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NATIONAL UNIVERSITY OF PHARMACY
Faculty for foreign citizen`s education
Department of Clinical Pharmacology and Clinical Pharmacy

QUALIFICATION WORK

on the topic: **«INFLUENCE MODERN PHARMACOTHERAPY OF ARTERIAL HYPERTENSION ON PATIENT'S ADHERENCE»**

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ANNOTATION

In the master's thesis, the application of the modern strategy of pharmacotherapy of arterial hypertension was studied, the impact of this strategy on the adherence of hypertensive patients was evaluated, and possible ways of improving the compliance of patients with the participation of pharmacists were proposed. The qualification work presented on 40 pages, includes 5 tables, 12 figures, 35 literature sources and 2 applications.

Key words: arterial hypertension, modern strategy of pharmacotherapy, compliance, hypertensive patients, blood pressure control.

АННОТАЦІЯ

У кваліфікаційній роботі було вивчено застосування сучасної стратегії фармакотерапії артеріальної гіпертензії, оцінено вплив цієї стратегії на комплаєнс пацієнтів з артеріальною гіпертензією, запропоновано можливі шляхи поліпшення комплаєнсу пацієнтів за участю фармацевтів. Кваліфікаційна робота викладена на 40 сторінках, включає 5 таблиць, 12 малюнків, 35 джерел літератури та 2 додатки.

Ключові слова: артеріальна гіпертензія, сучасна стратегія фармакотерапії, комплаєнс, хворі на артеріальну гіпертензію, контроль артеріального тиску.

LIST OF CONTENTS

ABBREVIATIONS LIST

ACE inhibitors — angiotensin-converting enzyme inhibitors

AH — arterial hypertension

AHA — American Heart Association

ARBs — angiotensin II receptor blockers

BB — Beta-blockers

BP — blood pressure

CCBs — calcium channel blockers

CVDs — cardiovascular diseases

ESC — European Society of Cardiology

ESH — European Society of Arterial Hypertension

M — arithmetic means

MMAS — Morisky-Green adherence scale

SD — standard deviations

TD — Thiazide diuretics

WHO — World Health Organization

INTRODUCTION

Relevance of the topic. Arterial hypertension is an urgent medical and social problem. More than 40% of the world's population has high blood pressure, every third person in the world, and in some countries every second person suffers from arterial hypertension. Despite the decrease in the number of people with elevated total cholesterol and low-density lipoproteins, the spread of smoking cessation, the number of cardiovascular events that lead to increased mortality in patients does not decrease. This is probably due to the increase in the prevalence of arterial hypertension, the lack of achievement of the "target" level of blood pressure, the epidemic of diabetes and obesity.

In recent years, scientists around the world are actively developing new strategies for the pharmacotherapy of arterial hypertension. One of them is the use of combined therapy with the use of fixed combinations of antihypertensive drugs in “single pill”. Despite the presence in the arsenal of doctors of highly effective drugs for lowering blood pressure, leading cardiologists estimate the effectiveness of pharmacotherapy of arterial hypertension as insufficient. Among the reasons for insufficient control of blood pressure are low adherence to treatment of patients with arterial hypertension, lack of information about arterial hypertension and complications to which it can lead, an increasing number of medications taken, and an increase in the frequency of taking medications.

Adherence to treatment is a vital factor that can affect blood pressure control. Low adherence to medical treatment leads to deterioration of the course of arterial hypertension, significant fluctuations in blood pressure, increases the likelihood of severe complications, primarily acute cerebro- and cardiovascular events, and leads to a significant increase in treatment costs.

The study of new clinical strategies for the pharmacotherapy of arterial hypertension for patient adherence is an element of a complex approach to solving the problems of treating arterial hypertension. The results of such a study can serve as a basis for the development and implementation of programs to increase

adherence to treatment, which will eventually lead to improved blood pressure control, improved prognosis of arterial hypertension, and reduced health care costs for the country.

Purpose of the research. The purpose of the master's thesis was to study the influence of modern strategies of pharmacotherapy on the adherence of patients with arterial hypertension.

Research objectives:

1. Develop a questionnaire to survey hypertensive patients.

2. Describe the sociodemographic characteristics of hypertensive patients.

3. To analyze the structure of antihypertensive therapy for hypertensive patients and evaluate the adherence of the choice of antihypertensive drugs with modern international recommendations for the selection of drugs for pharmacotherapy of arterial hypertension.

4. To assess the level of blood pressure control among hypertensive patients.

5. To assess the adherence of hypertensive patients; identify groups of hypertensive patients with the highest adherence.

6. To study the influence of the modern strategy of pharmacotherapy of arterial hypertension on the adherence of hypertensive patients.

7. Based on the results obtained, suggest possible ways to improve the adherence of hypertensive patients.

Object of research. The object of research is arterial hypertension.

Subject of research. The subject of research is the study of the influence of modern strategy of pharmacotherapy of arterial hypertension on the adherence of patients.

Research methods. To assess the impact of modern pharmacotherapy strategies, a patient survey method was used. The MMAS-8 Scale was used to assess adherence in hypertensive patients. Statistical methods were used to analyze the results obtained. Statistical analysis of the results was carried out using Microsoft Excel.

Practical significance of the obtained results. The result of the master's thesis was to determine the influence of the modern strategy of pharmacotherapy of arterial hypertension on patients' adherence to treatment. The results obtained allowed us to propose additional approaches to increasing adherence in hypertensive patients with the participation of pharmacists.

Approbation of research results and publication. The results of the study were published in abstracts (Application A):

1. Impact of pharmacological drug selection on adherence of patients with arterial hypertension / Redouane Ait-Kaddour, scientific supervisor: Associated Professor Zhabotynska N.V. // Актуальні питання створення нових лікарських засобів: матеріали XXX міжнародної науково-практичної конференції молодих вчених та студентів (17-19 квітня 2024 р., м. Харків). – Харків: НФаУ, 2024. – С. 349.

Structure and volume of master’s thesis. The master’s thesis consists of an introduction, 3 chapters: literature review, description of research methods, research results and their analysis; conclusions. The master’s thesis is presented on 40 pages, includes 5 tables, 12 figures, 35 sources of literature and 2 applications.

CHAPTER 1
LITERATURE REVIEW

1.1. Unresolved problems in the treatment of AH

The concept of the cardiovascular continuum, created by the American scientist, Nobel Prize winner Eugene Braunwald, is fundamental in modern cardiology and is based on the laws of development of pathological processes, including the influence of risk factors, damage to the main target organs — the heart, blood vessels, brain, and in it the most dramatic events for a cardiovascular patient, especially at high risk, are the development of myocardial infarction and cerebral stroke. Arterial hypertension (AH) makes a significant contribution to these processes and plays a leading role in developed a lot of cardiovascular diseases (CVDs), negatively affecting the final outcomes of a healthy population [1].

In recent years, global changes have occurred in the pharmacotherapy of CVDs and AH in particular, which have significantly reduced morbidity and mortality among patients. A wide range of new antihypertensive drugs have been developed that can suppress various pathophysiological mechanisms of the development of increased blood pressure (BP) and prevent the development of complications and deaths in patients with hypertension. However, despite significant scientific advances in practical activities, it is not always possible to achieve target BP levels.

Factors influencing the effectiveness of pharmacotherapy for AH are divided into three groups: sociodemographic factors [2], health-related behavior, and obesity [3]. Sociodemographic characteristics include age, education level, income level, and work status [2 ,4, 5, 6]. Health-related characteristics included alcohol use, current smoking status, aerobic physical activity practice, sedentary lifestyle, dietary control, type of weight control, physical examination, perceived stress, obesity, limitation of daily activities, identification of AH, and treatment of AH [7].

Other reasons for the low level of effectiveness of antihypertensive therapy include the following:

• Inadequate updating of treatment. Many patients continue to receive monotherapy and/or suboptimal doses of drugs despite inadequate BP control [8];

• Low adherence to pharmacotherapy of AH [5, 9];

• Insufficient use of combination pharmacotherapy. BP is a multi-regulated indicator; therefore, combinations of drugs that affect various mechanisms of BP increase are necessary to reduce BP in most patients with AH. Thus, monotherapy is likely to be insufficient for most patients [6, 8];

• In some patients receiving antihypertensive therapy, hypertension turns out to be resistant to pharmacotherapy [9, 10];

• Insufficient perception of information in doctor-patient communication, which is determined by the peculiarities of the presentation of information by the doctor and the patient's leading perceiving system [10];

• Complexity of current treatment strategies [9, 10].

Thus, the effectiveness of pharmacotherapy, along with organizational, economic, and medical factors, depends on the adherence of patients to therapy. It is believed that controlling the course of the disease allows the fulfillment of 80% or more of the appointments [11]. However, in practice, compliance remains mostly low. According to the research data of A.K.Mohiuddin [12], the long-term adherence of patients to any treatment, regardless of the disease, does not exceed 50%, and the majorities of patients suffering from chronic diseases take less medication after six months than when, or stop taking them altogether. The presence of a sufficiently large number of various factors that have an impact on the effectiveness of pharmacotherapy of AH requires their further, more detailed study.

1.2. Prevalence of AH

AH is one of the most common chronic nonspecific human diseases According to the World Health Organization (WHO), in 2021, 1.28 billion adults

between the ages of 30 and 79 suffered from AH [13]. Elevated BP is a major factor in premature death and is responsible for almost 10 million deaths and more than 200 million cases of disability worldwide [8, 14, 15]. An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths [16] AH is one of the major cardiovascular risk factors for the CVDs and its incidence continues to rise. The prevalence of AH among adults is 30–45%, and it does not depend on income level and is the same in countries with low, middle and high standards of living [17].

In Morocco, in 2018, the prevalence of AH was 29.6% [18, 19, 20]. The prevalence of AH among male and female in Morocco was 26.3% and 28.0%, respectively [21]. AH was higher among rural residents compared to urban residents (54.0% vs 46%) [22]. Another study conducted in Eastern Morocco estimated a regional prevalence of hypertension with higher frequency among rural residents than urban residents (39.9% vs 29.0% $p<0.001$) [22]. In 2017, 73% of hypertensive people in Meknes, Morocco, had uncontrolled BP [20]. Among the complications, AH were most often diagnosed CDCs (45.42%), stroke (25.55%), retinopathy (17.98%) and nephropathy (10.41%) [22].

Systolic BP level ≥140 mm Hg is associated with an increased risk of mortality and disability in 70% of cases, while the largest number of deaths during the year associated with the level of systolic BP occur due to coronary artery disease, ischemic and hemorrhagic strokes [8, 14, 15]. There is a direct relationship between blood pressure levels and CVDs risk. This relationship begins with relatively low values — 110-115 mm Hg for systolic BP and 70-75 mm Hg for diastolic BP [8, 14, 15]. AH is a leading risk factor for the development of CVDs (myocardial infarction, coronary heart disease, chronic heart failure), cerebrovascular (ischemic or hemorrhagic stroke, transient ischemic attack) and renal (chronic kidney disease) diseases [8, 14 ,15]. Therefore, improving the effectiveness of pharmacotherapy for AH can lead to increased control of BP levels and, therefore, can reduce mortality from complications of AH.

1.3. Modern strategy of pharmacotherapy of AH

The main goal of pharmacotherapy for AH is to reduce the overall risk of developing CVDs and death by correcting all modifiable risk factors through non-drug and drug interventions [8, 14, 15].

Over the last decade, the concept of "target" BP levels has changed. For adults with confirmed hypertension and known CVDs, or 10-year atherosclerotic CVDs event risk of 10% or higher, a BP goal of less than 130/80 mm Hg is recommended. For adults without additional markers of increased CVDs risk, a BP goal of less than 130/80 mm Hg may also be reasonable. The totality of the available information provides evidence that a lower BP target is generally better than a higher BP target. The systolic BP target recommended in the new guideline (<130 mm Hg) is higher than that which was used in the SPRINT trial (<120 mm Hg) [15].

As a non-drug intervention, lifestyle modification is recommended, which consists of the following areas [23, 24]:

• Reducing or normalizing body weight (preferably until a body mass index is less than 25 kg/m^2) by reducing the total calorie content of food and fat consumption.

• Regular daily moderate to vigorous aerobic physical activity for 30–60 minutes or 150 minutes per week. A rationally selected exercise regimen can lead to a decrease in systolic BP by 6.4 mm Hg, diastolic — by 6.9 mm Hg.

• Adults should be advised to limit their sodium intake to no more than 2,400 mg per day (equivalent to around 5 gm/1 teaspoon of table salt per day). Further reduction of sodium intake to 1,500 mg per day is desirable because it is associated with an even greater reduction in BP. It is advisable to include in the diet foods rich in potassium, magnesium, microelements, vitamins, dietary fiber (vegetables, fruits, herbs, wholemeal bread, and bran).

• Reducing the consumption of foods containing saturated fats and replacing them with polyunsaturated or monounsaturated fats.

• Limiting alcohol intake (less than 30 g per day for men and 20 g for women in terms of pure alcohol). The possible undesirable interaction of alcohol with antihypertensive drugs should be taken into account.

• Tobacco cessation is one of the most effective ways to reduce your overall risk of CVDs. Although quitting smoking itself has little effect on BP levels.

In accordance with the 2018 recommendations of the European Association of Cardiology (ESC/ESH) [8] and the American Heart Association (AHA) [15], drug pharmacotherapy with antihypertensive drugs should be started in the following situations:

• Patients with AH stage 2 and 3, regardless of the level of CVDs risk, after a few weeks or simultaneously with the start of lifestyle modification (level of evidence I A).

- In patients with AH stage 1 in the presence of a high overall cardiovascular risk due to damage to target organs, diabetes, CVDs or chronic kidney disease (level of evidence I B).
- In patients with AH stage 1 with low to moderate cardiovascular risk, if BP remains in the high range for several visits to the doctor or BP is elevated according to outpatient criteria and remains elevated despite the implementation of lifestyle modification for a sufficient amount of time (level evidence IIa).
- In elderly hypertensive patients, drug pharmacotherapy is recommended to begin when systolic BP is ≥160 mmHg.

Today, 5 main classes of antihypertensive drugs are recommended for the pharmacotherapy of AH, which have proven effectiveness in reducing the level of blood pressure, cardiovascular risk, and mortality from CVDs [8, 14, 15, 23].

I. Angiotensin-converting enzyme inhibitors (ACE inhibitors)
   - Enalapril, Lisinopril, Perindopril, Ramipril, Captopril

II. Angiotensin II receptor blockers (ARBs)
   - Losartan, Candesartan, Telmisartan, Irbesartan

III. Calcium channel blockers (CCBs)

- derivatives of dihydropyridines: Amlodipine, Isradipine, Nifedipine long-acting
- benzothiazepines: Diltiazem
- phenylalkylamines: Verapamil

IV. Thiazide diuretics (TD)

- Hydrochlorothiazide, Chlorthalidone, and Indapamide

V. Beta-blockers (BB)

- Metoprolol, Bisoprolol, Atenolol, Carvedilol

According to modern guidelines for the treatment of AH [6, 8, 14, 15, 23], it is currently recommended to carry out combined therapy using fixed combinations of drugs in single-pill. Scientists conducted a number of studies in which they compared the effectiveness of treatment depending on how many tablets a person takes per day: “single-pill” with a fixed combination of medicines or several different drugs. It turned out that when a person takes 1 tablet a day with a fixed combination of medicines, the effectiveness of treatment increases by 25% [25].

As a rule, medicines for the treatment of AH have different mechanisms of development and, as a result, affect various components of the pathogenesis of the disease. The problem is that, even with the help of a special examination, it is very difficult to tell which part of BP regulation is broken. That is why it is most expedient to influence two different components of the pathogenesis of AH from the very beginning. This approach makes it possible to achieve such high efficiency in 70% of patients. In addition, with the help of a fixed combination, it is possible to get a faster blood pressure reduction from the very beginning. This is a very important factor that affects the likelihood of future cardiovascular complications [6, 8, 14, 15, 23].

A combination of renin-angiotensin system blockers (ACE inhibitors or ARBs) with a TD or BB (level of evidence IA) [6, 8, 14, 15, 23] is preferred. In addition to prescribing fixed combinations of drugs in singl-pill, doctors can

further improve adherence by prescribing a larger number of pills per prescription to reduce the frequency of repeated visits to the doctor [26].

The modern strategy for the treatment of AH is presented in the Figure 1.1.

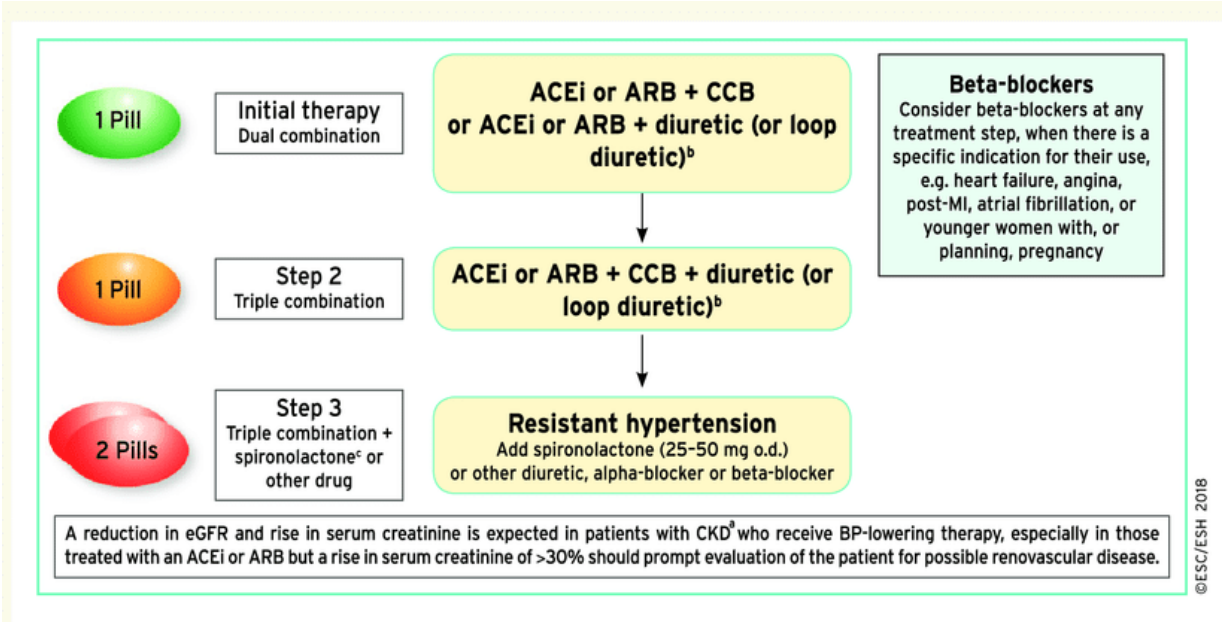

Fig.1.1. Modern drug treatment strategy for AH [23]

Among patients selected for antihypertensive drug treatment, therapy should be initiated with either one drug (ie, monotherapy) or two drugs (ie, combination therapy, preferably in a single pill to improve adherence) [23, 27].

Although initiating therapy with more than two antihypertensive agents has been examined in some trials (ie, with a "polypill") [27, 28], the experience with this approach is limited and is therefore not recommended.

Treatment of AH on with one drug (monotherapy) is allowed only in patients with stage 1 AH (systolic BP from 130 to 139 mm Hg and/or diastolic BP from 80 to 89 mm Hg). In addition, some but not all experts initiate monotherapy if the systolic BP is between 140 and 149 mmHg and the diastolic BP is <90 mmHg [27].

Treatment of AH with two mediciness (combined therapy) is recommended for all patients with a systolic BP of 10–20 mm Hg [27]. Combination therapy lowers BP more than monotherapy and increases the likelihood that target BP will

be achieved in a reasonable time period. In addition, using two medicines may lead to attainment of goal BP with lower doses of each medication, and this reduces the risk of dose-related side effects.

If in 3–6 months of regular intake of a double combination of antihypertensive agents in “single-pill”, the target BP level was not achieved, it is recommended triple combination. The choice of drugs for combined treatment depends on the damage to the target organs and comorbid conditions.

Effective treatment must confront three challenges [29]:

- diagnostic uncertainty —not knowing if a condition exits;
- therapeutic inertia — failure to initiate or escalate treatment when patients are not at goal;
- treatment non-adherence — failure of patients to follow a prescribed plan, including both medication and lifestyle changes.

1.4. Review of adherence studies in hypertensive patients

If goal blood pressure is not attained with initial therapy, adherence should be assessed. Non-adherence to medication is a common contributor to why an individual's blood pressure remains uncontrolled despite prescription of antihypertensive drug therapy. In one meta-analysis, for example, 45% of all patients with AH were partially or completely non-adherent to antihypertensive therapy; the prevalence of partial or complete non-adherence was 84% among those with uncontrolled blood pressure [30]. Another meta-analysis concluded that approximately 30 % of patients with apparent treatment resistance were non-adherent, but there was a high degree of heterogeneity, with non-adherence rates of 3% to 86%, depending upon the individual study [31].

The study of adherence in patients with AH has long attracted the attention of researchers. Daniele Braz da Silva Lima et al [32] studied the association between adherence to antihypertensive medications and types of cardiovascular complications in patients with AH and showed the need to monitor patient

adherence in order to prevent the development of cardiovascular complications. Iancu M.A. et al showed that increased adherence to antihypertensive therapy is associated with the degree of patient awareness of the consequences of hypertension if BP is not controlled, which emphasizes the role of the therapist in counselling on secondary prevention [33].

Researchers have also suggested strategies to prevent non-adherence in AH patients [27]:

- Prescribe long-acting rather than short-acting medications and specifically those that are dosed once daily.
- Prescribe single-pill combinations rather than free equivalents (ie, combination therapy as separate pills).
- Synchronize prescriptions so as to minimize the need for repeated trips to the pharmacy for refills.
- Counsel patients that, as their BP falls, they may have symptoms of fatigue, but that these symptoms are typically transient and that the medications should be continued.

Conclusion to Chapter 1.

AH is one of the most widespread diseases of the cardiovascular system, which leads to damage to target organs, with the development of severe complications and increased mortality in the population all over the world. To date, there are non-pharmacological and medicinal directions for the treatment of AH. The guidelines recommend 5 pharmacological classes of first-line antihypertensive drugs for the initial pharmacotherapy of AH. But, unfortunately, it is not always possible to achieve hypertension control. Different researchers distinguish several groups of factors that affect the effectiveness of pharmacotherapy of AH. Chief among these factors is patient adherence. Various researchers are actively studying the adherence of patients with AH, but in the literature there is not enough

information on the effect on treatment adherence of the use of a modern strategy of pharmacotherapy for AH using fixed combinations of medicines in “single-pill”.

CHAPTER 2
RESEARCH METHODS

There are various methods for assessing adherence, each of which has significant limitations [34]: direct patient queries, structured questionnaires, pill counts, electronic surveillance of prescription refill data, direct observation of pill taking, electronic monitoring systems, measurement of drug effects (eg, ACE in serum), and direct measurement of drug levels in either blood or urine.

In our research to study adherence, we chose the questionnaire method. A questionnaire consisting of several chapters was created.

Chapter I consisted of the socio-demographic characteristics of patients with AH: age, sex, education level, and work status. The survey was conducted anonymously.

Chapter II concerned the medical history: duration of BP increase, presence of comorbid conditions, characteristics of the BP level (maximum and target BP levels).

Chapter III of the questionnaire was based on the treatment of AH, how to treat illnesses. Participants were asked to enter into the questionnaire the name of the dose of drugs they take, the frequency of their use, and the severity of taking a particular drug.

Chapter IV of the questionnaire consisted of scale questions to assess the adherence of patients with AH. One of the most universal and frequently used scales, the validated Morisky-Green adherence scale, was used to assess adherence in the questionnaire. The scale is named after one of the authors who developed it in 1985. This scale is intended to assess the adherence of patients with chronic diseases. The scale has two variations: 4 questions (MMAS-4) and 8 questions (MMAS-8). The patient answers the questions "yes" or "no". 0 points are awarded for the "yes" answer, 1 point for the "no" answer. The scores of the MMAS-8 range from 0 to 8. A score below 6 indicates low adherence, a score between 6 < 8 medium adherences and a score of 8 high adherence [35]. The 8-item MMAS has

established a second level criterion related validity. We used the Scale MMAS-8 (Table 2.1).

Table 2.1

Scale MMAS-8 [35]

№ question	Question
1.	Do you sometimes forget to take your antihypertensive pills?
2.	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your antihypertensive medicine?
3.	Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?
4.	When you travel or leave home, do you sometimes forget to bring along your antihypertensive medication?
5.	Did you take your antihypertensive medicine yesterday?
6.	When you feel like your antihypertensive is under control, do you sometimes stop taking your medicine?
7.	Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your antihypertensive treatment plan?
8.	How often do you have difficulty remembering to take all your medications?

We included patients who were known to have AH, who had received antihypertensive treatment for at least six months, and who agreed to participate in the study.

The results obtained in the study were analyzed using statistical methods using Microsoft Excel programs from the Microsoft Office suite of office programs.

Conclusion to Chapter 2.

When carrying out research for the master's thesis, the survey method was used. To assess the adherence of patients was used Scale MMAS-8. Statistical methods were used to analyze the results obtained. Statistical analysis of the results was carried out using the Microsoft Excel program.

CHAPTER 3
THE RESULTS OF THE RESEARCH. THE DISCUSSION OF THE RESULTS

3.1. Sociodemographic characteristics of hypertensive patients

The research included 46 patients: 28 female and 18 male aged from 38 to 78 years (average age was 57.36 ± 13.18 years).

According to the work status, the patients were divided according to the current rank: 14 patients (30.43%) work full-time, 4 (8.7%) work hourly, 23 (50%) patients are retired persons, and disabled patients — 5 (10.87 %). At the same time, the prevalence of AH in people of working age (18 patients under 60 years old) was 1.48 times lower than the average compared to people of retirement age (28 people over 60 years old). This prevalence of AH on the gender and age of patients is generally consistent with the literature data.

By marital status, the patients were divided as follows: married — 36 (78.26%), unmarried — 7 (15.22%), and divorced — 3 (6.52%) patients.

According to the level of education, the patients were distributed as follows: 20 (43.47%) patients had a higher education, 16 (34.78%) had a secondary education, and 10 (21.75%) had a primary school education.

The duration of the BP increase ranged from 6 months up to 27 years. At the same time, the duration of the BP increase up to 1 year was observed in 2 patients (4.34%), from 1 year to 5 years — in 4 patients (8.7%); number of patients with elevated BP from 5 to 10 years; from 10 to 15 years; from 15 to 20 years and more than 20 years were distributed equally and amounted to 10 patients in each group (21.74%) (Fig. 3.1.).

Sociodemographic characteristics of hypertensive patients who took part in the survey: predominantly female of working age, married, with higher education, with duration of BP increased from 5 to 20 years. The predominance of female among hypertensive patients with coincides with literature data on a wider prevalence of AH among female.

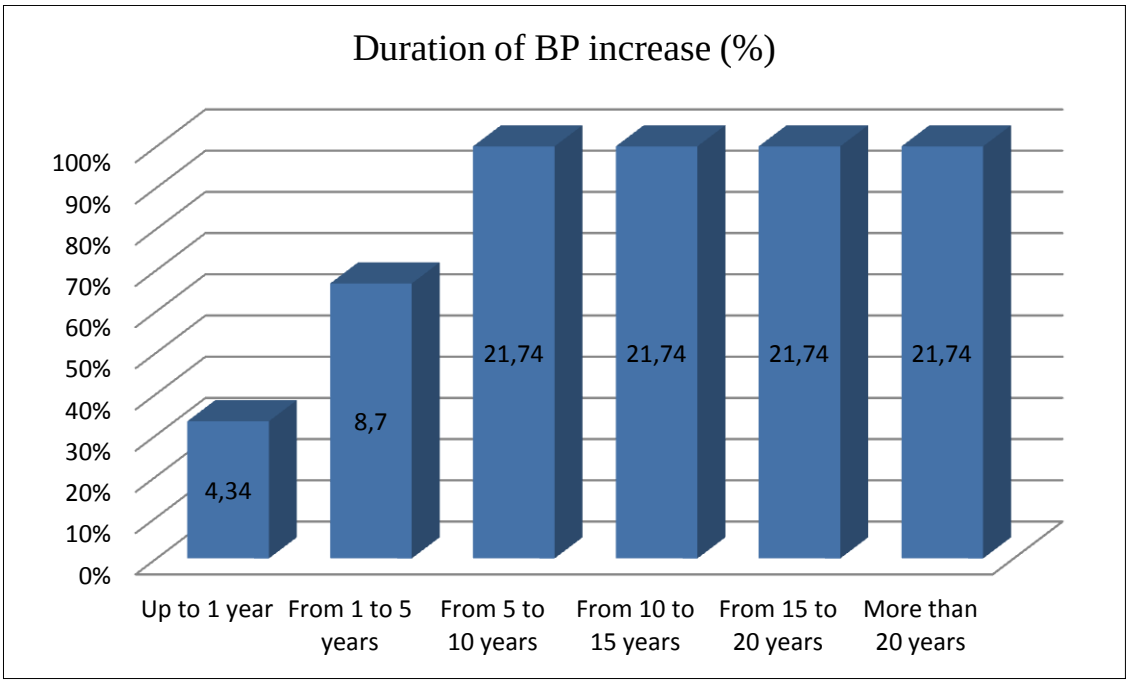

Fig. 3.1. Duration of BP increase

3.2. Study of the features of the clinical course of AH and comorbid conditions in hypertensive patients

When analyzing the degree of BP increase (Fig. 3.2.), it was revealed that the majority of patients had grade III AH, that is, BP was ≥ 180/110 mm Hg.

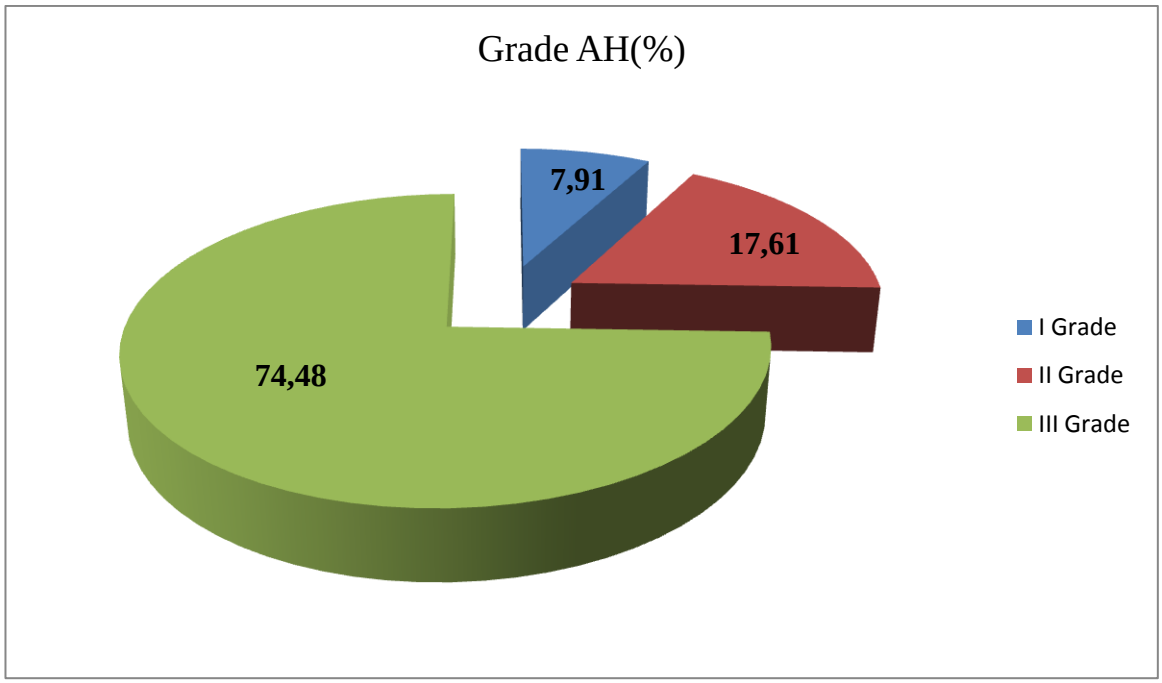

Fig. 3.2. Distribution of patients by grade of AH

When assessing the stage of AH in the surveyed patients, it was found that in terms of the presence of target organ damage, there were more patients with stage II AH, but the number of patients with stage I was 2.09 times greater than patients with stage III AH. The distribution of patients by stage of AH is presented in Fig. 3.3.

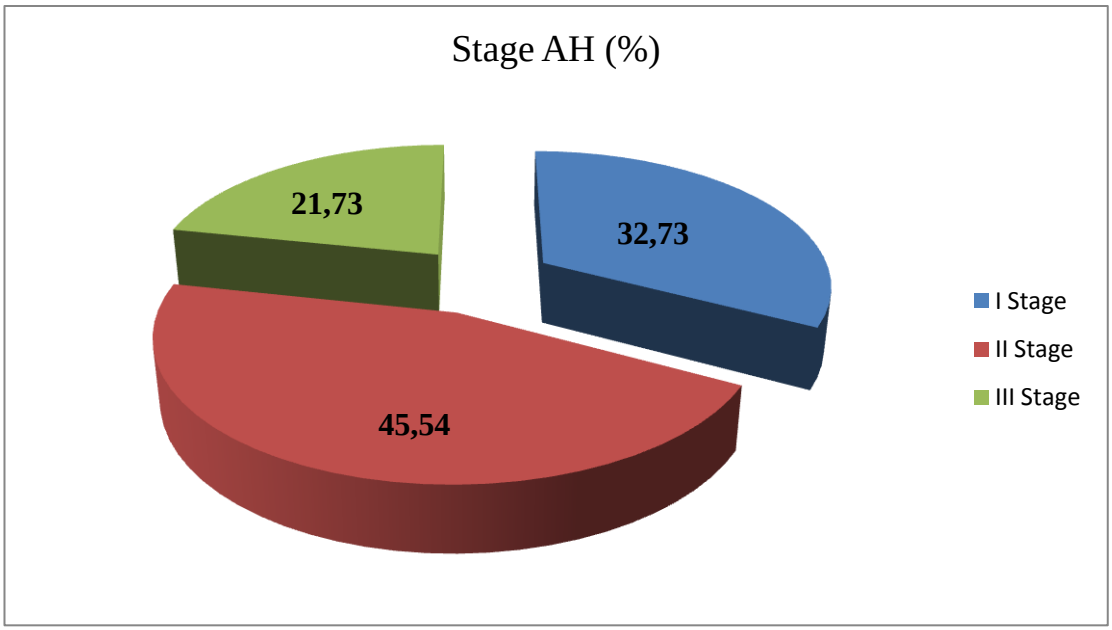

Fig. 3.3 Distribution of patients by stage of AH

The results of the study of comorbid conditions are presented in Table 3.1

Table 3.1

Distribution of patients by comorbid conditions

Comorbid conditions	Ischemic heart disease	Diabetes type 2	Stroke	Heart attack	Chronic kidney disease
Number of patients	27 (58,69%)	9 (19,56%)	3 (6,52%)	3 (6,52%)	4 (8,71%)

When assessing the presence of comorbid conditions in patients, it was revealed that 18 (39.14%) patients did not have comorbid conditions, and 28

(60.86%) patients had comorbid conditions. At the same time, 1 comorbid condition was identified in 9 (32.14%) patients, 2 comorbid conditions — in 15 (53.57%) patients, 3 comorbid conditions — in 4 (14.29%) patients. We see that the overwhelming majority of patients had comorbid conditions, represented by a combination of AH and ischemic heart disease, the main manifestation of which was stable angina.

"Target" BP level < 130/80 mm Hg was achieved in 28 patients, which accounted for 60.86% of all examined patients. The remaining 18 patients (39.14%) had BP ≥ 140/90 mmHg (Fig. 3.4). There was no significant difference between the achievement of BP control in male and female.

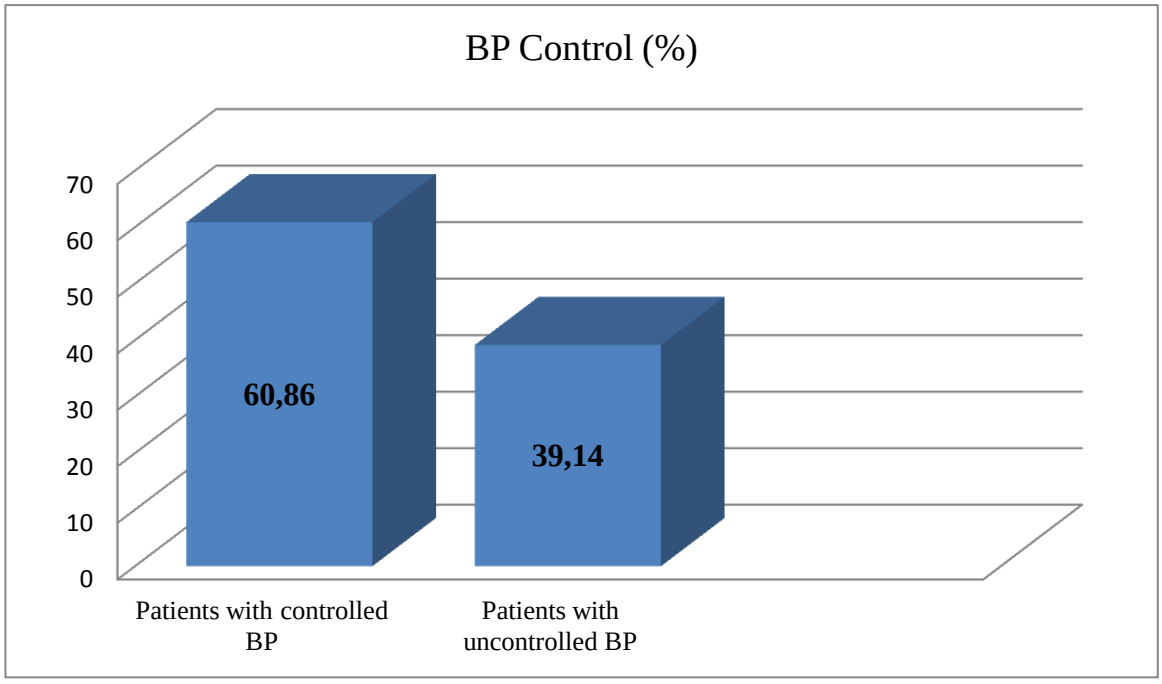

Fig. 3.4. Assessment of the achievement of BP control in patients who took part in the survey

Thus, among the patients who took part in the survey, in terms of the level of increase in BP, patients with grade III AH and comorbid ischemic heart disease prevailed; in terms of the presence of target organs damage, patients with stage II and III AH with insufficient BP control prevailed among the surveyed patients.

However, information about BP control in more than 60% of patients exceeds the literature data on achieving target BP values.

3.3. Structure of antihypertensive therapy received by hypertensive patients

After analyzing the antihypertensive therapy that the patients received, it was revealed that 12 (26.08%) patients received monotherapy, and 34 (73.92%) patients received combination therapy (Fig. 3.5.). 27 patients (79.41%) received a combination of two medicines, and 7 patients (20.59%) received a combination of three medicines.

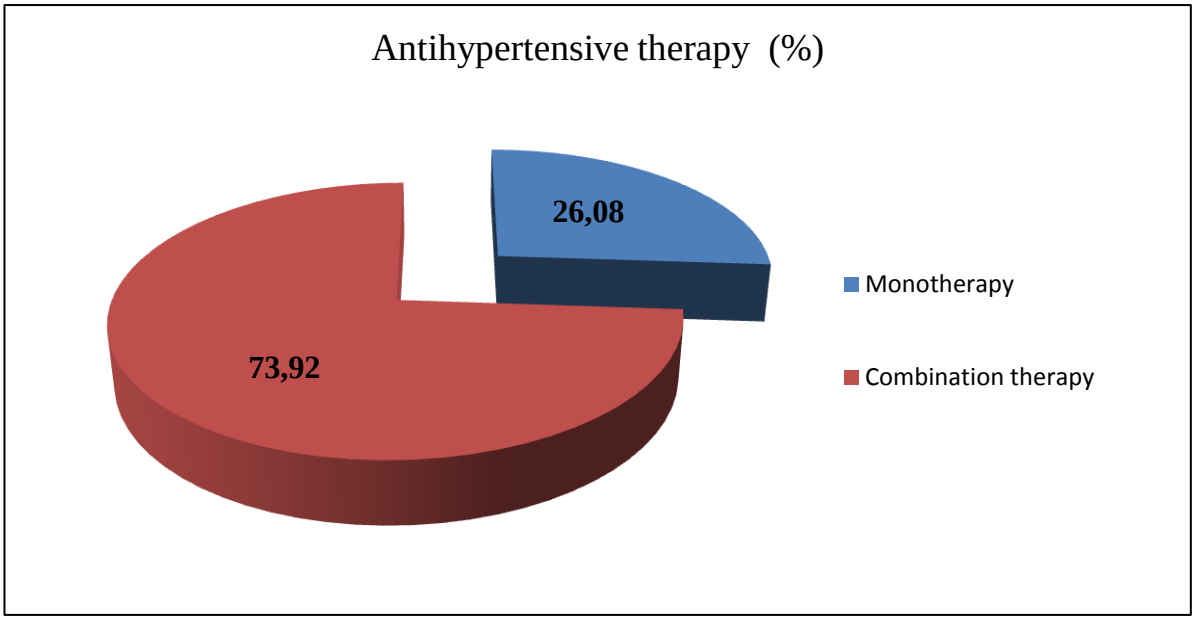

Fig. 3.5. Analysis of antihypertensive therapy received by patients with AH

When analyzing the choice of medicines for antihypertensive therapy, it was found that the following classes of medicines were used for monotherapy: ACE inhibitors in 4 patients (33.33%); ARB — in 5 patients (41.66%); BB — in 3 patients (25.01%) (Fig. 3.6.). All these pharmacological classes of medicines are included in the guidelines for pharmacotherapy of AH. Other groups of first-line antihypertensive medicines were not used for monotherapy. Second-line pharmacological classes were also not used for monotherapy.

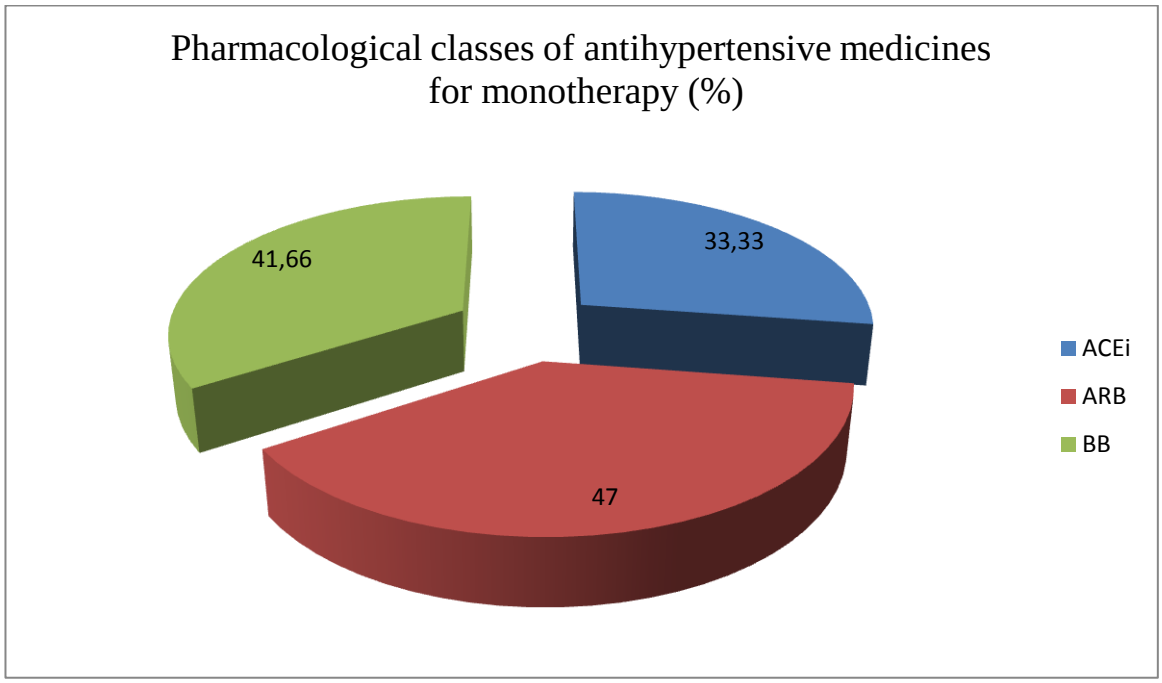

Fig. 3.6. Analysis of the choice of pharmacological classes of antihypertensive medicines for monotherapy

For combination therapy, all recommended pharmacological classes of first-line antihypertensive drugs were used (Fig. 3.7.): ACE inhibitors — in 14 patients; ARB — in 16; CCBs — 11; BB — in 13; TD — in 12 patients. All pharmacological classes were used for both double combination therapy and triple combination therapy. For combination therapy, all recommended pharmacological classes of first-line antihypertensive medicines were used without exception. Second-line medicines for combination therapy were not used.

Analysis of the choice of medicines from a specific pharmacological class showed that Enalapril, Lisinopril were used from the class of ACE inhibitors; from the class ARB were used Valsartan, Losartan; from the BB class were used Metoprolol, Bisoprolol.

Analysis of the choice of medicines from a specific pharmacological classes for dual combination therapy (Table 3.2) showed that combinations of ARBs and CCBs (a combination of Losartan or Valsartan with Amlodipine) were most often used; combinations of ACE inhibitors and CCBs (combination of Ramipril or

Enalapril with Amlodipine). But no significant difference was found between the uses of various combinations of pharmacological classes.

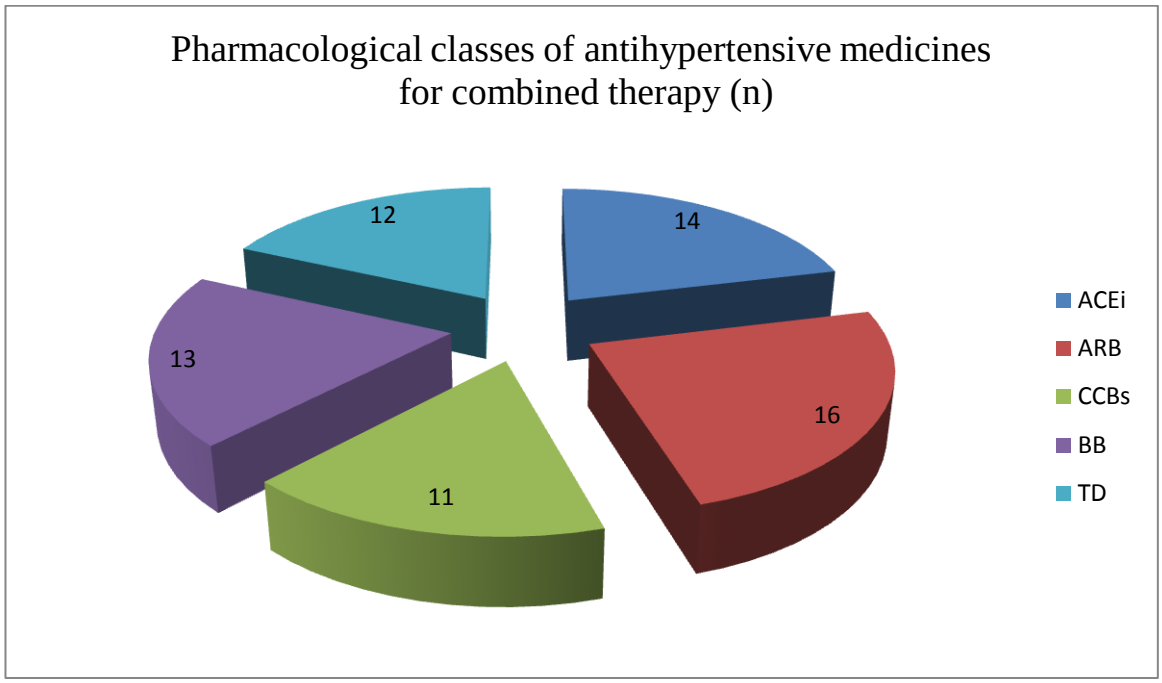

Fig. 3.7. Analysis of the choice of pharmacological classes of antihypertensive medicines for combination therapy

Table 3.2

Characteristics of dual combination antihypertensive therapy

Classes of antihypertensive medicines	Number of patients with AH using these classes	The most common medicines combinations
ACE inhibitors + BB	4 (14,81%)	Lisinopril, Captopril + Nebivolol, Bisoprolol, Metoprolol
ACE inhibitors + CCBs	5 (18,53%)	Ramipril, Enalapril + Amlodipine
ARB + CCBs	6 (22,24%)	Losartan, Valsartan + Amlodipine

Table 3.2 (continuation)

Classes of antihypertensive medicines	Number of patients with AH using these classes	The most common medicines combinations
ARB + BB	4 (14,81%)	Losartan + Bisoprolol
TD + BB	2 (7,4%)	Hydrochlorothiazide, chlorthalidone + bisoprolol, atenolol
TD + BB	4 (14,81%)	Hydrochlorothiazide + Losartan
TD + ACE inhibitors	2 (7,4%)	Hydrochlorothiazide + Lisipopril

Analysis of the choice of medicines from a specific pharmacological class for triple combination therapy (Table 3.3) showed that there was no significant difference between the uses of various combinations of pharmacological classes.

Table 3.3

Characteristics of triple combination antihypertensive therapy

Classes of antihypertensive medicines	Number of patients with AH using these classes	The most common medicines combinations
ARBs + TD + CCBs	2 (28,57%)	Valsartan + Hydrochlorothiazide + Amlodipine
ACE inhibitors + BB + CCBs	3(42,86%)	Lisinopril + Bisoprolol + Amlodipine
TD + CCBs + ACE inhibitors	2 (28,57%)	Indapamide + Amlodipine + Perindopril

The most commonly used combination of ACE inhibitors with BB and CCBs (a combination of Lisipopril with Bisoprolol and Amlodipine).

An analysis of the choice of classes of medicines for antihypertensive pharmacotherapy showed that the leading positions among antihypertensive medicines for both monotherapy and combination pharmacotherapy are occupied by medicines that affect the renin-angiotensin system: ACE inhibitors and ARBs. At the same time, for dual combination therapy, combinations of ARBs with CCBs and ACE inhibitors with BB or CCBs were mainly used. In the structure of the use of combination therapy using three classes of medicines, combinations of CCBs with TD and ACE inhibitors or ARBs, as well as combinations of CCBs with ACE inhibitors and BB, were evenly distributed.

It should be noted that all antihypertensive medicines that patients received in the study comply with modern recommendations for the selection of medicines for pharmacotherapy of AH set out in domestic and international guidelines for the provision of medical care for AH. The predominant use of medicines that affect the renin-angiotensin system (ACE inhibitors and ARBs) both in monotherapy and in combination therapy corresponds to current recommendations with level of evidence IA for the use of antihypertensive medicines.

The basis of the modern strategy for pharmacotherapy of AH is the use of fixed combinations in “single pill”, so analysis of the use of such a strategy is relevant. Assessing adherence with modern recommendations for the use of fixed combinations of medicines per “single pill”, it was found that only 13 (38.23%) patients receive the recommended therapy. At the same time, fixed combinations of two active ingredients were used for pharmacotherapy of AH only in 4 (30.76%), combinations of three active ingredients — in 9 (69.23%) of the total number of patients receiving combination antihypertensive therapy.

Antihypertensive therapy with fixed combinations of medicines in “single pill” is a unique technology that allows you to influence several pathogenetic mechanisms of increase BP development at once and achieve more effective BP control. Unfortunately, the data obtained on the use of fixed combinations of drugs

in “single pill” are not reassuring and indicate an absolutely low adherence with modern recommendations for antihypertensive therapy. In our opinion, both doctors and pharmacists play a leading role in the development of this situation. If we consider this issue from a legal point of view, then pharmacotherapy is prescribed by a doctor, and the pharmacist has no right to change it. However, as you know, doctor’s prescriptions often contain international names of active ingredients. In this regard, the pharmacist has the opportunity to offer medicines that include the necessary molecules in “single pill” and at a price that suits the patient. That is, the doctor’s task is to prescribe molecules, and the pharmacist’s task is to offer the patient available drugs that comply with modern recommendations for the treatment of AH.

Assessing the level of achievement of “target” BP levels in patients who received monotherapy with an antihypertensive medicine, it was found that in 4 patients (33.33%) BP levels exceeded 140/90 mm Hg. i.e. BP control was not achieved. Among the remaining 66.66% of patients who received monotherapy and achieved BP control, it was revealed that their AH duration was up to 5 years and they had no comorbode condition. That is, these are patients who, in accordance with the temporary pharmacotherapy strategy, are allowed to use monotherapy. But it should be noted that such effectiveness of monotherapy may also be associated with individual high sensitivity to the selected antihypertensive medicine. However, it should be noted that the effect of one antihypertensive medicine very rarely manifests itself in a decrease in BP by more than 20/10 mm Hg. Art. That is, if the patient’s BP level is 160/100 mm Hg, then with the help of one medicine it will not be possible to achieve BP level below 140/90 mm Hg. There is nothing to say about the recommended reduction in BP to 130/80 mm Hg. Thus, in patients receiving monotherapy with antihypertensive medicines, the risks of developing cardiovascular complications must be assessed and the pharmacotherapy of AH must be adjusted for more careful BP control.

In the process of analyzing the structure of drugs for antihypertensive therapy, it was revealed that 6 (13.04%) patients used the short-acting CCBs

nifedipine to relieve hypertensive crises, and in one case (2.17%) — as monotherapy for continuous use, which is completely unacceptable in accordance with modern guidelines for providing medical care to patients with AH. Also, 12 (26.08%) patients indicated that, against the background of antihypertensive pharmacotherapy, they constantly take medicines from other groups: loop diuretics or metabolic drugs.

3.4. Analysis of the effect of antihypertensive therapy on the adherence of hypertension patients

To assess the adherence of patients with AH, 4 parts of the questionnaire were developed using a items MMAS-8 Scale. When analyzing the results of a survey of patients using the MMAS-8 Scale, it was revealed that the degree of compliance of patients with AH was 61.84% (Table 3.4).

Table 3.4

The results of a survey of patients using the MMAS-8 Scale

№ Question	Question	M±SD
1.	Do you sometimes forget to take your antihypertensive pills?	3,13±0,52
2.	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your antihypertensive medicine?	3,33±0,71
3.	Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?	3,32±0,69
4.	When you travel or leave home, do you sometimes forget to bring along your antihypertensive medication?	3,23±0,8
5.	Did you take your antihypertensive medicine yesterday?	2,78±0,64

Table 3.4 (continuation)

№ Question	Question	M±SD
6.	When you feel like your antihypertensive is under control, do you sometimes stop taking your medicine?	2,76±0,96
7.	Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your antihypertensive treatment plan?	3,08±1,18
8.	How often do you have difficulty remembering to take all your medications?	3,02±1,11

The MMAS-8 scale allows a more detailed assessment of the level of patient compliance: a score below 6 indicates low adherence, a score between 6 < 8 medium adherences and a score of 8 high adherences. According to the level of compliance, all patients with hypertension can be divided into 2 groups (Fig. 3.8.).

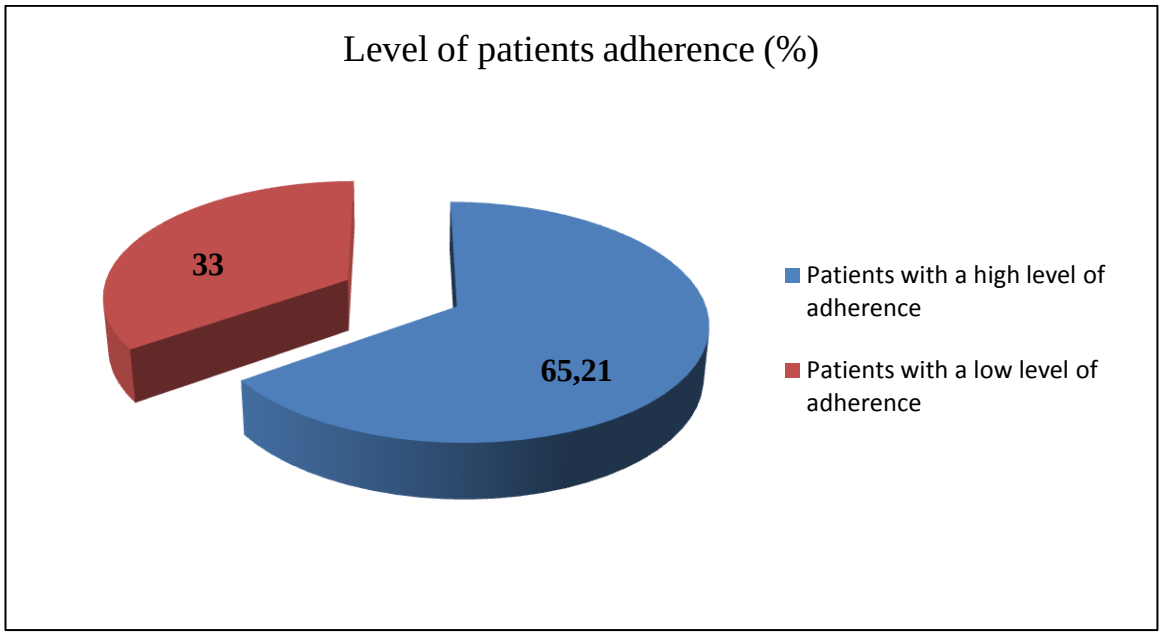

Fig. 3.8 Level of patient adherence

The group of patients with a high level of adherence (48.88±3.69) consisted of 30 patients (65.21%). The group of patients with insufficient adherence (36.87±3.9) consisted of 16 patients (34.79%). It is noteworthy that among the surveyed patients with AH, no patients with low adherence or no adherence at all were identified.

Next, we analyzed the dependence of the adherence of patients with AH on the achievement of BP control. In patients with controlled BP levels, adherence was 74.52%, and in patients who did not achieve BP control while taking antihypertensive medicines, adherence was 52.7% (Fig. 3.9.). The results of assessing the relationship between patient adherence and the achievement of BP control showed that in patients with controlled BP, adherence was 1.41 higher than in patients with uncontrolled BP. This study result is consistent with literature data on the significant influence of patient adherence on the achievement of BP control.

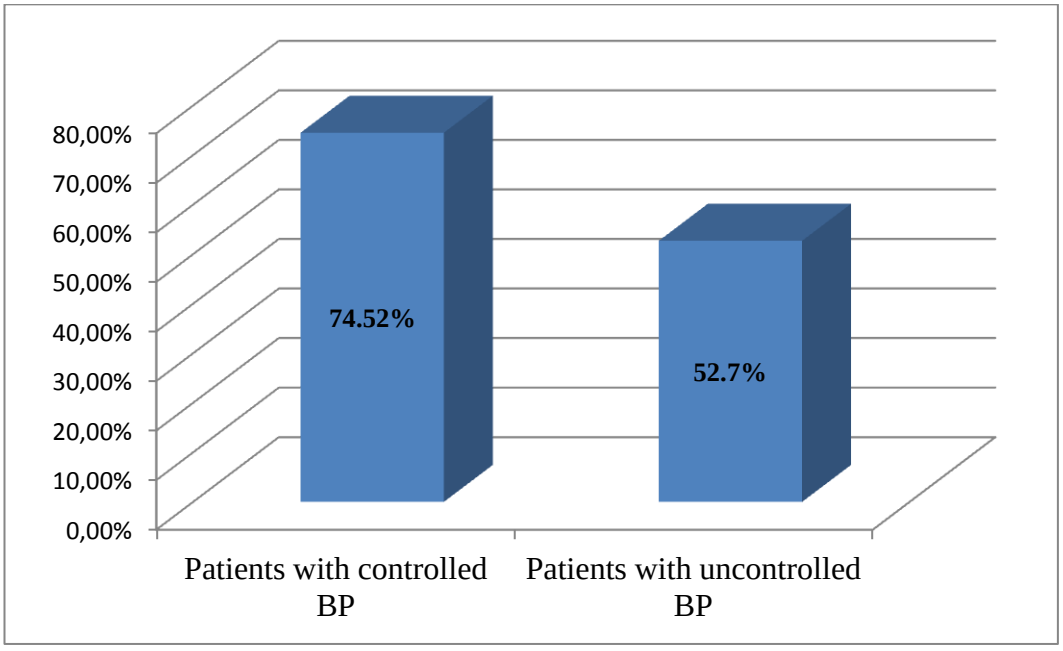

Fig. 3.9. Patient adherence depending on the degree of BP control

One of the main elements of the modern strategy for pharmacotherapy of AH is the use of combination therapy. Therefore, the effect of the use of the type of pharmacotherapy on the adherence of patients with AH was analyzed. The

results showed (Fig. 3.10.) that the adherence of patients receiving monotherapy was 10% lower than the adherence of patients receiving combination therapy, but this difference was not statistically significant. These results differ somewhat from the literature, which demonstrates higher patient adherence to monotherapy.

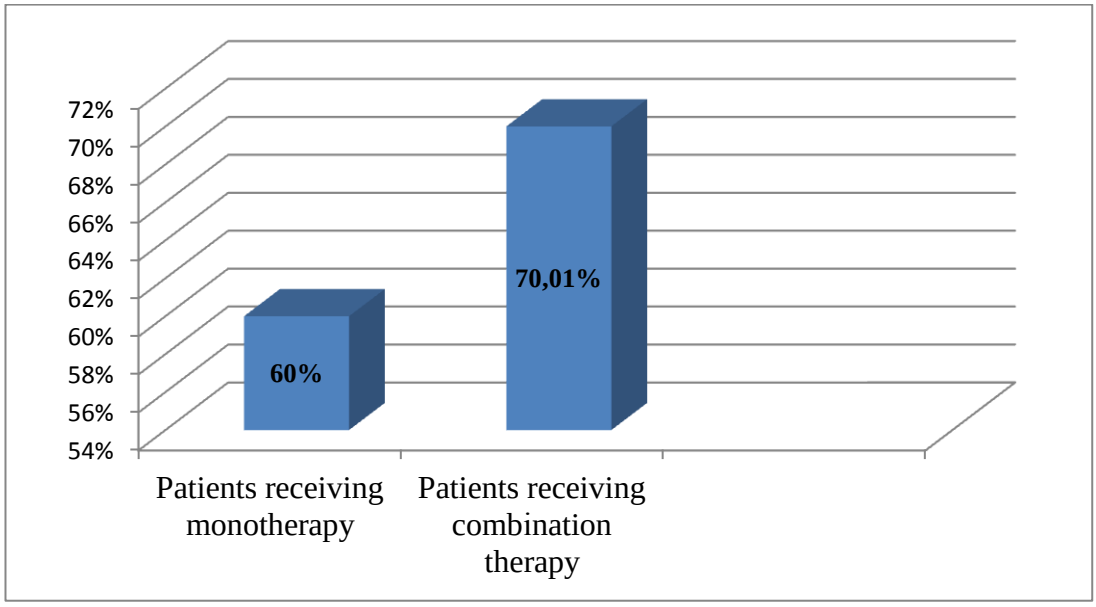

Fig. 3.10. Patient adherence depending on the type of pharmacotherapy of AH

The ambiguity of the data obtained necessitated an adherence analysis depending on the number of tablets taken by the patient. Analyzing the adherence of patients depending on the number of tablets received, it was found that in patients receiving combination therapy of several medicines, adherence was 68.75%; and the adherence of patients receiving “single pill” combinations of antihypertensive medicines was 71.43% (Fig. 3.11.).

When assessing the influence of the choice of mono- or combined antihypertensive pharmacotherapy on the adherence of hypertensive patients, a correlation was established between adherence and the number of pills taken by the patient, while in patients with low adherence it was weak positive ($r = 0.36$) significant ($p \leq 0\ .05$), and in patients with high adherence it had the character of a weak negative ($r = -0.18$) significant ($p \leq 0.05$) correlation.

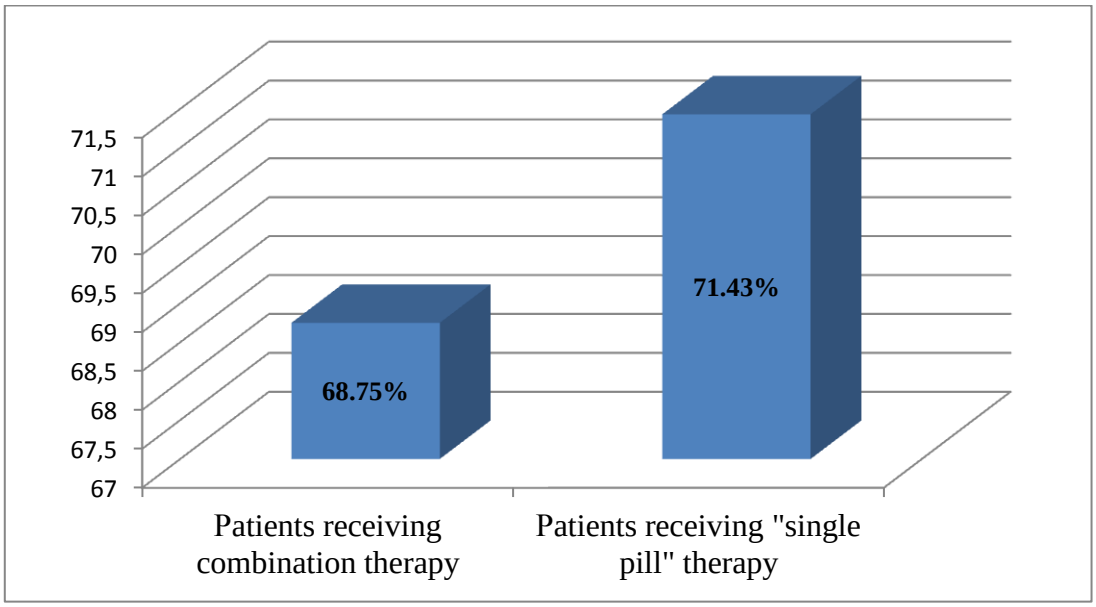

Fig. 3.11. The adherence of patients depending on the number of tablets

In our opinion, one of the most significant factors determining the high adherence of patients and their achievement of “target” BP levels is the presence of a significant correlation between adherence and the number of pills taken to lower BP. Thus, the number of pills taken by the patient affects his adherence and reducing their number can lead to an increase in adherence, and, consequently, the effectiveness of the therapy. This assumption is confirmed by our data that in patients receiving fixed combinations of antihypertensive medicines in “single pill”, adherence was significantly ($p \leq 0.05$) higher by 11.43% higher than in patients receiving monotherapy with antihypertensive medicines and 2.68% non significantly higher than in patients receiving combination therapy of several antihypertensive medicines.

The obtained results of patient adherence with antihypertensive therapy indicate its rather low level, since the andherence of hypertensive patients turned out to be significantly lower than the minimum of 80% proposed by a number of researchers. However, it should be noted that there were no patients with low adherence to antihypertensive therapy, which indicates a global understanding among hypertensive patients of the need to control BP to prevent the development of fatal cardiovascular complications.

Several studies have shown that knowledge of BP levels considered high and good knowledge of medications taken are associated with good adherence to treatment regimens. It has also been shown that improving patients' knowledge about their illnesses or the medications they are taking leads to better adherence with their medications. Involving patients in their care by imparting relevant knowledge often helps patients take better care of their health. This can be achieved through greater interaction between patients and healthcare professionals, particularly pharmacists. Pharmacists can provide consultations to help patients manage their medications. For example, this can be achieved by scheduling medications around certain activities such as eating, or by setting certain alarms on electronic devices (mobile phones, smart watches, alarm clocks) to go off when taking medications at the initial stages of their therapy. It is necessary to use all possible means to improve the memory of patients, which will help them comply with the dosage and intake of medications prescribed to them to lower BP. In addition, a simple medication regimen will promote better medication adherence in hypertensive patients. Simplicity of the medicines regimen can be achieved through the wider use of fixed combinations of antihypertensive drugs in “single pill”. The results obtained during the master's thesis demonstrated the positive impact of the modern strategy of pharmacotherapy of arterial hypertension using combination therapy using “single pill”. Patients receiving “single pill” had higher rates of achieving BP control. Also, these patients had significantly higher adherence compared to patients who received monotherapy or combination therapy from several medicines.

Thus, the importance of improving patient adherence to achieve the full benefits of treatment is clear. Efforts should always be made to improve adherence among hypertensive patients, identify the causes of non-adherence to pharmacotherapy, and organize the actions that need to be taken to eliminate these causes by improving communication between healthcare providers (pharmacist) and patients. To improve adherence and, in turn, improve BP control, it is necessary to develop intervention programs that address some of the identified

factors. A multidisciplinary approach with greater patient involvement in the management of their conditions should be adopted to promote better adherence with any prescribed treatment regimen.

Conclusions to Chapter 3

Sociodemographic characteristics of hypertensive patients who took part in the survey: predominantly female of working age, married, with higher education, with duration of BP increased from 5 to 20 years. Among the patients who took part in the survey, in terms of the level of increase in BP, patients with grade III AH and comorbid ischemic heart disease prevailed; in terms of the presence of target organs damage, patients with stage II and III AH with insufficient BP control prevailed among the surveyed patients. However, information about BP control in more than 60% of patients exceeds the literature data on achieving target BP levels.

Analysis of antihypertensive therapy received by patients with hypertension revealed that 26.08% of patients received monotherapy, and 73.92% of patients received combination therapy. An analysis of the choice of classes of medicines for antihypertensive pharmacotherapy showed that the leading positions among antihypertensive medicines for both monotherapy and combination pharmacotherapy are occupied by medicines that affect the renin-angiotensin system: ACE inhibitors and ARBs. At the same time, for dual combination therapy, combinations of ARBs with CCBs and ACE inhibitors with BB or CCBs were mainly used. In the structure of the use of combination therapy using three classes of medicines, combinations of CCBs with TD and ACE inhibitors or ARBs, as well as combinations of CCBs with ACE inhibitors and BB, were evenly distributed.

The results of the master's thesis demonstrated the positive impact of the modern strategy of pharmacotherapy of AH using combination therapy using “single pill”. Patients receiving “single pill” had significantly ($p \leq 0.05$) higher adherence compared to patients who received monotherapy or combination therapy

from several drugs. That is, the use of a modern strategy for pharmacotherapy of AH with the active participation of pharmacists can increase patient adherence and, accordingly, the effectiveness of treatment of AH.

Thus, the purposes and objectives set when planning the master's thesis were achieved.

CONCLUSIONS

1. To assess the impact of the modern pharmacotherapy strategy, a questionnaire was developed to survey patients. The questionnaire was based on a MMAS-8 Scale for studying compliance.

2. Sociodemographic characteristics of hypertensive patients who took part in the survey: predominantly female of working age, married, with higher education, with duration of BP increased from 5 to 20 years. Patients with grade III AH; stage II and III AH with insufficient BP and comorbid ischemic heart disease prevailed among the surveyed patients.

3. Analysis of antihypertensive therapy received by patients with hypertension revealed that 26.08% of patients received monotherapy, and 73.92% of patients received combination therapy. The leading positions among antihypertensive medicines for both monotherapy and combination pharmacotherapy are occupied by medicines that affect the renin-angiotensin system: ACE inhibitors and ARBs.

4. BP control was achieved only in 60.85% of hypertensive patients. There was no significant difference between the achievement of BP control in male and female.

5. The results of the study showed that the compliance of patients with hypertension was 63.64%, which is much lower than the minimum required compliance to achieve a therapeutic effect. Based on the results of the study, groups of patients were identified that had the highest (patients who achieved blood pressure control using a fixed combination of antihypertensive drugs in “single pill” tablet.

6. The modern strategy of pharmacotherapy of AH using combination therapy using “single pill” has the positive impact on the adherence hypertensive patients. Patients receiving “single pill” had significantly ($p \leq 0.05$) higher adherence compared to patients who received monotherapy or combination therapy from several drugs.

7. Possible ways to increase the adherence of hypertensive patients with were identified as follows: improving interaction between pharmacists and patients, increasing patient awareness of the disease and recommended medications, wider use of the technology for treating hypertension with fixed combinations of antihypertensive drugs in “single pill”.

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APPLICATIONS

APPLICATION A

XXX Міжнародна науково-практична конференція молодих вчених та студентів
«АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ»

IMPACT OF PHARMACOLOGICAL DRUG SELECTION ON ADHERENCE OF PATIENTS WITH ARTERIAL HYPERTENSION

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Introduction. According to the results of recent researchers, regardless of the region of the world, high or low economic level, the quality of medical care, only 40% of patients with hypertension receive treatment and only a total of 35% of patients with hypertension receiving treatment reach the target office systolic blood pressure < 140 mm Hg. Thus, today one of the most important problems is the improvement of blood pressure (BP) control in patients with hypertension. One reason why the current hypertension treatment strategy failed to achieve higher BP control scores is low patient compliance.

Aim. The aim of the work was to study was to analyze the literature on the impact of modern recommendations on the pharmacotherapy of arterial hypertension on patient`s adherence.

Materials and methods. Recommendations of the European Society for Arterial Hypertension and the European Society of Cardiology were analyzed. Also, the data of 3 International investigations on the study of adherence of patients with arterial hypertension were summarized.

Results and discussion. To date, there is a lot of evidence that patient adherence to treatment is a very important factor in achieving adequate BP control. According to American studies, about 33% of patients do not comply with doctor's recommendations. Moreover, 1 hour after talking with a doctor, 60% patients cannot remember and say what the doctor specifically recommended them. Adherences influenced by both undesirable reactions to the drug and the need to change their behaviour or habits when conducting therapy. Treatment adherence assessment studies have unambiguously shown a direct inverse relationship between pill count and treatment attachment. Low adherence level in antihypertensive therapy is dangerous because in irregular therapy among the development of uncontrolled arterial hypertension.

The current algorithm for selecting antihypertensive pharmacological drugs is based on several key recommendations. First of all, most patients need to start treatment with one tablet containing two active substances. Such selection will ensure increase of speed, efficiency and predictability of BP control. Preference should be given to two-component combinations: angiotensin II receptor blocker (ARB) with calcium antagonist (CA) or diuretic. The use of a three-component combination in a single tablet containing an ARB, CA and a diuretic is recommended in cases where the use of two drugs in a single tablet cannot be controlled by BP. The main advantage of combinations in one tablet as a conventional therapeutic approach in arterial hypertension is that patients can receive one, two or three drugs while remaining on a simple regimen with a single tablet.

Conclusions. The strategy for the drug treatment of arterial hypertension, presented in the recommendations of the European Society for Arterial Hypertension and the European Society of Cardiology, will contribute to improving patient adherence and, as a result, improving the effectiveness of BP control, preventing vital complications of this disease and improving the prognosis of patients.

APPLICATION B