**Ministry of health of the Republic of Belarus**
**Educational institution**
**«Gomel State Medical University»**

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# METHODOLOGICAL RECOMMENDATIONS

for a practical lesson on the discipline "Clinical pharmacology"
with six-year students of the Faculty of Foreign Students,
studying at the specialty 1-79 01 01 "General medicine"

## TOPIC 4: « CLINICAL PHARMACOLOGY OF CARDIOLOGICAL DRUGS»

Time: 7 hours

Approved at the meeting of the department of general and clinical pharmacology

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2023

## LEARNING AND EDUCATIONAL GOALS, OBJECTIVES, MOTIVATION FOR LEARNING THE TOPIC

Cardiovascular diseases are among the most pressing problems of modern medicine. According to the World Health Organization, they are comparable with a pandemic in the developed countries of the world. They are associated with a large social burden due to temporary and permanent disability, reduced quality of life and premature death. However, despite the relevance, pharmacological developments, international guidelines and recommendations for the treatment of respiratory diseases, the problem is far from being solved, and often patients do not receive adequate care. For this reason, knowledge and skillful use of drugs used in cardiovascular disease is one of the most important tasks of modern pharmacology.

**Learning objective:**

– formation of scientific knowledge about the pharmacokinetics and pharmacodynamics of drugs on the topic of the class in order to master the rational and differentiated pharmacotherapy of cardiovascular diseases.

**Educational purpose:**

– to develop their value-personal, spiritual potential, to form the qualities of a patriot and citizen, ready for active participation in the economic, industrial, socio-cultural and public life of the country; to realize the social significance of their future professional activities, to learn to follow academic and work discipline, standards of medical ethics and deontology.

**Tasks:**

As a result of the study lesson, the student should

**know:**

– clinical and pharmacological classification of drugs used in the treatment of diseases on the topic of the lesson, their pharmacokinetic and pharmacodynamic features;

– indications and contraindications for the prescription of drugs on the theme of the class, the features of their use in different age groups and in various concomitant diseases; dosage regimen of drugs and their interaction with other pharmacological groups;

– principles of control over the effectiveness and safety of the respective drugs, possible side effects, ways to prevent and correct them;

**be able to**:

– choose the most effective and safe medications on the topic of the lesson, taking into account their basic pharmacokinetic and pharmacodynamic characteristics, possible side effects and drug interactions, on the one hand, the characteristics of the disease, age and gender of the patient, the presence of concomitant pathology and the degree of impairment of the basic functions of the body, on the other hand;

– conduct objective monitoring of the effectiveness and safety of the medicines on the study topic, analyze their pharmacokinetic parameters and use the data to calculate single and course doses;

– determine the optimal route of administration of the medicines on the theme of the class, prescribe them taking into account the time of day, intake and composition of

food, predict, prevent and detect side effects of medicines, avoid polypragmasy and irrational combination of different medicines;

– prescribe medications on the topic of the class in the prescription;

– inform patients about the nature of the action of the medicines on the topic of the class, the rules of their administration and possible side effects;

– evaluate scientific information about the effectiveness of the studied drugs, work with reference and other literature on the topic of the class;

**possess:**

– skills ability and willingness to analyze the characteristics of absorption, distribution, biotransformation and excretion of drugs on the topic of the class;

– ability and readiness to rationally dose a medication on the topic of the class, including the choice of dosage form, routes of administration and dosing regimen;

– skills to use medicines on the topic of the class in the treatment, rehabilitation and prevention of relevant diseases and pathological conditions, taking into account the main pharmacodynamic parameters;

– skills to search, analyze and summarize information on the use and effects of various medicines on the topic of the class.

**Motivation for learning the topic:**

– the specifics of training doctors in this specialty determines the need for purposeful study of students' knowledge of the pharmacokinetics and pharmacodynamics of drugs on the topic of the class and the ability to justify and conduct a rational differentiated pharmacotherapy of the relevant diseases and pathological conditions.

## MATERIAL EQUIPMENT

Reference and informational literature, charts, tables, presentations, patient histories, package of regulatory documents, collection of medications.

## CONTROL QUESTIONS FROM RELATED DISCIPLINES

- **biochemistry and physiology:** physical properties and structure of cell membranes, transport of substances through biological membranes in norm and pathology;

- **general and bioorganic chemistry:** basics of chemical kinetics and catalysis, buffer solutions and systems, pH calculation;

- **from biochemistry:** kinetics of enzymatic reactions, Michaelis-Menten kinetics equation, the concept of enzyme inhibitors, types of enzyme inhibitors;

- **from pathological physiology:** cell damage, disorders of protein, fat, carbohydrate and mineral metabolism, disorders of local and general circulation, immunopathological processes, allergies, inflammation, pathology of heart and vascular organs;

- **from Latin:** basic rules for coordinating parts of speech and drawing up prescriptions when prescribing medicines;

- **from pharmacology:** general questions of pharmacology, pharmacokinetics and pharmacodynamics of drugs, general prescription and prescription rules;

- **from internal diseases:** features of clinical and anamnestic data in patients with diseases of the cardiovascular system, etiopathogenesis and modern approaches to the diagnosis of major diseases with heart and vascular lesions, emergency conditions in

cardiology and the principles of their relief.

## CONTROL QUESTIONS ON THE TOPIC OF THE CLASS

1. Clinical and pharmacological characteristics of drugs for treatment of chronic heart failure (cardiac glycosides, drugs non-glycosides).

2. Clinical and pharmacological characteristics of antihypertensive drugs: diuretics, beta-adrenoblockers, slow calcium channels, angiotensin-converting enzyme inhibitors, blockers angiotensin receptor agonists, central alpha2- and imidazoline receptors. Representatives of other groups of hypotensive drugs: alpha-adrenoblockers, inhibitors of renin synthesis, direct aldosterone antagonists, etc.

3. Principles of modern pharmacotherapy of arterial hypertension.

4. Clinical and pharmacological characteristics of antianginal and anti-ischemic drugs: beta-adrenoblockers, blockers slow calcium channel blockers, nitrates, sidnonimines, cardiocytoprotectors.

5. Drugs that correct lipid metabolism (statins, fibrates, polyunsaturated fatty acids).

6. Modern principles of treatment of coronary heart disease.

7. Clinical and pharmacological characteristics of antiarrhythmic drugs, Vaughan-Williams classification, mechanisms of Antiarrhythmic action, indications and contraindications for their use, safety control. Drugs used in the treatment of disorders of the conduction system of the heart.

## PROCESS OF THE STUDY

**1.**

**2.**

**3.**

**4.**

**5.**

**Theoretical part**

Theoretical questions are described in the appendix to the methodological recommendations.

**Practical part**

1. Take notes on theoretical material demonstrated by the teacher.

2. Master the methods of solving the tasks and writing out prescriptions on the topic of the class.

**Theme learning control**

Conducted in the form of independent written work ( solution of practical problems and prescriptions for individual task).

## METHODOLOGICAL RECOMMENDATIONS FOR ORGANIZATION AND EXECUTION OF STUDENTS' INDEPENDENT WORK (SIW)

**The time given for independent work can be used by students for:**

- preparing for the practical classes;
- completing the tasks on the topic of the class in the workbook;
- preparing thematic reports, essays and presentations;

– taking notes from academic literature.

**The main methods of organizing independent work:**

- completing tests and practical tasks of the electronic educational-methodical complex (EEMC) for self-monitoring and self-assessment;
- writing a case history.

**The list of tasks of the SIW:**

- solving practical problems in the EEMC;
- completing the test tasks of the EEMC;
- writing a case history.

**Control of the SIW is carried out in the form of:**

- assessment of an oral answer to a question, report, report, or solution of a task in a practical class;
- individual conversation;
- checking a case history.

## METHODOLOGICAL RECOMMENDATIONS FOR ORGANIZATION AND EXECUTION OF CONTROLLED INDEPENDENT WORK OF STUDENTS (CIWS)

**Recommended forms of CIWS organization:**

- writing a case history;
- writing an essay on a given topic;
- preparing a report and a multimedia presentation on a given topic.

**The list of tasks of the CIWS:**

Topics of essays / multimedia presentations:

1. Clinical pharmacology of potassium channel activators (nicorandil, minoxidil, pinacidil).
2. Arterial hypertension in pregnant women: diagnosis, management tactics and treatment approaches.
3. Current approaches to the treatment of arterial hypertension in childhood and old age.

**Forms of control of CIWS realization:**

- checking a case history;
- checking and grading an essay on a given topic;
- checking and grading a multimedia presentation on a given topic.

## LIST OF REFERENCES


1. Kharkevitch, D.A. Pharmacology: textbook for med. students: transl. of 12th ed. of Russ. textbook "Pharmacology" (2017) / D.A. Kharkevitch. - 2nd ed. - Москва: ГЭОТАР-Медиа, 2019. - 676 с.: ил., табл. - Рек. ФГАУ "ФИРО". – Режим доступа: http://www.studmedlib.ru/book/ISBN5970402648.html – Дата доступа: 23.05.2022.
2. Кратко о лекарственных средствах: учебно – методическое пособие для студентов 3 и 6 курсов факультета иностранных студентов, учреждений высшего

мед. образования: в 2 ч.=Drugs in short: partical workbook for 3 and 6 year students Faculty for International Students of medical higher educational institutions: in 2 parts / Е.И. Михайлова [и др.]. – Ч. 1. – Гомель: ГомГМУ, 2020. – 56с. – Режим доступа: http://elib.gsmu.by/xmlui/handle/GomSMU/7128 – Дата доступа: 23.05.2022.

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4. Rang and Dale's Pharmacology / J.M. Ritter [et al.]. - 9th ed. - Edinburg [et al.]: Elsevier, 2020. - xvi, 789 p.: ill., tab. + Student consult online.

## AGENTS FOR HEART FAILURE. INOTROPICS (CARDIOTONICS) [1-4]

**Inotropics** are drugs that affect the strength of cardiac contraction

| Classification | Cardiac glycosides | | Non-glycoside agents | |
|---|---|---|---|---|
| | | | **Adrenergic drugs** | **Phosphodiesterase inhibitors** |
| **Drugs** | ***Drugs of digitalis:***<br>1. Digoxin (Lanicore, Dilacor)<br>2. Digitoxine (Cardiotoxin)<br>3. Lanatoside (Celanide, Isolanide)<br>4. Methylldigoxine (Bemecor, Digi-cor) | ***Drugs of strophant:***<br>5. Strofantin<br>6. Strofantin G<br>***Drugs of lily of the valley:***<br>7. Corglycon<br>***Drugs of Adonis:***<br>8. Adonisid | 9. Dobutamine (Dobutrex)<br>10. Dopamine | 11. Amrinon (Vincoram, Inocor)<br>12. Milrinon (Primacor, Corothrop) |
| **Mechanism of action** | Block of SH-group of Na+/$K^+$-ATPase → violation of $Na^+$ and $K^+$ flowinside the cell ↓ $K^+$ and ↑ $Na^+$ → ↓ difference between intra- andextracellular concentration of $Na^+$→ ↓ transmembrane $Na^+/Ca^{2+}$ metabolism → ↓ elimination of $Ca^{2+}$ from the celland ↑ its intracellular concentration; Ions of $Ca^{2+}$ interact with the troponin complex and eliminateits inhibitory effect on contractile proteins of the myocardium → there is an interaction of actin with myosin → rapid and severe myocardial contraction. | | 1. See "Adrenergic drugs" (9)<br>2. Stimulation of peripheral dopamine receptors, ß1-, α-adrenergic receptors (10) | Inhibition of phosphodiesterase (III) → ↑ cAMP → ↑ intake of Ca2+ into myocardial cells and stimulation of the function of contractileproteins |
| **Pharmacological effects** | ***Cardiac:***<br>1. Positive inotropic effect (strengthening and shortening of the systole, ↑ minute and stroke volume of the heart);<br>2. Positive bathmotropic effect (↑ excitability of the myocardium);<br>3. Negative chronotropic effect (bradycardia → elongation of the diastole);<br>4. Negative dromotropic effect (↓ conduction of the myocardium).<br>***Extra-cardiac:***<br>5. ↑ *diuresis* (inhibition of Na+/$K^+$-ATPase in the cells of the epithelium of the renal tubules and ↓ reabsorption of Na+),<br>6. ↑ *glomerular filtration* (improvement of renal circulation by increasing the impact and minute volume of the heart),<br>*7.* ↓ *edema* (↑glomerular filtration and diuresis);<br>8. *Vasodilating effect and* ↓ *activity of RAAS* (due to the depression of the sympathoadrenal system),<br>9. ↑ *smooth muscle tone* (Inhibition of Na+/$K^+$-ATPase of smooth muscle cells). | | 1. Positive inotropic effect<br>2. Positive chronotropic effect<br>3. ↑ blood flow in internal organs (10) | 1. Positive inotropic effect<br>2. Vasodilating effect |
| **Indications** | 1. Acute heart failure (3.5-7)<br>2. Chronic heart failure (1-4,8)<br>3. Supraventricular tachyarrhythmias (1,2,7) | | 1. Acute heart failure<br>2. Chronic heart failure (CHF), exacerbation<br>According to some data, the use of PDE inhibitors in chronic heart failure leadstoanincrease in the death rate of patients. | |
| **Side effects** | 1. Extrasystole, bradycardia, AV blockade<br>2. Nausea, vomiting, diarrhea<br>3. Visual impairment (↓ acuity, impaired perception of the spectrum, ↓ visualfields) | | 1. Tachyarrhythmias, headache<br>2. Exacerbation of existing myocardial ischemia | 1. Tachyarrhythmia, ↓ BP<br>2. Thrombocytopenia, hepatotoxicity<br>3. Nausea, vomiting |

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|---|---|---|---|
| **Contraindications** | 1. Digital intoxication<br>2. Severe bradycardia, WPW syndrome and sick sinus syndrome<br>3. Acute myocarditis, endocarditis, unstable angina<br>4. Hypertrophic and restrictive cardiomyopathy<br>5. Paroxysmal ventricular tachycardia | 1. Cardiac tamponade, pericarditis, severe aortic stenosis<br>2. Ventricular arrhythmias | 1. Obstructive cardiomyopathy<br>2. Acute hypovolemia |
| **NB!** | Physico-chemical structure of cardiac glycosides: polar glycosides (strophanthin, corglycon), relatively polar (digoxin, celanide), nonpolar (digitoxin). Polar drugs are administered parenterally, act briefly, have a predominant systolic effect; non-polar act for a long time, are administered orally, have a predominant diastolic effect.<br>Disadvantages of cardiac glycosides: narrow therapeutic window → possibility of intoxication; no effect in hyperthyroidism, mitral stenosis, chronic pulmonary heart. | | |
| | In decompensation of CHF and acute heart failure, levosimendan can be used. This substance increase sencitivity of contractile proteins to calcium ions. Currently, levosimendan has not yet become wide spread in the clinic. | | |
| **Drug interactions** | 1. antacids and lipid-lowering drugs (cholestyramine) ↓ cardiac glycosides absorption (due to ↑ GIT motility)<br>2. anticholinergics ↑ absorption (↓ peristalsis).<br>3. beta-blockers, reserpine, quinidine, calcium channel blockers: ↓ HR.<br>4. diuretics, reserpine, clonidine, and calcium antagonists ↑ arrhythmogenicity | Dobutamine + cardiac glycozides: synergistic inotropic effect and increased risk of arrhythmia;<br>ACE inhibitors: cardiac pain, arrhythmias;<br>Alpha-blockers: ↓ or prevent increased systemic vascular resistance;<br>Tricyclic antiderpressants ↑ vasoconstriction. | 1. Milrinone not to be mixed with furosemide and bumetanide in one container (pharmaceutical interaction).<br>2. Milrinone ↑ inotropic effect of beta-agonists. |

## Glycoside intoxication

| Clinics: | Treatment: |
|---|---|
| 1. CVS: arrhrythmias (AV blockade, ventricular extrasystoles, etc.)<br>2. GIT: anorexia, nausea, vomiting and diarrhea<br>3. Central nervous system: dizziness, headache, hallucinations, etc.<br>4. Visual function: xantopsy (visual impairment, in which all objects appear yellow-colored), photophobia, loss of visual fields, mydriasis. | 1. The withdrawal of the drug;<br>2. Antidotes for cardiac glycosides: digitalis-antidote (antibodies to cardiac glycosides), unitiol (donor of SH-groups that binds cardiac glycosides) and EDTA (binds calcium ions);<br>3. Preparations of $K^+$: KCl (1-1.5 g in 100 ml of 5% glucose + 4 units of insulin, up to 8 g of potassium chloride per day) into the vein, or tablets "Asparcam", "Panangin";<br>4. Antiarrhythmics: lidocaine, phenytoin (difenin), β-adrenoblockers, in AV blockade – muscarinic antagonists (atropine). |

## ß-BLOCKERS

**ß-antagonists (ß- blockers)** – drugs directly blocking ß-adrenergic receptors.

| Classification | ß1, ß2- blockers | ß1- blockers | Mixed-action ß- blockers | ß- blockers with ISA |
|---|---|---|---|---|
| **Drugs** | 1. Propranolol<br>2. Pindolol<br>3. Sotalol<br>4. Timolol<br>5. Nadolol | 6. Atenolol<br>7. Metoprolol<br>8. Bisoprolol<br>9. Talinolol<br>10. Betaxolol<br>11. Nebivolol | 12. Labetalol<br>13. Carvedilol | 14. Pindolol<br>15. Acebutalol<br>16. Celiprolol |
| **Mechanism of action** | 1. Block ß1 and ß2-adrenergic receptors | 1. Block ß1-adrenergic receptors (6-10)<br>2. Affects the release of NO in vessels → vasodilation (11) | 1. Block α1 and ß1 adrenergic receptors | 1. Slightly stimulate ß1 or ß2-adrenoreceptors.<br>**NB!** With an excess of catecholamines, such a weak stimulation is equal to the blockade of these receptors. |
| **Pharmacological effects** | 1. Hypotensive (Block of ß1-adrenoreceptors of renal juxtaglomerular apparatus → ↓ renin secretion → ↓ tonus of peripheral vessels; Block of ß1-adrenergic receptors of the heart → ↓ systolic blood pressure; Depression of the central links of the sympathetic nervous system → ↓ of the tone of the peripheral vessels)<br>2. Antianginal (Blockage of ß1-adrenergic receptors of the heart and suppression of the central links of the sympathetic nervous system → ↓ heart rate → ↓ stroke and minute output → ↓ myocardial oxygen demand)<br>3. Antiarrhythmic (Block ß1-adrenoreceptors of the conduction system of the heart → ↓ automatism, conduction and excitability of the myocardium)<br>4. ↓ IOP (1, 4, 10) | | | |
| **Indications for use** | 1. AH, 2. IHD, 3. Tachyarrhythmias, 4. Thyrotoxicosis, 5. Glaucoma (1, 4, 10), 6. Acute myocardial infarction (6-9), 7. CHF (7, 8,13) | | | |
| **Side effects** | 1. Bronchospasm<br>2. Bradycardia, AV blockade<br>3. The withdrawal syndrome<br>4. Dyspepsia | | | |
| **Contraindications** | 1. Bronchial asthma<br>2. Bradycardia, AV-blockade, SA-blockade II-III degree, sick sinus syndrome<br>3. Arterial hypotension<br>4. Severe heart failure<br>5. Pregnancy (relative contraindication) | | | |

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| **Drug interactions** | 1. Rational combinations:<br>- α-blockers, nitrates (especially when arterial hypertension + IHD: it ↑ hypotensive effect and β-blocker-induced bradicardia is eliminated by nitrates).<br>- diuretics (their action is ↑ by inhibiting β-blockers release of renin in the kidney).<br>- ACE inhibitors, angiotensin receptor blockers.<br>Permissible combination: low doses of calcium channel blockers from the group of dihydropyridines (nifedipine).<br>2. Irrational and dangerous combinations: slow calcium channel blockers from the verapamil group (in this case, ↓ heart rate and deterioration of AV conduction are potentiated; excessive bradycardia and hypotension, AV block, acute left ventricular failure are possible), with sympatholytics, for example, reserpine and octadine (due to the weakening of sympathetic effects on myocardium ), cardiac glycosides (the risk of bradyarrhythmias, blockades and even cardiac arrest is increased), direct muscarinic agonists and anticholinesterase agents, tricyclic antidepressants, for example, imipramine ( for the same reasons), insulin and oral hypoglycemic agents (developing excessive hypoglycemic effect) |

**Antiarrhythmic agents** are drugs used to treat heart rhythm disturbances (arrhythmias) [1-4]

| Classification | **Class I** ($Na^+$-channel blockers) | | | **Class II** (ß-blockers) | **Class III** ($K^+$-channel blocker) | **Class IV** ($Ca^{2+}$-channel blockers) |
|---|---|---|---|---|---|---|
| | **IA** | **IB** | **IC** | | | |
| **Drugs** | 1. Quinidine<br>2. Procainamide<br>3. Dysopyramide | 4. Lidocaine<br>5. Phenytoin | 6. Propaphenone<br>7. Ethacizine | 8. Propranolol<br>9. Atenolol<br>10. Metoprolol | 11. Amiodarone<br>12. Bretiliumtosylate | 13. Verapamil |
| **Mechanism of action** | ↓ Permeability of membranes for $Na^+$and$Ca^{2+}$ ions→↓ Depolarization rate; ↓ automaticity and conductivity; ↑ repolarization. | Blockage of $Na^+$ entry in the phase 4 and ↑ permeability of membranes for $K^+$ions in the phase 3 → ↓ automaticity; ↓ duration of repolarization. *Do not affect the conductivity and heart beat strength* | $Na^+$-channel blockage→ ↓ depolarization and automatism. *Do not affect repolarization.* | See the topic «Adrenergic drugs» | 1. ↓ permeability of the cardiomyocyte membrane for potassium ions, delay repolarization (11)<br>2. Noradrenaline synaptic release blockage and ↓ of the effect of the neurotransmitter on adrenoceptors (12) | The slow transmembrane current of Ca 2+ ions is blocked in the cell → phase 0 inhibition in the cells with "slow response" → ↓ automaticity of SA- and AV-nodes and ectopic foci. |
| **Pharmacological effects** | 1. Antiarrhythmic<br>2. Anticonvulsant (5)<br>3. Local anesthetizing (4) | | | | 1. Antiarrhythmic<br>2. Antianginal (11)<br>3. Hypotensive (12) | 1. Antiarrhythmic<br>2. Antianginal<br>3. Hypotensive |
| **Indications** | 1. Atrialfibrillation (1, 2)<br>2. Ventricular tachycardia<br>3. Supraventricular paroxysmal tachycardia (1-3, 7)<br>4. Atrialfibrillation / flutter (2, 6) | | | | 1. Supraventricular and ventricular tachyarrhythmia, including life threatening<br>2. Refractory arrhythmias | 1. Supraventricular tachyarrhythmia and extrasystoles<br>2. Angina pectoris<br>3. Arterial hypertension |
| **Side effects** | 1. Negative inotropic effect<br>2. Nausea, vomiting<br>3. Antimuscarinic effect<br>4.α-blocking effect (1) | 1. Headache, dizziness<br>2. Tremor<br>3. Gingival enlargement (5) | 1. Negative inotropic effect<br>2.Proarrhythmogenicaction<br>3. Headache | | 1. Intestinal pneumonia;<br>2. Hypo- / hyperthyroidism (11)<br>3. Hypotension<br>4. Ataxia, tremor (11)<br>5. Deposition of lipofuscin in the cornea (11) | 1. Nausea, vomiting<br>2. Hyperemia of the face<br>3. Bradycardia, AV blockade<br>4. Peripheral edema<br>5. Constipation |
| **Contraindications** | 1. Intra cardiac blockades<br>2. Decompensation of heart failure | 1. Sick sinus syndrome<br>2. Liver diseases | 1. Sick sinus syndrome<br>2. Severe heart failure | | 1. Sick sinus syndrome (11)<br>2. Violation of thyroid function (11)<br>3. Arterial hypotension (12) | 1. Sick sinus syndrome, bradycardia<br>2. Arterial hypotension<br>3. Cardiogenic shock, MI |

**NB!**

• Treatment of bradyarrhythmia: *muscarinic antagonists* (eliminate the influence of the vagus nerve); *ß1-agonists* (dobutamine, dopamine).

• Additional drugs for the treatment of arrhythmias: *cardiac glycosides* for supraventricular arrhythmias, *potassium* preparations (panangin, asparcam) in arrhythmias to prevent hypokalemia; *dihydropyridine calcium channel blockers* (nifedipine, amlodipine, etc.) in brady-dependent arrhythmias (↑ heart rate); inhibitors of angiotensin-converting enzyme (captopril, enalapril, etc.) for ventricular arrhythmias.

| | | | | | | |
|---|---|---|---|---|---|---|
| **Drug interactions** | 1. Do not combine drugs from the same class<br>2. Quinidine ↑ effect of warfarine. | 1.ß-blockers: ↑ risk of hypotension and bradycardia.<br>2. Antiarrhythmics (amiodarone, quinidine) ↑ cardiosupression.<br>3. Lidocaine + with procaindamide: can cause CNS excitement and hallucinations.<br>4. Anticoagulants ↑ the risk of bleeding. | 1.Not to combine ethacizine with other IC and IA class antiaritmics, and MAO inhibitors.<br>2. ß-blockers + ethacizine: ↑ antiarrhythmic effect (especially in case of stress or physical effort induced arrythmias). This combination allows the use of a smaller doses of ethacizine and ↓ side effects: it's used for the treatment and prophylaxis of paroxysmal tachycardia including ventricular one.<br>3. Propafenone ↑ the effect of indirect anticoagulants but requires prothrombin time monitoring.<br>4. Propafenone +amiodarone: can cause conduction and repolarization disturbances and accompanied by arrhythmogenic effect. | See ß-blockers | 1. IA class antiarrhythmics, tricyclic antidepressants, sotalol ↑ risk of torsades de pointes.<br>2. Amiodarone: do not combine with fluoroquinolones.<br>3.Do not combine with HR-decreasing drugs.<br>4.Laxatives provoking hypokalemia: ↑ the risk of ventricular arrhythmia.<br>5.Digoxine: ↑ the risk of digitalis intoxication.<br>6. Combination with systemic GCs and diuretics causing hypokalemia requires caution | 1. Vasodilators, thiazide diuretics, ACE inhibitors: mutually ↑ antihypertensive action;<br>2.ß-blockers, antiarrhythmics, inhalation anesthetics ↑ the risk of Brady-cardia, AV-blockade, severe arterial hypotension, and heart failure<br>3. Nitrates ↑ antianginal action of verapamil<br>4.Amiodarone ↑ the risk of negative inotropic effects, bradycardia, conduction disturbances, and AV-blockade.<br>5.Verapamil IV for patients who have recently received ß-blockers: a risk of severe hypotension and asystole. |

## ANTIANGINAL AGENTS [1-4]

**Antianginal drugs** are substances used for angina pectoris – pain in the heart due to ischemia (usually because of coronary atherosclerosis).

| Classification | Nitrates and *sydnonimine derivatives | ß-adrenoblockers | Calcium channel blockers |
|---|---|---|---|
| **Drugs** | 1. Nitroglycerine<br>*Short-acting (*tablets Nitrolingual, Nitrostat; spray Nitromist)<br>*Long-acting* (buccal form Nitrogard; patch Minitran)<br>2. Isosorbide dinitrate (Isordil)<br>3. Isosorbide-5-mononitrate (Imdur, Ismo)<br>*4. Molsidomine | *Non-selective ß-blockers:*<br>5. Propranolol<br>*Selective ß1-blockers:*<br>6. Atenolol, Metoprolol, Bisoprolol<br>*ß1, α1-blockers with vasodilating activity:*<br>7. Carvedilol, Labetalol<br>*With ISA (intrinsic sympathomimetic activity)*<br>8. Acebutalol, Talinolol | *Dihydropyridine:*<br>9. Nifedipine<br>10. Amlodipine<br>*Phenylalkylamine:*<br>11. Verapamil<br>*Benzothiazepine:*<br>12. Diltiazem |
| **Mechanism of action** | SH-groups → are metabolized into S-nitrosothiols with NO release → activate guanylate cyclase, intracellular cGMP is accumulated → ↓ flow into the cells and accelerates the release of $Ca^{2+}$, relaxes the smooth muscles of the veins and arterioles (including the coronary vessels) (1-3).<br>*Is converted to NO, does not form S-nitrosothiols (4). | Blockage of ß-adrenergic receptors → ↓ cAMP → ↓ $Ca^{2+}$entry and ↓ intracellular concentration of $Ca^{2+}$→ ↓ force of the heart contractions. | Blockade of slow calcium channels ↓ entry of $Ca^{2+}$ions into the cell → ↓ conversion of phosphate energy into mechanical work → muscle fiber does not develop sufficient mechanical stress. |
| **Pharmacological effects** | 1.Antianginal (↓pre- and afterload)<br>2. Antiplatelet | 1. Antianginal<br>2. Hypotensive<br>3. Antiarrhythmic | 1. Antianginal<br>2. Hypotensive<br>3. Antiarrhythmic (11,12) |
| **Indications** | 1. Angina pectoris (all kinds)<br>2. Acute myocardial infarction (i/v 1, 2)<br>3. Chronic heart failure (2-4)<br>4. Pulmonary edema (1) | 1. Angina pectoris<br>2. Arterial hypertension<br>3. CHF<br>4. Tachyarrhythmia<br>5. Migraines | 1. Angina pectoris, vasospastic angina<br>2. Arterial hypertension<br>3. Supraventricular tachyarrhythmias (11, 12) |
| **Side effects** | 1. Headache, tinnitus, reflex tachycardia<br>2. Hypotension, orthostatic collapse<br>3. Nausea, vomiting<br>4. Tolerance (1-3)<br>5. ↑ intraocular and intracranial pressure | 1. Bronchospasm<br>2. Hypotonia<br>3. Bradycardia, AV blockade | 1. Headache, dizziness, skin hyperemia, tachycardia, legs edema (9, 10)<br>2. Bradycardia, AV blockage (11)<br>3. Tachy-, bradycardia (12) |
| **Contraindications** | 1. Allergy<br>2. Arterial hypotension<br>3. ↑ intraocular pressure<br>4. Closed-angle glaucoma | 1. Bronchial asthma<br>2. Bradycardia, AV blockade<br>3. Arterial hypotension, severe CHF<br>4. Pregnancy | 1. Severe hypotension<br>2. Acute MI, progressive HF<br>3. Sick sinus syndrome |

| | | | |
|---|---|---|---|
| **NB!** | Angina attack treatment: nitroglycerine sublingually. | New drugs: ivabradine (funny channel blocker, ↓HR, doesn't affect BP conductivity) | Metabolic therapy: trimetazidine (preductal), nicorandil, meldonium (mildronate). |
| **Drug interactions** | 1.ßblockers, verapamil, cordarone enhance the antianginal effect of nitrates, these are rational combinations.<br>2. Dihydroergotamine can reduce the antianginal effect of nitrates.<br>3. Novocainamide, quinidine, alcohol can cause hypotension and collapse.<br>4. Acetylsalicylic acid promotes ↑ plasma nitroglycerin levels.<br>5. Nitrates ↓ pressor action of adrenergic agonists. | 1. Quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone, pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, erythromycin ↑ decrease in heart rate and ↑ QT.<br>2. Ketoconazole, itraconazole, clarithromycin, erythromycin, josamycin, telithromycin, nelfinavir, ritonavir, nefazodone: contraindicated due to the ↑ risk of developing excessive bradycardia.<br>3. Diltiazem or verapamil increase ↓ heart rate. These combinations are not recommended.<br>4. Rifampicin, barbiturates, phenytoin and herbal preparations containing St. John's wort (Hypericum perforatum), when used together with ivabradine ↓ its concentration.<br>5. Thiazide and loop diuretics, ↑ risk of arrhythmia.<br>6. Grapefruit juice ↑ concentration of ivabradine in the blood 2 times. | 1.ß-blockers can potentiate bradycardia and impaired AV conduction caused by blockers of slow calcium channels.<br>2. Antihypertensive drugs and diuretics can enhance the hypotensive effect of slow calcium channel blockers.<br>3. Halotan potentiates the inhibitory effect of diltiazem on heart activity. |

## LIPID-LOWERING DRUGS [1-4]

**Lipid-lowering drugs** – agents decreasing level of plasma lipids.

| Classification | Statins | Bile acid sequestrants | Fibrates | Derivatives of nicotinic acid | Inhibitors of sterol intestinal absorption | Other |
|---|---|---|---|---|---|---|
| **Drugs** | 1. Atorvastatin<br>2. Lovastatin<br>3. Pravastatin<br>4. Simvastatin | 5. Cholestyramine<br>6. Colestypol | 7. Fenofibrate<br>8. Gemfibrozil<br>9. Ciprofibrate | 10. Nicotinic acid (niacin) | 11. Ezetimibe | 12. Probucol |
| **Mechanism of action** | 1. ↓ synthesis of cholesterol in the liver due to competitive inhibition of the enzyme HMG-CoA reductase → ↑ number of receptors for LDL → ↑ capture of cholesterol from the plasma<br>2. The LDL particles also contain triglycerides (TG) → ↓ TG | ↑catabolism and excretion of bile acids and cholesterol | 1. Violate lipid metabolism → stimulated lipoprotein lipase and ↑ catabolism of VLDL<br>2. Inhibit acetyl-CoA carboxylase, inhibition of lipolysis → ↓ synthesis of TG<br>3. ↑ intake of cholesterol and TG by HDL | 1. Directly inhibits hepatic VLDL → ↓ synthesis of TG<br>2. ↓ plasma cholesterol level | Selectively inhibits the absorption of phytosterol and cholesterol in the small intestine | Inhibits the synthesis of lipids, ↓ absorption of cholesterol and atherogenic properties of lipoproteins |
| **Pharmacological effects** | 1. ↓ total cholesterol plasma level<br>2. ↓ triglycerides plasma level (1-4, 7-10)<br>3. ↑ HDLP level (1-4, 7-9, 12)<br>4. Antiplatelet (1-4) | | | | | |
| **Indications** | 1. Atherosclerosis,<br>2. Hyperlipoproteinemia IIa; IIb (1-4, 7-12); III and IV (1-4, 7-9, 10),<br>3. Hypercholesterolemia (1-6, 10, 11)<br>4. Hypertriglyceridemia (1-4, 7-10) | | | | | |
| **Side effects** | 1. Dyspepsia<br>2. Liver function impairment<br>3. Myalgia, myosite | 1. Constipation, bloating<br>2. Malabsorbtion | 1. Nausea, vomiting, diarrhea<br>2. ↑ bile cholesterol level → ↑ cholelythiasis risk<br>3. ↑ ALT, AST | 1. Skin hyperemia<br>2. Hepatotoxicity<br>3. Hyperuricemia | 1. Liver function impairment | 1. Diarrhea, bloating, nausea<br>2. QT widening |
| **Contraindications** | 1. ↑ ALT, AST<br>2. ↑ creatinkynase<br>3. Pregnancy, lactation, age before 18 | 1. Severe hypertriglyceridemia | 1. Hepatitis<br>2. Cholelithiasis | 1. Gastroduodenal ulcers<br>2. Liver function impairment<br>3. Gout | 1. Hepatic diseases<br>2. Hypersensibility | 1. QT widening, ventricular tachyarrhythmia<br>2. Pregnancy, lactation |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Drug interactions** | 1. To prevent binding to anion exchange resins statins are taken in 4 hours after cholestyramine.<br>2. Cimetidine, ranitidine and omeprazole can ↑ the bioavailability of the statins. 3. The combination of statins with fibrates can ↑ the risk of myopathy.<br>4. Statins can ↑ warfarin and digoxin concentration, it requires clinical monitoring. | 1. Can ↓ absorption of other drugs, therefore they should be taken in 4 hours before or 1 hour after taking any other drug | 1. Fibrates sometimes ↑ the effect of indirect anticoagulants, so the dosage of the latter should be ↓ twice. | 1. Can ↑ the action of antihypertensive drugs, which leads to a sudden BP ↓ | 1.No data | 1. Terfenadine ↑ QT-interval, ↑ risk of severe heart rhythm disorders.<br>2. Tricyclic antidepressants, I-III classes antiarrythmics, phenothiazine ↑ risk of QT interval elongation<br>3. ↓ ciclosporin plasma concentration |
| **NB!** | 1. The basic treatment of hyperlipidemia is the DIET, not the drugs!<br>2. Bile acid sequestrants should be taken during meal.<br>3. Statins are taken in the evening before going to bed because cholesterol is synthesized in the night.<br>4. Omega-3 polyunsaturated fatty acids have lipid-lowering (↓ TG, VLDL), antiplatelet, anti-inflammatory effects. Can be used as a supplement for lipid-lowering therapy. | | | | | |

**Myocardial infarction management** (MI is ischemic necrosis miocardium because of prolonged lack of oxygen supply – ischemia) [1-4]

| Aim | Group | Drugs |
|---|---|---|
| 1. Pain management | 1.1*Opioid analgesics*<br>1.2 Neuroleptanalgesia<br>1.3 Inhalation anesthesia | Morphine, Promedol, Fentanyl<br>Fentanyl + droperidol<br>Nitrous oxide (80 vol% N2O and 20 vol% O2) |
| 2.Restoration of coronary blood flow(trombolysis) and thrombi formation prevention | 2.1 *Fibrinolytics*<br>2.2 *Anticoagulants*<br>2.3 *Antiplatelets* | Alteplase, Tenteplase (no antigenicity); Streptokinase<br>Heparin, Enoxaparin, Fondaparinux<br>Acetylsalicylic acid (250-500 mg to be chewed), Clopidogrel 300 mg |
| 3. Necrosis zone restriction | 3.1 *Nitrates (в/в)* | Nitroglycerin, isosorbide dinitrate |
| 4. Acute cardiac uploading | 4.1 *β-blockers*<br>4.2 *ACE inhibitors* | Metoprolol, Bisoprolol, Carvedilol, Atenolol<br>Captopril, Enalapril, Lisinopril, Perindopril |
| 5. Atherosclerotic plaque stabilization | 5.1 *Statins* | Atorvastatin, Rosuvastatin |

**Current principles of treatment of stable coronary heart disease (European Society of Cardiology ESC) [1-4].**
**SIHD is a disease manifested by exercise- or stress-induced chest symptoms associated with left main coronary artery stenosis ≥50% and one or more major coronary arteries ≥70%**

| Цели лечения | Препарат |
|---|---|
| **Management of angina symptoms, which is done in two steps:** | |
| **1.Curing the symptoms of angina after the onset of an attack** | Short-acting **nitrates** for stopping angina attacks:<br>**Nitroglycerin** (0.3-0.6 mg sublingually every 5 minutes. dose max 1.2mg !)<br>**Isosorbide dinitrate** (5mg sublingually) is long-lasting. |
| **2.During the period when it may occur.** | **β-adrenoreceptor blockers** ↑ perfusion of ischemic areas by prolonging diastole and ↑ vascular resistance:<br>**Metoprolol , bisoprolol, atenolol, nebivolol.** |
| | **Calcium antagonists** (vasodilation and ↓ of peripheral vascular resistance, sinus node suppression):<br>**Amlodipine, nifedipine, felodipine. verapamil, diltiazem.** |
| | **If-channel inhibitors** (reduce heart rate by reducing myocardial oxygen demand):<br>**Ivabradine (Bravadine)** |
| | **Potassium channel agonist** (vasodilation of epicardial coronary arteries):<br>**Nicorandil(Icorel)** |
| **2 Antischemic medications** | **Trimetazidine, molsidomine.** |
| **Preventing the development of cardiovascular events such as:**<br>Thrombosis, in case of plaque rupture and erosion | **Antiplatelet agents** (↓platelet aggregation): **Aspirin** (75mg/day) |
| | **P2Y12 receptor inhibitors** (↓ platelet aggregation): **Clopidogrel, Prasugrel, Ticagrelor.** |
| Plaque progression | **Statins** (hypolipidemic agents): **Atorvastatin**, etc. |
| Development of ventricular dysfunction | **RAAS blockers: ACE inhibitors, ATR-blockers** |

## ANTIHYPERTENSIVE AGENTS [1-4]

**Antihypertensives** are medicines used for the treatment of hypertension.
I$^{st}$ line drugs are used in the first complaints of the patient.

| Classification | Drugs affecting the RAAS | | Diuretics | β-blockers | Calcium channel blockers (calcium antagonists, CCB) |
|---|---|---|---|---|---|
| | **Angiotensin converting enzyme inhibitors (ACE inhibitors)** | **Angiotensin II receptor antagonists (sartans)** | | | |
| **Drugs** | ***Sulfhydryl-containing agents:***<br>1. Captopril (Capoten)<br>***Dicarboxylate-containing agents:***<br>2. Enalapril (Enap)<br>3. Lisinopril (Diroton)<br>4. Ramipril (Tritace)<br>***Phosphonate-containing agents:***<br>5. Fosinopril (Monopril)<br>***Hydroxame-containing agents:***<br>6. Idrapril | 7. Losartan (Cozaar)<br>8. Valsartan (Diovan)<br>9. Irbesartan (Aprovel)<br>10. Candesartan (Atacand)<br>11. Eprosartan (Teveten)<br>12. Telmisartan (Micardis) | See the topic «Diuretics» | See the topic «Adrenergic drugs» | See the topic «Anti-anginal and hypolipidemic agents» |
| **Mechanism of action** | 1. Inhibition of ACE → violation of the conversion of angiotensin I to angiotensin II → vasodilation, ↓ retension of Na and $H_2O$, ↓ stimulating effect on the sympathetic innervation → ↓ BP.<br>2. Inhibition of ACE → ↓ inactivation of bradykinin→ vasodilation. | 1. Antagonists of the angiotensin receptors → eliminate all the effects of angiotensin II (vasopressor action, ↑ production of aldosterone, stimulation of adrenergic innervation) | | | |
| **Pharmacological effects** | 1. Hypotensive<br>2. Protection of organs (cardio, angio - and nephroprotective action) | | | | |
| **Indications** | 1. Arterial hypertension<br>2. Diabetic nephropathy<br>3. CHF<br>4. Postinfarction condition<br>5. Intolerance to ACE inhibitors (7-12) | | | | |
| **Side effects** | 1. Dry cough, bronchospasm<br>2. Hyperkalemia<br>3. Deterioration of renal function in chronic renal failure. Hypotension | *Rarely:*<br>1. Hypotension<br>2. Dyspepsia<br>3. Hyperkalemia | | | |
| **Contraindications** | 1. Pregnancy and lactation<br>2. Stenosis of the renal arteries<br>3. Severe and chronic renal failure or hyperkalemia | 1. Pregnancy and lactation<br>2. Hyperkalemia | | | |

| | | | | |
|---|---|---|---|---|
| **NB!** | Classification of ACE inhibitors by duration of action: short-acting (captopril), intermediate-acting (enalapril), long-acting (ramipril, lisinopril).<br>The majority of ACE inhibitors (except captopril and lisinopril) are prodrugs. | | | |
| **Drug interactions** | - **A**ntidiabetic drugs: ↑ hypoglycemic action;<br>- diuretics (except potassium-sparing): ↑ the risk of hypotension;<br>- potassium-sparing diuretics or potassium preparations: ↑ the risk of hyperkalemia;<br>- β-blockers: ↑ cardioprotective and hypotensive action;<br>- α-blockers or Ca channel blockers: ↑ hypotensive action;<br>- sartans: ↑ antihypertensive, cardiovascular and renoprotective effects;<br>- - neuroleptics and tricyclic antidepressants: ↑ hypotensive effects, and possibility of postural hypotension;<br>- NSAIDs: ↓ hypotensive action;<br>- allopurinol, cytostatics, im immunosupressants, GCs, novocaineamide: ↑ risk of leucopenia;<br>- inhalation anesthetics: the possibility of significant blood pressure ↓. | - diuretics in high doses: possible arterial hypotension<br>- potassium-sparing diuretics or potassium preparations: ↑ the risk of hyperkalemia;<br>- indomethacin: ↓ the effectiveness of losartan.<br>- there is a report on the development of lithium toxicity after one-time use with lithium carbonate. | See the corresponding topics | - Valsartan and metformine ↓ Cmax and AUK of aliskiren for 28%.<br>Amlodipine, cimetidine ↑ Cmax and AUK of aliskiren for 29% and 19% respectively. Atotvastatin ↑ Cmax and AUK of aliskiren for 50%.<br>Ketoconazole ↑ Cmax and AUK of aliskiren for 80%.<br>Cyclosporine ↑ Cmax and AUK of aliskiren 2.5 and 5-fold, respectively.<br>Therefore, concomitant use of these drugs is not recommended.<br>2. Simultaneous use of aliskiren with potassium-sparing diuretics or potassium preparations can lead to hyperkalemia. |

## Antihypertensives (continued)

II[nd] line drugs are used when the I[st] line drugs are non-effective.

| Classification | Central-acting drugs | Ganglionic blockers | α-adrenoblockers | Sympatholytics | Potassium channels openers |
|---|---|---|---|---|---|
| **Drugs** | 1. Clonidine hydrochloride (Clopheline)<br>2. Moxonidine<br>3. Methyldopha (Dopegit, Aldomet) | ***Quaternary ammonium compounds:***<br>4. Hygronium<br>5. Azamethonium bromide<br>6. Hexamethonium<br>***Amines*:**<br>7. Pempidine | ***Selective α1-adrenergic blockers:***<br>8. Prazosin (Minipress)<br>9. Doxazosin (Cardura)<br>10. Terazosin (Kornam) | 11. Reserpine (Serpasil)<br>12. Octavin | 13. Minoxidil<br>14. Diazoxide |
| **Mechanism of action** | 1. Effect on α2-adrenoreceptors (1,3) and imidazoline I1 receptors (1,2) of solitary tract nuclei → oppression of VMC and ↑ tonus of the vagus nerve → ↓ cardiac workput, ↓ release of renin and ↓ TPR → ↓ AD (1-3)<br>2. Stimulation of peripheral pre-synaptic α2-adrenergic receptors → ↓ of norepi-nephrine release in synaptic cleft (1) | | | Violate noradrenalin storing in the vesicles → ↓amount of the mediator released in response to nerve impulses | Open potassium channels in the smooth muscle vessels → vasodilation and ↓ BP. |
| **Pharmacological effects** | 1. Hypotensive<br>2. Sedative (1,3)<br>3. ↓ IOP | See the topic «Cholinergic drugs. Nicotinic receptor agonicts. Nicotinic receptor antagonists (ganglionic blockers, neuromuscular blockers)» | See the topic «Adrenergic drugs» | 1. Hypotensive<br>2. ↓IOP (12)<br>3. Sedative, antipsyhotic (11) | 1. Hypotensive |
| **Indications** | 1. Resistant AH<br>2. Hypertensive crisis<br>3. Glaucoma (1)<br>4. AH in pregnant women (3)<br>5. Abstinence syndrome (1) | | | 1. Resistant AH | 1. Resistant AH<br>2. Hypertensivecrisis |
| **Side effects** | 1. Arterial hypotension<br>2. The withdrawal syndrome (1.3)<br>3. Drymouth (1,3)<br>4. Drowsiness | | | 1. Peripheral edema<br>2. Pain in the chest<br>3. Bradycardia<br>4. Dyspepsia | 1. Peripheraledema<br>2.Tachycardia, arrhythmia |
| **Contraindications** | 1. Arterial hypotension<br>2. Depression<br>3. Sick sinus syndrome, AV-blockade | Not for long-time administration | | 1. Acute stroke, MI<br>2. Arterial hypotension | 1. Pheochromocytoma |
| **NB!** | Other drugs with antihypertensive action: nitrates, dibazol, magnesium sulfate. | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Drug interactions** | 1. tricyclic antidepressants ↓ the effectiveness of antihypertensive drugs of the central action, the latter ↑ efficacy of tricyclic antidepressants<br>2. ↑ sedative effect of benzodiazepines (2)<br>3. β-blockers ↑ the risk of orthostatic hypotension (3)<br>4. NSAIDs ↓ hypotensive effect (3) | 1. Indomethacin and its analogs, glucocorticoids ↓ hypotensive effect.<br>2. Thiazide diuretics, other antihypertensives, H1–histamine receptor blockers, hypnotics, antipsychotics, narcotics analgesics, tricyclic antidepressants, local anesthetics ↑ hypotensive effect | 1. Other antihypertensive drugs and diuretics ↑ hypotensive effect<br>2. Estrogens, oral contraceptives, sympathomimetics, NSAIDs ↓ hypotensive effect | 1. Do not combine with MAO inhibitors<br>2.Digoxine ↑ the risk of bradycardia, arrhythmia, unconsciousness (11)<br>3. Barbiturates, ethanol ↑ CNS supression<br>4. NSAIDs ↓ hypotensive effect.<br>5. Combination with levodopa ↓ its effect. | 1. Nitrates, diuretics, β-blockers ↑ hypotensive effect.<br>2. Estrogens, oral contraceptives, sympathomimetics, NSAIDs ↓ hypotensive effect |

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**Antihypotensive drugs –** drugs increasing BP [1-4].

| Group | Drug |
|---|---|
| 1. α-adrenomimetics | Phenylephrine (Mezaton), Midodrine |
| 2. $\beta_1$-adrenomimetics | Dobutamine |
| 3. Dopaminomimetics | Dopamine |
| 4. Analeptics | Nikethamide (Coramine), Caffeine |
| 5. Non-selective α- and β-adrenomimetics | Epinephrine, Ethylphrine |
| 6. Plant stimulants | Extracts and tinctures of ginseng and eleutherococcus |

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**Hypertensive crisis management**

**Hypertensive crisis** an umbrella term for hypertensive urgency and hypertensive emergency. These two conditions occur when blood pressure becomes very high, possibly causing organ damage.

| *Hypertensive urgency (*no impairment of organ systems*)* | |
|---|---|
| Captopril | 12,5-50 мг orally or-sublingually |
| Nifedipine | 5-20 mg sublingually |
| Metoprolol | 25-50mg orally |
| Propranolol | 10-40 mg orally |
| Clonidine (clonidine) | 0,075-0,15 mg orally |
| Moxonidine | 0,4 mg orally |
| *Hypertensive emergency (*acute life-threatening impairment of organ systems, especially the CNS, cardiovascular systems or the kidneys. Management depends on complications*)* | |
| Sodium nitroprusside (for pulmonary edema, aortic dissection) | 0,25-10 mkg/kg/mini/v slowly |
| Nitroglycerine (for pulmonary edema, aortic dissection) | 50-200 mkg/mini/v slowly |
| Enalapril (for pulmonary edema, ischemic stroke, subarachnoid hemorrhage) | 1,25-5 mgi/v quickly |
| Labetalol (for aortic dissection, ischemic stroke, subarachnoid hemorrhage) | 20-80 mgquickly, 1-2 mg/minquickly |
| Furosemide (for pulmonary edema) | 40-200 mgi/v |
| Magnesium sulfate (for convulsions, eclampsia – complication of pregnancy) | 5-20 ml 20% solution i/v quickly |
| Clonidine | i/v 0,5-1,0 ml 0,01% solutionori/m 0,5-2,0 ml 0,01% solution |

## DIURETICS [1-4]

**Diuretics** are medicinal substances that increase diuresis

| Classification | Loop | Thiazide | Thiazide-like | Osmotic | Inhibitors of carbonic anhydrase |
|---|---|---|---|---|---|
| **Drugs** | 1. Furosemide<br>2. Torasemide<br>3. Ethacrynic acid | 4. Hydrochlorothiazide | 5. Chlorthalidone<br>6. Indapamide<br>7. Clopamide | 8. Mannitol | 9. Acetazolamide |
| **Mechanism of action** | Inhibit active transport of chloride ions in the ascending part of the loop Henle → reduce reabsorption $Na^+$, $K^+$, $Mg^{2+}$ and $Ca^{2+}$ | Inhibit the active transport of chloride ions in the distal tubules → reduce reabsorption $Na^+$, $K^+$ and $Mg^{2+}$, but $Ca^{2+}$ retention | | Increase osmolarity of urine in the proximal renal tubules and, to a lesser extent, in the descending part of the Henle loop → reduce water reabsorption | Inhibits carbonic anhydrase enzyme in the proximal tubules → reduces reabsorption of bicarbonate $Na^+$, promotes $K^+$, $Ca^{2+}$ elimination and acidosis |
| **Pharmacological effects** | 1. Diuretic (1-9). 2. Hypotensive (1-7). 3. Dehydration (8). 4. Decrease in intraocular and intracranial pressure (1-3, 8, 9). | | | | |
| **Indications** | 1. Hypertensive crisis (1, 3).<br>2. Arterial hypertension (1-7).<br>3. Forced diuresis (1, 3-5)<br>4. Heart failure, cirrhosis, toxicosis of pregnant women, nephrosis, nephritis (1-7).<br>5. Diabetes insipidus, glaucoma (4-7).<br>6. Edema of the brain and lungs, acute and chronic renal failure (1,3). | | | 1. Cerebral and pulmonary edema, glaucoma (8, 9).<br>2. Forced diuresis (in poisoning with water-soluble poisons) (8).<br>3. Edema associated with chronic heart failure, craniocerebral trauma, epilepsy, pulmonary emphysema, salicylate poisoning, severe hyperphosphatemia, metabolic alkalosis (9). | |
| **Side effects** | - Hypokalemia (1-7,9), - hypocalcemia (1-3), - hypochloremic alkalosis (1-7),<br>- hyponatremia (1-8), - hypervolemia (8), - metabolic acidosis (9),<br>- hypercalcemia (4-7), - hyperuricemia, hyperglycemia (1-4), - ototoxicity, (1-3). | | | | |
| **Contraindications** | - Allergy to sulfonamide-containing drugs<br>- anuria<br>- hypovolemia | - Allergy to sulfonamide-containing drugs<br>- Severe renal failure<br>- gout<br>- Hyperuricemia, hypokalemia | | - heart failure<br>- Severe renal insufficiency<br>- Anuria | - Severe forms of COPD<br>- Acute renal failure<br>- liver failure<br>- acidosis<br>- pregnancy |
| **NB!** | Incompatible with amino glycosides - risk of hearing loss. Eliminate $K^+$ and increases sensitivity to cardiac glycosides → exclude combination | Delay uric acid → danger of gout attack | | Has local irritating effect → isn't administered subcutaneously and intramuscularly | Do not take more than 5 days → metabolic acidosis. |
| | Alcohol intensifies the cardiotoxic effect of diuretics. To be taken before meal: 1, 5, 6. to be taken after meal: 2, 3, 4, 7. | | | | |

| | | | | |
|---|---|---|---|---|
| **Drug interactions** | 1.Aminoglycozides ↑ ototoxicity.<br>2. Cardiac glycosides ↑ risk of glycoside intoxication.<br>3. Anticoagulants ↑ the risk of bleeding. | 1. Antihypertensives: ↑ hypotensive effect.<br>2. ↑ effect of loop diuretics, vitamin D, cardiac glycosides, diazoxide, lithium preparations, anesthetics.<br>3. ↓ insulin action, hypoglycemic sulfonylurea derivatives, anticoagulants, uricosuric agents.<br>4. Glucocorticoids, amphotericin B ↑ risk of hypokalemia.<br>5. NSAIDs, anion exchange resins ↓ efficiency of thiazides<br>6. Quinidine ↑ the risk of torsades de pointes. | 1. combination with cardiac glycosides ↑ risk of toxicity associated with hypokalemia (8) | 1. diuretics: ↑ diuretic action<br>2. ↑ hypoglycemic effect of insulin and oral hypoglycemic agents.<br>3. Salicylates, digitalis drugs, ephedrine, carbamazepine, non-depolarizing neuromuscular relaxants ↑ toxic effects. |

## **Diuretics** (continued)

| **Classification** | **Potassium-sparing** | **Different groups with a diuretic effect** | **Vegetable agents: Monopreparations and combined *** |
|---|---|---|---|
| **Drugs** | 1. Spironolactone<br>2. Triamterene<br>3. Amyloride | **1.** Aminophylline<br>**2.** Cardiac glycosides (Digoxin, Digitoxine, Strophantine, etc.) | 6. Leaves of cranberries<br>7. Bearberry Leaves<br>8. Grass horsetail field<br>9. Artichoke extract (hofitol)<br>10. Kanefron *<br>11. Phytolysin *<br>12. Cyston * |
| **Mechanism of action** | 2. Blocks aldosterone receptors in collective and distal tubules → reduces reabsorption $Na^+$, $Cl^-$ and water, detain $K^+$, $Mg^{2+}$ (1).<br>3. Reduces the permeability of epithelial membranes of collecting tubules for ions $Na^+$ (2,3) | 2. Improve renal circulation and filtration processes in the glomeruli | Contain biologically active substances that improve kidney circulation and filtration processes, partially affect tubular reabsorption |
| **Pharmacological effects** | 1. Diuretic (1-12). 2. Hypoazotemic (9-12). 3. Anti-inflammatory, antimicrobial, spasmolytic (6, 7, 10-12).<br>4. Choleretic (6,7). 5. The vasodilator (4,5). 6. Hypotensive (1-4). | | |
| **Indication** | 2. Hyperaldehydronism, liver cirrhosis (1).<br>3. Together with saluretic, cardiac glycosides for prophylaxis of hypokalemia, chronic heart failure, arterial hypertension, nephritis (1-3) | 2. Complex therapy of edema in cardiac and renal insufficiency (4, 5).<br>3. Disorders of cerebral circulation, broncho-obstructive processes (4). | 1. Prevention of edema in cardiovascular and renal pathology (6-12).<br>2. Inflammatory processes of the urinary bladder and urinary tract, nephritis (6, 7, 10-12).<br>3. Urolithiasis disease (6).<br>4. Cholocystitis, chronic hepatitis (9). |
| **Side effects** | - Hyperkalemia, hyponatremia (1-3), - gynecomastia, thrombosis (1),<br>- hyperglycemia, hyperuricemia (2), - nausea, vomiting, headache, lowering blood pressure (1-4,10). | | |
| **Contraindications** | - Hyperkalemia,<br>- Acute renal failure,<br>- Liver cirrhosis,<br>- Macrocytic anemia (3). | - Acute myocardial infarction,<br>- Epilepsy, stomach and duodenal ulcer (4),<br>-intoxication with glycosides, unstable angina, pronounced bradycardia, AV blockade (5). | - Hypersensitivity<br>- glomerulonephritis, phosphate nefrourolithiasis (11). |
| **NB!** | - do not combine with ACE inhibitors (risk of hyperkalemia). -reinforcing the action of thiazide diuretic. | **Aminophylline** is forbidden to be taken simultaneously with the xanthenes-containing products, glucose solution. **Cardiac glycosides** can easily provoke glycoside intoxication! | During the storage of Kanefron's solution, slight turbidity or precipitation of a slight precipitate is possible; it does not affect the effectiveness of the drug. |
| | Diuretics are recommended to be taken in the morning to avoid nocturia. Also development of tolerance is possible. After meal: 2, 6, 11, 12. During meal: 7. | | |

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| **Drug interactions** | 1. NSAIDs: ↓ diuretic and Na-uretic effects, ↑ risk of renal failure<br>2. Combination with anticoagulants: ↓ anticoagulant action<br>3. ACE inhibitors, potassium drugs ↑ the risk of hyperkalemia | 1. Quinolons ↑ the risk of seizures (4)<br>2. Sympathomimetics lead to synergism and ↑ arrhythmia risk (4)<br>3. The combination with cardiac glycosides: their toxicity ↑ (4)<br>4. Glucocorticosteroids lead to mutual ↑ in adverse effects (4)<br>5. Diuretics ↑ the risk of hypokalemia (4) | 1. ↑ effects of anticoagulants, NSAIDs, hypoglycemic drugs, medicines containing lithium salts and MAO inhibitors (11)<br>3. Prolongs action of phentobarbital and paracetamol (11)<br>4. Can ↓ absorption of drugs in the small intestine, including β-carotene, α-tocopherol (11)<br>5. In connection with a diuretic drug (11) you should consider the possibility of accelerating the elimination of other drugs. |

## DRUGS ACTIVATING AND CORRECTS METABOLISM (CARDIOCYTOPROTECTORS)

| Drugs | Trimethazidine | Meldinoum | Thiotriazoline |
|---|---|---|---|
| **Mechanism of action** | inhibits the β-oxidation of fatty acids by inhibiting 3-ketoacyl-CoA thiolase, has membrane stabilizing action | inhibits the formation of carnitine, which provides transport of FFA to mitochondria | optimizing the energy intracellular exchange aimed at reducing oxygen demand during synthesis of ATP |
| **Pharmacological effects** | - antianginal<br>- anti-ischemic<br>- anti-hypoxic<br>- cytoprotective | - antianginal<br>- anti-ischemic<br>- anti-hypoxic<br>- cytoprotective<br>- improving efficiency, reducing the symptoms of mental and physical stress<br>- activation of tissue and humoral immunity | - antianginal<br>- anti-ischemic<br>- anti-hypoxic<br>- cytoprotective<br>- activation of tissue and humoral immunity |
| **Indications** | 1. IHD: prevention of stable angina attacks (in the combined therapy); | 1. CHD (angina, myocardial infarction)<br>2. Chronic heart failure<br>3. dishormonal cardiomyopathy | 1. IHD (AMI, angina)<br>2. CHF - cardiomyopathy<br>3. functional diseases of CVS |
| **Side effects** | 1. extrapyramidal disorder<br>2. orthostatic hypotension<br>3. dyspeptic symptoms<br>4. skin rash, itching, hives, hyperemia | 1. tachycardia, changes in blood pressure<br>2. psychomotor agitation<br>3. dyspeptic symptoms<br>4. itching, redness, rash, swelling, | 1. tachycardia, changes in blood pressure<br>2. breathlessness and suffocation<br>3. dyspeptic symptoms<br>4. itching, redness, rash, swelling |
| **Contraindications** | 1. hypersensitivity<br>2. Pregnancy, lactation<br>3. age before 18 years | 1. increased intracranial pressure<br>2. Pregnancy, lactation<br>3. age of 18 years | 1. hypersensitivity<br>2. Pregnancy, lactation<br>3. age before 18 years |
| **Drug interactions** | No data | 1.↑ effect of antianginal drugs, some antihypertensive drugs, cardiac glycosides.<br>2.nitroglycerin, nifedipine, alfa-blockers, and peripheral vasodilators mild tachy-cardia, hypotension can appear (combination requires caution). | 1. ↑ the effectiveness of anti-arrhythmic, antianginal and initropic drugs. |