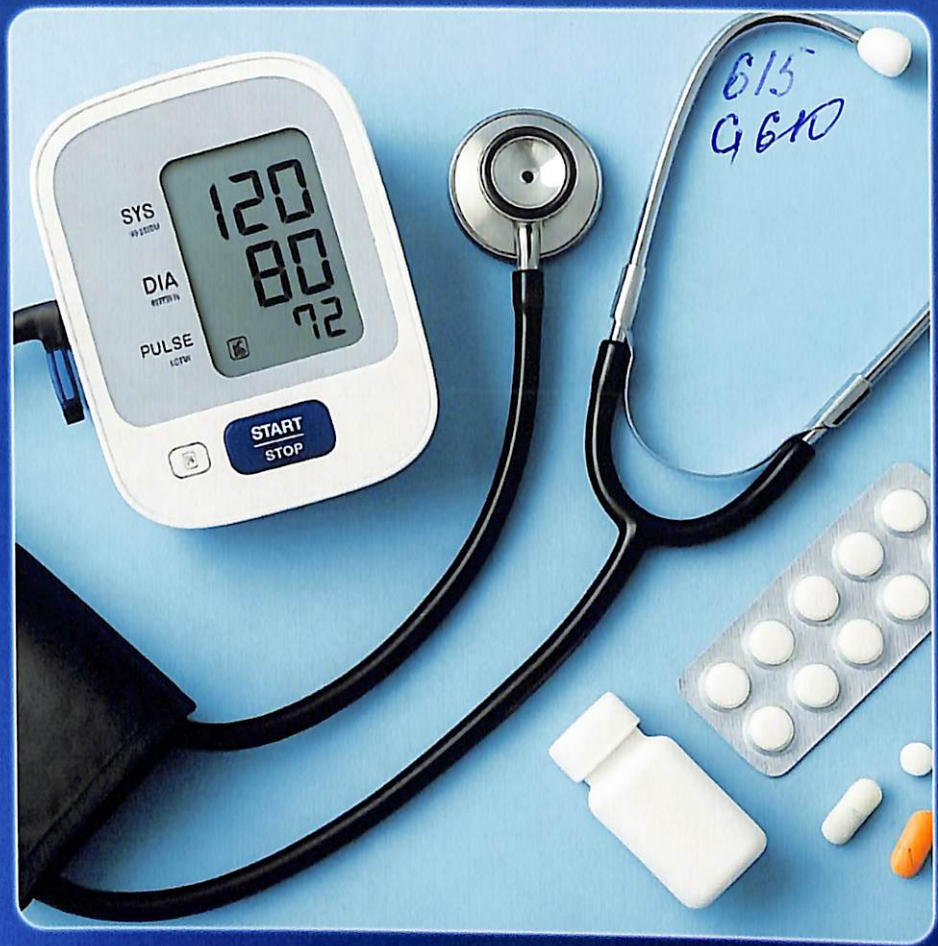
Siddikov O.A. Abdukodirova Sh.B.
Nuraliyeva R.M. Davurova L.Sh. Usmonova Z.M.

CLINICAL PHARMACOLOGY ANTI-HYPERTENSIVE DRUGS

Study guide



REPUBLIC OF UZBEKISTAN
MINISTRY OF HEALTH
SAMARKAND STATE MEDICAL UNIVERSITY

DEPARTMENT OF CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY
ANTI-HYPERTENSIVE DRUGS

Study guide

SAMARKAND 2025

UDC: 615.03(075.8)

BBC: 52.81ya73

CLINICAL PHARMACOLOGY ANTI-HYPERTENSIVE DRUGS, SIDDIKOV O.A., ABDUKODIROVA SH.B., NURALIYEVA R.M., DAVUROVA L.SH., USMONOVA Z.M., SAMARKAND 2025/ARTEX NASHR

Authors:

Siddikov O.A. - head of the department of clinical pharmacology, PhD

Abdukodirova Sh.B. - assistant of the department of clinical pharmacology

Nuraliyeva R.M. - assistant of the department of clinical pharmacology

Davurova L.Sh. - assistant of the department of clinical pharmacology

Usmonova Z.M. - assistant of the department of clinical pharmacology

Reviewers:

Nasirova A.A. - Samarkand State Medical University, Department of Internal Medicine , Faculty of Pediatrics PhD, Assoc. Prof

Nurbaev F.E. - Bukhara State Medical Institute, head of Internal Medicine propaedeutic department DSc, dots

ISBN: 978-9910-8396-4-1

2812

Annotation

This tutorial is necessary for students of the 5th year of general medicine, pharmacy, and professional education, 6th year of pediatric work, 4th year of Dentistry, 2nd year of higher nursing, as well as graduate and clinical residency students to thoroughly master the clinical pharmacology of antihypertensive drugs. It includes questions for the theoretical part, the practical part of the topic of Clinical Pharmacology of antihypertensive drugs, and the control related to this topic, based on the science of Clinical Pharmacology.

CONTEXT-SPECIFIC SHORT FORMS

AEB - Angiotensin enzyme blockers

BPRE - Blood pressure–regulating enzyme

MAP - Mean arterial pressure

AVN - AV node

BAB - Beta-adrenoblockers

BBB – blood-brain barrier

VLDLP - very low-density lipoproteins

LDLP - low-density lipoproteins

HDLP - high-density lipoproteins

ISMA - intrinsic sympathomimetic activity

MAO - monoamine oxidase

MCRA - mineralocorticoid receptor antagonists

GIT - gastrointestinal tract

RAAS - renin-angiotensin-aldosterone system

SAS - sympathoadrenal system

ChHF - chronic heart failure

EF is ejection fraction

FD – pharmacodynamics

FC - pharmacokinetics

SGA - supraglomerular apparatus

IHD is an ischemic heart disease

HR – heart rate

WPW – Wolff-Parkinson-White

INTRODUCTION

One of the main tasks set out in the National Training Program is the training of highly qualified, all–around, mature medical personnel. An important place in this is occupied by improving the quality of teaching, preparing literature according to the requirements of the time.

It is of great importance to teach clinical pharmacology to students studying in the medical direction, since it is necessary that future doctors can master the properties of drugs and apply this knowledge in clinical practice. The doctor should know the principles of conducting not only effective, but also safe pharmacotherapy.

According to research, hypertension is one of the main causes of disability on our planet. One of the most dangerous causes of ischemic heart disease, acute myocardial infarction, and cerebral stroke is arterial hypertension. Arterial hypertension problems account for 9.5 million fatalities worldwide each year. According to research, arterial hypertension affects 20% to 30% of the elderly population. Effective treatment of arterial hypertension can control blood pressure and prevent complications. In the treatment of Arterial hypertension, mainly 5 groups of antihypertensive drugs are used. Although the only feature for them is an effective lowering of blood pressure, each group of drugs has its own characteristics. When conducting effective and safe pharmacotherapy, when choosing an individual drug for the patient, it is necessary to know these properties and use them rationally.

In addition to providing detailed information on the pharmacodynamics, pharmacokinetics, indications for use, adverse effects, contraindications, and interaction with other drugs, this tutorial also provides up-to-date information on specific aspects of the use of antihypertensive drugs in clinical practice.

The key to treating arterial hypertension safely and effectively is having a thorough understanding of the pharmacodynamic, pharmacokinetic, and nonspecific effects of medications. As a result, it becomes feasible to properly choose antihypertensive medications, decide on the best way to take them, evaluate their efficacy and safety, and avoid any unintended side effects. The manual also sets up

control questions on the subject so that antihypertensive drugs can be thoroughly mastered the clinical pharmacology.

The tutorial, created by the authors, is designed for students in the Faculty of Pediatrics, 5th-year students of general medicine, pharmacy, professional education, 2nd-year students of higher nursing, clinical internships, and master's programs, who are specializing in Medicine. We hope that it will aid students in thoroughly understanding the clinical pharmacology of antihypertensive drugs.

CLINICAL PHARMACOLOGY OF β -ADRENOBLOCATORS

β-adrenoblocators (BABs) are medicines that exhibit their effects by blocking β – β-adrenoreceptors located in various organs and tissues β-adrenoblocators have been used in clinical practice since the 60s of the last century [22].

β-adrenoblocators have antianginal, antiischemic, hypotensive, antiarrhythmic, and organoprotective effects.

The following types of β-adrenoreceptors exist - β1-and β2-adrenoreceptors.

Blocking β1-adrenoreceptors results in the following pharmacodynamic effects:

A reduction in heart rate (negative chronotropic or bradycardic effect)

A decrease in myocardial excitability (negative dromotropic, antiarrhythmic effect)

A reduction in myocardial contractility (negative inotropic, antiarrhythmic effect) - Reduces pressure in the Portal vein system (at the expense of reducing blood circulation in the liver and mesenteric arteries);

- Reduces intraocular fluid formation (decreases intraocular pressure);

- Psychotropic effect (typical for BAB passing through BBB – impotence, drowsiness, depression, insomnia, nightmares, hallucinations, etc.;

- When taking a short-acting BAB is suddenly touched, a "cancel" syndrome develops (hypertensive reaction, recurrence of coronary insufficiency, non-stable stenocardia, acute myocardial infarction, or sudden death).

As a result of partial or full blockage of β2-adrenoreceptors, the following pharmacodynamic effects are observed:

- increased tone of the bronchi's smooth muscles, which can lead to bronchospasm in extreme circumstances [22];
- gluconeogenesis and the stoppage of glycogenolysis, which disrupt the flow of glucose from the liver to the blood (as a result of enhancing the effect of insulin and other blood sugar-lowering medicines);

- Increased arterial smooth muscle tone- arterial vasoconstriction (resulting in increased peripheral vascular tone), coronary spasm, decreased blood circulation in the kidneys, and decreased blood circulation in the limbs [22].

Table 1.1

Location of β-adrenoreceptors in organs and tissues, β1 / β2 ratio, stimulation result

Organ and tissue	Receptor	Stimulation results in
In synapses at the end of the nerve	β_2	Increased norepinephrine separation
Cholinergic nerve endings	β_2	Increased acetylcholine separation
Eye	β_1	Increased formation of intraocular fluid
Tear glands	β_2	Increased tear fluid separation
Heart (myocardium)	$\beta_1 > \beta_2$	Increase myocardial contraction force, number, and excitability, AV-permeability
	β_2	Increase in myocardial contraction force and number.
Blood-vessels	β_2, β_1	Coronary artery dilation
	β_2	Expansion of other arteries and veins
Kidneys (JuGA)	β_2, β_1	Increased Renin secretion Ingestion of sodium is reabsorbed in the ducts
Bronchi	$\beta_2 > \beta_1$	Bronchodilation
Salivary glands	β_1	Increased amylase secretion
Esophagus	β_2, β_1	Decreased esophageal peristalsis, decreased esophageal inferior sphincter tone
Stomach	β_2, β_1	Attenuation of gastric peristalsis, decreased secretion of hydrochloric acid
Intestines	β_2, β_1	Attenuation of intestinal peristalsis
Bladder	β_2	Detrusor contraction

Uterus	β_2	Relaxation of the muscles of the uterus (in pregnancy) [22].
Skeletal muscle	$\beta_2 > \beta_1$	Glycogenolysis and tremor enhancement
Liver	$\beta_2 > \beta_1$	Increased gluconeogenesis and glycogenolysis (increased blood glucose levels)
Pancreas	$\beta_2 > \beta_1$	Increased secretion of Insulin, glucagon somatostatin, and inhibition of external secretory function
Adipose tissue	β_2	Increased lipolysis

The molecular structure of β-adrenoreceptors consists of a sequence of anino acids. Stimulation of β-adrenoreceptors activate the G-protein, which in turn stimulates the enzyme adenylate cyclase. This activation of adenylate cyclase leads to the production of cyclic AMP from ATP. The increase in cyclic AMP activates protein kinase, which then phosphorylates calcium channels, enhancing the entry of calcium into the cell during voltage-gated depolarization, this leads to a calcium "flash" and the release of calcium from the sarcoplasmic reticulum (the storage depot) increases, as does cytosolic calcium. An increase in cytosolic calcium increases the frequency and effectiveness of impulse transmission, as well as the strength of muscle contraction.

BAB prevents the stimulating effect of β-agonists on β-adrenoreceptors, causing the development of negative chronotropic, dromotropic, batmo, and inotropic effects [22].

Pharmacological effects of BAB.

Cardiac effects:

1. Reduced cardiac contraction force (negative inotropic effect)
2. Decrease in the number of heart contractions (negative chronotropic effect)
3. Conduction attenuation (negative dromotropic effect)

4. Decrease in automatism (negative batmotropic effect-mainly to the sinus and AV node)

5. Reduces the release of renin into the blood (by blocking β1-receptors in the Yuga), which reduces blood pressure by reducing the formation of angiotensin II.

6. The left ventricle helps reduce myocardial hypertrophy.

7. Antianginal effect: It decreases myocardial oxygen demand by reducing inflammation and lowering blood pressure [22];

- improves coronary blood circulation (improves diastolic perfusion);

- Collateral improves blood circulation (improves blood supply to the ischemic zone);

- strengthens cells and lysosomal membranes;

- improves oxygen separation from oxyhemoglobin;

- reduce platelet aggregation.

Lipophilic β-adrenoblocators (lacking internal sympathomimetic activity) can prevent myocardial infarction, which can develop after stenocardia.

Hydrophilic β-adrenoblocators (with intrinsic sympathomimetic activity) do not affect the prognosis of ischemic heart disease.

8. *Antihypertensive effect:*

- reduces blood from the heart (slows down the shortening activity of the left ventricle and reduces the number of heart contractions)

- reducing renal secretion

-blocks presynaptic β2-adrenoreceptors to reduce norepinephrine release from postganglionic sympathetic nerve endings (selective unbranched β-adrenoblocators)

increases the excretion of vascular dilators (E2 and I2 prostaglandins, nitric oxide, components of natriuretic factor)

- reduces peripheral resistance (carvedilol, propranolol, nebivolol, pindolol)

The elongate acts on the vascular propulsion center in the brain (lipophilic β-adrenoblocators).

9. Vasodilating effects of β-adrenoblocators include the following linkage:

- because it has both β-adrenoblocking and α-adrenoblocking effects (carvedilol, propranolol)

- for causing nitrogen oxide separation from endothelial cells (nebivolol)

- for having intrinsic sympathomimetic activity to β2-receptors of blood vessels (pindolol) [22].

Extracardial effects:

1. Bronchospasm (blocking β2-adrenoreceptors in the bronchi reduces the stimulating effect of the GS protein on adenylate cyclase, which reduces cAMP synthesis. Depletion of cAMP within the cell leads to inactivation of the cAMP-binding protein kinase, which leads to increased activity of myosin light chain kinase. The Light chains of myosin are phosphorylated by myosin light chain kinase, causing contraction of smooth muscle. Bind to actin, causing the ciliary muscles to contract.)
2. Increases the tone of the uterine muscle (through the same mechanism as mentioned above).
3. Stimulates the gastrointestinal system, leading to abdominal pain, diarrhea, and nausea, and vomiting.
4. Narrowing the arterioles and venules increases peripheral resistance (up to Reyno syndrome)
5. The level of triglycerides in the blood increases, and the level of cholesterol in lipoproteins with low density increases (atherogenic property).
6. Hypoglycemia results from an increase in the liver's production of glycogen from glucose.
7. The pancreas blocks β2-receptors in the Langerhans islets, reducing insulin secretion, leading to hyperglycemia (the effect on carbohydrate metabolism is not observed in healthy people).

Table 1.2

The effect of β1-adrenoblocators on lipid metabolism.

The drug	Lipids and lipoproteins in the blood		
	General triglycerides or triglycerides in lipoproteins with very low density	Cholesterol in total cholesterol or low-density lipoproteins	The density of cholesterol in your low-density lipoproteins
Atenolol	↑	0	0/↓
Betaxolol	0/↑	0	0/↓
Bisoprolol	↑	0	0/↓
Carvedilol	0/↓	0/↓	0/↑
Metoprolol	↑	0	0/↓
Nadolol	↑	0	0/↓
Pindolol	0	0	↓/0/↑
Propranolol	↑	0	↓
Sotalol	↑	0	↓
Timolol	↑	0	↓
Celiprolol	0/↓	0/↓	0/↓

Note: ↑ -increase; ↓ - decrease; ↓/0/↑ - the information in the literature is different.

Tible 1.3

Comparative description of the pharmacodynamic effects of β-blockers

The drug	Selectivity	ISMA	Membrane stabilizing effect	VHR	Reaction of the heart to physical	Cardiac contractility	Total peripheral	Arterial pressure	Atrioventricular conduction	Antiarrhythmic effect
Atenolol	+	-	-	↓	↓	↓	↑/0	↓	↓	strong
Metoprolol	+	-	?	↓	↓	↓	↑/0	↓	↓	strong
Nadolol	-	-	moderate	↓	↓	↓	↑	↓	↓	strong
Pindolol	-	strong	Powerless	0	↓	0/↓	↓	↓	0/↓	strong
Propranolol	-	-	moderate	↓	↓	↓	↑	↓	↓	strong
Talinolol	+	weak	weak	↓	↓	↓	↑	↓	↓	strong
Timolol	-	-	-	↓	↓	↓	↑	↓	↓	strong

Eslatma: ↑ - depletion;↓ - increase; 0 – does not affect; ? – No information.

Factors affecting the pharmacological parameters of β1-adrenoblocators:

- β1-selectivity (cardioselectivity) and selectivity levels;

- membrane-stabilizing effect;
- degree of lipophilicity;
- intrinsic sympathomimetic activity;
- additional vasodilating effect;
- Duration of action of the drug [22].

Table 1.4

β1-adrenoblocator cardioselectivity index

The drug	**β1 / β2 ratio**
Propranolol	1,8:1 (nonselective)
Metoprolol	1:20
Atenolol	1:35
Betaksolol	1:35
Bisoprolol	1:75
Nebivalol	1:300

Prolonged use of BABs leads to an increase in the number of β-adrenoreceptors, which is why the effect of BAB gradually increases, and when they are suddenly stopped, a strong sympathomimetic (especially in the short-acting BAB) [22] effect of catecholamines in the blood is observed.

Table 1.5

Classification of β-adrenoblocators

Nonselective beta-adrenoblocators			**Cardioselective beta-adrenoblocators**		
No specific adrenomimetic activity	*Has specific adrenomimetic activity*	*Vasodilating effect has*	*Specific adrenomimetic activism non*	*Specific Intrinsic sympathomimetic activity*	*has Vasodilating effect*
Propranolol Nadolol Sotalol Timolol	Oxprenolol Bopindolol Pindolol	Pindolol	Atenolol Bisoprolol Metoprolol Esmolol Betaxolol	Alprenolol Acebutolol Talinolol	Carvedilol Nebivolol (Bivolol) Labetalol Proxodolol

Some BAB have intrinsic sympathomimetic activity (ISMA) properties – alprenolol, asebutalol, oxprenolol, penbutolol, pindolol, practolol, talinolol. The intrinsic sympathomimetic activity characteristic is strong in Pindolol. The nature of BAB's intrinsic sympathomimetic activity prevents the heart from decreasing the number of contractions in a calm state. This makes it possible to use BAB, which has a characteristic of intrinsic sympathomimetic activity in patients with a low number of heart contractions, but such BAB cannot be used in patients with early morning heart attacks.

The selectivity of selective BAB depends on their dosage, which means that as the dose of the drug increases, their selectivity decreases.

BAB – propranolol, betaxolol, bisoprolol, oxprenolol, pindolol, talinolol, which have antiarrhythmic, membrane-stabilizing effects [22].

All β-adrenoblocators are divided into 3 groups:

- lipophilus;
- hydrophilic;
- both lipophilic and hydrophilic.

Betaxolol, carvedilol, metoprolol, oxprenolol, propranolol, and timolol are examples of lipophilic β-blockers.

Sotalol, nadolol, and atenolol are hydrophilic β-blockers.

Asebutalol, bisoprolol, pindolol, and seliprolol are β-blockers that are both hydrophilic and lipophilic.

Lipophilic BAB has a short half-life (T½), is metabolized in the liver (80–100%), and is primarily eliminated from the body through the liver. It is also quickly and nearly entirely absorbed (more than 90%) from the digestive system [22].

Table 1.6

Pharmacokinetic indicators of lipophilic BAB

The drug	β_1-Selec-Tivity	ISMA/α-adrenob locada	T½ clock	Plasma protein binding% %	Elimination	
					Throug h the liver	Throug h the kidney
Alprenolol	0	+2/0	2-3	85	100	0
Bevantolol	+2	0/0	2-4	95	100	0
Nebivolol	+8	0/0	10-50	98	99,5	0,5
Betaxolol	+2	0/0	16-22	50	85	15
Carvedilol	+1	0/+1	6-7	?	100	0
Labetalol	0	$+1\beta_2/+2$	3-4	10	100	0
Metoprolol	+2	0/0	3-4	10	100	0
Oxprenolol	0	$+2\beta_1 = \beta_2$	1-4	80	100	0
Propranolol	0	0/0	2-5	93	100	0
Timolol	0	0/0	4-5	10	80	20

The condition of blood circulation in the liver affects the metabolism of the BAB, the frequency of delivery and the single dose. When treating individuals with heart failure, liver cirrhosis, and advanced age, this should be considered. Because the rate of BAB clearance in severe liver failure is precisely related to the level of liver function, the rate of BAB elimination falls by the same percentage as the decline in liver function. Lipophilic BAB reduces blood circulation in the liver when applied for a long time, as a result of which it reduces both its metabolism and the metabolism of other lipophilic drugs. This can cause the BAB to extend its half-release period, reduce the single or daily dose or daily frequency of administration, or increase the effect of the BAB or increase the dose in the blood. Taking high smoking, alcohol, rifampicin, barbiturates, diphenhydramine, and other hepatoinductors speeds up the metabolism and elimination of BAB. Preparations that slow blood circulation in the liver, hepatoingibitors, slow down the metabolism

and elimination of BAB. Therefore, in severe disorders of liver function, the dose of BAB is corrected.

The lipophilic BAB passes well from the blood-brain barrier, the histoplasntar barrier, to the ocular chambers.

Hydrophilic BAB is excreted mostly unchanged (40-70%) by the kidneys and has a long (6-24 hours) half-release period. They are poorly absorbed from the gastrointestinal tract, and are also not absorbed in one rhythm.

A decrease in the rate of ball filtration in the kidneys (in elderly patients, in chronic kidney failure) slows the elimination of hydrophilic BAB, which is why it is required to reduce their dose or frequency of administration, that is, when dosing BAB [22], it is possible to target the amount of creatinine in blood plasma or creatinine clearance. How many times the creatinine clearance decreases from the norm should the dose or frequency of administration of BAB be reduced so many times?

Table 1.7

Pharmacokinetic indicators of hydrophilic BAB

The drug	β_1-selectivity	ISMA /α-adrenoblocada	T½ clock	Plasma protein binding% %	Elimination	
					Through the liver	Through the kidney
Atenolol	+2	0/0	6-9	5	10	90
Carteolol	0	+1/0	5-6	25	10	90
Nadolol	0	0/0	14-24	25	0	100
Penbutolol	0	+1/0	24-27	98	5	95
Sotalol	0	0/0	7-18	0	20	80
Talinolol	+2	+1/0	?	?	10	90
Esmolol	+2	0/0	9 min	55	0	0

Impaired renal function does not require a dose correction of penbutalol from hydrophilic BAB. Nadolol does not reduce blood circulation in the kidney and the rate of blood filtration, as it has a vasodilating effect on renal blood vessels.

BAB, whose effect is very short, breaks down in the blood under the action of esterase, and they are only injected intravenously. The half-release period of BAB, which breaks down under the action of esterase in the blood, is very short, 30 minutes after the intravenous drip is stopped [22]. After the effect disappears. Such preparations are mainly used in acute cases (acute ischemia, during operationalism, or in control of ventricular rhythm in postoperative ventricular paroxysmal tachycardia). Patients with hypotonia or heart failure are considered safe to use the short-acting BAB, while those with bronchoobstruction are considered safe to use β1-selective BAB (esmolol).

Amphiphilic BAB (asebutolol, bisoprolol, pindolol, seliprolol) is also fat-soluble in water [22], which is excreted from the body both through the liver and through the kidneys.

Table 1.8

Pharmacokinetic indications of amphiphilic BAB

The drug	β_1-selektivity	ISMA /α-adrenoblocada	T½ clock	Plasma protein binding %	Elimination	
					Through the liver	Through the kidney
Acebutolol	+1	$+1\beta_1/0$	3-4	25	60	40
Bisoprolol	+3	0/0	10-12	30	50	50
Pindolol	0	$+3\beta_2$	3-4	57	60	40
Celiprolol	+2	$+2\beta_2/+1$	5-6	30	40	60

Since amphiphilic beta-blockers are eliminated from the body via both the liver and kidneys, they can be safely used in individuals with mild liver or kidney dysfunction. Excretion of these drugs from the body is only impaired in severe kidney and liver failure. In such cases, the daily dose of amphiphilic BAB isreduced to 1.5-2 barovars. Pindolol from amphiphil BAB can increase blood circulation in the kidneys in chronic kidney failure [22].

The number of heart contractions, blood pressure, AV-permeability, and clinical effect are all taken into consideration while choosing the dosage of BAB. BAB should be administered at a starting dose of 1/8 to 1/4 of the typical therapeutic dose. The drug's dosage is raised every three to seven days to an average therapeutic level when there is insufficient clinical effect. In this instance, when the patient is vertical, the heart contracts 55–60 times per minute, and the systolic blood pressure is 100 mm, which shouldn't be lower [22]. When BAB is taken consistently, its full effects are shown after four to six weeks. The hypotensive and bradycardiac effects of BAB last longer than the antianginal effects.

Table 1.9

Pharmacokinetic indications of BAB

The drug	Dosage mg/day	Absorption %	Biological appropriateness %	T1/2 clock	Protein binding, %	Release		Active metabolite
						Through the liver	Through the kidney	
Alprenolol	400	90-100	10	2-3	85	100	0	+
Atenolol	100	46-62	40-50	6-9	5	10	90	-
Asebutalol	600-1200	90-100	40-60	3-4	25	60	40	+
Betaxolol	-	-	80-90	15-20	50	85	15	-
Bisoprolol	-	-	85	10-12	30	50	50	?

Carvedilol	-	-	?	6-7	?	100	0	?
Labetolol	600-1200	90-100	?	3-4	50	100	0	-
Metoprolol	150-300	95-100	50	3-4	10	100	0	-
Nadolol	80-240	15-25	30	14-24	25	0	100	-
Oxprenolol	120-400	70-95	30-50	1-4	80	100	0	-
Penbutolol	-	-	?	24-27	98	5	95	-
Pindolol	7,5-22,5	90-100	90	3-4	57	60	40	-
Propranolol	120-400	95-100	30	2-5	93	100	0	+
Sotalol	-	-	60-70	7-18	0	20	80	-
Talinolol	100-300	70-75	?	10-14	60	40	60	-
Timolol	15-45	90-100	70	4-5	10	80	20	-
Seliprolol	-	-	30-70	5-6	30	40	60	+
Esmolol	-	-	-	9 min	55	0	0	-

Effects of bab in ischemic heart disease and stenocardia.

BAB has antianginal and antiischemic effects. The mechanism of origin of these effects is due to their action on hemodynamic parameters, that is, BAB lowers blood pressure, reduces heart function and the number of heart contractions, prolongs the diastole period, resulting in a decrease in myocardial oxygen demand.

A decrease in systemic blood pressure reduces myocardial contraction, reduces the central adrenergic effect (drugs passing through GEB), and renin activity in blood plasma (up to 60%).

Internal simpatomimethicity reduces overall mortality, sudden death, and risk of re-myocardial infarction by having cardioprotective effects in patients with lipophilic BAB (regardless of selectivity), acute myocardial infarction without activity. The cardioprotective effect is mainly characteristic of metoprolol, propranolol, and timolol. Lipophilic BAB with intrinsic sympathomimethicity activity has few cardioprotective effects. The cardioprotective effects of carvedilol and bisoprolol are the same as metoprolol. Hydrophilic BAB (atenolol and sotalol) does not affect the rate of sudden death and overall mortality in ischemic heart disease.

Table 1.10

Cardioprotective effect of BAB in patients with myocardial infarction

BAB teams	Reduced risk of death
Hydrophilic BAB (atenolol and sotalol)	10
ISMA BAB (alprenolol, oxprenolol, pindolol, practolol)	11
ISMA mortality BAB	28 ($p < 0,05$)
Non-selective BAB (propranolol, sotalol, thymolol)	27 ($p < 0,05$)
β_1-selektivity BAB [22] (atenolol va metoprolol)	31 ($p < 0,05$)
Lipophilic BAB (metoprolol, propranolol, timolol)	30 ($p < 0,05$)

Beta-blockers are recommended for secondary prevention in all patients with ischemic heart disease, with Q-tooth myocardial infarction, for at least 3 years without indication against this group of drugs, especially in patients over 50 years of age, left ventricular anterior wall infarction, early postinfarct stenocardia, when the number of heart contractions is high, cardiac ventricular rhythm disturbances, when there are manifestations of stable heart failure [22].

Effects of bab in chronic heart failure.

In the treatment of chronic heart failure, BAB enters the main group of drugs when the volume of ejection fraction (EF) is equal to or small at 35% (proof rate a).

The therapeutic effect of BAB in the treatment of chronic heart failure is due to the additional effects of the neurogumoral mechanism, sympathoadrenal (SAS) and renin-angiotensin-aldosterone systems (RAAS) in the development of chronic heart failure. Activation of SAS can lead to increased myocardial oxygen needs, increased ischemia, cardiac arrhythmias, myocardial remodeling, hypertrophy, apoptosis, and necrosis. The additional effect of BAB also includes the positive effect on left ventricular remodeling and the volume of ejection fraction . BAB has an anti-ischemic effect, which means it is effective in reducing the risk of sudden death (bisoprolol), as well as its use in chronic heart failure, leading to a rapid decrease in mortality (for any reason).

The positive effects of beta-adrenoblockers (BAB) in chronic heart failure include:

- Reduces the death and dysfunction of cardiomyocytes caused by necrosis and apoptosis.
- Decreases the number of cardiomyocytes in a dormant (hibernating) state.
- Increases β-adrenoreceptor activity;
- reduces myocardial hypertrophy.
- Reduces the number of heart contractions, especially in the swinging arrhythmia observed in physical exertion;
- Reduces myocardial ischemia in peace and especially in physical exertion;
- Slightly reduces the frequency of ventricular arrhythmias;
- Has an antifibrillator effect, reducing the risk of sudden death.

Several randomized clinical trials have shown that the early addition of beta-adrenoblockers (BAB) to standard therapy — including diuretics, digoxin, and angiotensin-converting enzyme (ACE) inhibitors — is effective in treating stable mild to moderate chronic heart failure, as well as severe cases, prolongs patient life expectancy, reduces the frequency of inpatient treatment, improves patient quality of life, improves patient condition (disease severity A). The best results in reducing the incidence of sudden death in chronic heart failure were reported in BAB-bisoprolol, metoprolol (with prolonged effect), and carvedilol.

It should be noted that BAB is not among the "ambulance" tools; it cannot exclude patients from the state of decompensation and hyperhydration. BAB can be used in the treatment of chronic heart failure as a supplement to ACE inhibitors when the patient's condition is stable.

Contraindications to the use of BAB in chronic heart failure:

- Severe bronchial pathologies accompanied by exacerbation of symptoms of bronchoobstructive syndrome when bronchial asthma or BAB is used;
- Bradycardia (<50pcs / min;

- Hypotonia (<85 mmHg.);
- Grade II and higher AV-blockade;
- Severe obliterating endarteritis.

BAB is an indication for patients with chronic heart failure and type 2 diabetes mellitus, in which all their positive effects are maintained. Carvedilol, from nonselective β-adrenergic blockers with α1-adrenoblocking action, is the choice drug for such patients, as carvedilol increases the sensitivity of peripheral tissues to insulin (degree of provability A).

Indications for the use of BAB:

- Arterial hypertension
- Ischemic heart disease
- Exertional (stable) angina
- Chronic heart failure
- Cardiac arrhythmias

In the treatment of arterial hypertension, BABs help prevent the long-term complications of the disease. However, in recent years, their usage has become more selective due to observed negative metabolic effects — such as an increased risk of metabolic syndrome and the development of diabetes mellitus in monotherapy or combination with thiazide diuretics in patients at high risk of developing diabetes in the treatment of arterial hypertension is limited.

Table 1.11

Basic guidelines for the use of β-adrenoblocators

Instruction	**Degree of provability**
Arterial hypertension	A
Tension stenocardia: - Anamnesis has no myocardial infarction: prolongs life expectancy, prevents myocardial infarction, and controls ischemia;	A C B A

- - Anamnesis had myocardial infarction: prolongs life expectancy, prevents re-myocardial infarction, and controls ischemia.	
In acute myocardial infarction, beta-adrenoblockers (BAB) provide several benefits: - Reduce the size of the infarcted (damaged) area - When administered intravenously, they help relieve pain, control blood pressure, and reduce heart rate - Prevent sudden death; - Intravenous administration for the treatment of tachyarrhythmia.	A A B C
Had myocardial infarction (secondary prevention): - prolongs life expectancy; - prevents myocardial infarction again; - Prevents sudden death; - Prevents arrhythmia.	A A A A B
Acute coronary syndrome (ST-segment not elevated. (reduces ischemia, prevents acute myocardial infarction, secondary prevention)	B
Chronic heart failure Asymptomatic dysfunction of the left ventricle after acute myocardial infarction	A A
Ventricular arrhythmia Compartment fibrillation (prevention, control of the number of heart contractions) Sinus rhythm revival Supraventricular arrhythmia(non-paroxysmal tachycardia, WPW Q-T syndrome	A A B C S

Note: Grade A: Based on meta-analyses or multiple randomized clinical trials.

Grade B: Based on a single randomized clinical trial or non-randomized clinical studies.

Grade C: Based on expert opinions or small-scale studies.

BAB, which has a vasodilating effect when an aortic aneurysm is at risk of stratification against the background of increased blood pressure, is the choice drug. Labetalol in the treatment of hypertonic crisis, which is complicated by acute coronary insufficiency, is a nonselective BAB selective drug used parenterally in cardiac rhythm disturbances or tachycardia-induced. Labetalol and esmolol are the drugs of choice in cranial trauma, which is complicated by hypertensive crisis. Labetalol and oxprenolol are the choice drugs when blood pressure rises in pregnant people (methyldopa is used if the patient is unable to tolerate labetalol and oxprenolol). Prolonged use of atenolol in pregnant people with Arterial hypertension leads to a decrease in fetal and placental weight, which is due to the increase (narrowing) of the tone of the aorta of atenolol and the umbilical artery of the fetus.

In the treatment of stenocardia, BAB is among the main antianginal drugs that improve the symptoms and prognosis of the disease.

In the treatment of chronic heart failure, BAB enters the main group of drugs when the volume of rapidly erupting blood (FE) is equal to or less than 35% (proof rate a).

Only 3 BABs (bisoprolol, methoprolol with prolonged action, carvedilol) can improve the prognosis of chronic heart failure; efficacy, safety are confirmed, carvedilol (α-β-adrenoblocator) has a positive effect on left ventricular relaxation rates in heart failure with rapid cardiac output (FE) [22].

BAB is used as a neurohormonal modulator in functional classes II-IV of chronic heart failure, and with ACE inhibitors are indicated when the ejection fraction (EF) — the volume of blood pumped out of the heart — is equal to or less than 35%. In the treatment of chronic heart failure, atenolol and metoprolol tartrate are contraindicated (evidence level A).

For elderly patients over 70 years of age with chronic heart failure, nebivolol may be used. This is a Grade II recommendation, supported by Grade C (expert opinion or limited evidence).

Other indications for the use of BAB:

- For the Prevention of ischemia and arrhythmia in surgical procedures in patients at high risk of cardiovascular disease (degree of provenance a);- In the treatment of Arterial hypertension, ischemia, and arrhythmia (degree of provability V);
- In hypertrophic cardiomyopathy (to relieve symptoms, control heart rate, treat arrhythmia and chronic heart failure, and reduce the risk of sudden death):
- In tyrotoxicosis (to relieve the symptoms of tyrotoxicosis):
- For the Prevention of Migraines.

Negative effects of BAB:

The origin of the negative effects of BAB depends on their selectivity, lipophilicity (observed by the central nervous system).

Table 1.12

Negative effects of BAB

β_1-receptor blocking	*Clinical:* coldness of the limbs, heart failure, occasionally bronchospasm, and bradycardia
	Biochemical: a slight change in the amount of potassium, uric acid, sugar, and triglycerides in the blood, an increase in insulin resistance, and a slight decrease in the amount of high-density lipoproteins
β_2-receptor blocking	*Clinical:* weakness, cooling of the limbs, bronchospasm, hypertensive reactions
	Biochemical: higher levels of potassium, uric acid, sugar, and triglycerides in the blood, increased insulin resistance, and slightly lower levels of high-density lipoproteins [22]
Lipophilicity	Negative effects observed by the central nervous system, including sleep disturbances, depression, and dreaming

Sinus bradycardia, AV-blockade development or elevated blockade levels, latent heart failure manifestation, excitation of bronchial asthma or other obstructive lung diseases, hypoglycemia, male sexual dysfunction, angiospasm (in different

forms), general weakness, drowsiness, depression, dizziness, impaired reactions, and the development of "withdrawal" syndrome (primarily in short-acting BAB) are the main adverse effects of BAB [22].

Control of therapy with BAB

In patients with angina pectoris (stenocardia), the target heart rate should be 55–60 beats per minute, measured 2 hours after taking the medication while atrest. In cases of chronic heart failure, the target heart rate may vary depending on clinical condition and treatment goals. The target heart rate should be 65-74 beats per minute; in most patients, around 70 bpm is optimal. It is recommended to be. When the drug is taken regularly, a hypotensive effect is observed after 3-4 weeks. Since BAB reduces AV permeability, It is advised that BAB sufferers have their ECGs controlled. For patients who exhibit symptoms of latent heart failure (fatigue, weight gain, hoarseness, and wheezing in the lungs), the duration of BAB dosage (therapeutic dose determination) should be extended to avoid decompensation.

Principles of bab dosage in chronic heart failure.

In chronic heart failure, initiating treatment with selective β1-adrenoceptor blockers is considered appropriate, particularly in cases characterized by severe tachycardia and normal or low systolic blood pressure. In such cases, ACE inhibitors may be added to the pharmacotherapy at a later stage. Small doses of BAB cause increased peripheral vascular resistance, decreased myocardial systolic function in the first 2-3 months, which requires a re-dosing of BAB [22]. The application of BAB requires dynamic monitoring of the course of the disease. If symptoms of decompensation are manifested by diuretics, it is recommended to increase the dose of ACE inhibitors [22], use drugs with positive inotropic effects (small doses of cardiac glycosides or calcium sensitizers - levosimendan), and taper the dose of BAB more slowly. The goal of using BAB in chronic heart failure, where rapid cardiac output (FE) has decreased or maintained blood volume, is to reduce the number of heart contractions and left ventricular hypertrophy.

In the treatment of chronic heart failure, treatment with BAB should begin with 1/8 of the therapeutic dose, and an overdose should be carried out 1 time every 2 weeks (in which the patient must have taken the previous dose well):

Bisoprolol: 1.25 mg – 2 weeks; 2.5 mg – up to 4 weeks; 3.75 mg – up to 6 Weeks; 5 mg – up to 8 weeks; 7.5 mg – up to 10 weeks; then 10 mg dan every day.

Carvedilol: 3,125 mg. from 2 times, then 6.25 mg. from 2 times, then 12.5 mg. from 2 times; then 18.75 mg. from 2 times; then 25 mg. from 2 times every day.

Metoprolol Succinate: 12.5 mg – 25 mg – 50 mg – 75 mg – 100 mg – 200 mg 1 time per day.

Nebivolol: 1.25 mg – 2.5 mg – 5 mg – 7.5 mg – 10 mg 1 time per day.

Table 1.13

Dosage of β-adrenoblocators for the treatment of chronic heart failure

The drug	Dosage, mg, and frequency of administration		
	initial	therapeutic	Max.
Bisoprolol	1,25 × 1	10 × 1	10 × 1
Metoprolol Succinate	12,5 × 1	100 × 1	200 × 1
Carvedilol	3,125 × 1	25 × 1	25 × 1
Nebivolol (In patients over 70 years of age)	1,25 × 1	10 × 1	10 × 1

Tactics of ordering BAB.

- Before treatment with BAB, the patient must be taking ACE inhibitors, mineralocorticoid receptor antagonists (MCRA - spironolactone I eplerenone), and diuretics. Usually, in the treatment of chronic heart failure, ACE inhibitors are prescribed in almost all cases. The dose of ACE inhibitors should not be high when BAB is prescribed (to titrate the dose of BABs).
- It is always necessary to start with the initial dose;
- The dose of BAB should be increased gradually (1 time every 2 weeks);

- All the time, it is necessary to try to achieve the targeted dose; if this is not possible, it is necessary to prescribe the maximum dose that the patient can carry.

- It is better to prescribe them at the minimum dose than not to prescribe BAB.

- It is necessary to constantly monitor the patient's personality, the number of heart contractions, and blood pressure.

- Biochemical analysis of the patient should be carried out after 1-2 weeks of sung at the beginning of treatment, and 1-2 weeks after the last dosage is carried out.

- The patient needs to be measured in body weight; if the body weight increases sharply, the dose of diuretics and ACE inhibitors should be increased (until the body weight returns to the norm again).

Extensional measures.

1. Increased symptoms of chronic heart failure (e.g., wheezing, rapid fatigue, increased swelling, increased body weight):

- Increase the dose of diuretics and/or reduce the dose of beta-adrenoblockers (BAB) by half if swelling increases and diuretics are ineffective at higher doses.

- If severe weakness develops, consider reducing the BAB dose.

- If the symptoms of chronic heart failure worsen and the patient's condition worsens after the prescription of BAB, reduce or cancel the dose of BAB by 2 times.

- After 1-2 weeks of treatment, a cardiologist should consult again if the patient's condition does not improve.

2. Bradycardia:

- Reduction of the dose of BAB by 2 times, cancellation in severe cases, if the symptoms of acute heart failure are increased < 50 pcs/min, and in chronic heart failure.

- Of course, to conduct an ECG examination (to exclude AV-blockade and conduction disorders);

- Consider prescribing other medications (e.g., ivabradine, digoxin, amiodarone).

3. Asymptomatic hypotonia: No change in Pharmacotherapy is required.

4. Symptomatic hypotonia:

- Revision of the need to take other drugs that dilate blood vessels;

- Consider reducing diuretics and the dose of ACE inhibitors in the absence of signs of edema;

- If the above does not help to consider a cardiologist's consultation again.

BAB is contraindicated in bronchial asthma, can be used in chronic pulmonary obstructive disease and chronic bronchitis, especially selective β_1-adrenoblocators (bisoprolol, metoprolol Succinate, nebivolol) can be used. BAB should be canceled if bronchoobstruction is triggered when BAB is applied. The choice in BOS is the drug bisoprolol (degree of provability S).

Table 1.14

These interactions involve changes in the absorption, distribution, metabolism, or excretion of β-adrenoblockers, affecting their overall effectiveness or toxicity.

Drug group	**Co-operation**
Nitrorvazodilators	The potentiation of antianginal and antiischemic effects occurs when beta-adrenoblockers (BAB) and nitrates are used together. This combination helps reduce the negative side effects associated with each drug group: Tachycardia and headache (common negative effects of nitrates) Bradycardia and limb numbness (common negative effects of BAB)
Cardiac glycosides, clonidine	Negative Chrono and Dromotropic effects of drugs are enhanced (potentiated)
Slow calcium channel blockers: verapamil, diltiazem Antiarrhythmics	Conduction, contractility functions of the heart are weakened, the number of heart contractions is reduced (there is a possibility of developing asystole, high-level AV-blockade, bradycardia, collapse, development of heart failure

Diuretics, slow calcium channel blockers (dihydropyridines), α-adrenoblocators, ACE inhibitors, A2RA [22].	The hypotensive effect is potentiated.
MAO inhibitors	Risk of impaired conduction activity of the heart, collapse, increased blood pressure (BAB can be prescribed 15 days after the abolition of MAO inhibitors) [22]
Insulin, hypoglycemic drugs	Exacerbation of hypoglycemic effects, symptoms of hypoglycemia (nivelirovanie): tachycardia, sweating, muscle tension
Iodine-contrast agents	Attenuation of cardiovascular compensatory reactions in hypotonia
NSAIDS, corticosteroids, sympathomimetics	Reduced hypotensive effect
Neuroleptics, antidepressants	Increased hypotensive effect
Liver metabolism enhancers (hepatoinducers), such as smoking, alcohol, rifampicin, barbiturates, and diphenhydramine, accelerate the metabolism of lipophilic drugs in the liver, thereby reducing the effectiveness of beta-adrenoblockers (BAB) etc.	Metabolism of lipophilic drugs in the liver is accelerated, and the effect of BAB is reduced.
Liver metabolic attenuators (hepatoingibitors)	BAB's effect increases

Remedies for narcosis (except fluorotane)	BAB's effect increases
Verapamil, diltiazem, digoxin, amiodarone [22]	It is not recommended to prescribe at the same time as BAB.

Control questions.

1. What pharmacodynamic effects are observed as a result of blocking β_1-adrenoreceptors?
2. What pharmacodynamic effects are observed as a result of partial or full blockage of β_2-adrenoreceptors?
3. Tell us the classification of β-adrenoblocators.
4. State the pharmacodynamics of BAB.
5. What pharmacological effects does BAB have?
6. What hemodynamic indicators does BAB affect, and how do they change?
7. Explain the clinical significance of the pharmacokinetic indicators of BAB.
8. List the instructions for applying BAB.
9. What effects does BAB have in ischemic heart disease and stenocardia?
10. What effects does BAB have in chronic heart failure?
11. List the negative effects of BAB.
12. List the instructions against applying BAB.
13. Give examples of BABs ' interactions with other drugs.

CLINICAL PHARMACOLOGY OF A-ADRENOBLOCATORS

Drugs that influence the adrenergic system in regulating vascular tone are classified into two groups: α-adrenoblockers, which reduce vascular tone by acting on the central nervous system. α1-adrenoblockers, which lower blood pressure by targeting the peripheral nervous system.

Adrenoreceptors are common in various organs and tissues of the body, performing various functions. α-adrenoblocators are of 2 types: α-and β-adrenoblocators. There will also be 2 types of each of them. They differ from each other in the number of organs and tissues, the function they perform, and their sensitivity to norepinephrine and adrenaline [22].

Table 1.1

Location of adrenoreceptors in various organs and tissues

Organs and tissues	Receptor type	Function to perform
Postsynaptic α_1-adrenoreceptors		
Blood-vascular smooth muscle	α_1 α_2- postsynaptic	Vasoconstriction Vasoconstriction
Urogenital tract smooth muscle	α_1 A (uroselective receptor) [22].	Contraction
Heart	α_1	Inotropic effect
Liver	α_1	Glycogenolysis
Adipose tissue	α_1 α_2- postsynaptic	Glyconeogenesis Activation of lipolysis
CNS	α_1 α_2- postsynaptic	Stimulation Arterial pressure drop
Endocrine glands	α_1	Secretion stimulation
β-cells of the pancreas	α_2- postsynaptic	Insulin secretion thinning
Intestinal enterocytes	α_1 α_2- postsynaptic	Stimulation of fluid and electrolyte transport
Platelets	α_2- postsynaptic	Aggregation
Presynaptic α_2-adrenoreceptors [22].		
Noradrenergic neurons	α_2	Norepinephrine release thinning
Cholinergic neurons	α_2	Inhibition of acetylcholine release
Serotoninergic neurons	α_2	Serotonin release inhibition [22].

α - and β-adrenoreceptors located at the end of the vascular narrowing nerve are involved in the regulation of vascular tone. From the ends of such a nerve, norepinephrine is released [22]. Norepinephrine released from the presynaptic nerve endings into the synaptic cleft causes vasoconstriction by stimulating postsynaptic α1-adrenoreceptors, which are more numerous than β1-adrenoreceptors in the vascular walls. Presynaptic α2 and β2-adrenoreceptors regulate the reuptake and release of norepinephrine. Stimulation of α2-adrenoreceptors promotes the reaccumulation of norepinephrine into vesicles at the presynaptic nerve endings, thus preventing its release (a negative "re-binding" mechanism). Stimulation of β2-adrenoreceptors, on the other hand, enhances the release of norepinephrine into the synaptic cleft (a positive "re-binding" mechanism) [22]. α-Adrenoblockers are classified into two groups: Nonselective α-adrenoblockers (acting on both α1 and α2 adrenoreceptors), such as fentolamine. Selective α1-adrenoblockers (primarily acting on α1-adrenoreceptors), such as prazosin, doxazosin, and terazosin. Fentolamine, a nonselective α-adrenoblocker, causes a temporary decrease in blood pressure because it blocks both α1 and α2-adrenoreceptors, preventing the normal negative re-binding of norepinephrine. However, its effect is short-lived, so it is mainly used in the treatment of hypertensive crises.

1st generation of selective α_1-adrenoblocators (short acting) – prozazine; 2nd generation (long acting)-doxazosin, terazosin; uroselective α_{1A} – adrenoblocators-alfuzosine, tamsulosine.

Pharmacodynamics of α1-adrenoblocators.

Pharmacological effects of α_1-adrenoblocators.

Pharmacodynamic effects of α_1-adrenoblocators: hypotensive, hypolipidemic, and *improve urine output (flow)* [22].

Of selective α_1-adrenoblocators:

- Hypotension
- Reduces total cholesterol levels in the blood.
- Increases the amount of lipoproteins with high density.
- Reduced triglyceride levels

- Increases tissue sensitivity to insulin.

- Breaks platelet aggregation.

- Improves urination in prostate adenoma..

- Improves sexual activity (improves erectile disorders in erection)

- Prolonged use of α1-adrenoblockers, such as doxazosin, may lead to the regression of left ventricular hypertrophy. However, in some cases, long-term use may contribute to the development of heart failure.

The hypotensive effect of α1-adrenoblockers results from their ability to dilate both arterial and venous blood vessels, leading to a reduction in peripheral vascular resistance and a subsequent decrease in blood pressure. Tachycardia (reflector) is observed as a result of the simultaneous expansion of both the artery and the venous blood vessels, but the force of the outflow of blood from the heart does not increase. The hypotensive effect of α_1-adrenoblocators does not increase the activity of renin in the blood.

Table 1.2

Comparison of hemodynamic effects of α - and β-adrenoblocators

Hemodynamic indicators	α- adrenoblocators	β- adrenoblocators
Heart rate	↑	↓↓
blood pressure	↓	↓
AV-conductivity	↔	↓↓
Myocardial contractility	↔↑	↓↓
Total peripheral resistance	↓↓	↓
Blood circulation in the kidneys	↑	↓

Note: ↑ - increases; ↓ - declines; ↔ - does not affect.

Blood pressure drops well when dose 1 is taken, especially if taken while standing. Reflector tachycardia is observed when α_1-adrenoblocators are taken, especially if dose 1 is taken standing. while the heart rate contractions remains virtually unchanged when subsequent doses are taken. When Arterial hypertension is accompanied by left ventricular hypertrophy, α_1-adrenoblocators call for left ventricular hypertrophy regression (reverse) when used long-term in monotherapy (not more than 10% on average), but are next to sluggish calcium channel blockers

and ACE inhibitors in terms of calling left ventricular hypertrophy regression. α_1-adrenoblocators do not affect blood circulation and electrolyte excretion in the kidneys, but doxazosin reduces microalbuminuria (as evidenced by its nephroprotective effects). α_1-adrenoblocators have a positive effect on lipid and carbohydrate metabolism, meaning that they reliably (up to 30%) lower total cholesterol, very low density lipoproteins, and especially triglycerides, while simultaneously increasing the amount of very high density lipoproteins. The hypolipidemic mechanism of action reduces CoA-reductase Activity 3-hydroxy-3-methyl-glutaryl (GMG), which plays a key role in cholesterol synthesis in the liver by blocking α_1-adrenoreceptors, resulting in reduced cholesterol and triglyceride formation, as well as increased activity of receptors that bind very low density lipoproteins, decreased endothelial lipoproteinlipase activity involved in triglyceride catabolism, stimulated apolipoprotein A_1synthesis (high density being the main component of lipoproteins, high density leads to an increase in the amount of lipoproteins), and at the expense of these, cholesterol levels are reduced by up to 40% [22].

α_1-adrenoblocators reduce blood glucose and insulin levels by increasing tissue sensitivity to glucose when used long-term, as well as increasing insulin-dependent utilization (transfer) of glucose to tissues [22]. The mechanism of origin of this condition can be arterial hypotension on the one hand, and an improvement in blood circulation in the muscles on the other.

Pharmacokinetics of α1-adrenoblocators.

α_1-adrenoblocators are lipophilic drugs. When they are taken for drinking, the stomach is well and completely absorbed from the intestinal tract. Biological uptake is 50-90%. The liver undergoes biotransformation under the action of microsomal enzymes (cytochrome R450). The patient's age and kidney function do not affect the pharmacokinetics of α-adrenoblocators.

Table 1.3

Comparative pharmacokinetic indicators of α_1 α1-drenoblocators

The drug	Biological appropriateness, %	Protein binding, %	Time to achieve maximum concentration Maximum exposure time, clock	Duration of exposure, hours	Occurrence of biotransformation in the liver	T½ hours	Elimination,%, liver/kidney, unchanged %
Prozazin	50-85	97	1-3 2-4	7-10	+* (active metabolites)	2-3	90 (5-11%)/6-10
Terazosin	90	90-94	1 2-3	24	+ (active metabolites)	12	60 (20%)/40 (10%)
Doxazosin	65	98-99	1.5-3,6 5-6	24	+ (active metabolites)	19-22	63-65 (5%)/9

Note: * - the drug undergoes metabolism metabolized [22].

Table 1.4

α_1-adrenoblocator exposure time indicators

The way to send	The beginning of its influence	Maximum exposure start time	Duration of action
Prozazine			
Into admission	30-180 min	2-4 hours	6-8 hours
Doxazosin			
Into admission	1-2 hours	2-6 hours	18-36 hours
Terazozine			
Into admission	5-10 min	15-30 min	12-24 hours
Alfuzozine			
Into admission	?	3 hours	8-12 hours
Tamsulozine			
Into admission	?	6-12 hours	22-24 hours

Instructions for use.

In Arterial hypertension (is a 2nd line drug);

In Benign Prostatic Hyperplasia (doxazosin, alfuzosin, tamsulosin).

Contraindications.

- High sensitivity (hypersensitivity) to the drug
- Advanced coronary and cerebral atherosclerosis (increased risk of ischemic events)
- Severe tachycardia, especially with nonselective α-adrenoblockers
- Aortic stenosis (risk of sudden drop in blood pressure)
- Patent ductus arteriosus (open Botallov duct)
- Severe hypotension
- Heart valve defects – particularly when left ventricular outflow is impaired (e.g., with prazosin)
- Severe renal failure – caution with fentolamine
- Severe hepatic failure – caution with doxazosin
- Pregnancy and lactation – relative contraindications for prazosin and doxazosin
- Systolic dysfunction of the left ventricle (risk of worsening heart failure)
- Elderly patients – increased risk of orthostatic hypotension
- Diabetic nephropathy – requires careful monitoring due to renal involvement

Negative effects.

Hypotension and orthostatic hypotension (in 2-10% of cases) (mainly observed when taking dose 1 of prozasin), this negative effect is called the "first dose" phenomenon, this negative effect depends on the dose and is observed 2-6 hours after taking the drug (during the period when the maximum hypotensive effect is developed), from this lesson the first dose of α1-adrenoblocators (prozasin) should be taken while the patient is lying down, and; tumors can be observed (in 4% of

cases), mainly swelling of the nasal mucosa (runny nose, the development of rhinitis symptoms); rapid heartbeat (in 2% of cases); the development of "cancellation" syndrome when the drug is canceled (mainly when it is quickly canceled) (5-10%).

Interaction with other drugs.

Antihypertensive drugs and diuretics increase the action of α_1-adrenoblocators; NSAIDs, estrogens, and sympathomimetics reduce the action of α_1-adrenoblocators (Table 1.4).

Table 1.4

Prazosin, Doxazosin	Benzogexonium, dibazole, guanetidine, papaverine	Pharmacodynamic interaction, summation of effects-decreased vascular smooth muscle tone, increased hypotensive effect
	α - drenomimetiklar, angiotensinamide	Pharmacodynamic interaction, reduced interactions Reduced hypotensive effect
	Calcium antagonists	Pharmacodynamic interaction, summation of effects – increased hypotensive effect, increased risk of developing orthostatic hypotension
Prazosin	β-adrenoblocators	Pharmacodynamic interaction involves the summation of antihypertensive effects [22], reducing pre- and post-cardiac strain and minute volume. The antagonistic effect on heart rate leads to a decrease in the risk of reflex tachycardia. However, this also increases the risk of the "first-dose effect", which may cause a sudden drop in blood pressure.
Terazosin	Sotalol	In pharmacodynamic interaction, the antihypertensive effect is enhanced.

Control questions.

1. state the classification of α1-adrenoblocators.
2. explain the the pharmacodynamics of α1-adrenoblocators.
3. α_1-what pharmacological effects do α1-adrenoblocators have?
4. α_1-what hemodynamic indicators do α1-adrenoblocators affect, and how do they change?
5. α_1-explain the clinical significance of pharmacokinetic indicators of α1-adrenoblocators.
6. α_1-list instructions for the use of α1-adrenoblocators.
7. α_1-list the negative effects of α1-adrenoblocators.
8. α_1-list instructions against the use of α1-adrenoblocators.
9. α_1-give examples of interactions of α1-adrenoblocators with other drugs.

SLUGGISH CALCIUM CHANNEL BLOCKERS OR CALCIUM ANTAGONISTS.

Calcium antagonists have antihypertensive, antianginal, anti-ischaemic, antiarrhythmic, and organ protective effects.

Pharmacodynamics.

Calcium channels:

L-type (located in the cytoplasmic membrane of the respiratory cardiomyocytes, sinus node cells, AV node, tuberculosis, and skeletal muscles)

T-type fetal heart, sinus node cell, Purkinje fibers, and smooth muscle cells are located in the cytoplasmic membrane.

P–type
N–type located in neurons, they are little studied.
R–type

Calcium antagonists are present in various organs and tissues, including the sinoatrial node, atrioventricular node, Purkinje fibers, cardiomyocytes, vascular smooth muscle, and skeletal muscle. They act as selective blockers of slow calcium channels (L-type, or voltage-dependent).

It is divided into 3 groups according to its chemical structure:

Calcium antagonists are classified based on their chemical structure into:

Phenylalkylamines – e.g., verapamil Benzothiazepines – e.g., diltiazem Dihydropyridines – divided into three generations: 1st generation: e.g., nifedipine 2nd generation: e.g., felodipine 3rd generation: e.g., amlodipine, nitrendipine, nimodipine, lercanidipine/

Due to their varying chemical structures, these calcium antagonists bind to calcium channels in different ways, resulting in distinct selectivity and pharmacological effects on different tissues. For example, verapamil and diltiazem both affect calcium channels in the myocardium as well, whereas calcium antagonists in the dihydropyridine group mainly affect calcium channels in the blood vessels.

While the blockage of slow calcium channels in cardiomyocytes, conductive pathways of the heart, causes cardio depressive effects, the blockage of calcium channels in smooth muscles in the blood vessel wall causes vasodilation. Verapamil has negative inotropic, Chronotropic, and dromotropic effect with weak vasodilating properties. Diltiazem exhibits weak cardiodepressant and weak vasodilating effects.

Table 1.1

Tissue selectivity of calcium antagonists

The drug	Cardiomyocytes	Conductive system of the heart	Smooth muscles of the blood vessels
Verapamil	+	+	+
Diltiazem	+	+	+
Nifedipine	+	-	++
Nitrendipine	+	-	+++
Nicardipine	+	-	++++
Nisoldipin	+	-	++++ (coronary)
Nimodypine	+	-	++++ (brain)
Felodipine	+	-	++++
Amlodipine	+	-	++++
Lasidipine	+	-	++++
Lerkanidipine	+	-	++++

Table 1.2

Pharmacodynamic effects of calcium antagonists

Effect	Verapamil	Nifedipine	Diltiazem
Sine node automatism	↔↓	↑(↔*)	↓
Myocardial contractility	↓↓	↔	↓
AV-node conduction	↓↓	↔	↓
Peripheral vasodilation	↑	↑↑	↑

Note: ↑ - increases; ↓ - declines; ↔ - does not affect; * specific for long-acting dihydropyridine unums.

Table 1.3

Classification of calcium antagonists (Toyo-Oka T., Mayer W. G., 1995, modified).

Group	1st generation	2nd generation		3rd generation
		2a	2b	
Dihydropyridines Artery > myocardium	Nifedipine	Nifedipine SR / GITS Felodipine or Nikardipine SR	Benidipine Felodipine Nikardipine Isradipine Manidipine Nilvadipine Nimodipine Nisoldipine Nitrendipine	Amlodipine Lasidipin Lercanidipine
Benzodiazepines Artery = myocardium	Diltiazem	Diltiazem SR	-	-
Phenylalkylamines Artery < myocardium	Verapamil	Verapamil SR	-	-

Note: SR – sustained release; ER – extended release; GITS – gastrointestinal therapeutic system.

Table 1.4

Comparative description of pharmacological properties of 3rd generation calcium antagonists

Feature	Amlodipine	Lasidipin	Lercanidipine
Lipophilicity	High	High	High
Binding to " receptors	Slow	Slow	Slow
Gradual onset and long duration of action: present (+)	+	+	+
Lack of effect on the sympatho-adrenal system	+	+	+
Hemodynamic pressure gradient between pre- and post-capillaries	High	Low	Low
Additional features	-	Powerful antioxidant effect	Vasodilation of the afferent and efferent arterioles of the kidney

Pharmacological effects of calcium antagonists.

Cardiac effects.

For phenylalkylamines:

1. Negative inotropic (reduces myocardial contractility
2. Negative batmotropic (reduces excitability in pacemaker cells in the sinus node)
3. Negative Dromotropic (AV reduces permeability in the Node
4. Antiarrhythmic effect.

For dihydropyridines:

1. Blood vessels (including coronary vessels) dilate.
2. Reflex tachycardia is commonly induced, especially in earlier generations.

For benzothiazepines-similar to phenylalkylamines.

Extracardiac effects.

1. Antiatherosclerosis (smooth muscle slows the proliferation of cells, relieves hyperplasia of the intima layer of vessels, reduces monocyte adhesion, stabilizes the cytoplasmic membrane, and limits free cholesterol access to the vessel wall, improves the HDL/LDL cholesterol ratio).
2. Verapamil has a nephroprotective effect, improving blood circulation in the kidneys. Phenylalkylamine (e.g., verapamil) reduces proteinuria in diabetic and hypertensive nephropathy, while amlodipine also demonstrates a nephroprotective effect.
3. Hyperglycemia (dihydropyridine unums-reduce insulin secretion, phenylalkylamines-have a good effect on carbohydrate metabolism-hepatocytes have increased glucose retention colic).
4. It has an antihypercholesterolemic effect (density reduces micdorin of low lipoproteins by 8%, density decreases micdorin of very low lipoproteins by 11%, density increases the amount of high lipoproteins by 6-15%)
5. Antiplatelet agents act by reducing the synthesis of thromboxane A2, increasing the synthesis of prostacyclin in the endothelium, and stimulating the production of endothelial-derived vasodilator factors, leading to a strong antiplatelet effect.
6. The brain dilates blood vessels (nimodipine-nimotope, synnarizine, flunarizine).

Clinical effects of calcium antagonists: antianginal, antiischemic, antiarrhythmic, hypotensive, organoprotective, antiatherogenic, extracardial.

The Antianginal effect is related to the direct pharmacodynamic effects of calcium antagonists, i.e., cardiodepressive, vasodilating (also coronary blood vessels), and effects on peripheral hemodynamics. By preventing calcium ions from entering cardiomyocytes, calcium antagonists decrease myocardial contractility and Increased coronary circulation improves myocardial oxygenation, while the dilation of peripheral arteries reduces peripheral resistance and lowers blood pressure. This leads to a decrease in cardiac workload and oxygen demand, Verapamil and diltiazem reduce the number of heart contractions (pulse), which also leads to a decrease in heart function.

The antiarrhythmic effect is observed when verapamil and diltiazem are used. In cardiomyocytes, the blocking of slow calcium channels reduces automatism and permeability, prolonging the sinoatrial and AV-node refractory period.

The hypotensive effect of calcium antagonists is primarily due to peripheral vasodilation, which not only decreases peripheral resistance and arterial pressure, but also improves blood flow to vital organs (such as the heart, brain, and kidneys). This effect is accompanied by a mild natriuretic and diuretic effect, further contributing to the reduction in peripheral resistance and circulating blood volume. Additionally, calcium antagonists have a beneficial impact on the structural and functional changes in both the blood vessel walls and target organs in arterial hypertension, organoprotective (cardioprotective, nephroprotective, cerebroprotective). As a result of the drop in blood pressure, calcium antagonists can trigger activation of the sympathoadrenal and renin-angiotensin-aldosteron systems. This triggering effect may lead to the reflex development of tachycardia. This effect is especially characteristic of the short-acting nifedipine, which can not only cause tachycardia but also exacerbate stenocardial attacks. Trigger effects on the sympathoadrenal system are hardly observed in long-acting diuretics (Generation II and Generation III).

The cardioprotective effects of calcium antagonists are associated with the regression of left ventricular hypertrophy in patients with arterial hypertension and an improvement in diastolic myocardial function. These effects are based on the hemodynamic impact of calcium antagonists and the reduction of cardiomyocyte overload with calcium ions.

Table 1.5

Comparison of the effect of antihypertensive drugs of different groups on the regression of the left ventricle (meta-analysis results)

Drug classes	Left ventricular regression (Decrease in index LVMM,%)				
	109 ta CS (1992)	39 ta CS (1996)	32 ta CS (1997)	50 ta CS (1998)	80 ta CS (2003)
Calcium antagonists	8.5	9	14.3	11.1	11
ACE inhibitors	15	13	11.9	11.1	10
Diuretics	11.3	7	10.1	8.6	8
β-blockers	8	6	6.5	4.5	6

Note: left ventricular myocardial mass index.

Nephroprotective effects of calcium antagonists include:

It has a positive effect on intra-renal hemodynamics, exerting a direct vasodilatory effect on renal blood vessels by blocking the vasoconstrictive action of angiotensin II (AT II). It reduces the proliferation and hypertrophy of mesangial cells in the renal glomerulus and prevents nephrocalcinosis by inhibiting the periglomerular migration of renal parenchymal cells with calcium ions.

The antiatherogenic effects of calcium antagonists are pleiotropic (multiple), and calcium antagonists, when applied for a long time, break the exacerbation of the atherosclerotic process in the coronary arteries (in ischemic heart disease) and carotid arteries (in arterial hypertension). The mechanism of antiatherogenic action of calcium antagonists comes at the expense of antioxidant (reducing inflammation), antiproliferative (in smooth muscles), and endothelial dysfunction enhancement (at

the expense of NO production) effects. Meta-analysis results showed that BABwith calcium antagonists, thiazide diuretics, and calcium antagonists were found to prevail when comparing ACE-inhibitors with calcium antagonists according to a reduction in the thickness of the carotid artery wall (intima-media) [22].

The cerebroprotective effects of calcium antagonists (mainly dihydropyridines) are manifested by preventing the origin of stroke in patients with arterial hypertension (reducing by 10%, mostly typical of dihydropyridines). While it is superior to Bab in preventing the origin of stroke, ACE is next only to inhibitors and diuretics. The effect of calcium antagonists on blood vessel stiffness and atherosclerotic processes explains their therapeutic benefits. Treatment with calcium antagonists leads to a decrease in central aortic pressure, which in turn reduces complications observed in the cranial region. Additionally, calcium antagonistshelp prevent and mitigate the development and exacerbation of dementia and vascular encephalopathy in patients with arterial hypertension. Extracardial effects of calcium antagonists, particularly those specific to dihydropyridines, include lowering pressure in the pulmonary arteries, dilating the bronchi, and reducing platelet aggregation.

Pharmacokinetics of calcium antagonists.

The majority of calcium antagonists are taken orally, while nimodipine isalso given intravenously. Lipophilia is a property of calcium antagonists. When consumed, it is quickly absorbed, but as it moves through the liver, it experiences a "primary transition effect" (presystemic metabolism), which makes it biodegradable. Calcium antagonists have a strong affinity for blood proteins, particularly albumins. The drug form and generation determine the maximum plasma concentration (Cmax), half-life (T½), and the time to reach maximum concentration (Tmax) of calcium antagonists. These drugs are eliminated by the kidneys as inactive metabolites after being metabolized in the liver. Typically, dose adjustments are not required in cases of chronic renal failure. The hemodynamic effects of calcium antagonists depend on the drug's concentration in the blood,with each pharmacokinetic parameter playing a crucial role.

Table 1.6

Comparative pharmacokinetic parameters of CaS

The drug	Biological appropriateness, %	T ½, hours	Elimination route	Reception number
Verapamil SR	10-35	5-9	Liver	1-2
Diltiazem SR	30-45	5-8	Liver	1-2
Nifedipin SR. GITS	30-50	4-5	Liver	1-2
Isradipine SRO	15-24	5-8	Liver	1-2
Felodipine ER	22	15	Liver	1-2
Amlodipine	60-65	35-45	Liver	1
Lasidipin	10	13-19	Liver	1
Lercanidipine	90	8-10	Liver	1

Indications for the use of calcium antagonists.

Basic guidelines:

1. *Ischemic heart disease:*

- Stable stenocardia (mainly phenylalkylamine and benzathiazepine unums are used. Short-acting nifedipine is not used);

– Vasospastic stenocardia (variant stenocardia, Prinsmetal stenocardia) - I, II, III generations of dihydropyridine products are used (mainly II, III generations) (their effects dilating blood vessels, especially coronary blood vessels, are stronger);

-Non-stable stenocardia (verapamil and diltiazem can be used when indicated against β-blockers;

-Myocardial infarction (verapamil and diltiazem can be used when indicated against β-blockers).

2. *Arterial hypertension:*

- Limited systolic arterial hypertension in elderly patients (when diuretics are contraindicated, or if they have a negative effect or are ineffective).

- In cases of myocardial infarction, the effects of long-acting verapamil and diltiazem can be utilized (especially when β-blockers are contraindicated).
- When arterial hypertension is accompanied by stenocardia (particularly when β-blockers are contraindicated).
- In patients with diabetic nephropathy (when ACE inhibitors are contraindicated or if they cause serious adverse effects).3. *Heart rhythm disturbances.*

3. *Hypertrophic cardiomyopathy.*

Further instructions:

1. In primary and secondary pulmonary hypertension (dihydropyridine derivatives).
2. In Reyno syndrome (to prevent vasospastic attacks) (dihydropyridine derivatives).
3. In the Prevention of migraine attacks (verapamil).
4. In the treatment of ischemic and hemorrhagic (complications) stroke (nimodipine).
5. Diffuse spasm of the esophagus and in Cardial achalasia (nifedipine and diltiazem).
6. Colon irritation syndrome is accompanied by diarrhea (verapamil).

Calcium antagonists are commonly used to treat arterial hypertension, stenocardia, tachycardia, and vasospastic diseases. Calcium antagonists are used to treat arterial hypertension and stenocardia, and they are listed in line 1 formulations (both monotherapy and combination therapy) in both international and national recommendations

Table 1.7

Indications for the use of calcium antagonists (according to the degree of provability)

Instructions	Verapamil	Nifedipine and dihydropyridines	Diltiazem
Arterial hypertension	+A	+A	+A
Tension stenocardia	+A	+A	+A
Vasospastic stenocardia	+V	+V	+V
To prevent coronary blood-vessel spasm during surgical or diagnostic procedures	-	+V	+S
Reyno syndrome	+	+V	+
Ventricular superior tachyarrhythmia	+V	-	+V
Bubble swing (mersanie)	+A	-	+A
Hypertrophic cardiomyopathy	+	-	+
Pulmonary hypertension	+S	+V	+V

Note: the degree of provability is derived from large randomized clinical trials where A–data is controlled; the degree of provability is derived from randomized clinical trials where the number of V–data controlled patients is limited; the degree of provability is derived from S–data non-randomized trials.

In arterial hypertension, calcium antagonists have a beneficial effect on the outcomes of the disease, reducing overall mortality, complications associated with the cardiovascular system, and the incidence of stroke.

In recommendations for the treatment of stenocardia, calcium antagonists are listed among the drugs that reduce myocardial ischemia and stenocardia. They reduce the frequency of myocardial ischemia episodes, hospital treatment with stenocardia, and the need for revascularization (reliable). They are especially effective in vasospastic stenocardia (Prinzmetal stenocardia).

In ventricular superior rhythm disturbances (tachyarrhythmias), mainly verapamil is used. Verapamil is effective in cardiac rhythm oscillating (atrial fibrillation) arrhythmia type disorders.

Contraindications for the use of calcium antagonists include:

- Arterial hypotension.
- Severe heart failure or a significant decrease in myocardial function (except for amlodipine).
- Acute myocardial infarction (with left ventricular insufficiency).
- Nifedipine is not used in aortic and subaortic stenosis, or in unstable angina due to its significant effect on hemodynamics.

In severe dysfunction of the left ventricle, WPW syndrome, sinus node retardation syndrome, AV conduction disorders, bradycardia, verapamil and diltiazem are contraindications.

Calcium antagonists fall under category S under the FDA classification of drugs that can be used in pregnancy. There is little data on the safety of calcium antagonists in pregnancy; they are considered relatively safe in the III trimester of pregnancy, with no teratogenic and embryotoxic effects detected in the I trimester. Calcium antagonists have a tocolytic effect and prevent the risk of fetal miscarriage. In the treatment of arterial hypertension during pregnancy, Nifedipine SR can be used in the II and III trimesters.

Common adverse effects associated with calcium antagonists include:

- Negative effects related to peripheral blood vessel vasodilation, such as headache, redness of the skin on the neck and face, coughing, overheating, tachycardia, ankle swelling, and arterial hypotension.
- Conduction disorders, including bradycardia and AV block.
- Gastrointestinal disturbances, most commonly constipation.

When short-acting forms of nifedipine are used, tachycardia and proishemic reaction (stenocardial syndrome) can be observed, while when applied for a long time, the risk of death increases, or complications observed by the cardiovascular system come with extimoli kupaydi. Bradycardia, AV-blockade can be observed when Verapamil and diltiazem are used. Arterial hypotension can be observed in acute cardiovascular diseases as well as when the drug (verapamil) is administered parenterally. Drug forms in which the effect of Kalar is prolonged are better tolerated by patients than their normal forms.

The most commonly observed adverse effect from dihydropyridines, especially amlodipine, is swelling of the ankles. The mechanism of origin of this negative effect is due to the high pressure gradient in the pre- and postcapillaries of the legs. S-amlodipine (levamlodipine) was produced in an attempt to counteract this negative effect. Such negative effects from Lasidipin and lercanidipin are poorly observed.

Table 1.8

Adverse effects of calcium antagonists

Adverse effects	Frequency of occurrence, %		
	Verapamil	Nifedipine	Diltiazem
Overheating, redness of the face	1,7	6-25	0-3
Headache	2-6	10-34	4-9
Heart play, tachycardia	0	7-25	0
Bradycardia	1,4	0	1,5-6
Dizziness	7	10-27	3-7
Constipation	34	0	4
A rash	0-2	sometimes	sometimes
Swellings	2-6	10-30	6-8

Table 1.9

Comparison of negative effects of amlodipine and lercanidipine (%)

Adverse effects	Amlodipine 5-10 mg	Lerkanidipine 10-20 mg	Placebo
Heel spur	3-10	0,9	0,6-1,3
Dizziness	3,4	0,4	0,4-1,5
Casting	1,4-2,6	1,1	0,4
Heart play, tachycardia	1,4-4,5	0,6	0,4-0,6

Table 1.10

Interaction of calcium antagonists with other drugs.

The drug used in cooperation	Result	Calcium antagonist
Pharmacodynamic interaction		
β-adrenoblockers	Cardiodepressive effect increases (bradycardia, AV block, heart failure)	Verapamil, diltiazem
α-adrenoblockers, diuretics, nitrates, ACE inhibitors, ARA	Antihypertensive effect increases	All calcium antagonists
Class I antiarrhythmic drugs	Cardiodepressant effect increases, QT interval lengthens.	Verapamil, diltiazem, felodipine
NSaIDS, corticosteroids, sympathomimetics	Antihypertensive effect decreases	All calcium antagonists
Means for inhalation anesthesia	Hypotonia increases	All calcium antagonists
Neuroleptics, antidepressants	Antihypertensive effect increases	All calcium antagonists
Pharmacokinetic interactions		
Hepatoinhibitors	The metabolism of CAs in the liver slows down	All calcium antagonists
Hepatoinducers	Metabolism of CAs in the liver is accelerated	All calcium antagonists

Cardiac glycosides	The concentration of cardiac glycosides in the blood increases, and the risk of poisoning and negative effects increases.	Verapamil, diltiazem, felodipin
Theophylline, quinidine, valproates, carbamazepine	Drug metabolism slows down, blood concentration rises, and the danger of poisoning and negative side effects increases.	Verapamil, diltiazem
Drugs that bind a lot to blood plasma proteins (quinidine, anticoagulants, NSAIDs, anticonvulsants)	Binding of drugs with plasma proteins is disrupted, blood concentration increases, and the risk of poisoning and negative effects increases.	

Review questions.

1. Tell the classification of calcium antagonists.
2. State the pharmacodynamics of calcium antagonists.
3. Tell the cardiac and extracardiac effects of calcium antagonists.
4. What is the mechanism of the hypotensive effect of calcium antagonists?
5. What is the mechanism of antianginal action of calcium antagonists?
6. Explain the clinical significance of the pharmacokinetic indicators of calcium antagonists.
7. List the indications for the use of calcium antagonists.
8. List the negative effects of calcium antagonists.
9. List the contraindications to the use of calcium antagonists.
10. Give examples of the interaction of calcium antagonists with other drugs.

CLINICAL PHARMACOLOGY OF NITROVASODILATORS.

Nitrovasodilators (NV) are drugs that show their effect by producing nitric oxide (NO), which include glyceryl trinitrate (nitroglycerin), isosorbide dinitrate, isosorbide mononitrate, and sympathomimetics.

Classification of nitrovasodilators.

- Nitroglycerin preparations:
- Short-acting: Nitroglycerin.
- Prolonged effect: Sustak, Sustonit, Nitrong, Trinitrong, Nitroderm TTS.
- Isosorbide dinitrate preparations:
- Short-acting: Nitrosorbide, Iso Mak, Isodinitrate.
- Prolonged effect: Cardix, Cardiket, Cardonite, Cardiograd SR, Iso Mak Retard.

Isosorbide mononitrate preparations:

Short-acting - mono mak;

Extended effect - cardix mono, mono mak depo.

Nitrate-like compounds - molsidomine, sodium nitroprusside.

Action mechanism of NV.

NV has a similar effect to the effect of endothelial relaxing factor. When endothelial dysfunction occurs, endogenous nitric oxide production from the endothelium decreases (except for septic shock), as a result of which an imbalance develops between reducing and relaxing factors. Nitropreparations are exogenous donors of nitric oxide. Nitric oxide stimulates guanylate cyclase. Cyclic guanosine monophosphate is formed from guanosine triphosphate under the action of guanylate cyclase, and cyclic guanosine monophosphate reduces the amount of calcium in the cell, as a result of which the muscle relaxes.

Pharmacological effects of NV.

1. Dilates blood vessels.
2. Inhibits platelet aggregation.

3. Increases the formation of prostacyclin in the walls of blood vessels (improves microcirculation).

4. Reduces the pre- and post-load of the heart, and reduces the oxygen demand of the heart.

5. Lowers blood pressure.

6. Causes reflex tachycardia (not observed in heart failure).

7. It has an antianginal effect, which includes expanding coronary vessels, opening collateral vessels, reducing the heart's oxygen demand, decreasing neuronal activity in the brain, and inhibiting sympathetic impulses.

8. Dilates blood vessels of the brain (headache and dizziness are observed).

9. Having a sympatholytic effect on internal organs, it relaxes the muscles of the OIT, bronchi, urinary tract, and uterus.

10. Increases the secretion of catecholamines during long-term use.

The primary effect of nitrates is the relaxation of smooth muscles in various organs (such as blood vessels, the gastrointestinal tract, and the respiratory tract). By dilating blood vessels (mainly veins), nitrates reduce preload and afterload on the heart, leading to decreased cardiac workload and reduced oxygen demand.

Also, the end-diastolic pressure of the left ventricle decreases (by 25% at rest, by 19% during stress), and the volume of blood ejected from the left ventricle increases (from 50% to 60% at rest, from 36% to 48% during stress).

Decreasing preload in the ventricles and reducing the filling of heart chambers during diastole improves blood circulation in the subendocardial and intramural layers of the myocardium, enhancing circulation in ischemic areas. Additionally, the anti-ischemic effect of nitrates is further attributed to a dose-dependent dilation of coronary blood vessels; that is, nitrates improve coronary blood circulation by dilating coronary collaterals. Nitrates cannot dilate stenosed blood vessels without smooth muscle in atherosclerosis. Nitroglycerin dilates normal coronary arteries by 20% when administered sublingually, and by 40% when injected intracoronarily. There is also information that nitrates can restore endothelial function when used in small doses.

Nitrates also have an antiplatelet effect (by reducing the amount of calcium in platelets). Nitric oxide also acts as an antithrombotic barrier. The antiaggregation effect is common to all nitrates. In patients with angina pectoris, the antiaggregatory effect of nitrates is reduced (up to 100 times in vivo). Also, the antiplatelet effect is related to the synergism of nitrates in the local production of prostacyclin, that is, prostacyclin is an activator of adenylation cyclase, adenylation cyclase increases the amount of cyclic adenosine monophosphate (cAMP), and an increase in the amount of cAMP in platelets blocks the receptor-dependent increase in the amount of calcium and prevents aggregation and adhesion. Nitrates also have anticoagulant and fibrinolytic effects.

Cydnonitroamines differ from nitrates in terms of their chemical structure; that is, they have several nitrogen atoms in their molecule.

Nitro vasodilators are prodrugs, which are converted into the active substance, nitric oxide, in the smooth muscle cells of blood vessels.

Description (characteristics) of nitrovasodilators.

Nitrates are available in various forms, including parenteral, aerosol, transdermal, buccal, and oral. Nitroglycerin and isosorbide dinitrate are used to relieve and prevent anginal pain, while isosorbide mononitrate is primarily used to prevent angina attacks (parenteral forms can also be used for immediate relief). In addition to tablets, nitroglycerin also has extended-release forms, i.e., microcapsules for drinking, application forms, and intravenous solution for parenteral use.

The duration of action of isosorbide dinitrate is average, and its hemodynamic and antianginal effect is directly related to itself and its metabolites (isosorbide mononitrate, isosorbide-2-mononitrate, and isosorbide-5-mononitrate).

Isosorbide dinitrate is available as an infusion solution, oral form (tablets and capsules), and transdermal drug forms (plasters and discs).

Isosorbide mononitrate is an active metabolite of isosorbide dinitrate and is formed as a result of presystemic metabolism of isosorbide dinitrate. After a short time after taking isosorbide dinitrate, isosorbide dinitrate and its metabolites (isosorbide-2-mononitrate and isosorbide-5-mononitrate) are present in the blood

plasma in the following ratio - 1:4:18. Isosorbide-2-mononitrate is a "short-lived" metabolite of isosorbide dinitrate and, like the intravenous form of nitroglycerin, has a rapid, potent, and short-lived antianginal effect. Isosorbide dinitrate is due to isosorbide-2-mononitrate, which develops a rapid antianginal effect when used sublingually to relieve an attack of angina pectoris.

Isosorbide-5-mononitrate is a long-acting metabolite of isosorbide dinitrate, providing a prolonged antianginal and anti-ischemic effect, extending the benefits of isosorbide dinitrate.

Isosorbide-5-mononitrate drugs are available in the form of simple and slow-dissolving (matrix tablets, microgranule capsules with the active substance) dosage forms for oral administration (providing a long-term effect), as well as in the form of intravenous solution.

Pharmacokinetics of nitrates.

Nitroglycerin, isosorbide dinitrate, and isosorbide-5-mononitrate preparations from the group of nitrates are widely used in practice. They differ from each other in their pharmacokinetic parameters.

Table 1.1

Comparison of pharmacokinetic parameters of nitrates

Parameters	Nitroglycerin	Isosorbide dinitrate	Isosorbide-5-mononitrate
"Primary pass effect" in the liver	occurs	occurs	does not occur
Biological absorption	less (sublingual – 50%)	less (sublingual - 50%, oral - 22%)	high 100%
Duration of effect	short (sublingual – 10-30 min)	medium (sublingual - 30-60 min, oral - 180-360 min)	long (oral – 300-360 min)
T ½	2-4 min	30-40 min	240-360 min

With sublingual and buccal administration, nitrates are well absorbed through the oral mucosa, do not undergo a "first-pass effect" in the liver, and quickly enter the large blood circulation and quickly reach the coronary vessels.

When given orally, nitrates undergo a "first-pass effect" in the liver, which reduces their bioavailability.

Pharmacokinetics of nitroglycerin.

When nitroglycerin 0.5 mg is taken sublingually, it is detected in the blood after 5 seconds, after 5 minutes it reaches its maximum concentration (3 ng/ml), and after 7.5 minutes its concentration in the blood decreases by 2 times (1.4 ng/ml). When taken sublingually, its bioavailability is 50%. T ½ - 2-5 min. It is metabolized in the liver (undergoing presystematic metabolism when taken orally), and its metabolites are excreted through the urine.

The duration of the effect of nitroglycerin is short, 10-30 minutes.

Nitroglycerin is initially administered intravenously at a rate of 10 μg/min, with the dose increased by 5-10 μg/min every 5-10 minutes until the desired hemodynamic effect is achieved. The clinical effect may take some time to become apparent. When administered at doses of 30-40 μg/min, nitroglycerin predominantly dilates veins. At doses of 150-500 μg/min, it primarily dilates arterioles. While there is no officially recommended maximum dose for nitroglycerin, it typically does not exceed 200 μg/min.

Isosorbide Dinitrate Pharmacokinetics Isosorbide dinitrate is rapidly and completely absorbed when administered sublingually, perorally, or transdermally. When taken orally, it is detectable in the blood within 15-20 minutes and reaches its maximum concentration after approximately 1 hour. However, during its first pass through the liver, the drug undergoes significant metabolism. The half-life (T½) of a single dose is 30-60 minutes, and approximately 7 hours after multiple doses.

Pharmacokinetics of isosorbide-5-mononitrate.

Simple tablets of isosorbide-5-mononitrate are quickly and completely absorbed from the gastrointestinal tract and are detected in the blood after 15-20 minutes, and after 1 hour, they form a maximum concentration. The therapeutically effective concentration in the blood is maintained for 10-13 hours. Isosorbide-5-mononitrate is 100% bioabsorbable when given orally because it does not undergo the "first pass effect" in the liver. The drug is mainly excreted in the urine in the form of metabolites. Retarded forms of isosorbide-5-mononitrate are taken 1 time a day.

Transdermal drug forms of nitrates.

Nitrate transdermal drug forms (TTDF) are in the form of ointment, patch, disk, and have different technical specifications. TTDF is placed on healthy skin, where the integrity of the skin is not damaged. In this case, nitrates enter the blood continuously in a dose close to the minimum therapeutic dose. Their disadvantage is that the bioavailability of TTDFs is unstable. Long-term use of TTDFs leads to the development of tolerance to nitrates, so TTDFs should not be used for more than 12 hours.

Molsidomine. Molsidomine is absorbed orally. When isosorbide dinitrate passes through the liver for the first time, approximately 30% is converted into various metabolites. The drug's effect begins within 15-20 minutes, though food may delay the onset of its effect without affecting its bioavailability. The maximum concentration in the blood is typically reached within 30-60 minutes. In liver diseases, the amount of the drug in the blood may increase slightly. The drug is 2-4 mg. Antianginal effect lasts for an average of 3-4 hours (from 1 hour to 6 hours). The effective dose of the drug is 2 mg in 30-40% of patients, 4 mg in 40-50% of patients, and 6-8 mg in 10-20% of patients (sometimes even higher). 2 mg when starting treatment with molsidomine. It is necessary to start with a dose, and if the patient accepts the drug well, then the dose can be increased to 6-8 mg. The effectiveness of the drug is determined by the systolic arterial pressure; that is, after 1-1.5 hours after taking the drug, the systolic arterial pressure is 15-20 (sometimes 25) mm Hg. Decreases. Molsidomine is available in tablets for oral and sublingual use, as well as ampoules for intravenous administration.

Nitrovasodilators are effective in preventing and eliminating myocardial ischemia, in emergencies related to arterial hypertension, and in heart failure.

Indications for Nitroglycerin Infusion:

- Unstable Angina: In cases resistant to β-adrenoblockers.
- Persistent Anginal Attacks: When anginal attacks are not alleviated by other treatments.
- Myocardial Infarction: To manage symptoms and reduce heart workload

- acute left ventricular failure;

- when there is a need for controlled hypotension during surgery;

- in extracorporeal blood circulation, during surgery and anesthesia, and in controlling preoperative arterial hypertension that occurs during intubation.

Instructions for Use of Nitrates:

- Sublingual Nitroglycerin or Spray Form: Used to eliminate or alleviate angina attacks.
- Long-Acting Nitrates: For Angina Pectoris Treatment: Used as part of combined therapy when there is an indication against the long-term use of β-blockers and calcium antagonists. Combination Therapy: If β-blockers or calcium antagonists are ineffective as monotherapy, long-acting nitrates are used in combination with them.

- Long-acting nitrates are used as part of combined therapy in case of sinus node dysfunction or severe AV-conduction disorders.

Antianginal dose and frequency of use of nitrovasodilators in stable angina pectoris.

Table 1.2

Nitrates and nitrate-like preparations

Active substance	Duration of effect	The drug	Usual dose in angina pectoris
Nitroglycerin (glyceryl trinitrate)	Short acting	Nitromint Nitrocor Nitrospray	0.3-1.5 mg under the tongue in angina attacks
	Long acting	Nitrogen forte	6.5-13* mg 2-4 times a day
Isosorbide dinitrate	Short acting	Izoket spray	1.25-3.75 mg sublingually
	Medium-range effect	Isolong Cardiket 20 Izo Mak 20 Nitrosorbide	20-80 mg per day
	Long acting	Cardiket 40 Cardiket 60 Cardiket 120 Izo Mak retard	40-120 mg per day
Isosorbide mononitrate	Medium-range effect	Mononite Monosan Monochinkwe	40-120 mg per day
	Long acting	Olicard retard Monochinkve retard Pectrol Efox long	40-240 mg per day
Molsidomine	Short acting	Corvaton Sydnofarm	4-12 mg per day
	Medium-range effect	Dilasidom	2-4* mg 2-3 times a day
	Long acting	Dilasidom retard	8* mg 1-2 times a day

* - 1 single dose

Dosing procedure for nitrates in angina pectoris:

- Nitrates are used intermittently in type I FC of exertional angina pectoris, mainly before physical exertion. Short-acting nitrates (buccal tablets, tablets, nitrates

in aerosol form, and isosorbide dinitrate) are used for this purpose. They should be used 5-10 minutes before expected physical exertion. It is not advisable to use long-acting forms.

- Nitrates are used intermittently in II FC of angina pectoris. Nitrates of short and medium duration are used in this.

- In III FC of angina pectoris, nitrates (used in the third place after β-blockers and calcium antagonists) are used continuously, but with a break of 5-6 hours (nitrate-free period), that is, they are prescribed every day.

- Nitrates are used continuously (without a nitrate-free period) in IV FC of angina pectoris, i.e., they are used every day; the concentration in the blood should be maintained at a therapeutic dose throughout the day. For this, it is necessary to use nitrates 3-4 times (short-acting nitrates) or prolonged nitrates.

Contraindications to the use of nitrovasodilators.

- If the systolic arterial pressure is below 90 mmHg;

- If the number of heart contractions is less than 50 per minute;

- Strong tachycardia;

- Severe dysfunction of right ventricular contractility associated with right ventricular preload;

- if sildenafil was used (nitrates should be used 24 hours after sildenafil);

- Severe aortic stenosis (when nitrates are used, there is a high risk of a sharp drop in arterial pressure and loss of appetite);

- Hypertrophic obstructive cardiomyopathy (when nitrates are used, obstruction and mitral regurgitation may increase).

Tolerance to nitrovasodilators.

When nitrovasodilators are re-used in a standard dose, their anti-anginal, anti-ischemic, and hypotensive effects decrease in strength and duration is called tolerance. The origin of tolerance depends on the dose of the drug and the duration of treatment. The mechanism of development of tolerance to nitrates depends on various factors.

There are 2 types of tolerance: *false (vascular stone) tolerance and true (vascular) tolerance*. False (vascular) tolerance develops as a result of a violation of neurohormonal regulation of blood vessels and an increase in blood volume in blood vessels, while true (vascular) tolerance occurs as a result of a decrease in the function of vascular smooth muscle cells to convert nitrates into nitric oxide.

The neurohormonal activity in response to nitrates is influenced by their dose, and it plays a crucial role in their long-term effectiveness. Here's a more detailed breakdown of how this works: Decreased Arterial Pressure: Nitrates dilate blood vessels, particularly veins, leading to reduced preload and a decrease in arterial pressure. Baroreflex Stimulation: When the blood pressure drops, the body compensates by activating baroreceptors in the blood vessels, which stimulate the sympathetic nervous system to release more catecholamines (like adrenaline). This action raises the heart rate and constricts blood vessels to counteract the pressure drop. Increased Vasopressin: As part of the compensatory response, the body releases vasopressin, which promotes water retention by the kidneys, increasing blood volume and indirectly raising blood pressure. Activation of the Renin-Angiotensin-Aldosterone System (RAAS): Reduced blood pressure also activates renin, which starts a cascade of reactions leading to the formation of angiotensin II. Angiotensin II raises blood pressure by constricting blood vessels and stimulating aldosterone secretion, which retains sodium and water, further increasing blood volume. Dose-Dependent Neurohormonal Stimulation: The degree of neurohormonal stimulation depends on the dose of nitrates. Higher doses of nitrates lead to more profound baroreflex activation and greater fluid retention, which can make the body less responsive to the vasodilatory effects of nitrates over time, a phenomenon known as tolerance.

The result of these neurohormonal responses can be increased blood volume and vascular tone, which may counteract the initial effects of the nitrates and reduce their effectiveness, especially with prolonged use. This mechanism is why nitrate tolerance can develop, necessitating strategies like nitrate-free intervals to mitigate this effect.

Ways to prevent or reverse nitrate tolerance:

- Nitrates should be prescribed with a break during the day, i.e., the interval of taking nitrates should be 10-12 hours. Nitrates should be taken at the same time. Taking nitrates at different times can lead to the development of "ricochet" syndrome, the appearance of anginal attacks, and even the development of painless myocardial infarction.

- Contraindication of nitrates with calcium antagonists.

- Introduction of SH-group donors into the body. One of the most effective NO-group donors is N-acetylcysteine. Also, NO-group donors include NO-group-preserving ACE inhibitors (captopril).

- Use of nitrates in combination with ACE inhibitors that do not retain the SH group.

- Use of nitrates together with calcium antagonists and/or BAB.

Alternative ways to overcome tolerance:

- Application of molsidomine, that is, molsidomine has a significant hemodynamic effect when tolerance to nitrates develops;

- Use of nicorandil, that is, nicorandil strongly expands coronary arteries without affecting pre- and post-load, the drug expands arteries of different diameters, increases the body's resistance to load, reduces the number of anginal pains and the need for nitrates (nitroglycerin). Nicorandil also has an antiplatelet effect.

- Application of new vasodilators (tolerance-resistant nitrates - furoxans, sodium channel regulators - KRN2391).

Table 1.3

Interaction of nitrovasodilators with other drugs

The drug	The essence of cooperation
BAB	Enhancement of antianginal and antiischemic effects, reduction of adverse effects of both groups of drugs (tachycardia and headache caused by nitrates, bradycardia and coldness of limbs caused by BAB) [22].
If-channel inhibitors	The enhancement of antianginal and antiischemic effects, as well as the reduction of negative effects, occurs when certain drug classes are used in combination. Specifically, the interaction between nitrates (which have vasodilatory properties) and If-channel inhibitors (which affect heart rate and rhythm) can optimize treatment for conditions like angina or ischemia.
Calcium antagonists (verapamil, diltiazem)	Enhancement of antianginal and antiischemic effects, reduction of adverse effects of both groups of drugs (tachycardia and headache caused by nitrates, conduction, contractility, heart rhythm disturbances, bradycardia, occurrence or exacerbation of heart failure caused by verapamil, diltiazem)
Calcium antagonists (dihydropyridine group)	Potentiation of antianginal and antiischemic effects, tachycardia increases.
Cytoprotectors	Enhancement of antianginal and antiischemic effects
Hypotensive drugs of other groups, antiarrhythmics, tricyclic antidepressants, ethyl alcohol, MAO inhibitors	Potentiation of hypotensive effect

AAF inhibitors, ARA, diuretics	The hypotensive effect increases, and the risk of developing tolerance to nitrovasodilators decreases.
Cardiac glycosides, hydralazine	Heart failure decreases, and tachycardia increases when used together with hydralazine.
Aspirin	The amount of nitroglycerin in the blood plasma increases, and the antiaggregation effect increases.
Heparin	Against the background of nitroglycerin, the effect of intravenous heparin decreases; the dose of heparin should be adjusted after the cancellation of nitrates
Hepatoinducers (smoking, alcohol, rifampicin, barbiturates, diflunisal)	The metabolism of nitrovasodilators is accelerated, and the strength and duration of the effect of nitrovasodilators are reduced
Hepatorinhibitors	The metabolism of nitrovasodilators slows down, and their effect increases.
α-adrenomimetics, pituitrin, dihydroergotamine, M-cholinelytics	Decreased effect of nitrovasodilators

Review questions.

1. Describe the classification of nitrovasodilators.
2. State the cardiac and extracardiac effects of nitrovasodilators.
3. What is the hypotensive effect mechanism of nitrovasodilators?
4. What is the mechanism of the antianginal effect of nitrovasodilators?
5. Explain the clinical significance of the pharmacokinetic indicators of nitrovasodilators.
6. List the indications for the use of nitrovasodilators.
7. List the negative effects of nitrovasodilators.
8. What are the causes of tolerance to nitrovasodilators, and how are they eliminated? What is the prevention of tolerance?
9. List the contraindications to the use of nitrovasodilators.
10. Give examples of the interaction of nitrovasodilators with other drugs.

MIXED VASODILATOR (SODIUM NITROPRUSSIDE).

Pharmacological effects.

Reduces peripheral resistance, lowers blood pressure (by dilating arteries and veins).

Reduces the pre- and post-tension of the heart, increasing the ejection of blood from the heart.

Improves blood circulation within the small blood vessels.

It causes reflex tachycardia; in some cases, bradycardia develops. It does not affect blood circulation and glomerular filtration in the kidney, but renin secretion increases.

Pharmacodynamics.

Sodium nitroprusside is a short-acting peripheral vasodilator that dilates arteries and veins.

Sodium nitroprusside combines with the sulfhydryl group of the cell membrane, disrupts the synthesis of cyclic nucleotides, and reduces calcium entry.

Pharmacokinetics.

Sodium nitroprusside is given intravenously. Sodium nitroprusside is metabolized into cyanides under the influence of erythrocyte enzymes, and into thiocyanate (active metabolite) under the influence of liver rhodanese. Thiocyanate causes metabolic acidosis. The T ½ period of thiocyanate is 84-156 hours. It is excreted through the kidneys. The effect starts after 0.5-1 min., the maximum effect starts after 5 min., and the duration of the effect is 5-10 min.

Instructions for use.

To eliminate severe hypertensive crises.

Administering hypotonia during surgical operations.

Negative effects.

Sudden drop in blood pressure: cold sweat, muscle tremors, nausea, vomiting, rapid heartbeat, shortness of breath, blurred vision, drowsiness.

Thiocyanate poisoning: general weakness, hyperreflexia, speech disorder, convulsions, psychosis, coma.

Contraindications.

Hyperthyroidism.

In severe liver and kidney disorders

Interaction with other drugs.

Sodium nitroprusside + ganglioblockers, anesthetics = hypotensive effect is potentiated.

Sodium nitroprusside + methyldopa = increases blood pressure, causes bradycardia.

Sodium nitroprusside + digoxin = bradycardia develops.

Clinical pharmacology of ivabradine.

Ivabradine is a specific inhibitor of If-channels in the sinoatrial node and has a selective effect on If-channels. Ivabradine has an anti-anginal and anti-ischemic effect by reducing the number of heart contractions. In ischemic heart disease, the increase in the number of heart contractions increases the oxygen demand of the myocardium.

The following are related to the number of heart contractions:

- Oxygen demand of the heart and ischemic threshold of the myocardium;

- Filling time of coronary arteries during diastole and coronary blood circulation time;

- Proatherogenic effect.

A high number of heart contractions is a factor indicating slow physical development or a factor indicating poor health of the patient. Patients with a higher number of heart contractions have a higher rate of sudden death or death from cardiovascular disease.

Mechanism of action of ivabradine.

Ivabradine reduces the number of heart contractions by blocking If channels in the sinus node, which control spontaneous diastolic depolarization and control heart contractions. Ivabradine does not affect heart conduction (impulse transmission from chambers, ventricles, and AV node) and contractility.

Pharmacokinetics of ivabradine.

Ivabradine is taken orally, and the gastrointestinal tract absorbs it quickly. After 1 to 1.5 hours, the blood's maximal concentration is seen. The drug's bioavailability is 40%. 70% attaches to proteins in the blood. It is broken down in the liver and then eliminated from the body as a metabolite via the kidneys and liver 1 (none of it is eliminated unaltered in the urine). When using the medicine consistently, its half-life is two hours.

Effect of ivabradine on hemodynamics. Ivabradine does not reduce average arterial pressure, nor does not affect myocardial contractility.

Effect of ivabradine on QT interval. The risk of death rises when the QT interval lengthens. The QT interval is not prolonged by ivabradine. Quinidine, disopyramide, bepredil, sotalol, ibutilide, amiodarone, pimozide, ziprazide, sertindole, mefloxine, halofantrine, pentamidine, cisapride, and erythromycin are among the medications that prolong the QT interval and should not be taken with Ivabradine.

Antianginal and antiischemic effects of ivabradine.

The antianginal and antiischemic effect of ivabradine is the same as the antianginal and antiischemic effect of atenolol and amlodipine, but the negative effects of ivabradine are less observed. The antianginal effect of ivabradine is preserved even with long-term use; that is, pharmacological tolerance does not develop, and "withdrawal" syndrome does not develop when the drug is stopped. Ivabradine can be used if there is an indication against BAB.

Use of ivabradine in chronic heart failure. Ivabradine is recommended for patients in II-IV functional class of chronic heart failure with sinus rhythm, cardiac ejection fraction equal to or less than 35%, heart rate equal to or greater than 70 per minute (treated with BAB, ACE inhibitors, ARA, CA) (recommendation class IIa, level of evidence V). In cases where it is not possible to use BAB in patients of this category, ivabradine can be prescribed instead.

The starting dose of ivabradine is 5 mg twice daily, and after two weeks, the dose may be increased to 7.5 mg twice daily. For elderly patients, the dose may be lowered.

Adverse effects of ivabradine.

- Visual impairment (photopsia) is one of the most frequent (in 14.5% of cases) side effects, which is low-level and resolves on its own during treatment. Photopsia is a transient change in clarity in a limited part of the field of vision, observed when the intensity of light changes suddenly, compared to a shiny object in broad daylight. Photopsia occurs as a result of the inhibition of the If-channels in the retina.

- Blurred (blurry, diffuse) vision - the drug is canceled when this negative effect is observed in patients who work in jobs that require high attention (driving a vehicle, working on a machine tool, etc.).

- From the cardiovascular system: often observed - bradycardia, AV block I-degree, ventricular extrasystole; sometimes - palpitations, ventricular extrasystole.

- Gastrointestinal tract: in rare cases, nausea, constipation, diarrhea.

- General changes: often observed - headache, dizziness; sometimes - parting, muscle tension.

- Laboratory changes: sometimes - hyperuricemia, eosinophilia, increase in blood creatinine.

Contraindications and precautions for the use of ivabradine.

It should be prescribed with caution:

- Sinus arrhythmia, AV- and interventricular conduction disorders;

- When used together with other drugs that reduce the number of heart contractions.

- Arterial hypotonia;

- In the acute period of a stroke;

- In cases of severe liver failure

- In cases of severe kidney failure

- In pigmentary retinal dehydration

- Not recommended for children under 14 years of age (the drug's efficacy and safety in children have not been studied).

Contraindications to use:

- Hypersensitivity to the drug;

- If the number of heart contractions is less than 60 per minute while standing still;

- Sinus node laxity syndrome;

- Sinoarterial blockade;

- AV block II degree;

- If the artificial rhythm is the controller;

- Acute myocardial infarction;

- Cardiogenic shock;

- Unstable angina pectoris;

- In severe arterial hypotension (AB below 90/50 mm sym.ust) [22];

- Chronic heart failure stage III-IV according to NYIA;

- Severe liver failure (if it is higher than 9 according to the Child-Pugh classification);

- Use together with strong hepatoinhibitors (ketoconazole, intraconazole, clarithromycin, erythromycin, josamycin, telithromycin, nelfinavir, ritonavir, nefazodone);

- Pregnancy, lactation period.

Clinical pharmacology of nicorandil.

Nicorandil, an ATP-dependent potassium channel opener, is used as a second-line treatment for ischemic heart disease. The drug is prescribed when first-line drugs are ineffective or cannot be used. Nicorandil is effective in the treatment of all types of angina pectoris, including tension, rest, variant, post-infarction, and microvessels.

Mechanism of action of nicorandil.

Nicorandil is an ester of nicotinamide according to its chemical structure, and contains nicotinic acid amide and a nitrate group in its molecule. Activation of ATP-dependent potassium channels in vascular smooth muscle leads to relaxation of smooth muscles, a decrease in peripheral vascular resistance, and a tone of narrowed coronary vessels. Also, nicorandil expands venous blood vessels and coronary blood vessels due to the increased amount of nitric oxide, reduces the post- and pre-

angiogenic pressure of the heart, and improves the delivery of oxygen to the myocardium. The drug opens ATP-dependent potassium channels, increases the entry of potassium into mitochondria, causes depolarization of the inner membrane of mitochondria, reduces tension with calcium ions (peregruzka), and reduces swelling of mitochondria during myocardial ischemia. As a result, it increases the resistance of cardiomyocytes to ischemia and reduces their death.

When studying the hemodynamic effect of nicorandil, when the drug is administered intravenously in the amount of 4-12 mg to patients with congestive heart failure, the average arterial pressure decreases by 5-15%, the total peripheral blood vessel resistance decreases by 8-27%, the pressure in the capillaries of the aorta decreases by 25-41%, the end-diastolic pressure in the left ventricle decreases by 8-18%, the blood pumping power of the heart decreases by 8-18%. Increases.The above indications show that nicorandil can be used in acute heart failure.

Long-term use of nicorandil at 5 mg 3 times a day (2,558 patients participated in a study conducted in Japan, the average duration of observation was 2.7 years) reduced the risk of death due to coronary blood vessels by 56%, death from acute myocardial infarction by 56%, the risk of developing ischemic stroke by 71%, and the risk of developing congestive heart failure by 33%. Also, positive results were obtained in the assessment of stabilization of atherosclerotic plaques. Positive changes in the parameters of erectile function were found in the patients taking Nicorandil.

Pharmacokinetics of nicorandil.

Nicorandil is quickly and completely absorbed from the gastrointestinal tract. The drug creates a maximum concentration in the blood 0.5-1 hour after drinking. It is less bound to blood plasma proteins, and the free fraction in blood is 75%.The drug is not metabolized in the liver. T ½ 50 min. It is excreted from the body mainly through the kidneys.

Interaction of nicorandil with other drugs.

Nicorandil's antianginal action is enhanced when it is used with antidepressants, phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil), vasodilators, hypotensive medications, MAO inhibitors, and ethanol.

Instructions for the use of Nicorandil.

- In the prevention of stable angina attacks (if the 1st-line drugs cannot be used or are ineffective, they are used as monotherapy or can be used together with other antianginal drugs). The drug is prescribed to be taken 10-20 mg 2-3 times a day, regardless of food.

- To eliminate angina attacks. 20 mg of the drug as soon as the first signs of an angina attack appear. The dose should be placed under the tongue and held until completely absorbed without swallowing. The maximum daily dose of the drug is 80 mg.

Contraindications to use.

- In case of hypersensitivity to the drug;

- Cardiogenic shock, collapse;

- Strong bradycardia (when the number of heart contractions is less than 50 per minute);

- II and III degree atrioventricular blockade;

- Left ventricular failure (with low-pressure filling);

- Arterial hypotension (when the systolic blood pressure is lower than 100 mm Hg);

- simultaneous use with phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil);

- Pregnancy and lactation period;

- Children under 18 years of age (the effectiveness and safety of the drug have not been studied).

The drug should be used with caution in the following cases:

- Heart rhythm disturbances;

- in atrioventricular block of the 1st degree;

- in Prinsmetal's angina pectoris;
- Arterial hypotension;
- Liver and kidney function disorders;
- in hypovolemia;
- In pulmonary edema;
- In angle-closure glaucoma;
- in hyperkalemia;
- In anemia.

Negative effects of nicorandil.

- Cardiovascular system:

palpitations, tachycardia, drop in arterial pressure, feeling of blood "pouring" on the skin of the face, peripheral edema;

- Central nervous system:

weakness, headache (reduce the initial dose), dizziness, ringing in the ears, insomnia;

- Gastrointestinal tract:

nausea, vomiting, stomach discomfort, feeling of fullness (satiety), stomatitis

Drug overdose and help.

When the dose of the drug is exceeded, the following symptoms may be observed: drop in arterial pressure, tachycardia.

Treatment: gastric lavage, activated charcoal administration (especially during the first 2 hours), cardiovascular monitoring and support, leg elevation, symptomatic therapy, intravenous calcium gluconate and dopamine, hemodialysis if necessary.

Features of Nicorandil application.

While taking the drug, it is necessary to monitor arterial pressure, ECG indicators, the amount of potassium and sodium in the blood, as the patient's heart rhythm disorder may increase.

It is necessary to be careful when using the drug on patients working in jobsthat require high attention.

Clinical pharmacology of trimetazidine.

In recent years, there has been an increasing interest in drugs with metabolic effects in the treatment of ischemic heart disease. The use of drugs with a metabolic effect makes it possible to develop additional antianginal and antiischemic effects. Unlike other anti-anginal and anti-ischemic drugs (BAB, CA, nitrovasodilators), hemodynamic negative effects are not observed when using drugs with a metabolic effect.

Myocardial cytoprotectors with metabolic effects include trimetazidine.

Pharmacodynamics of drugs with metabolic antiischemic effect.

Trimetazidine has an anti-anginal/anti-ischemic and cytoprotective effect due to optimization of energy exchange in cardiomyocytes in conditions of ischemia. Myocardium receives energy in the form of an adenosine triphosphate (ATP) molecule, and ATP is synthesized in mitochondria. With the use of ATP, its synthesis is always in balance. The main part (2/3) of ATP is synthesized from fatty acids, and the rest (1/3) from glucose and lactate.

Accumulation of fatty acids and their metabolites in cardiomyocytes under conditions of hypoxia has a cytotoxic effect on the cell membrane. An increase in the amount of fatty acids reduces the synthesis of ATP. Using glucose instead of fatty acids as an energy substrate protects cardiomyocytes from ischemic damage and increases the efficiency of heart work. Drugs that limit the use of fatty acids as an energy substrate are called antianginal and antiischemic cytoprotectors with metabolic effects.

Trimetazidine is a partial inhibitor of beta-oxidation of fatty acids.

Trimetazidine is available in regular and slow-release dosage forms.

Preductal is a slowly released (modified) form of trimetazidine, a myocardial cytoprotector recommended by experts of the Russian, European, and American associations of cardiologists in In the treatment of angina pectoris, according to the recommendations of the Russian Association of Cardiologists, other antianginal medications may be considered alongside the primary treatment options(BAB, CA,

nitrovasodilators) can be prescribed to enhance the antianginal and antiischemic effects of preductal stable tension angina at any stage. If the patient cannot use BAB, CA, nitrovasodilators, preductal can be used with If-channel inhibitors (ivabradine) or other antianginal drugs. When other antianginal drugs cannot be used, it can be prescribed as monotherapy in the treatment of preductal angina.

Indications for the use of trimetazidine in the treatment of stable angina pectoris:

- When other antianginal drugs cannot be used;
- when CID is accompanied by diabetes;
- In case of chronic heart failure;
- When angina functional class I (FC) is accompanied by bradycardia, when other antianginal drugs cannot be combined in treatment, for combined therapy, or monotherapy use;

- In cases where angina of functional class I (FC) is accompanied by hypotension and other antianginal medications cannot be combined, it may be used either as part of a combined therapy or as a monotherapy option.
- If the antianginal or antiischemic effect of other medications is insufficient in treating angina pectoris of functional class I (FC), this drug may be considered as an alternative.

Effects of trimetazidine in the treatment of angina pectoris.

According to the findings of the trimetazidine study with original medications, the drug consistently reduces the frequency of angina attacks while also increasing the body's resilience to physical stress.

Extended-release trimetazidine is prescribed at 35 mg twice a day, in the morning and evening, with meals. When the medicine is taken regularly, the effect appears after 15 days.

According to the results of a test done to minimize the frequency of angina attacks and raise the body's resilience to physical effort, propranolol was more successful when taken with trimetazidine than when used with isosorbide dinitrate.

Effect of trimetazidine in chronic heart failure.

Administering trimetazidine to patients with chronic heart failure led to an improvement in the myocardium's local contractility, an increase in the left ventricle's blood ejection volume both at rest and during physical activity. Additionally, it resulted in a reduction in the functional class of angina pectoris and chronic heart failure, as well as an improvement in the 6-minute walk distance. The ESA 2016 recommendations indicate long-acting trimetazidine for pharmacological therapy when stable angina is accompanied by heart failure with reduced ejection fraction (NYHA functional class II-IV) (Recommendation class IIB, level of evidence A).

Table 1.1

Pharmacokinetics of trimetazidine.

Parameters	**Regular dosage form of trimetazidine, 20 mg**	**Trimetazidine extended-release dosage form, 35 mg**
"Primary pass effect" in the liver	have (happens)	have (happens)
Time to reach maximum concentration in blood plasma	2 hours	3 hours
Maximum concentration in blood plasma	55 mg/ml	55 mg/ml
Time to reach the same concentration in blood plasma	24-36 hours	60 hours
Binding to blood plasma proteins	less (16%)	less (16%)
T ½	6 hours	7 hours; 12 hours (over 65)
Excretion from the body [22].	through the kidneys [22]	through the kidneys [22].

Trimetazidine is quickly and completely absorbed after oral administration. Biological absorption is 90%. It easily passes through histological barriers. The drug

is removed from the body through the kidneys (on average, 60% unchanged). Excretion of the drug from the body through the kidneys is directly proportional to creatinine clearance.

Instructions for use of trimetazidine.

- Trimetazidine is a 2nd-line drug in the treatment of stable ischemic heart disease (Recommendation class IIA, level of evidence V).

- In case of stable angina pectoris with heart failure with reduced ejection fraction (NYHA functional class II-IV), extended-release trimetazidine is recommended for drug therapy (Recommendation class IIB, level of evidence A).

Side effects and contraindications.

In rare cases, nausea, vomiting, and allergic reactions can be observed.

The drug is contraindicated during pregnancy and lactation (the safety and effectiveness of the drug during these periods have not been studied).

Review questions.

1. Explain the mechanism of antiischemic action of trimetazidine.
2. Explain the clinical significance of the pharmacokinetic parameters of trimetazidine.
3. Tell the effects of trimetazidine in the treatment of angina pectoris.
4. Tell the effect of trimetazidine in chronic heart failure.
5. Tell the instructions for the use of trimetazidine.
6. Tell the side effects and contraindications of trimetazidine.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)

The renin-angiotensin-aldosterone system (RAAS) plays a crucial role in regulating blood pressure [22]. The primary substance in RAAS, angiotensin II (AII), has a potent vasoconstrictor effect. AII primarily targets arteries, raising peripheral resistance, stimulating aldosterone secretion, promoting fluid retention, increasing circulating blood volume, and enhancing the release of catecholamines. AII is a "growth" factor for cardiomyocytes and smooth muscle, which causes muscle hypertrophy.

Table 1.1

Classification of ACEIs

1st class	Lipophilic drugs - captopril, alacepril, fentiapril
2nd class	Lipophilic prodrugs:
Group 2A	The kidneys eliminate the active metabolites of the following medications: cilazapril, benazepril, quinapril, perindopril, and enalapril.
Group 2V	Medications whose active metabolites are eliminated in two ways: fosinopril, trandolapril, spirapril, ramipril, and moexipril
3rd class	Hydrophilic drugs - lisinopril, libenzapril, seronapril

Table 1.2

Effects of angiotensin II.

Organs and tissues	Effects of angiotensin II.
Blood vessels	Vasoconstriction (secretion of noradrenaline, vasopressin, endothelin I), inactivation of nitric oxide
Heart	Positive inotropic and chronotropic effect Coronary artery spasm
Kidneys	Renal vasospasm (mainly efferent arterioles) Reduction and proliferation of mesangial cells Na2+ reabsorption, K+ excretion Decreased renin secretion
Adrenal gland	Adrenaline and aldosterone secretion
The brain	Antidiuretic hormone and vasopressin secretion Activation of the sympathetic nervous system, stimulation of the thirst center
Platelets	Stimulation of aggregation and adhesion
Inflammation	Macrophage activation and migration Expression of cytokine (IL-6), chemotaxis [22], and adhesion factors
Trophic factors	Hypertrophy of smooth muscles and cardiomyocytes Growth factor and protooncogene stimulation Increased synthesis of metalloproteinase and intracellular matrix components [22].

The key enzyme in the renin-angiotensin-aldosterone system (RAAS) is angiotensin-converting enzyme (ACE), which converts angiotensin I (AT I) into angiotensin II (AT II). ACE is primarily found in the blood, where it forms AT II, which has a short-term hemodynamic effect. In tissues, AT II is also produced not only by ACE but also through the action of other enzymes such as chymase, endoperoxidase, and cathepsin G [22].

ACE is similar to the enzyme kininase II, which is involved in the breakdown of bradykinin. Bradykinin is a powerful vasodilator and participates in ion transport and microcirculation control. The effect of bradykinin is very short and has a local effect. Bradykinin increases intracellular calcium, a cofactor of nitric oxide

(endothelial relaxing factor). Endothelial relaxing factor relaxes the muscles of blood vessels, prevents platelet aggregation, inhibits smooth muscle proliferation and mitosis (resulting in an antiatherogenic effect). Also, bradykinin stimulates the synthesis of PGE2 and PGI2 (prostacyclin) in the endothelium of blood vessels, which are powerful vasodilators and platelet antiaggregants [22].

The kinin system is a system opposed to RAAS. Inhibition of ACE causes an increase in the amount of kinins in various tissues, which accelerates blood flow, increases diuresis, and develops anti-ischemic, anti-proliferative, anti-atherogenic, and anti-aggregant effects.

Arterial hypertension, chronic heart failure, and acute myocardial infarction can cause RAAS activation.

Table 1.3

Functions of RAAS components

RAAS components	**Main functions**
AT I	Less active (100 times less active than AT II) [22].
AT III	It has the same effect as AT II, but its pressor effect is 4 times less than AT II.
AT IV	Involved in the release of tissue activator inhibitor of plasminogen, the main inhibitor of fibrinolysis, is a predictor of death from acute myocardial infarction.
FN 1-7	A degradation product of AT I and AT II, an endogenous inhibitor of the pathological effects of AT II: - binds to AT2-receptors and specific CNS-receptors; - affects the prostaglandin-bradykinin-NO system; - Has an antiproliferative effect; - It has a vasodilator effect; - Prevents reperfusion arrhythmia; - Prevents cardiac remodeling after acute myocardial infarction.

Table 1.4

Different factions of RAAS and their effects

Organs	Circulating RAAS (humoral)	Fabric RAAS
	Immediate effects	Slow effects
Kidneys	Aldosterone stimulation	Intraglomerular hypertension, arteriolo-nephrosclerosis
Blood vessels	Vasoconstriction	Blood vessel wall hypertrophy, blood vessel remodeling
Heart	Arrhythmogenic effect	Myocardial hypertrophy [22], cardiac remodeling

Mechanism of action of ACE inhibitors (ACEI).

The pharmacodynamic effects of ACEI include inhibition of ACE and reduction of formation of AT II in tissues, elimination of pressor and neurohumoral effects of AT II, as well as preventing the breakdown of bradykinin and enhancing the formation of vasodilating factors (prostaglandin, nitric oxide).

Table 1.5

Results of RAAS blockade

Effects associated with a decrease in the formation of AT II	Effects associated with reducing the breakdown of bradykinin
vasoconstriction	vasodilatation
monocyte adhesion	against monocyte adhesion
smooth muscle proliferation	expression of nitric oxide
activation of tissue activator inhibitor of thrombogenesis and plasminogen	tissue activator of plasminogen and fibrinolysis
production of free radicals	anti-remodulation effect
apoptosis	apoptosis
endothelial dysfunction	protective function of the endothelium

Table 1.6

ACEI description

Drug	Chemical group	Activity	Effect on tissue RAAS [22].
Captopril	SH-group	Active drug	no
Zofenopril	2SH-group	Prodrug	+
Enalapril	Carboxy-	Prodrug	no
Benazepril	Carboxy-	Prodrug	+
Quinapril	Carboxy-	Prodrug	+
Lisinopril	Carboxy-	Active drug	no
Moexipril	Carboxy-	Prodrug	+
Perindopril	Carboxy-	Prodrug	+
Ramipril	Carboxy-	Prodrug	+
Spirapril	Carboxy-	Prodrug	+
Trandolapril	Carboxy-	Prodrug	+
Fosinopril	Phospho-	Prodrug	+
Cilazapril	Carboxy-	Prodrug	+

The distribution of ACEIs into tissues depends on their lipophilicity. ACEIs are ranked in the following order of affinity (from strongest to weakest):

Quinaprilat = Benazeprilat = Trandolaprilat = Cilazaprilat = Ramiprilat = Perindoprilat > Lisinopril > Enalaprilat > Fosinoprilat > Captopril [22].

The affinity (similarity, structural similarity) of ACEIs with ACE determines the strength and duration of ACE inhibition by ACEIs, and the hemodynamic effects of ACEIs depend on this [22]. The hypotensive effect of ACEIs is more likely to be due to inhibition of tissue ACE than to inhibition of humoral ACE. The long-term hypotensive and organoprotective effects of ACEIs are associated with inhibition of tissue ACE.

According to the modern understanding of the mechanism of action of ACEIs, their mechanism of action is associated not only with their affinity for AAF but also

with their different active domains - N and C-terminal domains. Each of these domains can selectively bind to AT 1 and block the conversion of AT 1 to AT 2, but both domains must be involved for binding to bradykinin. Experimental studies have shown that the bradykinin/AT1 index varies in different drugs, i.e., in enalaprilat - 1.0; in perindopril - 1.44; in ramipril - 1.16. This indicates that perindopril and ramipril have an active effect on bradykinin. The effect of ACEIs on bradykinin increases the activity and expression of NO-synthetase, inhibits apoptosis of myocardial and endothelial cells. The greater the effect on bradykinin, the greater the organoprotective effect of ACEIs (vasodilating, vasoprotective, antiischemic, antiatherogenic).

Table 1.7

Pharmacodynamic effects of AceIs

Cardiovascular effects	- Arterial vasodilation (reduction of afterload, hypotensive effect) - Venous vasodilation (reduction of preload) - Coronary vasodilation - Prevents left ventricular dilatation and cardiac remodeling (cardioprotection)Chap qorincha gipertrofiyasini kamaytiradi (kardioproteksiya) - Reduces arterial wall hypertrophy, improves endothelial function (vasoprotection) - Reduces the frequency of reperfusion arrhythmias - Potentiates the effect of nitrates (prevents the development of tolerance) [22, .
Effects observed by the kidneys	- Dilation of afferent and efferent arterioles (reduces intravascular hypertension) - Increases diuresis and natriuresis - Retains potassium in the body - Nephroprotection (has an antiproliferative effect on mesengial cells) [22].

Metabolic effects	- Reduces insulin resistance, increases tissue sensitivity to insulin - Reduces atherogenic lipids (low-density lipoproteins, TH) and increases the amount of antiatherogenic lipids (high-density lipoproteins) - Has an antioxidant effect - Has an anti-inflammatory effect [22]

Hypotensive effect of AAFIs [22].

The hypotensive effect of ACEIs is due to the inhibition of ACE, which results in the formation of AT2 from AT1 and the reduction of bradykinin degradation.

Table 1.8

Duration of the hypotensive effect of ACEIs

Drug	Onset of effect, hours	Maximum exposure time, hours	Duration of effect, hours
Benazepril	< 1	2-4	16-24 [22].
Kaptopril	< 0,5	1	4-12
Kvinapril	< 1	2-4	24
Lizinopril	< 1	4-6	> 24
Moeksipril	1	3-6	24
Perindopril	1	4-6	24
Ramipril	1-2	4-6	> 24
Spirapril	1	4	24
Trandolapril	1	6	Up to 48 hours
Fozinopril	1	2-6	24
Zofenopril	1	4-6	24
Enalapril	< 1	6-8	24

Cardioprotective effect.

ACE inhibitors (ACEIs) exert their cardioprotective effects by reducing left ventricular hypertrophy, preventing myocardial ischemia and reperfusion injury, and promoting beneficial cardiac remodeling. In addition to reducing the trophic effect of AT2 on the myocardium, ACEIs also modulate sympathetic activity, which is responsible for the cardioprotective effect. AT2 is crucial in regulating catecholamine release, and a decrease in AT2 formation helps mitigate the sympathetic nervous system's impact on the cardiovascular system. Additionally, kinins, particularly bradykinin and prostaglandins, contribute to the cardioprotective effect. Their anti-ischemic properties and ability to dilate capillaries enhance microcirculation, improve oxygen delivery and metabolism in the myocardium, and reduce left ventricular hypertrophy by about 10%. This reduction indicates the antiproliferative effects of ACE inhibitors, leading to better myocardial pumping function in post-infarction recovery and with left ventricular hypertrophy [22].

ACE inhibitors (ACEIs) have been shown to reduce the risk of death by 23% and the risk of atrial fibrillation by 28%. Furthermore, according to numerous randomized clinical trials, ACEIs prevented the development of chronic heart failure in approximately 26% of patients. In cases of acute myocardial infarction, ACEIs help prevent cardiac remodeling induced by RAAS activation, which is a major factor contributing to the onset of heart failure and left ventricular contractile dysfunction. Meta-analyses have shown that the use of ACEIs in acute myocardial infarction, both early (within the first 24 hours) and late (after 48 hours), lowers mortality from acute myocardial infarction by 26%, reinfarction by 20%, and rehospitalization in chronic heart failure by 27%. However, there is no evidence of a significant therapeutic effect of ACEIs in chronic heart failure with FV>40% (without reduced left ventricular contractile function).

ACEIs have an anti-ischemic effect, which is associated with blocking the neurohumoral effect of AT2 (reduces the release of catecholamines, prevents myocardial damage caused by catecholamines), as well as with bradykinin effects.

According to the results of the meta-analysis by S. Yusuf, a decrease in mortality in stable forms of ischemic heart disease (OR = 0.86) was found.

Vasoprotective and antiatherogenic effects.

AT2 has a trophic effect not only on the myocardium but also on the vascular wall, i.e., it causes hypertrophy/hyperplasia of the muscle layer, inhibition of endothelial cell growth, and, as a result, endothelial dysfunction. AT2 also stimulates other growth factors (platelet-derived growth factor, endothelin-1), leading not only to hypertrophy of the vascular wall but also to atherosclerosis.

The vasoprotective effect of ACEs is mediated both by blocking the negative effects of AT2 on blood vessels and by bradykinin.

Table 1.9

Effect of ACEIs on endothelial dysfunction (meta-analysis results)

Groups and sub-groups	Increased endothelium-dependent vasodilation of the brachial artery
ACEI and placebo	+1,26% r = 0,002
ACEI and other groups of hypotensive drugs	+0,89% r = 0,009
ACEI and BAB	+0,59% r = 0,03
ACEI and CA	+2,15% r = 0,009
ACEI and A2RA	+0,21% r = no information

According to the results of the meta-analysis, ACEIs have a positive effect on arterial stiffness, reducing arterial stiffness and reducing the development of atherosclerosis in the carotid and coronary arteries.

Nephroprotective effect.

Activation of RAAS is a key step in diabetic and non-diabetic kidney damage. The development of nephropathy is based on damage to the renal vascular endothelium. By influencing RAAS, ACEIs lower proteinuria and stop renal failure from worsening. In individuals with diabetic and hypertensive nephropathy, dilatation of the renal tubules' efferent arterioles lowers intraglomerular filtration

pressure, filtration fraction, and hyperfiltration, which in turn lessens nephropathy. The nephroprotective effect of ACEIs is also based on their anti-inflammatory and antiproliferative effects.

Cerebroprotective effect.

ACEIs do not lower the risk of stroke, according to the findings of extensive meta-analyses. Perindopril and ramipril have been demonstrated in certain clinical trials to stop the recurrence of brain-related problems [22].

Metabolic effects.

RAAS plays an important role in the development of metabolic disorders. RAAS inhibitors or blockers are considered neutral drugs. According to the results of meta-analyses, it was found that ACEIs reduce the risk of developing diabetes by 22% to 33%. This is because ACEIs increase the sensitivity of tissues to insulin and improve glucose uptake by tissues due to improved blood circulation.

Pharmacokinetics of ACEIs.

The lipophilicity of ACEIs provides their effect on tissue RAAS and their organ-protective effect.

Table 1.10

Lipophilicity index of active forms of ACEIs

The drug	Lipophilicity index
Zofenopril	3,5
Fosinoprilat	> 2,00
Trandolaprilat	1,46
Quinaprilat	1,42
Ramiprilat	0,92
Perindoprilat	0,87
Enalaprilat	0,11
Captopril	0,08
Lisinopril	-2,44

Note: a negative value indicates the hydrophilicity of the drug.

The majority of ACEIs are prodrugs that undergo liver metabolism to produce an active metabolite. After one to two hours, the blood's ACEI concentration reaches its maximum. The table displays the ACEIs' pharmacokinetic parameters.

Table 1.11

Instructions for using ACEIs.

Instructions for use	**Level of evidence**
Arterial hypertension	A
Chronic heart failure	A
Left ventricular systolic dysfunction	A
Acute myocardial infarction	A
Diabetes mellitus, diabetic nephropathy	A
HID without symptoms of chronic heart failure, with a high risk of cardiovascular complications (perindopril, ramipril) [22].	V

Note: Level of evidence A – evidence is from large controlled randomized clinical trials; Level of evidence V – evidence is from limited (some or small number) patients, controlled randomized clinical trials

Arterial hypertension.

ACEIs have a hypotensive impact in practically all types of AH, regardless of renin activity in the plasma. ACEIs are considered first-line treatment for AH. When taken alone, they are successful in 50% of patients. In addition to the hypotensive impact, ACEIs in the treatment of AH lower cardiovascular complications and mortality. They are the preferred treatment, especially when AH is associated with diabetes mellitus [22].

Table 1.12

Pharmacokinetic parameters of ACEIs.

Drug	Absorption, %	Bioavailability, %	Plasma protein binding, %	T ½, hours	Metabolism/active metabolite	Elimination (kidney/liver)
Benazepril	37	37	95	10-11	+/+	Kidney (more than 70%)
Captopril	75 (30-55 after meals)	75 (decreases after meals)	25-30	2	+/-	Kidney (up to 50% active)
Zofenopril	No information	93	88	5,5	+/+	69/26
Quinapril	60	38	97	2	+/+	60/40
Lisinopril	25 (6-60)	25-60	< 10	12	-	Kidney – 100%
Moexipril	22 (decreases after meals)	13 (decreases after meals)	50-70	2-9	+/+	50/50
Perindopril	60-80	65-75	20-30	3-10	+/+	Kidney – more than 70%
Ramipril	50-60	50-60	56	9-17	+/+	60/40
Spirapril	45	50	90	2-40	+/+	40/60
Trandolapril	40-60	10	80-95	10	+/+	33/66
Fosinopril	25-36	25-30	97-98	11,5	+/+	50/50
Cilazapril	No information	45	90	7-11	+/+	Kidney – 100%
Enalapril	60	60	50-60	11	+/+	Kidney – 70%

Chronic heart failure and left ventricular systolic dysfunction.

ACEIs should be recommended to patients with left ventricular dysfunction, even if there are no symptoms of heart failure. ACEIs prevent and decrease the course of chronic heart failure, minimize the risk of acute myocardial infarction and

sudden death, and lessen the requirement for hospitalization. ACEIs diminish left ventricular dilation and myocardial remodeling, hence lowering atherosclerosis [22].

Acute myocardial infarction.

The use of ACEIs in the early stages of myocardial infarction lowers mortality, particularly when it occurs in the presence of arterial hypertension, diabetes mellitus, or in people in high-risk groups [22].

Diabetes and diabetic nephropathy.

All ACEIs, independent of blood pressure, reduce the course of kidney damage in type 1 and type 2 diabetes, as well as chronic renal failure in other nephropathies. Long-term usage of ACEIs decreases diabetic and cardiovascular problems more than other antihypertensive medications [22].

Main contraindications.

- Bilateral renal artery stenosis or stenosis of a single kidney; - Renal failure following kidney transplantation.

- Severe renal failure (plasma creatinine levels exceeding 265 mol/l).

- Hyperkalemia (above 6 mmol/l) - Severe aortic stenosis (causing hemodynamic disturbances)

- Angioedema (even after using another ACE)

- Arterial hypotension;

- Pregnancy (embryotoxic effect: in the first trimester, may cause heart, blood vessel, kidney, and brain defects; in the second and third trimesters, may cause fetal hypotension, skull hypoplasia, renal failure, anuria, and fetal mortality) [22].

It should be used with caution in the following cases:

- Autoimmune diseases;

- Collagen diseases, especially systemic lupus erythematosus and scleroderma (increased risk of neutropenia and agranulocytosis);

- Bone marrow dysfunction [22].

Dosing principles. ACEIs should be started at a low dose and then titrated gradually, i.e., every 1-2 weeks, to the required dose. The patient should not be in

an upright position when taking the first dose of ACEIs (as "first dose" hypotension may occur).

Adverse effects of ACEIs and safe use.

Most common - hypotension, cough, hyperkalemia, rash;

Rare - impaired renal function (in patients with renal artery stenosis and patients with ChHF taking diuretics), angioedema, impaired blood production [22], taste disturbance.

Hypotension.

Hypotension is a common side effect of ARBs, particularly in elderly individuals, patients with high plasma renin activity (such as those with renal artery stenosis), patients with chronic heart failure, those on diuretics, or individuals with hyponatremia. The occurrence of hypotension is about 2% in healthy individuals and 10% in those with chronic heart failure. To avoid hypotension, ACEIs should be begun at a low dose and increased gradually.

Cough.

Coughing may occur in 5- 20% of individuals using ACEIs. Cough is frequently dose-dependent and more common in women. Cough is caused by the kinin system, which triggers pro-inflammatory peptides (e.g., substance P, neuropeptide Y) that have accumulated in the bronchial walls, as well as bradykinin and histamine. Histamine affects bronchial motility and causes coughing. When coughing occurs, switching from one ACE to another does not assist since coughing is connected with the mechanism of action of ACEIs, which is the same for all ACEIs. When coughing occurs, ACEIs should be withdrawn; the cough will eventually dissipate.

Hyperkalemia (above 5.5 mmol/l). The occurrence of hyperkalemia is associated with the mechanism of action of ACEIs, i.e., blocking the formation of AT2 leads to a decrease in aldosterone In patients with chronic renal failure (including latent chronic renal failure) and other kidney conditions like diabetic nephropathy, the risk of hyperkalemia is elevated when potassium-sparing diuretics or potassium supplements are used. This is because these conditions impair the regulation of potassium, leading to retention, and NSAID drugs are used together.

Skin rashes and angioedema are associated with increased levels of bradykinin. Renal dysfunction may manifest as azotemia (blood creatinine increases by 10-20%), proteinuria [22], and even acute renal failure. Impaired renal function is mainly observed in patients with renal vascular pathology (bilateral renal artery stenosis, solitary renal artery stenosis, occult renal vascular pathology), as well as in patients taking diuretics and NSAIDs as a result of impaired glomerular filtration. An increase in plasma creatinine levels may occur at the beginning of treatment with ACEIs (during the first 2-3 months) and is transient, with subsequent normalization of creatinine levels, not requiring dose reduction or discontinuation of the drug.

Neutropenia, thrombocytopenia, and agranulocytosis occur very rarely (less than 0.5%).

Table 1.13

Safe use of ACEIs

Diseases, syndromes, and pathological conditions	**Predictable complications**	**Control methods**
Uncomplicated arterial hypertension and chronic heart failure	Arterial hypotension ("first dose" effect), transient increase in creatinine and potassium levels in blood plasma [22].	Monitoring blood pressure and the levels of creatinine and potassium in the blood plasma [22]
Kidney failure	Development of severe hypotension, hyperkalemia, and increased creatinine levels [22].	Determination of creatinine and potassium levels in blood plasma, determination of glomerular filtration rate in the kidneys
Renal artery stenosis	Development of acute hypotension ("first dose" effect)	Small doses of the drug control arterial pressure in both vertical and horizontal positions
Diabetes mellitus	Hypokalemia may be observed [22].	Blood glucose control [22].
Autoimmune diseases	Cytopenia may be observed.	Monitoring the number of erythrocytes, platelets, leukocytes, and leukocyte formula in the blood

Table 1.14

Interaction with other drugs.

Concomitant drug	Mechanism of action	The result of cooperation
Diuretics: - thiazide, loop diuretics	Sodium and fluid deficiency	Acute hypotonia, risk of kidney failure
- potassium-sparing	Reduced aldosterone formation	Hyperkalemia
Antihypertensive drugs	Increased Renin activity or increased sympathetic activity	Increased hypotensive effect
Sympathomimetics	Vasoconstriction	Reduced hypotensive effect
NSaIDS (specifically indomethacin	Decreased synthesis of prostaglandins in the kidneys, and fluid retention in the body [22].	Reduced hypotensive effect [22].
ACEI+Diuretiks + NSAIDs (trio "dangerous")	The kidney negatively affects blood circulation, potentiates (strengthens) dehydration, and hypovolemia.	As nephrotoxicity increases, the risk of acute kidney failure increases.
Potassium preparations, potassium-sparing foods, and food additives	Pharmacodynamic	Hyperkalemia
Preparations that reduce blood production	Pharmacodynamic	Risk of developing neutropenia and Agranulocytosis
Esterogenes	Fluid retention in the body	Reduced hypotensive effect [22].

Pharmacodynamic interoperability is mainly observed when using ACEIs along with other drugs. The use of ACEIs together with antihypertensives, diuretics, anti-inflammatory nonsteroidal drugs, and potassium preparations is of clinical importance.

When ACEIs are used simultaneously with other antihypertensive drugs, their hypotensive effect is enhanced, which is especially useful in the treatment of arterial hypertension.

When used together with thiazide diuretics, the hypotensive effect is enhanced, but the risk of developing hypotension ("first dose" effect) and acute renal failure increases [22].

When using ACEIs together with aldosterone antagonists [22], potassium preparations, the risk of developing hyperkalemia increases; therefore, in such cases, it is necessary to monitor the level of potassium in the blood plasma.

When ACEIs are used together with NSAIDs (except when aspirin is used as an antiplatelet agent at a dose of less than 150 mg/day), NSAIDs reduce prostaglandin synthesis in the kidneys, reduce glomerular filtration, fluid retention in the body, narrowing of the afferent renal arteries, and as a result, the hypotensive effect of ACEIs is reduced.

When ACEIs are used together with NSAIDs (except when aspirin is used as an antiplatelet agent at a dose of less than 150 mg/day), NSAIDs reduce prostaglandin synthesis in the kidneys, reduce glomerular filtration, fluid retention in the body, narrowing of the afferent renal arteries, and as a result, the hypotensive effect of ACEIs is reduced.

One of the most dangerous combinations is ACE + NSAID + Diuretic. In this case, iatrogenic acute renal failure develops in 50% of cases, and death occurs in 10%.

Estrogens reduce the hypotensive effect of ACE.

When ACE inhibitors are used together with blood sugar-lowering drugs, hypoglycemia may increase.

ACE should be used with caution with drugs that have a myelosuppressive effect.

Questions for control.

1. Explain the structure and function of the renin-angiotensin-aldosterone system (RAAS).

2. Give examples of the effects of angiotensin II on organs and tissues [22].

3. Describe the classification of angiotensin-converting enzyme inhibitors.

4. What is the mechanism of hypotensive action of angiotensin-converting enzyme inhibitors?

5. What is the mechanism of nephroprotective action of angiotensin-converting enzyme inhibitors?

6. Explain the clinical significance of the pharmacokinetic parameters of angiotensin-converting enzyme inhibitors.

7. List the indications for the use of angiotensin-converting enzyme inhibitors.

8. List the adverse effects of angiotensin-converting enzyme inhibitors.

9. List the contraindications to the use of angiotensin-converting enzyme inhibitors.

10. Give examples of interactions between angiotensin-converting enzyme inhibitors and other drugs.

CLINICAL PHARMACOLOGY OF ANGIOTENSIN 2 RECEPTOR ANTAGONISTS.

A2RAs (sartans) are a group of drugs that affect RAAS, block the action of AT2 more completely than ACEIs, and are well tolerated by patients.

Mechanism of action of A2RAs. Two types of receptors are sensitive to AT2 and perform different functions: AT1-type and AT2-type receptors.

AT1-type receptors are found in the walls of blood vessels, adrenal glands, and liver. AT2 receptors exert their negative effects through AT1 receptors, causing vasoconstriction, aldosterone release, vasopressin, and noradrenaline release, activation of the sympathetic nervous system, fluid retention, cardiomyocyte and smooth muscle cell proliferation, and renin formation due to negative feedback. AT2 receptors are widely distributed across the body, including the central nervous system, endothelial cells of blood vessels, adrenal glands, reproductive organs (like the uterus and ovaries), and the fetus, where they are more abundant than in adults. Stimulation of AT2 receptors has positive effects, including vasodilation, tissue repair and regeneration, antiproliferative effects, and support of embryonic cell development and differentiation. The number of AT2 receptors in tissues increases significantly when cells are damaged and repair is needed.

Table 1.1

	Functions of AT2 receptors
AT1-type receptors	Vasoconstriction
	Stimulates the synthesis and secretion of aldosterone
	Stimulates the reabsorption of sodium by the tubules
	Slows down the blood circulation in the kidneys
	Proliferation of vascular smooth muscle cells
	Hypertrophy of the heart muscle
	Increased release of noradrenaline
	Stimulates the release of vasopressin, endothelin-I
	Inhibits the release of renin
AT2-type receptors	Vasodilation
	Natriuretic effect
	Release of nitric oxide and prostacyclins
	Antiproliferative effect
	Stimulates apoptosis
	Involved in the development and differentiation of embryonic tissues [22].

A2RAs are highly selective for AT1-type receptors and block the negative effects of AT2. As a result of blocking the negative feedback mechanism, the amount ofAT2 and its other degradation products (AT3, AT4, AT1-7) increases, and AT2-type receptors are stimulated [22].

Table 1.2

Humoral effects of A2RAs and ACEIs

RAAS components	A2RA	ACEI
Renin	↑	↑
Angiotensinogen	↑	↓
ACE (kinase)	↔	↓
Himaza	↓	↔
Angiotensin I, 1-7	↑	↑
Angiotensin II	↑	↓
Angiotensin III, IV	↑	↓
Aldosterone	↓	↓
Brady's	↔	↑

A2RAs not only block AT1-type receptors, but also have a sympatholytic effect, that is, they increase the release of noradrenaline in the central nervous systemand reduce the release of noradrenaline from sympathetic nerve endings.

A2RAs, unlike ACEIs, can eliminate the effects of AT2 by blocking AT1 receptors. AAFIs cannot sufficiently inhibit RAAS activity, since with ACE inhibition, AT2 is also formed through other alternative (chemase, endothelialand renal peptidase, TAP) pathways. A2RAs do not affect the kinin system; the origin of the negative effects of AAFIs is also associated with the activation of the kinin system. Another important difference between AAFIs and A2RAs is their effect on the amount of AT4 (a dehydration product of AT2, which is involved in the release of the main inhibitor of fibrinolysis, PAI-1, a predictor of death from myocardial infarction).

The maximum concentration of A2RAs in the blood is typically reached 1-2 hours after oral administration, with steady-state concentrations achieved after 5-7 days of consistent use [22]. A2RAs are highly protein-bound (over 90%), mainly to albumin. The volume of distribution of A2RAs is influenced by their lipophilicity, with telmisartan having the largest volume of distribution among them.

Table 1/13

Lipophilicity coefficient of A2RAs

The drug	**Lipophilicity coefficient**
Losartan (E3174)	-2,45 (1,19)
Valsartan	-0,95
Candesartan (CV11974)	-0,96
Azilsartan	-0,29
Eprosartan	0,047
Irbesartan	1,48
Telmisartan	3,20

Note: A "negative" number indicates hydrophilicity.

The pharmacokinetic parameters of sartans indicate that they are metabolized in the liver and predominantly excreted through the liver. This is of significant practical importance, as it allows the use of sartans in patients with impaired renal function, a condition often seen in individuals with arterial hypertension, as the kidneys are the primary target organ affected in this condition. Also, in severe liver failure, the bioavailability of sartans increases, and their elimination slows down, therefore, biliary obstruction and severe liver failure are contraindicated for the use of sartans, but mild and moderate liver failure do not require dose adjustment of sartans. Sartans should be used with caution in severe chronic renal failure.

Table 1.14

Pharmacokinetic properties of sartans

The drug	Receptor binding	Selectivity for AT1 type receptors (relative to AT2 type receptors)	Degree of inhibition of the pressor effect of AT2, %
Losartan	competitive	1000	25-40
Valsartan	noncompetitive	20000	30
Irbesartan	noncompetitive	8500	40
Candesartan	noncompetitive	10000	65
Telmisartan	noncompetitive	3000	40
Eprosartan	competitive	1000	30
Olmesartan	noncompetitive	12500	61
Azilsartan	noncompetitive	10000	100

Table 1.14

Pharmacokinetics of sartans

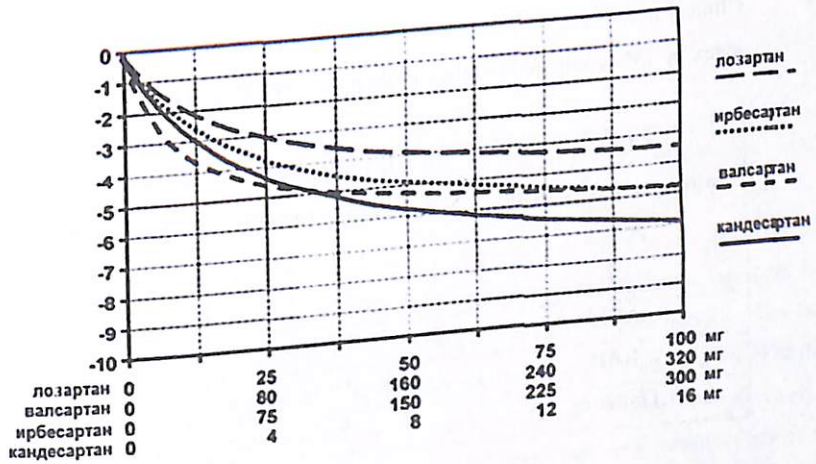
The drug	Bioavailability, %	T ½, hour	Enzymes involved in metabolism	Metabolism, %	Excretion	
					through the liver	through the kidney
Losartan (EXP-3174)	30-40	1-3 (5-10)	CYP2C9, CYP3A4	14	65	35
Valsartan	10-35	6-7	CYP2C9, CYP2C8, not cytochrome P450	20	80	20
Irbesartan	60-80	11-18	CYP2C9, glucuronidation	9	80	20
Candesartan	15	5-13	CYP2C9, glucuronidation a	Minimum	67	33
Telmisartan	30-60	21-38	glucuronidation	15	98	2
Eprosartan	13	5-9	no	Minimum	90	10
Olmesartan	25	12-18	no	Minimum	60	40
Azilsartan	60	11	CYP2C9	50	55	42

In the elderly, the bioavailability of sartans increases, which can lead to a 2-fold increase in their concentration in the blood plasma (a decrease in albumin levels in the elderly can also cause this condition), as well as a slowdown in intestinal absorption, which leads to a prolongation of the time it takes for sartans to reach their maximum concentration in the blood and the duration of their effect. In this case, a reduction in the dose of the drug is not required, since sartans have a large therapeutic range.

Hypotensive effect.

The mechanism of hypotensive action of A2RAs is due to the blockade of the vasoconstrictor effect of AT2 and the induction of vasodilation by reducing the tone of the SAS, as well as the natriuretic effect. The hypotensive effect of sartans is poorly dose-dependent; that is, ½ or ¼ of the average therapeutic dose provides a therapeutic effect, but increasing the dose to the maximum does not lead to a significant increase in the therapeutic effect.

Dose dependence of the hypotensive effect of sartans



1-rasm

Table 1.16

Comparison of the hypotensive effects of sartans

The drug	Dose, mg/day	ΔSAP / ΔDAP
Losartan	50-100	-8,0 / -5,5
Valsartan	80-160	-7,5 / -4,0
Irbesartan	150-300	-10,0 / -6,5
Candesartan	8-32	-10,0 / -6,0
Telmisartan	20-80	-9,5 / -6,0
Eprosartan	400-1200	-7,5 / -4,5

Note: SAP-systolic arterial pressure; DAP-diastolic arterial pressure The strongest hypotensive effect was observed with candesartan and irbesartan.

Cardioprotective effect.

In patients with left ventricular hypertrophy, numerous RCTs have shown that sartans have a regression effect on left ventricular hypertrophy. The effect of sartans on left ventricular hypertrophy is linked to their hemodynamic action, antiproliferative, and antifibrotic effects, and their reduction in cardiac remodeling. Clinical trials have shown that sartans reduce the left ventricular myocardial mass index by 13% compared to other antihypertensive drugs (Table 1.17).

Table 1.17

Class of antihypertensive drugs	Δ left ventricular myocardial mass index, %	
	80 CT results (n=4116)	75 CT results (n=6001)
A2RA	13	12,6
CA	11	12,8
ACEI	10	11,4
BAB	6	8,8
Diuretics	8	7,6

According to several meta-analyses examining the effectiveness of sartans in chronic heart failure, compared with placebo, sartans reduced the risk of death by

17% and hospitalization for CHHF by 36% in patients with CHHF who had CHHF and were at risk of developing acute myocardial infarction, but no advantage was found compared with ACEIs.

The development of atrial fibrillation in patients with AH and CHHF negatively affects the prognosis of the disease, increases the risk of thromboembolism, stroke, and cardiovascular disease, and increases the risk of death by 2-5 times. According to the results of a meta-analysis, sartans reduced the incidence of atrial fibrillation by 29%.

Nephroprotective effects.

The effects of A2RAs on the kidney are similar to those of ACEIs, but there are some differences (Table 1.18).

Table 1.18

Parameters	A2RA	ACEI
Afferent arteriolar tone	↓ minimum	↓ minimum
Efferent arteriolar tone	↓	↓↓
Globular filtration rate	↓	↓
Filtration fraction	↓	↓↓
Potassium content	↑	↑↑

One important factor is that A2RAs do not affect the amount of bradykinin, while an increase in the amount of bradykinin under the influence of ACEIs leads to a decrease in the tone of the renal arteries, which leads to a sharp decrease in intraglomerular pressure, filtration fraction, and glomerular filtration rate (this is considered an undesirable condition) [22]. A2RAs have a less pronounced effect on efferent arteriolar tone than ACEIs, A2RAs improve renal blood flow more than ACEIs, and have little effect on glomerular filtration rate. As a result, intraglomerular pressure and filtration fraction decrease, and nephroprotective effects occur [22]. These effects are especially beneficial in patients with AH with CHRF. The nephroprotective effect of A2RAs is observed at doses below those that cause hypotensive effects. This property of A2RAs is of clinical importance in

severe CHRF or heart failure, since even low doses of ACEIs cause azotemia and severe hypotension. The nephroprotective effect of A2RAs is manifested by a decrease in microalbuminuria in patients with AH and diabetic nephropathy. This effect has been studied and confirmed in several meta-analyses.

Neuroprotection.

A meta-analysis found that A2RAs reduced the risk of stroke by 21% compared with other antihypertensive drugs. A2RAs have also been shown to have pleiotropic cerebroprotective effects in preventing dementia and Alzheimer's disease in cohort studies.

Metabolic effects.

According to two large meta-analyses, in patients with AH, the incidence of new-onset diabetes mellitus was 20-25% lower with A2RAs compared with other antihypertensive drugs [22]. Losartan also has a strong uricosuric effect, while candesartan and telmisartan slightly increase uric acid levels. Several studies are being conducted to study the effect of sartans on uric acid, and the data obtained show that the effect of sartans on uric acid is different, and clarification of the data is required.

Indications for use of A2RAs.

A2RAs are well tolerated by patients. They are less likely to cause hypotension and collapse than other antihypertensive drugs. "First-dose" hypotension occurs in 1% of cases, and the development of cough is 3 times less common than with ACEIs.

Table 1.19

Instructions	**Level of evidence**
Arterial hypertension	A
Chronic heart failure (instead of ARBs) (losartan, valsartan, candesartan)	V
Diabetic nephropathy (losartan, irbesartan)	A
Acute myocardial infarction with left ventricular dysfunction (valsartan)	V

Note: Level of evidence A – Evidence from large controlled randomized clinical trials provides a high level of evidence (Level I), while evidence from limited (some or small number of) patients in controlled randomized clinical trials is considered Level V.

There is evidence that A2RAs may increase the risk of developing cancer (mainly lung cancer), but clinical trials are underway to clarify this information.

Table 1.20

Interaction with other drugs.

Concomitant drug	A2RA	The result of cooperation
Pharmacodynamic interactions		
Alcohol	Losartan, Valsartan, Eprosartan	Increased hypotensive effect
Hypotension drugs, diuretics	All	Increased hypotensive effect
NSAIDs, estrogens, sympathomimetics	All	Reduced hypotensive effect
Potassium-sparing diuretics, K-sparing drugs [22].	All	Hyperkalemia
Pharmacokinetic interaction		
Warfarin	Valsartan, Telmisartan	Decreased Cmax, prolonged prothrombin time [22].
Digoxin	Telmisartan	Increased Cmax

Control questions.

1. Describe the classification of angiotensin 2 receptor antagonists.

2. Explain the mechanism of action of angiotensin 2 receptor antagonists.

3. What is the mechanism of hypotensive action of angiotensin 2 receptor antagonists?

4. What is the mechanism of nephroprotective action of angiotensin 2 receptor antagonists?

5. Explain the clinical significance of the pharmacokinetic parameters of angiotensin 2 receptor antagonists.

6. List the indications for the use of angiotensin 2 receptor antagonists.

7. List the adverse effects of angiotensin 2 receptor antagonists.

8. List the contraindications to the use of angiotensin 2 receptor antagonists.

9. Give examples of interactions of angiotensin 2 receptor antagonists with other drugs.

CLINICAL PHARMACOLOGY OF DRUGS THAT LOWER BLOOD PRESSURE BY AFFECTING THE CENTRAL NERVOUS SYSTEM.

Control of the cardiovascular system by the nervous system.

The autonomic nervous system regulates circulatory activity: the parasympathetic nervous system has a depressive effect, while the sympathetic nervous system has a stimulating effect. Afferent impulses from the limbic and hypothalamic systems regulate the sympathetic nervous system's activation. The nucleus of the solitary tract of the medulla oblongata provides information to the parasympathetic nervous system. In addition to participating in baroreceptor, volume-receptor, and chemoreceptor modulation of the cardiovascular system, the nucleus of the solitary tract dampens the rostral-ventro-lateral portion of the medulla oblongata.

Activation of the sympathetic nervous system leads to vasoconstriction, impairs glucose transport to muscle tissue, contributing to insulin resistance and hyperinsulinemia. It also slows lipid metabolism in the liver, causing hyperlipidemia. Additionally, sympathetic activation promotes a trophic effect, resulting in the growth of smooth muscle and myocardial enlargement.

Central α2-adrenoreceptors and I1-imidazoline receptors are responsible for the central nervous system's control of the circulatory system. Although α2-adrenoceptors can be found throughout the brain, the majority of them are found in the solitary tract nucleus. The RVLM and chromaffin cells in the adrenal gland's brain layer are the primary locations for I1-imidazoline receptors.

The first generation of centrally acting hypotensive drugs (methyldopa, guanfacine) The newer generation drugs, such as moxonidine and rilmenidine, primarily act as agonists of I1-imidazoline receptors in the rostral ventrolateral medulla (RVLM), while clonidine is an agonist of both α2-adrenoreceptors and I1-imidazoline receptors. These receptors are located in the nucleus of the solitary tract in the brainstem.

Table 1.1

The drug	**Effects on receptors**
Methyldopa	α_2-adrenoreceptors >> I1-imidazoline receptors
Guanabenz	α_2-adrenoreceptors >> I1-imidazoline receptors
Guanfacin	α_2-adrenoreceptors >> I1-imidazoline receptors
Clonidine	α_2-adrenoreceptors = I1-imidazoline receptors
Moxonidine	I1-imidazoline receptors >> α_2-adrenoreceptors
Rilmenidine	I1-imidazoline receptors >> α_2-adrenoreceptors [22].

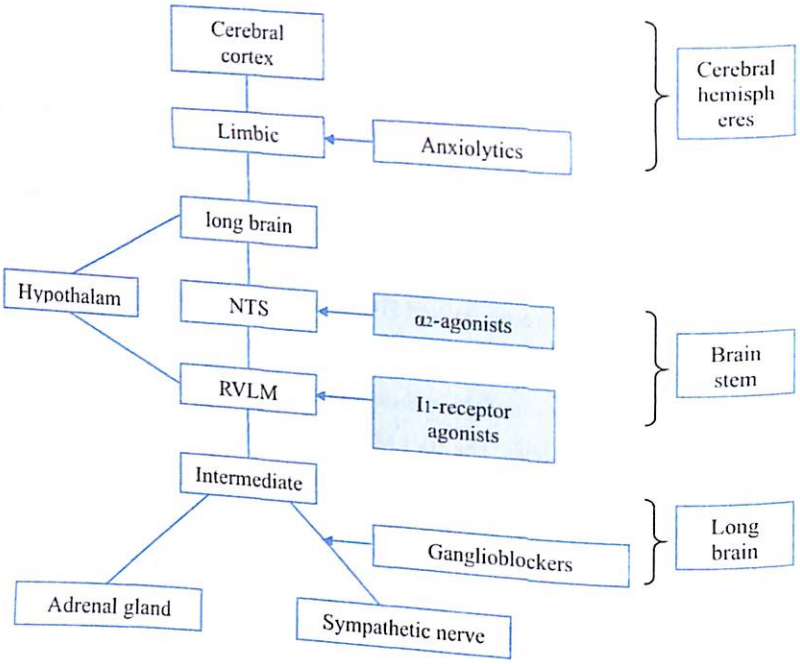


Figure 2. Mechanism of action of centrally acting hypotensive drugs.

Central α2-agonists.

Central α2-agonists stimulate α2-adrenoceptors of the blood-vessel center in the medulla oblongata, as a result of which the sympathetic impulse from the central nervous system to the periphery decreases.

All central α2-agonists have the following pharmacodynamic (hemodynamic) effects:

- The activity of the sympathoadrenal system decreases and reduces the amount of noradrenaline in the blood;

- reduces the total peripheral resistance of blood vessels, arterial pressure, to a lesser extent, the number of heart contractions, and blood pumping by the heart;

- reduces the intensity of the baroreceptor reflex, which is controlled by the sympathetic nervous system and participates in the compensatory mechanism (bradycardia development) that is activated when arterial pressure decreases;

- reduces the amount and formation of renin in the blood plasma (reduces the activity of RAAS);

- does not change blood circulation in the kidney even when blood pressure decreases;

- retains fluid and sodium in the body (increases circulating blood volume).

This group has 2 adverse effects associated with blood pressure control due to the receptor-related mechanism of action: withdrawal syndrome (increased blood pressure or hypertensive crisis when the drug is stopped suddenly, tachycardia, arrhythmia, insomnia) and tachyphylaxis syndrome ("bypass" syndrome or transient hypertension - increased blood pressure when the drug is taken for a long time). Their sedative effect is related to the effect on central α2-adrenoreceptors.

Table 1.2

The drug	Bioavailability, %	Protein binding, %	T ½, hours	Metabolism, %	Excretion (liver/kidney) %
Methyldopa	50	15	1-3	+	30/70
Guanfacin	80	70	10-30	+	60/40
Clonidine	=100	20-40	12-16	+50	20/60
Moxonidine	88	7	2	+20	>1/90
Rilmenidine	90	kam	8	-	30/65

Instructions for use.

The main indication for the use of central α2-agonists is arterial hypertension (it is the second-line drug for long-term therapy). Because clonidine and guanfacine lower intraocular pressure, they are used topically (eye drops) as an adjunct in the treatment of primary open-angle glaucoma.

Negative effects.

Sedative effect, numbness, drowsiness, dry mouth, depression, bradycardia, orthostatic hypotension, fluid retention in the body, withdrawal syndrome (after 2-7 days).

Interaction with other drugs.

When used with other antihypertensive drugs, the hypotensive effect increases; when used with tricyclic antidepressants, the hypotensive effect decreases; when used together with BAB, clinical signs of bradycardia and withdrawal syndrome increase; when used together with psychotropic drugs, depression increases.

Review questions.

1. Explain that the cardiovascular system is controlled by the nervous system.

2. Which drugs are central α2-agonists?

3. Explain the mechanism of action of central α2-agonists.

4. Explain the clinical significance of the pharmacokinetic indicators of central α2-agonists.

5. List the indications for the use of central α2-agonists.

6. List the negative effects of central α2-agonists.

7. List the contraindications to the use of central α2-agonists.

8. Give examples of interactions of central α2-agonists with other drugs.

I1-IMIDAZOLINE RECEPTOR AGONISTS.

Activation of imidazoline receptors in the central nervous system reduces the activity of the blood-vessel center and decreases peripheral vascular resistance. Selective agonists of I1-imidazoline receptors produce similar hemodynamic effects as α2-adrenoreceptor agonists: they lower arterial pressure by decreasing sympathetic nervous system activity and reducing peripheral vascular resistance, without affecting heart output or the number of heartbeats. RAAS activity decreases, fluid retention in the body does not change. However, unlike α2-adrenoceptor agonists, it has a positive metabolic effect: it reduces glycemia, insulin resistance, enhances lipolysis, and has a neutral effect on lipid metabolism, which is clinically important in the treatment of metabolic syndrome.

Table 1.3

Interaction of drugs that lower blood pressure by affecting the CNS with other drugs

Concomitant drug	Central sympatholytics	The result of cooperation
MAO inhibitors	α_2-agonists	Hypertensive crisis occurs
Tricyclic antidepressants, sympathomimetics, NSAIDs, estrogens	α_2-agonists	Hypotensive effect decreases
Haloperidol, lithium preparations	Methyldopa	The toxicity of drugs increases
α-adrenoblocators	α_2-agonists	Antagonism of hypotensive effect
β-adrenoblockers, cardiac glycosides	Clonidine, an I1-receptor agonist	Bradycardia, conduction disturbances
Alcohol, anxiolytics	α_2-agonists, I1-receptor agonists	Severe depression of the MNT activity, severe hypotension
Vasodilators, diuretics	α_2-agonists	Increased hypotensive effect
Other antihypertensive drugs	I1-receptor agonists	Increased hypotensive effect

I_1-receptor agonists do not cause the same adverse effects (sedation, depression, dry mouth) as α_2-agonists.

Moxonidine is a selective agonist of I_1-receptors. Moxonidine reduces the activity of SAS, reduces the content of noradrenaline in the blood plasma by 34%, reduces peripheral vascular resistance, and reduces the activity of AT_2 and renin in the blood plasma. Does not change the blood circulation in the kidneys and the glomerular filtration rate. Has a positive effect on carbohydrate metabolism: reduces hyperglycemia and insulin resistance, is neutral with lipid metabolism, but can reduce the level of total cholesterol.

When taken orally, bioavailability is 90%, and the maximum concentration in the blood plasma is reached after 1 hour. 10-20% of moxonidine is metabolized, forming a less active metabolite. More than 90% of the drug administered is excreted from the body through the kidneys (75% of it unchanged). T ½ is 2.2-2.3 hours, but its therapeutic effect reaches 24 hours. In chronic renal failure, T ½ is prolonged by 2-3 times, which requires dose adjustment.

Moxonidine is contraindicated in individuals with sick sinus syndrome, grade 2-3 AV conduction disorders, bradycardia (heart rate less than 50 beats per minute), poorly controlled arrhythmias, stage 3 chronic heart failure, severe coronary insufficiency, severe liver disease, severe renal dysfunction (glomerular filtration rate less than 30 ml/min or plasma creatinine level greater than 1.8 mg/dl), and angioedema.

Adverse effects.

Dry mouth (in 14-23% of cases), fatigue and headache (in 10% of cases), sometimes dizziness, sleep disturbances, and insomnia. Such adverse effects usually disappear with prolonged use of the drug. It does not cause a "cancellation" syndrome, and blood pressure returns to normal within 3-5 days after discontinuation of the drug.

Rilmenidine is similar in its mechanism of action and pharmacodynamic effects to moxonidine.

Questions for control.

1. Which drugs are included in the class of I_1-imidazoline receptor agonists?

2. Explain the mechanism of action of I_1-imidazoline receptor agonists.

3. Explain the clinical significance of the pharmacokinetic parameters of I_1-imidazoline receptor agonists.

4. List the indications for the use of I_1-imidazoline receptor agonists.

5. List the adverse effects of I_1-imidazoline receptor agonists.

6. List the contraindications for the use of I_1-imidazoline receptor agonists.

7. Give examples of interactions of I_1-imidazoline receptor agonists with other drugs.

CLINICAL PHARMACOLOGY OF DIURETIC DRUGS.

Diuretics are medications used to manage fluid levels in the body by reducing the reabsorption of water and salt in the renal tubules, thereby increasing their excretion. Prolonged use of diuretics can have negative effects as they alter the excretion of electrolytes such as potassium, calcium, magnesium, chloride, phosphates, bicarbonates, and sodium, in addition to water. Diuretics vary in their mechanism of action, potency, duration, onset of effect, and impact on acid-base balance. They are commonly prescribed in medical practice, particularly in cardiology, where they are frequently used to treat hypertension. They have a hypotensive impact in addition to a diuretic effect, and they also intensify the effects of nearly all hypotensive medications. The significance of diuretics in acute and chronic heart failure is increased when pulmonary edema and venous congestion are eliminated. Due to their extrarenal effects, diuretics can be utilized for a variety of purposes.

Physiological mechanism of diuresis.

Urine production begins with the formation of a protein-free ultrafiltrate from blood plasma. The glomerular capillaries filter around 120-125 ml of fluid per minute, but 99% of this is reabsorbed as it passes through the renal tubules, leaving only about 1% (1 ml) to form urine.

The rate of ultrafiltrate formation depends on the differences in hydrostatic and oncotic pressures on either side of the capillary walls, the blood flow rate in the glomeruli, and the number of filtering glomeruli. The composition of the ultrafiltrate differs from blood plasma as it lacks proteins and fats, and drugs bound to proteins cannot pass through the capillary barrier. Water and electrolytes in the ultrafiltrate are reabsorbed in the renal tubules, leading to urine formation. The tubules are divided into four zones based on their role in absorption. The fourth zone consists of the distal convoluted tubules and the collecting duct system. This zone absorbs sodium by the exchange of a small amount of potassium and hydrogen. This process is regulated by aldosterone. Decreased sodium absorption through the tubules increases the quantity of sodium in the fourth zone, accelerating the exchange of

sodium with potassium and causing potassium loss from the body. The antidiuretic hormone regulates the reabsorption of water in this zone. The collecting ducts flow through the kidney's medullary layer, which has a high concentration of salts. The permeability of the collecting tubules to water increases when antidiuretic hormone is present; as a result, water from low osmotic pressure areas flows to high osmotic pressure areas, resulting in the formation of concentrated urine.

Table 1.1

Classification of diuretics.

Group name	The drug	The main place of influence	Power of influence	Chemical structure
Diuretics that affect the bladder	Furosemide Torasemide Ethacrynic acid Bumetanide Piretanide	The ascending part of the Henley basin	Strong	Sulfonamide products (all except ethacrynic acids)
Thiazide and thiazide diuretics	Hydrochlorothiazide Chlorthalidone Clopamide* Indapamide	Distal tubules	Average	Sulfonamide products with and without thiazides
Carbonic anhydrase inhibitors	Acetazolamide	Proximal tubule	Weak	Sulfonamide product
Potassium-sparing diuretics	Triamterene* Amiloride	The last part of the proximal tubule and the collecting ducts	Weak	A non-sulfonamide product
Mineralocorticoid (aldosterone) receptor antagonists	Spironolactone Eplerenone	The last part of the proximal tubule and the collecting ducts	Weak	Steroid compound

Note: * - as part of complex preparations

Diuretics that have a laxative effect or are strong. The effect of diuretics of this group is strong, but short; only the effect of torasemide is long ($T_{1/2}$ is 2 times longer than other drugs).

Mechanism of action.

Blocks the active reabsorption of these ions by inhibiting the transport proteins that transport sodium, potassium chloride ions through the epithelial cells of the renal tubules.

Pharmacodynamic effects.

Enhances excretion of electrolytes (sodium, potassium, chlorine, magnesium) and other compounds. As a result of blocking carbonic anhydrase (except torasemide, bumetanide, piretanide) increases the excretion of bicarbonate and phosphates increases.

Drugs of this group increase uric acid excretion when taken once, and decrease it when taken continuously.

The diuretic effect of drugs of this group does not depend on the change in the acid-alkaline balance of the blood. Also, the diuretic effect does not change in renal failure, even when the rate of glomerular filtration decreases to 2 ml/min, the effect remains.

Effect on renal hemodynamics. Diuretics that act on the kidneys accelerate blood circulation in the kidneys. This effect is associated with an increase in the amount of prostacyclins, because drugs of this group increase the synthesis of prostacyclins in the kidneys. The balls do not change the filtration rate.

Other pharmacodynamic effects. All loop diuretics have a weak vasodilating effect. This effect is related to prostacyclins, which reduce the amount of calcium in the endothelial cells of blood vessels and dilate venous blood vessels, reducing left ventricular filling (reducing blood filling pressure) [22]. This effect is particularly strong in furosemide and appears before the diuretic effect in pulmonary edema. Vasodilatation and a decrease in circulating blood volume cause a hypotensive effect.

All short-acting strong diuretics can activate the sympathetic nervous system, so long-term use can worsen the course of ischemic heart disease. Strong diuretics dramatically increase the production of renin, which in turn increases the synthesis of aldosterone, which can cause a decrease in the effect of these diuretics. Unlike other strong diuretics, torasemide does not activate the sympathetic nervous system, but dose-dependently reduces the activity of RAAS. Torasemide blocks aldosterone receptors in the renal tubule epithelium, so hypokalemia is less likely than with other strong diuretics. Blocking of aldosterone receptors in the myocardium inhibits the development of myocardial fibrosis, which causes the organoprotective effect of torasemide in chronic heart failure. Long-term use of torasemide results in a reduction of arterial pressure, inhibition of myocardial fibrosis development, and a decrease in left ventricular myocardial hypertrophy.

When used at high doses, loop diuretics interfere with electrolyte transport not only in the kidneys but also in other organs. The clinical consequence of this is the ototoxic effect, which occurs due to disruption of the endolymph in the inner ear. The severity of this effect is dose-dependent.

Table 1.3

Pharmacokinetics.

The drug	Absorption from OIT, %	T ½, hour	It is excreted unchanged through the kidneys
Furosemide	10-90	0,3-3,4	60
Torasemide	79-91	0,8-6,0	30
Ethacrynic acid	~ 100	0,5-1,0	65
Piretanide	~ 8	0,6-1,5	50
Bumetanide	59-89	0,3-1,5	65

After the rapid and strong natriuretic effect of short-acting loop diuretics ends, retention of sodium ions in the body due to compensatory mechanisms (ricochet syndrome) is observed [22]. A daily rapid decrease in the volume of circulating

blood causes its rapid recovery, and this leads to the activation of angiotensin 2 and angiotensin 2 plays an important role in the pathogenesis of the development of chronic heart failure and hypertension; that is, it hinders the course of these pathologies.

Among loop diuretics, the effect of torasemide lasts for a long time, especially when its slow-release forms are used, the compensatory mechanisms mentioned above do not come into play, and patients accept this drug well.

Diuretics that have a diuretic effect are rapidly metabolized in the liver. Because they are well bound to proteins, they are not filtered through the globules, but are secreted through the transport mechanisms in the proximal part of the tubules and reach the corresponding part of the tubule unchanged.

Instructions for the use of diuretics that have a diuretic effect.

Drugs in this group are primarily used to treat conditions associated with sodium retention in the body, such as chronic heart failure, chronic kidney failure, nephrotic syndrome, swelling in liver cirrhosis, and ascites.

The effect of potent diuretics on pulmonary edema is due to their ability to rapidly dilate venous blood vessels and decrease circulating blood volume, which in turn reduces left ventricular filling pressure and enhances heart function.

Torasemide is a drug that has a positive effect on disease prognosis in chronic kidney failure due to reducing the activity of RAAS and reducing the death from cardiovascular diseases. Short-acting strong diuretics (except torasemide) are not the first-line drug of choice in arterial hypertension, but they are used in hypertensive crisis or to enhance the effect of other hypotensive drugs. Torasemide can be used in the long-term treatment of arterial hypertension, chronic heart failure, and ascites in liver cirrhosis.

The strong diuretic effect of diuretics, which affects the kidneys, is used in poisoning from drugs that are excreted through the kidneys. The use of loop-acting diuretics in acute renal failure can cause a transition from oliguric to non-oliguric form of acute renal failure. It is also possible to use diuretics that have a diuretic

effect in hypercalcemia, in which they are administered with an isotonic solution of sodium chloride to prevent excess water and electrolytes from leaving the body.

Negative effects.

One of the primary negative effects of diuretics on the kidneys is the disruption of water and electrolyte balance. In patients with liver disease, a reduction in sodium and extracellular fluid levels can lead to complications such as hepatic encephalopathy, vascular collapse, thromboembolic issues, hypotension, and impaired glomerular filtration.

Hypokalemia and hypomagnesemia can trigger arrhythmias, especially in individuals taking cardiac glycosides. Hypocalcemia may also develop, with rare cases leading to seizures. When diuretics from this group are administered intravenously (as opposed to orally), they may cause hearing impairment or even deafness, although these effects are often reversible (but not always). Additionally, loop diuretics can lead to hyperuricemia and hyperglycemia. Long-term use of these drugs can also result in decreased high-density lipoproteins and increased triglycerides and low-density lipoproteins. Torasemid has little effect on lipid and carbohydrate metabolism and does not increase the excretion of calcium, phosphorus, or bicarbonates. Also, due to its antialdosterone effect, torasemide is less likely to cause hypokalemia than other strong diuretics. Other negative effects, such as skin rash, increased sensitivity to light, paresthesia, thrombocytopenia, agranulocytosis, and changes in the gastrointestinal tract, can also be observed.

Contraindications.

Hypovolemia, hyponatremia, hypokalemia, increased sensitivity to sulfonamides (allergic reaction), anuria, use of diuretics that affect the loop is not recommended if no effect is observed after the administered diuretic.

Interaction with other drugs.

Anticoagulants, antihypertensive agents, other diuretics, non-depolarizing myorelaxants, diuretics that affect blood flow, and diuretics that enhance the adverse effects of cardiac glycosides and aminoglycosides can all interact with certain

medications. Additionally, diuretics that increase potassium loss, glucocorticosteroids, and drugs that raise blood levels of lithium and propranolol while reducing the effects of oral hypoglycemic agents can also present risks oralter drug effectiveness. These interactions may lead to increased side effects or reduced therapeutic effects, requiring careful monitoring and adjustments in treatment. For instance, diuretics that affect potassium levels can exacerbate electrolyte imbalances when combined with certain medications, while drugs like glucocorticosteroidsmay interfere with diuretic efficacy and electrolyte balance. Similarly, combining diuretics with medications like lithium and propranolol can lead to complications, highlighting the need for vigilant management in polypharmacy settings. Combining diuretics that work on the loop with indomethacin and other NSAIDS lessenstheir effects.

Thiazide and thiazide diuretics.

Drugs of this group consist of sulfonamide derivatives of benzothiadiazine (hydrochlorothiazide, methyclothiazide) and non-thiazide sulfonamides (chlorthalidone, clopamide, indapamide). The main site of action of drugs of this group is the initial part of the distal convoluted tubules. Drugs of this group are moderately strong diuretics.

Mechanism of action.

Thiazide and thiazide-like diuretics work by blocking the protein responsible for transporting sodium and chloride in the tubular epithelial cells, which reduces the absorption of sodium and chloride from the distal end of the renal tubules. Only thiazide diuretics inhibit the enzyme carbonic anhydrase in the proximal tubules, leading to increased excretion of phosphate and bicarbonate.

The increase in sodium levels in the collecting ducts promotes the exchange of sodium for potassium, which can lead to hypokalemia. While these diuretics increase uric acid excretion after a single dose, long-term use, particularly with a reduced glomerular filtration rate, can decrease uric acid excretion. Additionally, thiazide and thiazide-like diuretics can cause mild magnesium excretion or

magnesiumuria, which is particularly important to monitor in older patients. On a regular basis, these diuretics reduce calcium excretion.

Pharmacodynamic effects.

Effects on renal hemodynamics - medicines in this class do not alter renal blood circulation but, in some cases, reduce the rate of glomerular filtration.

Other pharmacodynamic effects.

The reduction in blood vessel resistance and the hypotensive effect of thiazide and thiazide-like diuretics are linked to their saluretic action. This effect occurs because these diuretics decrease the amount of sodium in smooth muscle cells, which leads to vasodilation and a reduction in blood pressure, and the amount of calcium through sodium, which causes muscle relaxation.

Pharmacokinetics.

Medicines have a high bioavailability when taken orally, but food slows down the absorption of the medicine. Because drugs of this group are lipophilic and less bound to proteins, they pass well to various organs and tissues. Thiazide and thiazide-like diuretics are secreted from the proximal part of the renal tubules, competing with uric acid through an active transport mechanism, with only a small amount filtered via the renal glomeruli. Hydrochlorothiazide and chlorthalidone are minimally metabolized in the liver and are predominantly excreted unchanged through the kidneys. In contrast, indapamide is almost entirely metabolized in the liver, with only a small amount excreted in its active form via the kidneys. Drugs begin to have a diuretic effect after 1-2 hours and reach their peak after 3-6 hours. Thiazide sulfonamides and clopamide act for 6-15 hours, indapamide for about 24 hours, and chlorthalidone for 24-72 hours.

Some pharmacokinetic parameters of thiazide and thiazide-like diuretics

The drug	Absorption through OIT, %	T ½, hours	Renal excretion unchanged, %
Gidroxlorotiazid	65-75	10-12	> 95%
Indapamid	~ 100	10-12	~ 7
Xlortalidon	60-70	44	65%

Instructions for use.

Thiazide and thiazide-like diuretics are used to treat edema associated with conditions such as chronic heart failure (CHF), nephrotic syndrome, chronic kidney diseases, and acute glomerulonephritis. However, their effectiveness diminishes when the glomerular filtration rate (GFR) drops below 30-40 ml/min/1.73 m^2, and they are ineffective when the GFR is less than 10-30 ml/min/1.73 m^2.

Thiazide and thiazide-like diuretics are used for long-term treatment of arterial hypertension, in which the drugs are prescribed for a long time in small doses (hydrochlorothiazide and chlorthalidone in amounts less than 25 mg/day). Prescribing them in high doses increases the risk of sudden death. When the drugs are taken regularly, their hypotensive effect develops after 2-4 weeks.

Thiazide diuretics are sometimes prescribed to prevent the formation of urinary stones in cases of hypercalciuria and to help prevent calcium loss in osteoporosis. Additionally, in diabetes insipidus, thiazide diuretics are used to reduce polyuria, as they enhance water reabsorption in the proximal part of the renal tubules.

Negative effects.

The main negative effects of this group of drugs are related to changes in the balance of water and electrolytes in the blood (Table 1.5).

Table 1.5

Type of adverse effect	Appearance of adverse effects
Electrolyte disorders	Depletion of electrolytes in the extracellular fluid, hypotension, hypokalemia, hyponatremia, hypochloremia, metabolic alkalosis, hypomagnesemia, hypercalcemia, hyperuricemia
Changes by CNS	Dizziness, headache, weakness, paresthesia
Changes in the gastrointestinal tract	Anorexia, nausea, vomiting, colic, diarrhea, constipation, cholecystitis, pancreatitis
Sexual disorders	Impotence, decreased libido.
Hematological changes	Thrombocytopenia, agranulocytosis, thrombocytopenic purpura
Dermatological disorders	Skin rashes, photosensitivity
Other changes	Hyperglycemia, increased total cholesterol, triglycerides, and low-density lipoproteins in the blood.

One of the dangerous negative effects of drugs is hypokalemia, the origin of which depends on the dose of the drug. Long-term use of the drug in small doses can also cause hypokalemia. For this reason, they cannot be used together with antiarrhythmic drugs from the quinidine group, because polymorphic ventricular tachycardia can develop against the background of hypokalemia. In patients with chronic kidney disease, there is a risk of developing hyperuricemia during long-term use of thiazide diuretics.

Side effects observed by the central nervous system and gastrointestinal tract, as well as sexual, hematological, and dermatological adverse effects, are rarely observed. Drugs of this group can reduce glucose tolerance and manifest latent diabetes.

Contraindications.

In pregnancy, hypersensitivity to this category of medicines, specifically sulfonamides.

Interaction with other drugs.

Thiazide and thiazide-like diuretics can reduce the effectiveness of insulin, hypoglycemic sulfonylureas, and anti-gout medications. On the other hand, anesthetics, diazoxide, cardiac glycosides, and lithium can enhance the diuretic effect.

NSAIDS and cholestyramine inhibit the action of diuretics. Amphotericin V and glucocorticoids boost the hypokalemic impact of thiazide and thiazide-like diuretics.

Carbonic anhydrase inhibitors.

This group of drugs is rarely used in clinical practice; acetazolamide is the most commonly used. Acetazolamide acts as a mild diuretic, mostly affecting the proximal tubular epithelium.

Mechanism of action and, excretion of electrolytes.

Acetazolamide works by inhibiting the enzyme carbonic anhydrase, both in the membrane and cytoplasm of tubular epithelial cells. Carbonic anhydrase plays a crucial role in catalyzing the production of hydrogen ions within the cells. When hydrogen ions are secreted into the tubular fluid, they are exchanged for sodium ions, which are absorbed into the epithelial cells. This process helps regulate the balance of sodium and hydrogen ions. Additionally, carbonic anhydrase breaks down carbonic acid into carbon dioxide and a hydroxyl ion within the tubular lumen, facilitating the reabsorption of sodium and water. As a result of inhibiting the carbonic anhydrase enzyme, the formation of hydrogen ions decreases, and sodium cannot be exchanged with enough hydrogen ions. Acetazolamide increases the excretion of bicarbonates (hydrocarbons) in the urine, which leads to a rise in urine

pH to around 8 and can result in metabolic acidosis. The decreased reabsorption of sodium in the proximal tubules reduces water reabsorption as well. As sodium and chloride are not reabsorbed in the ultrafiltrate, they reach the distal tubules, where compensatory mechanisms increase the reabsorption of these ions. However, this increased reabsorption of sodium and chloride is accompanied by an exchange with potassium, leading to potassium being excreted through the urine. Thus, acetazolamide indirectly causes potassium loss from the body. Acetazolamide accelerates the excretion of phosphates through urine, but has little effect on the excretion of magnesium and calcium. If acetazolamide is used for 4 days without a break, metabolic acidosis develops in the extracellular fluid (metabolic acidosis leads to the development of refractoriness to diuretics). After a break of 1-2 days, the alkaline reserve is restored, therefore, it is recommended to use acetazolamide with breaks.

Pharmacodynamic effects.

Carbonic anhydrase inhibitors, such as acetazolamide, increase the resistance of afferent arterioles, which slows down blood flow through the kidneys and reduces the glomerular filtration rate (GFR). In addition to their renal effects, carbonic anhydrase inhibitors have other pharmacological actions due to the enzyme's presence in various organs. In the eye, inhibition of carbonic anhydrase reduces fluid secretion in the anterior chamber, which in turn lowers intraocular pressure, making acetazolamide useful in the treatment of glaucoma. In the central nervous system, acetazolamide's anticonvulsant effects are related to the development of metabolic acidosis, which may help in controlling seizures. This direct effect on brain activity, combined with the alteration in the body's acid-base balance, contributes to its clinical use in epilepsy.

Pharmacokinetics.

Acetazolamide is almost entirely absorbed through the gastrointestinal tract. It is 95% bound to plasma proteins. T ½ – 6-9 hours. Acetazolamide is not metabolized in the body and is eliminated unaltered by the kidney.

When taken orally, the drug's action starts after 1-1.5 hours, peaks after 2-4 hours, and lasts 6-12 hours.

Instructions for use.

Acetazolamide is primarily used to reduce intraocular pressure before surgery in cases of open-angle glaucoma, secondary glaucoma, and acute closed-angle glaucoma. This is due to its ability to inhibit carbonic anhydrase, thereby decreasing fluid production in the eye and lowering intraocular pressure.

Additionally, acetazolamide is employed as part of a combination therapy to treat edema associated with congestive heart failure. When used alongside other potent diuretics like loop diuretics and thiazides, acetazolamide helps to alleviate edema and also counters the metabolic alkalosis that can develop with prolonged use of these diuretics. It enhances the diuretic effect, contributing to more effective fluid management in patients with heart failure.

Acetazolamide can also be used in absence.

Due to the rapid development of tolerance to acetazolamide, its use as an anticonvulsant drug is limited.

Because acetazolamide causes metabolic acidosis and stimulates the respiratory center, it can be used in the medical correction of apnea-hypopnea syndrome of central origin in both adults and children.

Negative effects.

The primary negative effects of acetazolamide stem from its ability to induce metabolic acidosis and shift the urinary environment to an alkaline state. This can lead to several issues, including: Worsening encephalopathy in liver cirrhosis By slowing the release of ammonium, acetazolamide exacerbates encephalopathy in patients with liver cirrhosis. Increased risk of urinary stones and renal colic: The alkaline urine environment promotes phosphate accumulation, contributing to the formation of urinary stones and renal colic. Exacerbation of metabolic or respiratory

acidosis: In cases of severe respiratory failure or hyperchloremic acidosis, acetazolamide can worsen these conditions by increasing acidosis. These side effects highlight the need for careful monitoring when prescribing acetazolamide, especially in patients with liver cirrhosis or respiratory conditions.

The drug can cause hypokalemia and hyponatremia.

Severe toxic reactions (decreased blood production in the bone marrow, kidney damage) rarely develop. Since the drug has a sulfanilamide structure, a skin rash may occur. Due to the blocking of carbonic anhydrase in the CNS, high doses of acetazolamide may cause paresthesia and drowsiness.

Contraindications to use.

Pathological conditions or diseases with acidosis:

- uremia;

- the decompensation period of diabetes;

- severe shortness of breath.

Interaction with other drugs.

Acetazolamide enhances the diuretic, hypotensive, and hypokalemic effects of other diuretics, hypotensive drugs, and theophylline. Reduces metabolic alkalosis, which affects the kidneys and develops with long-term use of thiazide group diuretics. When insulin and oral hypoglycemic drugs are used together with acetazolamide, their effect increases.

Salicylates, cardiac glycosides (preparatov naperstyanki), carbamazepine, ephedrine, and myorelaxants (non-depolarizing) are used together with acetazolamide; their toxicity increases.

Potassium-sparing diuretics and mineralocorticoid receptor antagonists.

Triamterene, amiloride, spironolactone, and eplerenone are potassium-sparing diuretics that reduce renal potassium excretion. They affect the last part of the distal tubules and collecting ducts, and their diuretic effect is weak.

Diuretics that preserve potassium in the body are divided into 2 groups according to the mechanism of action:

- triamterene and amiloride, which inhibit sodium channels in kidney epithelial cells;

- mineralocorticoid receptor antagonists - spironolactone and eplerenone

Sodium channel blockers. Mechanism of action and pharmacological effects.

Blocks sodium channels in the end part of the distal tubules and the epithelial membrane of the collecting ducts. The transmembrane potential, an electromotive force important for the passage of potassium, hydrogen, calcium, and magnesium ions into the space of the tubules, decreases; as a result, sodium does not exchange with potassium, and potassium does not leave the body. Long-term use of drugs reduces the excretion of uric acid.

Effect on renal hemodynamics. Triamterene has almost no effect on renal hemodynamics.

Pharmacokinetics.

Absorption of triamterene ranges from 30% to 70%, and 56% is bound to blood plasma proteins. It undergoes rapid metabolism in the liver and forms an active metabolite. Both liver failure and kidney failure slow the elimination of triamterene from the body and increase its toxicity.

Instructions for use.

Due to its mild diuretic effect, thiazide is not typically used alone to treat edema or arterial hypertension. Triamterene is primarily used as part of combination therapy to enhance the effects of other diuretics and to prevent the hypokalemia they may cause. The effectiveness of triamterene is reduced when the glomerular filtration rate (GFR) is lower than 50 ml/min. Additionally, triamterene is effective in treating pseudohyperaldosteronism (such as Liddle's syndrome), a condition characterized by hypokalemic alkalosis and hypertension, despite low levels of aldosterone

Negative effects.

The most dangerous side effect of triamterene is hyperkalemia. For this reason, triamterene is contraindicated in hyperkalemia and diseases that cause hyperkalemia (CHRF, potassium-sparing or potassium-sparing diuretics, NSAIDs). When triamterene is prescribed to patients with cirrhosis of the liver, it may lead to megaloblastic anemia, as triamterene is a weak antagonist of folic acid. In rare cases, it can also reduce glucose tolerance, cause photosensitivity, and contribute to urolithiasis, as the drug has poor solubility in water and can precipitate in the urine. Other potential side effects include nausea, vomiting, dizziness, calf muscle cramps, and, in rare instances, blood dyscrasia.

Mineralocorticoid receptor antagonists. This group includes synthetic steroids - spironolactone (a competitive antagonist of aldosterone, progesterone, androgen receptors) and eplerenone (a selective antagonist of aldosterone receptors, 9-a, 11-a epoxy derivative of spironolactone).

Mechanism of diuretic action.

Aldosterone is a mineralocorticoid hormone that is released from the cortex of the adrenal gland and is one of the components of RAAT. Aldosterone participates not only in water-electrolyte exchange in the body, but also in myocardial

hypertrophy and myocardial remodulation in SUE, chronic kidney diseases, and arterial hypertension.

Aldosterone moves sodium from the tubular space into the interstitial space, and potassium and hydrogen ions into the tubular space.

Spironolactone and eplerenone are steroidal drugs that competitively bind to aldosterone receptors and do not develop the effects of aldosterone on the body. Eplerenone is 20 times weaker than spironolactone.

Pharmacological effects.

Mineralocorticoid receptor antagonists increase the excretion of sodium and chloride through urine while decreasing the excretion of potassium, hydrogen, calcium, and magnesium ions. Their effectiveness is dependent on the levels of aldosterone in the body, as they are not effective when aldosterone levels are normal.

In terms of renal hemodynamics, these drugs have minimal impact. Pharmacologically, aldosterone receptors are located in various tissues including kidney tubules, cardiomyocytes, vascular endothelium, smooth muscle cells, fibroblasts, and monocytes. By blocking these receptors, mineralocorticoid receptor antagonists help reduce myocardial hypertrophy, interstitial fibrosis, lower arterial pressure, and decrease proteinuria, especially in chronic kidney disease.

Spironolactone not only blocks aldosterone receptors but also acts on androgen and progesterone receptors. Its weak antiandrogenic effect can be beneficial in treating hirsutism caused by elevated androgen levels.

Eplerenone, on the other hand, selectively targets aldosterone receptors, with only minimal effects on progesterone and androgen receptors (1% and less than 0.1%, respectively). This results in fewer side effects, making eplerenone more suitable for long-term use.

Pharmacokinetics.

Spironolactone is quickly and completely absorbed from OIT, undergoes biotransformation (metabolism) during the first passage through the liver. In doing so, it produces several metabolites, 2 of which are canrenone and canrenone. They have the same pharmacological effect as spironolactone. Spironolactone and its metabolites are more than 90 percent bound to blood proteins. The half-life of spironolactone is short - 1.6 hours, and the half-life of its metabolites is 10-16. Spironolactone has a diuretic effect after 2-5 days of taking it. The diuretic effect of spironolactone is observed after 2-5 days of taking the drug, stable diuretic effect is observed from the 6th day of treatment. CHHF, the half-life of spironolactone can be extended to 24-58 hours in ascites in liver cirrhosis, but it does not accumulate in the body. The drug can accumulate in the body in chronic kidney disease and hyperkalemia. 10% of the taken drug is excreted unchanged, and 50% in the form of metabolites through the kidneys.

Table 1.6

Some pharmacokinetic indicators of mineralocorticoid receptor antagonists.

The drug	Bioavailability from OIT, %	Protein binding, %	T_{max}, hours	T ½, hours
Spironolactone	25	98 90	2,6 2-4	1,6 10-16
Canrenone (active metabolite)	69	50	1,5-2,0	3-5

Eplerenone is well absorbed from the gastrointestinal tract, its bioavailability is 69%. In blood plasma, it is mainly bound to α1-glycoproteins. A steady concentration in the blood is formed after 2 days.

Eplerenone is metabolized in the liver with the participation of the CYP3A4 isoenzyme and does not produce an active metabolite. When used together with inhibitors or inducers of the CYP3A4 isoenzyme, the concentration of the drug in the blood changes. Eplerenone is excreted from the body through the intestines (32%) and through the kidneys (67%). Only less than 5% is excreted unchanged from the body. Dose correction is not required in case of mild and moderate impairment of liver function and in elderly patients.

Instructions for use.

Like other potassium-sparing diuretics, spironolactone is used to enhance the effect of other diuretics and reduce potassium loss. The diuretic effect begins after 3-5 days and is maintained for another 2-3 days after stopping the drug. Spironolactone can be used as monotherapy to treat conditions like hyperuricemia, hypokalemia, and reduced glucose tolerance. It is primarily utilized in the management of both primary hyperaldosteronism (such as in adrenal adenoma or bilateral hyperplasia) and secondary hyperaldosteronism (caused by conditions like congestive heart failure, liver cirrhosis, and nephrotic syndrome). Spironolactone and eplerenone can also be used in arterial hypertension.

Use of mineralocorticoid receptor antagonists in cardiovascular diseases.

Chronic heart failure and myocardial infarction. Hyperactivation of mineralocorticoid receptors plays an important role in the pathogenesis of cardiac remodeling (development of cardiac fibrosis) after myocardial infarction and chronic heart failure. Currently, it is one of the main drugs (required to be taken) in the treatment of chronic heart failure II-IV functional class (according to NYHA) and left ventricular systolic dysfunction (regardless of taking ACEI, A2RA, or BABA). In chronic heart failure, prescribing MCRAs reduces the risk of early death from the disease and the frequency of hospital admissions due to the disease.

Arterial hypertension. MCRA has a weak antihypertensive effect. The greatest effect of MCRAs was observed in resistant arterial hypertension with low renin content.

Chronic kidney disease, proteinuria.

Mineralocorticoid receptor antagonists (MCRA) have a mild hypotensive effect and help reduce proteinuria in chronic kidney disease. The progression of proteinuria and kidney dysfunction in chronic kidney disease is linked to aldosterone, and proteinuria serves as an important predictor for the prognosis of both cardiovascular and kidney diseases. Drugs that reduce proteinuria are among the main drugs in the treatment of chronic kidney disease. Antialbuminuric effect increases when ACEI and A2RA are combined with MCRA from drugs that reduce proteinuria, but the risk of developing hyperkalemia increases, especially when the glomerular filtration rate is less than 30 ml/min.

Side effects and contraindications.

Hyperkalemia. Spironolactone and eplerenone dose-dependently induce or worsen hyperkalemia. The risk of hyperkalemia increases when MCRAs are used together with potassium-sparing drugs and drugs that preserve potassium in the body. When spironolactone and eplerenone are used, it is necessary to monitor the level of creatinine in the blood plasma, because MCRA can worsen kidney function.

The use of MCRA is contraindicated when the amount of potassium in the blood is more than 6.0 mmol/l, when the creatinine level is more than 310 μmol/l (3.5 mg/dL).

Because spironolactone is a structural analogue of progesterone, long-term use has been associated with breast pain, gynecomastia, erectile dysfunction in men, menstrual cycle disorders in women, and voice changes. Gynecomastia is dose-dependent; that is, gynecomastia was observed in men 7 times more often when the drug was used at a dose of 150 mg/day than when the drug was used at a dose of 25-50 mg/day.

Since eplerenone is highly selective for aldosterone receptors, it has little effect on progesterone and aldosterone receptors, so hormonal negative effects are rare.

Spironolactone can lead to metabolic acidosis in patients with liver cirrhosis. Additionally, it may cause side effects such as nausea, vomiting, diarrhea, gastritis, peptic ulcer, dizziness, headache, and, in rare cases, drowsiness, ataxia, skin rash, and blood dyscrasia. Use of spironolactone is contraindicated in pathological conditions with hyperkalemia, hyponatremia, acute kidney diseases with decreased glomerular filtration rate, severe forms of chronic kidney disease, and pregnancy (I trimester).

When using eplerenone, the amount of triglycerides, total cholesterol, creatinine, and liver transaminase may increase. Also, adverse effects such as diarrhea, nausea, constipation, calf muscle tension, drop in arterial pressure, fainting, dizziness, and kidney dysfunction can be observed. Most of these adverse effects depend on the dose of the drug.

Co-administration of eplerenone with CYP3A4 inhibitors or inducers is not recommended. The drug has not been studied in children under 18 years of age or in pregnancy.

Interaction with other drugs.

Spironolactone and eplerenone may increase the blood concentration of digoxin and may increase the risk of developing negative effects of digoxin. When used together with ACEI, A2RA, and potassium preparations, the risk of hyperkalemia increases, especially against the background of chronic kidney disease.

MCRA enhances the effect of antihypertensive drugs, diuretics, tricyclic antidepressants, and neuroleptics.

Spironolactone can reduce the effect of anticoagulants (heparin, coumarin products, indandione).

When eplerenone is used together with ketoconazole, erythromycin, or clarithromycin, the concentration of eplerenone in the blood can increase. If it is necessary to use such a combination, the dose of eplerenone should be reduced. When eplerenone is used with inducers of the CYP3A4 enzyme (rifampicin, carbamazepine, phenobarbital, phenytoin, etc.), the concentration of eplerenone in the blood may decrease.

Review questions.

1. Explain the physiological mechanism of diuresis.
2. Tell the classification of diuretics.
3. Explain the mechanism of action of diuretics.
4. Explain the pharmacodynamics of diuretics that affect the kidney.
5. Explain the clinical significance of the pharmacokinetic parameters of diuretics affecting the kidney.
6. List the indications for the use of diuretics that affect the colon.
7. List the negative effects of diuretics that affect the kidneys.
8. List the contraindications of diuretics that affect the bladder.
9. Give examples of the interaction of diuretics with a diuretic effect with other drugs.
10. Explain the mechanism of action of thiazides and thiazide diuretics.
11. Describe the clinical importance of the pharmacokinetic characteristics of thiazide and thiazide-like diuretics.
12. Identify the conditions for which thiazides and thiazide-like diuretics are prescribed.
13. List the side effects associated with thiazide and thiazide-like diuretics.
14. List the contraindications for the use of thiazide and thiazide-like diuretics.
15. Provide examples of drug interactions involving thiazide and thiazide-like diuretics.
16. Explain the action mechanism of carbonic anhydrase inhibitors.
17. Discuss the clinical significance of the pharmacokinetic characteristics of carbonic anhydrase inhibitors.

18. List the indications for prescribing carbonic anhydrase inhibitors.

19. Identify the negative effects of carbonic anhydrase inhibitors.

20. List the contraindications for using carbonic anhydrase inhibitors.

21. Provide examples of drug interactions involving carbonic anhydrase inhibitors.

22. Explain the mechanism of action of potassium-sparing diuretics and mineralocorticoid receptor antagonists.

23. Explain the clinical significance of the pharmacokinetic parameters of potassium-sparing diuretics and mineralocorticoid receptor antagonists.

24. List the indications for the use of potassium-sparing diuretics and mineralocorticoid receptor antagonists.

25. List the negative effects of diuretics and mineralocorticoid receptor antagonists that preserve potassium in the body.

26. Give examples of interactions of diuretics and mineralocorticoid receptor antagonists with other drugs that preserve potassium in the body.

LIST OF USED LITERATURE.

1. Леонова МВ, Явелов ИС, Упницкий АА и др. Клиническая фармакология в кардиологии: Практ. руководство для врачей. М.: Медицинское информационное агентство; 2023. 304 с.
2. Михайлов ИБ. Клиническая фармакология. 2019.
3. Кукес ВГ, Мосолов СН. Клиническая фармакология. 2017.
4. Коноплева Е. Клиническая фармакология в 2 ч. Ч.1. Учебник и практикум для вузов. М.: ЛитРес; 2020.
5. Андреев ДА, Аникин ГС, Архипов ВВ и др. Клиническая фармакология и фармакотерапия. 2020.
6. Хохлов АЛ. Клиническая фармакология: вчера, сегодня, завтра. 2017.
7. Зырянов СК, Бутранова ОИ. Антигипертензивная терапия: от клинической фармакологии до клинического результата. Сердце. 2017;16(4):286-96.
8. Цырлин ВА. Фармакология антигипертензивных средств. Регионарное кровообращение и микроциркуляция. 2020;19(2):75–88.
9. Пляшешников МА, Титова ЗА, Волкова ЮВ, Жгут ОГ. Фармакотерапия артериальной гипертонии у больных с ХБП. Клиническая фармакология и терапия. 2020;29(3).
10. Кобалава ЖД, Колесник ЭЛ, Троицкая ЕА. Европейские рекомендации по АГ. Клиническая фармакология и терапия. 2019;28(2):7–18.

11. Журавлева МВ, Лучинина ЕВ, Шелехова ТВ и др. Комбинированная терапия АГ: взгляд фармаколога. Рац. фармакотерапия в кардиологии. 2020;16(4):601–6.

12. Сименюра СС, Сизова ЖМ, Шиндряева НН, Легошина АВ. Влияние антигипертензивной терапии при низкой приверженности. Клиническая фармакология и терапия. 2022;31(3).

13. Гиляревский СР, Голшмид МВ, Захарова ГЮ и др. Гибкий режим комбинированной терапии. Рац. фармакотерапия в кардиологии. 2019;15(2):265–70.

14. Farmanovna IE, Ergashboevna AZ. ACE ингибиторларининг амалиётда қўлланилиши. Barqarorlik va yetakchi tadqiqotlar. 2022:513–7.

15. Реброва ЕВ, Ших ЕВ, Рязанова АЮ. Ирбесартан при ССЗ. Клиническая фармакология и терапия. 2022;31(2).

16. Абдусалимова ША. Антигипертензивная терапия у пациентов с метаболическим синдромом. Экономика и социум. 2021;(7(86)):193–6.

17. Стрыгин АВ, Толкачев БЕ, Стрыгина АО, Доценко АМ. Центральные антигипертензивные препараты. Рац. фармакотерапия в кардиологии. 2020;16(5):815–21.

18. Крутиков ЕС, Акаев РО, Цветков ВА. Комбинации антигипертензивных средств при СД 2 типа. Таврический медико-биологический вестник. 2021;24(1):25–32.

19. Джумаева GA, Рахматова MR, Жалолова BЗ, Юлдашева HM. Выбор препаратов при АГ. Биология и интегративная медицина. 2020;(4(44)):57–71.

20. Жалолова BЗ. Лечение артериальной гипертонии: клинико-фармакологические аспекты. Tadqiqotlar.uz. 2024;36(1):153–9.

21. Jo'raqulovna AM. Kardiotonik dori vositalari farmakokinetik ko'rsatkichlari. Int J of Scientific Researchers (IJSR). 2024;5(2):165–9.

22. Белоусов ЮБ, Кукес ВГ, Лепахин ВК, Петров ВИ, ред. Клиническая фармакология: национальное руководство. М.: ГЭОТАР-Медиа; 2014. 976 с.

CONTENTS

CLINICAL PHARMACOLOGY
ANTI-HYPERTENSIVE DRUGS

Study guide

ARTEX NASHRI

Mas'ul muharrir — Madina Mirzakarimova

Musahhih — Madina Mirzakarimova

Texnik muharrir — Raxmonov Shohimardon

Dizayner va sahifalovchi — Raxmonov Shahzod

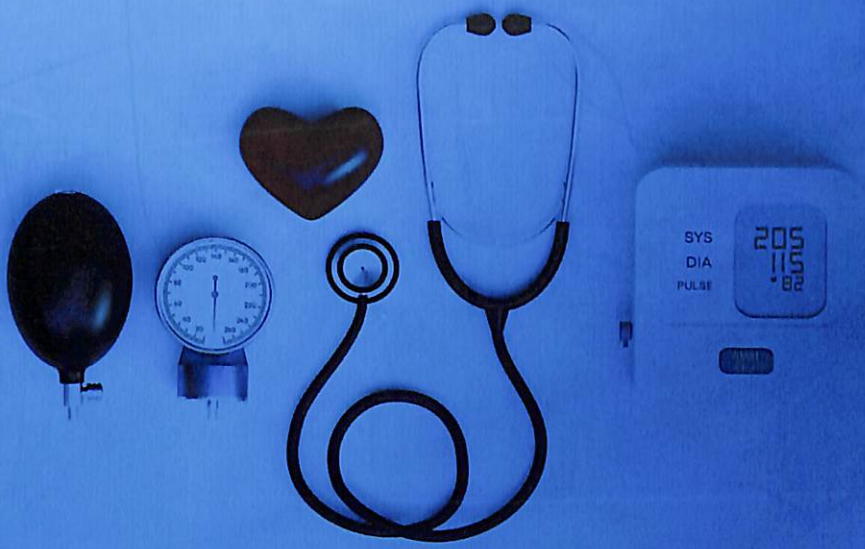
ARTEX NASHRI bosmaxonasida chop etildi.

Samarqand shahar, Alisher Navoiy ko'chasi 27 - uy

Bichimi 60x84 1/16. Times New Roman garniturasi. 20 bosma taboq.

Adadi: 200 nusxa. Buyurtma raqami: 114 /25.11.2025

Tel:(97) 897-80-00



9 789910 839641