Poltava State Medical University

DRUGS THAT AFFECT HEMOSTASIS

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1. Blood coagulation and fibrinolysis (physiology and pathology)
2. Direct and indirect coagulants
3. Pharmacology of heparin and other direct-acting anticoagulants
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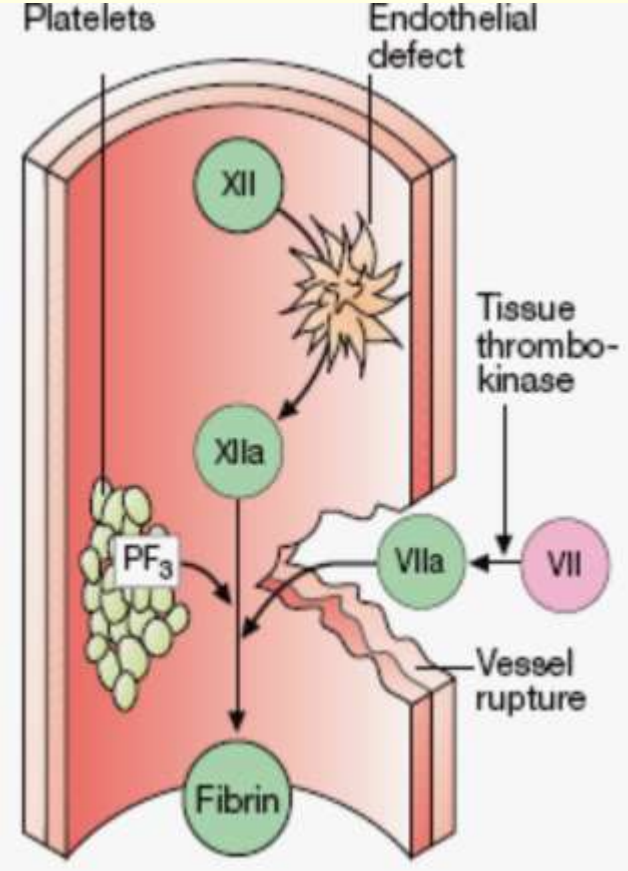
5. Antiplatelets and their use
6. Fibrinolytics and activators of fibrinolysis
7. Inhibitors of fibrinolysis
8. Control tasks

HEMOSTASIS (BLOOD COAGULATION)



Hemostasis is an arrest of bleeding from damaged blood vessels.

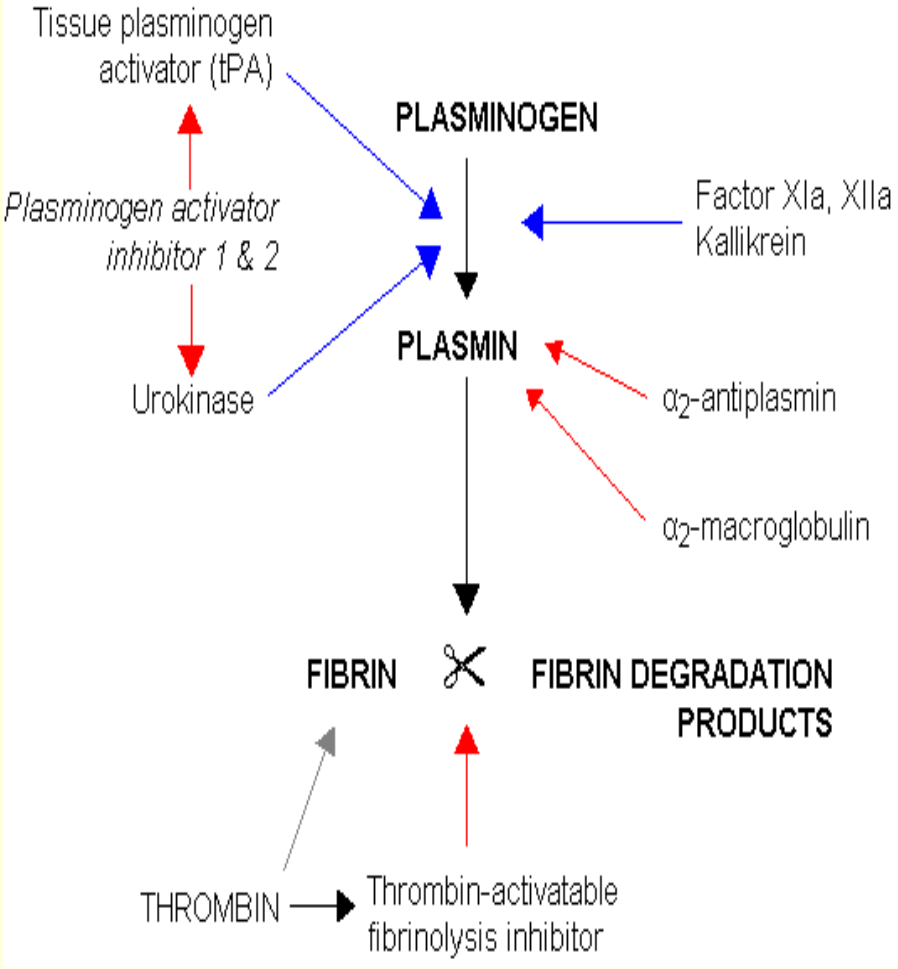
It is complex cascade of enzymatic reactions

Damage of blood vessel causes vasospasm, platelet aggregation and adhesion.

It is resulting in formation of platelet plug, activation of clotting factors, conversion of fibrinogen to insoluble fibrin, clot formation, and stop of bleeding

FIBRINOLYSIS

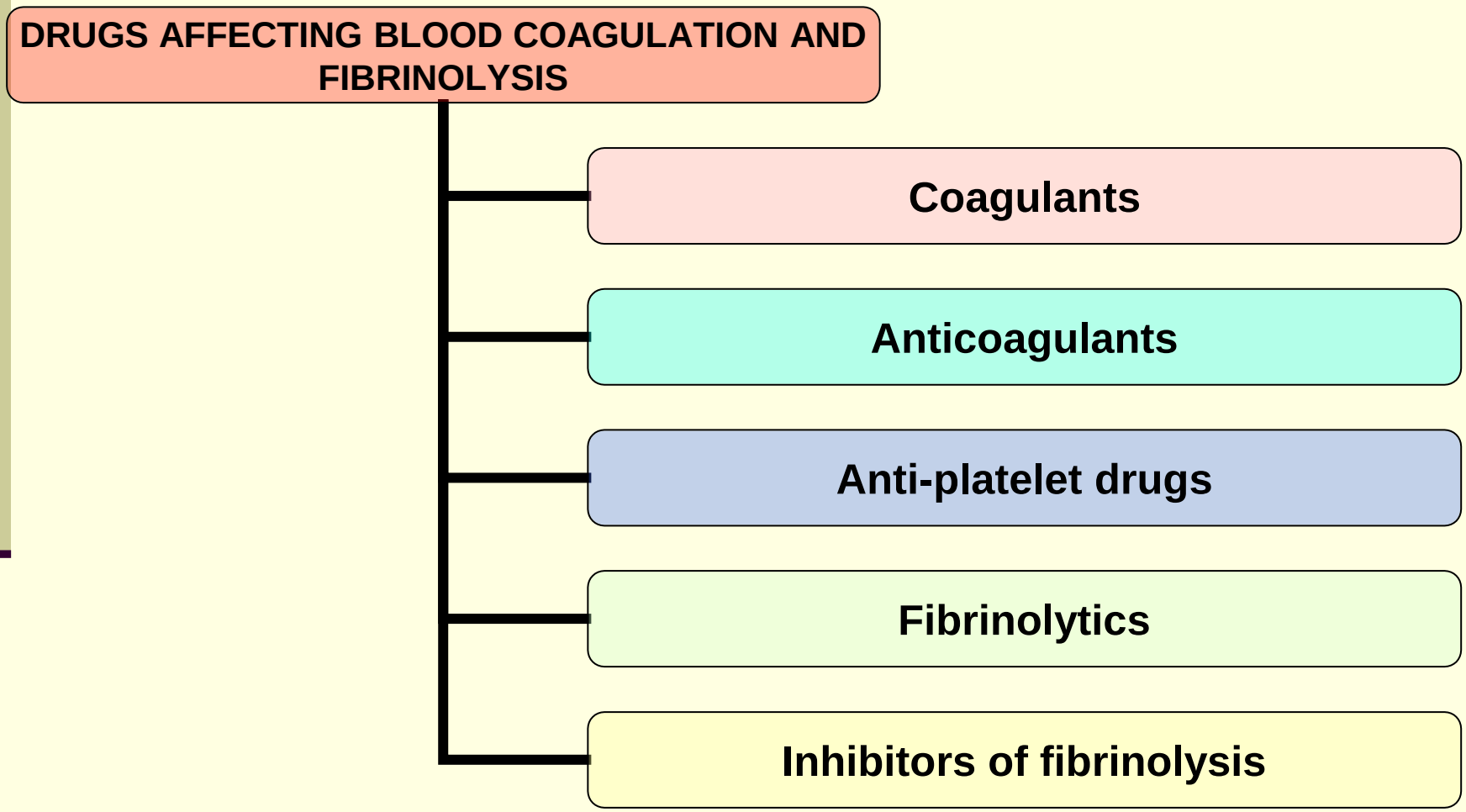
Fibrinolysis is a lysis of thrombus for restoration of blood flow: plasminogen (pro-fibrinolysin) converts into plasmin (fibrinolysin) and causes lysis of fibrin clot



PATHOLOGY OF HEMOSTASIS AND FIBRINOLYSIS

- Decrease in blood coagulation and (or) increase in fibrinolysis result in ***bleeding***
- Increase in blood coagulation and (or) decrease in fibrinolysis result in ***thrombosis, thromboembolism, syndrome of disseminated intravasal blood coagulation***

DRUGS AFFECTING BLOOD COAGULATION AND FIBRINOLYSIS



COAGULANTS

CLASSIFICATION

1. ***Direct-acting (are active in vivo, as well as in vitro)***
   - – Thrombin
   - – Hemostatic sponge (Spongia haemostatica)
   - – Fibrinogen
   - – Eptacog alfa (Novoseven)
   - – Calcium chloride
   - – Calcium gluconate
2. ***Indirect- acting (are active only in vivo)***
   - – Vitamin K (Phytomenadion)
   - – Vikasolum

DIRECT-ACTING COAGULANTS

- ***Thrombin*** is active compound of blood coagulation system, is used for bleeding from capillary vessels, is applied only topically (IV administration may cause disseminated thrombosis).
- ***Fibrinogen*** is non-active compound of blood coagulation system, is used by IV infusion for bleeding from bigger vessels, hypofibrinogenemia, disseminated intravasal blood coagulation.
- ***Calcium chloride, calcium gluconate*** contain calcium ions which are the components of blood coagulation system, stimulate formation of active clotting factors, are used parenteraly for bleeding, for prophylaxis of bleeding, or for decrease of capillary permeability.

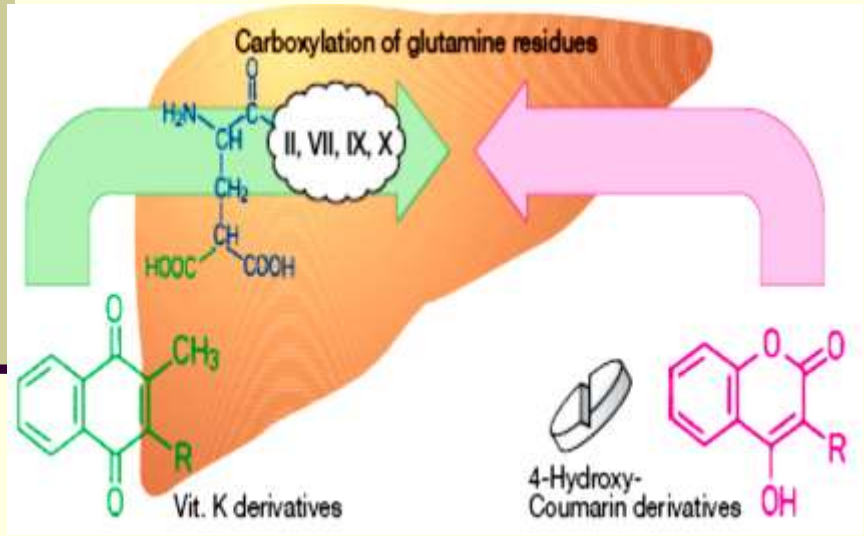
DIRECT-ACTING COAGULANTS

Eptacog alfa (NovoSeven)

- recombinant activated factor VII or eptacog alfa is similar to human plasma-derived coagulation factor VIIa
- is manufactured using DNA biotechnology
- interacts with thrombin-activated platelets to produce thrombin burst leading to accelerated fibrin clot formation localized to the site of vascular injury
- is approved for use as an intravenous hemostatic agent in patients with congenital hemophilia with inhibitors, for acquired hemophilia, factor VII deficiency, and Glanzmann thrombasthenia
- is not immunogenic in patients with hemophilia and has very low thrombogenicity

INDIRECT-ACTING COAGULANTS. VIKASOLUM

Mechanism of action of Vitamin K derivatives (Vikasolum) and their antagonists (coumarins)



- is indirect-acting coagulant, water-soluble synthetic vitamin K
- is administered orally, IM, rarely IV; develops therapeutic effect slowly in 12-18 hrs
- takes part in synthesis of clotting factors in the liver
- is used for prophylaxis of bleeding, for chronic and repeated bleedings, radiation sickness, liver diseases, overdose of indirect-acting anticoagulants
- is contraindicated to patients with hypercoagulation, thrombosis, thromboembolism

ANTICOAGULANTS

CLASSIFICATION

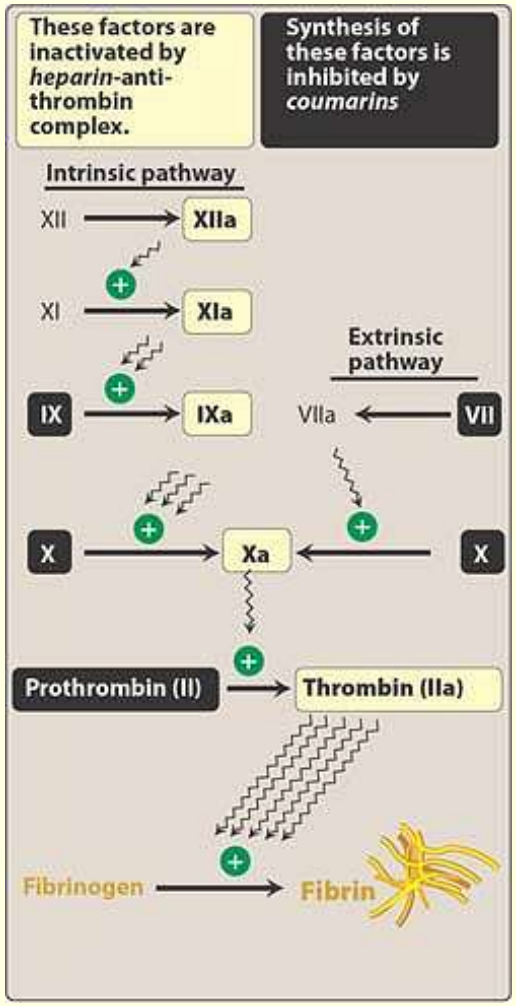
1. Direct-acting (are active in vivo, as well as in vitro)

– Heparin
– Fraxiparine
– Enoxaparin
– Fondaparinux
– Rivaroxaban

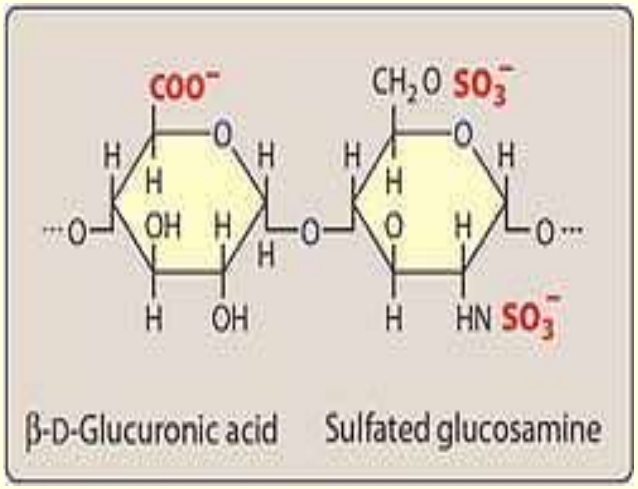
2. Indirect-acting (are active only in vivo)

– Warfarin
– Syncumar
– Neodicumarinum.

ANTICOAGULANTS: targets of action



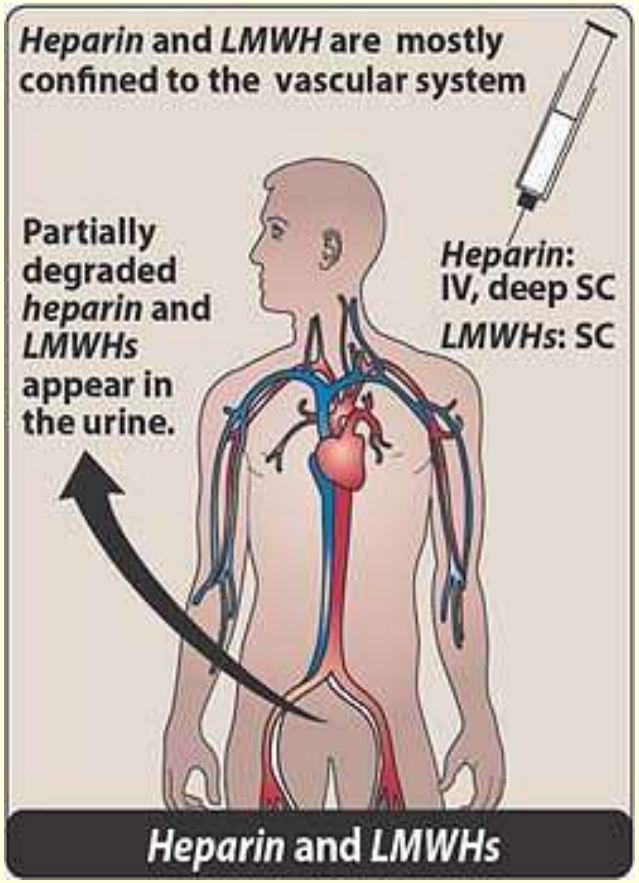
DIRECT-ACTING ANTICOAGULANTS. HEPARIN



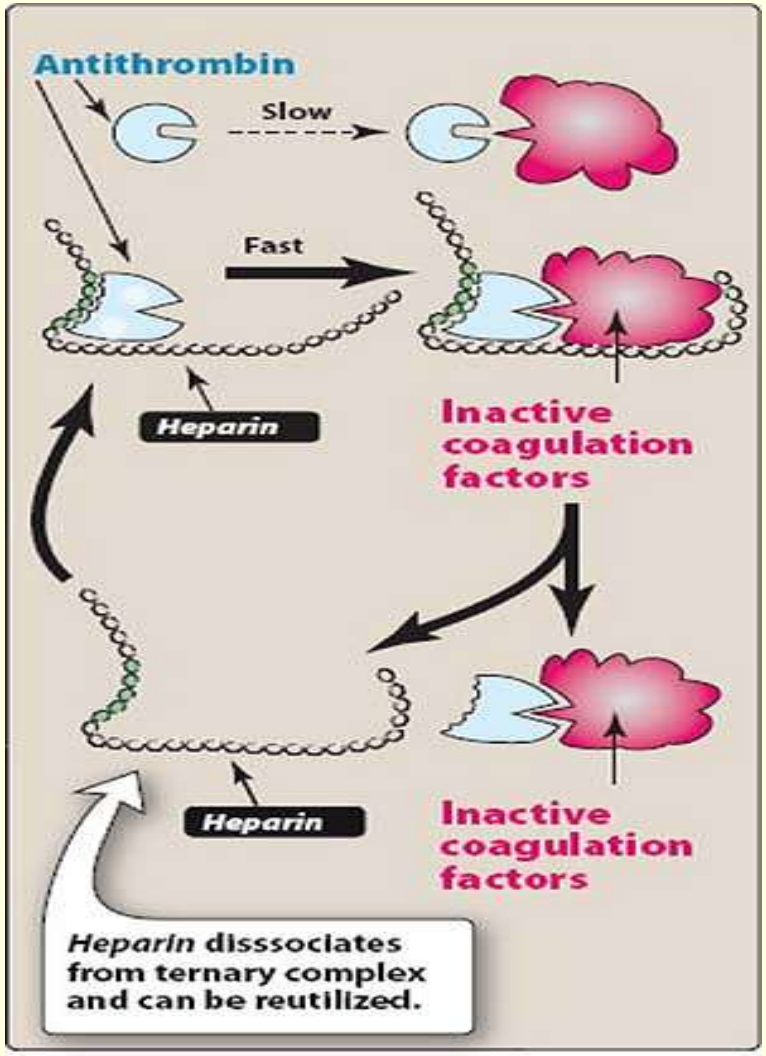
- ***Heparin*** is natural substance produced by mast cells.
- High concentration of heparin is observed in lungs and wall of intestine.
- It belongs to acidic mucopolysaccharides.
- Disaccharide component of heparin shows negative charges due to carboxyl and sulfate groups.

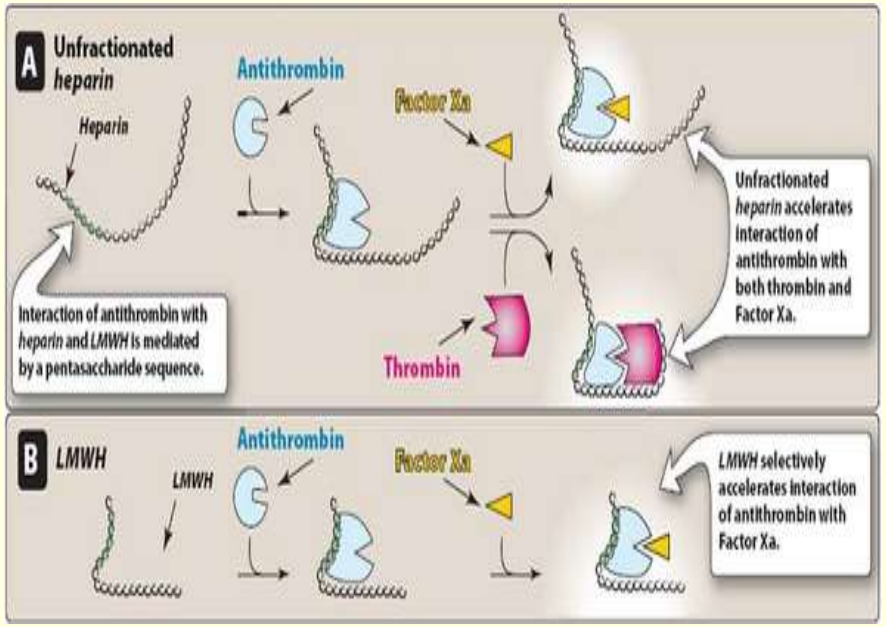
HEPARIN: pharmacokinetics

- is administered IV, IM, SC, topically
- begins to act immediately after IV administration and acts during 4-6 hrs
- begins to act in 15-30 min after IM administration and acts during 6-8 hrs
- begins to act in 30-60 min after SC administration and acts during 8-12 hrs
- is metabolized in the liver by heparinase
- is excreted with urine.



HEPARIN: mechanism of action





HEPARIN: pharmacodynamics

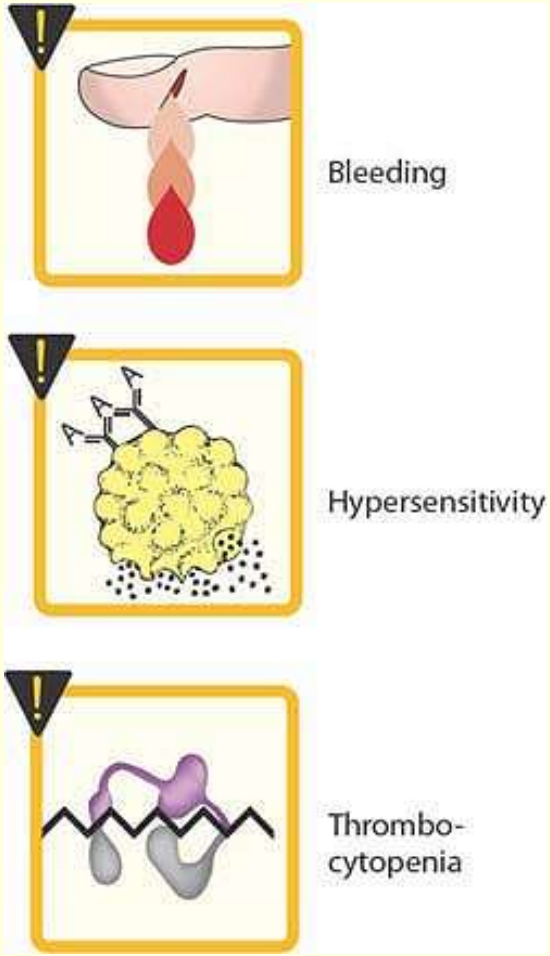
- strong rapid decrease in all stages of blood coagulation
- decrease in platelet aggregation
- improvement of microcirculation and coronary circulation
- decrease in lipids concentration in blood serum
- decrease in inflammation
- decrease in immunity
- increase in synthesis of surfactant in lungs
- decrease in blood pressure (in higher doses)
- decrease in glucose level in blood serum (in higher doses)
- increase in diuresis (in higher doses).

HEPARIN: indications

- Acute thrombosis and thromboembolism
- Myocardial infarction
- Ischemic stroke
- Prevention of thrombus formation after surgeries
- Hemodialysis or blood transfusion
- Thrombophlebitis
- Syndrome of disseminated intravasal blood coagulation
- Atherosclerosis
- Autoimmune diseases
- Chronic non-specific diseases of lungs.

The time of bleeding or the time of blood coagulation should be controlled!

HEPARIN: side-effects



- Bleeding
- Hematomes
- Hematuria
- Thrombocytopenia
- Allergy
- Osteoporosis
- Silvering of the hair.

In overdose – Protamine sulfate!

HEPARIN: contraindications

- Hemorrhages
- Hemorrhagic diathesis
- Leukemia
- Anemia
- Malignant diseases
- Gastric ulcer
- Hypertension
- Severe diseases of the liver and kidney.

FRAXIPARINE

- is ***low molecular weight heparin (LMWH)***
- is administered SC once a day; has bigger bioavailability, longer duration of action, less binding with plasma proteins
- depresses activated Stuart-Prauers factor more than thrombin
- is used for treatment of thrombophlebitis, prevention of thrombus formation after surgeries

ENOXAPARIN

- is ***low molecular weight heparin (LMWH)***
- is used to prevent or to treat deep vein thrombosis, therapy of unstable angina and myocardial infarction
- is given SC or IV
- Side-effects: thrombocytopenia, elevations in serum aminotransferases, hematuria, bleeding, anemia, ecchymosis, peripheral edema, injection site hemorrhage, injection site pain

FONDAPARINUX

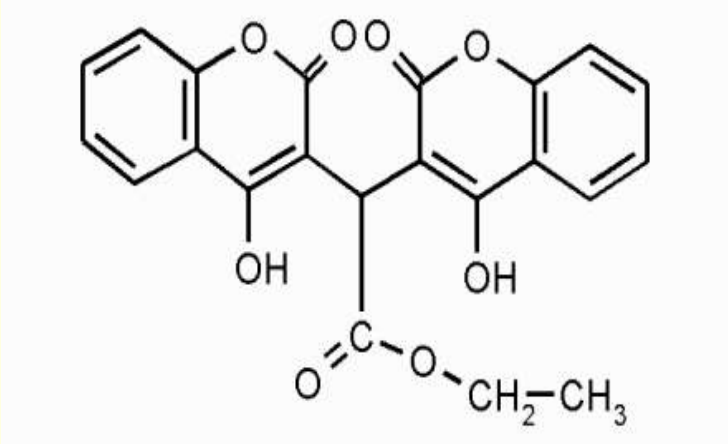
- is an anticoagulant medication chemically related to low molecular weight heparins
- is a synthetic pentasaccharide factor Xa inhibitor
- is given SC daily
- is used for the prevention of deep vein thrombosis in patients who have had orthopedic surgery, for the treatment of deep vein thrombosis and pulmonary embolism
- One potential advantage of fondaparinux over LMWH or unfractionated heparin is that the risk for heparin-induced thrombocytopenia is substantially lower

RIVAROXABAN

- is an oral anticoagulant
- is the first available orally active direct factor Xa inhibitor
- inhibits both free Factor Xa and Factor Xa bound in the prothrombinase complex
- is well absorbed from the gut and maximum inhibition of factor Xa occurs 4 h after a dose. The effects last 8–12 h, but factor Xa activity does not return to normal within 24 h so once-daily dosing is possible
- is used for prevention of venous thromboembolism in patients with atrial fibrillation, elective hip and knee replacement surgery
- side-effects: bleeding, including severe internal bleeding. *A possible antidote (andexanet alfa) is being investigated*.

INDIRECT-ACTING ANTICOAGULANTS. NEODICUMARINUM

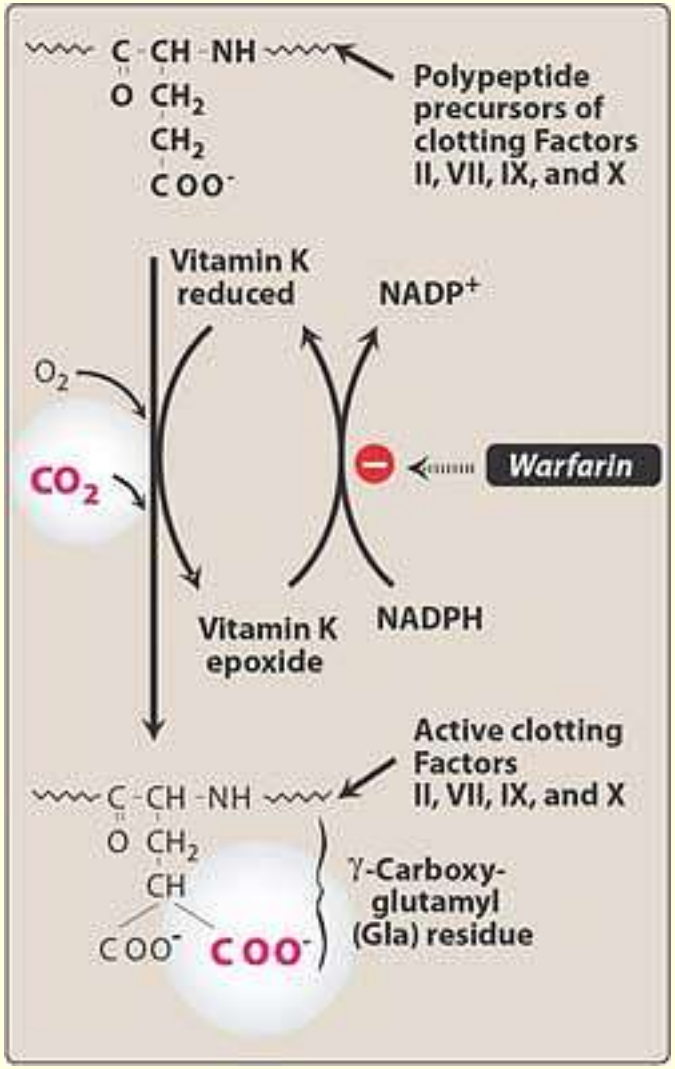
Neodicumarinum is indirect-acting anticoagulant, coumarin derivative



NEODICUMARINUM: pharmacokinetics

- is administered orally
- is absorbed in the GI tract
- binds to proteins in blood plasma
- is metabolized in the liver
- begins to act in 2-3 hrs after administration
- develops maximal action in 12-30 hrs after administration
- acts during 48 hrs after the end of treatment
- is excreted by urine.

NEODICUMARINUM: mechanism of action



NEODICUMARINUM: pharmacodynamics and indications

Pharmacodynamics

- decrease in blood coagulation
- increase in fibrinolysis
- decrease in lipids concentration in blood.

Indications

- Acute thrombosis (together or after of heparin's usage)
- Myocardial infarction
- Ischemic insult
- Thromboembolism
- Thrombophlebitis
- Prevention of thrombus formation after surgeries.

Index of prothrombin should be controlled!

NEODICUMARINUM: side-effects and contraindications

Side-effects

- Bleeding
- Forming of hematomes
- Hematuria
- Dyspepsia
- Oppression of liver function
- Allergy. decrease in blood coagulation

Contraindications

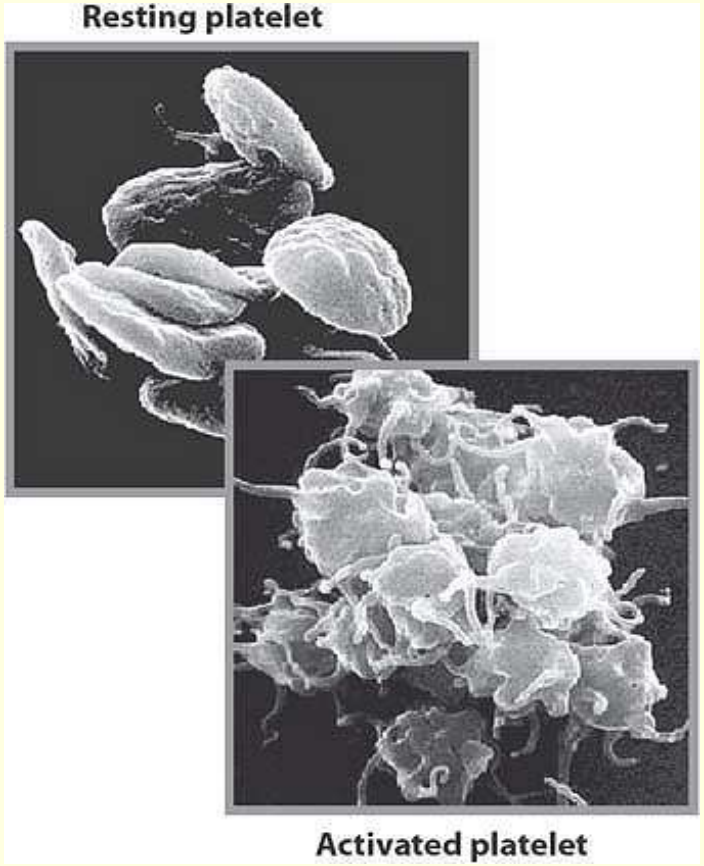
- Hemorrhages
- Hemorrhagic diathesis
- Gastric ulcer
- Malignant diseases
- Diseases of liver and kidney
- Pregnancy.

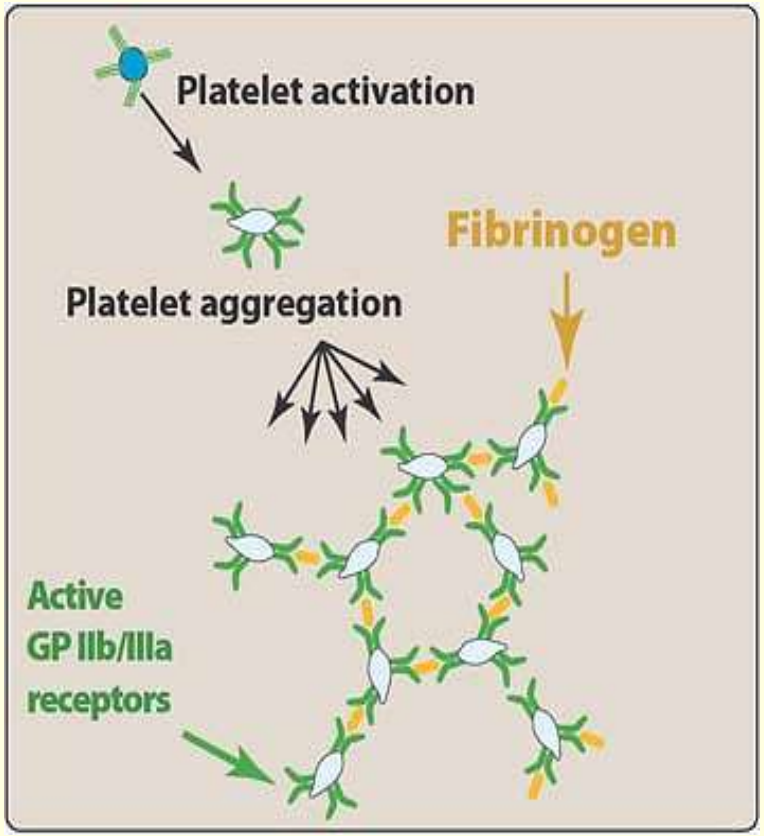
For treatment of overdose – Vikasolum!

WARFARIN

- decreases blood coagulation by inhibiting vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K1 to its reduced form after it has participated in the carboxylation of several blood coagulation proteins, mainly prothrombin and factor VII.
- the pharmacologic action may always be reversed by fresh vitamin K1
- does not anticoagulate blood immediately. Instead, onset of their effect requires about 2 to 3 days and the duration of action of a single dose of warfarin is 2 to 5 days. Reversal of warfarin's effect by discontinuing its use, or by administering vitamin K1, requires a similar period of time.

PLATELET AGGREGATION





ANTI-PLATELET DRUGS

CLASSIFICATION

1. COX-inhibitors

– Acetylsalicylic acid (Aspirin)

2. Inhibitors of phosphodiesterase

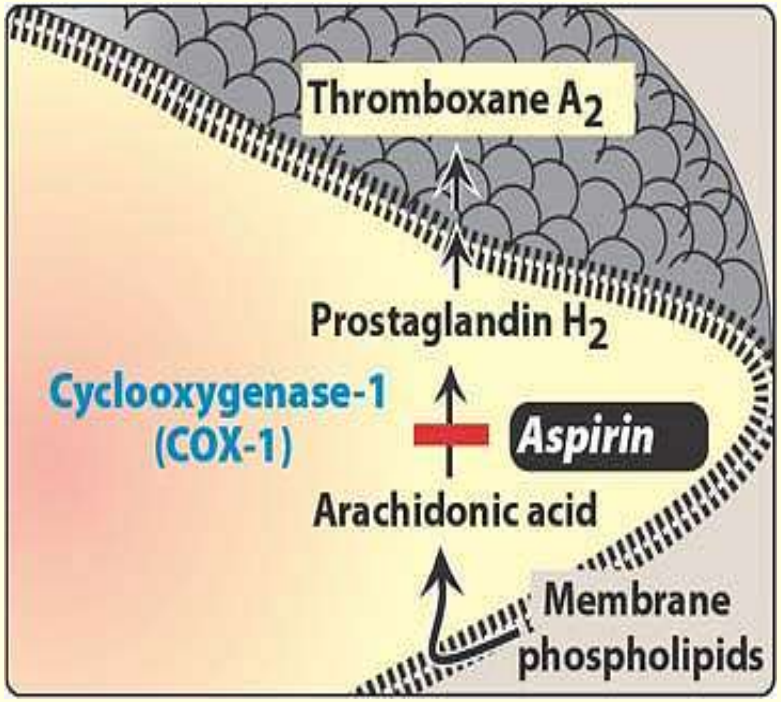
– Dipyridamole

3. Inhibitors of ADP-mediated aggregation

– Ticlopidine (Ticlide).

ASPIRIN

Aspirin irreversibly inhibits platelet COX-1. In such way, it prevents synthesis of thromboxane A2 and decreases platelet aggregation. This effect occurs in lower doses (less than 0,5 per day) and lasts more than 48 hrs (till 7 days). In higher doses aspirin also inhibits prostacycline synthesis.



DIPYRIDAMOLE

Dypiridamole inhibits adenosine desaminase and phosphodiesterase in platelets, increases cAMP concentration in cells and inhibits thromboxane A2 synthesis that leads to decrease in platelet aggregation. It also increases prostacycline level.

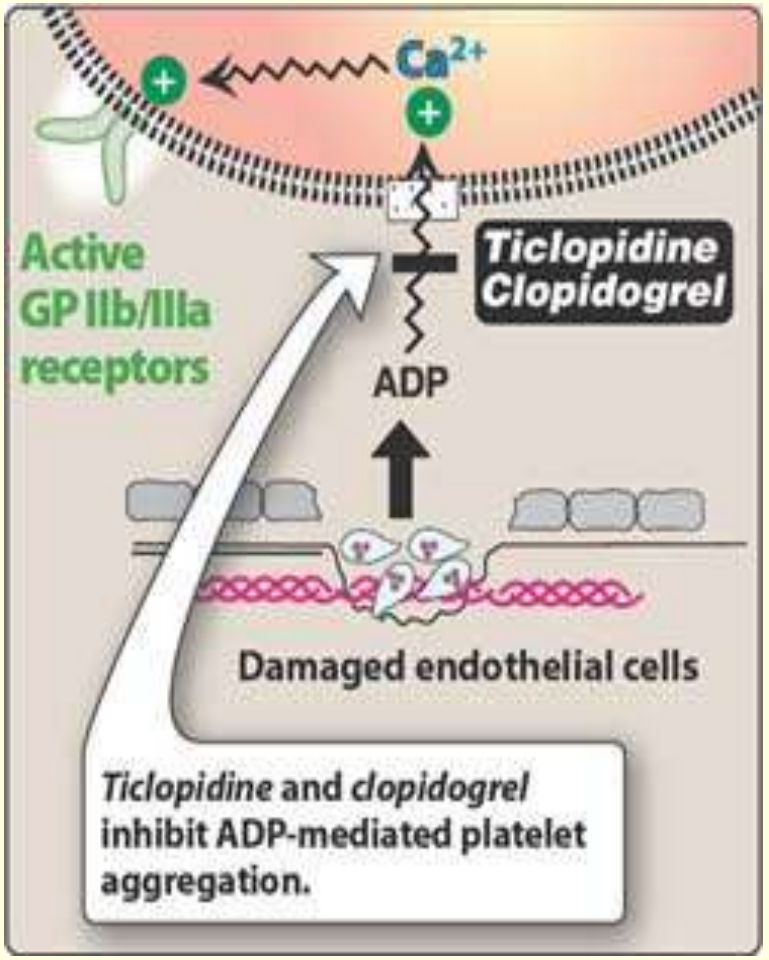
TICLOPIDINE

- is an antiplatelet drug
- is ADP receptor inhibitor
- is for preventing

strokes and coronary stent occlusion

- because of neutropenia

and thrombotic thrombocy-topenic purpura it is used If aspirin is not tolerated, or dual antiplatelet therapy Is desirable



ANTI-PLATLETS: indications

- Prevention of thrombosis and re-thrombosis (as discontinuation of anticoagulant therapy)
- Prophylaxis of myocardial infarction and stroke
- Prophylaxis of thrombosis after surgeries
- Angioplastics
- Prevention of thrombosis in patients with prosthetic cardiac valves
- Thrombophlebitis.

DRUGS AFFECTING FIBRINOLYSIS

CLASSIFICATION

A. Fibrinolytic drugs

1. Direct-acting

– Fibrinolysin

2. Indirect-acting (activators of pro-fibrinolysin)

a) non-selective

– Streptokinase

b) selective

– Alteplase

– Tenecteplase

B. Inhibitors of fibrinolysis

1. Direct-acting

– Contrykal

– Aprotinin

2. Indirect-acting

– Aminocaproic acid.

FIBRINOLYTICS. FIBRINOLYSIN

Fibrinolysin is the protein from donors' plasma, the active factor of fibrinolysis

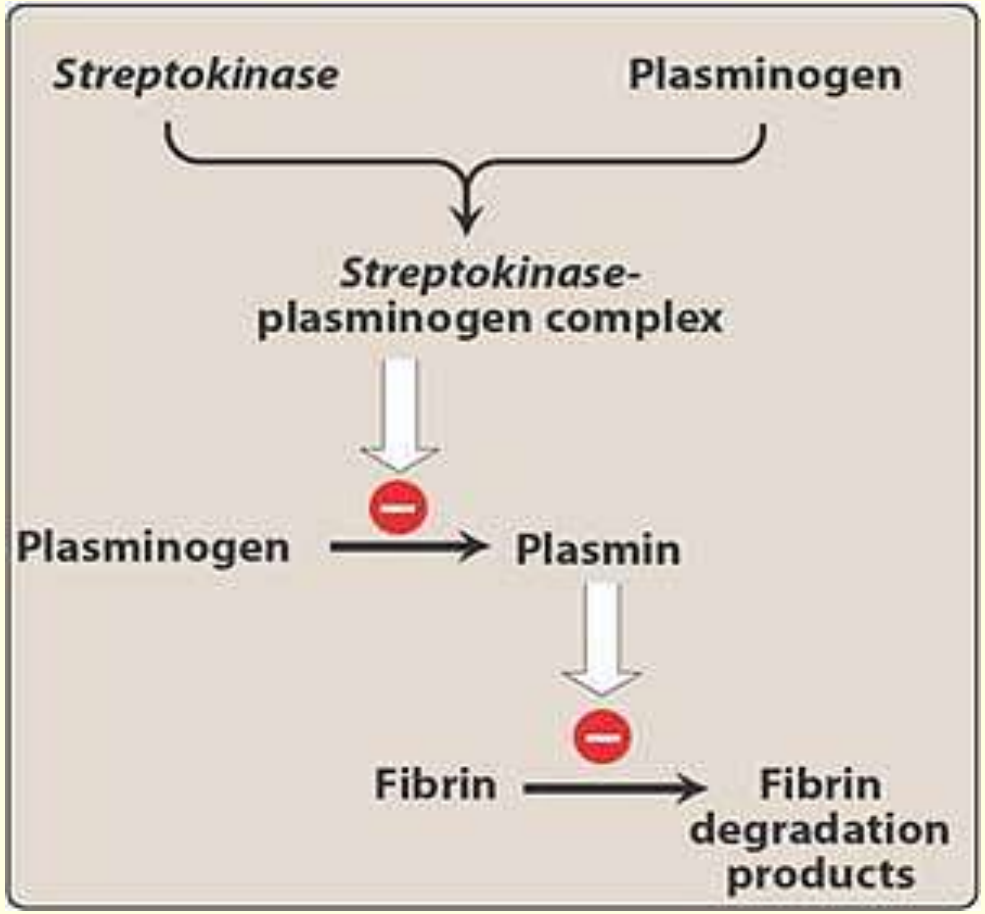
- is administered by IV infusion
- has direct action on fibrin and dissolves fibrin clot in the first hours after thrombosis
- is used for treatment of acute thrombosis, acute myocardial infarction, thrombophlebitis
- may cause bleeding resulting from increase in fibrinolysis, allergy, anaphylaxis, arrhythmia, hypotension
- is contraindicated in bleeding, cerebral vascular accident, recent trauma of brain, surgery, uncontrolled hypertension.

ACTIVATORS OF FIBRINOLYSIS

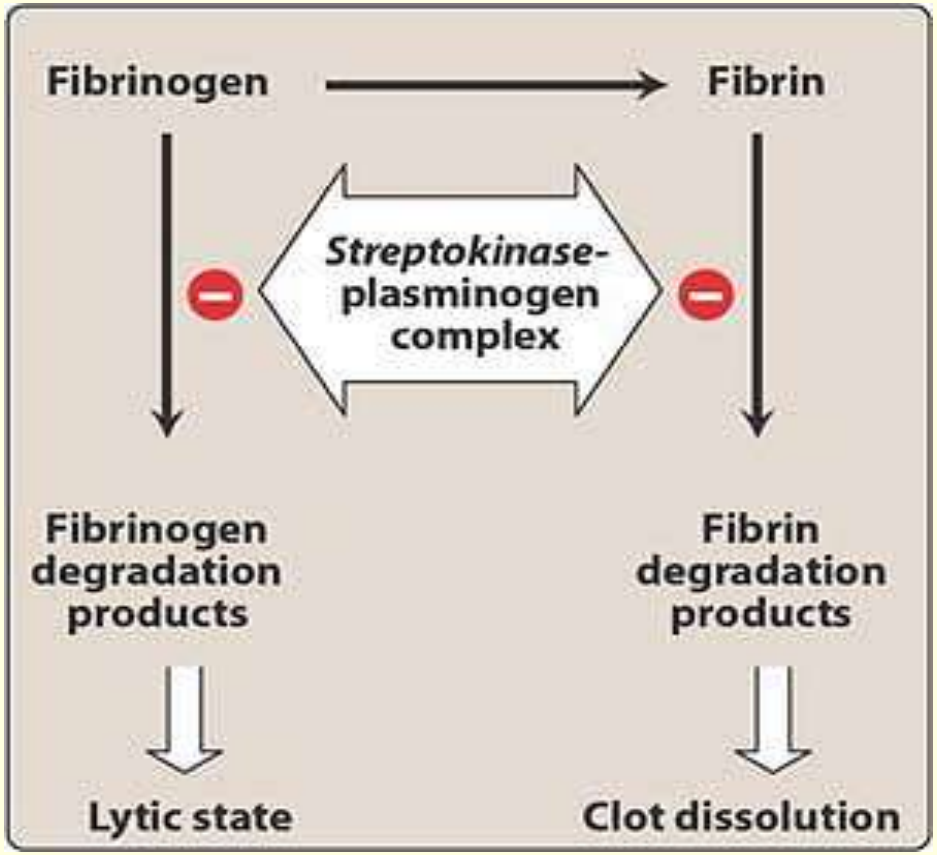
STEPTOKINASE

- is proteolytic enzyme from hemolytic streptococcus
- acts indirectly, promotes the conversion of plasminogen to plasmin, causes systemic activation of fibrinolysis and degradation both of fibrin and fibrinogen resulting in dissolving of thrombus
- has plasma half-life of 23 min; is administered by IV infusion (intracoronary infusion in myocardial infarction)
- is more potent than fibrinolysin
- does not cause arrhythmia.

ACTIVATORS OF FIBRINOLYSIS: mechanism of action of Streptokinase



ACTIVATORS OF FIBRINOLYSIS: non-selective action of Streptokinase



ACTIVATORS OF FIBRINOLYSIS

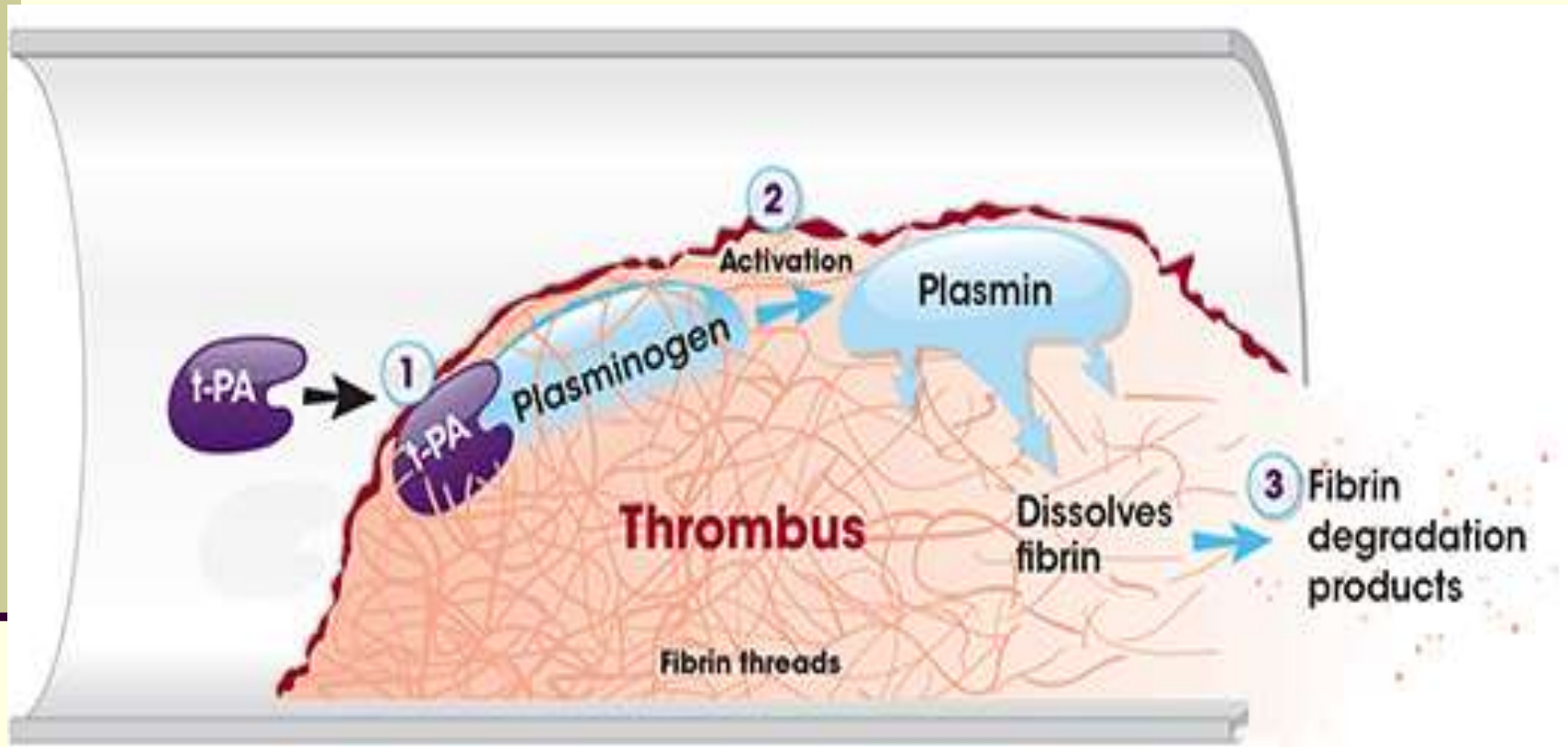
TENECTEPLASE

- is an enzyme used as a thrombolytic drug
- is a tissue plasminogen activator (t-PA) produced by recombinant DNA technology
- It binds to the fibrin component of the thrombus and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus; has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor compared to native t-PA.
- has plasma half-life of 20-24 min; is administered by IV infusion

ALTEPLASE (ACTILISE)

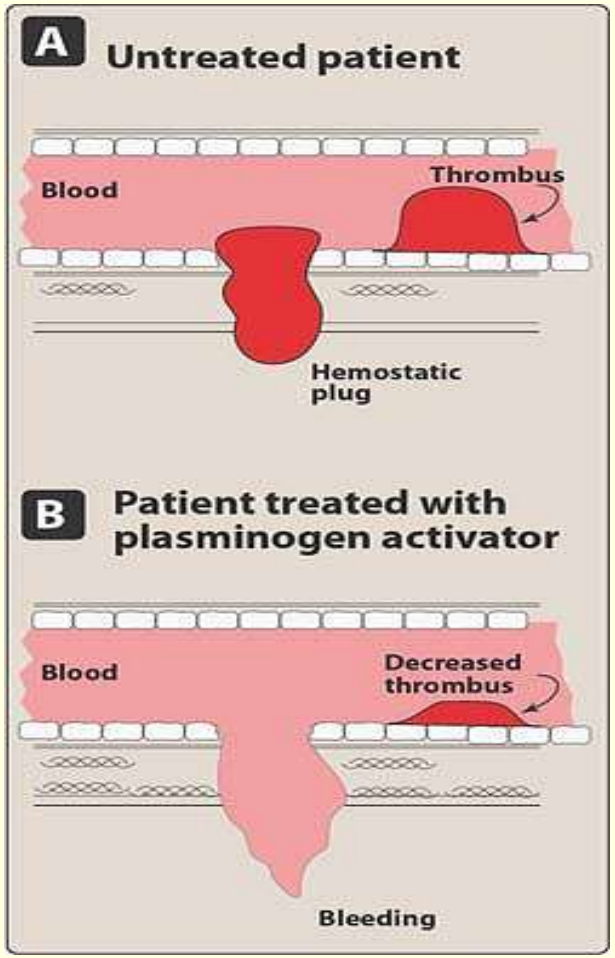
- is tissue plasminogen activator (t-PA), product of biotechnology
- has a half-life of 5 min, is administered by IV infusion
- has high affinity for fibrin and acts selectively on plasminogen bound with thrombus.

MECHANISM OF ACTION OF RECOMBINANT t-PA



1 Recombinant t-PA (alteplase) binds to fibrin in thrombus 2 converts entrapped plasminogen to plasmin that 3 initiates local fibrinolysis.

ACTIVATORS OF FIBRINOLYSIS: side-effects



INHIBITORS OF FIBRINOLYSIS. CONTRYKAL

- is direct-acting inhibitor of fibrinolysis and proteolysis
- is administered IV slowly or by IV infusion
- binds with plasmin and inactivates it, inhibits activity of trypsin inhibits fibrinilysis and stops bleeding caused by activation of fibrinolysis; inhibits proteolysis and inflammation
- is indicated in bleeding resulting from activation of fibrinolysis; myocardial infarction; acute pancreatitis; prophylaxis of proteolytic complications after surgeries on pancreas, thyroid glands, bigger salivary glands, and lungs
- may cause allergy, nausea, vomiting, hypotension, tachycardia.

INHIBITORS OF FIBRINOLYSIS. AMINOCAPROIC ACID

- is indirect-acting inhibitor of fibrinolysis
- is administered orally and by IV infusion, acts during 4-6 hrs, is not metabolized, is excreted with urine
- interacts with plasminogen and inhibits its transformation into plasmin, partly inhibits plasmin; inhibits proteolytic enzymes
- inhibits fibrinolysis and decreases bleeding caused by activation of fibrinolysis; oppresses proteolysis, decreases inflammation, has anti-allergic action, stimulates antitoxic function of the liver
- has indications which are similar to the same of contrykal; also is used in syndrome of disseminated intravasal blood coagulation, obstetrics pathology (ablation placenta, uterine hemorrhages), liver diseases, hypoplastic anemia
- may cause side-effects, such as dizziness, hypotension, bradycardia, arrhythmia, skin rash, vomiting, nausea.

CONTROL TASKS

- On discontinuation of heparin therapy in a patient with myocardial infarction, the administration of warfarin was started. What is the mechanism of anticoagulant effect of this preparation?

A. Blocking of calcium binding to clotting factors

B. Forming of complex with clotting factors

C. Inhibiting of pro-clotting factor synthesis in the liver

D. Breaking down of thrombin

E. Depolymerization of fibrin.

(C)

CONTROL TASKS

- A patient with acute thrombosis of femoral artery was delivered to a hospital. Immediately infusion of heparin has begun. What is the goal of this drug administration?

A. To prevent further thrombus formation

B. To cause the lysis of thrombus directly

C. To transform plasminogen into plasmin

D. To prevent platelets activation

E. To decrease the area of hypoxia in tissues.

(A)

CONTROL TASKS

- A patient with acute myocardial infarction was taken into resuscitation department 2 hours after the appearance of coronary thrombosis. Alteplase was administered by intravenous infusion. Which group is it from?

A. Direct anticoagulants

B. Indirect anticoagulants

C. Anti-platelets

D. Activators of fibrinolysis

E. Inhibitors of fibrinolysis.

(D)

THE END

Thank you for attention!