx of oxygen and nutrients reaches the ischemic cells. This abrupt change can disrupt cellular ion balance, leading to arrhythmias as the cells adjust to the rapid restoration of blood flow

3.Hypotension

Side Effects

4. Hypersensitivity:

Category	Bacterial Source Drugs	Human Source Drugs
Drug name	Streptokinase	Urokinase
composition	Purified from culture broths of streptococci	Exists naturally in human urine
Antigenicity	Antigenic (foreign body)	Non-antigenic
Clinical implications	- Common in people with prior streptococci infections, leading to antibodies against it. Streptokinase-antibody reaction can cause fever, hypersensitivity,&/ or therapy failure (complexed antibodies are pharmacologically inactive).	Used for patients hypersensitive to streptokinase
Related drug	Antistreplase (include streptokinase)	
Notes	Shares the same antigenic prosperities and hypersensitivity risks as streptokinase	

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	11	injectable drug that acts as a factor 2 inhibitor.	Injectable drug that acts as a factor X inhibitor.
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!