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COMPREHENSIVE EVALUATION OF COMBINED PHARMACOTHERAPY OF CARDIAC PATHOLOGY CONSIDERING EXOGENOUS AND PHARMACOGENETIC FACTORS

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Abstract. The study assessed changes in hemodynamic and biochemical parameters, vascular age and 5-year cardiovascular risk on the background of complex pharmacotherapy in patients with stable angina I-III functional class (FC), hypertension of I-III degree, chronic heart failure (CHF) II-III FC taking into account the influence of exogenous and pharmacogenetic factors. The study included 200 patients aged 45 – 65 years with concomitant cardiovascular diseases: hypertension of I-III degree, stable angina (I-III FC), with CHF (II-III FC). Patients of the 1st group (100 patients) received prestans, carvedilol, hydrochlorothiazide, verospiron, preparations of acetylsalicylic acid, atorvastatin. Patients of the 2nd group (100 patients) received monopril (fosinopril sodium), carvedilol, amlodipine, hydrochlorothiazide, verospiron, preparations of acetylsalicylic acid, atorvastatin.
In hypertensiology part of the study to the end of the observation period the positive dynamics of the main hemodynamic parameters found in both groups. The main indicators of lipid spectrum were improved. Assessment of the impact of pharmacogenetic factors on the effectiveness of the therapy showed no influence of ACE gene polymorphisms (rs4344) and CYP2D6 gene (rs1135840) for the basic hemodynamic parameters, whereas carriers of the genotype (G;G) of the gene CETP (rs4783961) in both groups was associated with a less significant increase of cholesterol of high density lipoproteins (HDL cholesterol) compared with carriers of the allele (A;A) and (A;G). The significant improvement noted in the analysis of the data of vascular age as an integral indicator of the state of the cardiovascular system, as well as a 5-year cardiovascular risk on the background of the combined pharmacotherapy. . However, there were not detected statistically significant differences between 1-St and 2-nd groups
Keywords: coronary heart disease, hypertension, heart failure, pharmacogenetic, lipid-transport system, the vascular age.

Introduction. Cardiovascular diseases are currently the subject of intense study because, despite significant advances in prevention and therapy, they remain one of the main causes of death and disability in most socially developed countries in the world [1, 2].

The main goal of treatment of patients with arterial hypertension (AH), coronary heart disease (CHD) is to reduce the risk of cardiovascular complications and death from them. To achieve this goal requires not only reduction in blood pressure (BP) to the target level, but the correction of all modifiable risk factors, and treatment of associated diseases – diabetes mellitus (DM), CHF, etc. In turn, the persistent commitment of these patients for continued medical treatment and lifestyle changes is a major factor in the success of treatment of chronic cardiovascular diseases [3, 4].

The term "vascular age" was developed a few years ago to promote the patient adherence to a permanent treatment and conscious self-control in the outpatient setting. This term allows the patient to present a risk of future disease and complications, expressed in years, not percentages that are more clear and accessible for most patients who do not have the medical education [5]. A modified scale SCORE (score 10-year risk of cardiovascular death) was the basis for the calculation. The modified scale SCORE for determining "vascular age" (VA) allows to focus on the individual exogenous risk factors of cardiovascular diseases and their complications (smoking, blood pressure, blood glucose, total cholesterol and high-density lipoproteins) [6, 7]. Strong and significant correlation of the percentages of the risk of cardiovascular complications with a calculated value of "vascular age" has already been demonstrated in some studies [8].

"Vascular age" could potentially be reduced, since among its components are modified, exogenous

indicators (blood pressure, smoking, levels of total cholesterol, lipoproteins of blood serum). Consequently, the motivation to lower your "vascular age" for a few years with smoking cessation, modification of diet and constant medication is likely to be the most effective for the Russian patient [9].

The question of the influence of genetic factors controlling the pharmacokinetics and pharmacodynamics of drugs, on the efficacy of pharmacotherapy is also being actively discussed in the world in recent years. Personalized medicine originated in the depths of clinical pharmacology has become one of the most promising approaches in optimizing pharmacotherapy of socially significant diseases. The successes of molecular biology, in particular, the sequencing of the human genome, has allowed and will allow in the future to identify the genes governing the functioning of body systems and determining the efficacy and safety of pharmacological interventions [10]. Thus, the pharmacogenetic approach is the most modern among the methods of personalized medicine and improves the efficiency and increase safety of treatment of cardiovascular disease, determining the prognosis of treatment. Unfortunately, only a few pharmacogenetic tests approved for use in the Russian Federation and in the world today, that are rarely used in clinical practice [11, 12]. The latter makes it relevant as a search for new alleles responsible for the pharmacokinetics and pharmacodynamics of drugs, and testing of pharmacogenetic studies have already identified the "alleles –candidates" in real clinical practice [13, 14]. In particular, the testing of pharmacogenetic tests in routine clinic allows you to answer the questions of whether genotyping for already proposed in world literature the alleles given the potential benefits from such testing, including the economic viability [15, 16, 17].

It should be noted that neither the methodology of "vascular age" or the methodology of pharmacogenetic personalization of comorbid pathology in the conditions of unorganized population not tested and possible benefit from their use is still under discussion, both at the international and Russian level. On the one hand, the dynamics of indicators of "vascular age" under the influence of the most commonly applied schemes of combination pharmacotherapy has not been studied. On the other hand, data on the use of pharmacogenetic testing in conditions typical practices only begin to accumulate in the scientific community. All of the above makes it relevant to the topic undertaken for the study.

The purpose of this study was to investigate the dynamics of the indicator of "vascular age" based on the modified SCORE scale and the 5-year vascular risk scale ASCORE in the composition of a comprehensive assessment of the various schemes of combined pharmacotherapy in patients with concomitant cardiac pathology, given the exogenous and pharmacogenetic factors.

Research tasks:

1) evaluation of the effectiveness of a 6-month combined therapy using a variety of angiotensin converting enzyme inhibitors (ACE-I) (perindopril arginine and fosinopril) in achieving the target BP values in patients with uncontrolled hypertension and concomitant cardiac pathology;

2) evaluation of the effect of 6-month combined therapy on lipid level: total cholesterol, high density lipoproteins (HDL) and low density lipoproteins (LDL), triglycerides (TG), creatinine and glucose serum;

3) assessment of the impact of pharmacogenetic factors, carriage of allelic variants of genes involved in the pharmacokinetics and pharmacodynamics of antihypertensive and hypolipidemic drugs on key indicators of cardiovascular and lipid-transport systems;

4) the calculation of the indicator "vascular age" definition of a 5-year risk of complications on a scale ASCORE and assessment of impact of combined therapy on these parameters in patients after 6 months of treatment.

Materials and methods.

The study included 200 patients aged 45 – 65 years with concomitant cardiovascular diseases: hypertension of I-III degree, stable angina (I-III FC), with CHF (II-III FC). Patients with myocardial infarction suffering for less than 6 months, acute coronary syndrome, unstable angina, arrhythmias, CHF terminal (IV FC), valvular heart defects, history of stroke, chronic obstructive pulmonary disease, DM of the 1st type or the decompensated 2nd type DM, pregnancy, patients who had serious cardiovascular disease or condition that affects duration of life (need for dialysis, cancer, drugs, etc.) were excluded from the study.

All patients randomized into two groups.

The main clinical characteristics of the study groups are presented in table 1.

Table1

Clinical characteristics of study groups

Parameter	1st group	2nd group
The number of patients • Men • Women	100 48 52	100 54 46
Average age, years	60,5 ± 4,3	56,04±6,7

Patients of the 1st group (100 patients) received a fixed combination of ACE inhibitors and calcium channel blocker (CCB) – prestans (perindopril arginine in a dose of 5-10 mg/day and amlodipine 5-10 mg/day), carvedilol at a dose of 12.5-50 mg/day, hydrochlorothiazide – 12,5-25 mg/day, verospiron 25 mg/day, acetylsalicylic acid drugs– 75 – 100 mg/day, atorvastatin at a dose of 20-40 mg/day.

Patients of the 2nd group (100 patients) received monopril (fosinopril sodium) at a dose of 10-40 mg/day, carvedilol in the dose 12,5-50 mg/day, amlodipine 5-10 mg/day, hydrochlorothiazide – 12,5-25 mg/day, verospiron 25 mg/day, acetylsalicylic acid drugs– 75 – 100 mg/day, atorvastatin 20-40 mg/day.

The criteria for titration of the doses of medicine were the target levels of hemodynamic, clinical and laboratory parameters.

The observation period was 6 months.

"Vascular age" was calculated by the modified SCORE table, taking into account gender, age, smoking status, blood pressure and total cholesterol of blood serum [5]. 5-year risk of cardiovascular complications was calculated on a scale ASCORE [5].

Pharmacogenetic testing for allelic variants of the genes was carried out in pharmacogenetic laboratory of the center for preclinical and clinical studies, national research university "BelSU", Belgorod, Russia. DNA extraction was performed using the reagents set ThermoFisherScientific 250 discharge, to assess the quality and quantity of obtained DNA was used, the system Qubit with the set of necessary reagents. Pharmacogenetic typing for alleles was conducted in real time with the use of high-performance systems FluidigmBioMark™ HD System using a standard set of boot reagents, customized set of synthesized primers and a universal chip format is 48x48. Processing of the obtained results was performed in the software package BiomarkDataAnalisys licensed to work in the laboratory [18].

Statistical data processing was carried out by methods of parametric and non-parametric statistics using Statistica 8.0. Differences were considered significant at values of bilateral $p<0.05$. Presenting the results of the parametric statistics used the format M±SD.

The results of the study and their discussion.

Combined therapy was well tolerated by all patients. The drugs cancellation and adverse drug reactions were not recorded.

In hypertensiological part of the study the positive dynamics of the main hemodynamic parameters were found in both groups by the end of the observation period (table 2). Patients in the intervention groups achieved the target levels for heart rate (HR) and blood pressure (BP) in result of titration of drug doses in all areas of pharmacotherapy.

Table 2

Change hemodynamic variables in groups of observations on the background of treatment (M±SD, n = 200)

Parameter	1st group (n=100)		2nd group (n=100)	
	At baseline	After 6 months	At baseline	After 6 months
Systolic BP, mm Hg.	152,7±10,9	134,2±7,6*	154,3±9,5	135,2±8,9*
Diastolic BP, mm Hg	92,2±7,6	81,1±6,3*	91,8±7,1	81,4±4,8*
HR, beats/min	74,3±6,5	65,9±4,0*	72,6±4,2	64,8±3,5*

Note: here and in table 4 the significance of differences of indicators in the process of treatment: * – $p< 0.05$, * * – $p< 0,01$.

Further analysis of the changes in hemodynamic parameters did not reveal statistically significant differences ($p > 0.05$) between the groups (table 3). It says comparable antihypertensive efficacy of the proposed regimens, but also emphasizes their sufficiency in absolute terms.

Table 3

Comparative analysis of efficiency of used pharmacotherapeutic schemes for changing the basic hemodynamic parameters (M±SD, n = 200)

Hemodynamic parameters	1st group (n=100)	2nd group (n=100)
ΔSystolic BP (%)	10,9±5,8	12,2±4,3
ΔDiastolic BP (%)	10,9±7,1	10,2±7,5
Δ HR (%)	8,9±4,5	10,7±4,4

Seemed interesting to assess in practice the influence of allelic variants of genes involved in the pharmacokinetics and pharmacodynamics of drugs on the efficacy of pharmacotherapy. The impact of the allelic variant of the gene is a target of ACE inhibitors – ACE allele (A/G) (rs4344) on the effectiveness of combination therapy containing ACE inhibitors – perindopril – in the 1st group, and fosinopril – in the 2nd group respectively were estimated . Choice of single nucleotide polymorphism rs 4344 caused, on the one hand, a small study of this polymorphism among alleles of the gene for the ACE, and on the other hand, contradictory data about its influence on the antihypertensive efficacy and safety of drugs that inhibit this enzyme [19, 20]. Comparative analysis of efficiency of used drug regimens subject to the carriage of allelic variants of the studied polymorphisms is presented in table 4.

Table 4

Comparative analysis of effectiveness of pharmacotherapy depending on the carriage of allelic variants of the gene ACE (rs4344) (M±SD, n=200)

Group	1st group (n=100)			2nd group (n=100)		
Allele	rs4344 (A;A), (n=23)	rs4344 (A;G), (n=55)	rs4344 (G;G), (n=22)	rs4344 (A;A), (n=26)	rs4344 (A;G), (n=53)	rs4344 (G;G), (n=21)
Δ Systolic BP, mm Hg.	18,2±6,5	16,8±7,8	18,8±7,5	19,8±+7,6	19,5±7,9	19,4±7,4
Δ Diastolic BP, mm Hg	11,3±6,2	9,4±5,2	11,8±6,5	9,8±5,6	9,4±5,4	9,5±4,0
Δ HR, beats/min	7,2±2,5	7,0±2,9	7,1±2,8	9,8±6,6	9,8±6,2	9,4±5,1

Note: Difference between groups on relevant allelic variants in all hemodynamic parameters was not revealed.

In the analysis of the data, within group genotypes (A;A), (A;G), (G;G), nor between groups on relevant allelic variants of statistically significant differences was not obtained (in all cases, the values of the two-way $p > 0.05$). This is consistent with some of the literature data about the absence of a clinically significant effect of this polymorphism for the realization of the hypotensive effect of ACE inhibitors.

Further seemed interesting to assess the influence of genetic factors on the implementation of another drug included in the scheme of pharmacotherapy in both groups of observation – carvedilol. It is well known that a major enzyme determining the pharmacokinetics, and as a consequence, the effectiveness of most beta-blockers is the cytochrome CYP2D6. The literature describes the impact of a number of alleles of this cytochrome on the efficacy and safety of pharmacotherapy with beta blockers. One of the most promising for the study is single nucleotide polymorphism rs 1135840 gene cytochrome CYP2D6, since in several studies it has been shown as sufficient frequency of mutant alleles, and its impact on the effectiveness of beta-blockers [21, 22]. In our study, we have attempted to evaluate the impact in terms of the Russian population (table 5).

Table 5

Comparative analysis of effectiveness of regimens depending on the carriage of allelic variants of CYP2D6 gene (rs1135840), (M±SD, n=200)

Group	1st group (n=100)			2nd group (n=100)		
Allele	rs1135840 (G;G), (n=81)	rs1135840 (G;C), (n=10)	rs1135840 (C;C), (n=9)	rs1135840 (G;G), (n=79)	rs1135840 (G;C), (n=11)	rs1135840 (C;C), (n=10)
Δ Systolic BP, mm Hg.	18,2±6,5	17,8±7,8	16,1±7,4	19,4±7,2	18,2±7,1	17,4±7,4
Δ Diastolic BP, mm Hg	11,4±6,2	11,1±5,2	9,5±6,4	9,5±5,4	9,2±5,3	9,5±4,0
Δ HR, beats/min	7,2±2,5	7,1±2,6	5,4±2,1	9,9±5,6	9,2±5,1	8,4±4,8

Note: Differences between groups on relevant allelic variants in all hemodynamic parameters

As can be seen from the table, or inside the group by genotype (G;G), (G;C), (C;C) nor between the groups on the respective allelic variants of statistically significant differences was not received (in all cases, the values of the two-way $p > 0.05$). In comparison of obtained results with available in the world literature it should be noted that in some cases carriers of the negative allele (C;C), this polymorphism was associated with increased activity of CYP2D6, resulting in decrease in the effect of metabolizing them drugs, while in others such laws has not been established.

In lipidological and biochemical part of the study evaluated the effect of the lipid-lowering and antihypertensive drug therapy on lipid and carbohydrate metabolism, levels of blood creatinine. As a result of 6-months therapy in both groups pharmacological intervention negative impact on the levels of glucose and blood creatinine was not observed, on the contrary, tended to their improvement. The main indicators of lipid spectrum were improved (table 6).

Table 6

Dynamics of the main biochemical parameters in the intervention groups (M±SD, n=200)

Parameter	1st group (n=100)		2nd group (n=100)	
Total cholesterol, mmol/l	5,37±0,71	4,62±0,63*	5,32±0,82	4,58±0,62*
HDL, mmol/l	1,57±0,41	1,82±0,45	1,6±0,47	1,77±0,43
LDL, mmol/l	3,18±0,66	2,33±0,76*	3,03±0,84	2,36±0,67*
Creatinine, mmol/l	85,5±9,8	87,0±7,7	89,3±9,9	88,4±9,3
Glucose, mmol/l	5,04±0,5	4,88±0,5	5,13±0,5	5,04±0,4

Comparative analysis of the effectiveness of lipid-lowering intervention in patients in both groups are presented in table 7. Note worthy adequate lipid-lowering effect on indicators of atherogenic fractions of lipoproteins of blood serum and the absence of statistically significant differences between the groups.

Table 7

Comparative analysis of the effectiveness of lipid-lowering intervention in patients with concomitant cardiac pathology (M±SD, n =200)

Parameters	1st group (n=100)	2nd group (n=100)
lowering of total cholesterol, %	13,4±2,2	13,9±2,26
increase HDL cholesterol, %	15,9±4,6	12,9±4,7
reduction LDL cholesterol, %	26,7±5,3	24,8±4,6

To assess the impact of genetic factors on the efficacy of lipid-lowering correction seemed interesting to assess the impact of protein gene polymorphism, transporting cholesterol esters CETP rs4783961 on the effectiveness of lipid-lowering correction in the groups of intervention.

This polymorphism choise is based on two premises: first, a sufficient frequency of "minor" allele, and secondly, available in the world literature data, not only about its effect on the lipid spectrum, but also on the risk of early development of non-fatal myocardial infarction [23, 24]. The results of the analysis of the influence of this allele on the basic parameters of lipid-transport system in patients in the intervention groups are presented in table 8.

Table 8

Dynamics of the main biochemical parameters depending on the carriage of allelic variants of the gene CETP (rs4783961), (M±SD, n = 200)

Group	1st group (n=100)			2nd group (n=100)		
Allele	rs4783961 (A;A), (n=22)	rs4783961 (A;G), (n=56)	rs4783961 (G;G), (n=22)	rs4783961 (A;A), (n=23)	rs4783961 (A;G), (n=53)	rs4783961 (G;G), (n=26)
lowering of total cholesterol, %	13,4±2,2	13,8±2,5	12,9±2,1	13,9±2,3	13,5±2,4	12,9±1,9
increase HDL cholesterol, %	15,9±4,6	15,1±4,3	10,1±4,0*	12,9±4,7	12,1±4,3	9,3±4,0*
reduction LDL cholesterol, %	26,7±5,3	26,2±5,1	25,4±5,2	24,8±4,6	24,1±4,3	25,2±4,1
Differences within groups for LDL cholesterol, p	(A;A) / (A;G): p>0,05 (н/д)			(A;A) / (A;G): p>0,05 (н/д)		
	(A;G) / (G;G): p>0,05 (н/д)			(A;G) / (G;G): p>0,05 (н/д)		
	(A;A) / (G;G): p>0,05 (н/д)			(A;A) / (G;G): p>0,05 (н/д)		
Differences within groups for HDL cholesterol, p	(A;A) / (A;G): p>0,05 (н/д)			(A;A) / (A;G): p>0,05 (н/д)		
	(A;G) / (G;G): p>0,05 (н/д)			(A;G) / (G;G): p>0,05 (н/д)		
	(A;A) / (G;G): p<0,05			(A;A) / (G;G): p<0,05		

Note: Differences between groups on the relevant alleles in the compared indicators were not identified.

As can be seen from the table, statistically significant differences in dynamics of indicators of HDL cholesterol have been identified as in the 1st and in the 2nd group. The carriers of the genotype (G;G), there was statistically significantly smaller increase of HDL cholesterol (10,1±4.0% in the first group, and 9.3±4.0% in the second group, respectively) compared with carriers of other alleles (15,9±4,6% and 15.1±4.3% for the allele (A;A) and (A;G), respectively in the first group, and 12.9±4.7% and 12,1±4.3% for the allele (A;A) and (A;G), respectively in the second group). These differences are a subject for further study, make genotyping for this polymorphism is clinically significant, and confirm hypotheses about the influence of this polymorphism on the risk of development of cardiovascular complications, since HDL cholesterol is "anti-risk" of coronary pathology.

In the part devoted to the assessment of the dynamics of vascular age, we obtained the following

results. As among men, and among women the estimated vascular age and 5-year risk of cardiovascular complications significantly decreased at 6 months treatment, with statistically significant gender differences were not found, so the following is summary data for groups in general. Comparative analysis of dynamics of parameters of vascular age and 5-year cardiovascular risk are presented in table 9.

Table 9

Dynamics of indices of vascular age and 5-year cardiovascular risk in the intervention groups (M±SD, n =200)

Parameters	1st group (n=100)		**2nd group (n=100)**		**p 1-2**
	At baseline	After 6 months	At baseline	After 6 months	
Vascular age	61,0 [55,8;66,0]	54,0** [50,0;62,0]	60,0 [52,8;65,0]	54,0** [49,5;61,0]	ns
5-year risk (abs.%)	2,7 [2,3;4,0]	2,0** [1,6;2,4]	3,0 [2,1;3,6]	2,4** [1,5;3,0]	ns

Notes: 1) abs.% – absolute (%) risk reduction, 2) the statistical significance of differences of indicators in dynamics in the same group: * p<0.05, * * p<0,01, 3) p 1-2 – intergroup differences in the indices, ns – the difference was not statistically significant.

In the analysis of the parameters of vascular age as an integral indicator of the state of the cardiovascular system, as well as a 5-year cardiovascular risk on the background of the conducted pharmacotherapy there is a strong positive trend. However, statistically significant differences between 1-St and 2-nd groups were not detected

Conclusion. Thus, the results of these studies point to the pronounced clinical efficacy of combined therapy in both groups, patients with concomitant cardiac pathology in the form of improved hemodynamic parameters (significant decrease in systolic and diastolic BP), parameters of the lipid spectrum, glucose and blood creatinine and significant decrease of the indicator "vascular age" and the 5-year cardiovascular risk. All this emphasizes the necessity for an integrated approach in the treatment of comorbid cardiovascular pathology, primarily due to correction of modifiable risk factors.

On the other hand, the data obtained on the contribution of pharmacogenetic factors in the variation of the effect of drugs, emphasize that in some cases in real life, this influence is not clinically significant (as it was shown for ACE-I and beta-blocker), others may have a clinical value as it was shown for lipid-lowering correction). The above confirms the necessity for further research in this direction.

References

1. Mareev V. Y., Ageev F. T., Arutyunov G. P. [et al.]. Diagnosis and treatment of chronic heart failure (IV revision). National recommendations. *Heart Failure.* Vol. 14 (2013): P. 379-472. (In Russian). [Full text]

2. Martsevich S. Y., Kutishenko N. P., Tolpygino S. N. [et al.]. The efficacy and safety of drug therapy in primary and secondary prevention of cardiovascular disease. National Recommendations / *Rational pharmacotherapy in cardiology*. Vol. 5.(2011): P. 5-72. (In Russian). [eLIBRARY]

3. Urazalina S. G., Rogoza A.N., Balahonova T.V. The relationship of "vascular age" with indicators of subclinical atherosclerotic lesion of the arterial wall in women with low and moderate cardiovascular risk on a scale of "SCORE". *Heart.* Vol. 5 (2010): P. 271-276. (In Russian).[eLIBRARY]

4. Chazova I. E, Oschepkova E. V., Zhernakova Y. V. Diagnosis and treatment of arterial hypertension. Clinical guidelines. *Cardiology*. (2015) : P 3–30. (In Russian). [Full text]

5. Karpov Yu. A. , Sorokin E. V.. Risk assessment of complications of arterial hypertension and vascular age: new tools to improve the quality of treatment and better understanding of patient and doctor. *News of cardiology*. Vol. 2 (2015): P 18-24. (In Russian). [eLIBRARY]

6. Cuende, J.I., Calaveras-Lagartos J. How to calculate vascular age with the SCORE project scales: a new method of cardiovascular risk evaluation. *Eur. Heart J.* Vol. 19 (2010): P. 2351-2358.[PubMed][Full text]

7. D'Agostino R.B., Vasan R.S., Pencina M.J. [et al.]. General cardiovascular risk profile for use in primary care. *The Framingham Heart Study. Circulation.* Vol.117 (2008): P.743–753.[PubMed][Full text]

8. Groenewegen K., den Ruijter H., Pasterkamp G. [et al].Vascular age to determine cardiovascular disease risk: A systematic review of its concepts, definitions, and clinical applications. *Eur. J. Prev. Cardiol.* Vol. 23 (2015): P. 264-274.[PubMed]

9. Karpov Yu. A., Sorokin E. V.. The effect of combined antihypertensive therapy on the risk of cardiovascular complications and vascular age: results of a multicenter open study ADVANT'AGE. *News of cardiology*. Vol. 3 (2015): P. 18-26 (In Russian). [eLIBRARY]

10. Caudle K.E., Dunnenberger H.V., Freimuth R.R.. [et al]. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical

Pharmacogenetics Implementation Consortium (CPIC). *Genet Med.* Vol. 21 (2016): P. 1-9.[PubMed][Full text]

11. Kukes V. G., Sychev D. A., Ignatiev I. V. Clinical pharmacogenetics and clinical practice: integration perspectives. *Biomedicine.* Vol. 5 (2006): P. 2-15 (In Russian). [eLIBRARY]

12. Filippenko N. G. Povetkin S. V., Kornilov A. A. [et al.]. The possibilities of personalization of pharmacotherapy for patients of a cardiological profile. *Cardio somatics.* Vol. 2 (2011): P. 58-62 (In Russian). [eLIBRARY]

13. Kornilov A. A, Filippenko N. G. Povetkin S. V. [et al.]. Prospects for personalization of pharmacotherapy of cardiovascular diseases. Materials of international scientific-practical conference dedicated to the 81st anniversary of the Kursk state medical University and the 50th anniversary of pharmaceutical faculty. Kursk Vol. 1 (2016): P. 372-377. (In Russian). [eLIBRARY]

14. Filippenko N. G. Povetkin S. V., Kornilov A. A. [et al.]. From applied pharmacokinetic research to the implementation of personalized pharmacotherapy in real clinical practice. *Biomedicine.* Vol. 3 (2010): P. 158-160. (In Russian). [eLIBRARY]

15. Haga, S.B. Challenges of development and implementation of point of care pharmacogenetictesting. *Expert Rev MolDiagn*. (2016): P.1-12. [PubMed]

16. Hicks J.K., Stowe D., Willner M.A. [et al]. Implementation of Clinical Pharmacogenomics within a Large Health System: From Electronic Health Record Decision Support to Consultation Services. *Pharmacotherapy* (2016): P.1-9.[PubMed]

17. Filippenko N. G. Povetkin S. V., Kornilov A. A. [et al.]. Experience in the implementation of pharmacogenetic studies at the University hospital. *Biomedicine.* Vol. 3 (2010): P. 79-80. (In Russian). [eLIBRARY]

18. BiomarkHDBrochure. [Electronic resource] // Fluidigm: site. – Mode of access: https://www.fluidigm.com/products/biomark-hd-system (date of access 24.07.2016.). [Full text]

19. Grilo A., Saes-Rosas M.P., Santos-Morano J. [et al]. Identification of genetic factors associated with susceptibility to angiotensin-converting enzyme inhibitors-induced cough. *Pharmacogenet Genomics.* Vol. 1 (2011): P. 7-10. [PubMed]

20. Bhatnagar V., O'Connor D.T.,. Schork N.J. [et al]. Angiotensin-converting enzyme gene polymorphism predicts the time-course of blood pressure response to angiotensin converting enzyme inhibition in the AASK trial. *J Hypertens.* Vol.10 (2007): P.1-20. [PubMed][Full text]

21. Yuan H., Yu M., Yang Y. [et al]. Association of CYP2D6 single-nucleotide polymorphism with response to ophthalmic timolol in primary open-angle Glaucoma--a pilot study. *Ocul. Pharmacol. Ther.* Vol. 5 (2010): P. 497-501. [PubMed]

22. Suarez-Kurtz G., Pena S.D., Struchiner C.J. [et al]. Pharmacogenomic Diversity among Brazilians: Influence of Ancestry, Self-Reported Color, and Geographical Origin. *Front Pharmacol.* Vol. 3 (2012): P. 191-198. [PubMed][Full text]

23. Sharafetdinova L.M., Ismagilova R.K., Maycova E.V. [et al]. The influence of the polymorphism in the promoter region of the gene CETP activity it protein in ischemic heart disease. *Cytology.* Vol. 6 (2014): P. 462-464 (In Russian). [PubMed]

24. Schierer A., Been L.F., Ralhan S. [et al]. Genetic variation in cholesterol ester transfer protein, serum CETP activity, and coronary artery disease risk in Asian Indian diabetic cohort. *Pharmacogenet Genomics.* Vol. 2 (2012): P. 95-104. [PubMed][Full text]