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CLINICAL AND PHARMACOLOGICAL ASPECTS OF THERAPY FOR ELDERLY PATIENTS

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Arterial hypertension (HTN) remains a leading cause of morbidity, disability , and mortality in most countries worldwide. A significant proportion of patients with hypertension are elderly, and treating it in them is associated with a number of challenges: high comorbidity , more frequent adverse reactions to medication, and poor adherence to treatment. Achieving target blood pressure levels in these patients often requires the use of two or more medications, which significantly complicates treatment and reduces adherence. The article examines the clinical and pharmacological features of therapy for elderly patients, taking into account age-related changes in organs and systems that affect the pharmacokinetics and pharmacodynamics of drugs.

Key words
antihypertensive therapy, frailty syndrome, orthostatic hypertension, pharmacokinetics , pharmacodynamics in the elderly

Arterial hypertension (AH) is the leading modifiable risk factor for cardiovascular complications in the elderly. According to the European guidelines Society of Cardiology and European Society of According to the European Society of Hypertension (2023), the prevalence of hypertension among individuals over 65 years of age exceeds 60–70%, and isolated systolic hypertension is the most common form. In the elderly, increased systolic pressure is associated with age-related vascular wall remodeling , decreased aortic elasticity, and increased pulse pressure. Adequate antihypertensive therapy significantly reduces the risk of stroke, myocardial infarction, heart failure, and overall mortality [1] .

Treatment of arterial hypertension in patients over 80 years of age deserves special discussion [2]. This age group is growing faster than any other, and life expectancy in these individuals has increased by 50% over the past 50 years [3]. Morbidity, comorbidity , and loss of self-care ability increase significantly after age 80.

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The high prevalence of hypertension among the elderly is due to etiopathogenetic features: decreased vascular elasticity; suppression of baroreceptor sensitivity ; weakening of the autoregulation system in the cerebral vessels; reduction of the capillary bed; changes in the functional state of hormonal systems; endothelial dysfunction [4].

Key clinical and pharmacological features in the elderly include decreased glomerular filtration, decreased hepatic blood flow, altered volume of distribution, and increased pharmacodynamic sensitivity to the hypotensive effect. This increases the risk of orthostatic hypotension, electrolyte disturbances, and drug interactions. Therefore, the " start " principle low — go slow » and mandatory monitoring of renal function and electrolytes are the basis of safe therapy.

The evidence base for the effectiveness of hypertension treatment in the elderly is convincingly presented in randomized trials. In the HYVET study (2008), which included patients aged ≥80 years, therapy with indapamide (with the possible addition of perindopril) reduced the risk of stroke by 30%, heart failure by 64%, and all-cause mortality by 21%. These data confirmed the need for active treatment even in the very elderly population, provided that the therapy is well tolerated. In the SPRINT study (2015), intensive SBP control (<120 mmHg) in patients aged ≥75 years was associated with a reduction in cardiovascular events and mortality, but increased the risk of hypotension and renal impairment, which emphasizes the importance of individualizing treatment goals.

Rational pharmacotherapy for arterial hypertension (HTN) and the optimal choice of antihypertensive medications are important and relevant for a wide range of patient groups, but they are particularly significant for patients with a variety of comorbid conditions, diseases, and risk factors. This is especially true for elderly and senile patients, who, in addition to hypertension, have a wide range of comorbidities. A rational choice of pharmacotherapy also requires consideration of a number of factors that influence the choice of a particular class of medications. In elderly and senile individuals, the development and pathogenesis of high blood pressure (BP) and the pharmacokinetics and pharmacodynamics of medications should be considered first and foremost.

Although the causes leading to the development of hypertension are the same in all patients regardless of age, in the elderly, during the aging process, additional prerequisites for the development of hypertension appear, such as hypoxic damage and age-related functional restructuring of the diencephalic- hypothalamic structures of the brain, age-related changes in the sympathoadrenal (SAS) and renin- angiotensin - aldosterone systems (RAAS); age-related decrease in elasticity, increase in rigidity, as well as atherosclerotic changes in the aorta and large arteries

[5]; worsening dysfunction of the vascular endothelium and a decrease in its ability to produce vasodilatory substances; ischemic changes in the kidneys and heart; deterioration of blood rheology [6], microcirculation and tissue metabolism; increase in body weight, decrease in physical activity, increase in the duration of bad habits.

A low plasma aldosterone concentration is observed, which correlates with the level of angiotensin and plasma renin activity [7]. All this determines the characteristics and development of the most common variant of hypertension in the elderly – isolated systolic hypertension (ISH), which is characterized by increased stiffness of the aorta and large arteries, an increase in systolic blood pressure (SBP) and a decrease in diastolic blood pressure (DBP) [8]. The prevalence of ISH is 0.1% among individuals under 40 years of age, 0.8% at the age of 40–49 years, 5% at the age of 50–59 years, 12.6% at the age of 60–69 years and 23.6% at the age of 70–80 years. This increase in the number of patients with ISH is associated with the fact that an increase in SBP occurs at least until the age of 80, while DBP after 50 years either remains at the same level or tends to decrease.

Features of pharmacokinetics and pharmacodynamics of drugs in the elderly

With age, processes progress that significantly impact the bioavailability and, ultimately, the efficacy of medications. Age-related changes in the gastrointestinal tract (gastric and intestinal hypomotility, atrophic changes in their mucous membranes, and decreased blood flow) are of great importance, ultimately leading to a slower rate of gastric emptying and a reduction in active absorption [9] .

Decreases in muscle mass, absorption, body water content, plasma volume, albumin concentration, and adipose tissue content, as well as age-related atherosclerotic changes in blood vessels, also contribute to a reduction in the volume of distribution of water-soluble and fat-soluble substances. The rate of pharmacokinetic processes, which determine both the rate of xenobiotic biotransformation due to decreased liver enzyme activity and reduced liver blood flow, and the rate of renal drug excretion, changes. With age, kidney mass, the number of functioning glomeruli, renal blood flow (in patients over 70 years of age, it is half that of middle-aged individuals), and glomerular filtration rate decrease.

Also, with age, the density of receptors, the dynamics of ion channels, the activity of enzymatic systems responsible for the formation of the pharmacological effect of drugs change, homeostatic mechanisms are weakened, which can often lead to hypotonic conditions during antihypertensive therapy, hypoglycemia during treatment with hypoglycemic agents.

In the elderly, especially those over 80 years of age, the incidence of frailty syndrome (FSS) is increasing. Frailty is an age-associated syndrome whose main

clinical manifestations are general weakness, slowness and/or unintentional weight loss, decreased physical and functional activity of many systems, and decreased adaptive and restorative reserves of the body [10]. FSS contributes to the development of dependence on outside assistance in everyday life, loss of the ability to self-care, and worsens the health prognosis. FSS includes a combination of the following components: weight loss (sarcopenia); decreased hand strength, proven by dynamometry; severe weakness and increased fatigue; decreased speed of movement; significant decrease in physical activity; FSS is established in the presence of more than 3 signs.

Prospective studies have found that at the age of 70-80 years, not only is high blood pressure (BP) associated with a decrease in walking speed, but also low BP is associated with a deterioration in physical condition, in particular, with a decrease in arm strength.

In older adults, decreased blood pressure (systolic and diastolic) is an indicator of cardiovascular aging, accompanied by hypoperfusion of vital organs, primarily the brain, and the progression of cognitive, physical, and functional impairments. High blood pressure in the very elderly may serve as a compensatory mechanism to maintain organ perfusion and, ultimately, prevent morbidity and functional decline.

Arterial hypertension (AH), especially if uncontrolled in the elderly, can contribute to the development of orthostatic hypotension and hypertension. To detect these blood pressure responses to standing, blood pressure and heart rate (HR) should be measured for at least 7 minutes in the supine position and 1, 2, and 3 minutes after standing.

Orthostatic hypertension has an unfavorable prognosis, increasing the risk of ischemic stroke by 2.5 times [11]. Orthostatic hypertension has been associated with age, hypertension, diabetes mellitus, and dyslipidemia. Differences in systolic blood pressure (SBP) between arms may also be significant in old age. A difference of more than 10 mmHg is considered a specific, although not sufficiently sensitive, sign of supra-aortic artery stenosis and is associated with the development of coronary heart disease in the future, an increased risk of stroke, and an increase in cardiovascular mortality.

Pseudohypertension in the elderly is a condition in which auscultatory blood pressure readings do not correspond to the true blood pressure measured intra-arterially [12]. The prevalence of this phenomenon is estimated at 3-4% among individuals over 80 years of age. This phenomenon is caused by the " non-compressibility " of peripheral vessels due to their calcification and can be detected using the Osler maneuver . This test requires inflating a cuff above the systolic

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blood pressure (SBP) level while simultaneously palpating the brachial or radial artery. The test is considered positive if pulsation is retained in at least one of these arteries. A more reliable method is ultrasound examination of the brachial artery.

Table 1. Recommendations for initiation of AHT and target BP levels in elderly and very elderly people

Patient category	Initiation of AHT and target BP values	Note
60-79 years without frailty	Initiation of AHT depending on the cardiovascular risk category. AHT is indicated for all patients with SBP>160 mmHg. The target BP level is 140-150 mmHg . Initiation of AHT may be considered at SBP>140 mmHg , provided that treatment is well tolerated.	In the development of frailty in patients aged 60–79 years, the recommendations for patients > 80 years with frailty apply. An orthostatic test is mandatory before and during AHT. If orthostatic hypotension is detected, contributing factors, concomitant treatment, malnutrition, and dehydration should be assessed.
> 80 years without senile asthenia	Start AHT at SBP > 160 mmHg or continue previous AHT if it is well tolerated. Target SBP is 140-150 mmHg . When SBP reaches < 130 mmHg . Drug doses should be reduced or discontinued. AHT should be initiated with a low dose of one drug. Combination AHT should be prescribed only if monotherapy is ineffective . Careful monitoring for signs of frailty is necessary.	Initiating AHT or changing medications and their doses increases the risk of falls.
> 80 years old with senile asthenia	An individualized approach based on the results of the clinical gastroscopy (CG) with target blood pressure values and antihypertensive therapy (AHT) strategy. AHT initiation begins with low doses and monotherapy under strict AHT monitoring.	For patients over 80 years of age with frailty, weight loss and salt restriction are not recommended as non-drug measures.

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Note: AHT – antihypertensive therapy. Orthostatic test – measurement of blood pressure and heart rate (HR) after at least 7 minutes in the supine position and 1, 2, and 3 minutes after moving to an upright position.

Modern cardiology has a large number of modern antihypertensive medications, the rational use of which undoubtedly leads to a reduction in the incidence of adverse outcomes. The issue of optimal and rational drug selection, taking into account the specific features of their action, is particularly relevant in primary healthcare, as the patient's prognosis depends on properly selected antihypertensive therapy in outpatient settings. Guidelines summarizing the evidence base for all classes of antihypertensive medications can be of great assistance to practitioners when choosing pharmacotherapy.

The latest revision of the European and national guidelines places particular emphasis on the target blood pressure level, which for elderly patients with SBP over 160 mmHg is 150–140 mmHg (class of recommendation I, level of evidence A) [13, 14]. For elderly patients under 80 years of age who lead an active lifestyle and whose treatment is well tolerated, the target SBP level may be less than 140 mmHg (class of recommendation IIb , level of evidence C). Five main classes of drugs that have a convincing evidence base for their effect on prognosis are recommended for the treatment of hypertension [15]. These are angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), calcium antagonists [16], β-blockers (BB) and diuretics, which can be prescribed both as monotherapy and as part of combination therapy [17,18]. All these classes of antihypertensive drugs can be used in elderly patients with hypertension; however, in isolated systolic hypertension, diuretics and calcium antagonists are advantageous (class of recommendation I, level of evidence A), and ACE inhibitors can be used.

A rational choice of pharmacotherapy also requires consideration of a number of factors that influence the choice of a particular class of drugs [19]. In elderly and senile individuals, the development and pathogenesis of high blood pressure (BP) and the pharmacokinetics and pharmacodynamics of drugs should be considered first and foremost.

The issues of rational pharmacotherapy of arterial hypertension (AH) and the optimal choice of antihypertensive drugs are important and relevant for a wide range of patient categories, but they are of particular importance for patients with a variety of concomitant conditions, diseases, and risk factors. Frequent concomitant diseases in them include coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), gastrointestinal diseases, thyroid pathology, metabolic

syndrome, etc. These diseases significantly increase the risk of overall and cardiovascular mortality, which requires improved management tactics for elderly patients [20].

Antihypertensive therapy for elderly patients must take into account: lipid metabolism; glucose metabolism; left ventricular hypertrophy; liver function; circadian rhythm chronopathology ; morning blood pressure elevation; and the patient's economic status. The primary goal of hypertension treatment in elderly patients is not only to lower blood pressure but also to prevent complications (often fatal), prolong life, and improve its quality by maintaining satisfactory physical, mental, and psychoemotional well-being.

Diuretics. Thiazide and thiazide-like diuretics (indapamide , chlorthalidone) remain first-line treatments for isolated systolic hypertension. Their efficacy has been demonstrated in the SHEP and HYVET trials. They reduce the risk of stroke and heart failure. Clinical and pharmacological considerations include the risk of hyponatremia, hypokalemia, and hyperuricemia, especially with reduced SCF. In the elderly, treatment should be started with minimal doses and electrolytes should be monitored regularly.

Loop diuretics are indicated primarily in patients with concomitant heart failure and reduced renal function. Their use requires monitoring of circulating blood volume to prevent dehydration and orthostatic hypotension.

ACE inhibitors and angiotensin II receptor blockers (ARBs). ACE inhibitors (enalapril , perindopril) and ARBs (losartan , valsartan) have been shown to reduce cardiovascular mortality and heart failure progression. In the HOPE study , ramipril reduced the risk of myocardial infarction, stroke, and death in high-risk patients, including the elderly. In individuals with diabetes and nephropathy, drugs in this group have a nephroprotective effect.

However, elderly patients have an increased risk of hyperkalemia and deterioration of renal function, especially when combined with NSAIDs or potassium-sparing diuretics. Creatinine and potassium levels should be monitored 1–2 weeks after initiation of therapy.

Calcium channel blockers (CCBs). Dihydropyridine CCBs (amlodipine) are particularly effective for isolated systolic hypertension due to their pronounced vasodilatory effect. In the ALLHAT study, amlodipine demonstrated comparable efficacy to diuretics in reducing cardiovascular outcomes. These drugs are well tolerated in the elderly but may cause peripheral edema and reflex tachycardia. Non-dihydropyridine CCBs (verapamil , diltiazem) are used sparingly due to the risk of bradycardia and atrioventricular block.

Beta-blockers. Beta-blockers are not considered first-line treatment for uncomplicated hypertension in the elderly, but are indicated for coronary artery disease, post-infarction states, and chronic heart failure. They reduce the risk of recurrent cardiovascular events but may contribute to bradycardia, worsen peripheral perfusion, and increase the risk of falls. Lipophilic agents (e.g., propranolol) are more likely to cause central side effects; selective agents (bisoprolol , nebivolol) are preferred.

Alpha-blockers and centrally acting agents. Alpha- blockers (doxazosin) are not recommended as initial therapy due to the increased risk of orthostatic hypotension (as demonstrated in ALLHAT). Centrally acting agents (clonidine , moxonidine) are used sparingly due to the risk of sedation and cognitive impairment.

Blood pressure targets. According to the 2023 ESC/ESH guidelines, the target SBP for patients aged 65–79 years is 130–139 mmHg, if well tolerated. For individuals aged 80 years or older, therapy is indicated for SBP ≥160 mmHg, with gradual reduction to 140–150 mmHg, taking into account functional status and risk of falls. Individualization of targets is particularly important in patients with frailty syndrome . Elderly patients often receive combination therapy (two- or three-component regimens). Fixed-dose combinations improve adherence but require consideration of renal function and potential interactions. Regular therapy reviews and orthostatic pressure assessment are essential to prevent falls and hospitalizations.

Conclusion. Antihypertensive therapy in elderly patients has a strong evidence base and significantly reduces the risk of stroke, heart failure, and mortality. The most well-founded groups are thiazide-like diuretics, CCBs, ACE inhibitors, and ARBs. The clinical and pharmacological approach is based on reducing starting doses, gradual titration, monitoring renal function and electrolytes, assessing orthostatic responses, and individualizing blood pressure targets. Balancing cardiovascular risk reduction and preventing hypotensive complications is a central principle in the care of elderly patients.

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