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Research Article

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# Multi-aspect approach to the optimization of pharmacotherapy of patients with arterial hypertension of high and very high risk

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## Abstract

**Introduction:** Personalization of pharmacotherapy of cardiovascular diseases is one of the urgent problems of cardiology.

**Material and methods**: The study includes 120 patients with grades 2-3 arterial hypertension with the criteria of high and very high risk of developing cardiovascular complications. The patients were randomized into three groups with differentstarting regimens of pharmacotherapy – fixed and free combinations of ACE inhibitors and dihydropyridine CCB. Evaluation of the efficacy, safety and individualization of a therapy was carried out by using pharmacokinetic, pharmacoeconomic, sonographic, and laboratory methods.

**Results and discussion**: Antihypertensive treatment with the inclusion of Amlodipine and Lisinopril or Ramipril in patients with arterial hypertension, having a slow and very slow oxidative metabolism phenotype, is characterized by the development of a more pronounced hypotensive effect in this group of patients ($p<0.05$-$0.001$) (Δ% SBP from 12.7 to 24.6 and from 19.6 to 27.9, respectively; Δ% DBP from 10.6 to 19.1 and from 15.9 to 23.6, respectively) in comparison to the group of patients with a fast phenotype (Δ% SBP from 6.42 to 9.34; Δ% DBP from 1.04 to 5.66), which allows administering a personalized pharmacotherapy. For patients with arterial hypertension of high and very high risk, the use of a fixed combination of Amlodipine and Lisinopril as a basic variant of the two-four-component therapy compared with treatment options based on free combinations of the studied drugs provided a significantly more pronounced decrease in systolic blood pressure (24.9%, 17.8 %, 19.0%, respectively, $p<0.01$), a greater degree of regression of left ventricular myocardial hypertrophy (8.70%, 5.67%, 5.84%, respectively, $p<0.05$), significant ($p<0.05$-$0.001$) improvement in a number of parameters of the patients' quality of life, and was characterized by the greatest economic efficiency according to various criteria of hypotensive action.

**Conclusion:** The results obtained in the study demonstrate the advantages of a fixed combination over free combinations of antihypertensive drugs and demonstrate the possibility of a pharmacokinetic approach to individualization of pharmacotherapy.

## Keywords

arterial hypertension, pharmacokinetics, combined pharmacotherapy.

# Introduction

The results of large controlled clinical studies indicate that in order to achieve the optimal control of blood pressure, a significant number of patients with high and very high risk hypertension have to at least two antihypertensive drugs at the same time take (Berglund 1989, Dyadik et al. 2013).

However, the complexity of the simultaneous administration of several drugs and the increased costs for them in some cases significantly reduce the patients' adherence to treatment. One of the ways to solve this problem is to use fixed combinations of drugs.

One of today's leading combinations providing a positive effect on the outcome for patients with hypertension is a combination of an ACE inhibitor and CCB. The efficacy of this combination of drugs, in particular the combination of Amlodipine and Lisinopril, due to their effect on surrogate and final points in patients with hypertension has been shown in many studies (Elliott 2006, Nedogoda et al. 2013, Protasov et al. 2009).

Despite this, approaches to individualization of pharmacotherapy of patients with high and very high hypertension by means of fixed combinations in comparison with free combinations of antihypertensive drugs are not well studied, either in terms of pharmacodynamic features affecting the quality of patients' life, or in terms of pharmacoeconomic analysis.

In the Russian Federation, the annual economic damage caused by temporary or permanent disability associated with hypertension or its complications, as well as the costs of treatment and rehabilitation of this category of patients exceed 30 billion rubles, and the costs are constantly increasing. In this regard, the choice of drugs optimal both in terms of clinical and pharmacoeconomic effectiveness is one of the most important medical and social problems (Chazova and Oshepkova 2013, Glezer et al. 2014, Karpov 2001).

At the same time, one of the possibilities to reduce patient's expenses for drug therapy is the use of fixed combinations of antihypertensive drugs (Kolosov and Proshin 2016). The studies mentioned earlier demonstrated the cost-effectiveness of such an approach. It turned out that the separate use of drugs compared with the fixed combinations of the same substances was accompanied by significantly higher total cost of patient management (Markova et al. 2012, Petrov 2002).

Despite numerous studies on this issue, a number of issues remains controversial and unresolved.

Along with clinical and social factors, one of the most important modern trends is the substantiation of the economic aspects of the strategy and tactics of treatment, including patients with hypertension. From this point of view, the task of comprehensive integrated assessment of the optimal ratio of the price of drugs and their efficacy requires its solution, which will contribute to the efficacy of treating patients with hypertension (Gilyarevsky and Golshmid 2016, Reshetko et al. 2015).

Development and implementation of personalized pharmacotherapy should use innovative techniques. Earlier studies have established heterogeneity of the humans in their ability to metabolize drugs. Currently, the individualization of pharmacotherapy of circulatory system diseases is mainly based on pharmacodynamic and pharmacogenetic approaches. The latter is the most promising, but technically more complex. Keeping in mind the coincidence of biotransformation pathways of antihypertensive drugs and markers, the evaluation of polymorphism of oxidative metabolism based on the study of pharmacokinetics of the test-drug, from a practical point of view, is one of the ways to personalize pharmacotherapy. Among the main classes of antihypertensive drugsб there are medicinal substances, pharmacodynamic effect from which is determined by the characteristics of their pharmacokinetics, in particular, the genetically determined rate of biotransformation processes. One of such drugs is Amlodipine. It seems practically important to study the intensity of pharmacodynamic effects of the combination therapy of Amlodipine and the representatives of one of the leading classes of antihypertensive agents – ACE inhibitors in patients with hypertension, having different oxidative metabolism phenotypes (Borodulin et al. 2012, Kazakov and Sycheva 2015, Knott et al. 1984, Sychev et al. 2011).

At the same time, the data available in the literature do not fully represent the whole range of possible approaches to the personalization of antihypertensive therapy in patients with high and very high risk hypertension, based on a systematic analysis of the intensity of the pharmacodynamic effect of treatment in various phenotypic groups of patients with different oxidative metabolism rate; the nature of the drugs used and their combinations; and the use of mathematical methods for predicting the hypotensive effect of the therapy.

The information above confirms the relevance of the problem under study and serves as a rationale for the research undertaken.

**Objective:** to conduct a comparative evaluation of the pharmacological and pharmacoeconomic efficacy of various regimens of the combined antihypertensive therapy in patients with high and very high risk arterial hypertension; to study the possibility of using a pharmacokinetic approach to personalize the pharmacotherapy in a specified contingent of patients.

# Material and methods

### General characteristics of patients

The design of the research is an open, randomized study in parallel groups of patients.

*Criteria for inclusion into the study:* men and women aged 45-65 years with grades 2-3 arterial hypertension, having a high and very high risk of developing cardiovascular complications (Diagnosis and Treatment of Hypertension. Russian Recommendations 2010).

*Criteria for exclusion from the study:* the presence of heart disease, myocardial infarction, stroke, classes III-IV stable exertional angina, during the examination or in the medical history; the presence of classes III-IV chronic heart failure, cardiac arrhythmias and conduction disturbances requiring antiarrhythmic therapy; symptomatic arterial hypertension; the presence of chronic bronchopulmonary pathology, diabetes; comorbidities requiring a constant medical therapy.

The study involved 120 patients. The average age of patients was 63.0 [58.0; 64.0] years; the duration of arterial hypertension was 10.6±2.89 years. Men made up 70% (84 people), women - 30% (36 people). Among the patients included in the study, the patients with grade 3 hypertension (95 people, 79.9.1%) prevailed, 25 patients (20.9%) had grade 2 hypertension. High risk was determined in 58 people (48.3%), very high – in 62 patients (51.7%). Class II stable angina pectoris was diagnosed in 32 patients (26.6%). In 36 patients (30%), class I CHF was registered, in 84 patients (70%) – class II CHF.

Clinical, laboratory and instrumental methods of the study were used in the patients eligible for inclusion into the main group over a three-day placebo period, and then the patients were randomized into three groups with different pharmacotherapy regimens (Fig. 1). The stratification criteria for randomization were: gender (men/women), age (below 55 years old/over 55 years old), grade of hypertension (2/3 grade), presence or absence of stable angina, functional class of CHF (class I/II). The patient groups were comparable ($p>0.05$) with one another by the parameters under study. All the patients prior to the introductory period had signed the informed consent on the participation in the study.

After the randomization, in each of the three groups, doses of drugs were titrated and the stages of therapy were changed with 2-week interval. The criteria for increasing doses of drugs or switching to a higher stage of pharmacotherapy was failure to achieve the target blood pressure – under 140/90 mm Hg – evaluated at the next patient's visit. Upon reaching the fourth stage of therapy, this scheme was followed for 6 weeks. The total duration of follow-up was 14 weeks.

For the pharmacological correction of hypertension, the following drugs were used: Amlodipine (Normodipine, Gedeon Richter Ltd., Hungary), Ramipril (Amprilan, KRKA Ltd., Slovenia), Lisinopril (Diroton, Gedeon Richter Ltd., Hungary), fixed combination of Amlodipine and Lisinopril (Eqvator, Gedeon Richter Ltd., Hungary), Bisoprolol (Bidop, Gedeon Richter Ltd., Hungary), Indapamid (Indapamid MV, STADA, Makiz-Pharma Ltd., Russia).

In addition to antihypertensive therapy, the patients received lipid-lowering therapy – statins (Atorvastatin or Rosuvastatin) in appropriately selected doses; antiplatelet agents (Acetylsalicylic acid, 75mg/day) when there no contraindications. In the screening period, if necessary, the patients could use Captopril and short-acting nitrovasodilators.

**Methods for assessing the morphofunctional parameters of the circulatory system, daily blood pressure profile, laboratory parameters, phenotype of oxidative metabolism, characteristics of the quality of life of patients with arterial hypertension**

Evaluation of casual ("office") values of blood pressure was carried out according to the existing methodological requirements. The initial level of systemic hemodynamic parameters were the ones recorded before the start of pharmacotherapy.

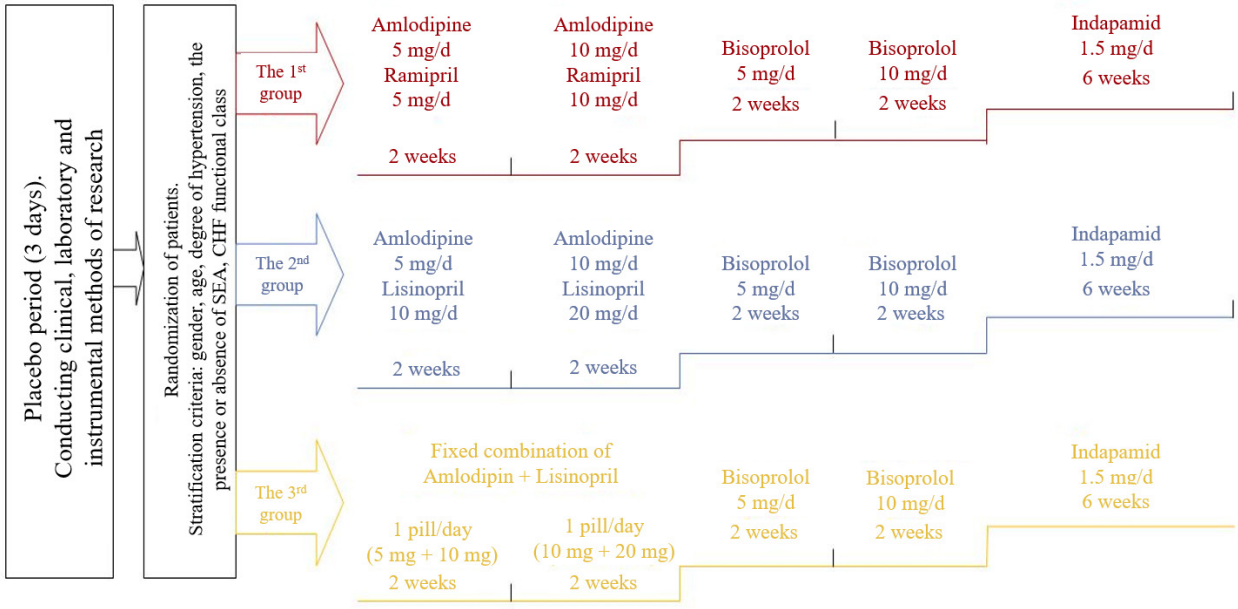


**Figure 1.** Design of an open, randomized study of pharmacological correction of hypertension in parallel groups of patients.

The diurnal profile of blood pressure was assessed using a BPLab MnSDP-1 monitor (Petr Telegin Ltd., Russia) according to the generally accepted method (Rogoza 1997), with the following parameters determined: the mean level of SBP, DBP, HR during daytime, nighttime and 34-hour periods; variability of SBP and DBP during daytime and nighttime; systolic and diastolic blood pressure loads; daily indices of SBP and DBP.

The study of the structural and functional parameters of the heart and blood vessels was performed by using a sonographic method on an SSI-8000 SonoScape ultrasound system (Sono Scape Co. Ltd, PRC). Doppler echocardiography was carried out according to the standard technique. When assessing the structural parameters of the brachiocephalic vessels, a transverse and longitudinal scanning of the middle third of the right and left common carotid arteries was performed, measuring the thickness of the intima-media complex and the subsequent calculation of the average values of the index (Atkov 2015, Devereux et al. 1986).

The laboratory tests included an assessment of complete blood and urine analyses; biochemical blood parameters (total cholesterol, triglycerides, HDL cholesterol, glucose, creatinine, sodium, potassium), determined by means of an automatic analyzer Furuno-CA-180 (Furuno Electric Co, Japan). The calculation of lipid-transport system parameters was carried out according to the standard formulas.

The quality of life of patients with hypertension was assessed using the SF-36 questionnaire. At the same time, psychosocial and physical status of patients was determined, described by the following scales: physical functioning (PF), role-based physical functioning (RPF), pain (P), vitality (V), social functioning (SF), role-based emotional functioning (REF), and mental health (MH) (Novik 2007).

The phenotype of oxidative metabolism was studied on the basis of the assessment of the pharmacokinetic parameters of the drug marker (Aminophylline), determined in biofluid (saliva) by the method of highly effective reversed-phase liquid chromatography (Milichrom chromatograph, Nauchpribor Ltd., Russia). The test indicator for determining the phenotype of oxidative metabolism was the half-life of the test drug: $T_{1/2}$ under 9 hours – patients with a rapid phenotype of oxidative metabolism; $T_{1/2}$ = 9–15 hours – people with a slow phenotype; $T_{1/2}$> 15 hours – patients with a very slow rate of oxidative metabolism (Kachmarskaya 1996).

The above research methods, as well as electrocardiography (electrocardiographs EK 12 T-01- RD, RF, SchillerAT-1, SCHILLERAG, Switzerland) were used in a placebo period and at the end of the 14th week of pharmacotherapy (except for the pharmacokinetic study). At the end of the 4th week of pharmacotherapy, the "office" values of blood pressure and heart rate were evaluated, and the 24-hour blood pressure monitoring was performed.

**Methods of pharmacoeconomic and statistical data analysis**

Pharmacoeconomic analysis was carried out using the method of "cost-effectiveness" (Industry Standard IS 91500.14.0001-2002 "Clinical and economic research. General provisions" 2002).

Due to the fact all the patients were placed in the equal conditions, provided by the design of the study and different only by the nature of the pharmacotherapy, direct expenses on medicines were considered as expenses. The data for calculating the expenses was obtained on the website www.apteka.ru from the price list adapted to Kursk region.

Mathematical data processing was carried out using the methods of parametric and non-parametric statistics, depending on the nature of the parameter distribution. The data in the study is presented in the form of M±SD (with a normal distribution) or the median and interquartile interval (with a distribution different from the norm). Differences were considered statistically significant with bilateral values of $p<0.05$. To eliminate erroneous estimates of the reliability of differences in parameters, in the multiple comparison of subgroups, the Bonferroni correction was used.

When comparing discrete quantities in a four-field table system using the $\chi 2$ criterion, the latter was evaluated with Yates' continuity correction. The presence and degree of the connection between the various parameters was assessed using a correlation analysis. To assess the significance of the influence of various factors on the studied parameters, we used analysis of variance. The determination of the degree of determinateness of the criterion (dependent) variable by predictors (independent variables), as well as the prediction of the value of the dependent variable using independent variables, was carried out using regression analysis.

## Results and discussion

**Comparative effectiveness of the studied pharmacotherapy regimens in patients with high and very high risk hypertension**

The pharmacodynamic effects of the studied pharmacotherapy regimens were evaluated at period of 4 (comparative evaluation of various options for the second stage of therapy) and 14 weeks (comparison of treatment regimens in the form of double, triple and quadrotherapy). In patients in each of the studied groups, both 4 and 14 weeks of therapy were accompanied by a significant decrease in blood pressure, heart rate, which was most pronounced at the end of the observation period (Table 1).

Comparative intergroup assessment of the intensity of the antihypertensive effect of different pharmacotherapy options at the end of the 4th week of treatment demonstrated the advantage of the fixed combination of Amlodipine

**Table 1.** Dynamics of Casual Values of Blood Pressure and Heart Rate in the Process of Pharmacotherapy in Patients of the Studied Groups.

| Indicators | Study period | | | p | | |
|---|---|---|---|---|---|---|
| | Before treatment | 4 weeks of treatment | 14 weeks of treatment | 1-2 | 1-3 | 2-3 |
| | 1 | 2 | 3 | | | |
| **Group 1** | | | | | | |
| SBP mm Hg | 183.0±10.2 | 160.2±12.2 | 148.0±14.3 | ***** | ********** | *** |
| DBP mm Hg | 106.8±6.59 | 96.0±6.22 | 88.7±9.18 | *** | *** | *** |
| Heart rate bpm | 82.0±6.39 | 79.1±8.74 | 72.3±9.90 | * | *** | *** |
| **Group 2** | | | | | | |
| SBP mm Hg | 180.0±5.41 | 158.0±10.8 | 148.0±14.9 | *** | **** | *** |
| DBP mm Hg | 106.6±5.79 | 95.8±6.39 | 87.7±9.53 | *** | *** | *** |
| Heart rate bpm | 79.4±6.71 | 76.7±5.05 | 70.3±7.85 | * | *** | *** |
| **Group 3** | | | | | | |
| SBP mm Hg | 183.1±9.16 | 145.7±17.3 | 137.5±19.1 | *** | *** | *** |
| DBP mm Hg | 104.7±6.27 | 89.6±9.96 | 84.5± 9.72 | *** | *** | *** |
| Heart rate bpm | 79.6±9.09 | 75.6±7.15 | 69.6±8.45 | ** | *** | *** |

and Lisinopril compared with their free combination, as well as with the combination of Amlodipine and Ramipril in relation to the degree of SBP reduction (-20.4%, -12.1%, -12.3 %, respectively, $p<0.001$). No significant differences between the groups by the DBP dynamics (-14.1%, -9.9%, -9.9%, respectively, $p>0.05$) and heart rate (-4.5%, -3.0%, -3.5%, respectively, $p>0.05$) were found. A similar pattern was notoced when comparing the degree of reduction in blood pressure and heart rate at the end of the 14th weeks of therapy. In the patients of Group 3, there was a significantly more pronounced decrease in SBP in comparison with the patients of Groups 1 and 2 (-24.9%, -19.0%, -17.8%, respectively, $p<0.01$), with insignificant differences in the degree of DBP (-19.1%, -16.6%, -17.4%, respectively, $p>0.05$) and heart rate (-12.1%, -11.7%, -11.1%, respectively, $p>0.05$).

The number of patients who reached the target level of blood pressure when using the second stage of pharmacotherapy was more significant in Group 3 (32.5%) compared with both Group 1 (10%, $p<0.05$) and Group 2 (12.5%, $p>0.05$). At the end of the 14th week of treatment, the difference between the groups in the number of patients having the target level of blood pressure was statistically unreliable (47.5%, 47.5%, 67.5%: in Groups 1, 2 and 3, respectively).

Evaluation of changes in the diurnal profile of blood pressure showed that all three groups had a positive reliable ($p<0.05$-$0.001$) dynamics of the main indicators of the 24-hour blood pressure monitoring in each of the analyzed periods of the day. Only the change in the daily index of blood pressure and parameters of blood pressure variability was insignificant ($p>0.05$). When conducting an intergroup comparison of the dynamics of ABPM indicators at the end of the 4-week therapy, significant differences were identified in relation to some parameters. In the patients of Group 3, in comparison with Group 1 and Group 2, the following parameters decreased more significantly: SBPd (Δ% 21.3 [11.5; 25.8], 11.9 [6.4; 18.5], 13.1 [7.2; 17.0], $p<0.01$, $p<0.01$, respectively), DBPd (Δ% 16.7 [7.0; 26.8], 12.3 [1.08; 18.9], 9.1 [2.5;14.7], $p>0.05$, $p<0.01$, respectively), TISBPd (Δ% 61.0 [15.5; 75.5], 12.8 [2.0; 34.0], 18.4 [3.0; 30.4], $p<0.001$, $p<0.001$, respectively), TIDBPd (Δ% 29.1 [13.3; 90.8], 24.3 [5.42; 52.9], 25.0 [5.2; 43.2], $p>0.05$, $p<0.05$, respectively), DBPn (Δ% 16.9 [6.7; 28.9], 11.4 [4.50; 22.4], 8.1 [-2.2; 18.9], $p>0.05$, $p<0.01$, respectively), SPB24h (Δ% 19.8 [10.2; 26.4], 13.4 [7.0; 17.9], 12.9 [7.5; 18.7], $p<0.01$, $p<0.01$, respectively), TISBP24h (Δ% 35.5 [7.6; 63.0], 11.6 [1.0; 31.0], 13.4 [2.5; 28.5], $p<0.01$, $p<0.01$, respectively). At the end of the 14th week of therapy, the differences between the groups were more leveled. In Group 3, comparing to Groups 1 and Group 2, the following parameters decreased more significantly: SBPd (Δ% 27.9 [14.3; 30.9], 17.6 [14.2; 25.9], 17.7 [11.3; 25.9], $p<0.05$, $p<0.05$, respectively), TISBPd (Δ% 86.7 [16.5; 93.6], 38.1 [7.5; 59.5], 43.4 [8.5; 70.0], $p<0.01$, $p<0.05$, respectively), TISBPn (Δ% 54.0 [3.5; 87.0], 22.0 [0.0; 52.5], 28.5 [0.0; 70.9], $p<0.05$, $p>0.05$, respectively), SBP24h (Δ% 26.0 [15.0; 31.9], 20.0 [11.1;25.8], 19.5 [12.2; 25.8], $p<0.01$, $p<0.05$, respectively).

The free combinations of Amlodipine and Lisinopril or Ramipril under study were comparable to one another in terms of pharmacodynamic effects both as the second stage of therapy in patients with high and very high risk

hypertension, and as the addition to the starting treatment regimens with beta-blockers and diuretics. However, both treatment options were inferior ($p<0.01–0.001$ to the fixed combination – Amlodipine and Lisinopril – in terms of the intensity of the hypotensive effect (degree of SBP reduction), frequency of early (by the end of the 4th week) achievement of the target level of BP. Moreover, this advantage was implemented with a more frequent prescription of the second stage of treatment to the patients of Group 3. A more pronounced and early achievement of a significant antihypertensive effect due to the optimization of combination therapy, is especially important for patients with grades 2-3 hypertension, because most of them have structural and functional changes in their target organs.

The results of the present study are comparable with the literature data showing that the fixed combination of Amlodipine and Lisinopril has high antihypertensive efficacy compared with other combinations of antihypertensive drugs. This fact was recorded both according to the daily monitoring of blood pressure, and during its routine measurement (Nedogoda et al. 2013, Ostroumova et al. 2017).

Thus, the use of a fixed combination of Amlodipine and Lisinopril, both as a starting therapy for patients with hypertension of high and very high risk, and in combination with drugs of the third and fourth stages of treatment, resulted in a more pronounced hypotensive effect and a more frequent early (at the end of the 4th week of therapy) achieving the target level of blood pressure.

**Assessment of the effect of the oxidative metabolism phenotype on the intensity of the hypotensive effect of drugs used in patients with high and very high risk hypertension**

The ability to conduct an analysis assessing the effect of a genetically determined rate of oxidative metabolism on the degree of hypotensive effect of the drugs used in the study was possible due to their pharmacokinetic characteristics. The latter was due to the fact that the only drug used (when implementing the second stage of pharmacotherapy), the pharmacodynamic effect of which depended on the rate of oxidative metabolism determined by the test drug, was Amlodipine. According to the literature, members of individual families and subfamilies, as well as individual isoenzymes of cytochrome P450, could have a "cross" substrate specificity, which made it possible to carry out an indirect assessment of the activity of one isoenzyme according to the test results of another using a marker drug (Beresford et al. 1988, Sychev et al 2007).

The data on the degree of reduction in blood pressure (presented in modular values) in different phenotypic groups in patients who had been receiving various options for the second stage of pharmacotherapy, are reflected in Table 2.

As follows from the data presented, the degree of BP reduction in patients with a slow and very slow phenotype of oxidative metabolism was significantly higher than that in patients with a fast variant of the oxidative process. The first two phenotypic groups also differed significantly from each other in terms of SBP reduction, except for the cohort of patients who had received a fixed combination of Amlodipine and Lisinopril. According to Δ% DBP, no significant differences between the slow and very slow oxidation phenotypes were found.

The degree of decrease in blood pressure in patients of Grup 1 with slow and very slow phenotypes of oxidative metabolism was significantly higher than that in patients with a fast variant of the oxidative process. The first two phenotypic groups also significantly differed by the degree of reduction of systolic blood pressure. In terms of a decrease in diastolic blood pressure, there were no significant differences between the slow and very slow phenotypes of oxidative metabolism.

Statistical analysis, evaluating the intensity of a decrease in blood pressure in various phenotypic groups in patients who received the free combination of Amlodipine and Lisinopril as starting therapy, revealed a relationship

**Table 2.** Degree (%) of Blood Pressure Reduction in Patients with Different Phenotypes of Oxidative Metabolism in the Studied Groups.

| Intervention groups | Indicators | Phenotypic groups | | | p | | |
|---|---|---|---|---|---|---|---|
| | | F | S | VS | 1-2 | 1-3 | 2-3 |
| | | 1 | 2 | 3 | | | |
| Group 1 | Δ%SBP | 6.42 [3.90;8.85] | 12.7±3.5 | 19.6±5.66 | ** | *** | *** |
| | Δ%DBP | 5.66 [0.39;8.16] | 10.6±6.39 | 16.6±5.14 | * | *** | na |
| Group 2 | Δ%SBP | 6.59 [4.07;6.59] | 13.1±1.73 | 21.6±3.09 | *** | *** | *** |
| | Δ%DBP | 5.66 [0.90;5.66] | 11.9±5.43 | 15.9±3.83 | *** | *** | na |
| Group 3 | Δ%SBP | 9.34 (6.25-14.1) | 24.6±4.41 | 27.9±6.54 | *** | *** | na |
| | Δ%DBP | 1.04 (-4.17-5.66) | 19.1±5.70 | 23.6±8.66 | *** | *** | na |

**Note.** F - fast phenotype of oxidative metabolism, S - slow phenotype of oxidative metabolism, VS - very slow phenotype of oxidative metabolism.

similar to the one observed in patients of the first intervention group. In Group 3, patients who had slow and very slow oxidative metabolism phenotypes were identical ($p > 0.05$) to each other in terms of blood pressure reduction in a 4-week therapy with a fixed combination of Amlodipine and Lisinopril and significantly outnumbered individuals with a high oxidation rate.

Gradations of the oxidative metabolism rate, considered as a determining factor when conducting analysis of variance, had a significant effect on the degree of reduction in SBP and DBP: for Group 1 – $F = 18.7$, $p<0.001$, $F = 9.89$, $p<0.001$, respectively; for Group 2 – $F = 46.1$, $p<0.001$, $F = 14.1$, $p<0.001$, respectively; for the patients of Group 3 – $F = 39.9$, $p<0.001$, $F = 33.0$, $p<0.001$, respectively.

A correlation analysis evaluating the interrelation of $T_{1/2}$ of the test drug and the degree of antihypertensive effect of therapy established a significant effect of the studied parameter on Δ% SBP and Δ% DBP in patients of Group 1 ($r = 0.59$, $p<0.001$; $r = 0.58$, $p<0.001$, respectively ); similar data were obtained from patients of Group 2 ($r = 0.83$, $p<0.001$; $r = 0.60$, $p<0.001$, respectively) and Group 3 ($r = 0.55$, $p<0.001$; $r = 0.64$, $p<0.001$, respectively).

The main objective of the regression analysis was the construction of regression equations, which make it possible to predict the intensity of the hypotensive effect with considerable probability when the second stage of therapy was used as the starting one, based on the free or fixed combination of Amlodipine with Lisinopril or Ramipril. In this case, the dependent parameter was the degree of reduction in SBP and DBP, and the half-life of the test drug and baseline BP values served as independent indicators. Regression analysis was performed with respect to the indicated parameters, assessed at the end of the 4-week therapy, since in that case the use of regression equations would allow to predict the efficacy of pharmacotherapy and optimize the choice of starting treatment options. The choice of parameters for regression analysis depended on the presence of a significant correlation between pharmacokinetic and hemodynamic parameters. In addition to the above-mentioned correlations between $T_{1/2}$ and Δ%BP, the latter was determined by its initial level. When evaluating the 4-week treatment of patients of Group 1, Δ% SBP reliably correlated with the initial value of the SBP ($r = 0.32$, $p<0.05$), Δ% DBP – with the initial level of DBP ($r = 0.63$, $p<0.001$). In Group 2, the initial levels of SBP and DBP were significantly correlated with the magnitude of their decrease ($r = 0.41$, $p<0.01$, $r = 0.54$, $p <0.001$, respectively). The initial SBP level in patients of Group 3 did not have a significant correlation with Δ% SBP ($r = 0.055$, $p>0.05$), while the baseline values of DBP significantly correlated with the magnitude of their decrease ($r = 0.45$, $p<0.01$).

Indicators of regression analysis carried out in the studied groups of patients, characterizing the intensity of the linear relationship between dependent (Δ% SBP, Δ% DBP) and independent ($T_{1/2}$ initial levels of SBP and DBP) variables indicate its reliability (Table 3).

The regression equations, allowing calculating the predicted hypotensive effect of the 4-week therapy, were as follows:

for the free combination of Amlodipine and Ramipril

$$\Delta\%SBP = -57.9+0.995\cdot T_{1/2}+0.318\cdot SBP_{ini};$$

$$\Delta\%DBP = -64.5+0.758\cdot T_{1/2}+0.611\cdot DBP_{ini,}$$

for the free combination of Amlodipine and Lisinopril

$$\Delta\%SBP = -62.9+1.032\cdot T_{1/2}+0.352\cdot SBP_{ini};$$

$$\Delta\%DBP = -83.8+0.967\cdot T_{1/2}+0.775\cdot DBP_{ini,,}$$

for the fixed combination of Amlodipine and Lisinopril

$$\Delta\%SBP = -37.4+1.149\cdot T_{1/2}+0.247\cdot SBP_{ini};$$

$$\Delta\%DBP = -78.7+1.398\cdot T_{1/2}+0.741\cdot DBP_{ini,}$$

where $SBP_{ini}$ и $DBP_{ini}$ – initial levels of SBP and DBP, respectively.

**Table 3.** Results of the Regression Analysis of the Dependence of Δ% BP on its Initial Level and the $T_{1/2}$ of Test Drug in the Studied Patients During the 4-week Pharmacotherapy.

| Regression Analysis Criteria | Δ%SBP | Δ%DBP |
|---|---|---|
| **Group 1** | | |
| Multiple correlation coefficient (R) | 0.778 | 0.791 |
| Determination coefficient ($R^2$) | 0.606 | 0.625 |
| F-criterion | 28.4 | 23.4 |
| $p_{F\text{-criterion}}$ | <0.001 | <0.001 |
| **Group 2** | | |
| Multiple correlation coefficient (R) | 0.880 | 0.860 |
| Determination coefficient ($R^2$) | 0.770 | 0.750 |
| F-criterion | 63.0 | 54.6 |
| $p_{F\text{-criterion}}$ | <0.001 | <0.001 |
| **Group 3** | | |
| Multiple correlation coefficient (R) | 0.60 | 0.770 |
| Determination coefficient ($R^2$) | 0.360 | 0.590 |
| F-criterion | 10.5 | 27.2 |
| $p_{F\text{-criterion}}$ | <0.001 | <0001 |

In the regression equations calculated for Groups 1 and 2, all β-coefficients of the equations were highly significant ($p<0.001$). The coefficient of determination explained more than 60% of variations of the dependent variable in Group 1 and not less than in ¾ patients of Group 2. In the formula for calculating Δ% SBP for Group 3, the intercept of the equation and the β-coefficient $SBP_{ini}$ were statistically insignificant. However, the exclusion of the initial values of the SBP from the parameters of the regression equation led to the deterioration of the latter, and therefore this indicator was left in the list of independent parameters of the regression equation. The constructed equation was not characterized by a high degree of coverage of the variation of Δ%SBP, but it was also reliable. The coefficient of determination of the equation for calculating the Δ% DBP in the Group 3 of patients explained the variations in the dependent variable in more than half of the patients in Group 3. All β - coefficients of this equation were highly significant ($p<0.001$).

The reduction of the forecast accuracy (by the variable component) of a decrease in blood pressure to the average value for all the three options of starting pharmacotherapy is characterized by a rather high percentage – 61.7% – of the sample of patients with high and very high risk of AH who will have a coincidence of theoretical and actual values Δ% BP.

Thus, the conducted multivariate analysis showed the dependence of the degree of blood pressure reduction on the phenotypic variant of oxidative metabolism, assessed during the 4-week treatment of hypertensive patients with different second-stage antihypertensive therapy with Amlodipine and Lisinopril or Ramipril. Personalization of antihypertensive therapy could be achieved by assessing the phenotype of oxidative metabolism in patients with hypertension using drugs, pharmakokinetics of which ensured the polymodal nature of the pharmacodynamic response of patients to pharmacological intervention. Adequate prediction of the hypotensive effect could be achieved in almost 2/3 of patients using regression equations obtained in the study.

**The influence of various variants of combined pharmacotherapy on the morphofunctional parameters of the cardiovascular system, laboratory parameters, quality of life of patients with high and very high risk hypertension**

The structural parameters of the left ventricle in patients with high and very high risk hypertension favorably changed during the 14-week therapy in all the three intervention groups. The main criterion of LV myocardial hypertrophy – MMI decreased in patients of Group 1 from 153.5326.2 to 144.8±27.3 g/m$^2$ ($p<0.001$), in Group 2 – from 153.7±25.6 to 144.9±24.8 g/m$^2$ ($p<0.001$), in Group 3 – from 150.5±28.7 to 137.4±28.0 g/m$^2$ ($p<0.001$). Intergroup analysis revealed the priority of the treatment regimen used in Group 3 of patients according to the impact on the degree of left ventricular IMM reduction in comparison with the pharmacotherapy options of patients in Groups 1 and 2. The integral parameter reflecting the systolic function of the LV – EF increased equally in each of the three studied groups of patients (in Group 1 from 62.9±4.13 to 63.7±4.73%, $p<0.05$; in Group 2 from 62.8±5.73 to 63.4±5.49%, $p<0.05$; in Group 3 from 63.3±4.69 to 64.5±4.51%, $p<0.01$). The thickness of the carotid intima-media complex did not significantly change during the observation period.

The study showed a positive effect of the used treatment regimens for patients with hypertension, on the structural indicators of the heart – regression of LV myocardial hypertrophy. The literature data on the timing of the development of LVH regression in patients with hypertension under the influence of pharmacotherapy is quite contradictory. Many researchers believe that a significant reduction in LVMM can be obtained at least after 6 months of treatment. At the same time, there are a number of studies, where an earlier (after 3-4 months) statistically significant change in the value of the structural parameters of the heart was shown.The study by Ostroumova et al. (2017) shows that fixed combinations (Amlodipine and Lisinopril; Bisoprolol and Hydrochlorothiazide) statistically significantly reduced the severity of LVH (moreover, the A/L combination did significantly better), having reduced the left ventricular myocardial mass index and left ventricular wall thickness, despite the relatively small period (12 weeks).

A fairly rapid and significant regression of the left ventricular MMI in patients with hypertension can be caused by various factors, in particular, the presence of baseline LVH, a combination of drugs that have the most pronounced effect on the regression of LV myocardial hypertrophy (Kakhramanova and Bakhshaliev 2008, Prokofyeva and Glezer 2015, Terpstra et al. 2001). The basic combinations of the drugs used in the study – ACE inhibitors and CCB – are leaders by their ability to reduce the LV myocardium mass (Fagard et al. 2009).

Dynamic control of biochemical blood parameters indicated the absence of a negative effect of the used pharmacotherapy on the studied parameters. A number of blood lipid spectrum indicators had a significant positive trend when using each of the three pharmacotherapy regimens: in Group 1, the cholesterol level decreased from 6.43±0.80 to 6.0±0.74 mmol/l ($p<0.001$), LDL – from 4.41±0.92 to 3.89±0.84 mmol/l ($p<0.001$); in Group 2, cholesterol – from 6.14±0.96 to 5.91±0.84 mmol/l ($p<0.01$), cholesterol LDL – from 3.97±0.91 to 3.80±0.82 mmol/l ($p<0.05$); in Group 3, cholesterol – from 6.36±0.86 to 5.81±0.79 mmol/l ($p<0.001$), cholesterol LDL – from 4.39±0.88 to 3.79±0.88 mmol/l ($p<0.001$). This effect was caused by several factors: the used lipid-lowering therapy, metabolic neutrality and pleiotropic effects of the hypotensive agents used. A more pronounced ($p<0.05$-$0.01$) decrease in LDL cholesterol was observed in patients of Groups 1 and 3 compared to the patients of Group 2.

The biochemical parameters evaluated in the present study did not undergo any negative changes in the treat-

ment process of each of the three studied treatment regimens. The positive dynamics of the indicators of the lipid and carbohydrate metabolism, recorded in the paper may be the result of the administration of the basic therapy (statins), the presence of metabolic neutrality and pleiotropic effects in the used drugs.

The indicators of the quality of life of patients, assessed over the entire observation period, were characterized by significant ($p<0.001$) positive dynamics in both mental and physical health parameters in each of the three observation groups. The use of a fixed combination of Amlodipine and Lisinopril as a basic treatment option for patients with hypertension compared to free combinations of ACE inhibitors and CCB allowed for a more significant improvement in a number of parameters of patients' quality of life: pain scale, general health, social functioning, and mental health (Fig. 2). The scale of physical functioning was significantly higher in patients of Group3 compared with Group 2.

In the study performed, the indicators of the quality of life of the examined patients, assessed over the entire observation period, were characterized by significant positive dynamics in both mental and physical health parameters in the three observation groups. The use of a fixed combination of Amlodipine and Lisinopril as a baseline of two-four component therapy for patients with high and very high risk of arterial hypertension, in comparison with the starting treatment regimens in the form of free combinations of Amlodipine and Lisinopril or Ramipril, was accompanied by significant ($p<0.05$-$0.001$) improvements in a number of parameters of the patients' quality of life: scales of physical functioning, pain, general health, social functioning, mental health. The indicated dynamics of the quality of life of patients with hypertension was associated with a significant ($p<0.001$) decrease in blood pressure in each of the studied groups at the end of the observation period.

Our data conceptually coincides with the results of the EXPERT program, which showed that the use of a fixed combination of Amlodipine and Lisinopril, as a replacement for previous therapy with various ACE inhibitors, sartans and CCB, led to a rapid, pronounced safe decrease in blood pressure, improved quality of life in the majority of patients with previously uncorrected blood pressure (Glezer et al. 2014).

Thus, complex antihypertensive therapy of patients with high and very high risk hypertension during 14 weeks improved the structural and functional parameters of the left ventricle, improved the quality of life of patients, and was safe in terms of influence on lipid, carbohydrate and electrolyte exchanges. The greater manifestation of the positive dynamics of the above parameters was characteristic of patients of Group 3 comparing to those of Groups 1 and 2.

## Pharmacoeconomic analysis of various options for complex pharmacotherapy of patients with high and very high risk hypertension

The following criteria of the efficacy of the treatment required for conducting a clinical and economic analysis were used: degree (mm Hg) of SBP and DBP reduction; the frequency of achieving target blood pressure in patients of Groups 1, 2 and 3 at the end of the 4th and 14th week of pharmacotherapy;

The total cost of pharmacotherapy in patients of Group 1 by the end of the 4th weeks of treatment was 31,012.8 rubles, at the end of the 14th weeks – 143890.6 rubles. (per patient – 775.3 rubles and 3597.3 rubles, respectively). For patients of Group 2, the corresponding indicators

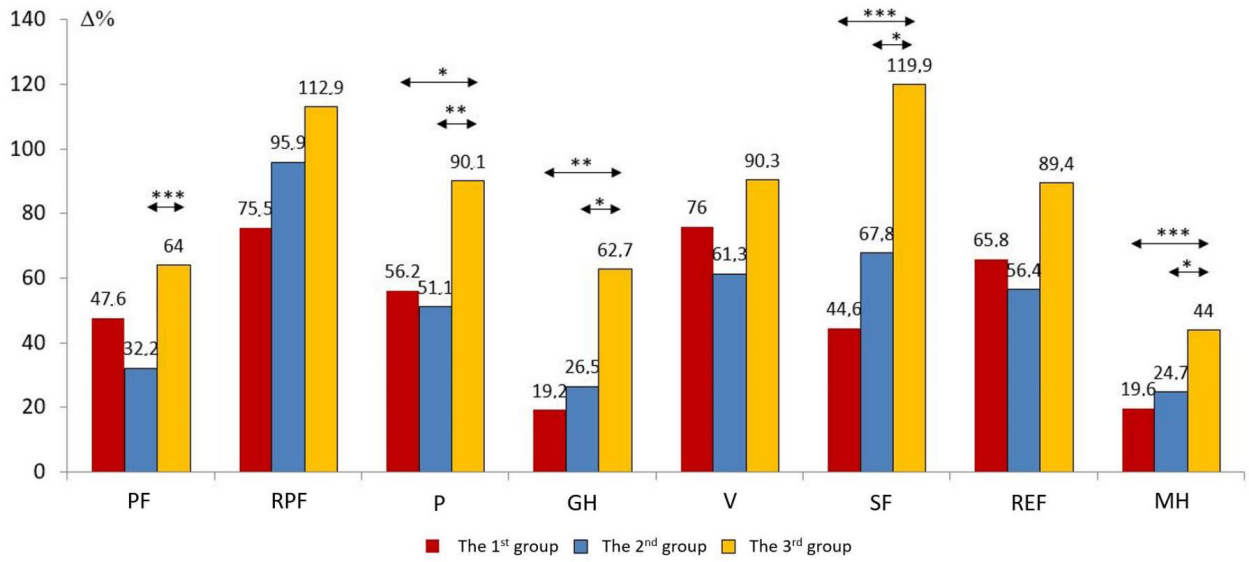


**Figure 2.** Comparative influence of various pharmacotherapy regimens on the quality of life of patients with hypertension.
Note. Δ% – degree of change in percentage, PF – physical functioning, RPF – role physical functioning, P – pain, GH – general health, V – vitality, SF – social functioning, REF – role emotional functioning, MH – mental health, * – significance of differences, $p<0.05$, ** – significance of differences, $p<0.01$, *** – significance of differences, $p<0.001$.

were equal to 31889.2 rubles and 150630.1 rubles (per patient – 797.2 rubles and 3765.7 rubles, respectively). In Group 3, the similar parameters amounted to 23753.8 rubles and 105723.8 rubles, respectively (per patient – 593.8 rubles and 2643.1 rubles, respectively). The results of the calculation by the method of "cost-effectiveness" of the cost of reducing blood pressure by 1 mm Hg and the cost of achieving the target level of blood pressure in one patient with the implementation of various options for pharmacotherapy in different periods of treatment are presented in Figure 3.

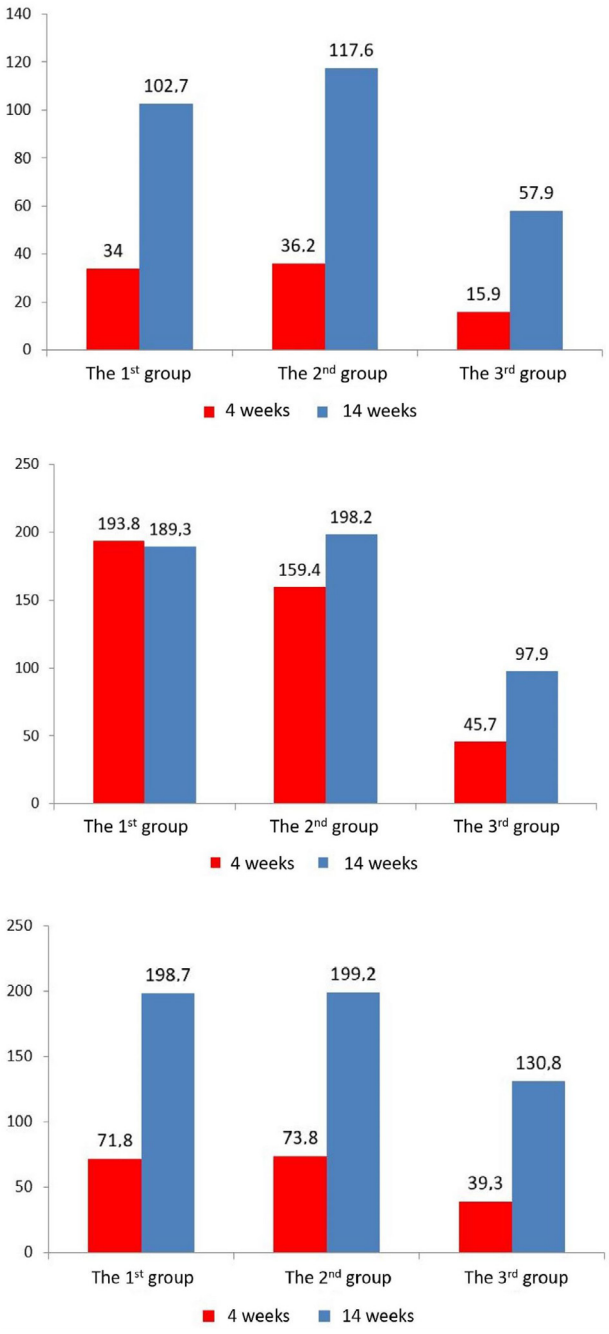


**Figure 3.** The average cost (rub.) of reducing SBP (A), DBP (B) by 1 mm Hg and the cost of achieving the target blood pressure (C) in one patient in each of the studied groups at different periods of observation.

Minimizing costs when using a fixed combination of Amlodipine and Lisinopril compared with the free combinations of Amlodipine with Ramipril or Lisinopril, depending on the chosen efficacy criterion, led to minimization of costs from 18.1 rubles to 148.1 rubles per patient.

Our data match the results of studies on assessing the introduction of fixed combinations of drugs in the management of patients with hypertension with both initial therapy and low effecacy of previous strategies. Those studies demonstrated the cost-effectiveness of such an approach. It turned out that the separate administration of drugs in comparison with the fixed combination of the same substances was accompanied by significantly bigger (up to 65%) total costs for patient management. At the same time, the patients' adherence to the treatment (calculated according to the implementation of prescription formulations in the pharmaceutical database) was by 14.4% higher in the group treated with the drugs in the form of fixed combinations (Filippi et al. 2009, Mori et al. 2006).

Different types of pharmacoeconomic studies indicate that when using fixed combinations of drugs, improvement in BP control is accompanied by a decrease in the total cost of providing medical care compared to the same, but separate combinations, primarily due to a decrease in the number of hospitalizations, visits to doctors, costs of other drugs (Kobalava et al. 2007).

Thus, the use of the fixed combination of Amlodipine and Lisinopril as a starting therapy, as well as when transferring patients with high and very high risk of hypertension to the third and fourth stages of treatment, in comparison with alternative pharmacotherapy regimens, provided the least expensive treatment option.

## Conclusion

The study investigated the method of personalization of pharmacotherapy of patients with high and very high risk arterial hypertension, based on the determination of the oxidative metabolism phenotype. When a slow or very slow phenotype of oxidative metabolism is detected in patients, it is preferable to administer Amlodipine with Lisinopril or Ramipril to ensure the greatest degree of hypotensive effect in this cohort, compared with patients in the phenotypic group with a high rate of oxidative biotransformation.

Using the developed regression equations allows determining the predicted degree of hypotensive effect of the studied options of starting pharmacotherapy (combination of Amlodipine with Lisinopril or Ramipril) of patients with arterial hypertension of high and very high risk, which makes it possible to further individualize the treatment of the specified patient population.

In patients with arterial hypertension of high and very high risk, the pharmacodynamic and pharmacoeconomic advantage of the fixed combination of Amlodipine and Lisinopril is shown both as a starting treatment opti-

on and in combination with drugs of the third and fourth stages of treatment, compared with the free combinations of the studied drugs. This advantage was expressed in a significantly more significant hypotensive effect, an earlier achievement of the target blood pressure level, a significantly higher degree of regression of left ventricular myocardial hypertrophy, a significant improvement in a number of patients' quality of life indicators: physical functioning, pain, general health, social functioning, mental health, and it was also characterized by the lowest cost-effectiveness ratios according to various criteria of the hypotensive effect.

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