

Prescription of Antihypertensive and Antianginal Medications within the Conditions of Outpatient Treatment of Patients with Ischemic Heart Disease Along with Hypertension

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Abstract

Cardiovascular morbidity leads the world in the morbidity rate structure. An arterial hypertension and a stable angina are widely occurring among the population and, in terms of medical and social significance, stand at the head of the circulatory system diseases. The combination of these diseases is observed in 2/3 of patients. An important challenge for cardiology is to ensure a rational approach to the choice of medications for effective antianginal and antihypertensive therapy, its compliance with accepted treatment quality standards, the development of clear and scientific-based criteria for the use of medications, improvement of the patients' quality of life while reducing the economic costs for medications supply. Purpose: To develop an approach to the optimization of medications supply for patients with ischemic heart disease in combination with arterial hypertension in inpatient and outpatient practice based on the use of pharmaco-economic and pharmaco-epidemiological researches. Materials and methods: To assess the prescription structure of the various groups of antihypertensive and antianginal medications, an analysis of the past medical history in patients with ischemic heart disease in combination with arterial hypertension was carried out. Variation statistics methods have been applied in mathematical data processing. Results: Beta-blockers prevailed, followed by angiotensin-converting enzyme inhibitors, calcium channel blockers, and diuretics were found in the structure of medicinal benefits when prescribing pharmacotherapy to patients with stable angina pectoris with arterial hypertension. Conclusions: As a result of the research, it was revealed that the combination therapy in most cases was based on beta-blockers, angiotensin-converting enzyme inhibitors, diuretics in various combinations with each other.

Keywords: *Arterial hypertension; Antihypertensive medications; Pharmacoepidemiological research.*

Introduction

The structure of prescriptions of antihypertensive and antianginal medications for the treatment in patients with ischemic heart disease (IHD) along with arterial hypertension (AH) on an outpatient basis differed from that at the inpatient one (Fig. 1).

Research Results

The leading groups of medications were beta-

adrenergic blocking agent (Beta-blockers), angiotensin-converting-enzyme inhibitor (ACE inhibitors), calcium channel blockers (CCBs), then nitrovasodilators (NVD) and diuretics [1-6]. Top requested medications from the Beta-blockers group were Bisoprolol, Metoprolol, Betaxolol (Fig. 2), which were prescribed in the amount of Concor (73%), Egilok and Betaloc (38% and 29%), Lokren (65%), respectively.

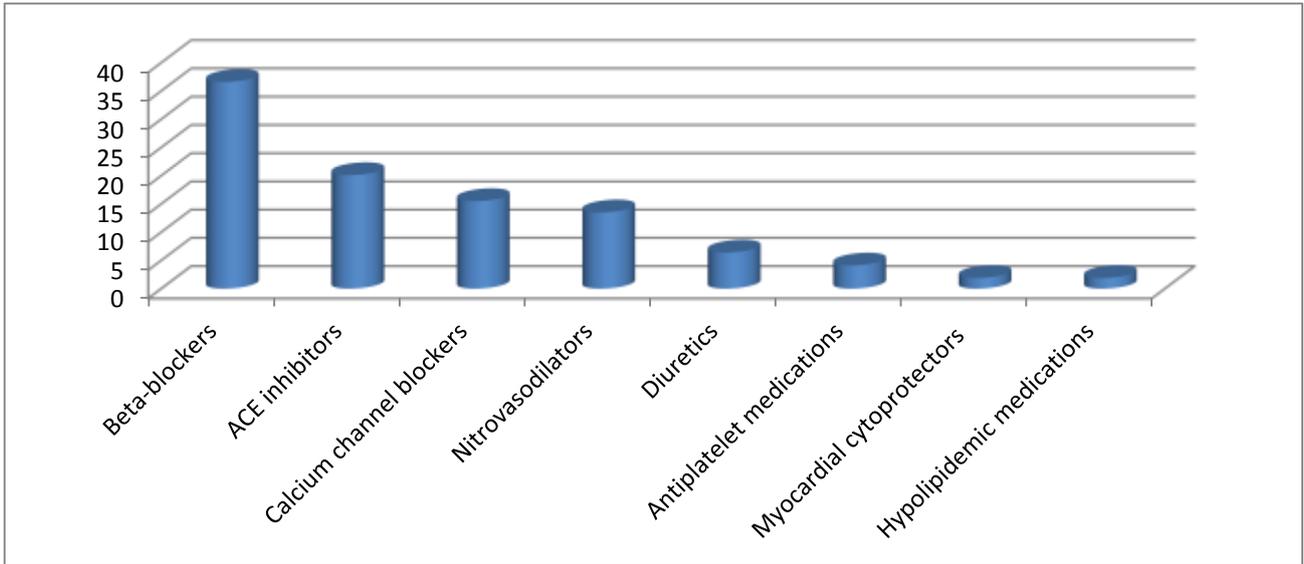


Figure 1: Structure (%) of antihypertensive and antianginal medications prescription to patients with IHD along with AH on an outpatient basis

The structure of ACE inhibitors prescription included five medications (M) (Fig. 3). Perindopril, Fosinopril and Enalapril were in the priority. The first one was prescribed as

an original medication (Prestarium), Fosinopril was used in 75% of cases as Monopril, and Enalapril was used in 100% of prescriptions as generics.

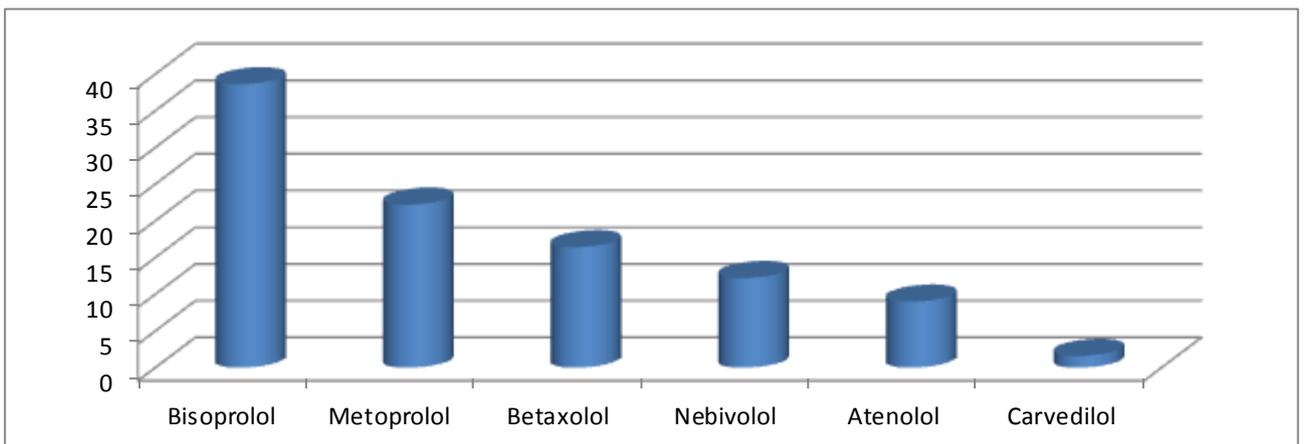


Figure 2: Structure (%) of Beta-blockers prescription to patients with IHD along with AH on an outpatient basis

CCBs were represented by six medications (Fig. 4). The leaders were dihydropyridine derivatives: Amlodipine and Nifedipine. The

first one was used in generic form in 60% of cases. Nifedipine was used in short-acting forms in 20% of prescriptions.

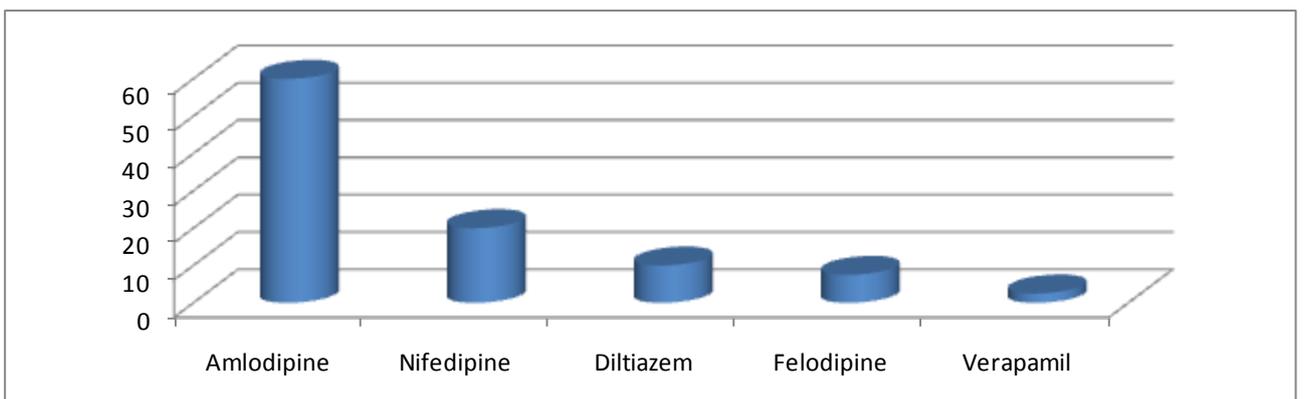


Figure 4: Structure (%) of CCBs prescription to patients with IHD along with AH on an outpatient basis

Isosorbide-5-mononitrate derivatives (5-ISMN) were the leader among NVDs - 67% of prescriptions; derivatives of isosorbide dinitrate (ISDN) (24 %) and nitroglycerin (NTG) (9 %) were used less frequently. 53% of the ISMN prescriptions were for Trimetazide, 46% - for Preductal. Among ISDN medicines, the most popular was Kardiket (59 %), less often-Nitrosorbide (24 %). The diuretic structure included three medications: Indapamide (85 %), Spironolactone (9 %) and Hydrochlorothiazide (6 %). Physicians prescribed Indapamide as Arifone (57 %), in other cases as generics.

Antiplatelet medications, in 100% of cases, were represented by various preparations of acetylsalicylic acid. Myocardial cytoprotectors were used in 80% of cases in the form of Preductal MR and in 20% in the form of the usual form of Trimetazidine. 100% simvastatin was prescribed as the hypolipidemic medications. Physicians chose between original medication and generic medications in favor of the latter (42% and 59%, respectively). Physicians' assessment of the clinical efficacy of the pharmacological groups in general revealed the following priorities (Fig. 5).

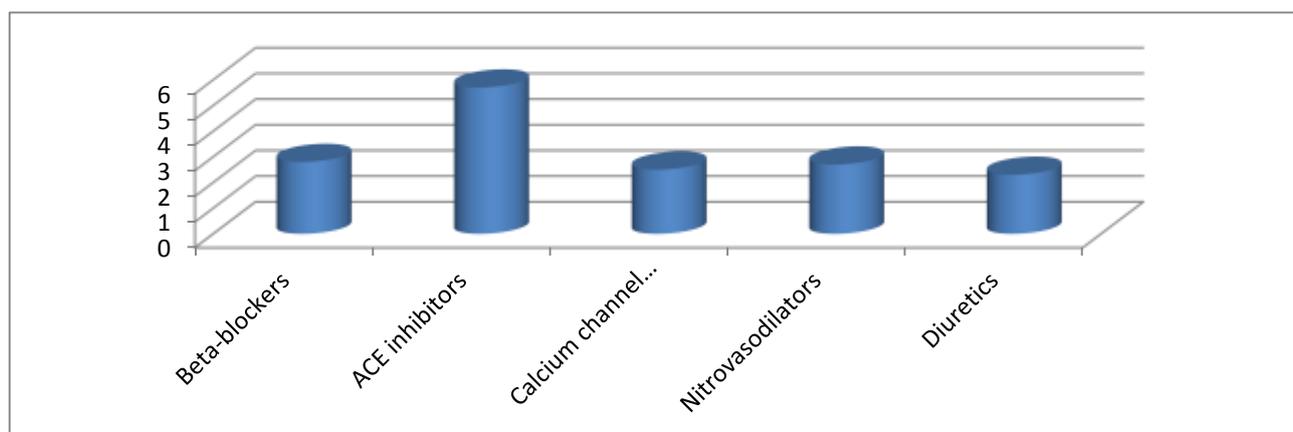


Figure 5: The value of clinical efficacy for different classes of antihypertensive and antianginal medications, determined by family physician

The leading position was occupied by Beta-blockers, less and almost equal level of effectiveness was characteristic for ACE inhibitors and NVDs, CCBs and diuretics were considered by the physicians as fewer effective. In a comprehensive evaluation of both the clinical efficacy and frequency of medication use, data were obtained (Fig. 6), which confirmed the above priorities among physicians for three M groups – Beta-blockers, ACE inhibitors, NVDs. Consideration of individual representatives of antianginal, antihypertensive M according

to the same criteria showed that the use of the M significance and use coefficient (MRSUC) is more adequate in this case, since it determines leaders among medications in terms of the highest frequency of prescriptions of highly effective medications (Table 1). The latter include Bisoprolol, Perindopril, Amlodipine, ISMN derivatives, Metoprolol, MRSUC of which was more than 1.0. The average level of the complex criterion was typical for Betaxolol, Indapamide, Nebivolol, Fosinopril, Enalapril, which MRSUC was among 0.5 and 1.0. Table 1.

The values of the CE and MRSUC for various antihypertensive and antianginal medications

Medications	CE	MRSUC
Bisoprolol	2.9	2.04
Metoprolol	2.8	1.13
Betaxolol	2.85	0.85
Nebivolol	2.9	0.64
Atenolol	2.6	0.42
Carvedilol	2.7	0.08
Perindopril	2.75	1.32
Fosinopril	2.55	0.56
Enalapril	2.45	0.52
Lisinopril	2.5	0.19
Quinapril	3	0.03

Amlodipine	2.65	1.22
Nifedipine	2.6	0.4
Diltiazem	2.4	0.18
Felodipine	2.7	0.15
Verapamil	2	0.04
ISMN derivatives	2.6	1.17
ISDN derivatives	2.6	0.42
NTG derivatives	2.8	0.16
Indapamide	2.6	0.7
Spirolactone	2.3	0.07
Hydrochlorothiazide	2	0.04

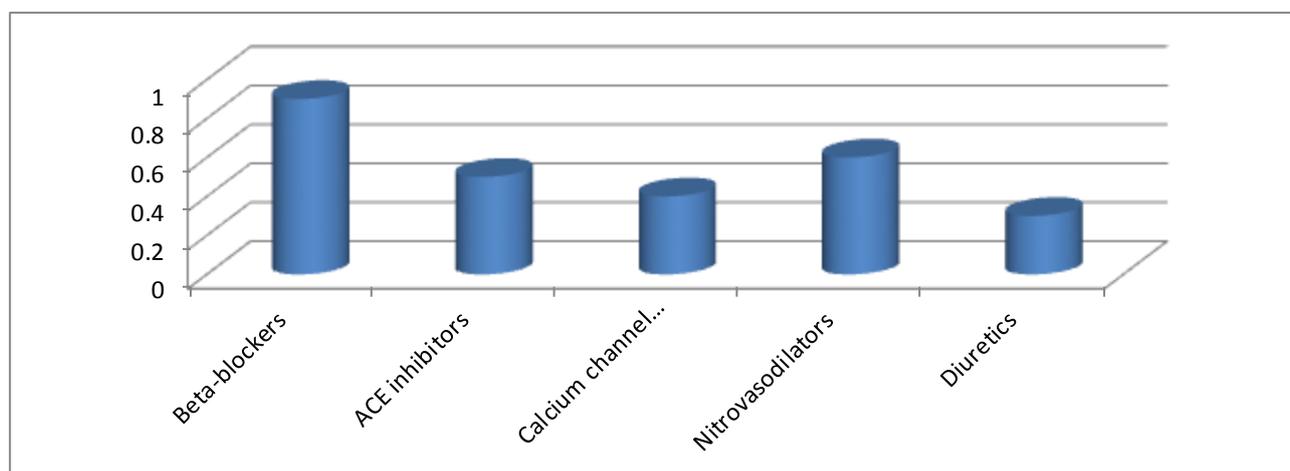


Figure 6: MRSUC value for various classes of antihypertensive and antianginal medications

Evaluation of approaches to the switch therapy in patients with angina pectoris along with the hypertension showed a natural increase in the number of medications prescribed as the severity of the disease (Table 2). The frequency of

prescription of the main classes of the studied medications during monotherapy almost did not differ from the general structure of the use of antihypertensive and antianginal medications (Fig. 7).

Table 2: Structure (%) of prescription of various levels of pharmacotherapy on an outpatient basis to patients with angina pectoris along with AH, depending on the severity thereof

Treatment level	Level 1 AH	Level 2 AH	Level 3 AH	Pharmacotherapy of angina pectoris Level II	Pharmacotherapy of angina pectoris Level III	Pharmacotherapy of angina pectoris Level IV
Monotherapy	84	16	1,5	42		
Combination of two medications	12	65	14	50	61	8
Combination of three medications	4	17	66	7	40	92
Combination of four medications		2	19			

Among all the combination therapy options, the following combinations were most in demand: Beta-blockers + ACE inhibitors + diuretics (34%), Beta-blockers + ACE inhibitors (26%), Beta-blockers + diuretics (23%), ACE inhibitors + diuretics (22%). The same combinations retained the lead in the corresponding treatment regimens. When using a combination of three medications, the following combinations were also quite often

used: Beta-blockers + ACE inhibitors + NVD, ACE inhibitors + Beta-blockers + diuretics. Among the combinations of the Pharmacotherapy Level IV for patients with AH and IHD, the following medication combinations were most often used: Beta-blockers + ACE inhibitors + NVD + diuretics (43%), Beta-blockers + ACE inhibitors + CCBs + NVD (22%), Beta-blockers + ACE inhibitors + CCBs + diuretics (19%).

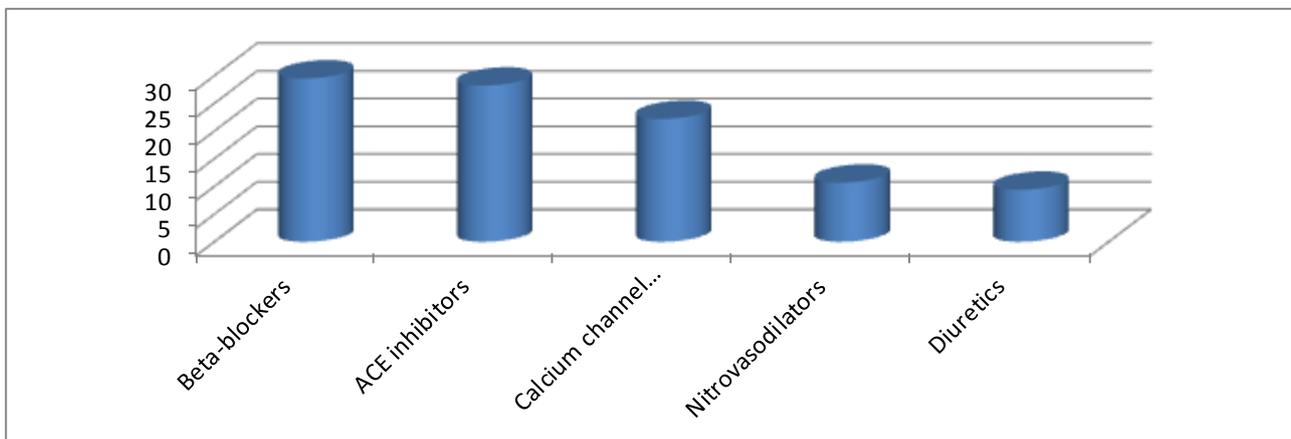


Figure 7: Structure (%) of monotherapy in patients with angina pectoris along with AH on an outpatient basis

The percentage of Beta-blockers among two-component pharmacotherapy regimens was 55%, in three-component regimens - 67%. For the ACEI inhibitors, the same indicator was 54% and 88%, respectively, for CCBs - 20% and 42% respectively, for NVD - 12% and 26% respectively, for diuretics - 48% and 70%) respectively.

The share of irrational M combinations (Beta-blockers + CCBs of nondihydropyridine) has reached 8%. Acceptable combinations of medications (CCBs dihydropyridine + NVD, CCBs dihydropyridine + CCBs of nondihydropyridine) were found in 4% of prescriptions. The physicians' preferences to create a combination therapy depending on mono- and bicomponent medications are shown in Figure 8. As an indicator used as a criterion for the optimal hypotensive effect,

38% of respondents noted a decrease in blood pressure less than 140/90 mm Hg, 24% of respondents - the achievement of the patient's "working pressure", 14% of respondents - a decrease in systolic and/or diastolic blood pressure by 20 and 10 mm Hg respectively, 13% of physicians - elimination of subjective symptoms in the patient and 11% - reduction of systolic or diastolic blood pressure by 10% from the initial level.

The indicator of the optimal antianginal effect for 50% of the respondents was the elimination of attacks of anginal pain in patients, for 34% of the surveyed physicians - a decrease in the frequency of attacks of anginal pain in patients by 50% per day, for 16% of respondents - a decrease in the amount of additional use of nitroglycerin tablets per day.

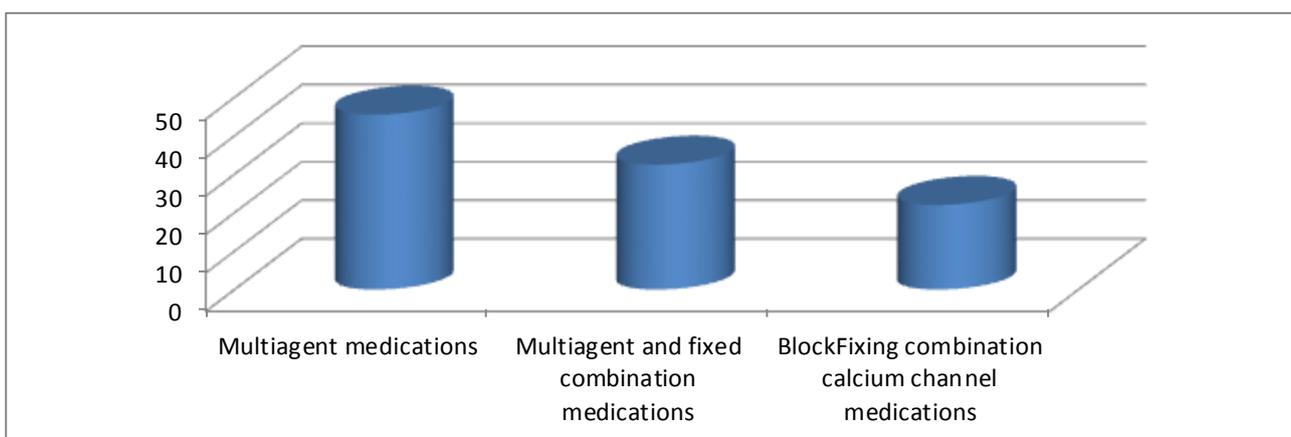


Figure 8: Structure (%) of combination therapy in patients with angina pectoris along with AH, depending on the combination of dosage forms

Most of the surveyed physicians (95%), when prescribing medications, took into account the financial capabilities of patients when 5% of respondents did not consider the pharmacotherapy's financial side. 7% of

respondents considered adequate the monthly cost of antihypertensive or antianginal therapy which is not more than UAH 1,000; 26% of physicians indicated this sum from UAH 800 to UAH 1,000; range

UAH 600-800 was acceptable for 41% of respondents, UAH 400-600 - for 19% of respondents, 7% of physicians prescribed treatment worth more than UAH 1,000 per month.

There were indicated the following pharmaceutical companies, whose products are most often preferred by physicians (in decreasing order of importance): Berlin Chemie, Servier, KRKA, Gedeon Richter, Nycomed, Pfizer, Polpharma, making up 86% of the total number of options. Thus, in the structure of medicinal benefits when prescribing pharmacotherapy to patients with stable angina along with AH, Beta-blockers prevailed, then ACE inhibitors, CCBs, NVD, and diuretics.

The most popular medications, with a high assessment of clinical efficacy, were Bisoprolol, Perindopril, Amlodipine, ISMN derivatives, Indapamide. The combination therapy in most cases was based on Beta-blockers, ACE inhibitors, diuretics in various combinations with each other. 2/3 of physicians considered the adequate monthly cost of pharmacotherapy in the range from UAH 200 to 500, while in most cases the use of generic medications was meant. No more than half of the respondents used adequate

criteria for evaluating antihypertensive and antianginal therapy in their work.

The Consumption Structure of Antihypertensive and Antianginal Medications at the Outpatient Level of Treatment in Patients with IHD and Hypertensive Disease

When considering the use structure of pharmacological agents in patients with stable angina along with AH, it was revealed that the leading positions were occupied by three groups of medications: ACE inhibitors, antiplatelet medications and Beta-blockers (Fig. 9). The average level of consumption accounted for NVD, diuretics, a lower percentage (less than 10%) of use was typical for lipid-lowering medications, CCBs, myocardial cytoprotectors and antiarrhythmic medications.

In this case, the frequency of use (of the total number of patients surveyed) of various classes of medications was as follows: ACE inhibitors (64%), antiplatelet medications (59%), Beta-blockers (58%), NVD (56%), diuretics (32%), lipid-lowering medications (24%), CCBs (22%), myocardial cytoprotectors (9%), antiarrhythmic medications (4%).

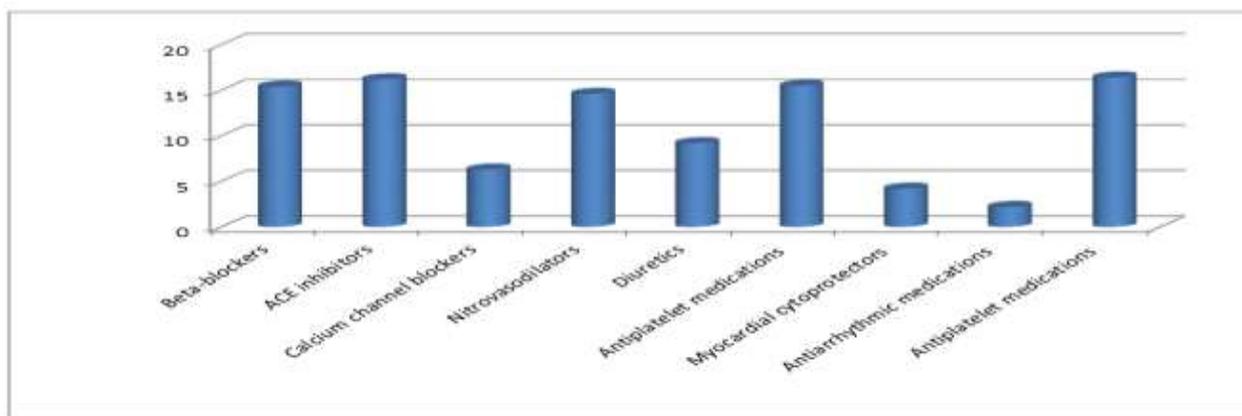


Figure 9: Consumption structure (%) of antihypertensive and antianginal medications by patients with stable angina along with AH on an outpatient basis

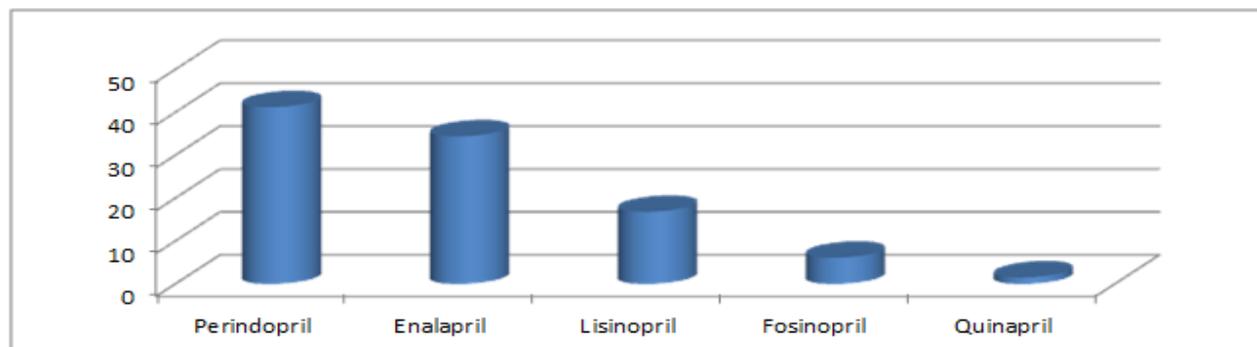


Figure 10: Consumption structure (%) of ACE inhibitors in patients with stable angina along with AH on an outpatient basis

The consumption structure of ACE inhibitors included five medications (Fig. 10). The priority in use belonged to Perindopril, Enalapril and Lisinopril. The first of them was prescribed in the form of original medications (Prestarium), Enalapril - in the form of generics (100% of prescriptions), Lisinopril was presented by Diroton (77%) and in 22% of cases by a medications from various companies. Anti-platelet medications

were represented by various preparations of acetylsalicylic acid. Pharmaceutically optimized forms - aspirin cardio and Cardiomagnyl - were used in 87% of cases. The most popular medications from the Beta-blockers group were Bisoprolol, Betaxolol, Metoprolol (Fig. 11), which were intended in the amount of Concor (50%), Lokren (52%), Vasocardin and Betaloc (39% and 35%), respectively.

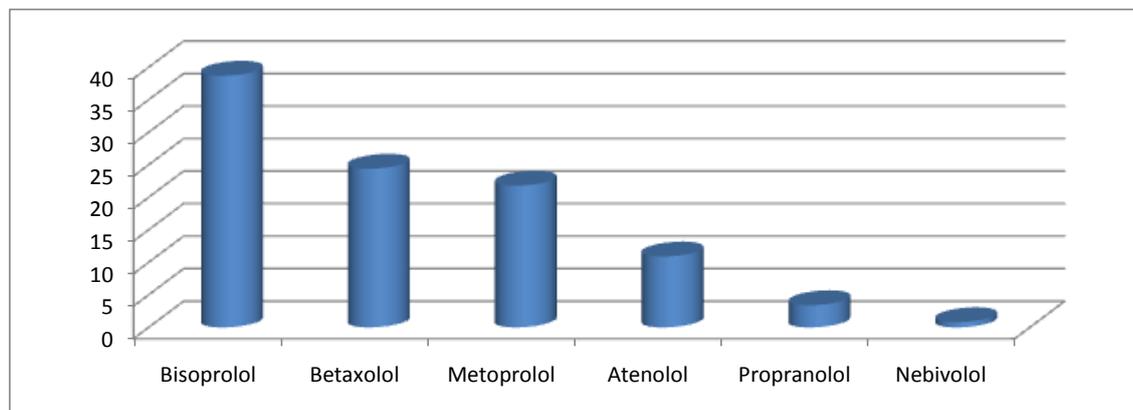


Figure 11: Consumption structure (%) of Beta-blockers in patients with stable angina along with AH on an outpatient basis

Among the NVDs, the leaders were ISDN derivatives (49%) and ISMN (41%) derivatives of prescriptions; NTG derivatives were used less frequently (10%). 57% of prescriptions were for Pektrol, 34% for Trimetazide within the ISMN medications. Kardiket Retard (66%) was among the most popular ISDN medications, less often - Nitrosorbide (23%). In the structure of diuretic prescriptions, Indapamide medications prevailed (64%), followed by Spironolactone (27%), and Hydrochlorothiazide was most rarely used (9%). Indapamide was used in 71% of cases as generics and in 29% as Arifone.

Lipid-lowering medications were represented by statins: Simvastatin (56% of prescriptions), Rosuvastatin (42%) and Atorvastatin (2%). Simvastatin and Atorvastatin were used in the form of generic medications (Vasilip, Simvacard and Liprimar, respectively), Rosuvastatin in the form of the original medication Crestor. CCBs were represented by three medications. The leaders were dihydropyridine derivatives: Nifedipine (56%) and Amlodipine (37%). The first was used in the form of generics in 100% of cases, and the retard form prevailed (Cardipin Retard and

Fenamon Retard - 63%). Amlodipine was also mainly used in generic form (81% of prescriptions). Verapamil was used less frequently among CCBs - 7% of prescriptions. Myocardial cytoprotectors were presented in 100% of cases as Preductal. Amiodarone was used as an anti-arrhythmic agent. In the structure of original and generic medications, the last group of medications prevailed (36% and 64%, respectively, $p < 0.05$).

The structure of combined pharmacotherapy with antianginal and antihypertensive medications in patients with IHD and AH was as follows: the second level of treatment was used in 46% of cases, the third level - in 28%, the fourth level - in 10%, the fifth level - in 1%. Monotherapy was used in 16% of cases. Among the options for the second-level treatment, schemes that included Beta-blockers (56%), NVD (47%) and ACE inhibitors (44%, of which 8% were combined with a diuretic) prevailed. The frequency of CCBs and diuretics use was less - 16% and 18%, respectively.

The combined use of Beta-blockers and ACE inhibitors was found in 27% of patients. Combinations of Beta-blockers + NVD (19%) and ACE inhibitors + NVD (19%) were used with almost the same frequency.

Other combinations were much less common (for example, NVD + diuretic - 4%). The third-level of pharmacotherapy was mainly represented by a combination of Beta-blockers + ACE inhibitors + NVD (44%), to a lesser extent - ACEI + NVD + diuretics (22%), Beta-blockers + NVD + diuretics (8%). Combinations of medications, including both Beta-blockers and ACE inhibitors, were found in 57% of cases. According to the frequency of use in various variants of the third level of therapy, antihypertensive and antianginal medications were distributed as follows: ACE inhibitors (86%), NVD (81%), Beta-blockers (69%), diuretics (43%), CCBs (16%).

Among the options on the fourth-level of pharmacotherapy, Beta-blockers were used in 100%, ACE inhibitors - in 89% (in all cases in combination with Beta-blockers), NVD and diuretics - in 77% each, CCBs - in 59% of cases. The most popular was the regime that included Beta-blockers + ACE inhibitors + diuretic + NVD (41%), less often used variants of Beta-blockers + ACE inhibitors + NVD + CCBs (23%), Beta-blockers + ACE inhibitors + diuretic + CCBs (18%). The fifth level of the therapy for IHD and AH included the use of Beta-blockers + ACE inhibitors +

diuretic + NVD + CCBs. Undesirable medications combinations were found mainly when using the second level of pharmacotherapy and were represented by a combination of a diuretic and NVD; NVD and CCBs, diuretic and CCBs (4%).

As monotherapy, with approximately the same frequency, patients used ACE inhibitors (28%), Beta-blockers (24%), NVD (21%), less often CCBs (17%) and diuretics (10%). The evaluation of the outpatient pharmacotherapy effectiveness in patients with IHD and AH, carried out on average for 58 days, revealed a significant ($p < 0.001$) decrease in SBP from 161.8 ± 21.5 to 141 ± 5.6 mm Hg, DBP from $97.3 \pm 10, 2$ up to 86.7 ± 8.2 mm Hg.

An increase in the number of antianginal and antihypertensive medicaments used did not lead to an increase in the level of blood pressure reduction; a statistically significant threshold is reached when performing multiple paired comparisons of indicators, with the exception of the dynamics of SBP in mono- and combined therapy (Table 2). There were no significant differences between the studied levels of pharmacotherapy in the duration of outpatient follow-up.

Table 2: Dynamics of blood pressure, duration of outpatient treatment in patients with IHD and AH, depending on the pharmacotherapy level

Treatment level	Average systolic blood pressure (SBP) reduction per course	Average diastolic blood pressure (DBP) reduction per course	Average observation duration (months)
1st level	$14.1 \pm 7.0^*$	6.8 ± 7.2	2.0 ± 1.7
2nd level	21.9 ± 17.1	9.9 ± 8.2	1.9 ± 1.7
3rd level	20.2 ± 18.5	11.5 ± 9.6	1.6 ± 1.3
4th level	21.7 ± 17.8	10.5 ± 8.2	2.1 ± 1.8
5th level	19.0 ± 13.7	9.5 ± 6.7	2.7 ± 2.9

Note * - a significance of differences compared to combination therapy options

When considering individual options for combined outpatient therapy for patients with IHD and AH, the most cost-effective (in terms of total CER) was the combination of Beta-blockers + diuretic among the options of the 2nd level of treatment.

Of the options for 3rd level of treatment, the least expensive was the combination of an ACE inhibitor + Beta-blockers + diuretic, among the 4th level regimens - the combination - Beta-blockers + CCBs + diuretic + ACE inhibitor (Table 3). The comparison of the hypotensive effect level in all inpatients and outpatients

showed that the decrease in blood pressure in the hospital was more significant ($p < 0.001$) than in the polyclinic: for SBP 29.0 ± 20.9 i 20.4 ± 16.6 mm Hg respectively, for DBP- 15.5 ± 9.6 i 10.6 ± 8.5 mm Hg respectively. At the same time, the initial blood pressure levels in inpatients were higher than in outpatients: SBP 166.8 ± 24.1 and 161.8 ± 21.5 mm hg ($p < 0.05$), for DBP $99; 7 \pm 10.9$ and 97.3 ± 10.2 mm Hg ($p < 0.01$).

When comparing the cost of one day of treatment of inpatient and outpatient patients, the outpatient treatment level was more costly in almost any combined variant

of medical correction of IHD and AH (Fig. 12).

Table 3: the value of the cost-effectiveness ratio for the main options for outpatient combined pharmacotherapy in patients with IHD and AH

Combinations of medications	CER SBP	CER DBP
NVD + ACE inhibitor	45.1±31.2	75.5±24.2
CCBs + ACE inhibitor	25.3±11.2	38.7±29.8
NVD + Beta-blockers	87.5±56.9	97.9±77.6
NVD + CCBs	37.9±24.9	69.8±48.7
Diuretic + ACE inhibitor	59.4±37.8	69.8±36.3
Diuretic + NVD	144.8±147.6	191.5±225.5
Beta-blockers + ACE inhibitor	62.2±51.7	99.5±72.0
Beta-blockers + diuretic	19.8±10.7	28.2±19.8
Beta-blockers + CCBs	37.8±32.7	49.8±53.5
NVD + ACE inhibitor + Beta-blockers	137.4±128.9	138.7±107.3
NVD + ACE inhibitor + diuretic	148.7±153.5	194.8±134.9
NVD + Beta-blockers + diuretic	99.4±123.9	144.3±131.2
ACE inhibitor + Beta-blockers + CCBs	93.6±108.9	85.3±120.6
ACE inhibitor + Beta-blockers + diuretic	39.4±22.5	60.3±62.1
ACE inhibitor + CCBs + diuretic	72.8±92.1	115.7±195.6
NVD + Beta-blockers + CCBs + ACE inhibitor	98.8±102.5	243.7±136.6
NVD + ACE inhibitor + Beta-blockers + diuretic	105.7±101.5	263.8±97.8
Beta-blockers + CCBs + diuretic + ACE inhibitor	90.4±58.7	136.5±91.2
NVD + Beta-blockers + CCBs + diuretic	115.7±32.8	284.7±163.4
NVD + ACE inhibitor + Beta-blockers + CCBs + diuretic	203.6±362.6	406.4±307.7

The cost-effectiveness ratio (CER) for reducing SBP and DBP by 1 mm Hg at the inpatient and outpatient levels of pharmacotherapy in patients with IHD and AH has testified to the greater profitability of the inpatient level of treatment

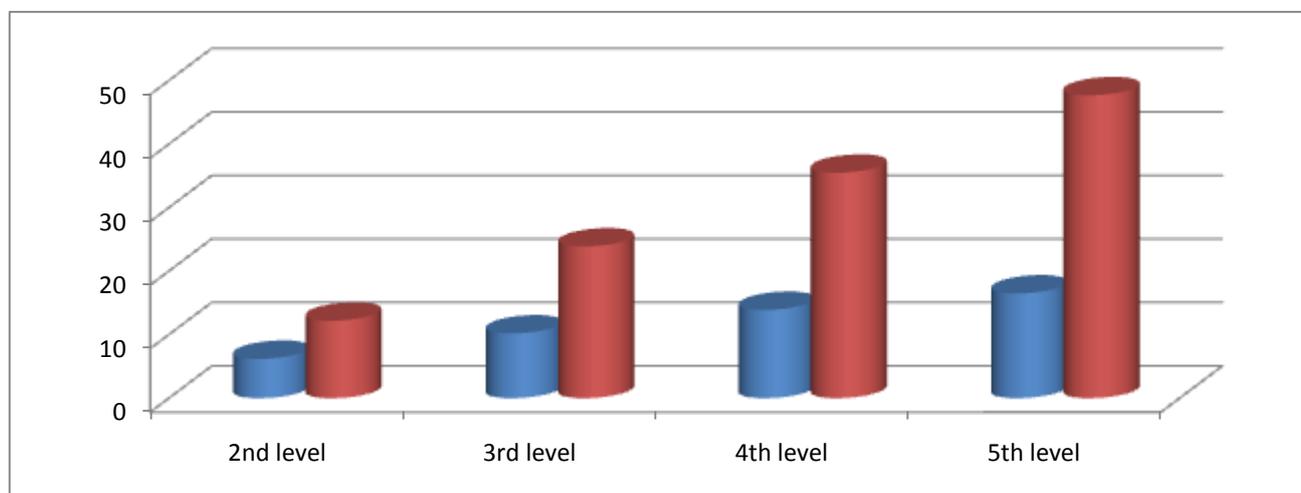


Figure 12: The cost of 1-day pharmacotherapy in patients with stable angina along with AH in inpatient and outpatient conditions using various treatment levels

Conclusions

Thus the leaders in the frequency of use in patients with IHD and AH were ACE inhibitors, antiplatelet medications, Beta-blockers, NVD, diuretics. The selection of medications from the indicated pharmacotherapeutic groups was based on: Perindopril, Aspirin, Bisoprolol, ISDN derivatives, Indapamide. The most popular

groups of medications for mono- and combination therapy were Beta-blockers, NVD, ACE inhibitors. The most cost-effective outpatient therapy regimens were: Beta-blockers + diuretic, ACE inhibitor + Beta-blockers + diuretic. Beta-blockers + CCBs + diuretic + ACE inhibitor. The outpatient level of treatment in patients with combined pathology was more costly according to the evaluated criteria than inpatient therapy.

References

1. Kvasha EA, Horbas IM, Smirnova IP, Sribnaia OV. Arterial hypertension: 35-year dynamics of the prevalence and the effectiveness of its control at the population level among males living in urban area. *Arterial hypertension*. 2016;3(47):18–23 (<http://www.mif-ua.com/archive/article/43044>).
2. Ministry of Health of Ukraine (2012) Unified clinical protocol for primary, emergency and secondary (specialized) medical care “Arterial hypertension” (http://mtd.dec.gov.ua/images/dodatki/384_2012/384_2012ykpmd_ag.pdf).
3. Copley JB, Rosario R. Hypertension: a review and rationale of treatment. *Dis. Mon.* 2005;51(10-11): 548-614.
4. Arterial hypertension. Updated and adapted evidence-based clinical guidelines. 2012.
5. Resistant Hypertension: Diagnosis, Evaluation, and Treatment. A scientific statement from the american heart association professional education committee of the council for high blood pressure research. *Hypertension*. 2008; 51:1403-1419
6. Lebedeva T. Guarantors of reliable information / T. Lebedeva // *Farm. vestn.* 2002; 13: 5.