

МЕДИЦИНСКИЕ НАУКИ

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CLINICAL AND PHARMACEUTICAL ANALYSIS OF APPLICATION OF ANTIHYPERTENSIVE MEDICATIONS IN PATIENTS WITH ARTERIAL HYPERTENSION IN THE REPUBLIC OF UZBEKISTAN

Summary. In order to determine the degree of compliance of the ongoing medicinal treatment of patients with arterial hypertension with current international recommendations, the prescription of medications in 136 patients of one of the regional multidisciplinary medical centers of Uzbekistan was retrospectively evaluated. Based on the analysis of patient histories an unreasonably underestimated frequency of use of beta-blockers (54% of the examined), ACE inhibitors (47.9%) and diuretics (32.3%) were found. In 27.4% of cases, the dosage of beta-blockers was insufficient, and in 15% of cases, an overdose of medications was noted. Calcium channel blockers were used quite widely, but in 7.4% of cases, their use was found to be not following the indications for patients with heart failure. Side effects were observed in 25.3% of patients, which in many cases were predictable and easily eliminated. It is concluded that in order to increase the rationality of arterial hypertension therapy, taking into account the concomitant pathology, a more complete consideration of modern recommendations on the use of antihypertensive medications and a thorough analysis of ongoing pharmacotherapy, as well as the need for a clinical pharmacist to participate in the treatment process are required.

Keywords: *arterial hypertension, antihypertensive medication, modern руководство, beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers, diuretics.*

Introduction. The cardiovascular disease currently holds a leading position as the main non-infectious causes of temporary or permanent loss of the working capacity of the population. As known, each year on the planet, they are a major cause of death in more than 17 million people. And by 2030, it is expected to increase of this indicator to 24.2 million per year. This total exceeds following them in the frequency oncological, respiratory diseases and diabetes mellitus. And all these groups' disease accounts for about 82% of deaths from non-infectious pathology [1, 2].

Arterial hypertension (AH) is the most common cardiovascular disease, which can take place in various embodiments - slowly progressing (benign) and fast progressing (malignant). In the vast majority of cases, the basis of the pathogenesis of hypertension is atherosclerosis with corresponding changes in the intima of large and medium-sized arteries [3, 4]. This, in turn, leads to the development of coronary heart disease (CHD), cerebrovascular accidents, the development of heart failure (HF) and their subsequent complications. It is known that the presence of AH accelerates the course of the atherosclerotic process in the patient and significantly increases the risk of complications. Only adequate therapeutic measures, including the use of appropriate medications, can reduce both cardiovascular morbidity and mortality in general, and improve the quality of life of patients with AH. However, in practice, the presence of concomitant diseases and conditions sometimes significantly limit the choice of antihypertensive drugs and even create contraindications to the use of some of them. At the

same time, for effective control of blood pressure and the prevention of complications of AH during medicinal treatment, it is important to use evidence-based medicine, which is contained in updated international guidelines for the treatment of AH and takes into account all the features of the course of the disease [1, 5].

The aim of the work was a clinical and pharmaceutical analysis of the treatment in hospitalized patients with arterial hypertension from the perspective of evidence-based medicine for the subsequent development of recommendations to improve the rationality of medicinal therapy.

Separate tasks were: 1) To study the frequency of use of the main groups of antihypertensive drugs (beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers, diuretics); 2) Conduct a clinical and pharmaceutical assessment of the compliance of the use of certain groups of these medications with modern international recommendations; 3) To determine directions for improving the rationality of medicinal therapy in patients with AH, including the presence of concomitant pathology and complications of the course of the disease.

Materials and methods. Following the intended purpose retrospectively analyzed 136 case histories of patients with AH stage II-III, were hospitalized at the Department of Cardiology one of the regional diversified medical centers of Uzbekistan. The study involved case histories of 61 men and 75 women aged 44 to 69 years (mean age 53 ± 3.7 years). All patients, in addition to the initial medical examination,

underwent an instrumental examination, including ultrasound, with the determination of myocardial function and the state of the great vessels, as well as the necessary laboratory tests. Particular attention was paid to the condition of the so-called "target organs" affected by common degrees of atherosclerosis - the heart, kidneys, major vessels of the limbs, the functions of the central nervous system.

Analysis of case histories was carried out according to a specially developed scheme (based on the protocols for providing medical care to patients with AH and CHD), which included aspects of rationality of the use of medications, their dosage, consideration of pharmacological and pharmaceutical compatibility, the presence of contraindications and the development of adverse reactions and side effects. Patients with significant concomitant systemic diseases (decompensated diabetes mellitus, rheumatic diseases in the active phase, severe renal or hepatic insufficiency, etc.) were excluded from the study. Similarly, patients with myocardial infarction suffered during the last 6 months were rejected from the study.

The use of certain antihypertensive medications was analyzed taking into account the latest recommendations of the European Societies for cardiology (European Society of Cardiology - ESC) and arterial hypertension (European Society of Hypertension – ESH) [5]. Peculiarities of the course of CHD were taken into account by the functional capacity classes (FCC) according to the 1994 New York Classification [6].

Results and discussion. The previous 2013 European Recommendations cited four effective medications groups for the treatment of AH and its concomitant diseases based on the proven ability to control blood pressure, a positive effect on complication rates and mortality. The first is a group that includes ACE inhibitors (iACE) and angiotensin II receptor blockers (ARB) that are largely similar in their mechanism of action, then beta-blockers (BAB), calcium channel blockers (CCB) and diuretics (thiazide and thiazide-like) followed. The same groups remain recommended in the 2018 European version of the recommendations, which take into account the data of randomized clinical trials (RCTs) conducted over the

past 6 years. The data of new meta-analyzes confirmed that the effect on the prognosis, complications of AH and related mortality for all four groups of medications is generally approximately the same. Other antihypertensive medications (centrally-acting medications, alpha-blockers, etc.) are used as an adjunct to therapy with inadequate blood pressure control against the background of the use of the main groups. In this case, certain considerations affect the efficiency of the treatment and the above-mentioned parameters in the presence of concomitant diseases and certain states for each group of medications [2, 7, 8].

The main differences between the 2018 ESC / ESH recommendations and the previous ones published in 2013 include the emergence of new thematic sections related to the medicinal treatment of patients with AH and associated pathologies and conditions. In particular, chronic obstructive pulmonary disease, various cardiac arrhythmias, the presence of concomitant oncological diseases, pregnancy and sexual dysfunction are first identified in separate chapters. Along with the recommendations for the use of antihypertensive medications in these and other patients with concomitant diseases, oral anticoagulant therapy, the administration of hypoglycemic preparations and the use of the antihyperglycemic diet in diabetes mellitus are separately discussed in detail. There are new sections of recommendations for antihypertensive treatment of thematic patients during surgical treatment, as well as for hypertensive crises, acute cerebrovascular accidents, as well as the peculiarities of using certain groups of medications and their dosages in various ethnic groups. The chapters on risk assessment and diagnosis of specific injuries of target organs to blood pressure targets have been substantially revised, the use of fixed tablet combinations of antihypertensive medications as initial therapy in most patients with a general simplification of therapeutic algorithms. Particular attention was paid to the specific initial treatment of elderly patients, as well as methods to increase patient adherence to blood pressure monitoring.

The distribution by type of cardiovascular pathology of the examined patients is presented in Table 1.

Table 1.

DISTRIBUTION BY TYPE OF MAIN CARDIOVASCULAR DISEASE AMONG MEN AND WOMEN

Cardiovascular disease	Men	Women	Total
Arterial hypertension stages II-III	11	28	39
Arterial hypertension + CHD including II-III FCC	34	41	75
	16	6	22
Total	61	75	136

As follows from the table 1, more than half of the patients (75 people or 55% of the examined) had a combination of diseases, which required taking these parameters into account to determine rational medicinal therapy. At the same time, the use of the following antihypertensive medications was established: beta-blockers - in 54% of patients, calcium channel blockers

- in 69.8%, ACE inhibitors - in 47.9%, diuretics - in 32.3%.

Beta-blockers. According to the prescription lists of case histories, this group of medications was prescribed to 73 patients (54% of the examined). Of these, 60 had CHD and other concomitant diseases, and only 13 had AH alone. BAB is especially indicated for patients with a combination of AH with

angina pectoris, heart failure, previous myocardial infarction. They are also recommended for primary use in the presence of various types of cardiac arrhythmias, including atrial flutter, etc. According to the analyzed case histories, the presence of contraindications for the use of BAB (bradycardia, atrioventricular block II-III degree, impaired glucose tolerance) was noted in 16 patients. Thus, although only 16% of patients with CHD had contraindications to the use of BAB, only 54% of patients took them.

Following current recommendations for patients with AH and concomitant coronary atherosclerosis (CHD with angina pectoris II-III FCC), BAB is the medications of choice in the absence of contraindications. The recommendations of ESC / ESH 2018 clarified that they are especially effective as first-line medications in the presence of LV hypertrophy and proteinuria. At the same time, the emphasis on the obligatory nature of their appointment, which took place in the recommendations of ESC / ESH 2013, is somewhat relaxed. This was done both because of the sufficient effectiveness of other groups of antihypertensive drugs, and because of the lesser effectiveness found in recent RCTs regarding the prevention of strokes, the reverse development of LV hypertrophy, aortic stiffness, and small vessel remodeling than iACE, ARB, and CCB. A negative

role is also played by the bad influence of BAB on sexual function (for men) and an increased risk of treatment withdrawal in real clinical practice. At the same time, the primary use of BAB for angina pectoris, arrhythmias, after myocardial infarction, the initial stages of heart failure, and as an alternative to iACE and ARB for young women planning a pregnancy or being of reproductive age is re-emphasized [6, 9, 10].

Of the 47 patients who have not prescribed BAB, 16 patients had angina attacks, 7 had a history of myocardial infarction, and 4 had an initial stage of heart failure. Thus, 27 patients with clear indications of BAB use did not receive these medications.

It should be borne in mind that the BAB group is heterogeneous in its effects, very different from one to another. But in the last decade, there has been a clear tendency to expand the use of the so-called "new beta-blockers" (or third-generation BAB), which have a vasodilating effect and have an increased safety profile (labetalol, bisoprolol, nebivolol, and carvedilol). In particular, due to the lack of risk of developing diabetes mellitus and the absence of negative effects on sexual function. At the same time, in total, this subgroup of BAB was used only in 37% of patients. That looks very insufficient in proportion [11, 12]. The range of BAB used in the examined patients is generally presented in Table 2.

Table 2.

THE USE OF BETA-BLOCKERS IN THE EXAMINED PATIENTS

Preparation	Number of patients
Atenolol	30
Metoprolol	16
Bisoprolol	16
Carvedilol	9
Nebivolol	2
Total	73

Dosing of medications in 25 cases out of 73 was insufficient, as indicated by heart rate, which was significantly higher than the recommended protocol 55-60 bpm. However, in 5 patients there was a pronounced tendency to hypotension, which was an obstacle to increasing the dose of the medications. Thus, the incidence of insufficient dosing of BAB, excluding patients with a tendency to hypotension, was 27.4%. On the other hand, in 11 patients, while taking BAB, bradycardia was lower than 55 bpm. And 6 people had a heart rate of less than 50 bpm. Therefore, the overdose of the medications was observed in 15% of patients. Two patients had a record of a dermatologist consultation in their case histories and a diagnosis of concomitant psoriasis was made. Taking BAB increases the risk of its exacerbation. In another seven patients with CHD who took metoprolol, sleep disturbances were observed, possibly as a manifestation of a side effect of these medications. More rational in these patients would be the use of atenolol, which is characterized by hydrophilicity and does not penetrate the blood-brain barrier [12, 13].

Thus, as a result of the analysis of case histories, it was found that BAB in the patients examined by us were limited (in 54%), their dose in 27.4% of cases was insufficient, and overdose was observed in 15%. Cases of irrational use of medications in patients with psoriasis, as well as the use of lipophilic metoprolol in patients with sleep disorders have been identified.

Calcium channel blockers in modern guidelines are confirmed to be particularly effective in combining AH with peripheral vascular atherosclerosis or stable angina pectoris. In addition to reducing systemic blood pressure, CCB reduces endothelial dysfunction, which is manifested by an antiatherogenic effect. They also reduce platelet aggregation and aldosterone secretion. At the same time, it is understood that the most acceptable in modern conditions among BCC are third-generation drugs - dihydropyridine derivatives (amlodipine and lacidipine), which are characterized by a long elimination half-life (up to 40-50 hours) and high tissue selectivity. It is the latter circumstance that gives a significant reduction in undesirable side effects. The latest RCTs have shown BCC to be more effective

compared with BAB in slowing the progression of coronary atherosclerosis, reducing LV hypertrophy and proteinuria [7, 14, 15].

When analyzing case histories, cases of irrational use of drugs in this group were established. So, in seven patients, against the background of

manifestations of HF, first-generation CCB was used, which does not correspond to modern recommendations for providing medical care to such patients. The list of used drugs of this group is presented in table 3.

Table 3.

THE USE OF CALCIUM CHANNEL BLOCKERS IN THE EXAMINED PATIENTS.

Preparation	Number of patients
Amlodipine	48
Nifedipine retard	18
Felodipine	11
Verapamil	9
Diltiazem	7
Lercanidipine	2
Total	95

According to the sheets of medical prescriptions, four patients taking nifedipine and one taking diltiazem had tachycardia. Also, laxatives were used in 12 patients to eliminate constipation (a possible side effect of the therapy). According to the records in the case histories, in 18 patients with the use of CCB (nifedipine, amlodipine, felodipine), the appearance of edema in the lower extremities was observed, which was regarded as a symptom of HF, but since there were no other signs of this pathology, edema should be considered a side effect of dihydropyridines [14, 16].

In general, the use of BCC in 7.4% of cases was not following the 2018 ESC / ESH recommendations for the provision of medical care for patients with heart failure. And in 25.3% of cases of using this group of medications, side effects were noted. A significant portion of these effects could be corrected. In particular, replacing drugs for which these effects are most characteristic, with CCB of other chemical groups, with less pronounced specific adverse reactions. For example, nifedipine rarely causes constipation, and for verapamil, this is a typical side effect. Increased heart rate is a typical side effect of dihydropyridine derivatives. It can be concluded that a more differentiated approach to assessing leg edema and prescribing adjustment will increase the effectiveness of treatment. The positive aspects of the use of BCC in our study include the widespread use of prolonged forms of nifedipine, which is important for controlling exacerbation of cardiovascular diseases in the first half of the day when they are most likely.

A feature of *ACE inhibitors*, which is confirmed in the recommendations of 2018, is their ability, in addition to lowering blood pressure, to not only prevent but also correct the negative consequences of the

prolonged existence of AH. This is especially important in patients predisposed to diabetes mellitus or having kidney pathology. Another important positive aspect of iACE in comparison with antihypertensive drugs of other groups is the effect of lowering blood pressure without impairing cerebral hemodynamics, which is especially important when they are used in elderly patients. ARB has many common characteristics with iACE. And the difference is those specific receptors are blocked at the tissue level, which provides a more complete blockade of the renin-angiotensin system. ARB also does not inhibit kinin cleavage; therefore, they do not cause a dry cough, which occurs in about 12-18% of patients treated with iACE. And this group occupies a leading position due to the extremely rare development of side effects among all other antihypertensive medications [6, 17, 18].

ACE inhibitors and ARB are of particular importance for elderly and senile patients, as well as in combination with AH and diabetes mellitus, as they contribute to a decrease in albuminuria and also effectively stop the progression of both diabetic and non-diabetic nephropathy. And the target patients for their appointment are those with LV hypertrophy, as well as other specific changes in the target organs. They are recommended for patients after myocardial infarction and patients with HF, which are frequent complications of the course of AH [10, 18].

According to the analysis of case histories, iACE was used in 65 people (47.9% of the examined). The list of medications used in this group is presented in table 4. Information on contraindications to iACE was available in case of histories only in 13 patients (11.4%).

Table 4.

THE USE OF ACE INHIBITORS IN THE EXAMINED PATIENTS.

Preparation	Number of patients
Lisinopril	21
Ramipril	17
Enalapril	14
Captopril	8
Perindopril	4
Total	65

It is noteworthy that medications of this group were not used in 14 patients with proteinuria and 11 people with chronic HF. At the same time, following the recommendations of the ESC / ESH of 2018, iACE is the medication of choice in these conditions. In this regard, their use as part of complex therapy at AH only in 47.9% cases, if there are contraindications in only 11.4%, indicates an insufficient assessment of this group of drugs [8, 18, 19].

Thus, as a result of the analysis of case histories, it was found that iACE was used with unreasonably low frequency in the examined patients, albeit in some cases (18.4%) their use was mandatory. Relatively rarely among iACE were prescribed ramipril (15.4%) and perindopril (7.7%), which have a positive safety profile and has additional evidence of improved prognosis in patients with CHD.

Diuretics currently remain effective first-line medications in the treatment of AH. And in the absence of contraindications, they should be prescribed to all patients. They are especially recommended in the treatment of elderly patients with systolic arterial hypertension, as well as concomitant HF. The 2018 ESC / ESH recommendations emphasize the reduction in complications of AH in elderly patients associated with diuretics, exceeding this indicator for BAB. Thiazide-like diuretics are the medications of choice for HF in the older age category, as well as in patients with concomitant osteoporosis and CHD [6, 20, 21].

According to the prescription lists of case histories, diuretics (hydrochlorothiazide, indapamide, furosemide) were taken by 44 people (32.4%). At the same time, according to case histories, contraindications to their prescriptions were detected only in 4 (3.5%) patients (gout, impaired glucose tolerance). Thus, as a result of the analysis of case histories, a low frequency of diuretics in patients of the studied profile with AH was found to be 32.3%, which indicates insufficient attention to this group of medications by both doctors and a low degree of patient compliance.

Based on the results, appropriate recommendations were developed to rationalize the use of medications. To increase the rationality of therapy in patients with AH of various age groups and with the presence of concomitant pathology, a more complete account of modern recommendations for the use of antihypertensive medications and a thorough analysis of the pharmacotherapy are necessary. This necessitates the participation of a clinical pharmacist in the treatment process.

Conclusions: 1. According to the results of the analysis of case histories of patients with AH, the use, as part of complex treatment, of medications was found: beta-blockers in 54%, calcium channel blockers in 69.8%, ACE inhibitors in 47.9%, diuretics in 32.3%. The frequency of use of beta-blockers, ACE inhibitors and diuretics was unreasonably underestimated in comparison with the existing international recommendations for the treatment of patients with this pathology.

2. Beta-blockers in patients with AH used were limited, their dose was insufficient in 27.4% of cases, and signs of overdose were observed in 15%. Seven cases of irrational use of metoprolol in patients with sleep disorders were identified.

3. Calcium channel blockers have been widely used to treat patients with AH. However, in 7.4% of cases, their use was found to be not by the protocol for the provision of medical care to patients with heart failure. Side effects were observed in 25.3% of patients, which in many cases were predictable and easily eliminated.

4. ACE inhibitors in patients with AH used were limited, although in 18.4% of the cases observed their use should have been mandatory. Rarely prescribed ramipril (15.4%) and perindopril (7.7%), which have additional evidence regarding the improvement of the prognosis of the disease in patients with concomitant CHD.

5. To increase the rationality of therapy in patients with AH, a more complete consideration of modern recommendations on the use of antihypertensive medications and a thorough analysis of the pharmacotherapy that requires the participation of a clinical pharmacist in the treatment process are necessary.

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