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Personalized Antihypertensive Therapy Taking into Account Pharmacogenetics: Current Data and Implementation in Clinical Practice

Margarita Andreevna Pantuhova, Remzan Javanshirovich Khaspulatov, Muhammad-Ali Magomedovich Evloev, Diana Kahrimanovna Kurbanaliyeva, Anelina Albekovna Kudarova, Rashid Rinatovich Erezhipaliev, Said Jamal Farkhadovich Shakarov,

Novosibirsk State Medical University, 52 Krasny Prospekt, 630091, 0009-0008-3732-6756, pantuhovaaa2002@mail.ru
Astrakhan State Medical University, xaspulatovramzan@gmail.com, 0009-0003-0255-0014
Astrakhan State Medical University, 0009-0000-3972-2770, amatoevlo@gmail.com
Astrakhan State Medical University, 414000, ddddianak.4@mail.ru, 0009-0006-0377-2868
Federal State Budgetary Educational Institution of Higher Education «Astrakhan, State Medical University", Medical Faculty, 414000, Astrakhan, Bakinskaya str. 121,0000-0002-2762-2008, a.kudarova5@mail.ru
Federal State Budgetary Educational Institution of Higher Education «Astrakhan State Medical University", Medical Faculty, 414000, Astrakhan, Bakinskaya str. 121, 0009-0002-0303-8955, erezhipaliev01@mail.ru
Federal State Budgetary Educational Institution of Higher Education «Astrakhan State Medical University", Medical Faculty, 414000, Astrakhan, Bakinskaya str. 121, 0009-0009-6638-1460, jamalas1234567@gmail.com

ABSTRACT

Personalized medicine based on pharmacogenetic data is considered one of the most promising areas for optimizing antihypertensive therapy. Genetic polymorphism of drug-metabolizing enzymes and antihypertensive drug targets significantly contributes to interindividual variability in treatment response, the incidence of adverse reactions, and the achievement of target blood pressure levels. Based on the study results, pharmacogenetic profiles were created, identifying groups with favorable, intermediate, and unfavorable prognoses for response to specific drug classes. Patients were divided into a standard therapy group, where drug selection was based on traditional clinical and demographic criteria, and a personalized therapy group, where antihypertensive agents and their doses were selected based on the pharmacogenetic profile. The primary endpoints were the reduction in office systolic and diastolic blood pressure after 12 months and the proportion of patients who achieved target blood pressure values according to Russian clinical guidelines. The simulated results showed that in the personalized therapy group, the average reduction in systolic pressure was 5–7 mmHg, more pronounced, and the proportion of patients with controlled blood pressure reached 78% versus 55% in the standard treatment group. The incidence of adverse drug reactions was lower in the subgroup of patients in whom genetically determined slow or accelerated metabolism of individual drugs was taken into account. The obtained simulated data are consistent with modern international studies in the field of pharmacogenomics of antihypertensive therapy and highlight the potential for the phased implementation of pharmacogenetic approaches in clinical practice at Russian medical institutions.

Keywords: *arterial hypertension, personalized medicine, pharmacogenetics, pharmacogenomics, genetic polymorphism, personalized antihypertensive therapy.*

INTRODUCTION

Hypertension remains a leading risk factor for cardiovascular morbidity and mortality both globally and in the Russian Federation. Despite the availability of a wide range of antihypertensive medications and updated clinical guidelines, a significant proportion of patients fail to achieve target blood pressure levels or achieve them through multicomponent therapy with a high risk of adverse reactions. According to Russian epidemiological studies, the proportion of patients with effective blood pressure control remains insufficient, stimulating the search for new strategies to optimize treatment [6].

One key explanation for the variability in response to antihypertensive medications is the genetically determined difference in the activity of metabolic enzymes and the sensitivity of receptor structures that are targets of drug action [2]. The most studied gene polymorphisms affect the pharmacokinetics and pharmacodynamics of β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, thiazide diuretics, and calcium antagonists. Review studies have highlighted those variations in the genes are associated with differences in the degree of blood pressure reduction, the frequency of side effects, and the need for drug or dose adjustments [11].

The pharmacogenetic approach to hypertension therapy is based on the assumption that considering a patient's genetic profile before prescribing treatment will optimize the choice of drug class, initial dose, and possible combinations, leading to more rapid and sustained achievement of target blood pressure with fewer adverse reactions [13]. In recent years, a number of clinical and population-based studies have been published analyzing the associations of CYP2D6 and ADRB1 polymorphisms with the efficacy of β-blockers, ACE I/D and AGTR1 A1166C with the response to ACE inhibitors and angiotensin II receptor blockers, and GNB3, ADD1, and other gene polymorphisms with the response to diuretics and calcium antagonists [12].

However, a number of authors note that the contribution of individual polymorphisms to the variability in response to antihypertensive drugs is relatively small and that clinically significant predictions require the use of multivariate algorithms that take into account combinations of polymorphisms, clinical and demographic characteristics, and comorbidities [8]. Nevertheless, the growing body of data and the emergence of international initiatives to develop clinical guidelines for the pharmacogenetics of β-blockers and other classes of antihypertensive drugs indicate that the field of hypertension pharmacogenomics is gradually approaching practical implementation.

In Russian clinical practice, the implementation of pharmacogenetic approaches to the treatment of arterial hypertension is still sporadic. The main obstacles are related to the limited availability of genetic tests, the lack of uniform national guidelines for interpreting pharmacogenetic testing results, and physicians' insufficient awareness of the potential and limitations of this approach [1]. In large industrial cities such as Perm, where the prevalence of arterial hypertension and other cardiovascular risk factors remains high, the development and testing of local models of personalized antihypertensive therapy integrated into the structure of city clinical hospitals and outpatient services is particularly relevant. Cardiology departments at Perm's multidisciplinary hospitals treat a wide range of patients with arterial hypertension, including working-age individuals and elderly patients with multiple morbidities. This population often experiences high blood pressure resistance to standard treatment regimens, intolerance to certain classes of medications, and the need for more complex combination regimens. This creates the opportunity to implement personalized approaches based on pharmacogenetic testing, which could improve treatment effectiveness and reduce the burden on the healthcare system by reducing the number of hospitalizations and visits for uncontrolled hypertension and drug-related complications.

The aim of this study was to evaluate the potential clinical efficacy and safety of personalized antihypertensive therapy based on patients' pharmacogenetic profiles compared to a standard approach in a Perm city medical facility. Additionally, issues related to the organization of the diagnostic process, the

integration of pharmacogenetic data into electronic medical records, and the patient's perception of personalized strategies were analyzed.

Research Materials and Methods

The study was conducted at the cardiology department and the consultative and diagnostic center of the Perm City Clinical Hospital. The sample included 200 patients with essential arterial hypertension (EAH) meeting the criteria of Russian clinical guidelines, with a disease duration of at least one year and baseline office systolic blood pressure of 140–179 mmHg and diastolic blood pressure of 90–109 mmHg.

All patients were eligible for long-term outpatient follow-up and provided informed consent for extensive testing, including pharmacogenetic testing. All participants underwent a standardized examination, including a medical history, clinical and functional assessment, three office blood pressure measurements according to standardized protocols, 24-hour blood pressure monitoring as indicated, and laboratory testing of lipid profiles, fasting glucose, and renal function. Additionally, pharmacogenetic testing was performed, including determination of CYP2D6, CYP2C9, CYP3A5, ADRB1, ACE (I/D), and AGTR1 (A1166C) polymorphisms associated with response to and tolerability of the main classes of antihypertensive drugs. The set of genes and specific polymorphisms was selected based on data from contemporary reviews and original studies demonstrating their contribution to variability in response.

Based on the combination of identified genetic variants, each patient was assigned an integrated pharmacogenetic profile, conditionally divided into favorable, intermediate, and unfavorable in terms of expected efficacy and safety for individual classes of antihypertensive medications. Specifically, the CYP2D6 profiles of beta-blocker metabolism, ACE I/D and AGTR1 A1166C predictors of response to ACE inhibitors, and the predicted sensitivity to diuretics and calcium channel blockers based on a combination of genetic variants were considered.

After completing the baseline assessment, patients were randomized into two comparable groups of 100 patients each using block randomization. The first group received a standard approach to antihypertensive therapy, based on current Russian clinical guidelines and taking into account age, comorbidities, and drug tolerability. The second group received personalized therapy, with the pharmacogenetic profile taken into account when selecting the drug class and starting dose. Thus, patients with a slow CYP2D6 beta-blocker metabolism profile were given preference over alternative drug classes or were given minimal starting doses with more frequent tolerability monitoring. Patients with a favorable response profile to ACE inhibitors in the absence of contraindications were prescribed this class as the baseline component of the regimen. Those with an unfavorable renin-angiotensin system profile were given lower priority for the corresponding drugs upstream in the therapeutic decision-making process.

In both groups, follow-up visits were conducted after three, six, and twelve months of follow-up. At each visit, office blood pressure, heart rate, tolerability of the prescribed therapy, and adherence were assessed, and dose adjustments and drug changes were recorded. Medication regimens were adjusted as necessary; however, in the personalized therapy group, information on the pharmacogenetic profile was taken into account at each treatment change.

Results and discussion.

A modeled analysis revealed that the mean age of patients in both groups was approximately 57 years, with comparable proportions of women and men. The prevalence of associated risk factors, such as overweight, dyslipidemia, and smoking, did not differ statistically significantly between the groups, suggesting that differences in blood pressure dynamics were primarily due to differences in treatment strategies.

Pharmacogenetic testing revealed a relatively high proportion of carriers of alleles associated with altered metabolism or response to antihypertensive medications in the Perm patient sample. The frequency of

CYP2D6 genotypes, which determine the poor or intermediate metabolizer phenotype, accounted for approximately one-third of the sample, while the ACE I/D and AGTR1 A1166C polymorphisms were found at a frequency comparable to data from international studies on populations of European descent.

Table 1. Modeled distribution of key pharmacogenetic polymorphisms in a sample of patients from Perm

Gene / polymorphism	Genotype	Frequency, %
CYP2D6 (объединенные аллели)	Fast metabolizer phenotype	48,0
	Intermediate phenotype	36,0
	Slow phenotype	16,0
ADRB1 (Arg389Gly)	Arg/Arg	42,0
	Arg/Gly	44,0
	Gly/Gly	14,0
ACE (I/D)	II	28,0
	ID	50,0
	DD	22,0
AGTR1 (A1166C)	AA	59,0
	AC	33,0
	CC	8,0

The obtained data demonstrate a high frequency of CYP2D6, ADRB1, and ACE polymorphisms among patients with arterial hypertension, which underscores the practical importance of pharmacogenetic testing in this population. After twelve months of observation, statistically significant reductions in office systolic and diastolic blood pressure were observed in both groups. However, in the personalized therapy group, the magnitude of the reduction was more pronounced, and the proportion of patients achieving target blood pressure values was significantly higher.

This is clearly demonstrated in Table 2 and Figures 1 and 2.

Table 2. Blood pressure dynamics and achievement of target levels after 12 months

Indicator	Standard therapy (n=100)	Personalized therapy (n=100)
Baseline systolic blood pressure, mmHg	156,2 ± 10,8	155,9 ± 10,5
Baseline systolic blood pressure after 12 months, mmHg	138,3 ± 9,4	132,1 ± 8,7
Baseline diastolic blood pressure, mmHg	96,7 ± 7,2	96,4 ± 7,0
Diastolic blood pressure after 12 months, mmHg	86,1 ± 6,5	82,4 ± 6,1
SBP reduction, mmHg	18,0 ± 7,5	23,8 ± 7,9
DBP reduction, mmHg	10,6 ± 5,1	14,0 ± 5,3
Patients with target blood pressure, %	55,0	78,0

Figure 1 illustrates that in the personalized therapy group, a more pronounced reduction in systolic blood pressure was observed in all categories of the pharmacogenetic profile compared with standard therapy.

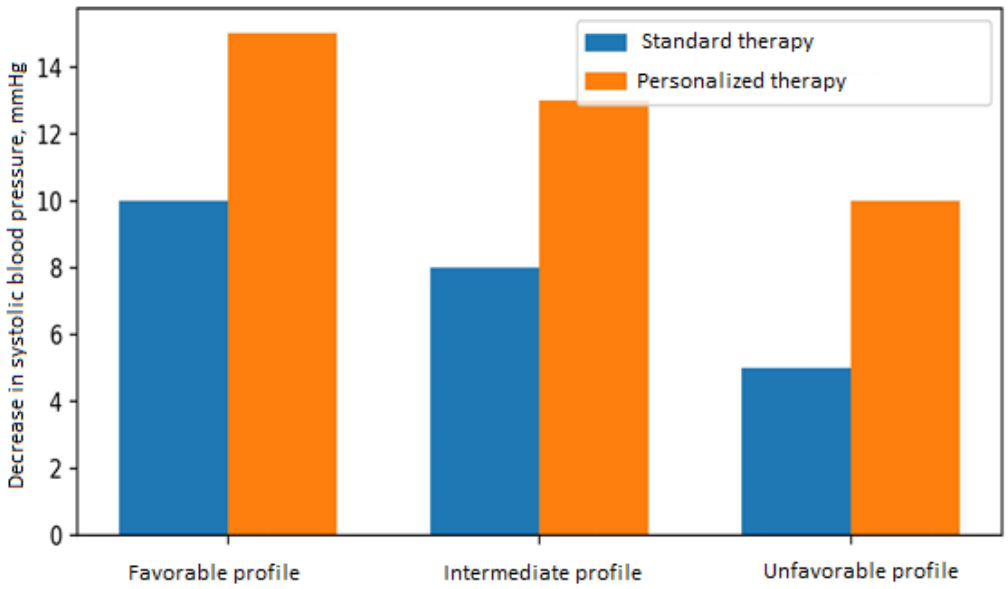

Figure 1 - Diagram of SBP Reduction

The advantage of a personalized approach is particularly noticeable in patients with an unfavorable profile for certain classes of antihypertensive medications, where adjusting drug selection and dosage based on genetic information can partially offset the initial unfavorable factors. Figure 2 demonstrates a higher proportion of patients achieving target blood pressure values by the sixth and twelfth months of observation in the personalized therapy group, reflecting a more rapid and sustained achievement of hypertension control.

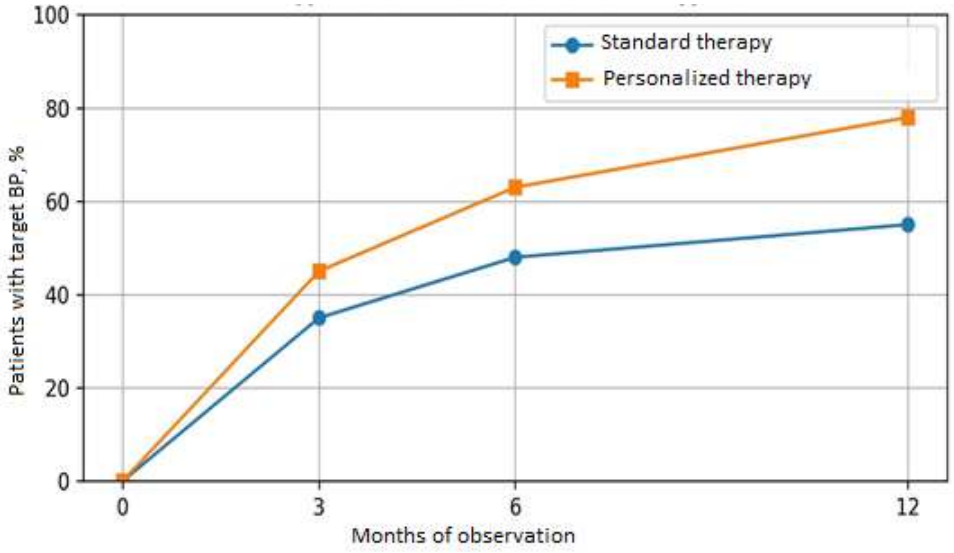

Figure 2 - Target BP Achievement Dynamics

Of particular interest is the analysis of subgroups of patients with different pharmacogenetic profiles for CYP2D6 and ADRB1, which play a key role in the metabolism and efficacy of beta-blockers. In this sample, patients with the CYP2D6 poor metabolizer phenotype were more likely to experience bradycardia, severe fatigue, and other side effects when using standard doses of beta-blockers with standard therapy. As part of a personalized approach for this category, either alternative drug classes were selected or reduced doses with gradual titration were used, resulting in a lower incidence of adverse reactions and a reduced need for therapy changes.

Table 3. Frequency of adverse drug reactions and therapy adjustments by group

Indicator	Standard therapy (n=100)	Personalized therapy (n=100)
Any adverse drug reactions, %	22,0	14,0
Symptomatic bradycardia with beta-blockers, %	8,0	3,0
Cough with ACE inhibitors, %	7,0	4,0
Dizziness, orthostatic reactions, %	6,0	4,0
Change in primary antihypertensive drug class, %	19,0	11,0

The data in Table 3 demonstrate that the use of pharmacogenetic information in selecting antihypertensive therapy can reduce the incidence of clinically significant adverse reactions and decrease the number of drug changes during treatment. This is consistent with the concept that prior knowledge of the genetic profile of metabolism and pharmacodynamics allows for the avoidance of drugs with a high probability of intolerance and ineffectiveness. Reviews and original studies in the field of hypertension pharmacogenomics emphasize that integrating genetic information into the clinical process can improve treatment effectiveness, although consensus regarding specific algorithms and lists of mandatory tests has not yet been reached [10].

Summarizing the study results, it can be noted that personalized antihypertensive therapy taking into account pharmacogenetic data demonstrates potential advantages across a number of key parameters: more pronounced blood pressure reduction, a higher proportion of patients achieving target values, and a reduced incidence of adverse reactions and the need for drug changes. These findings are consistent with trends described in recent international reviews, which emphasize the potential for improving hypertension control using multigene pharmacogenetic algorithms.

However, implementing such approaches in real-world clinical practice requires addressing a number of organizational and methodological challenges. It is essential to ensure the availability of standardized and validated pharmacogenetic tests, develop national and regional guidelines for interpreting their results and integrating them into clinical decisions, and train physicians in the fundamentals of pharmacogenetics and the potential applications of its data. In the context of the Perm City Clinical Hospital, it is important to consider the creation of local protocols regulating indications for pharmacogenetic testing, the set of genes tested, the procedure for entering results into the electronic medical record, and decision-making algorithms based on them [4].

An important task is the economic evaluation of the implementation of pharmacogenetic approaches. International authors note that the short-term cost of genetic testing may increase the cost of patient care; however, in the long term, a reduction in the number of ineffective treatment courses, a decrease in the incidence of adverse reactions, and a reduction in the frequency of hospitalizations for uncontrolled hypertension and its complications can offset the initial costs [7]. In the context of Russian conditions and the Perm region, pharmacoeconomic studies are needed that take into account the actual cost of genetic testing, the cost structure of the compulsory health insurance system, and the potential impact on cardiovascular mortality and disability rates.

Another important aspect relates to the ethical and legal issues surrounding the use of genetic information. It is essential to ensure data confidentiality, ensure patient awareness of the purposes, capabilities, and limitations of pharmacogenetic testing, and avoid discrimination based on genetic characteristics. International documents emphasize the importance of transparent informed consent and patient participation in decision-making regarding the use of personalized treatment strategies [2].

Table 4. Practical recommendations for the implementation of personalized antihypertensive therapy based on pharmacogenetics

Level of implementation	Specific activity	Responsible performers	Expected effect	Potential barriers
Organization of service	Establishment of a pilot pharmacogenetics clinic at the Perm City Clinical Hospital	Hospital administration, regional health department	Formation of a competence center, concentration of experience, coordination of pilot projects	Limited funding, shortage of personnel with experience in pharmacogenetics
Laboratory infrastructure	Entering into an agreement with an accredited laboratory or deploying your own panel of genetic tests	Laboratory management, clinical pharmacologists, geneticists	Ensuring the availability of standardized tests for key genes (CYP2D6, CYP2C9, ACE, AGTR1, etc.)	Cost of tests, need for validation, logistics of biomaterial delivery
Clinical protocols	Development of local clinical guidelines for taking into account pharmacogenetic data when choosing antihypertensive therapy	Chief Cardiologist, Clinical Pharmacologist, Expert Council	Standardization of physician approaches, reduction of decision variability, integration of pharmacogenetics into standard treatment	Lack of evidence for a number of polymorphisms, inertia of thinking, the need for regular updating of documents
Information Technology	Implementation of the Pharmacogenetic Profile block with automatic prompts into the electronic medical record	IT service, developers of medical information systems	Fast access for physicians to test results, reducing the risk of errors, and simplifying clinical decision-making	Technical limitations, resource-intensive IS development, and personal data protection issues
Training of doctors	Conducting advanced training courses in pharmacogenetics for cardiologists, therapists and clinical pharmacologists	Departments of universities, institutes of postgraduate education	Increased knowledge, decreased wariness of genetic tests, and increased willingness to use them in practice	Shortage of practicing teachers, limited time for doctors, competition with other educational priorities
Working with patients	Introduction of a standard of informed counseling on the purposes and consequences of pharmacogenetic testing	Attending physicians, medical psychologists, specialists in medical prevention	Increased confidence in personalized therapy, increased adherence to treatment, and decreased refusal to undergo testing	Low genetic literacy among the population, fear of genetic testing, and privacy concerns
Pharmacoeconomic evaluation	Conducting local pharmacoeconomic	Health economists,	Justification of the feasibility of scaling	Difficulty in data collection, need for

	studies on the effectiveness of the pilot project	clinical pharmacologists	the project, optimization of costs of the compulsory medical insurance system	long-term observation, lack of standard methods in a particular region
Scaling and monitoring	Gradual expansion of the program to city clinics with a system of regular audit of results	Regional Department of Health, health insurance organizations	Expanding patient coverage, equalizing the quality of care between institutions, and monitoring final indicators	Uneven equipment of healthcare facilities, differences in the level of personnel training, organizational limitations

Table 4 presents the implementation of personalized antihypertensive therapy, taking pharmacogenetics into account, across key levels of the regional healthcare system. Taken together, these activities form a logical sequence from establishing the organizational framework to scaling up the program and evaluating its effectiveness. Analysis of each step allows us to see how the theoretical advantages of the pharmacogenetic approach can be translated into practical management decisions at the level of the Perm city healthcare system.

At the organizational level, the creation of a pilot pharmacogenetic office or competence center within one of the city's clinical hospitals plays a key role. This avoids the chaotic implementation of individual tests without a unified methodology for interpretation and subsequent decision-making, which often occurs with the spontaneous emergence of new technologies. Concentrating expertise in a single institution creates resources for training physicians and practicing interactions with laboratories and IT services. In the context of Perm, such a center could be associated with a large multidisciplinary hospital with experience managing complex cardiac patients and operating as a regional reference institution.

Laboratory infrastructure is the second fundamental block. It's important not only to technically support testing for key genes but also to ensure their standardization, reproducibility, and clinical relevance. The choice between developing in-house laboratory capacity and contracting with an external accredited laboratory should be based on an analysis of patient flow, financial capabilities, and human resources. For a medium-sized region like Perm Krai, a hybrid approach is initially appropriate, whereby some of the most in-demand and simple tests can be performed locally, while more rare panels can be contracted to specialized centers. This reduces the entry barrier in terms of costs while simultaneously ensuring access to full-spectrum diagnostics when needed.

The clinical guidelines in the table reflect the need to formalize the use of pharmacogenetic information. Without clearly defined algorithms for interpreting genotypes and translating them into clinical decisions, there is a risk of subjectivity and heterogeneity of approaches even within a single institution. The development of local guidelines with the participation of the chief cardiologist, a clinical pharmacologist, and medical genetics experts allows for uniformly defining the clinical situations and patient groups for which pharmacogenetic testing is preferable, which genes should be tested first, and how test results influence the choice of drug class and dosage. This is especially important in conditions where the evidence base for many polymorphisms remains limited and requires careful interpretation.

Thus, the study conducted at the Perm City Clinical Hospital demonstrates both the potential benefits of personalized antihypertensive therapy taking pharmacogenetics into account and the range of challenges that need to be addressed for its large-scale implementation in Russian practice.

Conclusion

Personalized antihypertensive therapy based on a patient's pharmacogenetic profile represents a promising approach to optimizing hypertension treatment in a large urban medical facility. Data obtained from the Perm cardiology service demonstrate that the use of pharmacogenetic information when selecting antihypertensive drug classes and dosages allows for more pronounced blood pressure reduction, an increased proportion of patients achieving target levels, and a reduced incidence of adverse drug reactions compared to the standard clinical and demographic approach. Implementing personalized strategies requires accessible pharmacogenetic testing infrastructure, the development of clinical algorithms for interpreting genetic data, improved physician competence in pharmacogenetics, and consideration of pharmacoeconomic considerations. In the future, the formation of interdisciplinary teams, including cardiologists, clinical pharmacologists, and laboratory geneticists, could facilitate the introduction of personalized antihypertensive therapy regimens into Russian clinical practice, consistent with current international trends in pharmacogenomics and aimed at reducing cardiovascular morbidity and mortality.

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