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Antiplatelet drugs

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Antiplatelet drugs

= Antiaggregants

- The goal of antiplatelet therapy is primary or secondary prevention of atherothrombosis (that could lead to acute coronary syndrome, ischemic stroke, peripheral artery disease – critical limb ischemia etc.)
  = the most common causes of mortality in developed countries

Primary hemostasis

= Vasoconstriction, platelet adhesion, aggregation and platelet shape changes → formation of the primary platelet plug

- Platelets are involved
  - in platelet plug formation
  - formation of fibrin (secondary hemostasis)

I. Platelet adhesion

- endothelial injury – contact of platelets with exposed collagen in the subendothelial matrix → **platelet adhesion** to vessel wall (aid of adhesion molecules or surface receptors – direct binding or indirect via their ligand von Willebrand factor)

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Primary hemostasis

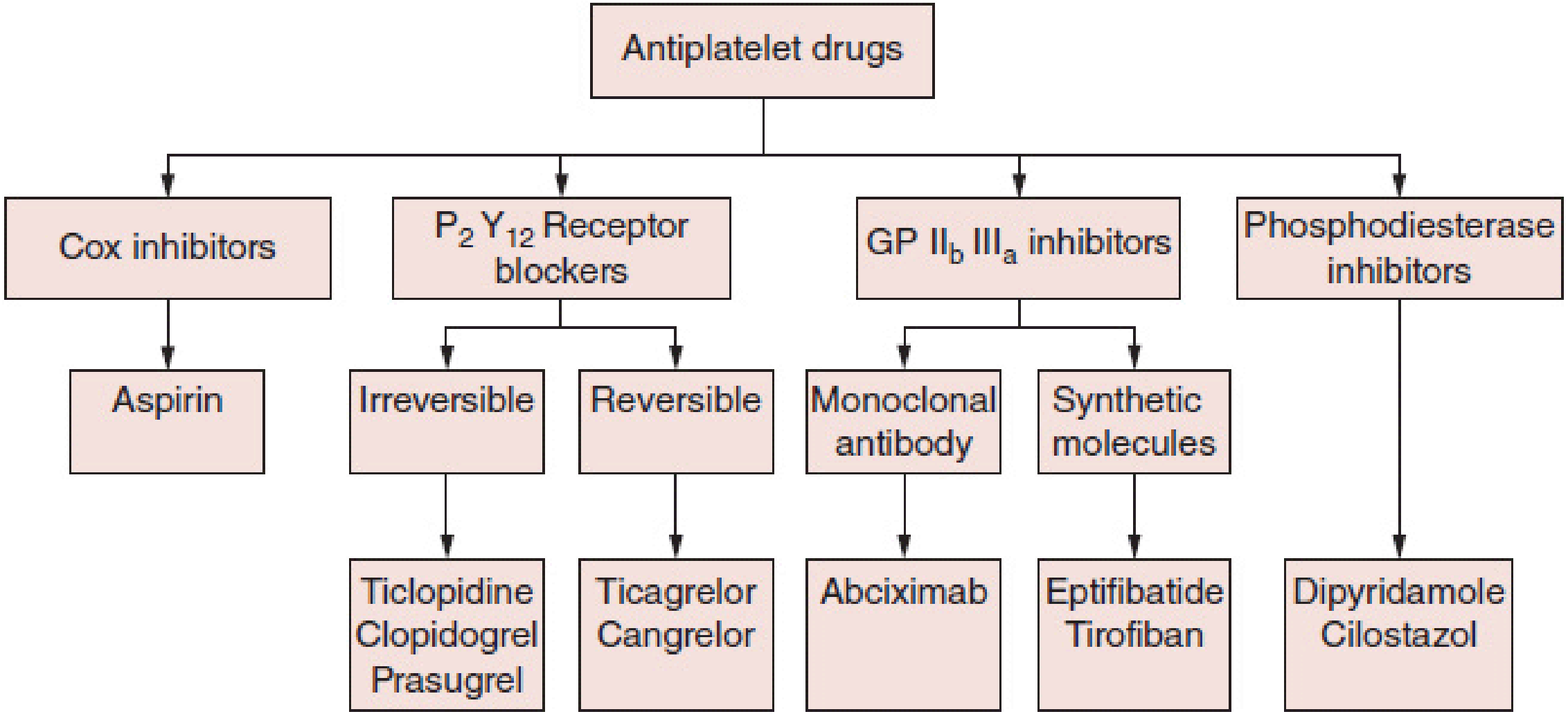
II. **Platelet activation** – the adhesion activates the platelets
- Shape change
- Degranulation – release of prothrombotic and vasoconstrictive substances
- Membrane metabolism – activation of phospholipase A2 → production of thromboxane A_2 by COX-1
- Activation of the fibrinogen receptor GP IIb/IIIa (allows fibrinogen to bind adjacent platelets → the process continues with aggregation)

III. **Platelet aggregation**
- Mediated by fibrinogen → binds to the activated fibrinogen receptor (GP IIb/IIIa) on platelets
- Formation of the primary plug

Targets for antiplatelet therapy

- Inhibition of **TXA2** synthesis
- Inhibition of **P2Y12 receptors** activated by ADP → blockage of platelet activation
- **Adenosine A_{2B}** receptor stimulated by adenosine (↑ concentration of adenosine by ↓ reabsorption of adenosine into the erythrocytes) → platelet stabilization

  (+ inhibition of phosphodiesterases)
- Inhibition of **GP IIb/IIIa receptors** → inhibition of connection between trombocytes → inhibition of aggregation



https://thoracickey.com/antiplatelet-therapy-2/

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Thromboxane synthesis inhibitors – Arachidonic acid metabolism

- Occurrence in the cell: not free, esterified in phospholipid cell membranes
- Upon injury or in inflammatory reaction, it is released from neutrophilic granulocytes, mast cells, endothelium, **platelets**
- Its metabolic products = eicosanoids with the properties of short-term hormones with local action
- Arachidonic acid is released from the membranes of phospholipids using activated **phospholipase A2** (PA2) → synthesis of eicosanoids from arachidonate

Arachidonic acid metabolism

– Arachidonic acid is metabolised in 3 ways:

I. **Cyclooxygenase** - formation of prostaglandins, prostacyclins, thromboxanes
II. **Lipoxygenase** - formation of leukotrienes, lipoxins, hepoxilins and 12- and 15-HETE (hydroxyeicosatetraenoic acid)
III. **Cytochrome P450** - the emergence of other HETE

Cyclooxygenases

- Isoenzymes:
- **COX-1** (constitutive) synthesizes prostanoids involved in physiological processes and inflammatory reactions: prostaglandins (e.g. PGE2, PGF2), **thromboxane A2** (**TXA2**)
- **COX-2** (inducible) is activated in inflammation (activation by pro-inflammatory factors e.g. IL-1, IL-2, TNF-α, oncogenes, etc.) mainly in macrophages, neutrophils, in the endothelium → inflammation, pain (nociceptor sensitization), fever
  - prostacyclin production (PGI2)
- **COX-3**: CNS and myocardium - role in the central mechanism of action of analgesic-antipyretics ??

Eicosanoids

- Short biological half-life, acts on autocrine and paracrine levels (x hormones)
- Physiological functions of eicosanoids:

1. Prostaglandins

- Inflammation mediators (vasodilation, increased vascular permeability)
- Pain and fever (hypothalamus) - increase the sensitivity of nociceptors to bradykinin, histamine, serotonin etc.
- Inhibition of gastric HCl secretion, promotion of gastric mucus secretion
- Vasodilation - reduces systemic arterial pressure
- They stimulate myometrial contractions
- They inhibit the resorption of water and Na^+ in the collecting duct

Eicosanoids

2. Prostacyclines

- Vasodilation (→ regulation also glomerular filtration)
- Decreased platelet aggregation

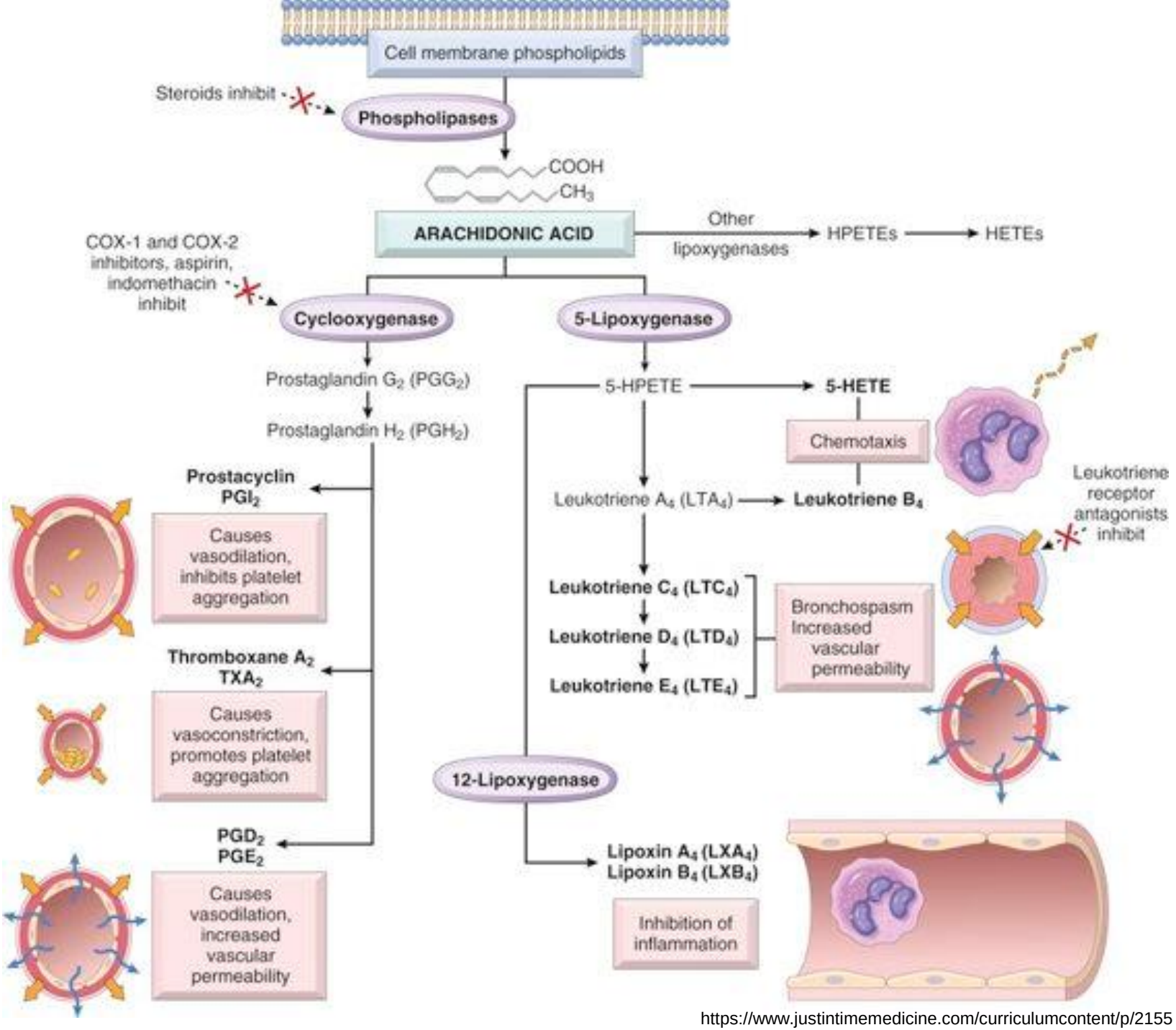
3. Thromboxanes - synthesized in platelets

- Vasoconstriction (**TXA2**)
- Increased platelet aggregation

Lipoxygenase pathway

- Lipoxygenase pathway
- The effect of neutrophil 5-lipoxygenase produces a group of leukotrienes
- (LTA4, LTB and LTC4, D4, E4)

- **Leukotrienes** have a very strong bronchoconstrictive effect; LTC4, LTD4 and LTE4
- They increase the permeability of blood vessels
- Chemotactive and activating functions on leukocytes (mainly eosinophils and monocytes)
- They regulate vasoconstriction



https://www.justintimemedicine.com/curriculumcontent/p/2155

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Acetylsalicylic acid

- Effects:
  - **Antiplatelet** starting at the dose of 50–100 mg/day (secondary prevention of myocardial infarction)
  - MA: by **irreversible** blockade of **COX1** inhibits **thromboxane A2** synthesis (acetylation of active site of COX1) → irreversibly inhibits platelet activation (they are not able to synthesize new cyclooxygenase) + inhibitory effect in secondary hemostasis
    - the effect lasts for the duration of platelet survival in the bloodstream (full disappearance of the effect 4-5 days)
  - Higher doses inhibits synthesis of other products of arachidonic acid metabolism
  - Antipyretic 500 mg; Analgesic 500 mg (minimal interval between doses 4–6 h)
  - Anti-inflammatory over 3 g per day
  - As the dose increases, so does the adverse effects

Acetylsalicylic acid

- Pharmacokinetics: absorption at pH < 3.5 (stomach or proximal part of the duodenum)
- Salicylic acid metabolite – acetylation of COX occurs in portal circulation (deacetylation may already be present in the GIT)

- Salicylate intoxication = salicylism (headache, dizziness, tinnitus, confusion, sweating, vomiting, diarrhea, fever)

- Adverse effects (for doses intended to achieve antiplatelet therapy): bleeding (the risk is comparable for all antiplatelet drugs), nauzea, vomiting, heartburn, bronchospasm

Acetylsalicylic acid

- KI: Asthma; gastroduodenal ulcer; doses > 100 mg/day during the third trimester of pregnancy; renal and liver failure
- children under 12 years - Reye's sy (hyperpyrexia, metabolic acidosis, vomiting, convulsions, neuropsychiatric disorders, hepatic dysfunction)

- Drug interactions:
  - Anticoagulants, antiplatelet drugs
  - NSAIDs (risk of ↑ GIT toxicity, bleeding; risk of ↓ irreversible acetylation of COX)
  - Proton pump inhibitors (↓ bioavailability of ASA)
  - Higher doses: antidiabetic drugs (risk of hypoglycemia); antihypertensives (risk of increased blood pressure)

Purinergic receptors

- P2Y12 receptors stimulation
  - Inhibits adenylylcyclase → ↓ cAMP

    → ↑ expression of GP IIb/IIIa receptors

Adenosine A_{2B} receptor stimulation

- Activation of adenylylcyclase → ↑ cAMP → platelet stabilisation

Inhibitors of ADP receptors P2Y12

- Dominant role of P2Y12 receptors in primary homeostasis
- Mechanism of action:
- Blockage of ADP receptors type P2Y12 → allows the synthesis of a sufficient amount of cAMP → phosphorylation of a regulatory protein VASP (vasodilator-stimulated phosphoprotein) → platelet stabilisation
- Ticagrelol – combined effect + inhibits the reabsorption of nucleosides into the erythrocytes → ↑ plasma adenosine concentration → ↑ activation of adenosine receptors → platelet stabilisation
  – but adenosine stimulates respiratory center in the central nervous system, ↓ excitation signals in the conduction system of the heart → shortness of breath

Inhibitors of ADP receptors P2Y12

- Classification:
  - **Irreversible** inhibitors of P2Y12 receptors – **clopidogrel**, **prasugrel**, ticlopidine (obsolent)
    - duration of effect – time of the survival of the platelet in circulation (platelets are not able to synthesize new receptors) → inhibition of primary hemostasis for 2 days
  - **Reversible** inhibitors of P2Y12 receptors – **ticagrelol**, **cangrelol**
    - duration of effect – for the time of the effective plasma levels (cangrelol – short-acting)
- I: prevention of atherothrombotic events (prophylaxis of arterial thrombosis → ischemic stroke, myocardial infarction – clopidogrel; secondary prophylaxis of acute coronary events – prasugrel, ticagrelol)
- Dual antiplatelet therapy – combination with ASA (secondary prevention of coronary artery disease)

Inhibitors of ADP receptors P2Y12

- Pharmacokinetics:
- Thienopyridines are prodrugs → activation by CYP450
  - **clopidogrel** (low bioavaibility, variable), **prasugrel**, **ticlopidine**
  - (polymorphism of CYP2C19 – variability in bioavaibility)
- Non-thienopyridines – not fully dependent on activation by CYP450
  - **ticagrelor**, **cangrelor**

- Onset of action – clopidogrel 6 hours, prasugrel, ticagrelor 30–60 minutes, cangrelol immediately (only for parenteral administration)

Inhibitors of ADP receptors P2Y12

- Adverse effects: ↑ incidence of bleeding (hematoma, epistaxis, bleeding into GIT), shortness of breath
- Ticlopidine – trombocytopenia, leucopenia

- Drug interactions: other antiplatelets drugs, antitrombotics; proton pump inhibitors (inhibitors of CYP2C19) → ↓ bioactivation of clopidogrel

Antagonists of receptors GP IIb/IIIa

- Glycoprotein receptors GP IIb/IIIa – role in platelet binding by bivalent proteins (fibrinogen and von Willebrand factor)

- Mechanism of action:
  - Blockage of the last step of primary hemostasis – independent of the way of the platelet activation
  - Antagonists bind to the receptors and block connection between trombocytes
  - Suitable for combination with ASA or ADP-receptor inhibitors
  - After the end of drug administration → temporary increase in hemostasis (rebound phemonenon) → only in combination with ASA or heparin

Antagonists of receptors GP IIb/IIIa

- **Abciximab** (parenteral)
- **Irreversible** blocator of GP IIb/IIIa receptors
- Fragment of monoclonal antibody againts GP IIb/IIIa receptor
- High afinity – long-acting (48 hours)
- I: prevention of ischemic cardiac complications in percutaneous coronary intervention; reduction of the risk of myocardial infarction in patients with unstable angina pectoris
- **Eptifibatid** (parenteral)
- **Reversible** blocator of GP IIb/IIIa receptors
- Cyclic heptapeptid
- Lower afinity – shorter duration of activity
- I: to prevent early myocardial infarction
- **Tirofiban**

Activators of adenosine A_2 receptors

Mechanism of action:

- inhibition of transporter ENT-1 → ↓ reabsorption of adenosine into the erythrocytes → ↑ plasma concentration of adenosine → stimulation of adenosine receptors → activation of adenylylcyclase → ↑ cAMP → platelet stabilisation
- + inhibition of phosphodiesterase → ↓ degradation of cAMP and cGMP (dipyridamol – inhibitor of $PDE_{3,5}$; cilostazol – selective inhibitor of PDE_3)

Dipyridamol

I: in combination with ASA secondary prophylaxis ischemic stroke

Cilostazol

I: peripheral artery disease – critical limb ischemia

+ vasodilatory effects

Other antiplatelet drugs

Vorapaxar

- Inhibitor of thrombin receptor PAR-1 – inhibition of thrombin-related platelet aggregation
- I: secondary prevention of myocardial infarction or in peripheral arterial disease
- Not registered in Czech republic

Naftidrofuryl

- Antagonist of 5-HT_{2A} receptors in trombocytes
- Lower antiplatelet effect, higher vasodilating effect

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Thank you for your attention