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**ANALYSIS OF DIAGNOSTIC AND THERAPEUTIC STRATEGIES
IN PATIENTS WITH ARTERIAL HYPERTENSION BY THE METHODS OF
MEASURING DRUG UTILIZATION
AND RATIONAL DRUG USE AT THE MACRO LEVEL
IN BULGARIA**

ABSTRACT

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The dissertation contains 124 pages and it is illustrated with 19 tables and 45 figures. The literature used includes 189 sources.

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Abbreviations used:	
ACE	Angiotensin-converting enzyme
AH	Arterial hypertension
ARB	Angiotensin receptor blocker
ATC code	Anatomical Therapeutic Chemical code
BiPAP	Bilevel positive airway pressure
BDA	Bulgarian Drug Agency
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CML	Central Medical Library
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
CPAP	Continuous positive airway pressure
DDD	Defined daily dose
EMA	European Medicines Agency
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GDP	Gross Domestic Product
HMOD	Hypertension-mediated organ damage
HTC	Hydrochlorothiazide
ICD	International classification of diseases
IHD	Ischemic heart disease
INN	International nonproprietary name
MA	Marketing authorisation
MoH	Ministry of Health
NCD	Non-communicable diseases
NCPHA	National Centre for Public Health and Analysis
NHIF	National Health Insurance Fund
PML	Positive medicinal list
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTRA	Percutaneous transluminal renal angioplasty
PVR	Peripheral vascular resistance
PWV	Pulse wave velocity
RCTs	Randomized clinical trials
WHO	World Health Organisation

I. INTRODUCTION

Arterial hypertension (AH) is defined as ambulatory measured systolic blood pressure \geq 140 mmHg, and/or diastolic blood pressure \geq 90 mmHg. Two main types of arterial hypertension are defined - primary and secondary.

Primary (essential) hypertension is of as yet unclear aetiology. It is unlikely that the diverse pathophysiological and haemodynamic disorders associated with it are the sole causative factor. A hereditary predisposition is thought to be present, but the exact mechanism is unclear. Hygienic and dietary factors - such as sodium intake, overweight and stress - appear to have an effect only or primarily on genetically predisposed individuals. Pathogenetic mechanisms ultimately lead to an increase in peripheral vascular resistance (PVR), causing vasoconstriction, increasing cardiac minute volume and/or both, leading to higher arterial pressure. Secondary hypertension is associated with diseases such as chronic glomerulonephritis or pyelonephritis, chronic kidney disease, pheochromocytoma, Cushing's syndrome, primary hyperaldosteronism, pregnancy, and others. In addition, it is also associated with excessive alcohol use, intake of oral contraceptives, sympathomimetics, corticosteroids and cocaine.

In primary hypertension, early pathological changes are not detected. In the course of the disease, generalized arteriolar sclerosis develops, characterized by medial hypertrophy, hyperplasia and hyalinization, affecting most often small arterioles - the fundus of the eye, and especially pronounced in the kidneys (nephrosclerosis). Left ventricular hypertrophy gradually develops. Hypertension accelerates atherogenesis and atherosclerosis is more frequent and pronounced in these patients.

Depending on the presence and degree of damage to the target organs, according to the WHO classification, arterial hypertension passes through three stages: Stage I - no organ damage; Stage II - mild organ damage - left ventricular hypertrophy, initial retinopathy, presence of protein in urine, slightly elevated creatinine; Stage III - severe organ damage - heart failure, stroke, hypertensive encephalopathy, renal failure.

Arterial hypertension occurs in about 25,000 people per 100,000 population. Its incidence increases with age, with over 50% in persons over 60 years of age and over 75% of the population over 65 years of age. About 5% of children have AH. In about 90% of cases, no etiology can be identified, and uncomplicated AH is most often asymptomatic. Persistently elevated blood pressure increases the overall risk of morbidity and mortality.

According to WHO, hypertension is one of the most serious socially significant diseases, leading to and increasing the risks of heart, brain, kidney and other complications. About 1.13 billion people worldwide have hypertension, most (2/3) of whom live in low- and middle-income countries. In 2015, 1 in 4 men and 1 in 5 women had hypertension. Fewer than 1 in 5 people with hypertension is in good control, with hypertension being a major cause of premature death worldwide. As far back as 2002, the WHO alarmed that the global epidemic of rising cardiovascular disease was linked to an increase in the number of overweight and obese individuals.

Interesting data is reported for the US - over 65 million of the population (1/5) have arterial hypertension, with 70% of them aware that they have a health problem, 59% undergoing treatment, with only 34% finding adequate control of hypertension.

In Bulgaria, the prevalence of hypertension is about 55%, compared to a European average of 30-45%. There are about 2 million hypertensives in our country, with about 37% adequately treated, with control achieved in recent years. Overweight, obesity and a sedentary lifestyle are considered to be major risk factors, not forgetting smoking and alcohol consumption.

According to the Bulgarian Society of Endocrinology, 34.93% of the population aged 20 years or older are obese, and 38.95% are overweight. This means that every second Bulgarian man (45%) and every third Bulgarian woman (32.4%) between the ages of 30-60 is overweight.

In 2014, smoking rates were the highest in the EU, with 28% of adults in Bulgaria smoking tobacco products every day.

The levels of episodic alcohol misuse (as a measure of excessive alcohol consumption) are lower than in other EU countries, but overall per capita alcohol consumption is the fifth highest.

The prevalence of obesity is low but increasing rapidly, especially among adolescents. Legislative efforts to mitigate risk factors have not been effective yet.

Life expectancy at birth was 74.7 years in 2015, the second lowest in the EU and almost 6 years below the EU average. Cardiovascular diseases and cancer cause more than four-fifths of all deaths.

Heart disease and strokes remain the leading causes of death. Cardiovascular mortality in Bulgaria is estimated at 56%, with stroke mortality estimated at 21%; ischemic heart disease (IHD) and myocardial infarction at 12% and other cardiovascular death at 23%.

According to this indicator, Bulgaria occupies the negative first place in the EU, with cardiovascular mortality 3 times higher than the average for the Member States.

We chose and formulated the dissertation topic because:

- 1. The measurement of macro-level indicators of drug utilization is an essential element in any national drug policy, especially in the formation of strategies for the prevention, diagnosis and treatment of socially important diseases.**
- 2. Early detection and diagnosis of essential hypertension is essential for cardiovascular disease prevention and cardiovascular mortality reduction.**
- 3. The national medicines utilisation parameters also enable the most appropriate assessment of rational medicines use, which requires that patients receive medicines appropriate to their clinical needs in doses that meet their individual needs for a sufficient period of time and at the lowest possible cost to them and their community.**
- 4. The analysis of rational drug use will enable us to assess the quality and effectiveness of the system for prevention and early detection of the disease, prevention and healthy lifestyle programs, compliance with national standards and recommendations of available and valid pharmacotherapeutic guidelines, compliance with established standards in actual clinical and pharmaceutical practice, and to measure the therapeutic effectiveness of different strategies.**

1. The analyses and corresponding results in this dissertation cover the period from 2017 to 2021. During this period, there was no pharmacotherapeutic guideline in cardiology approved by the NCPHA in Bulgaria. The pharmacotherapeutic guideline in cardiology has been adopted by Regulation No. 2 of 7 September 2023 on the adoption of pharmacotherapeutic guideline in cardiology and has been promulgated in State Gazette No. 80 of 19 September 2023. Therefore, all conclusions and generalisations can be considered reliable.
2. Part of the analyses and graphical representations contain trade names of medicinal products as authorised for use.
3. The dissertation is intended for presentation, discussion and dissemination, predominantly, among medical professionals, therefore we believe that the rules for promotion and advertising of medicinal products are not violated.
4. For the purposes of this dissertation, we believe that specifying the trade names enriches the applied value of the results and enables readers to reflect and search independently for additional reasons and corresponding motivations of prescribers as to why particular prescriptions predominate.
5. The place and role of beta-blockers in drug therapy according to different authors and standards continues to be debated. The author of this work has adopted the understanding that the choice should be well justified and more conservative due to the high rate of adverse drug reactions of beta-blockers.

II. AIMS AND OBJECTIVES

II.1. AIMS

The primary aim of the study is to analyze the drug utilization in the treatment of uncomplicated essential hypertension in Bulgaria using quantitative and qualitative measures at the national level.

Secondary aim - to evaluate the obtained data through the prism of rational drug use by determining the compliance of diagnostic and therapeutic strategies in patients with uncomplicated essential hypertension with treatment standards and valid national and international pharmacotherapeutic guidelines.

We will determine the proportion of patients with uncomplicated essential hypertension in the total proportion of hypertensive patients in Bulgaria, determine prevalence and morbidity using indirect quantitative parameters, and analyze the selected therapeutic approaches.

II.2. OBJECTIVES

The following tasks will be solved::

1. Analysis of national programs for prevention of arterial hypertension.
2. Determination of the total number of patients diagnosed with primary hypertension who are part of the drug therapy reimbursement system. Percentage of patients with different types of complication of primary essential hypertension (classified according to the International Classification of Diseases (ICD)).
3. Indication of the most prescribed medicines by INN according to the amounts paid by the NHIS budget.
4. Identification of the most prescribed medicinal products by INN, defined as absolute number of DDD.
5. Presentation of the cost of medicinal products calculated as number of packages.
6. Identification of the top 10 mono medicinal products by INN, quantity of active substance and number of tablets per pack, calculated according to the DDD/per patient/per year indicator.
7. Definition of the most prescribed combination medicinal products as cost containing fixed dosage forms by trade name and INN.
8. Specify the most prescribed combination medicinal products as DDD/year containing fixed dosage forms by trade name and INN.
9. Calculation of DDD per capita of the population for 1 year and DDD per 1000 capita of the population for 1 year.

III. MATERIALS AND METHODS

Study design - retrospective, observational study of information-data bases.

Study period January 2017 - December 2021.

We analyzed publicly available data from the registers of the National Health Insurance Fund (NHIF) related to arterial hypertension classified according to the International Classification of Diseases (ICD) with code I10 - Essential (primary) hypertension (Hypertensio arterialis essentialis (primaria)) - number of patients, reimbursement amount, types of medicinal products by INN (international non-proprietary name), products by trade names.

Drug utilization analyses were performed in accordance with the WHO ATC/DDD methodology.

The registration status of medicines was checked and was consistent with data from the public registries of the EMA and the BDA (Bulgarian drug agency).

The results were processed using descriptive statistical methods and presented in absolute and relative values, mean, median, mode.

Limitations and acceptable assumptions:

Due to a lack of publicly available data, analyses of drug utilization do not include demographics such as gender and age.

The average age for the onset of arterial hypertension, the duration of the disease, switching from one therapy to another has not been determined.

We assume that measuring DDD at the macro level is sufficient to assess whether there is adequate dosing, compliance with treatment standards, and evaluation of the therapeutic approach.

We chose to perform analyses only on ICD I10 because the cost of hypertension treatment in this segment is covered 100% by the NHIF, from the beginning of 2017 and we believe that this will ensure precision and credibility of calculations.

The study does not include secondary hypertension.

IV. ANALYSIS OF RESEARCH RESULTS

IV. 1. Results for Objective №1:

We performed a literature search using the keywords "arterial hypertension" on the websites of the competent authorities in the country - the Ministry of Health (MoH), the BDA and the NHIF. When analysing the data, it becomes clear that public efforts in Bulgaria aimed at preventing arterial hypertension are very limited. The search resulted in the discovery of three outcomes.

- Due to the proven causal relationship between modifiable risk factors (environmental and lifestyle factors) and the incidence of chronic non-communicable diseases (NCDs), in 2013 a decree of the Council of Ministers adopted the National Programme for the Prevention of Chronic NCDs.

According to the WHO, NCDs are among the leading causes of high rates of disability and death worldwide. Referring to statistical data, it is assumed that the incidence and severity of CHD is increasing. According to the WHO definition of NCDs, the following are considered as such - malignant neoplasms, COPD, diabetes, mental illnesses, but mainly diseases of the circulatory organs, i.e. the subject of this dissertation - arterial hypertension.

This Programme aims to track the impact of environmental factors on population health, cognition and patient behaviour, with the resulting information forming the basis for the development of future objectives and strategies. As part of the National Programme for the Prevention of NCD, annual educational campaigns are planned for both the patient population and health professionals, using different approaches and forms of training. The aim is to inform patients about possible preventive examinations and consultations. The free measurement of blood pressure is promoted in public places accessible to patients - pharmacies, community centres and pensioners' clubs. Initiate campaigns for free screening of smokers, set up healthy eating clubs and encourage regular physical activity.

Responsible for the monitoring and evaluation of activities related to the Programme is the National Programme Council, which includes representatives from the MoH, the National Centre for Public Health and Analysis (NCPHA), Regional Health Inspectorates, NHIF, NGOs and others. As this model of prevention is internationally recognised and evaluated as effective in other countries, the Council of Ministers approves the continuation of the Programme in the period 2021-2025. And within the framework of this continuation, in the long term, in the field of cardiovascular diseases among the main objectives is the reduction of the incidence of arterial hypertension in the age group 25 - 64 years by

- An information sheet designed for patients has been published on the NCPHA website, which describes the causes of AH and tips for maintaining an optimal BP level. This leaflet was produced in 2017 by the MoH in conjunction with the NCPHA, but there is no record of it being updated or its effect being monitored since then.
- As part of the activities related to the prevention of hypertension, World Hypertension Day is celebrated annually on 17 May. The campaign consists of free blood pressure measurements at specialised stations in regional towns and distribution of educational materials.

However, there is no clear evidence of a positive effect of the national prevention programme and accompanying events.

IV.2. Results for Objective №2 ÷ №9:

The classification of medicinal products in Bulgaria is in accordance with the WHO ATC/DDD classification system. It also serves as the basis for classification in authorisation procedures as well as in pricing and reimbursement procedures. We performed an analysis of the ratio of WHO ATC/DDD medicines used for the treatment of hypertension in general versus medicines included in the Bulgarian positive medicinal list (PML).

In accordance with the Law on Medicinal Products in Human Medicine (LMPHM), medicinal products may be placed on the market in Bulgaria only after they have received a marketing authorization (MA) under the relevant procedure and have a price registration. That is, a medicinal product can only be defined as available if it is authorised for use and has a registered price. The same medicinal product is defined as available if it is available and is included in the public reimbursement system.

The updated version of the ATC/DDD Index 2020 contains 121 Level IV codes and 609 Level V INNs. Of these, 41 Level IV codes and 102 Level V INNs can be considered as available in Bulgaria, as described in the PDS. The level IV ATC products in Bulgaria are 3 times less than all WHO ATC or 33.88%, and as level V products 6 times less or 16.74% (Table 1).

Table 1. Comparison between medicines included in the WHO ATC/DDD Index 2020 and medicines available in Bulgaria

Group	BG	WHO	BG	WHO
1. Cardiac therapy	7	18	12	140
2. Antihypertensive	7	28	13	74
3. Diuretics	5	20	7	72
4. Peripheral vasodilators	3	7	3	39
5. Vasoprotectors	0	10	0	49
6. Beta blockers	3	15	7	65
7. Calcium channel blockers	4	7	11	39
8. Substances acting on RAAS	9	9	40	67
9. Lipid modifiers	3	7	9	74
TOTAL	41/33.88%	121/100%	102/16.74%	609/100%

Diseases in Bulgaria are coded according to the ICD and all health institutions, including the only public health fund - NHIF use this system as the basis for their overall activities. The prescription and dispensing of prescription medicines is also carried out according to the ICD. The positive list of medicinal products, which is the basis for reimbursement of medicinal products, uses the ICD to determine the diseases whose treatment will be paid for, according to the therapeutic indications of the medicinal products. Reporting of the cost of drug therapies is prepared in accordance with the ICD.

According to the official data of the NHIF for 2017, the number of all patients with any primary hypertension who are included in the reimbursement system for treatment is 1 393 037. The patients with primary uncomplicated essential hypertension with ICD code I10 accounted of 185 671 or 13.33% of all hypertensive patients. The largest proportion of patients with hypertensive heart without (congestive) heart failure - 1 013 822 or 72.78%. The second place

is occupied by patients with hypertensive heart with (congestive) heart failure - 186 718 or 13.40%, followed by patients with complicated primary hypertension with combination of hypertensive heart with hypertensive kidney and with (congestive) heart failure - 4 733 people, the relative share of this group of hypertensives is less than 1%. The number of patients and their distribution according to the type of complications of primary essential hypertension classified by ICD are presented in Table 2.

Table 2. Number of patients in 2017 with different types of primary hypertension by ICD, treatment of which is paid by NHIF

Code	Types of primary arterial hypertension	Number of patients n / Relative proportion %
I10	Hypertensio arterialis essentialis (primaria)	185 671 / 13.33
I11	Morbus cordis hypertensivus	
I11.0	Morbus cordis hypertensivus cum insufficientia cordis (congestiva)	186 718 / 13.40
I11.9	Morbus cordis hypertensivus sine insufficientia cordis (congestiva)	1 013 822 / 72.78
I12	Morbus renalis hypertensivus	
I12.0	Morbus renalis hypertensivus cum insufficientia renis	574 / 0.04
I12.9	Morbus renalis hypertensivus sine insufficientia renis	564 / 0.04
I13	Morbus cordis et morbus renis hypertensivus	
I13.0	Morbus cordis et morbus renis hypertensivus cum insufficientia cordis (congestiva)	4 733 / 0.34
I13.1	Morbus cordis et morbus renis hypertensivus cum insufficientia renis	551 / 0.04
I13.2	Morbus cordis et morbus renis hypertensivum cum insufficientia cordis (congestiva) et insufficientia renis	404 / 0.03

To analyze drug utilization we used different qualitative indicators. As a baseline for all analyses, we used the total budget expenditure to pay for treatment for uncomplicated essential hypertension.

The 2017 NHIS expenditure (cost per year) for the disease (ICD I10) was BGN 9 796 940.12. The cost per patient per year (cost per capita per year) is BGN 52.76, the monthly cost (cost per month) is BGN 4.40 and the cost per treatment day (cost per treatment day) is BGN 0.14. The amount of BGN 9 796 940.12 is divided into two large groups - cost for mono products BGN 6 454 818.90 (relative share 65.88%) and cost for combination medicinal products BGN 3 342 121.22 (relative share 34.12%).

We recalculated the cost as a proportion of gross national product (GDP) per capita. GDP per capita for 2017 recalculated in purchasing power parity (PPP) is 13 600 euro. On this indicator, Bulgaria ranks last in the EU, with an EU average of 28 900 euro. The amount allocated by the NHIF for the treatment of essential hypertension per patient is equal to 0.19% of the gross product per capita. It would be important to add that 15.5% of the population lives below the EU poverty threshold.

Another important indicator for assessing drug utilisation is the calculation of cost as a proportion of total health cost. The total cost of reimbursement of drug treatment for outpatients in 2017 was BGN 798 571 600. The cost of medicines for the treatment of primary essential hypertension as a proportion of total health cost for NHIF medicines is equal to 1.23%. The studied segment is a reimbursement segment, with a clearly defined order of prescription and dispensing of medicines, therefore we assume that the cost of DDD (cost per

defined daily dose) and the cost of PDD (cost per prescribed daily dose) are identical. We defined one of the most important indicators, drug utilization (DU) 90% (90% drug utilization), by what is known in practice as a "top-ten list". In Figure 1, we present the top 10 INNs as a proportion of the amounts paid by the NHIF.

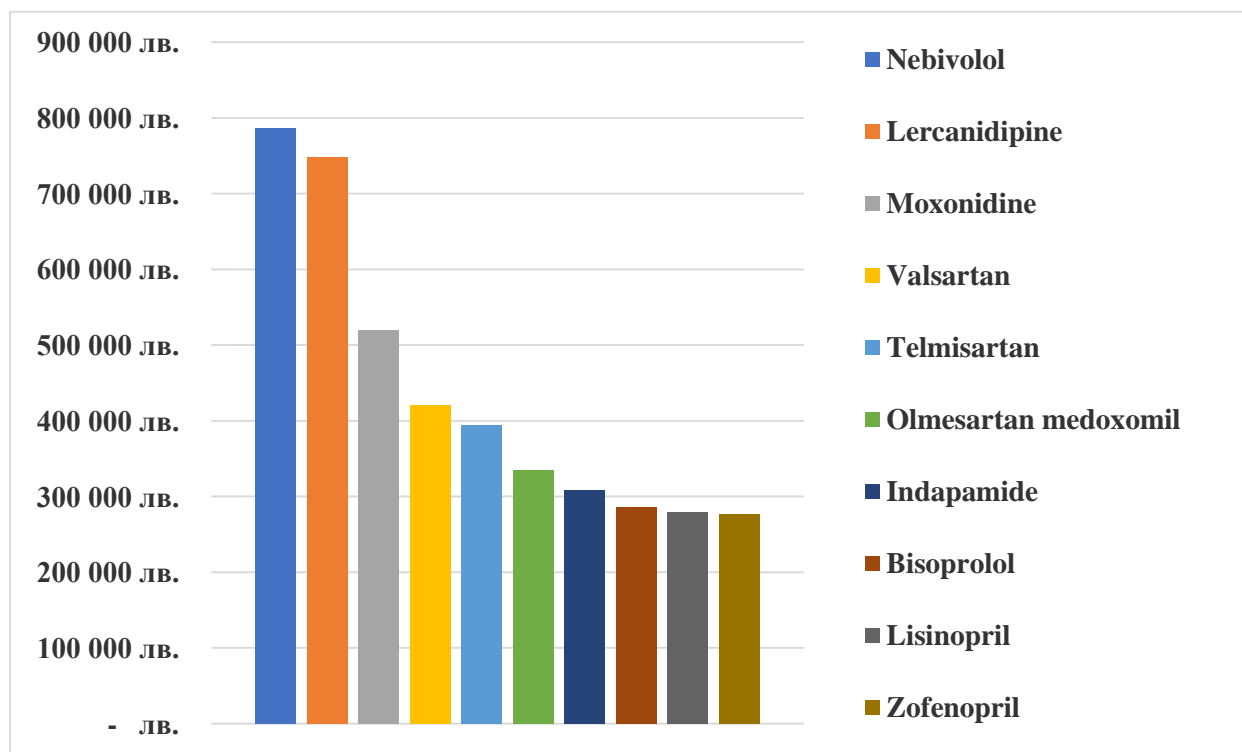


Figure 1. The most prescribed medicines by INN according to the amounts paid by the NHIF budget (top ten) in 2017.

Cost are shown in BGN (1 Euro=1.95583 BGN)

It is noteworthy that the most prescribed drugs by INN are beta-blockers (Nebivolol and Bisoprolol), ARBs (Valsartan, Telmisartan, Olmesartan) and ACE-inhibitors (Lisinopril, Zofenopril). The isolated, and very high, presence in the cost fraction of Ca-antagonist Lercanidipine, centrally acting Moxonidine and sulfonamide diuretic Indapamide is impressive. The cited medicinal products occupied a share of BGN 4 352 085.09 of the NHIF expenditures, about 1/2 of the total prescription or 44.42% of the expenditures for the treatment of primary essential arterial hypertension. We calculated the total number of DDD by INN paid by the NHIF (Figure 2). Lercanidipine had the highest utilization - 6 327 284 DDD in one year - or 1 in 10 patients took 1 DDD Lercanidipine/per day. The total number of DDDs for the first 10 products was 41 736 639 DDD/per year. Or each patient with essential hypertension takes at least 0.6 DDD of the top 10 most used drugs.

The prescription determined by the total number of DDDs shows differences with the prescription determined by the reimbursement amount, i.e., a difference is found between the prescription of medicines by reimbursement amount and DDDs, which is most likely due to the abundance of generic medicines. Two new international non-proprietary names (INNs), Amlodipine and Enalapril, appear in the top 10 group of medicines at the expense of Olmesartan medoxomil and Zofenopril. The displacement of the two products is due to the

higher registered prices in the PPS system for Olmesartan medoxomil and Zofinopril, which explains the higher budget outlay for them, against a lower number of defined daily doses.

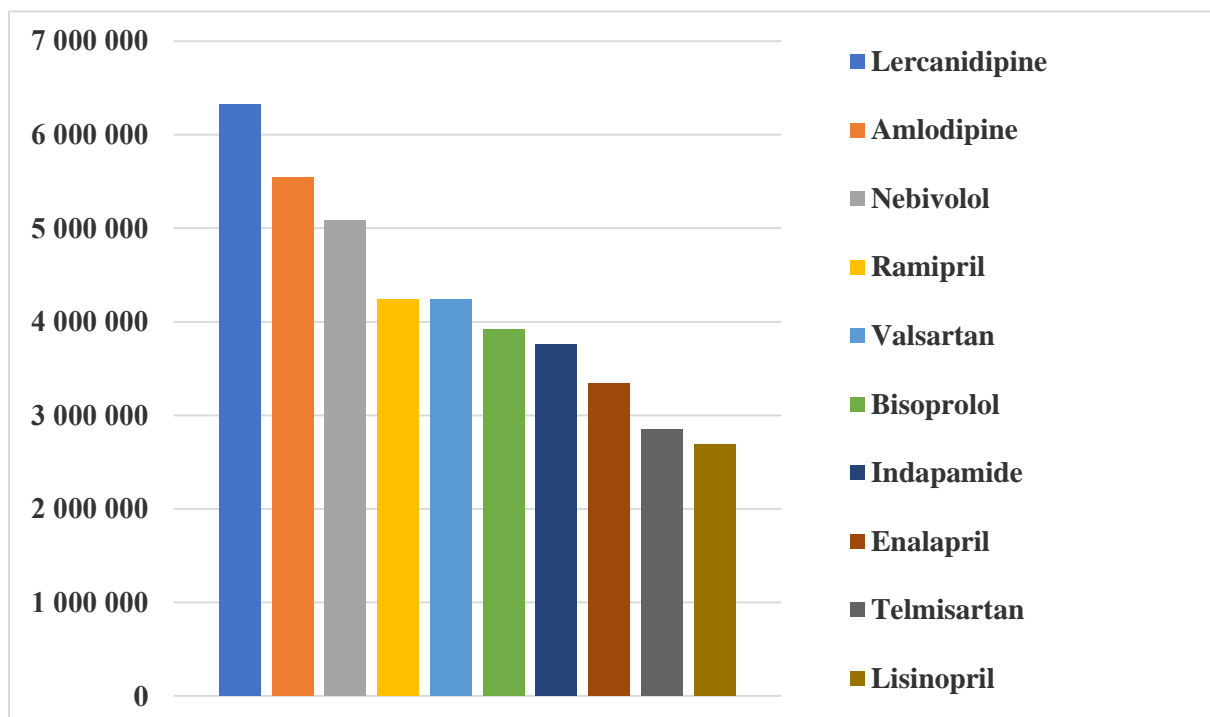


Figure 2. Top prescribed medicines by INN, defined as absolute number of DDD in 2017

We identified the top 10 most prescribed medicines in terms of number of packs according to the amounts paid from the NHIF budget. Calculations were indirect by converting total budget expenditures into expenditure per quantity of active drug substance and number of tablets per pack (Figure 3).

The most prescribed products were Nebivolol and Lercanidipine. The cost for the both presentations of Nebivolol approached BGN 750 000 and for Lercanidipine BGN 550 000. The share of these products of total consumption defined through packaging cost is 13.26 percent of total cost or 20.13 percent of mono-product cost. Noteworthy in this group is the significant presence of the two centrally acting anti-adrenergic agents Rilmenidine and Moxonidine, which together occupy third place in packaging expenditure, with a relative share of 7.00 per cent of total packaging expenditure on mono-products.

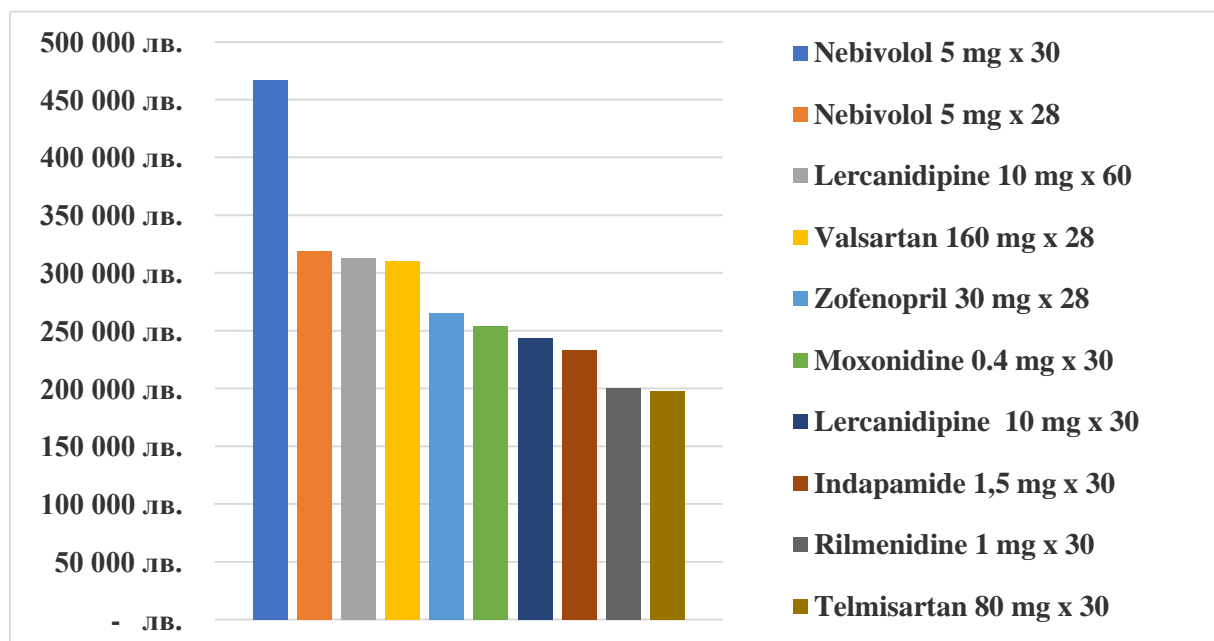


Figure 3. Medicines expenditure for 2017, calculated as number of packs

At Figure 4, we present the top 10 mono-drug products by INN, active substance amount and number of tablets per pack, and we calculated the DDD/per patient/per year. The group of calcium antagonists, Amlodipine and Lercanidipine, has the highest relative share in this parameter, followed by the beta-blockers Nebivolol and Bisoprolol. The third position is occupied by the only sartan included in this group - Valsartan, followed by the diuretic from the group of sulfonamides Indapamide.

As we have already pointed out, combination medicines account of 1/3 of the total consumption of medicines for the treatment of essential hypertension in the segment reimbursed by the health insurance fund. Figures 5 and 6 present the 10 most prescribed combination medicinal products by international non-proprietary names as reimbursement expenditure in leva and as DDD. The most used combination medicinal products contain combinations of sartans and thiazide diuretics. In the top 10, 6 such medicinal products are found. It is noteworthy the pronounced use of the combination Valsartan/Hydrochlorothiazide on both evaluated measures - cost in absolute value and DDD, compared to all other combination medicinal products. The quantitative prescription by DDD of Valsartan/Hydrochlorothiazide was significant at approximately 5 million DDD/per year or 0.07 DDD per patient per year, as the second ranked drug combination significantly behind with 1 250 000 DDD/per year.

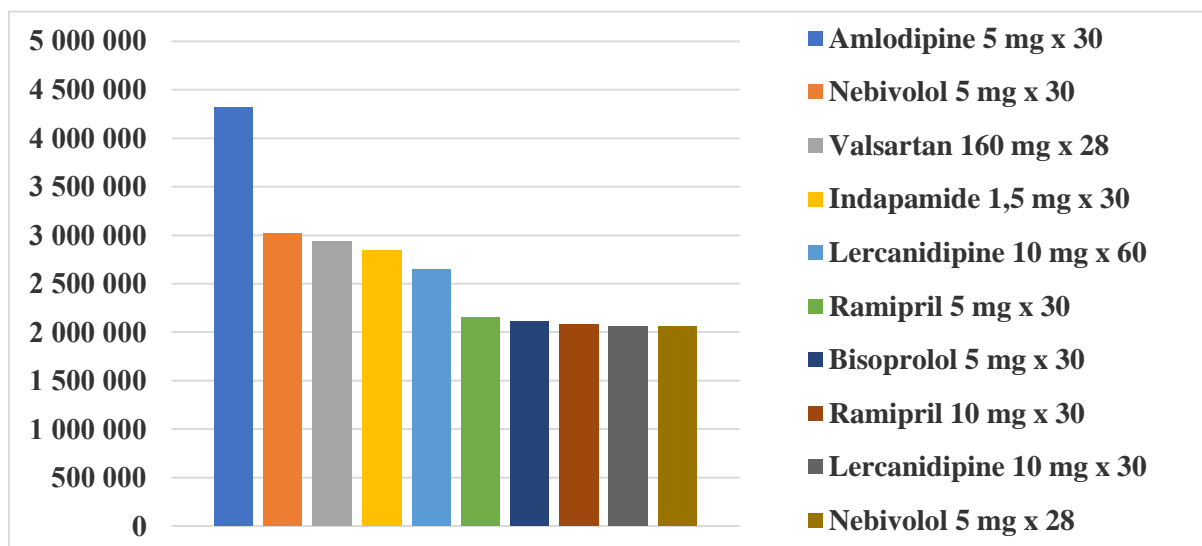


Figure 4. Top 10 medicines by INN, active substance quantity and number of tablets designated as DDD/year in 2017

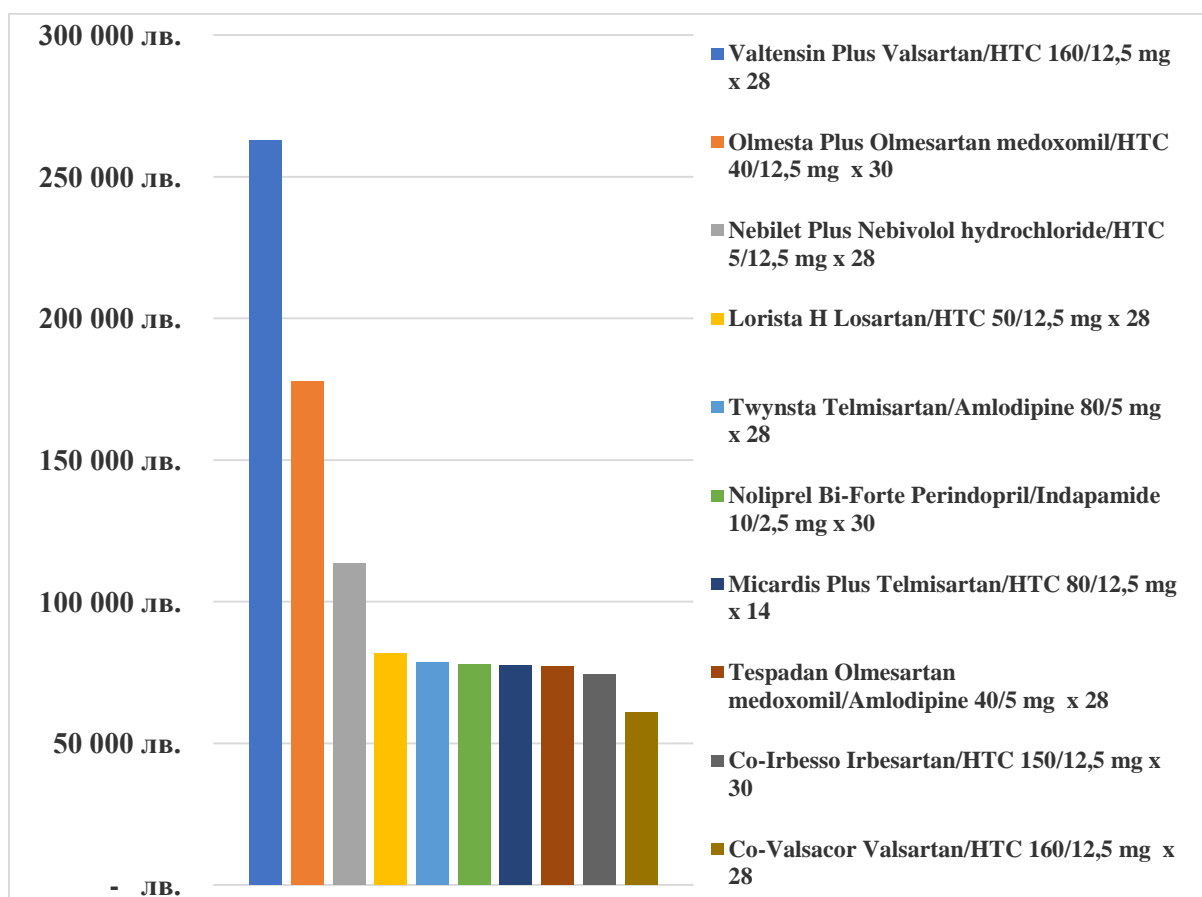


Figure 5. The most prescribed combination medicinal products as cost containing fixed dosage forms by trade name and INN in 2017

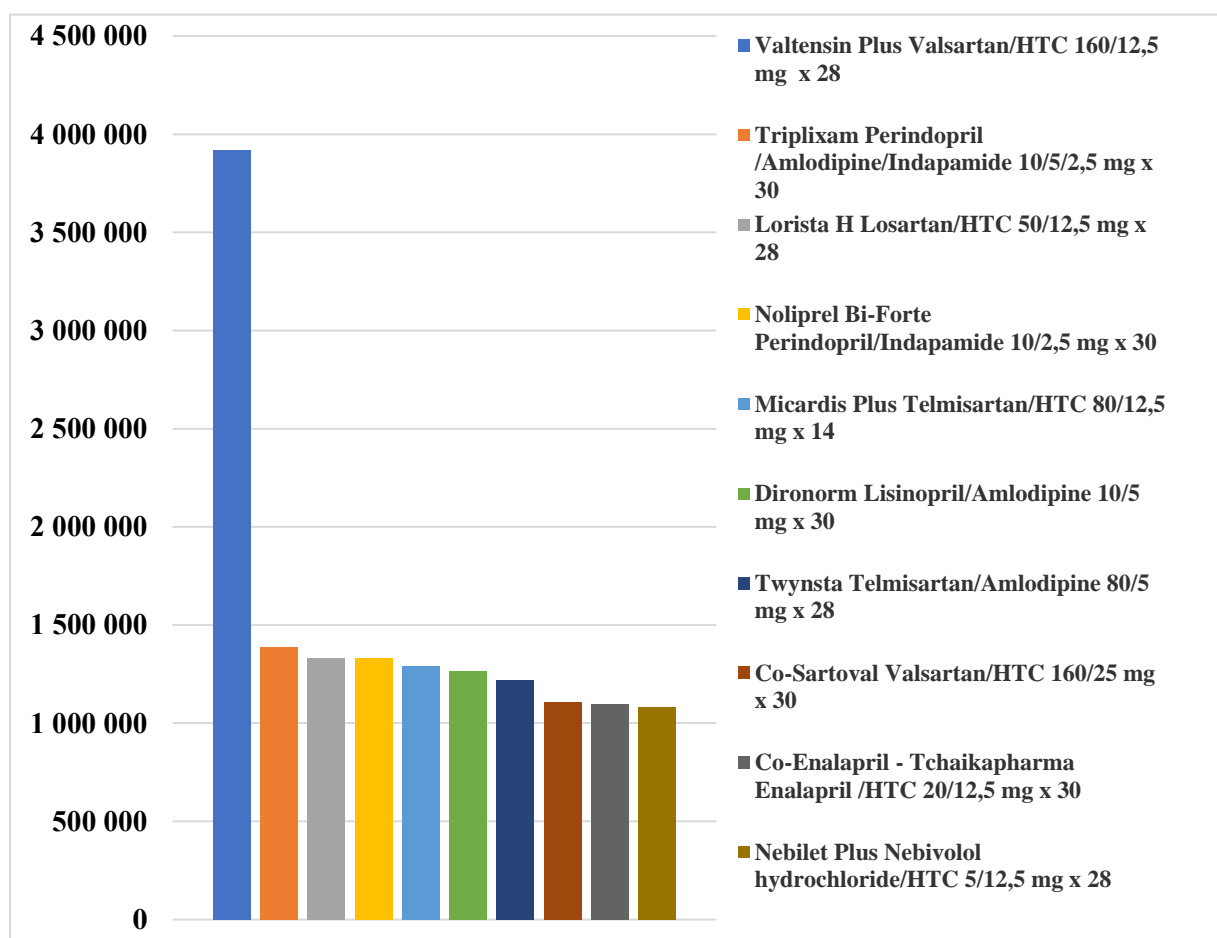


Figure 6. The most prescribed combination medicinal products as DDD/year containing fixed dosage forms by trade name and INN in 2017

We also calculated two other significant indicators of drug utilization, DDDs per capita per year (DDD per inhabitant per year) and DDDs per 1000 inhabitants per year (DDD per 1000 inhabitants per day) (Table 3).

The analyses are made to the Bulgarian population of 7 101 859 inhabitants as of 2017, according to Eurostat data.

Calcium antagonists and beta-blockers were in the top 3 positions, as Lercanidipine significantly ahead of the other drugs.

Table 3. DDD per capita per year (DDD per inhabitant per year) and DDD per 1000 inhabitants per day (DDD per 1000 inhabitants per day) for 2017

INN	DDD	DDD/inhabitant/year	DDD/1000/day
Lercanidipine	6 327 284	0.89	2.44
Amlodipine	5 543 138	0.78	2.14
Nebivolol	5 082 087	0.72	1.96
Ramipril	4 241 123	0.60	1.64
Valsartan	3 982 124	0.56	1.54
Bisoprolol	3 924 263	0.55	1.51
Indapamide	3 760 958	0.53	1.45
Enalapril	3 338 725	0.47	1.29
Telmisartan	2 850 469	0.40	1.10
Lisinopril	2 686 469	0.38	1.04

Similarly, we performed the analysis of the information provided by the NHIF electronic database for the entire period of our study. In 2018, the number of patients, regardless of the type of primary hypertension, whose treatment was paid for by the health insurance fund budget was 1 202 704. The patients who were diagnosed with primary uncomplicated essential hypertension (i.e. with ICD code I10) were 129 376 people or this makes a little over 10% of the total population of Bulgaria undergoing treatment for high blood pressure.

The share of the NHIF budget allocated for the provision of quality and effective therapy of patients with uncomplicated essential hypertension in 2018 amounts to BGN 8 437 096.38. After making a breakdown of these funds, it is found that the cost per patient per year (cost per capita per year) is BGN 65.21, the monthly cost (cost per month) is BGN 5.43, and the daily treatment cost (cost per treatment day) is BGN 0.18.

Compared to the previous year 2017, we found that the cost covered by the NHIF for ICD I10 has decreased, but the cost per patient per year has increased, respectively per month/day. The amount of BGN 8 437 096.38 covers to a greater extent the treatment of patients with mono products - BGN 5 703 224.74 (relative share 67.60%) and BGN 2 733 871.64 for treatment with combination products (relative share 32.40%).

Reimbursement cost for the treatment of outpatients for 2018 amounted to BGN 1 222 986 555. The cost of medicines for the treatment of primary essential hypertension, as a share of the total health expenditure on medicines of the NHIF, is equal to 0.69%.

The funds allocated by the NHIF for the treatment of uncomplicated essential hypertension per patient in 2018 are equal to 0.34% of the gross product per capita (which is 14 800 euros).

According to the "top-ten list" rule, the most prescribed and used INNs for treatment in 2018 were:

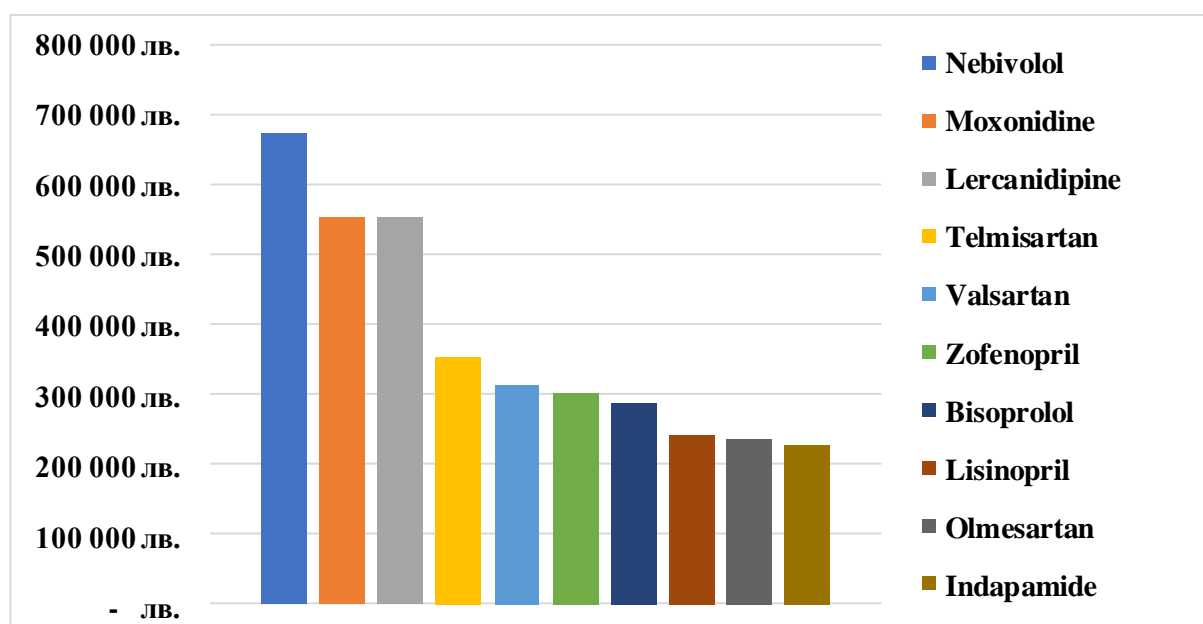


Figure 7. Top prescribed medicines by INN according to the amounts paid by the NHIF budget (top ten) in 2018.
Cost are shown in BGN (1 Euro=1.95583 BGN)

It is notable that there is no change in the top ten prescribed medicines by INN. Choices for the treatment of uncomplicated essential hypertension are: beta-blockers (Nebivolol, Bisoprolol), ACE-inhibitors (Zofenopril, Lisinopril), ARBs (Telmisartan, Valsartan, Olmesartan).

Again it is seen that in real Bulgarian practice Ca-antagonist Lercanidipine and centrally acting Moxonidine are also frequently prescribed. The sulfonamide diuretic Indapamide is also among the top ten, but compared to 2017 the total reimbursement amount that the NHIF pays for its treatment is lower.

The above medicines take up a share of BGN 3 732 673 of the NHIF budget, which is almost half of the total prescription or 44.24% of the cost for the treatment of primary essential hypertension.

Analogous to 2017, we calculated the total number of DDDs by INN paid by the NHIF (Figure 8). The top ten prescribed medicines by INN, defined by absolute number of DDDs were - Amlodipine, Nebivolol, Bisoprolol, Ramipril, Lercanidipine, Enalapril, Valsartan, Indapamide, Telmisartan and Moxonidine.

Compared to the previous year, Amlodipine had the highest utilization at 4 576 629 DDD in one year. In 2017 the first place was Lercanidipine, and in 2018 this product now occupies the fifth place and this leads to the conclusion that the prescription, respectively the dispensing and use of this product, is falling.

The total number of DDDs for the top 10 products is 34 823 113 DDD/per year, which represents 36.08% of the total absolute number of DDDs of mono and combination products. On this analysis criterion, there is another difference compared to 2017 - Lisinopril is not present, its position is "occupied" by

Moxonidine.

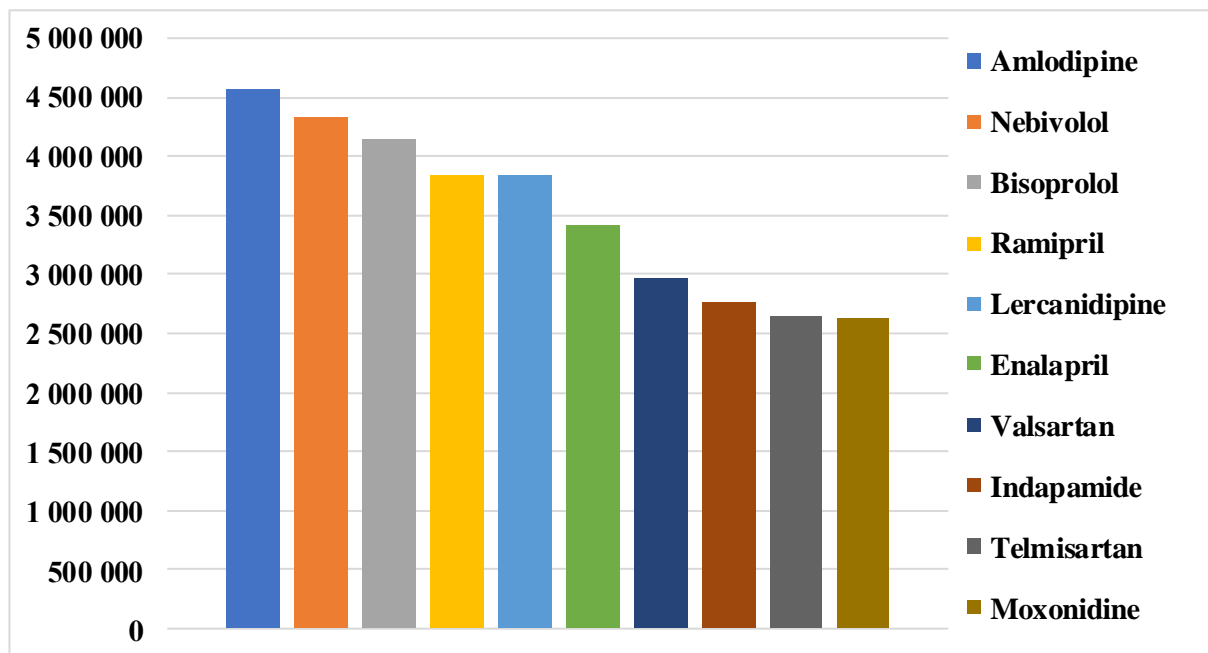


Figure 8. Top prescribed medicines by INN, defined as absolute number of DDD in 2018

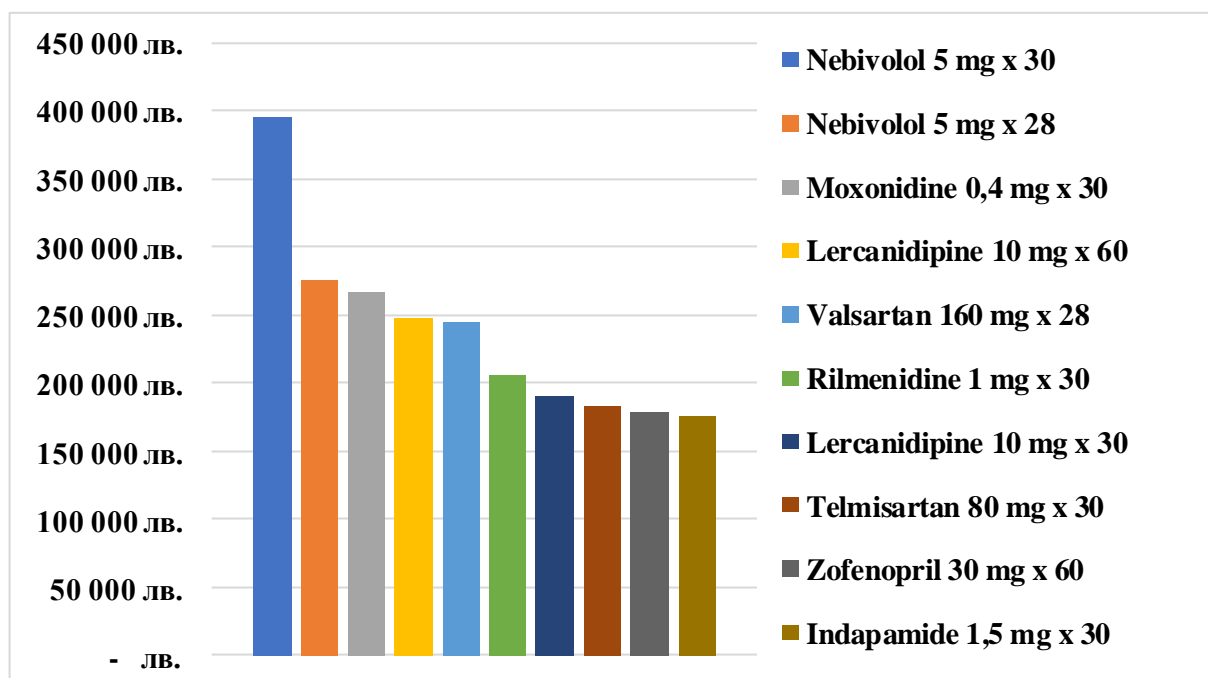


Figure 9. Medicines expenditure for 2018, calculated as number of packs

In order to study drug utilization in the uncomplicated essential hyperosthenia segment, we retrospectively identified the top 10 most prescribed drugs in terms of number of packs according to the amounts paid from the NHIS budget.

The most prescribed products were Nebivolol and Lercanidipine. The cost of the two variations of the INN Nebivolol 5 mg medicine pack was around BGN 670 880. The cost of

Lercanidipine is BGN 437 395. The total cost of the first two INNs, Nebivolol and Lercanidipine, is 1 108 275 BGN, which as a proportion of total consumption defined through packaging cost is 13.14% of total cost or 19.44% of mono-product cost.

Both in 2017 and 2018, the presence of the two centrally acting anti-adrenergic agents Rilmenidine and Moxonidine makes a strong impression. They retained third place in cost per number of packs with a share of 5.60% of total cost, or 8.30% of cost for medicinal products containing a single pharmacologically active substance.

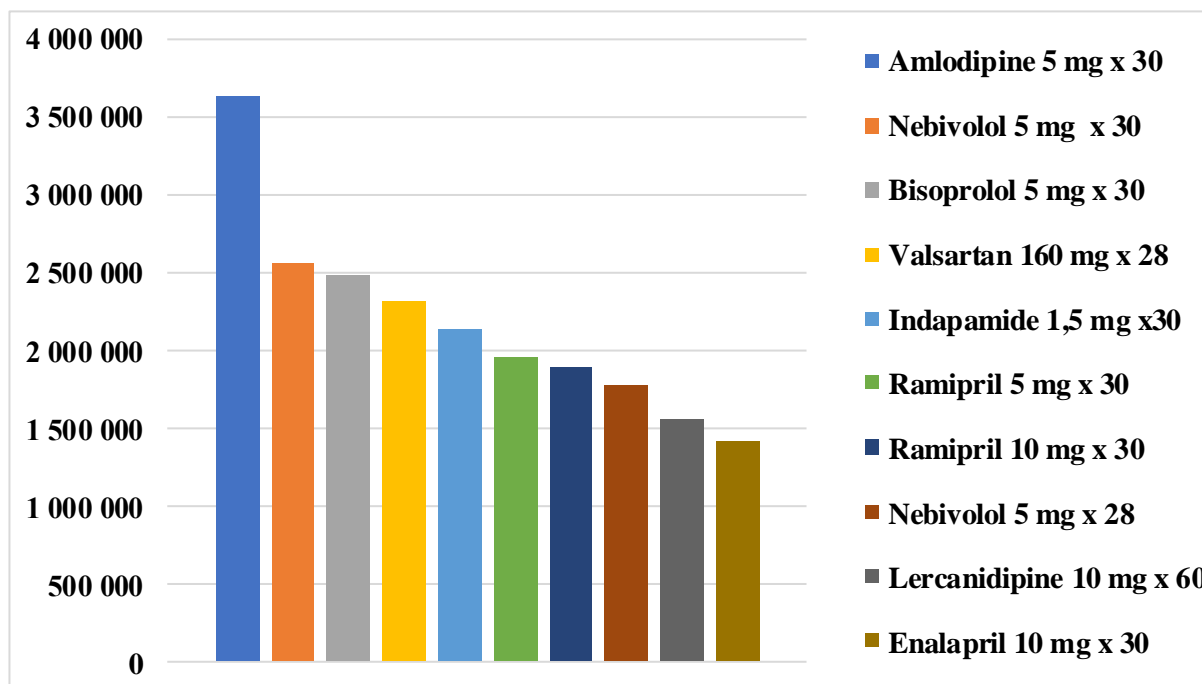


Figure 10. Top 10 medicinal products by INN, active substance quantity and number of tablets defined as DDD/year in 2018

In order to examine at a macro level whether there is or is not, respectively, a rational use of medicines in the treatment of patients with uncomplicated essential hypertension, for 2018 we also calculated the DDD/year indicator and identified the top mono medicines by INN, amount of active substance and number of tablets per pack.

In contrast to 2017, in 2018 the highest share in this indicator was occupied by the group of ACE-inhibitors - Enalapril and Ramipril. They displaced from the first place calcium antagonists - Amlodipine and Lercanidipine and the displaced group falls in 2018 to the third place. The second place is occupied by the group of beta-blockers - Nebivolol and Bisoprolol. Valsartan for another year remains the only representative of the group of ARBs. It maintains its relative share according to the above criteria. The situation is similar for the treatment with the only representative of sulfonamides - Indapamide.

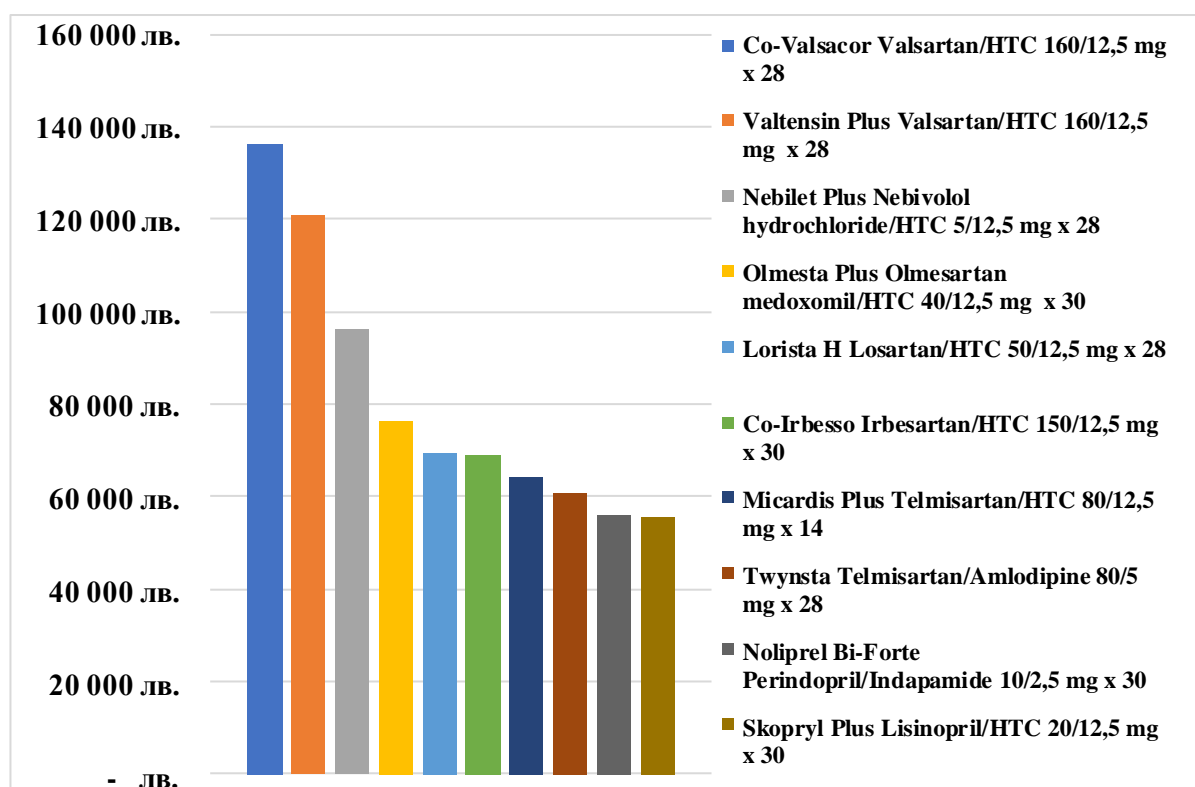


Figure 11. The most prescribed combination medicinal products as cost containing fixed dosage forms by trade name and INN in 2018

With regard to combination antihypertensive medicines as isobr for the treatment of ICD I10, the trend is maintained - they occupy a share of nearly 1/3 of the total consumption of medicines in the segment reimbursed by the health insurance fund. In the figure we present the Fmost prescribed combination medicinal products by international non-patent names as reimbursement expenditure in BGN.

The most frequently prescribed again are the medicinal products containing combinations of ARB and thiazide diuretic (Valsartan/Telmisartan/Irbesartan/Olmesartan/Losartan in combination with Hydrochlorothiazide), taking up a share of 6.35% of the total expenditure or 19.60% of the expenditure on combination medicinal products. Six of the top ten combinations were of an ARB and a thiazide diuretic, similar to 2017. By that criterion, the most common isobr for therapy was again Valsartan/Hydrochlorothiazide. At the same time, a significant increase in the use of the combination drug, Nebivolol/Hydrochlorothiazide, was also reported.

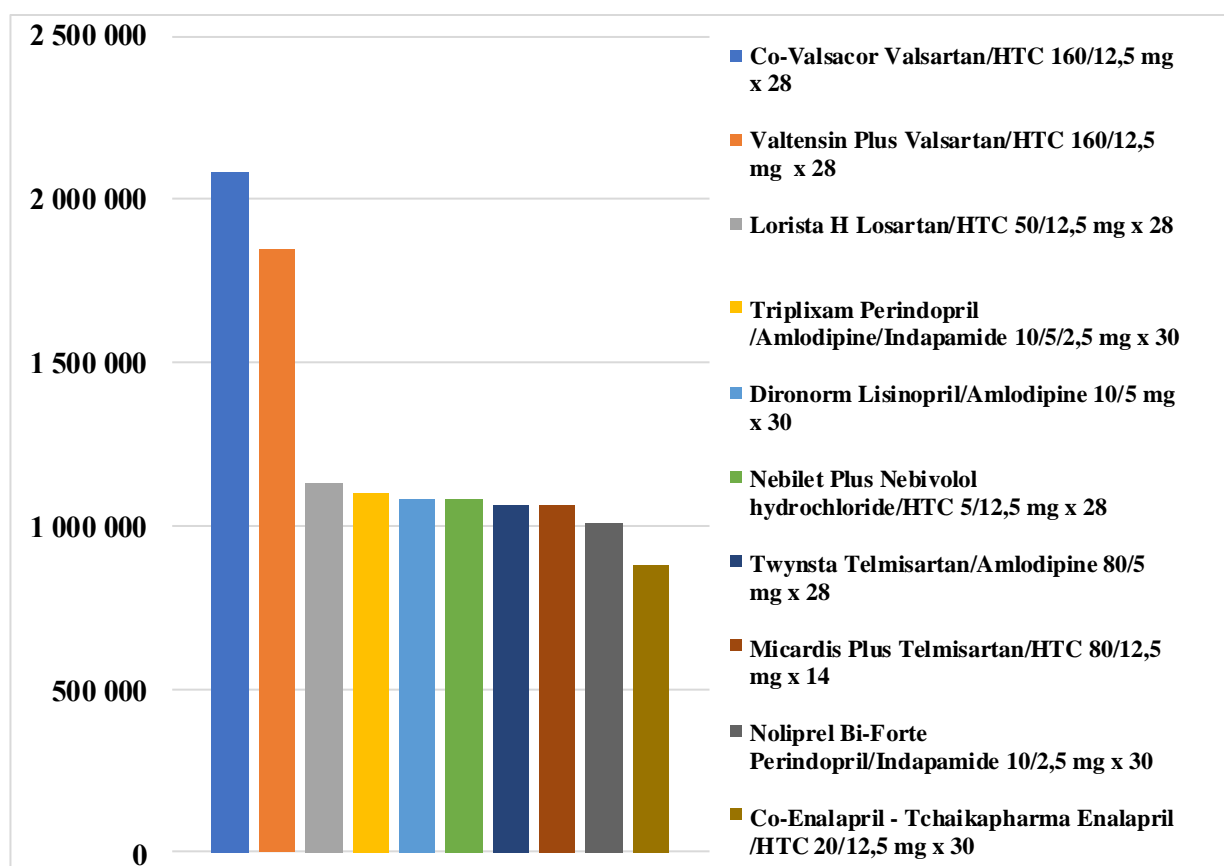


Figure 12. The most prescribed combination medicinal products as DDD/year containing fixed dosage forms by trade name and INN in 2018

We performed an analysis of the most prescribed combination drugs as DDD/year for 2018. We found that the top three positions are occupied by a drug that is a combination of an ARB and a thiazide diuretic, as the most prescribed being Valsartan/Hydrochlorothiazide and Losartan/Hydrochlorothiazide. The total number of DDD/year for these three products is 5 061 563 DDD. This represents a share of 5.24% of the total number of DDD/year or 10.47% of the share of combination products. We observe a similarity among the top ten representatives in 2018 compared to 2017 with the only differences determined by the difference in the total number of DDD/year for the respective drug products.

We also calculated two other significant indicators of drug utilization, DDDs per capita per year (DDD per inhabitant per year) and DDDs per 1 000 inhabitants per day (DDD per 1 000 inhabitants per day). The analyses are based on the 2018 population size of 7 000 039 inhabitants. The top 3 positions are calcium antagonist and beta blockers.

Table 4. DDDs per capita per year (DDD per inhabitant per year) and DDDs per 1000 inhabitants per day (DDD per 1000 inhabitants per day) for 2018

INN	DDD	DDD/inhabitant/year	DDD/1000/day
Amlodipine	4 576 629	0.65	1.79
Nebivolol	4 337 491	0.62	1.70
Bisoprolol	4 148 905	0.59	1.62
Ramipril	3 845 862	0.55	1.51
Lercanidipine	3 485 397	0.50	1.36
Enalapril	3 414 463	0.49	1.34
Valsartan	2 970 768	0.42	1.16
Indapamide	2 759 667	0.39	1.08
Telmisartan	2 651 718	0.38	1.04
Moxonidine	2 632 215	0.38	1.03

In the following calendar year, there was a decrease in the total number of patients diagnosed with primary essential hypertension whose outpatient treatment is paid by the NHIF budget - 1 181 706 people. The number of patients with uncomplicated essential hypertension was 119 240 people.

The funds needed to cover the treatment of these patients amount to BGN 8 029 776.18. Or that is BGN 67.34 per patient per calendar year, BGN 5.61 per thirty day period or just over BGN 0.18 on a daily basis. The amount of BGN 8 029 776.18 is predominantly used to provide treatment for patients with mono medicinal products - BGN 5 560 631.74 (relative share 69.25%), against BGN 2 425 658.41 for treatment with combination medicinal products (relative share 30.21%).

The money allocated by the NHIF for the treatment of uncomplicated essential hypertension per patient in 2019 is equal to 0.36% of the gross product per capita, calculated by purchasing power parity (14,800 euros). Compared to 2018, we find an increase of 0.04% in the funds allocated by the NHIF for the treatment of patients with essential hypertension.

The reimbursement cost for the treatment of outpatients for 2019 are BGN 1 313 770 234. The cost of medicines for the treatment of primary essential hypertension as a share of the total health expenditure on medicines of the NHIF is equal to 0.61%. There has been a decrease in the percentage of these expenditures compared to previous years, part of the thesis.

Following the already established procedure for tracking therapeutic strategies in hypertensive patients, we performed the same analyses for 2019.

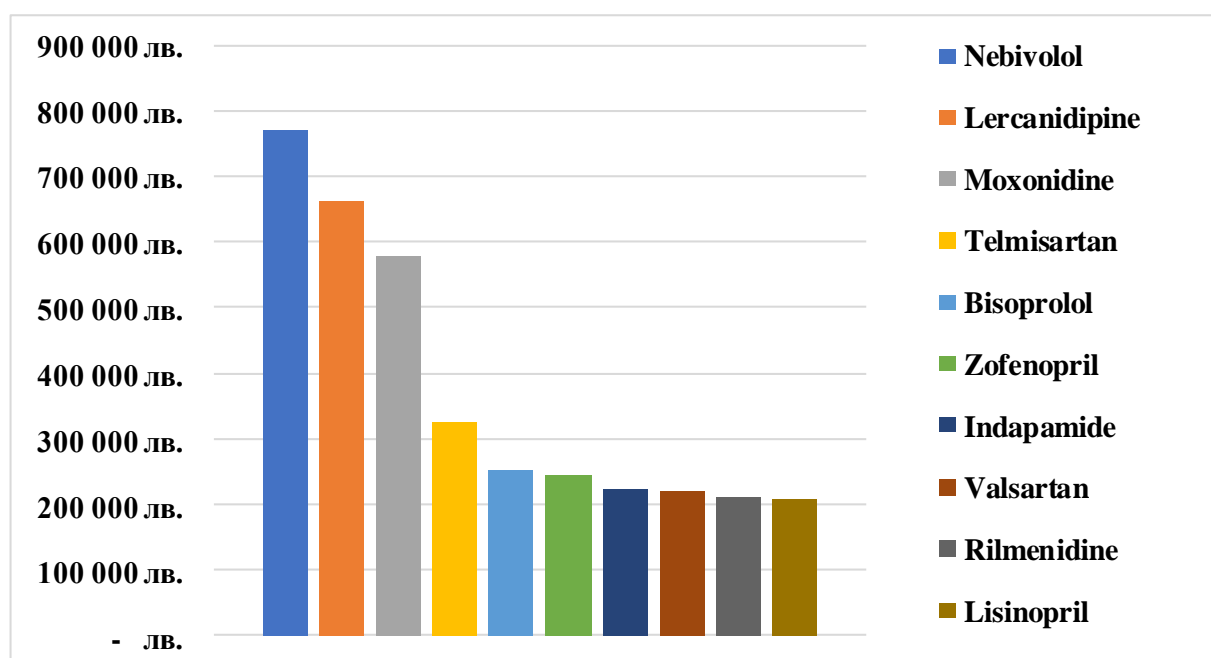


Figure 13. The most prescribed medicines by INN according to the amounts paid by the NHIF budget (top ten) in 2019.
Cost are shown in BGN (1 Euro=1.95583 BGN)

Among the top 10 medicines that are most prescribed, according to the amounts paid by the NHIF budget, are the following INN: Beta-blockers (Nebivolol, Bisoprolol), ARBs (Telmisartan, Valsartan), ACE-inhibitors (Zofenopril, Lisinopril), Ca-antagonists (Lercanidipine), centrally acting antihypertensives (Moxonidine, Rilmenidine), sulfonamide diuretics (Indapamide).

Comparing the data with those of 2018, we found that the INN Olmesartan, which according to the ESC and ESH recommendations for the management of arterial hypertension is among the first choices for treatment, is being displaced from the list of the top 10. Interestingly, another member of the group of centrally acting antihypertensive drugs, Rilmenidine, appears among the top 10.

The total value of the products listed in Figure 13 is BGN 3 698 612. Their share in relation to the total expenditure of the NHIF for 2019 for the treatment of primary essential hypertension is 46.06%, which represents an increase compared to 2018.

We examined which drugs were the most prescribed by INN based on absolute number of DDDs in 2019 (Figure 14). Amlodipine, Nebivolol, Bisoprolol, Ramipril, Lercanidipine, Enalapril, Valsartan, Indapamide, Telmisartan and Moxonidine participated in this ranking. There is no change in the products on this list compared to 2018. But unlike the previous year, in 2019 the first position in absolute number of DDD is Ca-antagonist Lercanidipine with 4 176 124 DDD. This shows that its usage in 2019 has increased and it from the fifth position, now occupies the first place. Second place is retained by the beta-blocker Nebivolol, and the Ca-antagonist Amlodipine stands in third position. Obviously, from the data it is clear that of the top three products, two are Ca-antagonists.

According to the recommendations of the European Society of Cardiology and the European Society of Hypertension, calcium antagonists are not the first choice for the treatment of arterial hypertension, including taking into account the risk of a number of adverse drug reactions. The total number of DDDs of the top 10 products was 31 551 773 DDDs,

representing a share of 35.28% of the total absolute number of DDDs of mono- and combination products for the treatment of essential hypertension (Figure 15).

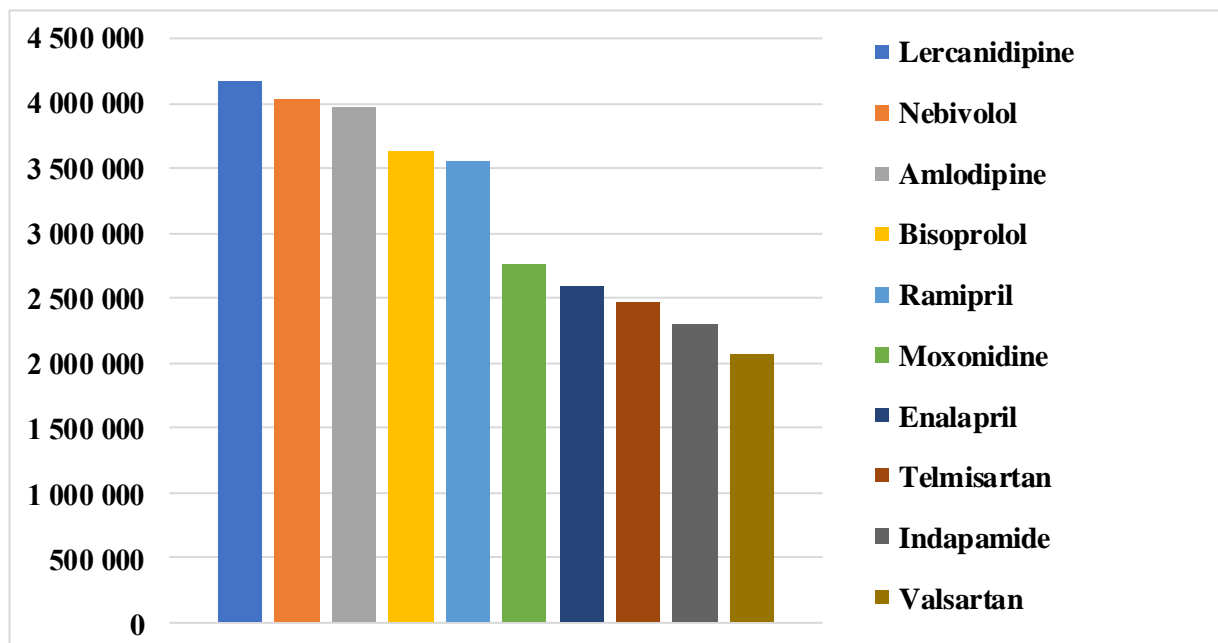


Figure 14. Top prescribed medicines by INN, defined as absolute number of DDD in 2019

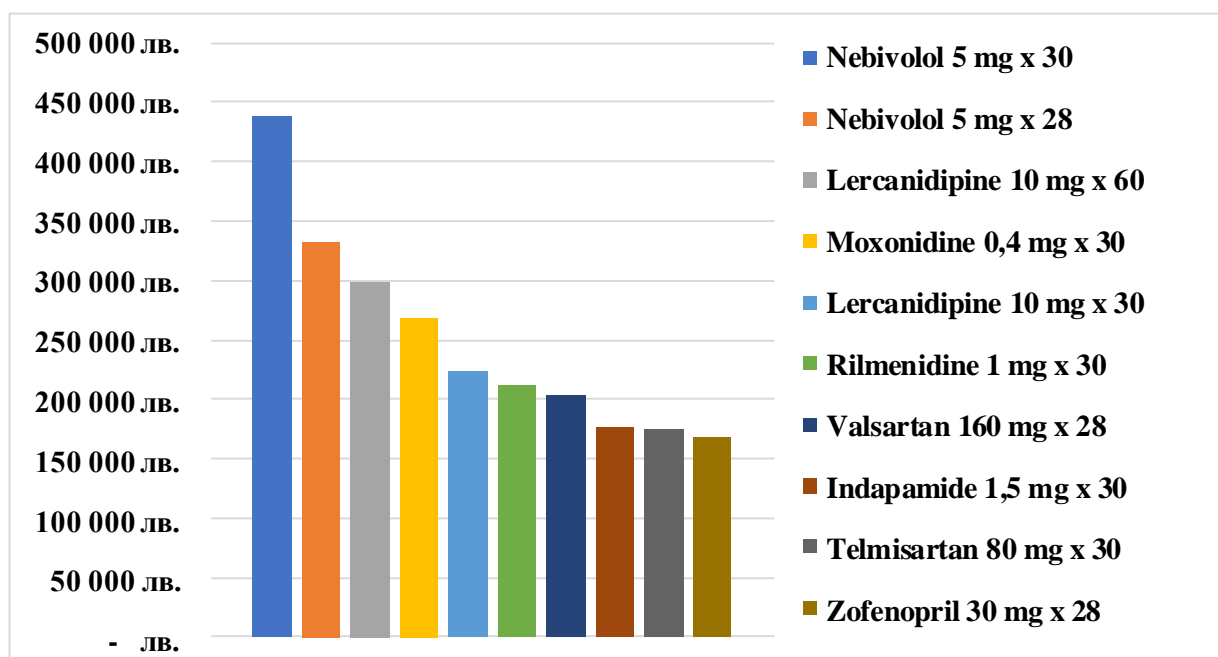


Figure 15. Medicines expenditure for 2019, calculated as number of packs

The next indicator, which we calculated for the current year, determines which medicines are the most prescribed and used for treatment in the segment in question, according to the number of packages the NHIF pays for.

There is no change in the products present in this list compared to 2018.

The first place in terms by total cost was again occupied of the beta-blocker Nebivolol through its varieties in the number of tablets per pack - BGN 770 567. In second place was the Ca-antagonist Lercanidipine with BGN 521 452. The third place is occupied by the centrally acting Moxonidine – BGN 269 244. The total value of the top two INNs, Nebivolol and Lercanidipine, is BGN 1 292 019, which is a significant increase on 2018. The share of these products was 16.09% of the total cost or 23.25% of the mono-product cost. The anti-adrenergic products Rilmenidine and Moxonidine retained the third place as a group and had a share of 5.99% of total cost or 8.65% of mono-product cost. This is indicative that there is medicinal utility of these products, contrary to the recommendations spelled out in European pharmacotherapeutic guidelines.

After an analysis of the top 10 drugs by INN, amount of active substance they contain, and number of tablets per pack, defined as DDD/year, we found that this group includes: beta-blockers - Bisoprolol and Nebivolol, Ca-antagonists - Amlodipine, Lercanidipine, ACE inhibitors - Ramipril, ARBs - Valsartan, and sulfonamide diuretics - Indapamide (Figure 16).

In contrast to 2018, in 2019, the ACE inhibitor Enalapril does not appear among the top 10, and in its place appears another variety of Ca-antagonist - Lercanidipine, a pack of 30 tablets.

In 2019, the beta-blockers Nebivolol and Bisoprolol have the highest share in this ranking - 6 403 221 DDD/year. They displace of the first place Ca-antagonists, which occupy the second position. The third place is again for the group of ACE-inhibitors. Once again, the only ARB in this analysis is Valsartan.

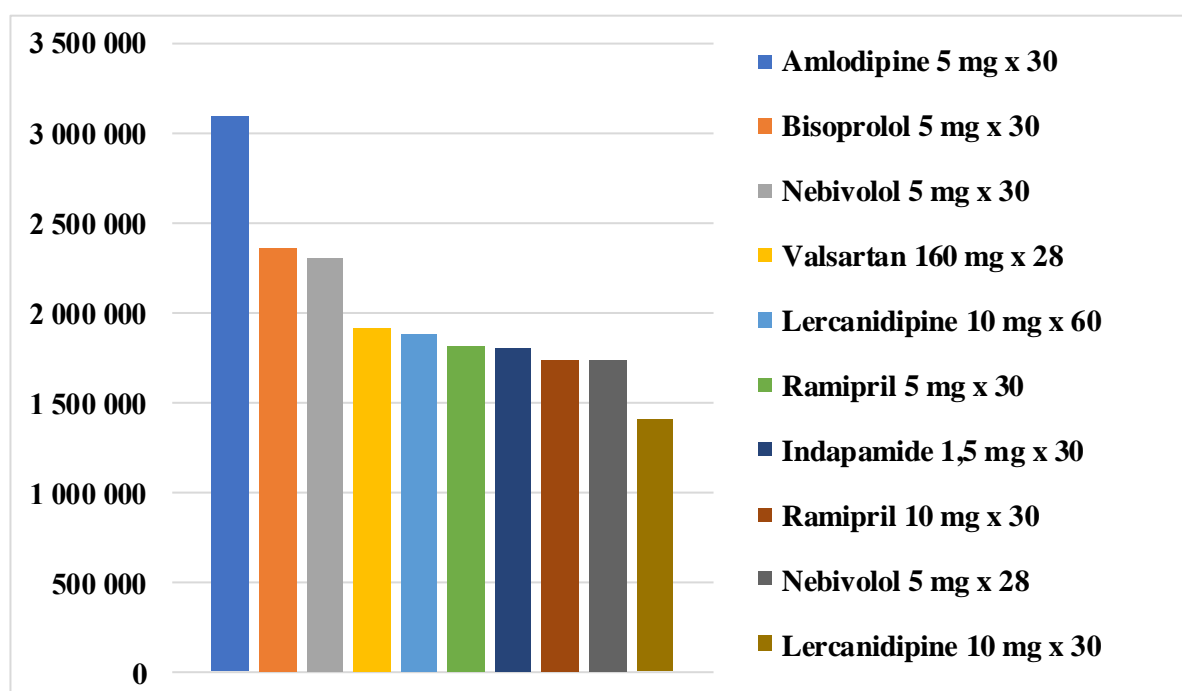


Figure 16. Top 10 medicines by INN, active substance quantity and number of tablets defined as DDD/year in 2019

Compared to 2018, this year we have a change in the top 10 most prescribed combination medicines by cost containing fixed dosage forms by trade name and INN (Figure 17).

The combination Valsartan/Hydrochlorothiazide (trade name - Co-Valsacor) was the most common treatment choice and saw a huge increase on the previous year. The combination

of a beta blocker and hydrochlorothiazide (trade name - Nebilet Plus) ranked second. Compared to 2018, it maintained its value.

A combination product containing Valsartan/Hydrochlorothiazide (trade name - Valtensin Plus) drops out of the top 10 and another medicinal product containing the same types of active substances appears - namely another combination of Losartan/Hydrochlorothiazide (trade name - Lozap H).

As in 2018, the number of combination products containing ARB/hydrochlorothiazide is six out of ten in 2019. They accounted for a 6.32% share of total spending or 20.92% of spending on combination drug products. Compared to 2018, this is an increase of nearly 1.32%. Apparently, this combination is becoming more preferred by practitioners.

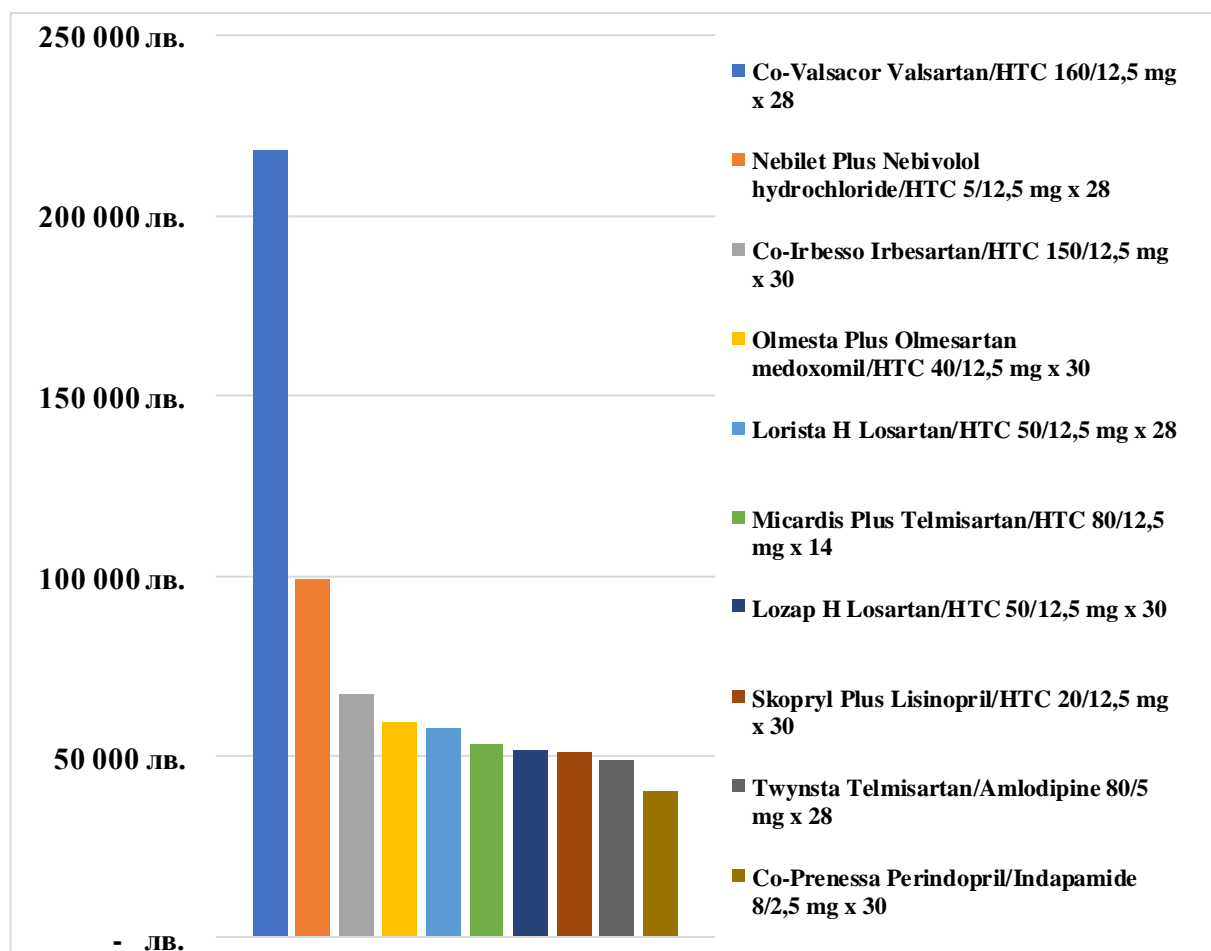


Figure 17. The most prescribed combination medicines as cost containing fixed dose forms by trade name and INN in 2019

After an analysis of the most prescribed combination drugs as DDD/year for 2019, we found that the first place is again occupied by the combination Valsartan/Hydrochlorothiazide (Co-Valsacor), which has a huge growth of nearly 62.59% compared to 2018. We have a change in the representatives occupying the second and third place (Figure 18).

In 2018, these places were occupied by Valtensin Plus (Valsartan/Hydrochlorothiazide) and Lorista H (Losartan/Hydrochlorothiazide) respectively, which are representatives of the ARB/Hydrochlorothiazide combination.

In 2019, Dironorm (Lisinopril/Amlodipine) and Nebilet Plus (Nebivolol/Hydrochlorothiazide) combinations stand in the second and third place.

In 2019, we have increased prescribing of combination products formulated with an ARB with a thiazide diuretic, with their number in the top 10 now at six, as opposed to 2018 when there were only 4 products.

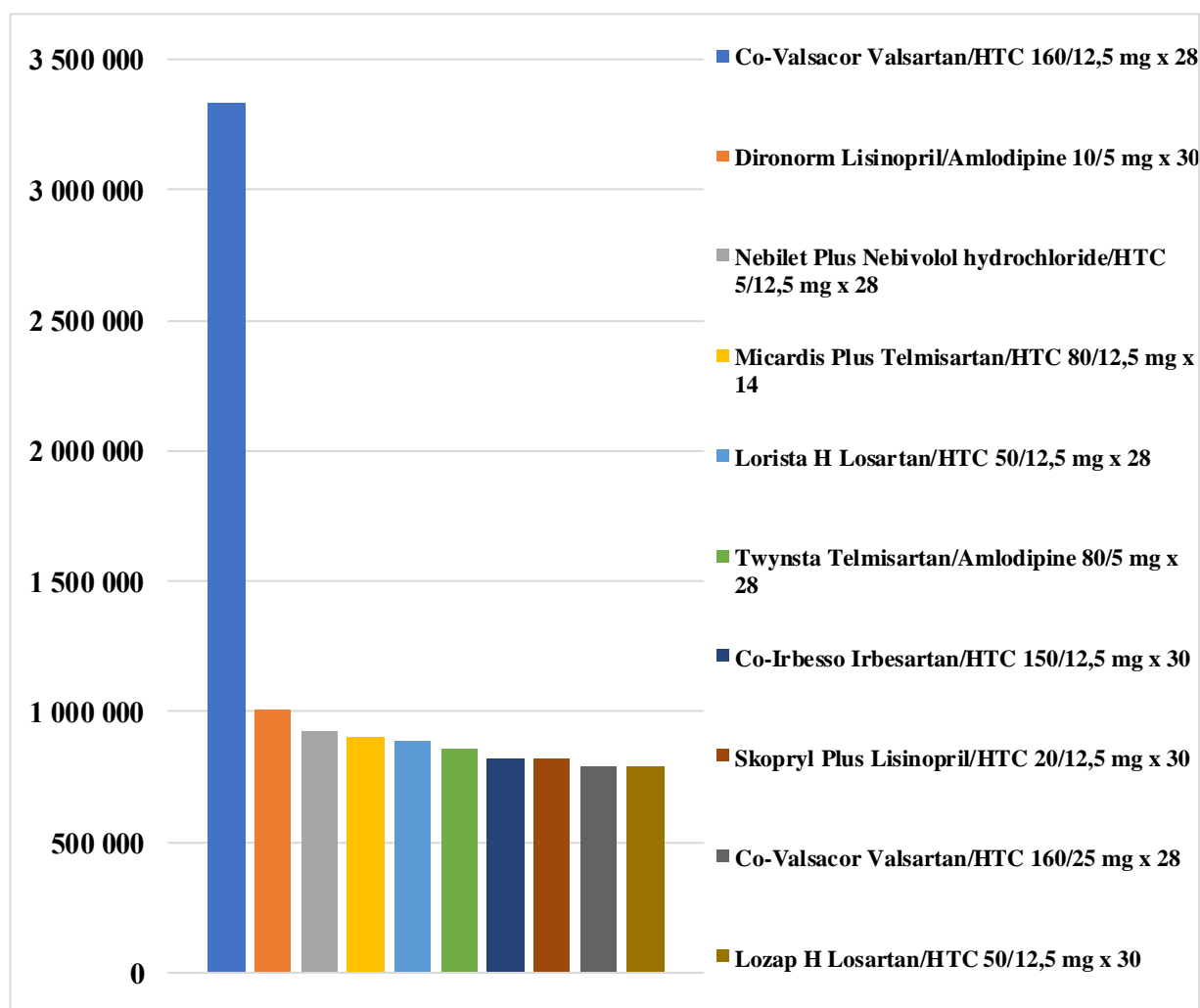


Figure 18. The most prescribed combination drug products as DDD/year containing fixed dose forms by trade name and INN in 2019

The analyses for the calculation of DDD per capita per year (DDD per inhabitant per year) and DDD per 1,000 inhabitants per day (DDD per 1,000 inhabitants per day) are made according to the population of Bulgaria as of December 2019, namely - 6 951 482 inhabitants.

The top 3 positions are calcium antagonists and beta blocker.

The use of Ca-antagonists has increased in 2019.

Table 5. DDDs per capita per year (DDD per inhabitant per year) and DDDs per 1000 inhabitants per day (DDD per 1000 inhabitants per day) for 2019

INN	DDD	DDD/inhabitant/year	DDD/1000/day
Lercanidipine	4 176 124	0.60	1.65
Nebivolol	4 041 366	0.58	1.59
Amlodipine	3 974 056	0.57	1.57
Bisoprolol	3 641 297	0.52	1.44
Ramipril	3 562 829	0.51	1.40
Moxonidine	2 754 901	0.40	1.09
Enalapril	2 581 859	0.37	1.02
Telmisartan	2 459 170	0.35	0.97
Indapamide	2 290 523	0.33	0.90
Valsartan	2 069 648	0.30	0.82

According to the data provided to us by the NHIF for 2020, the total number of patients with primary hypertension is 1 147 943 people. There continues to be a decline in the number of patients receiving treatment under the health insurance fund (about 33 000 fewer patients compared to 2019). Patients with primary uncomplicated essential hypertension with ICD code I10 accounted of 109 246 or 9.52% of all hypertensive patients.

Table 6. Number of patients in 2020 with different types of primary hypertension by ICD, treatment of which is paid by NHIF

Code	Types of primary arterial hypertension	Number of patients n / Relative proportion %
I10	Hypertensio arterialis essentialis (primaria)	109 246 / 9.52
I11	Morbus cordis hypertensivus	
I11.0	Morbus cordis hypertensivus cum insufficientia cordis (congestiva)	160 265 / 13.96
I11.9	Morbus cordis hypertensivus sine insufficientia cordis (congestiva)	873 373 / 76.08
I12	Morbus renalis hypertensivus	
I12.0	Morbus renalis hypertensivus cum insufficientia renis	399 / 0.03
I12.9	Morbus renalis hypertensivus sine insufficientia renis	398 / 0.03
I13	Morbus cordis et morbus renis hypertensivus	
I13.0	Morbus cordis et morbus renis hypertensivus cum insufficientia cordis (congestiva)	3 659 / 0.32
I13.1	Morbus cordis et morbus renis hypertensivus cum insufficientia renis	339 / 0.03
I13.2	Morbus cordis et morbus renis hypertensivum cum insufficientia cordis (congestiva) et insufficientia renis	264 / 0.02

The largest share was occupied by patients with hypertensive heart without (congestive) heart failure - 873 373 people or 76.08%. The second place was occupied by patients with hypertensive heart with (congestive) heart failure - 160 265 people or 13.96%. The number of patients and their distribution according to the type of complications of primary essential hypertension, classified by ICD, are presented in Table 6.

In 2020, the NHIF allocates BGN 7 728 217.13 from its budget for the treatment of the disease according to ICD I10. According to this amount, the cost per patient per year (cost per capita per year) is BGN 70.74, the monthly cost (cost per month) is BGN 5.90 and the cost per treatment day is BGN 0.19. Obviously, the cost per patient is increasing compared to previous years. The amount of BGN 7 728 217.13 is again divided into two large groups - cost for mono products BGN 5 322 141.85 (relative share 68.87%) and cost for combined medicinal products BGN 2 406 075.25 (relative share 31.13%).

The funds allocated by the NHIF for the treatment of uncomplicated essential hypertension per patient in 2020 are equal to 0.41% of the gross product per capita, calculated using purchasing power parity (€16 268). Compared to 2019, we find an increase of 0.05% in the funds allocated by the NHIF for the treatment of patients with essential hypertension.

The cost of reimbursement for the treatment of outpatients for 2020 is BGN 1 513 045 143. The cost of medicines for the treatment of primary essential hypertension as a share of the total health expenditure on medicines of the NHIF is equal to 0.51%. The downward trend in these expenditures compared to previous years continues in 2020.

Similar to previous years, our analysis of drug utilization in the study segment begins with a study of the most prescribed drugs by INN according to the amounts paid out of the NHIS budget. The top 10 rankings include: beta-blockers (Nebivolol, Bisoprolol), ARBs (Telmisartan, Valsartan), ACE-inhibitors (Zofenopril, Lisinopril), Ca-antagonists (Lercanidipine), centrally acting antihypertensives (Moxonidine, Rilmenidine), sulfonamide diuretics (Indapamide).

In the comparison made with 2019, we found that there was no change in the top-ten list. The total cost of the top 10 products is BGN 3 626 334 and, accordingly, their share in relation to the total cost of the NHIF for 2020 for the treatment of primary essential hypertension is 46.92%, which confirms the trend of growth in this indicator, since in 2019, their share was 46.06%, and in 2018 - 44.24%.

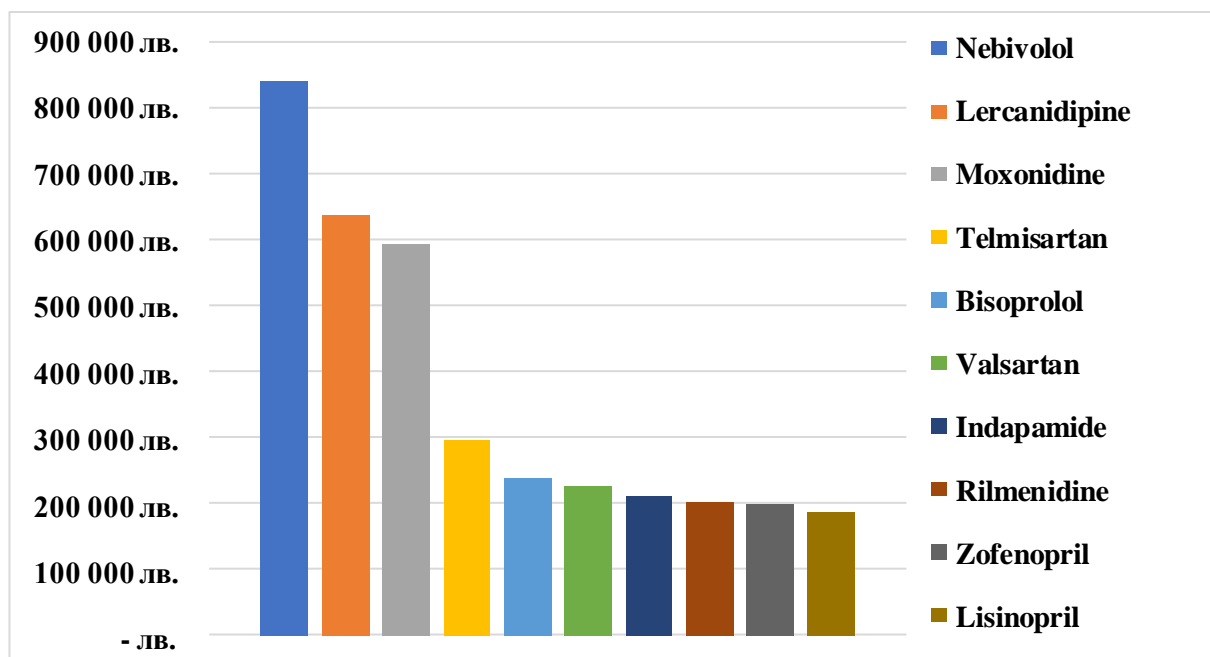


Figure 19. Top prescribed medicines by INN according to the amounts paid by the NHIF budget (top ten) in 2020.

Cost are shown in BGN (1 Euro=1.95583 BGN)

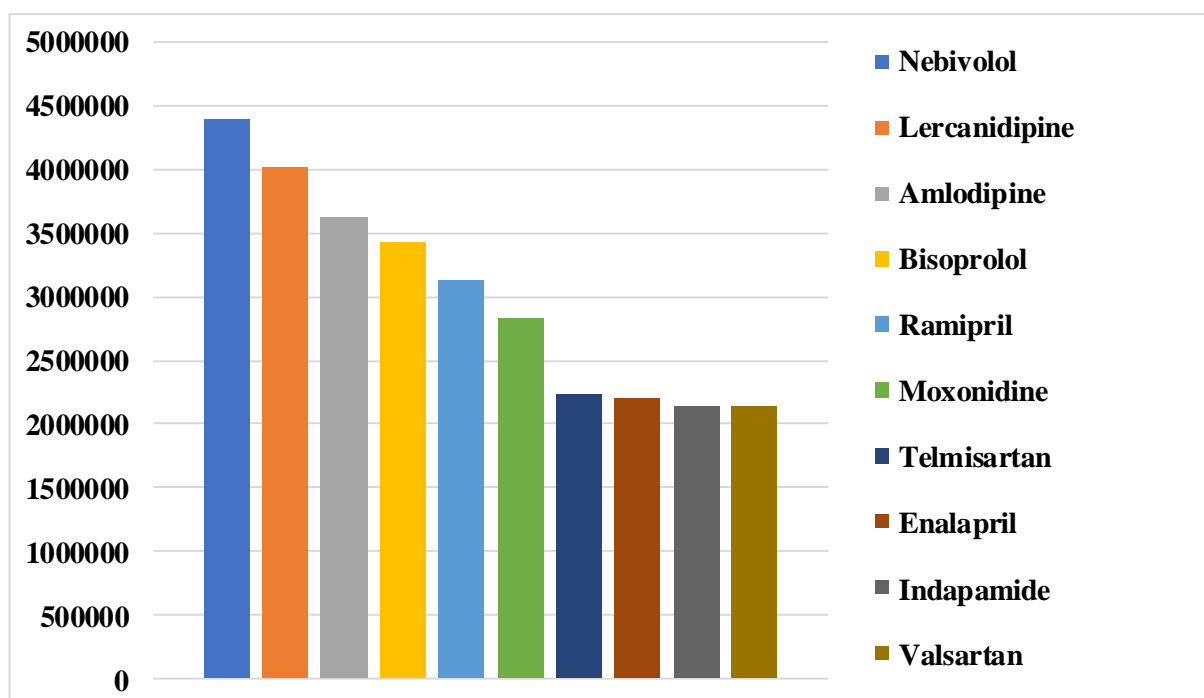


Figure 20. Top prescribed medicines by INN, defined as absolute number of DDD in 2020

In 2020, there is no change in the products contained in the list of the top 10 most prescribed medicines by INN, defined as absolute number of DDDs. In contrast to 2019, in 2020 the beta-blocker Nebivolol, with an absolute DDD count of 4 398 532, is in first place on

this indicator, displacing the Ca-antagonist Lercanidipine from the top spot. Lercanidipine takes second place in this ranking. The third position is retained by Ca-antagonist Amlodipine. Again, among the first three products we have two representatives of the group of Ca-antagonists, which are not considered as the first choice of treatment. The total absolute number of DDD of the first 10 products is 30 136 082 DDD, which represents 35.24% of the total absolute number of DDD of mono- and combination products for the treatment of essential arterial hypertension.

After measuring out-of-pocket drug spending calculated as number of packages, we found significant changes among the top 10 products compared to 2019 (Figure 21).

In 2020, this list does not include ARBs with the INN Telmisartan, which is among some of the first-line treatments for uncomplicated essential hypertension. The centrally acting anti-adrenergic Moxonidine now has two varieties among the top 10 products in the analysis.

First place is again occupied by the beta-blocker Nebivolol with a total value of – BGN 838,668. The second place goes to the group of centrally acting antihypertensive products with representatives - Moxonidine and Rilmenidine - BGN 628 892. They displace from the second place Ca-antagonist Lercanidipine, which already occupies the third place with a total value - BGN 513 988, but still remains with too high share of drug utilization. In terms of total cost - the first two groups of drugs have a total cost - BGN 1 467 560, which is 18.99% of the total cost or 27.57% of the cost of mono-products. Lercanidipine has a share of 6.65% of total cost or 9.66% of mono-product cost.

Contrary to internationally accepted recommendations, the utilization of non-first line therapy drugs for essential hypertension is increasing.

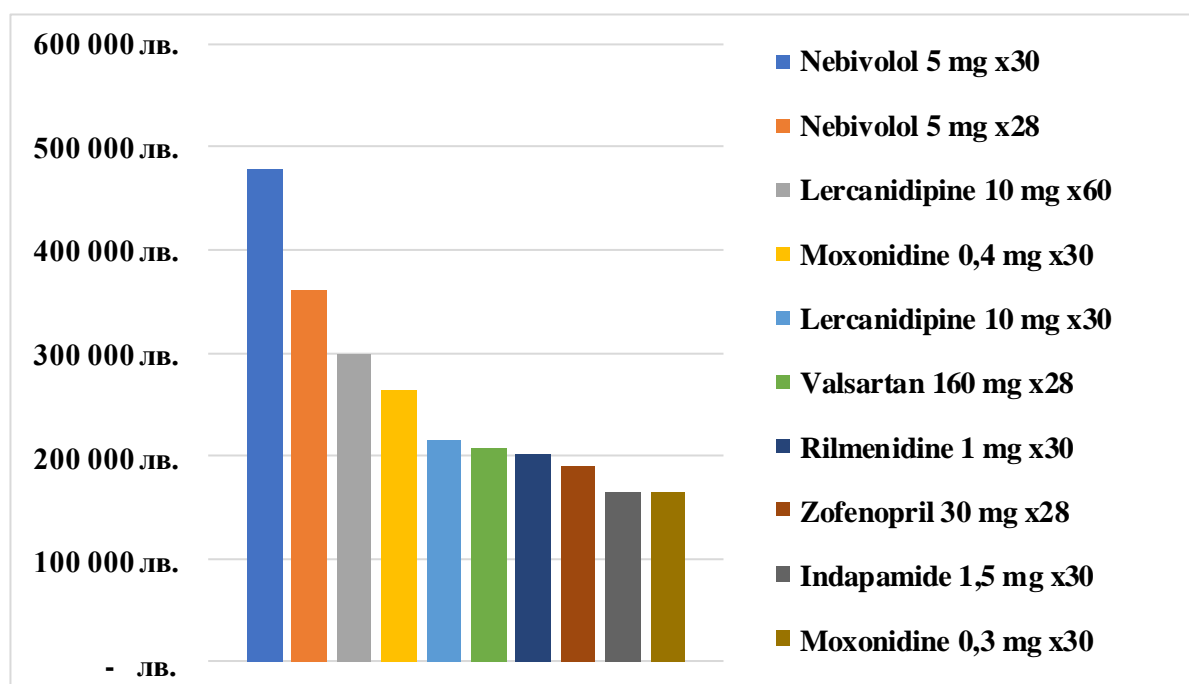


Figure 21. Medicines expenditure for 2020 calculated as number of packs

Figure 22 illustrates the comparison of the top 10 medicines by INN, active substance quantity and number of tablets defined as DDD/year for 2019 and 2020. We observe no change in the products present in this list. The most prescribed drugs are again the beta blockers Nebivolol and Bisoprolol - 6 509 899 DDD/year, which represents a significant increase compared to 2019.

Няма промяна във второто и третото място в тази класация. Valsartan запазва своя дял, като има малък ръст през 2020 година като относителна стойност. Идентичен е случаят и със сулфонамидния диуретик – Indapamide.

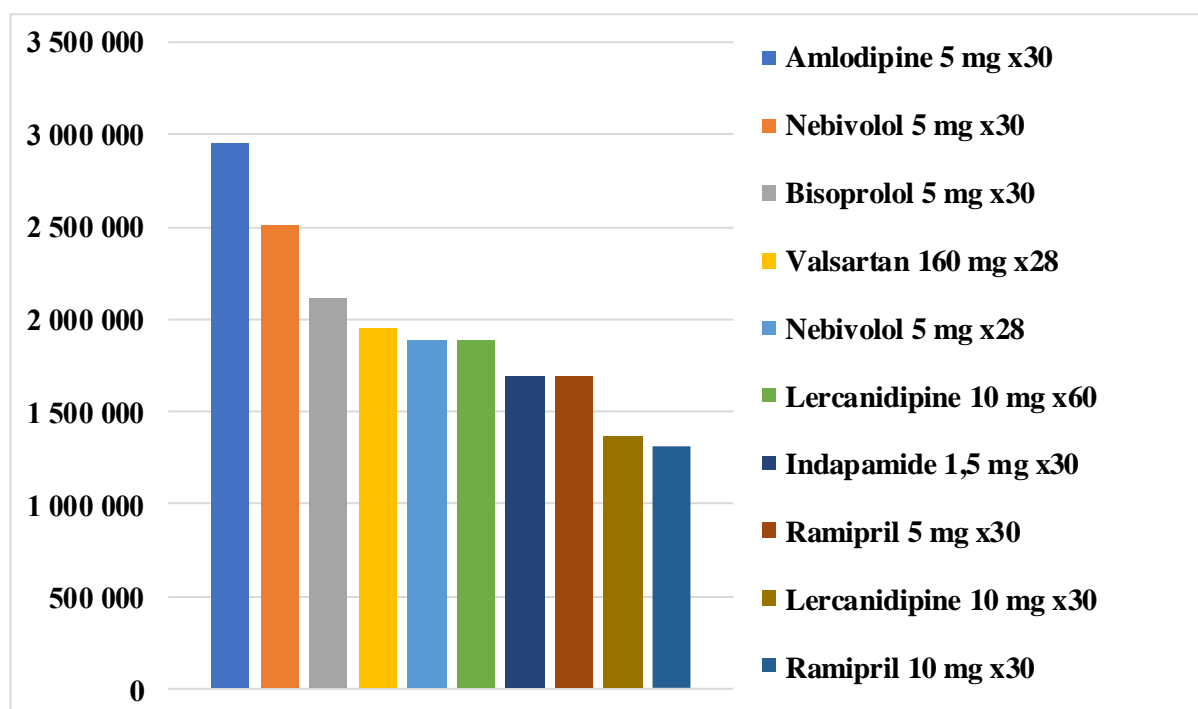


Figure 22. Top 10 medicines by INN, active substance quantity and number of tablets defined as DDD/year in 2020

The most prescribed combination medicines as cost containing fixed dose forms by trade name and INN for 2020 are ARB/hydrochlorothiazide combinations (Co-Valsacor, Lozap H, Co-Irbesso, Micardis Plus, Olmesta Plus 20/12.5 and Olmesta Plus 40/12.5), ACE inhibitor/thiazide diuretic (Skopryl Plus), beta-blocker/thiazide diuretic (Nebilet Plus), ARBs/Ca-antagonists (Twynsta) and the triple combination ACE inhibitor/Ca-antagonist/thiazide diuretic (Triplixam) - Figure 23.

The first place is again occupied by the combination Valsartan/Hydrochlorothiazide through the representative Co-Valsacor. In contrast to 2019, in 2020 one of the Losartan/Hydrochlorothiazide representatives does not enter the top 10 - under the trade name Lorista H, but a higher medicinal use of Olmesartan/Hydrochlorothiazide is reported and this combination now has two representatives in the top 10. Another interesting fact is that in 2020, for the first time, a triple fixed combination - Triplixam (Perindopril/Amlodipine/Indapamide) - appears in this measure.

According to the ESC/ESH guidelines, the combination of three active substances is used in cases of resistant hypertension, and in this case the proportion of this drug is significant. Another medicinal product, Perindopril/Amlodipine (Co-Prenesaa), is not among the top 10.

Combinations between ARB and thiazide diuretic occupied a share of 5.88% of the total cost for the treatment of uncomplicated arterial hypertension, or that is 18.90% of the cost for combination drugs.

Comparing to 2019 we find that there is a decrease of about 2% in prescribing and use of this drug combination.

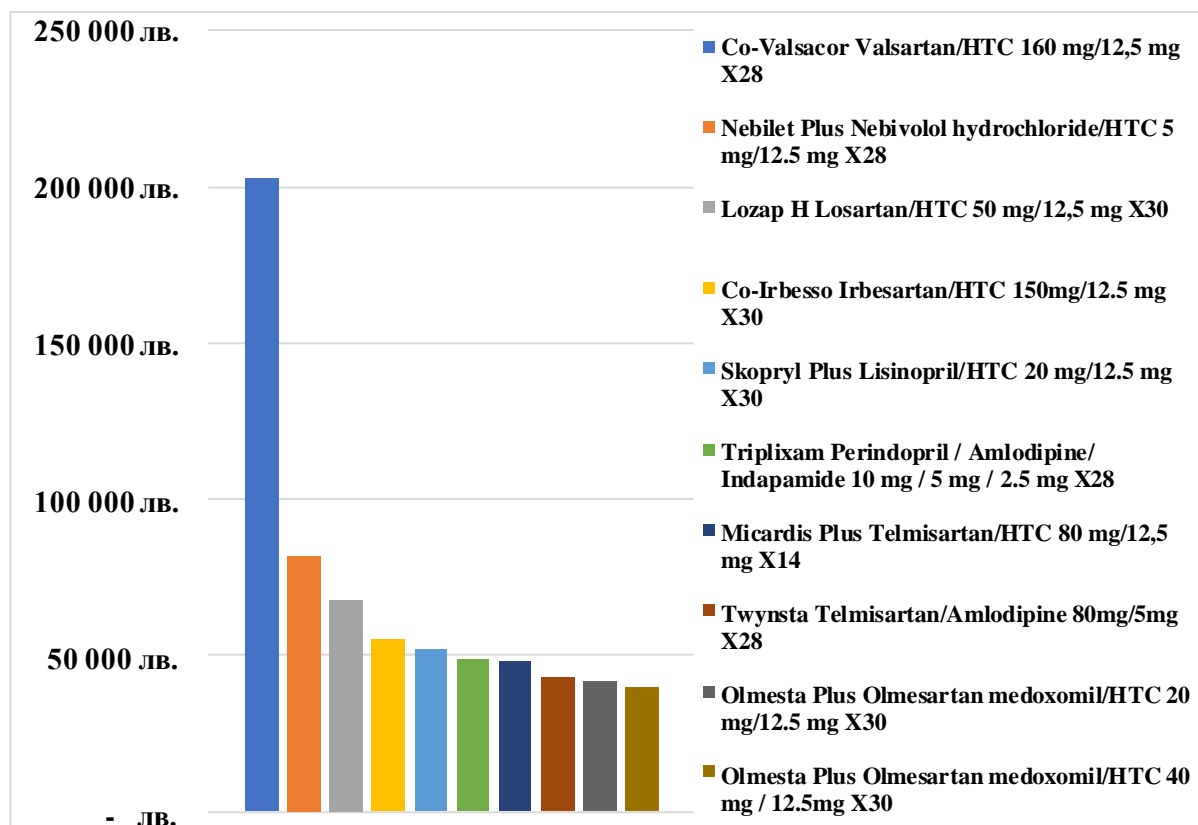


Figure 23. The most prescribed combination medicines as cost containing fixed dose forms by trade name and INN in 2020

In 2020, the most prescribed combination drugs as DDD/year are Valsartan/Hydrochlorothiazide (Co-Valsacor), the triple combination Perindopril/Amlodipine/Indapamide in two varieties (Triplixam), Losartan/Hydrochlorothiazide (Lozap H), Lisinopril/Amlodipine (Dironorm), Amlodipine/Valsartan (Walmox), Lisinopril/Hydrochlorothiazide (Scopryl Plus), Telmisartan/Hydrochlorothiazide (Micardis Plus), Nebivolol/Hydrochlorothiazide (Nebilet Plus) and Perindopril/Indapamide (Noliprel Bi-Forte), which can be seen in Figure 24.

The top spot is again occupied by Valsartan/Hydrochlorothiazide with 3 091 900 DDD/year - 3.62% of the total or 7.05% of the share of combination drugs on a DDD/year basis. Again, in this measure, we found increased prescribing of the combination of three active substances - Perindopril/Amlodipine/Indapamide (Triplixam) in 2020. Their total number of DDD/year is 1 936 481 DDD. This is 2.26% of the total or 4.42% of the share of combination drug products on a DDD/year basis.

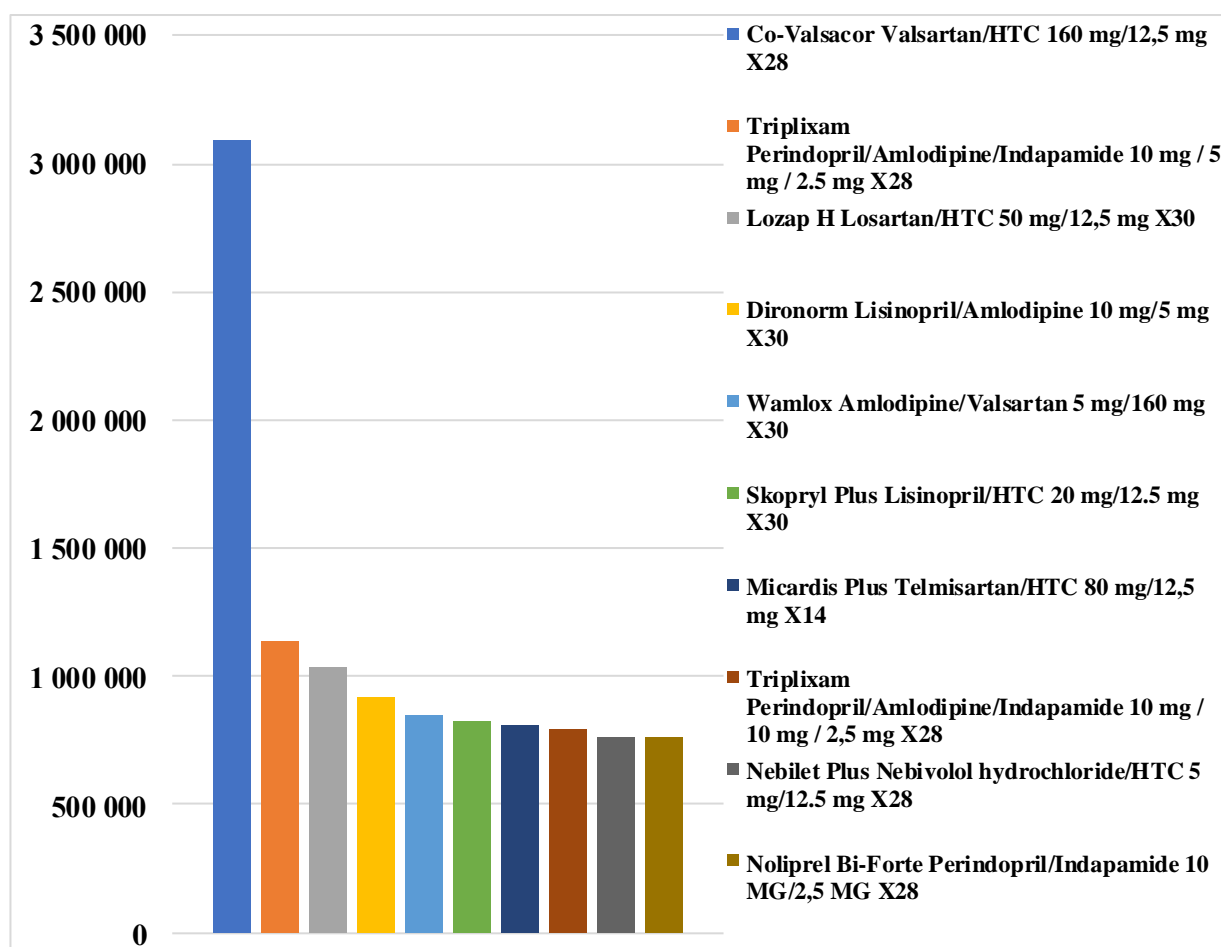


Figure 24. The most prescribed combination medicines as DDD/year containing fixed dosage forms by trade name and INN in 2020

In 2020 the population of Bulgaria was 6 916 548 inhabitants. Taking this value into account, we again calculated the DDD per capita in 1 year and the DDD per 1,000 people in 1 year. The top 3 positions are again calcium antagonists and beta-blocker. The use of Ca-antagonists is maintained in 2020.

Table 7. DDDs per inhabitant per year and DDDs per 1000 inhabitants per day for 2020

INN	DDD	DDD/inhabitant/year	DDD/1000/day
Nebivolol	4 398 532	0.64	1.74
Lercanidipine	4 025 066	0.58	1.59
Amlodipine	3 625 564	0.52	1.44
Bisoprolol	3 423 558	0.49	1.36
Ramipril	3 127 033	0.45	1.24
Moxonidine	2 825 210	0.41	1.12
Telmisartan	2 237 267	0.32	0.89
Enalapril	2 200 471	0.32	0.87
Indapamide	2 141 046	0.31	0.85
Valsartan	2 132 335	0.31	0.84

For the purposes of this dissertation, we investigated the prescribing and, respectively, the use of drugs for the control of uncomplicated essential hypertension in the year 2021. According to the NHIF system, for the said calendar year, funds were spent to pay for the treatment of 1 099 608 people diagnosed with all types of primary hypertension.

Table 8. Number of patients in 2021 with different types of primary hypertension by ICD, treatment of which is paid by NHIF

Code	Types of primary arterial hypertension	Number of patients n / Relative proportion %
I10	Hypertensio arterialis essentialis (primaria)	103 027 / 9.37
I11	Morbus cordis hypertensivus	
I11.0	Morbus cordis hypertensivus cum insufficientia cordis (congestiva)	149 936 / 13.64
I11.9	Morbus cordis hypertensivus sine insufficientia cordis (congestiva)	842 108 / 76.58
I12	Morbus renalis hypertensivus	
I12.0	Morbus renalis hypertensivus cum insufficientia renis	340 / 0.03
I12.9	Morbus renalis hypertensivus sine insufficientia renis	367 / 0.03
I13	Morbus cordis et morbus renis hypertensivus	
I13.0	Morbus cordis et morbus renis hypertensivus cum insufficientia cordis (congestiva)	3 306 / 0.30
I13.1	Morbus cordis et morbus renis hypertensivus cum insufficientia renis	307 / 0.03
I13.2	Morbus cordis et morbus renis hypertensivum cum insufficientia cordis (congestiva) et insufficientia renis	217 / 0.02

103 027 people had primary uncomplicated essential hypertension (ICD code I10), nearly 83 000 fewer than in the first year, part of our 5-year study period, and 6 000 fewer than in 2020.

The trend for the largest number of hypertensive patients without (congestive) heart failure was observed, with 842 108 or 76.58% of hypertensive patients.

The second place was taken by hypertensive heart patients with (congestive) heart failure - 149 936 or 13.64% of the total. The ICD classification of the number of patients according to the type of complications is detailed in Table 8.

The total expenditure from the NHIF budget for 2021 for the disease (ICD I10) is BGN 7 145 778.91.

The cost per patient per year (cost per capita per year) is again higher compared to previous years - BGN 69.36, the monthly cost (cost per month) is BGN 5.78, and the cost per treatment day remains the same - BGN 0.19.

For another year, it is observed that mono products have the predominance in the distribution of the NHIF funds - the treatment of patients with them amounted to BGN 4 838 944.43 or 67.72% of the total cost; respectively, the therapy including combined medicinal products costs the NHIF BGN 2 306 834.48 / 32.28%.

Calculating these expenditures again as a share of GDP per capita through purchasing power parity, it is found that the amounts allocated by the health insurance fund are 0.45% of the budget.

The cost paid by the NHIF for the treatment of outpatients in 2021 are BGN 1 630 016 055. The cost of medicines for the treatment of uncomplicated essential hypertension as a share of total health expenditure on medicines is equal to 0.44%.

In Figure 25, we have indicated one of the key indicators for determining drug utilization, the top 10 INNs, as a share of amounts paid by the NHIF.

Compared to 2020, there is no change in the products present in this list. The top spot continues to be the beta blocker Nebivolol. An interesting fact is that the second place goes to the centrally acting antihypertensive drug - Moxonidine, which in 2020 occupied the third place. In third place in 2021 is a Ca-antagonist - Lercanidipine.

But despite this shift in the rankings, we are again seeing a trend of massive prescribing of drugs that do not fall within the internationally recognized scientific and applied standards and accepted by the professional medical community as the first choice for the treatment of uncomplicated essential hypertension.

The total value of the products in the top-ten list is BGN 3 377 139, which represents a share of 47.26% of the total cost of the NHIF in 2021 for the treatment of primary essential hypertension and confirms the growth trend, as their share in 2020 was 46.92% and in 2019 - 46.06%.

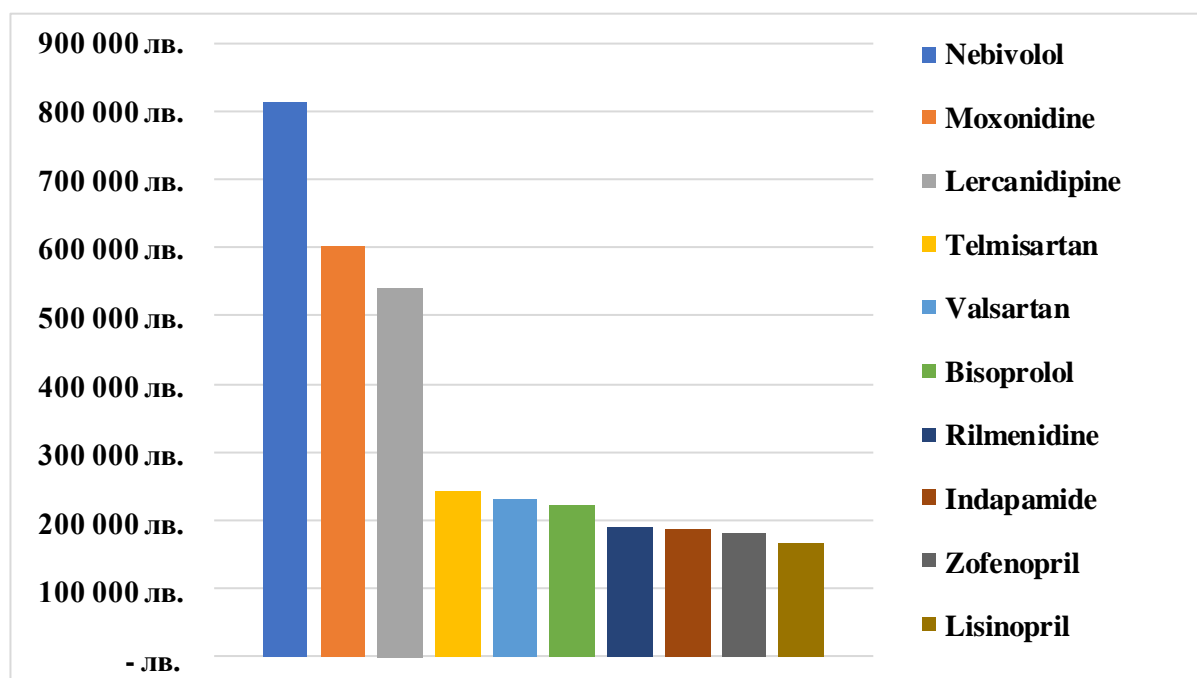


Figure 25. Top prescribed medicines by INN according to the amounts paid by the NHIF budget (top ten) in 2021.
Cost are shown in BGN (1 Euro=1.95583 BGN)

Following the pattern already established, we also examined the most prescribed drugs by INN, defined as absolute number of DDDs and presented in Figure 28.

In this arrangement, beta-blockers (Nebivolol, Bisoprolol), ACE-inhibitors (Ramipril, Enalapril), Ca-antagonists (Lercanidipine, Amlodipine), centrally acting antihypertensives

(Moxonidine), ARBs (Valsartan, Telmisartan) and sulfonamide diuretics (Indapamide) are present.

Making reference to 2020, we note that in 2021 this list does not change.

In first place again is the beta-blocker Nebivolol with an absolute number of DDD - 4 255 143. Lercanidipine takes the second place with an absolute number of DDD - 3 419 760.

The third position is retained by the Ca-antagonist Amlodipine with an absolute number of DDD - 3 260 970.

The tendency to have products in the top 3 that are not first-line treatments for essential hypertension is maintained.

The total absolute number of DDD of the top 10 products was 27 649 525, representing a share of 34.17% of the total.

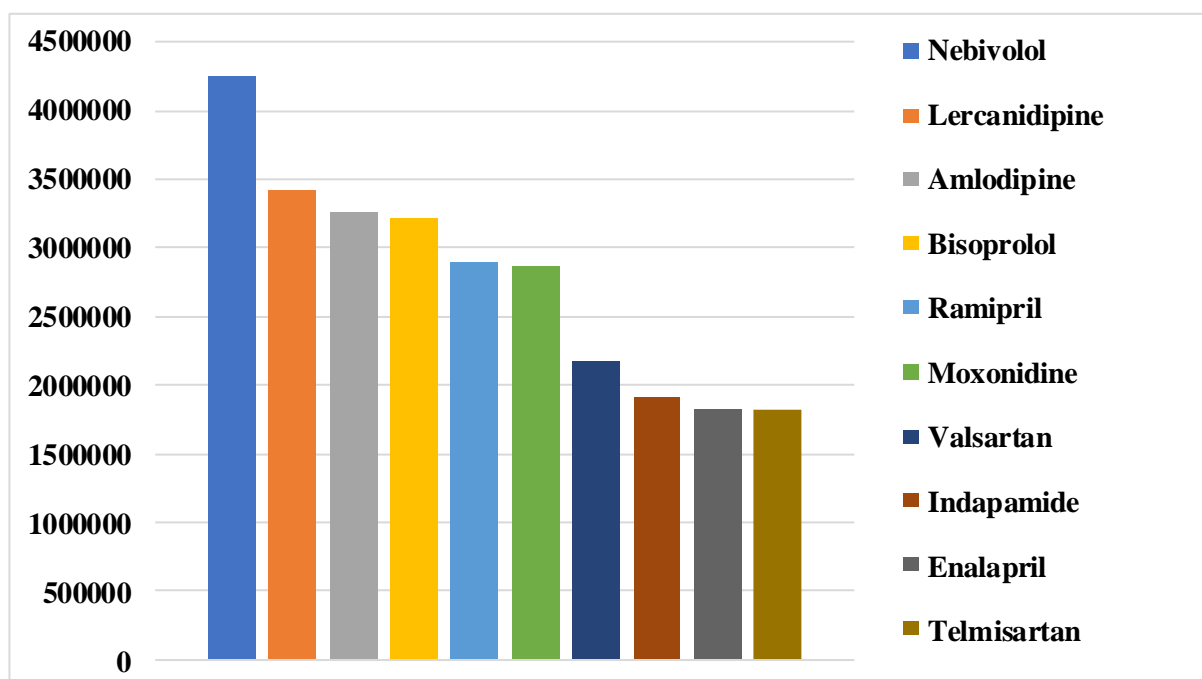


Figure 26. Top prescribed medicines by INN, defined as absolute number of DDD in 2021

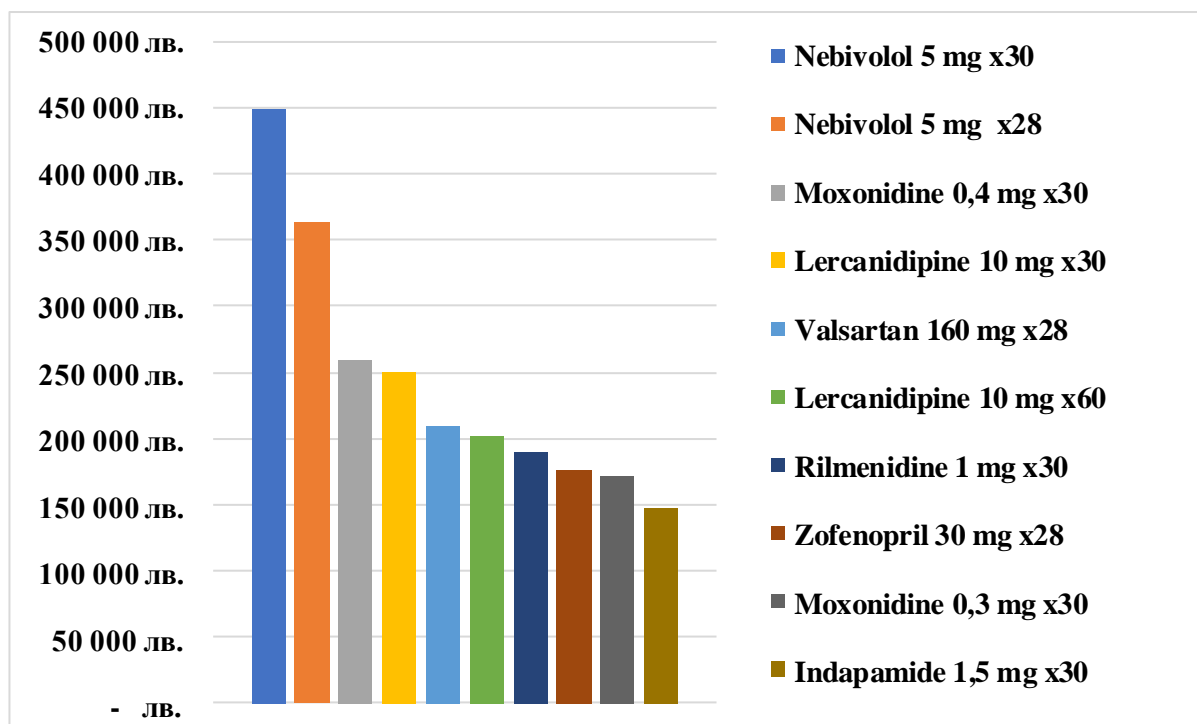


Figure 27. Medicines expenditure for 2021, calculated as number of packs

Stability also continues to be observed for the products occupying the top 10 positions, based on an analysis of the cost of medicines calculated as number of packs.

The first place is again occupied by the beta-blocker Nebivolol - BGN 811 328. The second place goes to the centrally acting antihypertensives - Moxonidine and Rilmenidine - BGN 620 788. The third place remains to Ca-antagonist Lercanidipine - BGN 451 262, with a share of 6.32% of total cost or 9.33% of mono-product cost. Here a decrease compared to 2020 is reported.

With a total cost of BGN 1,432,116, the first two groups of drugs have a share of 20.04% of total cost or 29.60% of mono-product cost. This is an increase compared to 2020.

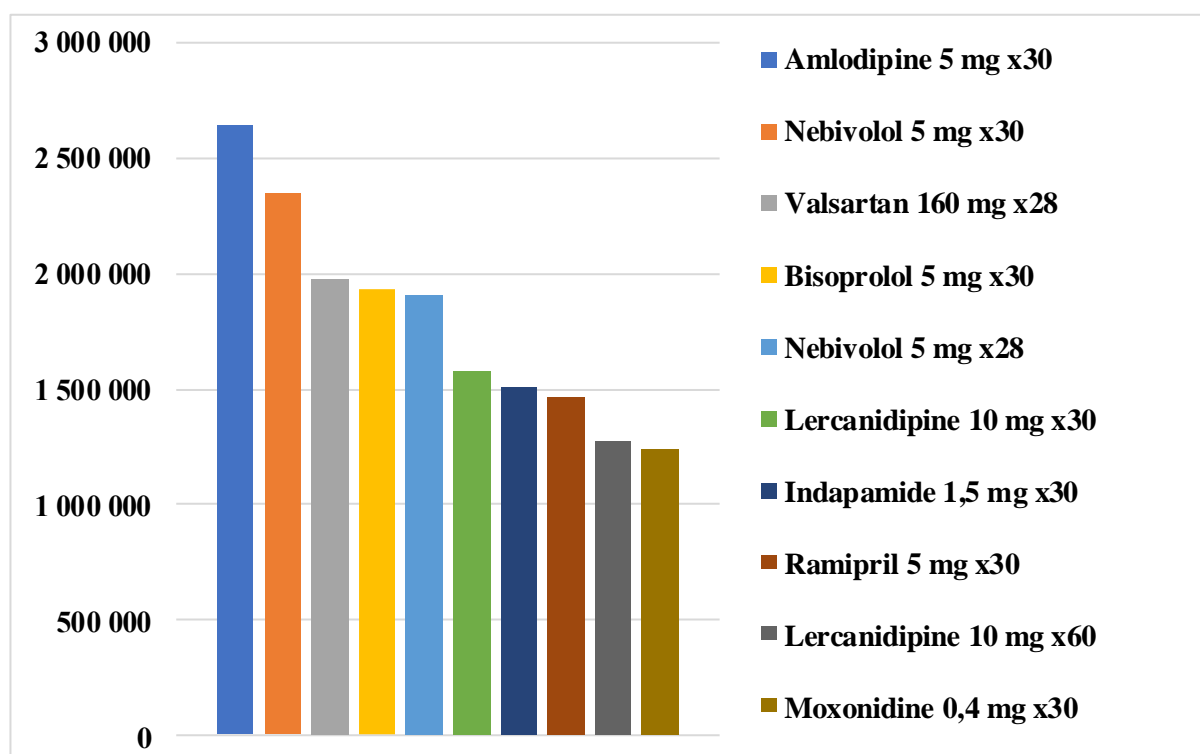


Figure 28. Top 10 medicines by INN, active substance quantity and number of tablets defined as DDD/year in 2021

In 2021, among the first drugs present, there is a change compared to 2020. A centrally acting anti-adrenergic agent, Moxonidine, enters the top 10, and a variation of the ACE-inhibitor Ramipril leaves this top-ten list.

We found a positive trend in the usage of Valsartan - its prescribing has increased compared to 2020 and in 2021, it takes third place.

The top spot remains again for the beta-blockers Nebivolol and Bisoprolol - 6 184 701 DDD/year. The second place is occupied by Ca-antagonists - Amlodipine and Lercanidipine.

The trend of maintaining the widespread use of non-first-line drugs for the treatment of uncomplicated essential hypertension is again present.

We performed an analysis of the most prescribed combination drugs as cost-containing fixed-dose formulations by trade name and INN for 2021.

Once again, the top spot is held by the combination Valsartan/Hydrochlorothiazide through the representative Co-Valsacor. We can see that in the top 10 we have only five representatives of the combination ARB with thiazide diuretic, in contrast to 2020, which had six representatives. Second place is occupied by the beta blocker/thiazide diuretic combination (Nebivolol/Hydrochlorothiazide - Nebilet Plus).

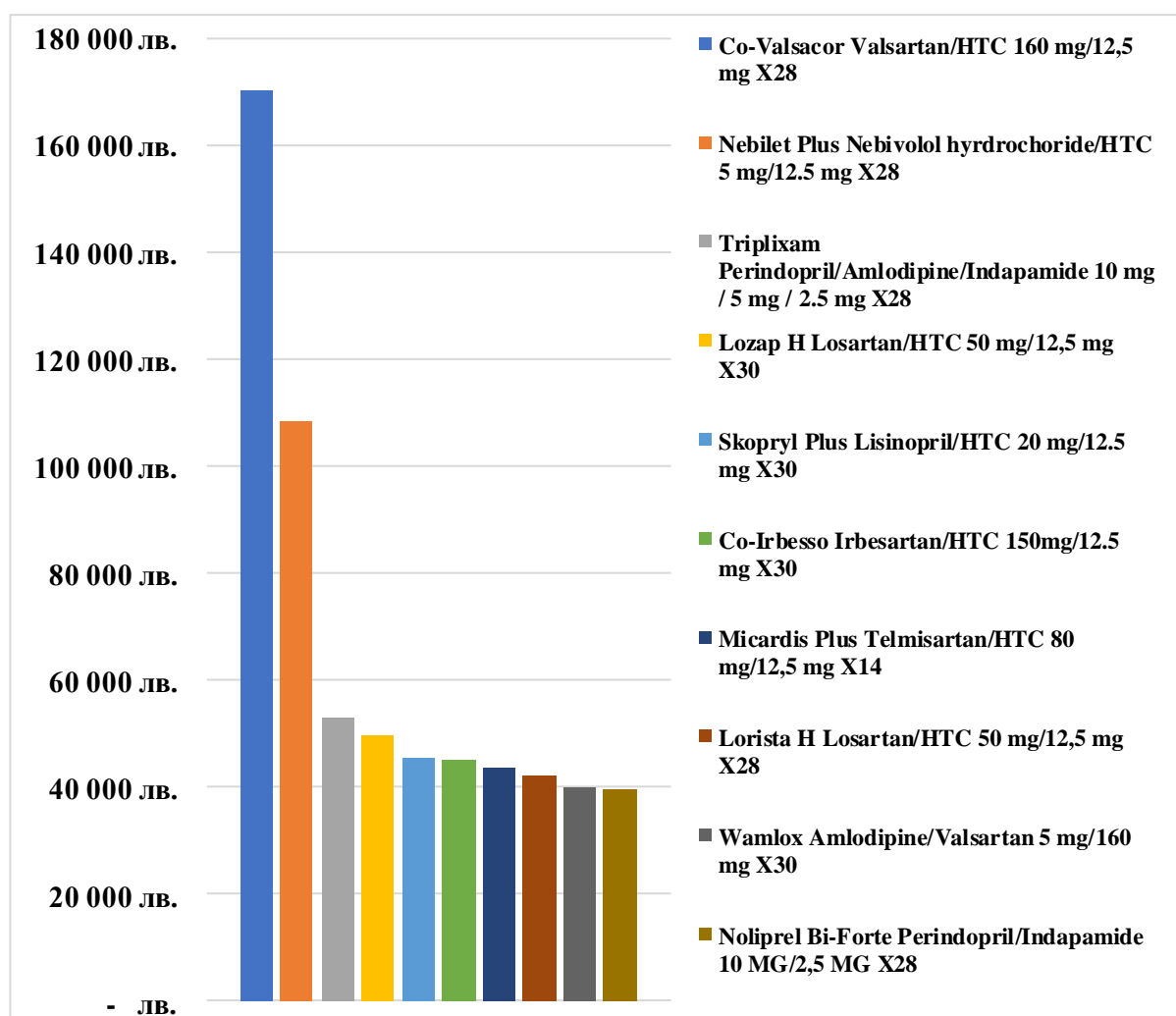


Figure 29. The most prescribed combination medicines as cost containing fixed dose forms by trade name and INN in 2021

For yet another year, we found increased prescribing of the triple-active drug Perindopril/Amlodipine/Indapamide (Triplixam). It ranked third in 2021, while in 2020 it was sixth in prescribing. The combination Telmisartan/Amlodipine (Twynsta) drops out of the top 10 by that criterion, and we found that there is increased prescribing of Valsartan/Amlodipine (Wamlox). The representatives of Olmesartan/Hydrochlorothiazide, which in 2020 occupied the ninth and tenth place, no longer appear in 2021 in the analysis made on the said indicator.

The top 10 in 2021 include Losartan/Hydrochlorothiazide (Lorista H) and Perindopril/Indapamide (Noliprel Bi-Forte). Representatives of the combination of an ARB with a thiazide diuretic (Hydrochlorothiazide) are now five of the top 10 combination drugs, in contrast to previous years when they were six of ten. In 2021, they account for 4.90% of total spending, or 15.18% of spending on combination medicines.

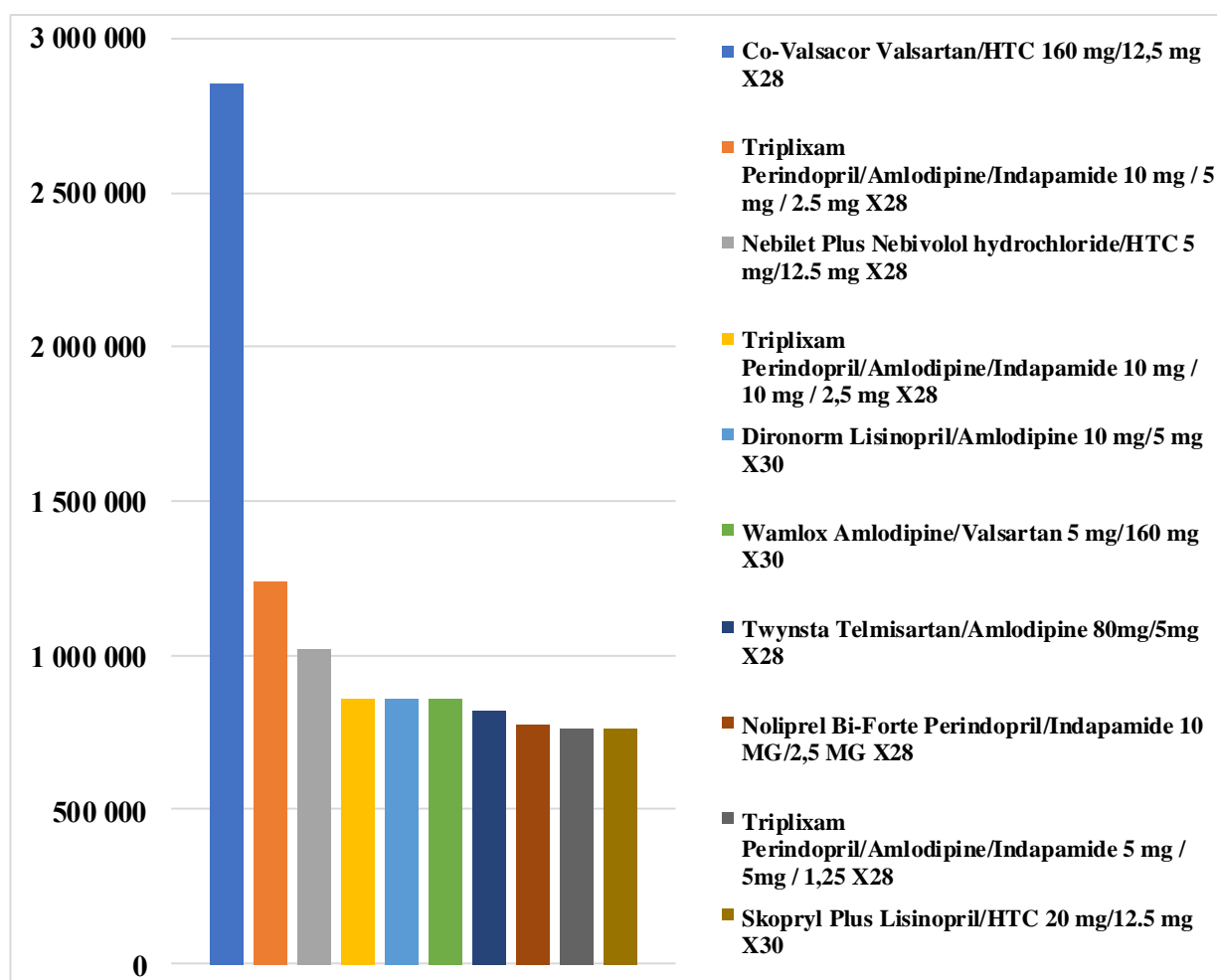


Figure 30. The most prescribed combination drug products as DDD/year containing fixed dosage forms by trade name and INN in 2021

After examining the last indicator for assessing the medication utilization and rational drug use in patients with uncomplicated essential hypertension, namely, determining the most prescribed combination drug products as DDD/year for the year 2021, we found that the first place is again occupied by the combination product Valsartan/Hydrochlorothiazide (Co-Valsacor) with a total number of DDD/year - 2 852 557, representing a share of 3.53% of the total share or 6.64% of the share of combination products based on total number of DDD/year. This is a significant decrease compared to 2020.

We found an increase in prescribing of the Nebivolol/ Hydrochlorothiazide (Nebilet Plus) combination, which went from ninth position in 2020 to third position in 2021. The frequency of treatment with the triple fixed combination Perindopril/Amlodipine/Indapamide (Triplixam) remained high again and the product maintained its position.

Unfortunately, the population continues to decline significantly and in 2021 already stands at 6 519 789 inhabitants. We have calculated the other two indicators that we have set as a necessary data source for the purpose of our study - DDD per capita in 1 year and DDD per 1000 capita in 1 year.

The top 3 items are calcium antagonists and beta-blocker.

Medication utilization of Ca-antagonists is maintained in 2021.

Table 9. DDDs per inhabitant per year and DDDs per 1000 inhabitants per day for 2021

INN	DDD	DDD/inhabitant/year	DDD/1000/day
Nebivolol	4 255 143	0.65	1.79
Lercanidipine	3 419 760	0.52	1.44
Amlodipine	3 260 970	0.50	1.37
Bisoprolol	3 217 302	0.49	1.35
Ramipril	2 900 357	0.44	1.22
Moxonidine	2 868 629	0.44	1.21
Valsartan	2 175 405	0.33	0.91
Indapamide	1 906 635	0.29	0.80
Enalapril	1 824 151	0.28	0.77
Telmisartan	1 821 173	0.28	0.77

To delineate the tendencies in the health insurance fund budget spending in the essential arterial hypertension segment, we computed share ratios and relationships for the selected 5-year analysis period.

Table 10. Ratio of ICD I10 patient treatment cost/total outpatient treatment cost

Year	2017	2018	2019	2020	2021
Total cost (BGN)	798 571 600	1 222 986 555	1 313 770 234	1 513 045 143	1 630 016 055
Cost (BGN) ICD I10	9 796 940	8 437 096	8 029 776	7 728 217	7 145 779
Cost ICD I10 / Total cost	1.23%	0.69%	0.61%	0.51%	0.44%

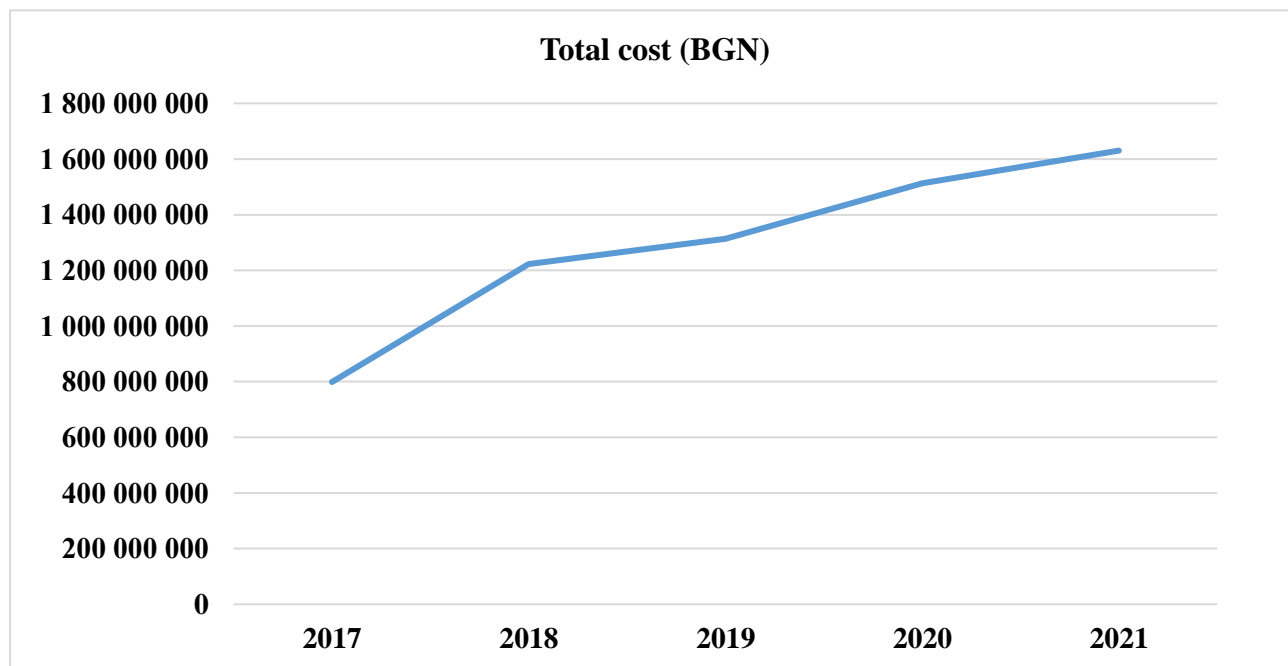


Figure 31. Outpatient treatment cost for the period 2017 - 2021

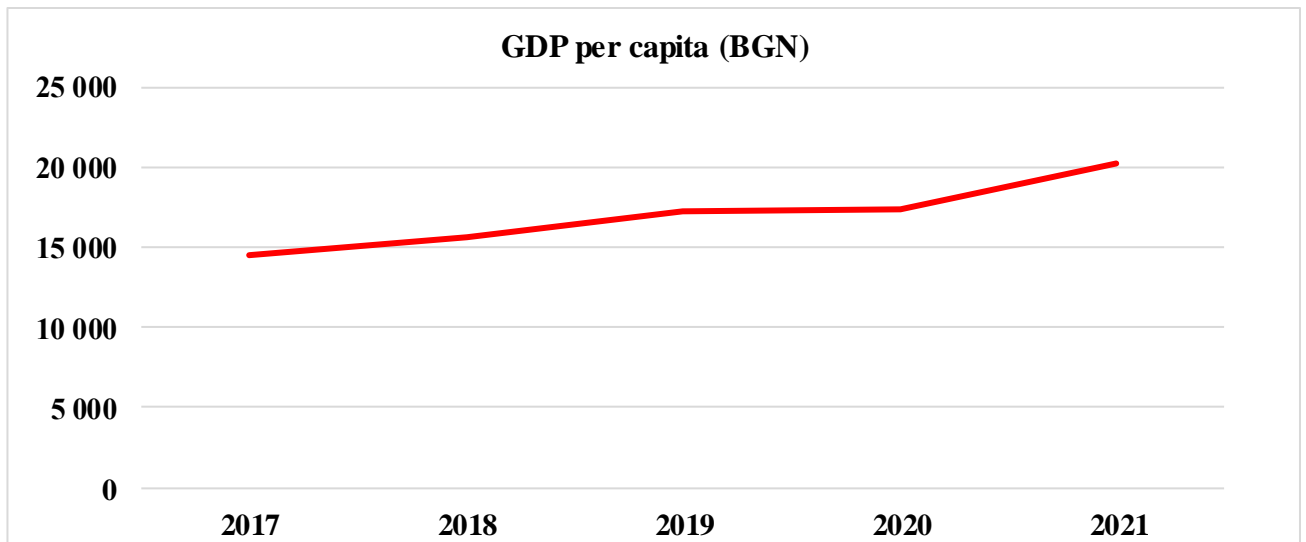


Figure 32. Change in GDP per capita for Bulgaria between 2017 and 2021

There has been an increase in the NHIF's reimbursement expenditure for the treatment of outpatients for the period 2017-2021. This is due to the emergence of new health technologies, but also to the increase in the gross domestic product per capita, which is an indicator of an increased state budget, respectively a larger financial share for the health care system. The inflation index is also important.

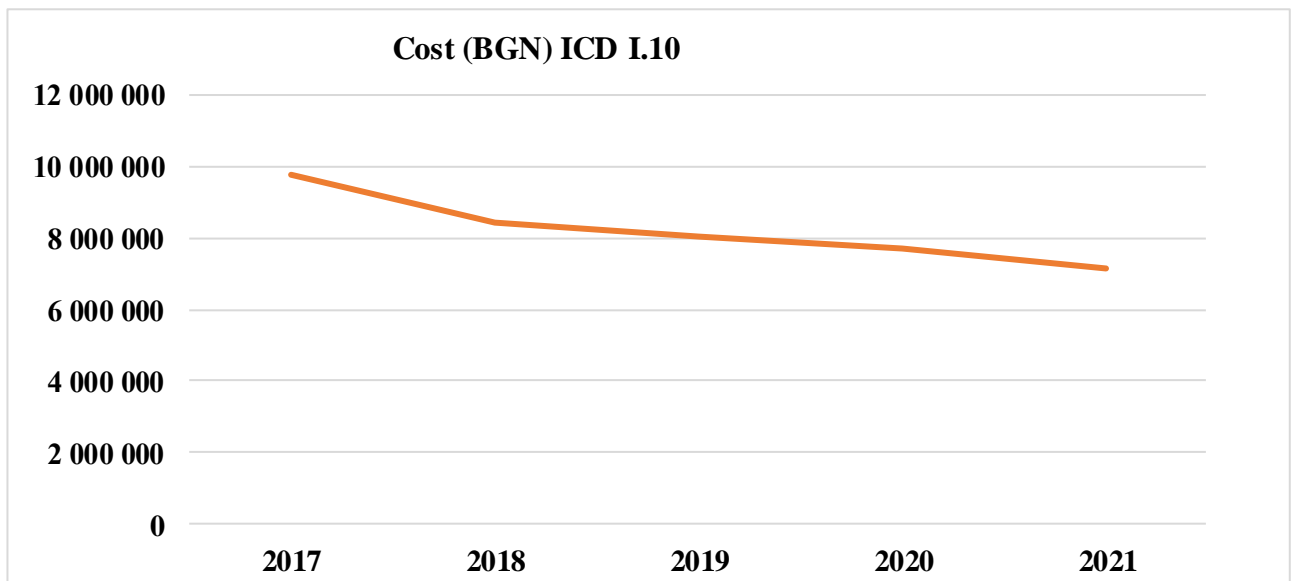


Figure 33. Cost of treatment of patients with essential hypertension in the period 2017 - 2021

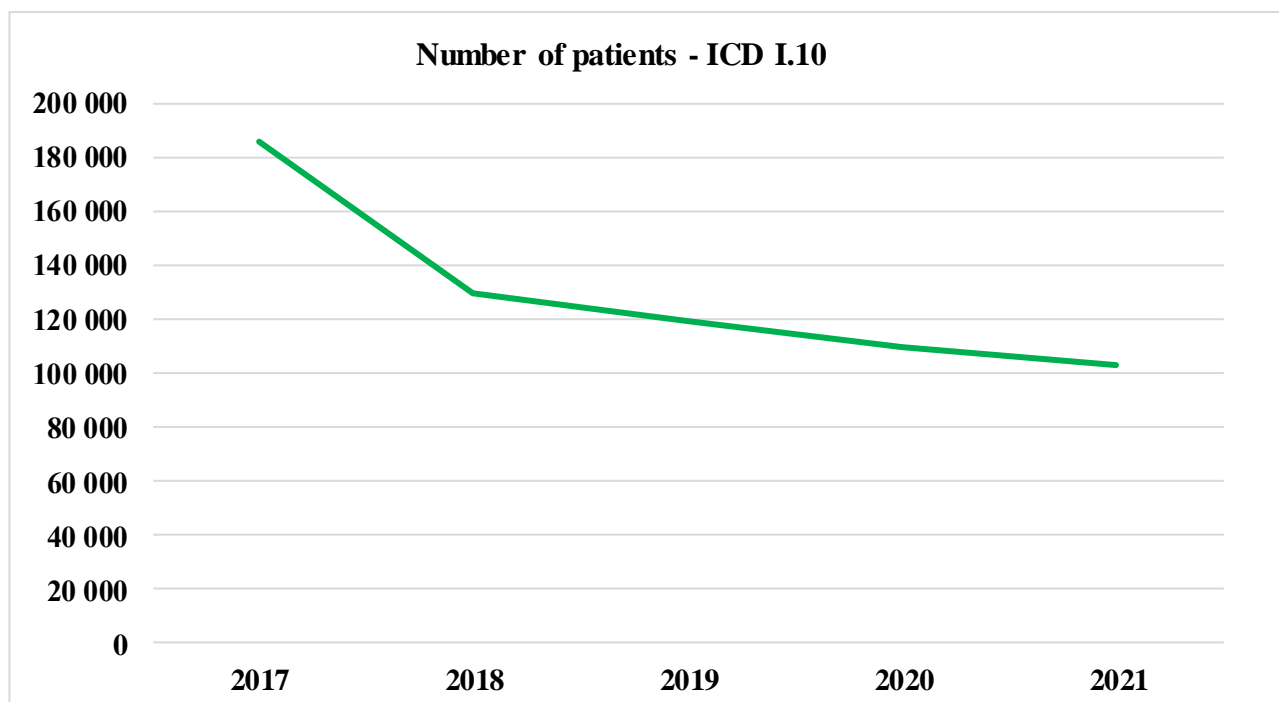


Figure 34. Number of patients with essential arterial hypertension (ICD I10)

Analyzing the data provided by the NHIF, a trend of a significant increase in the annual cost with which the health insurance fund covers home treatment of all patients emerges. Against this backdrop, the funds needed to pay for the treatment of patients with primary hypertension are decreasing year on year.

In proportion to this decline, the number of patients diagnosed with hypertension is also falling.

These results can be interpreted in three ways:

- It is possible that some of the newly diagnosed patients get their prescribed antihypertensive treatment through the so-called "free market" and thus do not fall into the statistics of the NHIF.

- The difference in the number of patients from one year to another may be due to undiagnosed hypertension.

- According to statistical data as of 2017, the mortality rate due to hypertension or IHD in patients under the age of 65 in Bulgaria is very high - almost four times higher than the EU average for AH, and 1.5 times higher than the EU average for IHD. For this reason, all activities related to health promotion and active prevention are encouraged. It is possible that progress has been made in this direction, leading to a fluctuation in the number of patients with ICD I10.

V. DISCUSSION OF THE RESULTS

In order to adequately assess medicines utilisation and the existence of rational medicines use, we need to answer a series of specific questions developed by WHO:

1. Why are these medicines prescribed?
2. Who are the prescribers?
3. Who are the prescribers prescribing for?
4. Are patients taking their medications correctly?
5. What are the benefits and risks of medications?

A fundamental basis for measuring rational use and drug utilization is the availability of accurate epidemiological data that can be derived from properly maintained disease registries at the national level.

Unfortunately, such registries are not maintained in Bulgaria and we refer to extrapolations from literature data and data from other countries comparable in demographic and socioeconomic development to Bulgaria.

According to epidemiological and literature data, there should be between 1 750 000 - 2 000 000 people with essential arterial hypertension, either uncomplicated or complicated, in Bulgaria.

According to the NHIF, the number of patients with different types of hypertension whose treatment is reimbursed is between 1 393 037 and 1 099 608.

There is a statistically significant deviation between epidemiological and reimbursement data in the range of 350 000 to 500 000 people.

A possible reason for this is that a large number of patients take antihypertensive treatment under the so-called "free market" and do not fall into the statistics of the NHIF or this difference is due to cases of undiagnosed hypertension. These suspected cases should be the subject of further research.

The cost of treating patients with essential hypertension (ICD I10) for the five-year period 2017-2021 amounted to BGN 41 137 809. The total budget for drug treatment of outpatients is BGN 6 478 389 587.

The relative share of NHIF expenditures on antihypertensive drugs is 0.64% of the total budget.

The level of reimbursement by the NHIF of medicinal products for the treatment of primary hypertension (ICD I10) is 100%, which means that patients diagnosed with this disease have access to free treatment.

However, the low relative share of antihypertensive drugs under the NHIF reinforces the thesis that a large percentage of people pay for their own treatment and/or are not diagnosed in a timely manner.

The analysis of the medicines included in the PML and INN in the WHO ATS/DDD Index 2020 shows that the medicines available on the market in Bulgaria provide adequate therapeutic choices for the treatment of patients with primary essential hypertension.

The large differences in the relative shares are due to the lack of vasoprotective drugs in the Bulgarian PFS, the dropping of non-selective beta-blockers from hypertension treatment strategies, the limitation of diuretic therapy mainly to hydrochlorothiazide from the group of thiazide diuretics, the reduced use of peripheral vasodilators and the products of the so-called cardiac therapy, which does not fall into the domain of drugs for the treatment of hypertension.

In the Bulgarian therapeutic practice in this segment - ICD I10.0 Hypertensio arterialis essentialis (primaria), no overprescription of drugs was found - on average over the five years, each patient took no more than 1 DDD/day.

Interesting trends were found in therapeutic management. In Bulgaria, there is still no national pharmacotherapeutic guideline for the management of arterial hypertension.

The Bulgarian Society of Cardiology recommends direct reference to European and American guidelines. According to these guidelines it would be advisable to start treatment with thiazide diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium antagonists.

Our data show that among the most prescribed products by INN one thiazide-like diuretic is found and there is a significant proportion of beta-blockers (Bisoprolol, Nebivolol).

The group includes 2 ACE-inhibitors, 3 receptor blockers, 1 calcium antagonist. There is relative compliance with recommendations. In the group of top 10 products by DDD, the same trend is maintained.

However, the cost per number of packs of the drugs set different trends - the most prescribed products are the beta blockers Nebivolol and Bisoprolol and the calcium antagonist Lercanidipine.

Of note is the large expenditure on the centrally acting anti-adrenergic agents Rilmenidine and Moxonidine. In this group, there is a marked discrepancy with the standards of therapy choice.

In a pooled analysis based on DDD, INN and cost per number of packs, it is striking that in Bulgarian therapeutic practice the most prescribed products are beta-blockers, calcium antagonists and centrally acting anti-adrenergic agents. ARBs are predominantly represented by Valsartan.

In all cross-sectional analyses across arms, the significant use of Lercanidipine is striking.

Medicinal products containing a single active drug substance are preferred for uncomplicated essential hypertension. They occupy 2/3 of the prescription compared to combination drugs although new trends are to start treatment of essential hypertension directly with fixed dose combinations.

The role of prophylaxis in the detection of socially relevant diseases is indisputably proven. In our literature searches and reviews, we found data on only one adopted National Chronic NCD Prevention Program. Within 38 pages, activities to reduce morbidity and mortality from various chronic NCDs are spelled out, with the issue of arterial hypertension only superficially addressed.

The pyramid of morbidity with different types of hypertension is reversed - for 2021, 9.7% are patients with essential hypertension, while patients with hypertensive disease with or without heart failure account for over 90% of all hypertensive patients. This distribution may be interpreted in different ways - lack of effective prophylaxis, late detection of hypertension, long latency period of asymptomatic hypertension, treatment outside the reimbursement system, incorrect coding and reporting of the disease, etc.

VI. MAIN CONCLUSIONS FROM THE DISSERTATION

- 1. In Bulgaria there is still no established national pharmacotherapeutic guideline for the treatment of arterial hypertension.**
- 2. Although the practice of direct reference of medical professionals to European and international standards has been adopted, the lack of an approved and mandatory for application Pharmacotherapeutic Guide by the National Council on Prices and Reimbursement of Medicinal Products is an anachronism and leads to deviations in actual practice.**
- 3. According to ESC and ESH recommendations, five main classes of drugs should be used to treat essential hypertension - ACE-inhibitors, ARBs, calcium antagonists, beta-blockers and thiazide diuretics. All types of medicinal products with therapeutic indications for the treatment of arterial hypertension are available and accessible on the Bulgarian pharmacy market.**
- 4. In clinical practice in Bulgaria, the real choice for the treatment of patients with essential hypertension (ICD I10) are mono-products - they occupy 2/3 of the total share of antihypertensive drugs.**
- 5. The cost of treating ICD I10 patients decreased each year during our 5-year study, in contrast to total NHIF cost, which showed an increasing trend.**
- 6. Contrary to the European recommendations for the management of primary arterial hypertension, in Bulgaria the preferred first choice for the treatment of patients is often a calcium antagonist - Lercanidipine.**
- 7. The group of centrally acting anti-adrenergic drugs (Moxonidine, Rilmenidine), which, however, according to the current ESC and ESH recommendations, can be used only in resistant hypertension when all alternatives are ineffective, occupies a serious share.**
- 8. In clinical practice, beta-blockers, respectively INN Nebivolol, occupy a significant share among the most prescribed medicinal products, determined through the cost of treatment of the NHIF, as well as by the number of packages. The choice of beta-blockers must be well justified, given the high rate of adverse drug reactions that would result from their use.**
- 9. There is no adequate mechanism for follow-up of patients with essential hypertension undergoing treatment through the so-called "free market".“.**
- 10. Our analyses raise the suspicion of late diagnosis of essential hypertension and late initiation of drug treatment, but we are unable to point to an adequate algorithm to prove these findings.**
- 11. In clinical practice, we do not find adequate prevention programmes in place that are population-oriented and yield positive results.**

12. Epidemiological data in the arterial hypertension arm are uncertain. We do not find logical correlations between real statistics, scientific research and extrapolation and generalization of data from European and world practice.

VII. CONTRIBUTIONS

CONTRIBUTIONS OF SCIENTIFIC AND THEORETICAL NATURE AND ORIGINALITY OF THE DISSERTATION

1. For the first time in Bulgaria an analysis of diagnostic and therapeutic strategies in patients with arterial hypertension is performed by measuring drug utilization and rational drug use.
2. For the first time, a systematic review of scientific publications on the PRISMA standard for assessing diagnostic and therapeutic strategies in patients with arterial hypertension.
3. For the first time in Bulgaria, a retrospective comparative analysis between epidemiological and reimbursement data is conducted to evaluate prevention and treatment effectiveness of socially important diseases..
4. The study reveals new theoretical and applied aspects of retrospective analyses of health insurance records and, in particular, how to use reimbursement data to rationalize drug therapies for socially important diseases.

METHODOLOGICAL CONTRIBUTIONS

1. An original setup is developed to assess the positive and inverse relationships between effective prevention, timely diagnosis, evidence-based treatment, reimbursement, cost-effective therapies and health outcomes by measuring drug utilization (quantitative parameters).

CONTRIBUTIONS OF SCIENTIFIC AND APPLIED NATURE

1. The study enriches the knowledge of medical professionals (physicians and pharmacists) on the practical application of drug utilization and rational drug use in the treatment of socially important diseases.
2. The study reveals the impact and opportunities for introducing rational use requirements at national level through statutory measures in pricing and reimbursement systems.
3. The study shows the existence of scientific and regulatory problems in the validation and implementation in real practice of pharmacotherapeutic guidelines by national competent authorities for the treatment of different groups of diseases.

CONFIRMATIVE CONTRIBUTIONS

- 1.** The introduction of rational use criteria in clinical practice and reimbursement systems should become a mandatory element of medicines policy.

VIII. SCIENTIFIC PUBLICATIONS RELATED TO THE DISSERTATION

Publications and reports published in scientific publications, referenced and indexed in world-renowned databases of scientific information

1. **Stoyanova S**, Yordanov E, Petrova L, Hristov E. Evaluation of the pharmacotherapeutic approaches for treatment of arterial hypertension by measuring the drug utilization. The 37th Balkan Medical Week “Perspectives of the Balkan Medicine in the Post COVID-19 Era” & The 8th Congress on Urology, Dialysis and Kidney Transplant from the Republic of Moldova with International Participation “New Horizons In Urology”, Balkan Medical Union. Chisinau, Republic of Moldova, June 7-9, (2023), p.38/Abstract book. Arch Balk Med Union.
2. Nachev N, **Stoyanova S**, Rangelov A, Yordanov E, Hristov E, Parvova I, Petkova V. Retrospective analysis of drug utilization and rational drug use in the treatment of uncomplicated essential arterial hypertension in Bulgaria. Journal of Generic Medicines. (2022), 18(2):88–98. <https://doi.org/10.1177/17411343211055896>

Publications and reports published in non-refereed peer-reviewed journals or published in edited collective volumes

1. **Stoyanova S**, Yordanov E, Hristov E, Parvova I. Modern approaches to the treatment of patients with arterial hypertension. // III National Student Conference on Pharmaceutical and Chemical Sciences, Faculty of Chemistry and Pharmacy, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria, 05-06 October 2022, ISBN 978-954-07-4639-5; ISSN 2738-8247 (Online)
2. Nachev N, **Stoyanova S**, Rangelov A, Yordanov E, Hristov E, Parvova I, Petkova V. Analysis of drug utilization and rational drug use in the treatment of essential arterial hypertension in Bulgaria. // III National Student Conference on Pharmaceutical and Chemical Sciences, Faculty of Chemistry and Pharmacy, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria, 05-06 October 2022, ISBN 978-954-07-4639-5; ISSN 2738-8247 (Online)
3. **Stoyanova S**, Hristov E. A retrospective, observational, longitudinal study of drug use for the treatment of uncomplicated essential arterial hypertension in Bulgaria. // First Scientific Congerence for students and PhD students „Pharma Nova, 16-17 December 2022, FF, MU-Sofia, Bulgaria
4. **Stoyanova S**, Nachev N, Yordanov E, Hristov E. Evaluation of pharmacotherapeutic approaches for the treatment of arterial hypertension by measuring drug utilization. // VIII Congress of Pharmacy, 27-30 April 2023, Hotel „Rila“, Bororvets, Bulgaria
5. Nachev N, **Stoyanova S**, Hristov E. Analysis of diagnostic and therapeutic strategies for the treatment of arterial hypertension - a systematic review. // Congress of Pharmacy, 27-30 April 2023, Hotel „Rila“, Bororvets, Bulgaria