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PHARMACOLOGY OF CARDIOVASCULAR SYSTEM
Part II

DRUGS ACTING ON HEMOSTASIS & FIBRINOLYSIS, ANEMIA

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ANEMIA

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Introduction

- Anemia = lower than normal quantity of hemoglobin (Hb) in the blood
- Low limit values:
  - Children up to 6 years: 110 g Hb/L
  - Children up to 14 years: 120 g Hb/L
  - Women: 120-165 g Hb/L
  - Men: 130-175 g Hb/L
- Also shape and size is mesured (MCV)

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Clinically important parameters

- **RBC:** Men 4,0-5,3 $\times 10^{12}$/L
  Women 3,8-4,8 $\times 10^{12}$/L
- **WBC:** 4,0-10 $\times 10^{9}$/L
- **Trombocytes:** 150-350 $\times 10^{9}$/L
- **aPTT** (reference range): 30-40 sec – intrinsic pathway
- **Prothrombin time** (Quick): 12-15 sec – extrinsic pathway
- **INR** (reference range): 0,8 – 1,2

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Types of anemia

Anemia due to loss of erythrocytes	- bleeding - hemolysis (ERY destruction)
Anemia due to decreased production of erythrocytes	- disorder of stem hematopoietic cells - deficient ERY production

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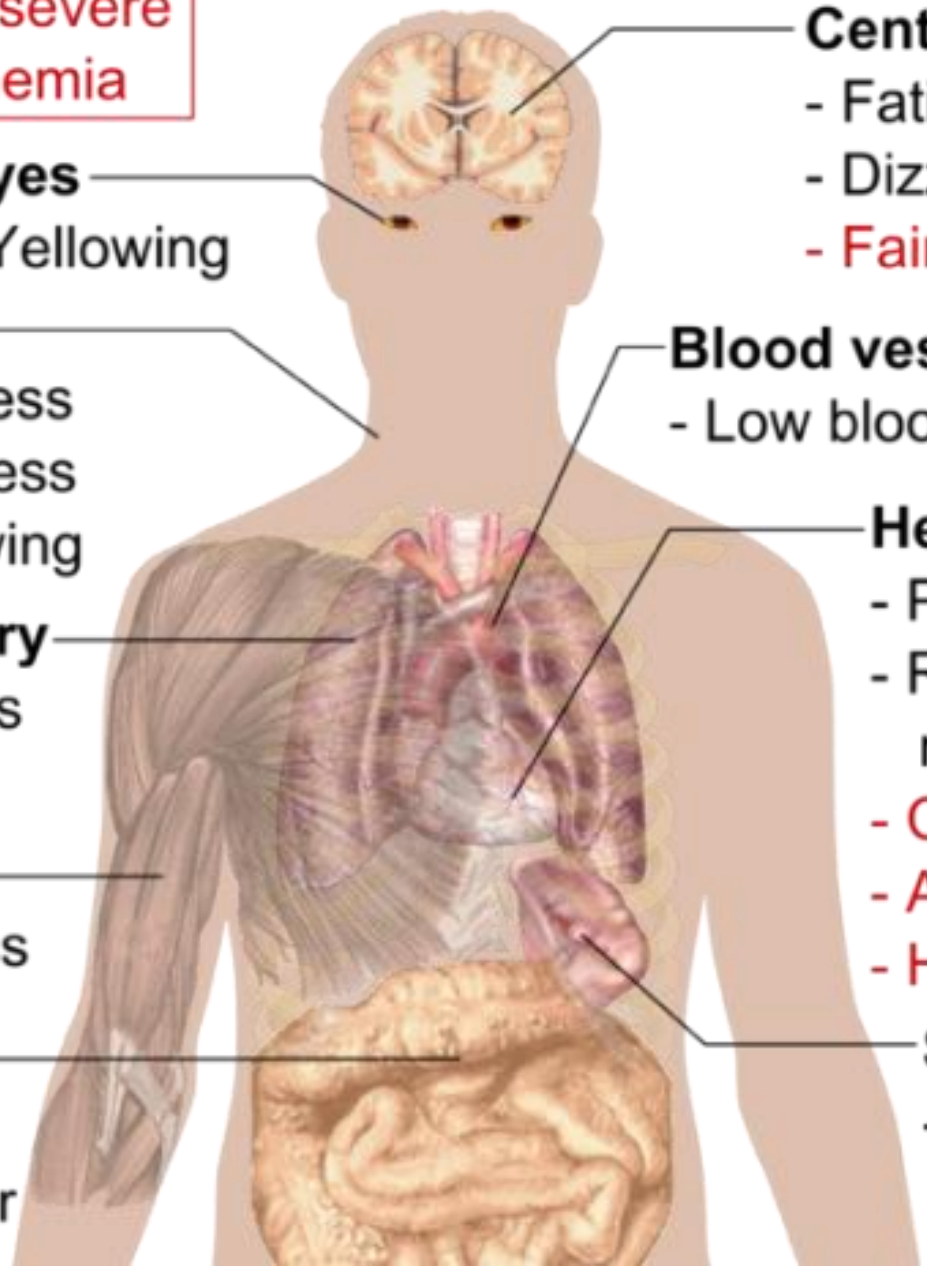
Symptoms of

Anemia

Red = In severe anemia



Central
- Fatigue
- Dizziness
- Fainting

Eyes
- Yellowing

Skin
- Paleness
- Coldness
- Yellowing

Blood vessels
- Low blood pressure

Heart
- Palpitations
- Rapid heart rate
- Chest pain
- Angina
- Heart attack

Respiratory
- Shortness of breath

Muscular
- Weakness

Intestinal
- Changed stool color

Spleen
- Enlarge-ment

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Anemia due to Iron (Fe) deficiency

- Supplementation with Fe
  - divalent ion (Fe2+)
  - trivalent ion (Fe3+)
- Intolerance of p.o. preparations
- Indications for parenteral drugs
  - malabsorption of Fe
  - GIT disorders

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Pharmacotherapy

– Fe preparations in CZ

Ferronat Retard tbl	**ferrous sulphate**	**105 mg/tbl**
Sorbifer Durules tbl	**ferrous sulphate**	**100 mg/tbl + 60 mg acidum ascorbicum**
Tardyferon tbl	**ferrous sulphate**	**80 mg/tbl + 30 mg acidum ascorbicum**
Aktiferrin cps	**ferrous sulphate**	**34,5 mg /tbl**
Ferrum Lek i.m.inj.	**ferric hydroxide**	**50 mg / ml**
Ferrlecit i.v.inj.	**ferric salt**	**12,5 mg /ml**

Anemia due to vitamin B_{12} deficiency

- Pernicious anemia = lack of „intrinsic factor“
- Deficiency of B_{12} (cyanocobalamin)

- Decrease in DNA synthesis ⟹ disruption of red blood cells development
- Epithelial disorders of the gastrointestinal tract (e.g. glossitis)
- Neurological disorders

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Pharmacotherapy

- Parenteral medication of B_{12}:
  - 300 – 1000 µg i.m. per day for 1 week
  - maintenance dose: 300 µg 1x /14 days or 1x /month

- Vitamin B_{12} 300 µg i.m. inj.
- Vitamin B_{12} 1000 µg i.m. inj.

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Anemia due to folic acid deficiency

- In malnutrition, malabsorption, premature babies, teens, pregnancy, folic ac. MTBsm disorder OR
- **SE** of drugs:
  - barbiturates, methotrexate, trimethoprim, sulfasalazine, some ATB, contraceptives
- Etiopathogenesis !!

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Pharmacotherapy

- Folic acid (tetrahydrofolate) DDD 10-20 mg p.o. (weeks),

  long-term therapy 10 mg every other day

- Special indications:
  - parenteral = Leucovorin (calcium salt of folinic acid)

    „*rescue therapy*“ = high-dose methotrexate

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Hemolytic anemia

– Classification of hemolytic anemia (HA):

- Hereditary (inherited) HA (spherocytosis, sickle-cell anemia and other hemoglobin defects)

- Acquired immune-mediated HA

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Pharmacotherapy

- Standard approach: corticosteroids, immunosuppressants, splenectomy
- Symptomatic therapy: blood transfusion
- Resistance to treatment: combination of corticosteroids and cytotoxic agents (azathioprine, 6-mercaptopurine, cyclophosphamide)
- Immunosuppressive therapy: cyclosporin A, mycophenolate mofetil

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Sickle cell anemia

- Pain in bones, joints and muscles, caused by sickle cells and thrombosis: therapy with an analgesics

- Hemoglobin (Hb) in oxidized form = less tendency to form sickle cells: therapy by increasing affinity of Hb to O_2 through the alkalization with Mg^{2+} glutamate or acetazolamide

Aplastic anemia

- Bone marrow doesn´t produce sufficient number of new blood cells
- Disorder of pluripotent stem cell proliferation; together with leucopenia and thrombocytopenia
- Known causes:
  - toxic effects (insecticides, viruses, …)
  - drugs: chloramphenicol, sulfonamides, aminosalicylates, and others

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Pharmacotherapy

- Transfusion
- Suppression of the immune system
- Androgens and anabolic steroids stimulate pluripotent stem cell (oxymetholon)
- In more severe cases: growth factors (filgrastim, EPO) or bone marrow transplant

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COAGULATION DISORDERS

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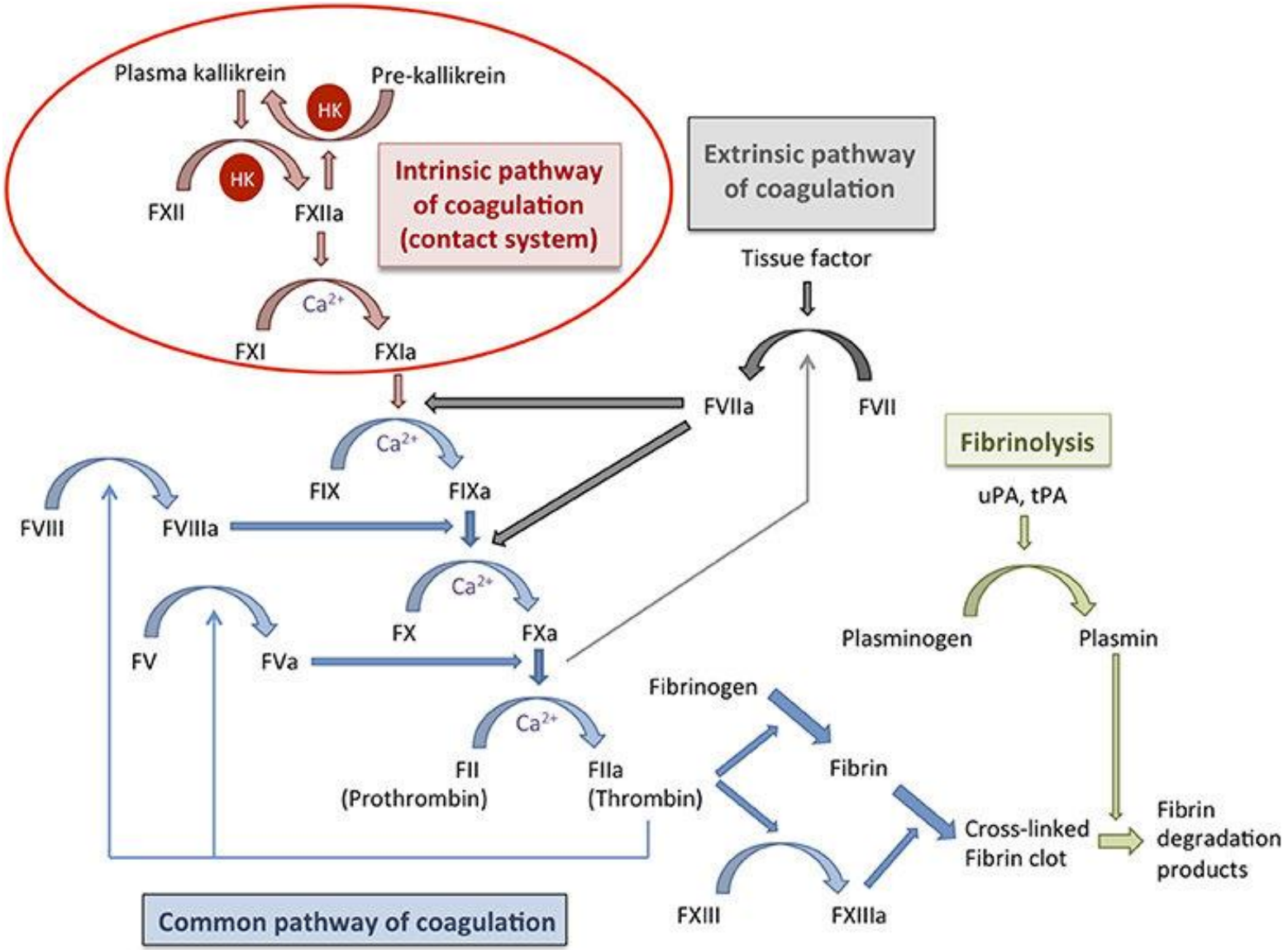
Coagulation cascade



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Coagulation tests

In vitro tests:

- Contact activation (intrinsic) pathway - activation of plasma contact factors:
  - evaluated by activated partial thromboplastin time (**aPTT**)
- Tissue factor (extrinsic) pathway - release of tissue factor:
  - evaluated by prothrombin time (**PT**) test (often reported as ratio **INR**)

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Pharmacotherapy

1. Anticoagulants
2. Fibrinolytics
3. Antiplatelet drugs (antiaggregants)
4. Hemostatic drugs
5. Antifibrinolytic drugs

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1. ANTICOAGULANTS

- **Direct:**
  - heparin
  - low molecular weight heparin (LMWH)
  - heparinoids - local application
- **Indirect:**
  - warfarin
- **New: Directly acting oral anticoagulants (DOACs):**
  - direct inhibitor of thrombin (dabigatran)
  - inhibitors of factor Xa (rivaroxaban, apixaban, edoxaban)

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Effect on coagulation

- heparin: activates antithrombin III, which blocks thrombin from clotting blood
- warfarin: inhibits vitamin K-dependent synthesis of active forms of the Ca-dependent clotting factors II, VII, IX and X

- **I:** atrial fibrillation, pulmonary embolism, deep vein thrombosis, or venous thromboembolism, congestive heart failure, stroke, MI

Heparin

- Not absorbed from GIT
- *i.v.* (immediate effect) or *s.c.* (effect after 1-2 h), effect lasts for 12-18 h; $t_{1/2}$ = 40-90 min
- After *i.v.* application neither leaves blood vessels nor passes the membranes
- Never *i.m.* - extensive hematoma at administration site!!
- **SE:** bleeding - requires protamine sulfate *i.v.;* osteoporosis (therapy > 6 months); thrombocytopenia

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LMWH (3.5 - 5 kDa)

- dalteparin; parnaparin; reviparin; tinzaparin
- nadroparin (FRAXIPARINE)
- enoxaparin (CLEXANE)
- bemiparin (ZIBOR)

- Characteristics:
  - effect is significant and prolonged
  - aPTT monitoring is not required (more predictable plasma levels) and have fewer SE
  - longer $t_{1/2}$ (3-6 h) – administration 1-2x /day

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Indications for LMWH

1. Early treatment of unstable angina
2. Prophylaxis of thromboembolic complications
3. Replace heparin in prophylaxis and treatment of venous thrombosis
4. Hemodialysis
5. Extracorporeal circulation

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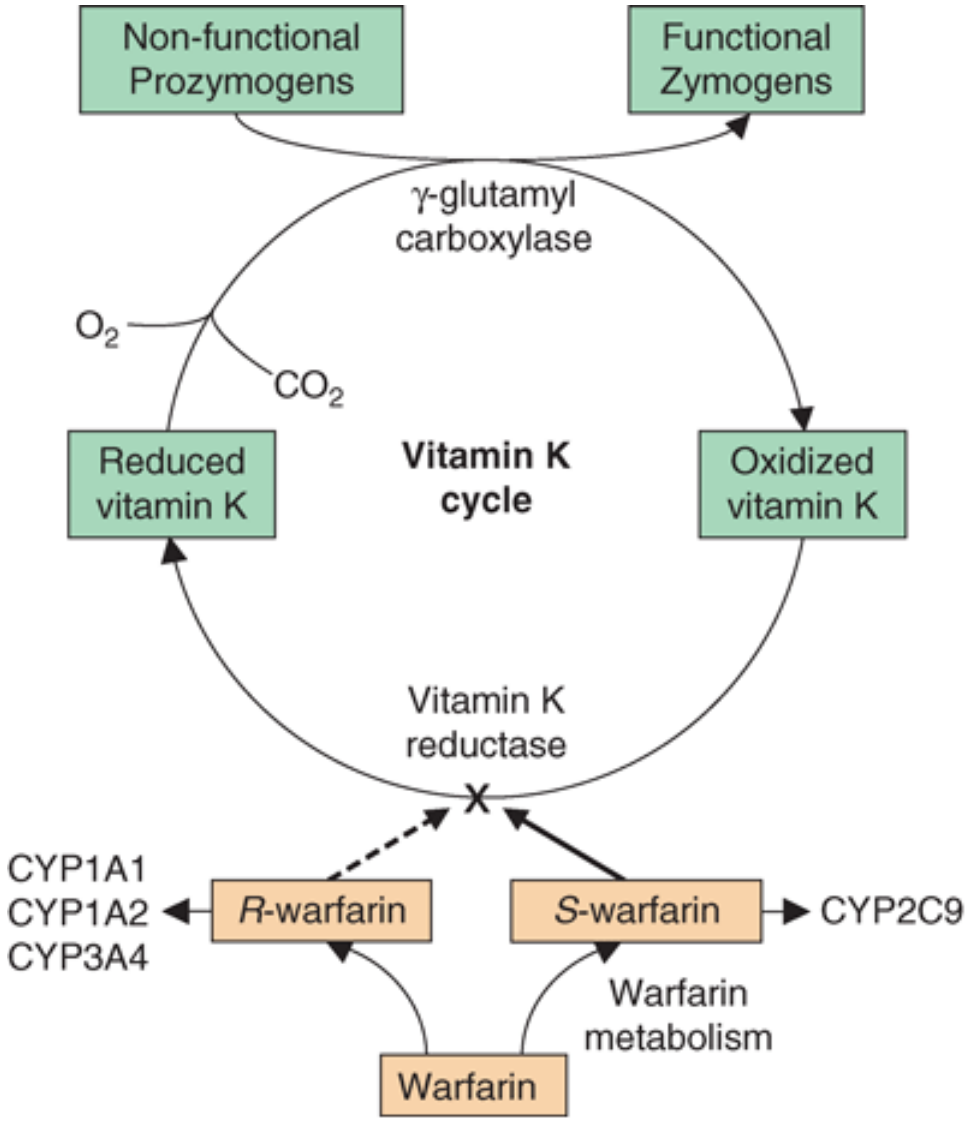
Warfarin

- Onset is slow; peak effect in about 3 days after administration, effect persists 5-7 days
- Passes through placental barrier and may cause bleeding in fetus (CI in pregnancy!)
- Does not pass into milk
- Biodegradation: CYP 450

Mechanism of action of warfarin



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

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Use of warfarin in practice

- Prophylaxis of thrombosis and embolism after surgery; therapy of thrombosis and thrombophlebitis
- Dosage under individual control of coagulation factors values (INR)
- Rapid withdrawal increases risk of excessive blood clotting -- Therapy should terminate gradually !!

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Interactions of warfarin

- eff. extended by: allopurinol, co-trimoxazole, SA, metronidazole
- eff. enhanced by: anabolics, fenothiazines, NSAIDs
- Factors influencing the effect of warfarin:
  - ↓ coagulation factors production – eg. in liver diseases
  - CYP450 inducers (AE) & inhibitors (amiodarone,co-trimoxazole)
  - competition for binding to plasma proteins: NSAID
  - ↓ vit K production: broad-spectrum ATB

Directly acting oral anticoagulants (DOACs)

- Recently, they have been gradually replacing warfarin
- Regular routine monitoring of the anticoagulant effect is not required
- Two main mechanisms of action:

I. direct inhibition of thrombin

II. inhibition of factor Xa

I. Direct inhibitor of thrombin – dabigatran

- Selective, reversible
- Inhibits both free and fibrin-bound thrombin → acts inside of the thrombus
- Inhibits thrombin-induced platelet aggregation
- Antidote (reversal agent): idarucizumab

II. Inhibitors of Factor Xa – rivaroxaban, apixaban, edoxaban, betrixaban

- Highly selective direct inhibition of Factor Xa by the intrinsic and extrinsic pathways of the coagulation cascade
- Good bioavailability after p.o. administration
- They inhibit both thrombin production and thrombus formation; do not inhibit thrombin (activated Factor IIa) or platelets
- They cross the placenta: CI in pregnancy

2. FIBRINOLYTICS (THROMBOLYTICS)

- Indications:
  - heart attack, massive pulmonary embolism, deep vein thrombosis

- After their use, anticoagulant treatment always follows: heparin

- Side effects:
  - bleeding, allergy, anaphylaxis

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I. generation thrombolytics (non-selective)

- Streptokinase
  - *indirectly* acting plasminogen activator
- Urokinase
  - polypeptide protease enzyme, converts plasminogen to the active plasmin *directly*
- Today, a whole generation is obsolete

II. generation thrombolytics (selective)

- Plasminogen activators; bind to fibrin clots on the surface - activity is limited to thrombus
- **t-PA** (recombinant tissue plasminogen activator)
- alteplase, reteplase, tenekteplase, brinase, saruplase, …

- **I:** acute MI, pulmonary embolism, stroke
- **SE:** bleeding, hypersensitivity

3. ANTIPLATELET DRUGS (ANTIAGGREGANTS)

– Indications:

- specific prophylaxis of arterial thrombosis

– Class include:

- ASA (Aspirin)
- ticlopidine, clopidogrel, prasugrel, tikagrelor, kangrelor
- cilostazol
- epoprostenol
- indobufen
- abciximab, eptifibatid – parenteral
- fibans – oral

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Mechanisms of action

Blockade of the thromboxane system
- irreversible: acetylsalicylic acid (ASA)
- reversible: indobufen

Inhibition of PDE-3A phosphodiesterase in platelets
- cilostazol increases cAMP and stabilizes the platelet

Inhibition of platelet aggregation by decreasing cytoplasmic Ca^{2+} conc.
- epoprostenol

Inhibition of the P2Y12 receptor – blockade of the ADP system
- thienopyridines (prodrug – activ. by CYP450): clopidogrel, prasugrel, ticlopidine
- non- thienopyridines (activ. by CYP450 not needed): ticagrelor, cangrelor

Antagonists of IIb/IIIa receptors
- monoclonal Ab – abciximab
- synthetic peptide inhibitors – eptifibatid
- non-peptide inhibitors (fibans) – tirofiban, roxifiban

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4. HEMOSTATIC DRUGS

1. Vascular vasoconstrictors: vasopressin, α-SM (A, NA)
2. Facilitation of platelet aggregation and platelet thrombus formation: ethamsylate
3. Induction of coagulation:

- locally: gelatin, collagen
- systemic eff.: plasma, coagulation factors, vit K and protamine sulfate (antidotes), desmopressin

4. During fibrinolysis - see Antifibrinolytics

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5. ANTIFIBRINOLYTIC DRUGS

- **Decrease plasminogen activation**
  - epsilon-aminocaproic acid (EACA)
  - para-aminomethylbenzooic acid (PAMBA)
- **Inhibit activated plasmin (protease inhibitors)**
  - aprotinin
- **I:** fibrinolytics (thrombolytics) overdose; surgery with a risk of activation of endogenous fibrinolysis activators

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Thank you
for your attention

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