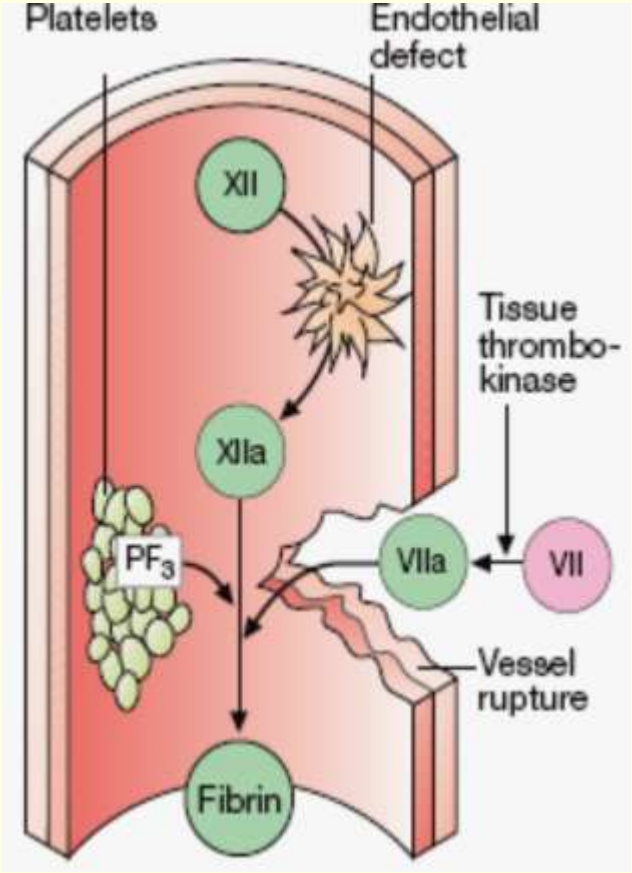
Poltava State Medical University
Department of Pharmacology, Clinical Pharmacology and Pharmacy

Pharmacology of Drugs Influencing Blood System:

Coagulants, Anticoagulants, Fibrinolytic Drugs, Fibrinolysis Inhibitors, Antiplatelets

CONTENTS

HEMOSTASIS (BLOOD COAGULATION)



Hemostasis is an arrest of bleeding from damaged blood vessels.

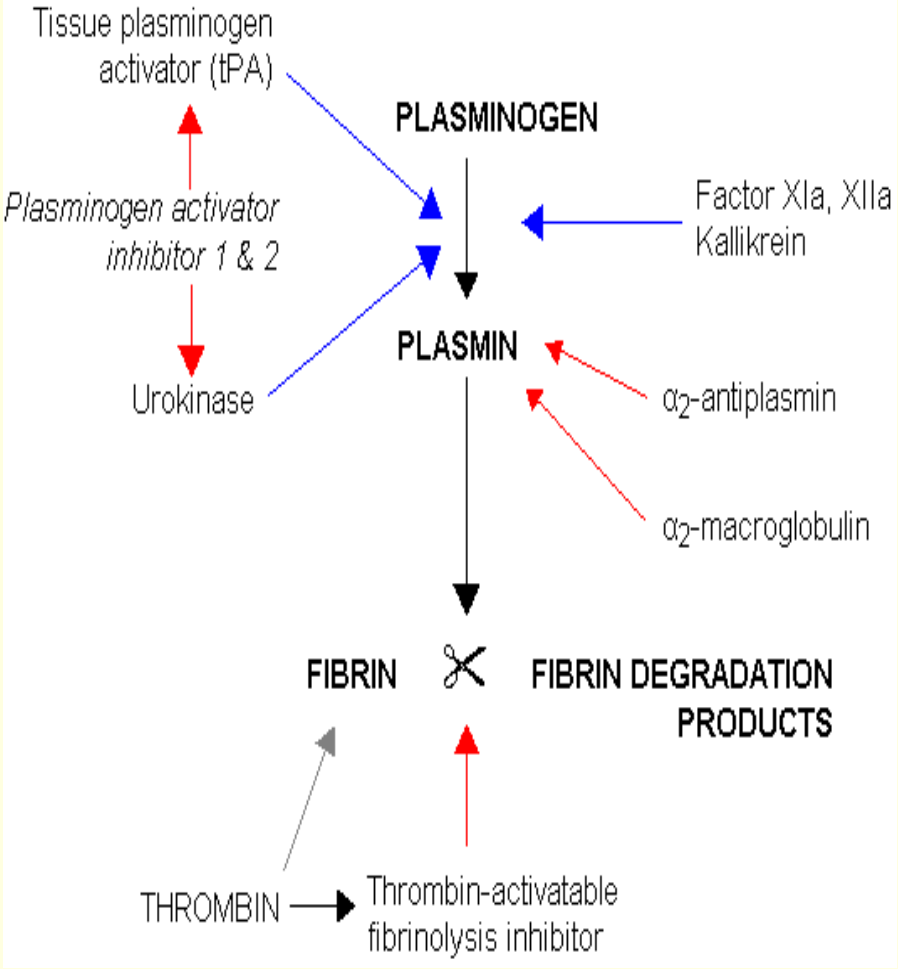
It is complex cascade of enzymatic reactions

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

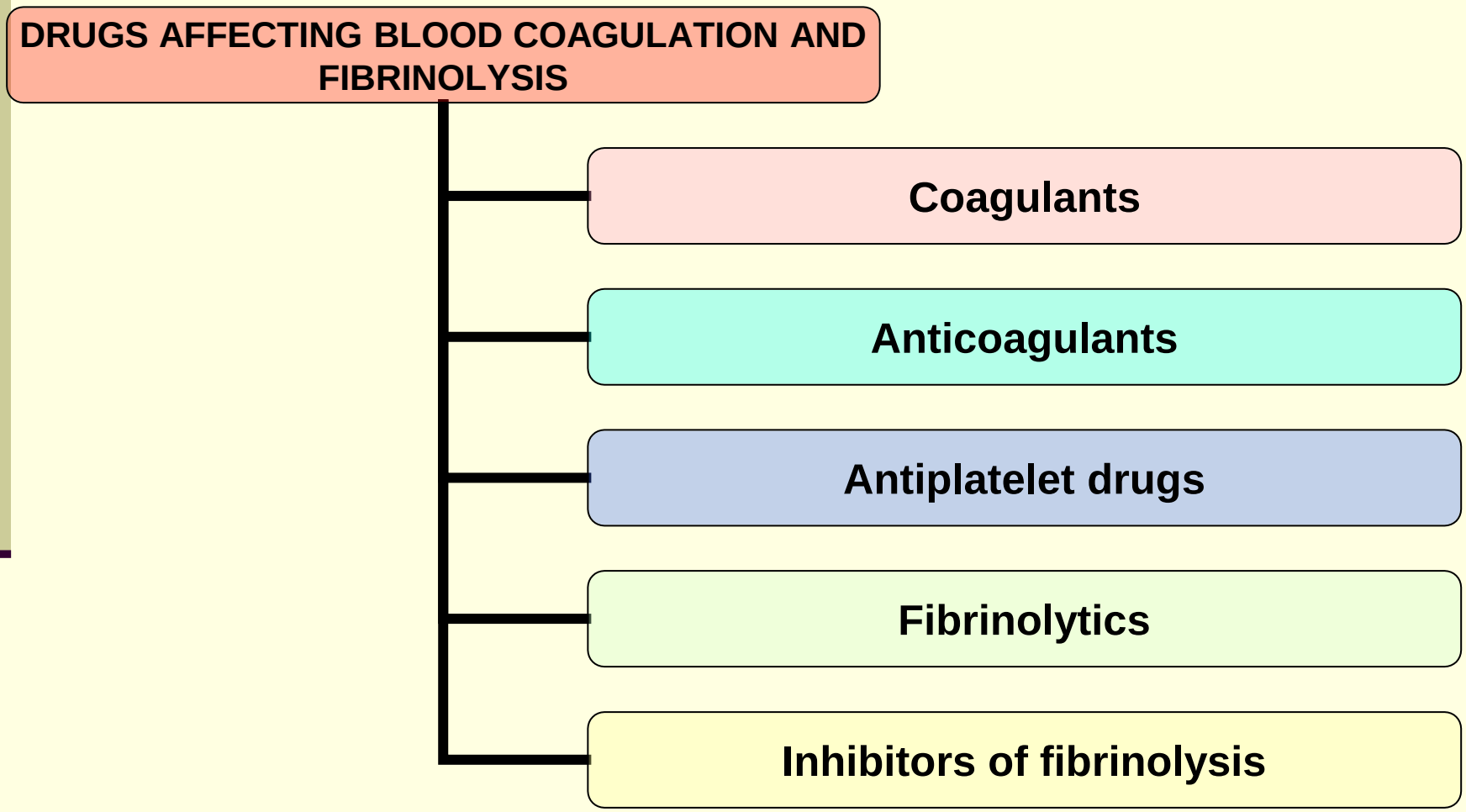
Fibrinolysis is a lysis of thrombus for restoration of blood flow: plasminogen (pro-fibrinolysin) converts into plasmin (fibrinolysin) and causes lysis of fibrin clot



PATHOLOGY OF HEMOSTASIS AND FIBRINOLYSIS

- A decrease in blood coagulation and (or) an increase in fibrinolysis result in ***bleeding***
- An increase in blood coagulation and (or) a decrease in fibrinolysis result in ***thrombosis, thromboembolism, syndrome of disseminated intravasal blood coagulation***

GROUPS OF DRUGS AFFECTING HEMOSTASIS AND FIBRINOLYSIS



COAGULANTS

CLASSIFICATION

1. ***Direct-acting (are active in vivo, as well as in vitro)***
   - – Thrombin
   - – Hemostatic sponge
   - – Fibrinogen
   - – Eptacog alfa
   - – Calcium chloride
   - – Calcium gluconate
2. ***Indirect-acting (are active only in vivo)***
   - – Vitamin K (Phytomenadione, Menadione)
   - – Vikasol

DIRECT-ACTING COAGULANTS

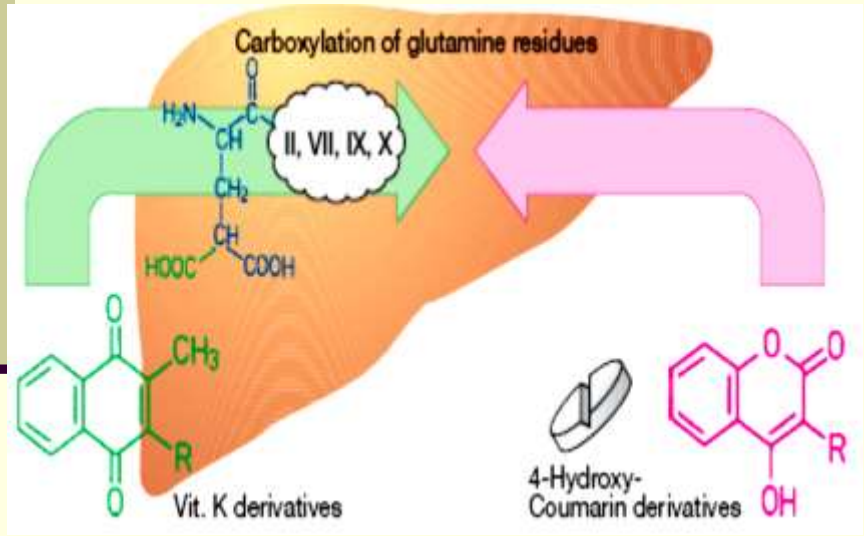
- ***Thrombin*** is an active compound of blood coagulation system, is used for bleeding from capillary vessels, is applied only topically (IV administration may cause disseminated thrombosis).
- ***Fibrinogen*** is a non-active compound of blood coagulation system, is used by IV infusion for bleeding 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 parenterally for bleeding, for prophylaxis of bleeding, or for a decrease of capillary permeability.

DIRECT-ACTING COAGULANTS. EPTACOG ALFA

- is a recombinant activated factor VII, 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, for acquired hemophilia, factor VII deficiency, and Glanzmann thrombasthenia
- is not immunogenic in patients with hemophilia and has very low thrombogenicity

INDIRECT-ACTING COAGULANTS. VIKASOL

Mechanism of action of Vitamin K, its derivatives (Vikasol) and their antagonists (coumarins)



- is an 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

INDIRECT-ACTING COAGULANTS. MENADIONE

- is an analogue of 1,4-naphthoquinone with a methyl group in the 2-position (vitamin K3)
- can serve as a precursor to various types of vitamin K
- for human use at pharmaceutical strength is available in some countries with lower income populations
- typical daily dose is 10 mg oral or 2 mg parenteral
- is used in the treatment of hypoprothrombinemia
- large doses can cause hemolytic anemia, neonatal brain or liver damage, neonatal death in some rare cases

ANTICOAGULANTS

CLASSIFICATION

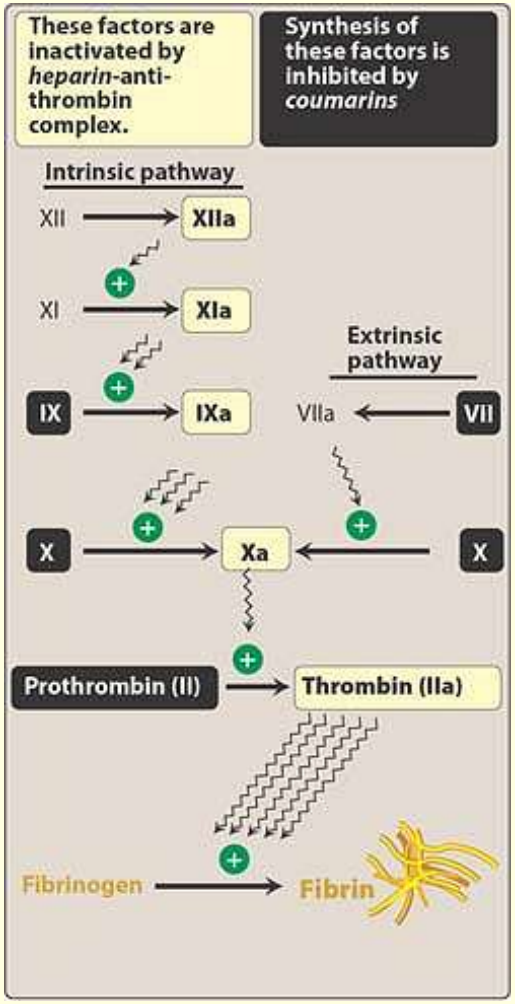
1. Direct-acting (are active in vivo, as well as in vitro)

- Heparin
- Fraxiparine
- Fondaparinux
- Rivaroxaban
- Dabigatran

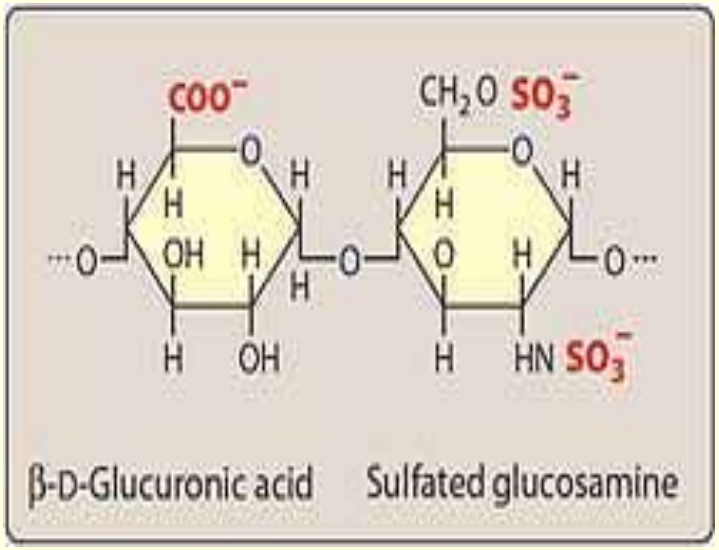
2. Indirect-acting (are active only in vivo)

- Warfarin

ANTICOAGULANTS: targets of action



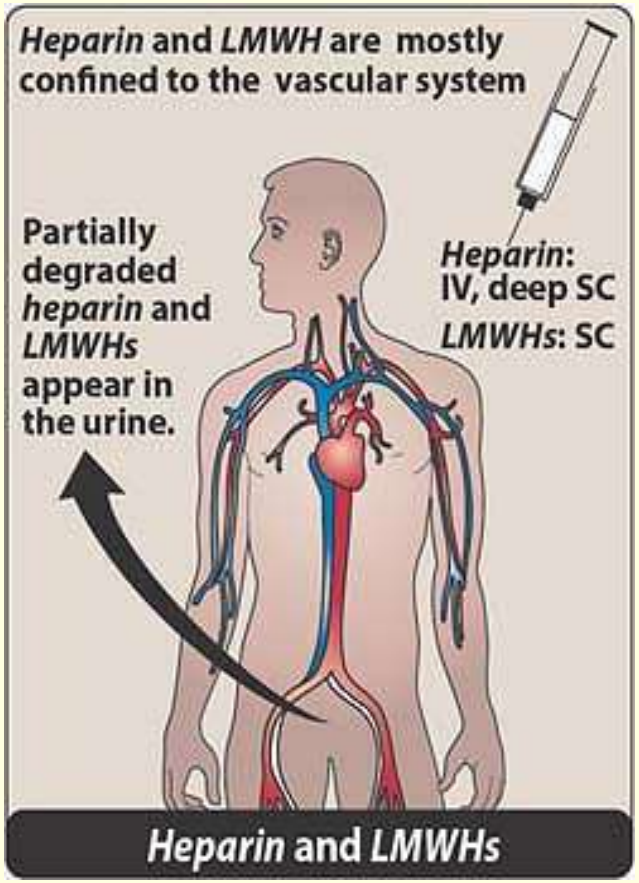
DIRECT-ACTING ANTICOAGULANTS. HEPARIN



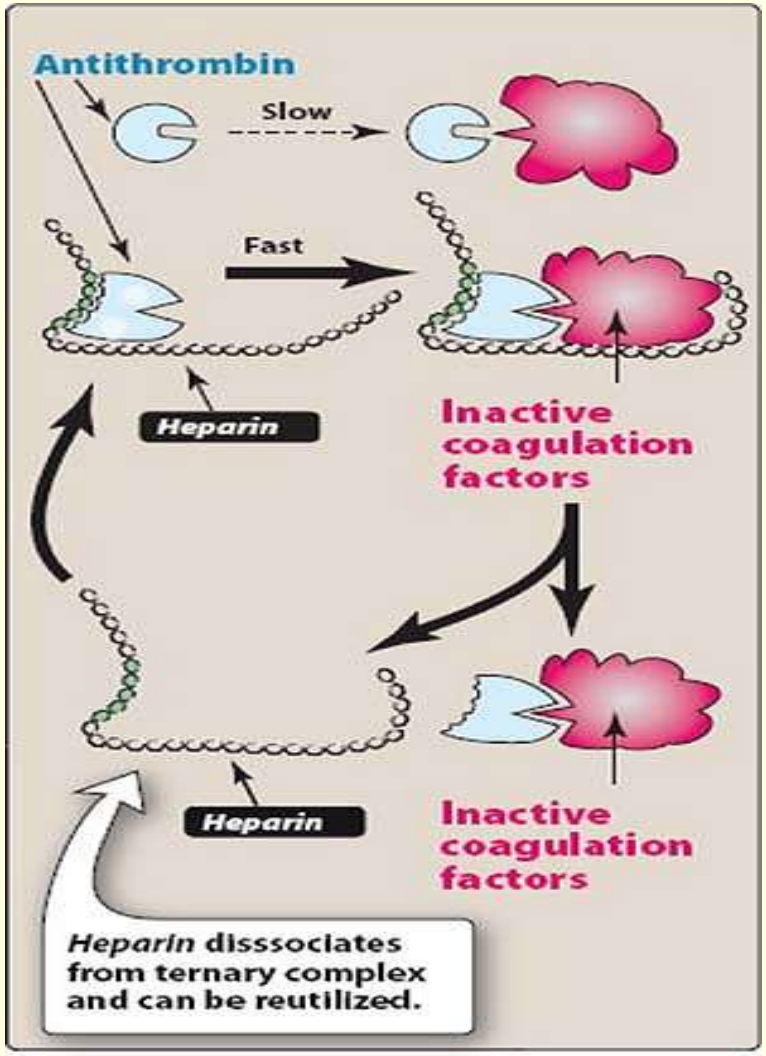
- ***Heparin*** is a natural substance produced by mast cells
- High concentration of heparin is observed in the lungs and wall of the intestine
- It belongs to acidic mucopolysaccharides
- Disaccharide component of heparin shows negative charges due to carboxyl and sulfate groups

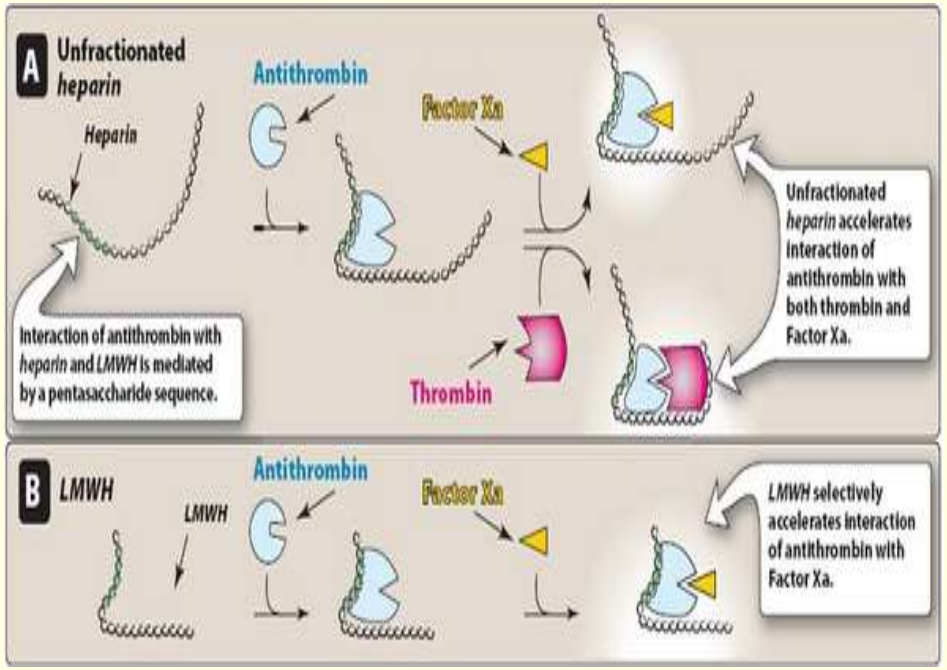
HEPARIN: pharmacokinetics

- 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

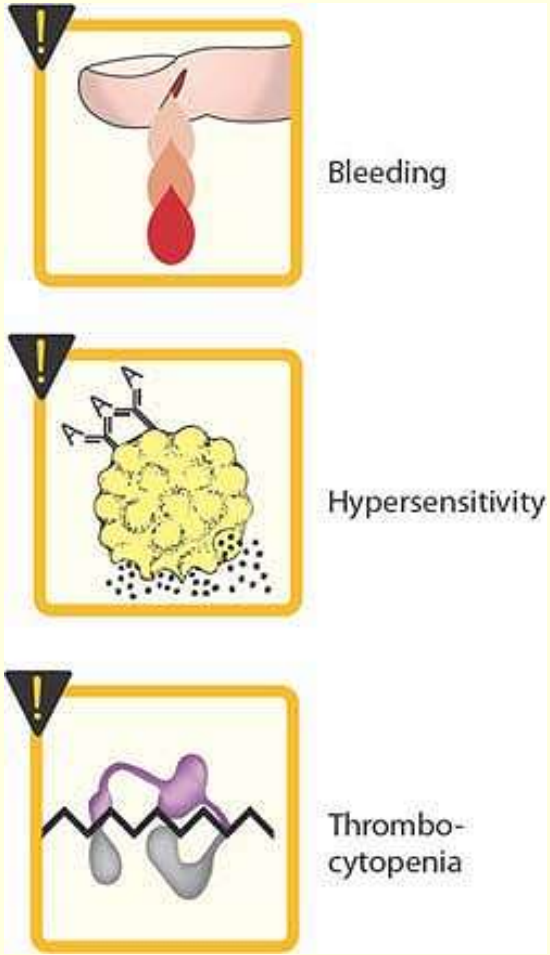
- a strong rapid decrease in all stages of blood coagulation
- a decrease in platelet aggregation
- improvement of microcirculation and coronary circulation
- a decrease in lipids concentration in blood serum
- a decrease in inflammation
- suppression of immunity
- an increase in synthesis of surfactant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

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

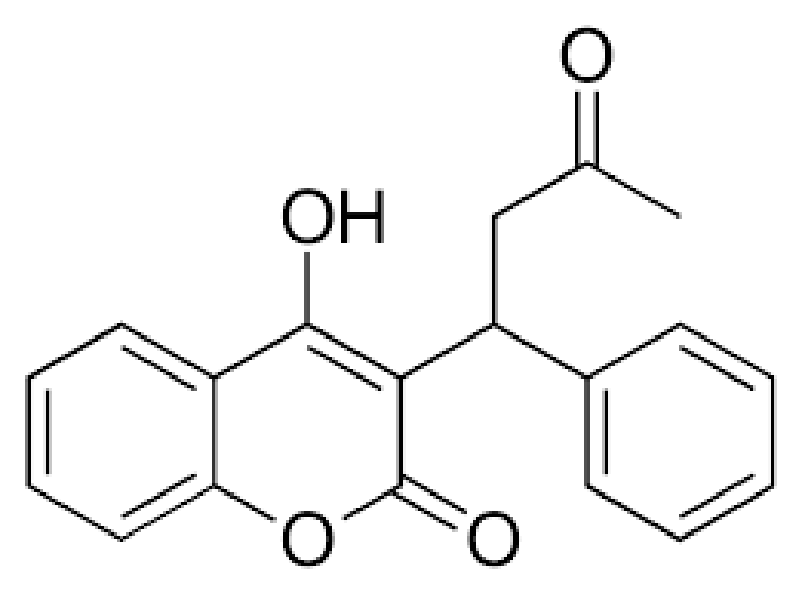
- is an oral anticoagulant
- is the first available orally active direct factor Xa inhibitor
- inhibits both free Factor Xa and Factor Xa bound in the prothrombinase complex
- is well absorbed from the gut and maximum inhibition of factor Xa occurs 4 h after a dose. The effects last 8–12 h, but factor 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*.

DABIGATRAN

- is a direct thrombin inhibitor.
- is taken by mouth
- reversibly binds to the active site on the thrombin molecule preventing thrombin-mediated activation of coagulation factors
- is an anticoagulant used to treat and prevent blood clots and to prevent stroke in people with atrial fibrillation
- is used as an alternative to warfarin and does not require monitoring by blood tests
- side effects include bleeding and gastritis, bleeding around the spine and allergic reactions such as anaphylaxis. In cases of severe bleeding, it can be reversed with the antidote idarucizumab
- is not recommended during pregnancy or breastfeeding.
- compared to warfarin it has fewer interactions with other medications

INDIRECT-ACTING ANTICOAGULANTS. WARFARIN

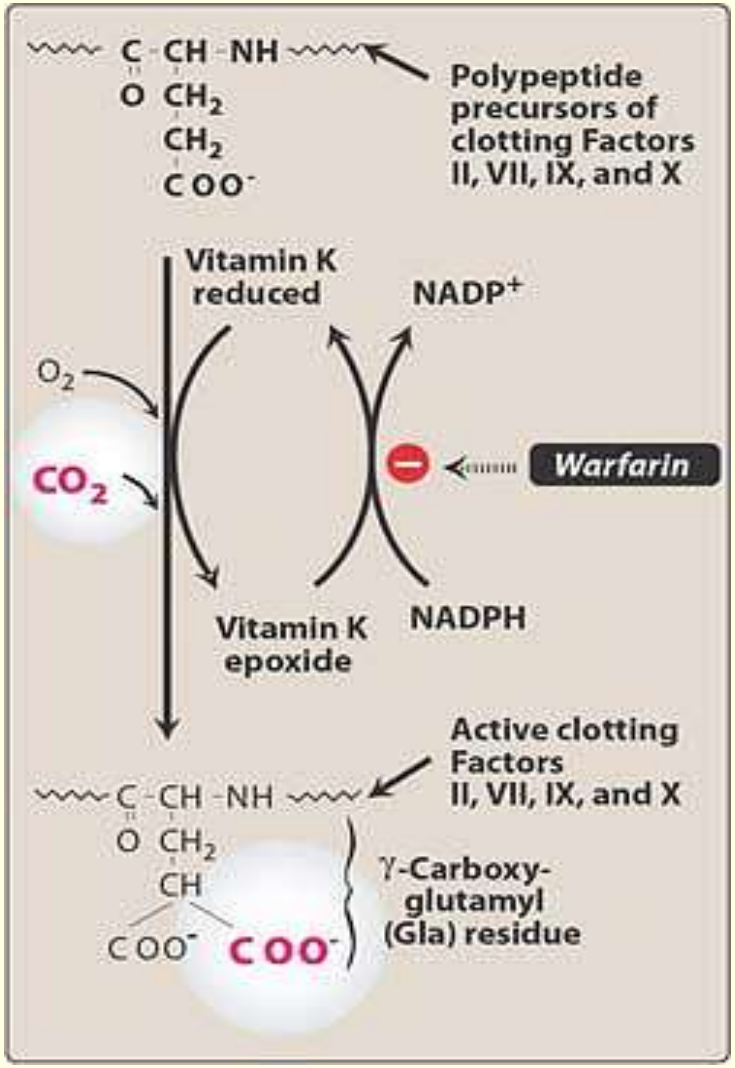
Warfarin is an indirect-acting anticoagulant, a coumarin derivative



WARFARIN: pharmacokinetics

- is administered orally (as a rule), may be injected IV
- is absorbed in the GI tract
- binds to proteins in blood plasma
- is metabolized in the liver
- does not anticoagulate blood immediately, onset of their effect requires about 2 to 3 days
- duration of action of a single dose of 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
- is excreted with urine
- many other medications and dietary factors can interact with warfarin, either increasing or decreasing its effectiveness due to hepatic metabolism

WARFARIN: mechanism of action



- 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 vitamin K1

WARFARIN: pharmacodynamics and indications

Pharmacodynamics

- Inhibition of the synthesis of clotting factors II, VII, IX, and X
- a decrease in blood coagulation

Indications

- Acute thrombosis (together or after of heparin's usage)
- Myocardial infarction, ischemic stroke
- Thromboembolism
- Thrombophlebitis
- Prevention of blood clots in people who have atrial fibrillation, valvular heart disease or artificial heart valves
- Prevention of thrombus formation after surgeries.

Index of prothrombin should be controlled!

WARFARIN: side effects and cotraindications

Side effects

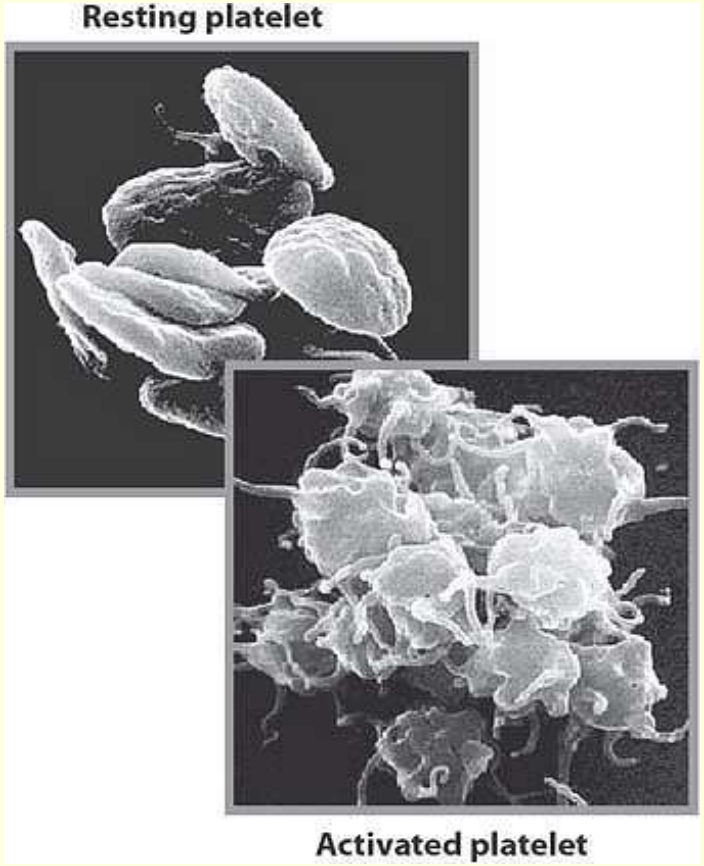
- Bleeding
- Forming of hematomes
- Hematuria
- Dyspepsia
- Areas of tissue damage
- Purple toes syndrome

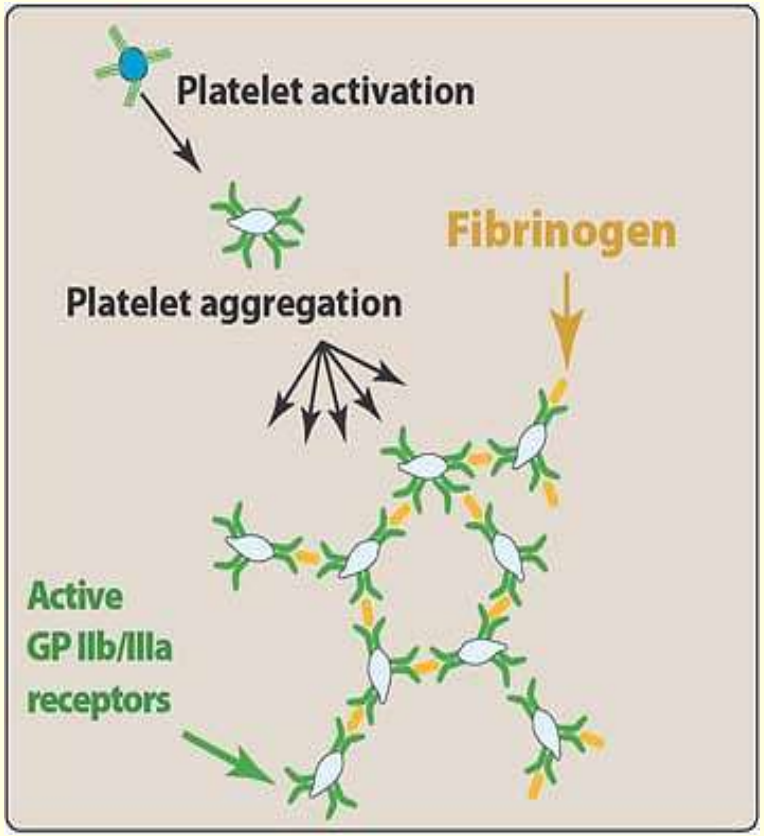
Contraindications

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

For treatment of overdose – vikasol or vitamin K1!

PLATELET AGGREGATION





ANTIPLATELET DRUGS

CLASSIFICATION

1. COX-inhibitors

– Acetylsalicylic acid (Aspirin)

2. Inhibitors of phosphodiesterase

– Dipyridamole

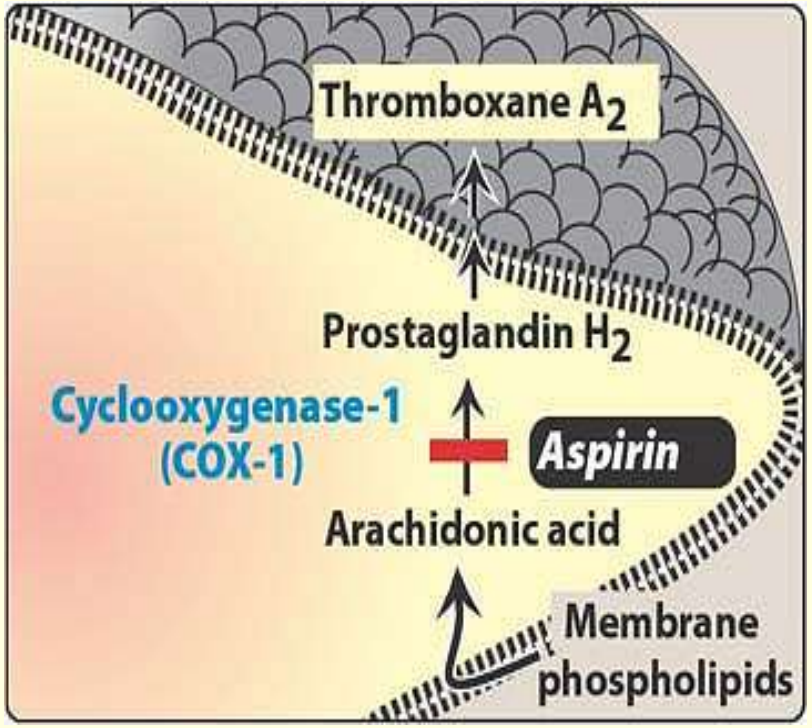
– Pentoxifylline

3. Inhibitors of ADP-mediated aggregation

– Clopidogrel

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



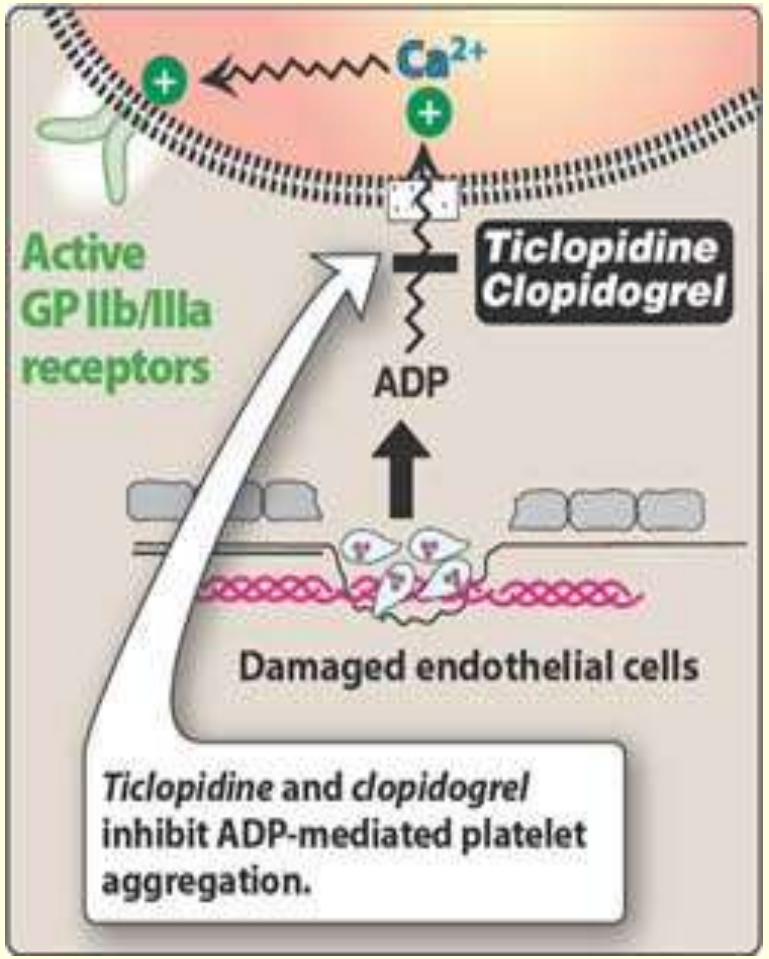
DIPYRIDAMOLE. PENTOXIFYLLINE

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.

Pentoxifylline is a competitive nonselective phosphodiesterase inhibitor which raises intracellular cAMP, improves red blood cell deformability (known as a haemorrheologic effect), reduces blood viscosity and decreases the potential for platelet aggregation and blood clot formation.

CLOPIDOGREL

- is a prodrug
- its active metabolite inhibits the P2Y12 subtype of ADP receptor, which is important in activation of platelets
- platelet inhibition is 2 h after a single dose of oral clopidogrel, but the onset of action is slow, so a loading dose is administered when a rapid effect is needed
- is used along with aspirin or as an alternative antiplatelet drug for people intolerant to aspirtin
- side effects include headache, nausea, easy bruising, itching, and heartburn, bleeding and thrombotic thrombocytopenic purpura



ANTIPLATLETS: 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
- Peripheral artery disease

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

B. Inhibitors of fibrinolysis

1. Direct-acting

– Contrykal

– Aprotinin

2. Indirect-acting

– Aminocaproic acid

– Tronexamic acid

FIBRINOLYTICS. FIBRINOLYSIN

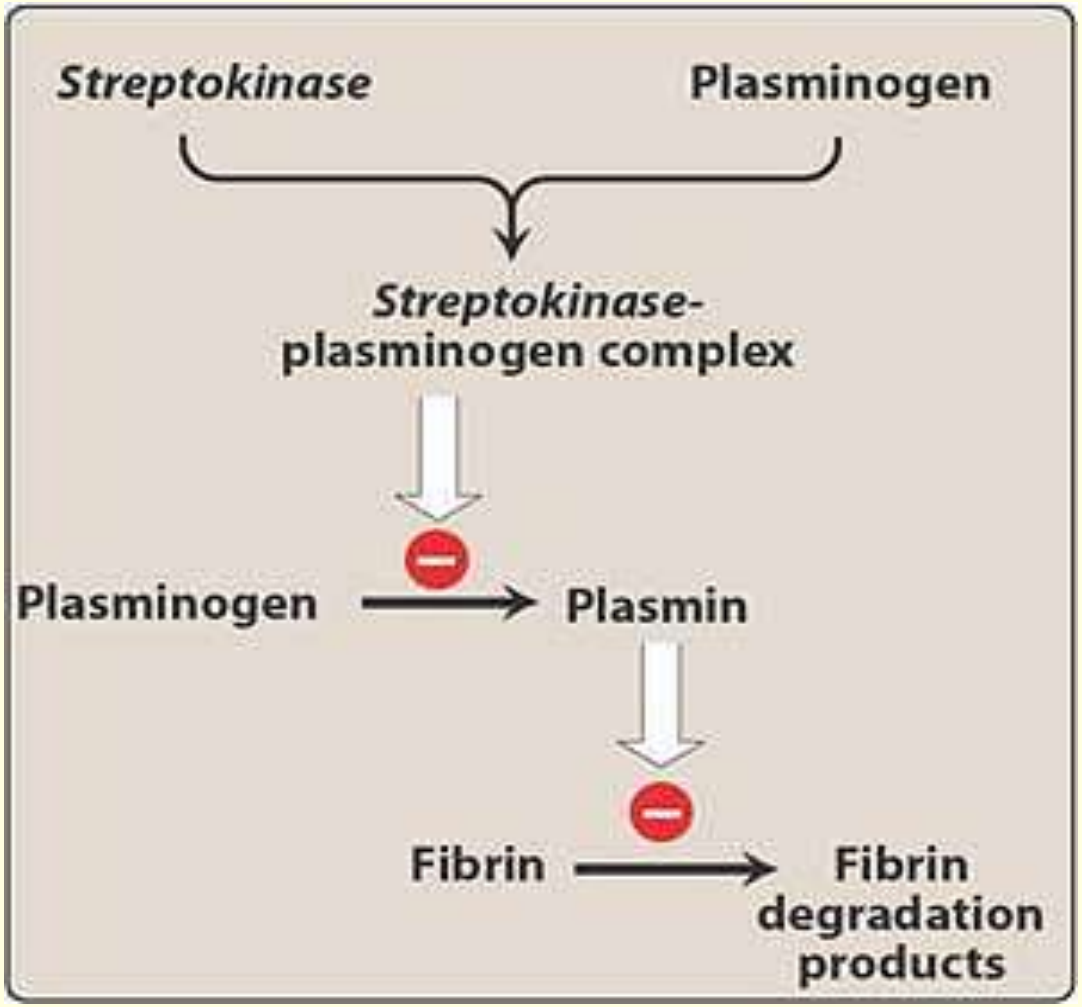
Fibrinolysin is a protein from donors' plasma, an active factor of fibrinolysis

- 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.

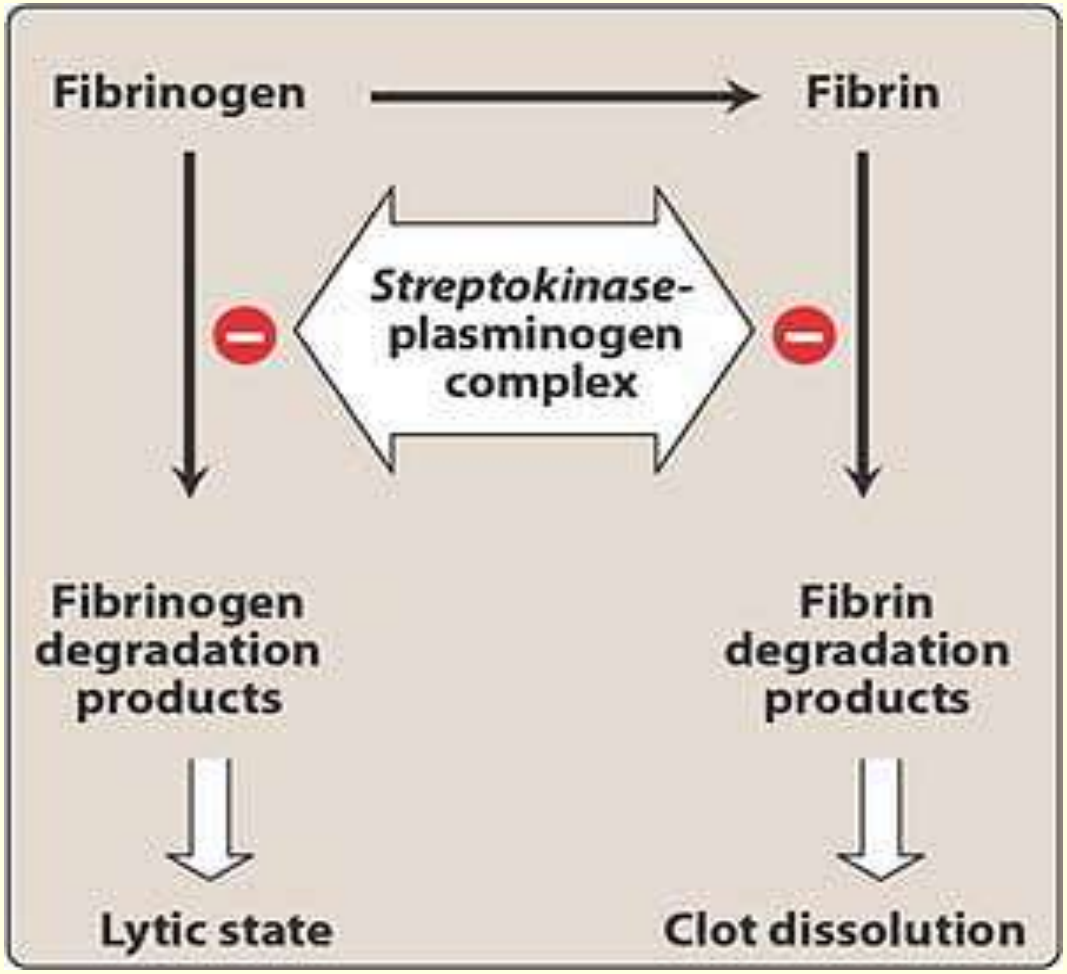
ACTIVATORS OF FIBRINOLYSIS. STREPTOKINASE

- is a 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 a 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



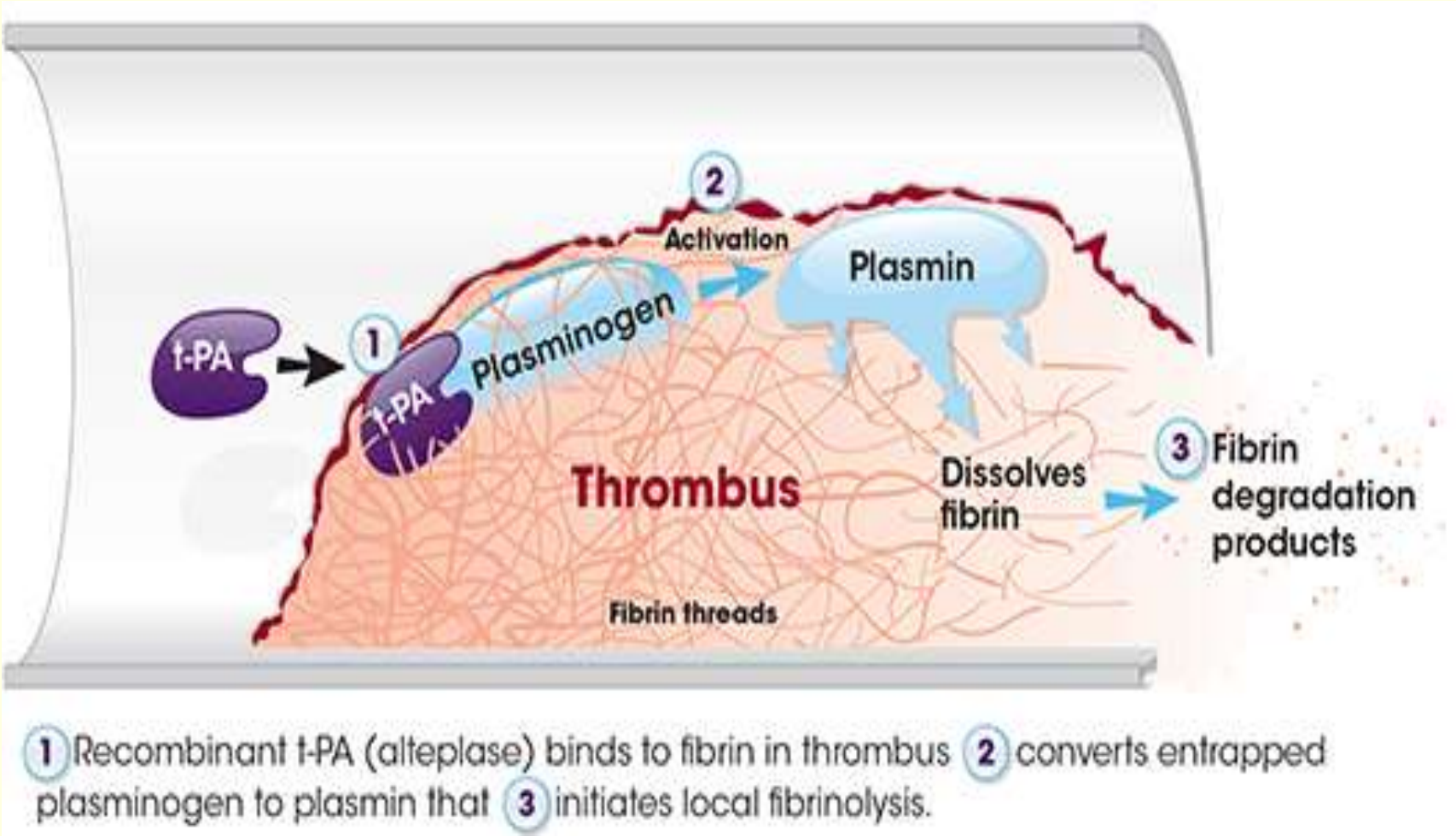
ACTIVATORS OF FIBRINOLYSIS: non-selective action of Streptokinase



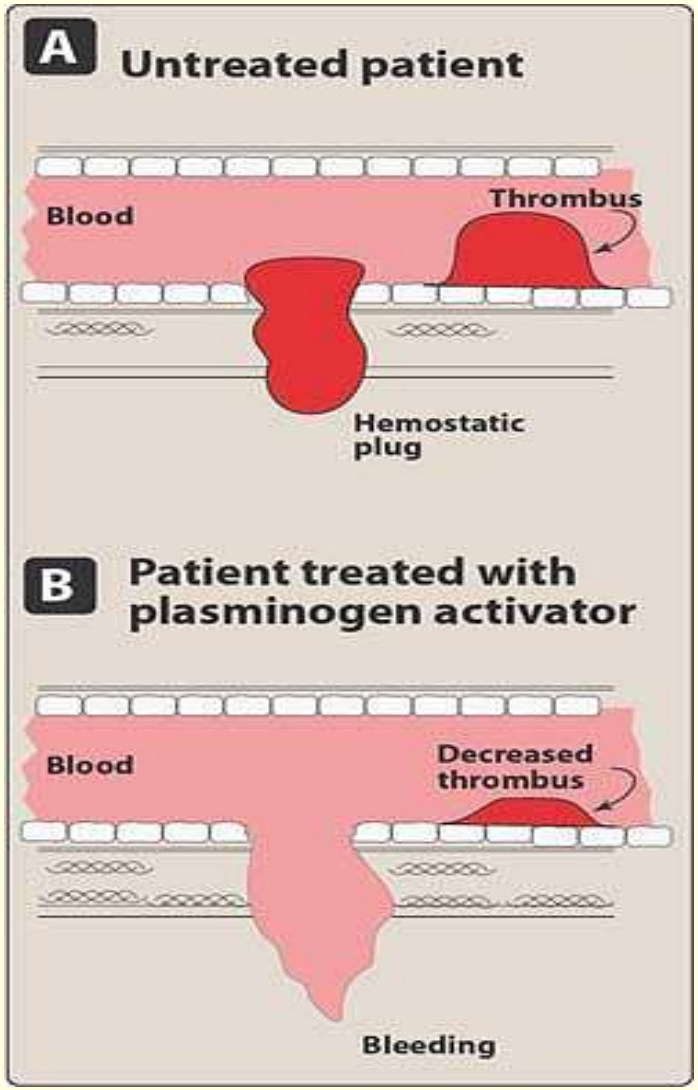
ACTIVATORS OF FIBRINOLYSIS. ALTEPLASE

- is a 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
- 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.

MECHANISM OF ACTION OF RECOMBINANT t-PA



ACTIVATORS OF FIBRINOLYSIS: side effects



INHIBITORS OF FIBRINOLYSIS. CONTRYKAL

- is a 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 the pancreas, thyroid glands, bigger salivary glands, and lungs
- may cause allergy, nausea, vomiting, hypotension, tachycardia.

INHIBITORS OF FIBRINOLYSIS. APROTININ

- is a small protein bovine pancreatic trypsin inhibitor, an antifibrinolytic molecule
- is used by injection to reduce bleeding during complex surgery
- its main effect is the slowing down of fibrinolysis
- is a competitive inhibitor of several serine proteases, specifically trypsin, chymotrypsin and plasmin, and kallikrein Its action on kallikrein leads to the inhibition of the formation of factor XIIa. As a result, both the intrinsic pathway of coagulation and fibrinolysis are inhibited. Its action on plasmin independently slows fibrinolysis
- the aim in its use is to decrease the need for blood transfusions during surgery, as well as end-organ damage due to hypotension as a result of marked blood loss
- is used in cardiac surgery with a high risk of significant blood loss, in high-risk orthopedic surgery, liver transplantation
- can cause anaphylaxis, thrombosis, presumably from overactive inhibition of the fibrinolytic system, a risk of acute renal failure, myocardial infarction and heart failure, as well as stroke and encephalopathy

INHIBITORS OF FIBRINOLYSIS. AMINOCAPROIC ACID

- is an 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.

INHIBITORS OF FIBRINOLYSIS. TRONEXAMIC ACID

- is a synthetic analog of the amino acid lysine
- is taken either orally or by injection into a vein
- serves as an antifibrinolytic by reversibly binding four to five lysin receptor sites on plasminogen. This decreases the conversion of plasminogen to plasmin, preventing fibrin degradation and preserving the framework of fibrin's matrix structure
- has roughly eight times the antifibrinolytic activity of the aminocaproic acid.
- is used to treat or prevent excessive blood loss from major trauma, postpartum bleeding, surgery, tooth removal, nosebleeds, and heavy menstruation, hereditary angioedema
- side effects are rare and include changes in color vision, blood clots, and allergic reactions. Greater caution is recommended in people with kidney disease
- appears to be safe for use during pregnancy and breastfeeding
- is approved for short-term use in people with severe bleeding disorders who are about to have dental surgery. Tranexamic acid is used in dentistry in the form of a 5% mouth rinse after extractions or surgery in patients with prolonged bleeding time

DRUGS FOR TERMINATION OF BLEEDING AFTER TOOTH EXTRACTION

- Thrombin (a coagulant)
- Hemostatic sponge (a coagulant)
- Aminocaproic acid (an antifibriolytic)
- Tronexamic acid (an antifibriolytic)
- Epinephrine (an adrenomimetic, acts due to vasoconstriction)
- Phenylephrine (an adrenomimetic, acts due to vasoconstriction)
- Hydrogen peroxide (an antiseptic, acts due to film of proteins)

All these agents are used topically!

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. Antiplatelets

D. Activators of fibrinolysis

E. Inhibitors of fibrinolysis.

(D)

CONTROL TASKS

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(D)

CONTROL TASKS

- A man with a liver disease has hypoprothrombinemia and is prone to bleedings. At the same time, he needs tooth extraction. Which indirect-acting coagulant should be prescribed for prevention of post-extracting bleeding?

A. Aminocaproic acid

B. Thrombin

C. Phytomenadione

D. Aspirin

E. Alteplase.

(D)

CONTROL TASKS

- A young woman has prolonged bleeding after the removal of the wisdom tooth. Which inhibitor of fibrinolysis useid as a rinse will be effective in the termination of this post-extracting bleeding?

A. Tronexamic acid

B. Aprotinin

C. Heparin

D. Aspirin

E. Clopidogrel.

(A)

THE END

Thank you for attention!