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THE ASSOCIATIONS OF β-ADRENORECEPTORS GENES POLYMORPHISMS WITH THE COURSE OF HEART FAILURE AND WITH THE LOW TRIIODOTHYRONINE SYNDROME (literature review and own observations)*

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The HF is one of the most common causes of hospitalization and death of patients. In many countries of the world, research is underway to study the molecular genetic factors of HF development, search for susceptibility genes and analyze the relationship of their polymorphisms with the risk of adverse outcome and co-morbidities [1]. In clinical practice, the human genome is more often studied by molecular testing to identify so-called susceptibility genes or candidate genes [1]. Their polymorphic variants have relatively little effect on the function of the proteins they encode. Their functioning is compatible with life, but in combination with the action of adverse external factors can cause various diseases. The most common cause of differences in the structure of genes are point mutations — substitutions of single nucleotides, or the so-called single-nucleotide polymorphism (SNP). Less common are other genetic changes, such as different number of repetitions of the same short sections of the gene, as well as deletions of nucleotides or small fragments of the gene. The frequency of nucleotide substitutions as a result of replication is more than 1 %. Thus, given the presence of approximately 3 billion nucleotides in the human genome, a particular individual may have several million SNPs. A lot of data has been accumulated that SNPs are responsible for the formation of specific gene alleles to produce a complex of phenotypic differences between people. This also includes personal characteristics of the development of protective reactions and predisposition to a number of diseases [2].

Many works are devoted to the study of associations of gene polymorphisms with the most common cardiovascular diseases (CVD) and the effectiveness of appropriate therapy. According to the analysis of a lot of studies

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in this area, the greatest attention is paid to the study of polymorphisms of genes encoding proteins — structural components of enzymes, hormones, receptors of neurohumoral systems involved in the development and progression of most CVDs, including HF. Such systems primarily include ß-AR genes.

The low triiodothyronine syndrome (Low T_3 syndrome, peripheral dysthyroidism syndrome) is observed in some patients with HF. Disruption of the activity of thyroxin (T_4) conversion to triiodothyronine (T_3) by peripheral deiodinases (DD) is associated with the clinical course of the HF. The activity of DD, among other factors, is also affected by hypercatecholemia, which is inherent in HF. The hypercatecholemia in HF, on the one hand, is an adaptive mechanism, but subsequently it leads to disorder in many systems. These effects are realized through the ß-adrenergic receptors' system. There is extremely little data in literature regarding the effect of ß-AR gene polymorphisms on the development of LT_3S and many contradictory results about their association with HF course. This encourages new research in this area.

The aim of this article is to systematize literature data on the associations of ß-AR genes polymorphisms with the course of HF and with the development of LT_3S and to present the results of own research.

MATERIALS AND METHODS

The narrative review represents an assessment of the most pertinent literary sources published in English language from 1990 to 2021, which dealt with the issues of the associations of ß-AR genes polymorphisms with the course of HF and with the development of LT_3S. Also, the results of own research were presented.

REVIEW AND DISCUSSION

When the perfusion of vital organs is impaired, or when there is a need for increased blood supply, for example, during exercise or stress, the body reacts by activating the sympatho-adrenal system (SAS) [3]. The increase in cardiac output is due to the activation of ß-AR on the cardiomyocyte membrane. SAS provides an adaptive response of the heart to the action of short-term (acute) needs (stimuli), which corresponds to the law of «fight or flight» [3]. However, excessive activation of the corresponding regulatory system under conditions of chronic stress can lead to pathological consequences.

HF is characterized by high SAS activity, which is primarily an increase in the concentration of norepinephrine (NE) due to its increased release from the presynaptic terminals of axons innervating the heart. With chronic ß-AR activation, the heart works in an enhanced mode - an excessive increase in the frequency and force of contractions, which leads to depletion of metabolic reserves, in particular, a decrease in contractility and eventually to decompensation of patients with HF. ß-adrenergic blockers (ß-AB) have been shown to have a positive effect in HF, disrupting this cycle by antagonizing the effects of NE on myocardial ß-ARs [3]. Under the condition of correct ß-AB titration, cardiac energy improves, cardiotoxic effects of chronic ß-AR stimulation decrease, and the so-called «reverse reconstruction» of the processes that led to a decrease in myocardial inotropic function occurs. Under these conditions, changes in gene expression are also observed. This ultimately leads to the normalization of the heart, increasing the survival rate of patients [4]. With the improvement of heart function, perfusion of vital organs and systems is restored, which leads to a decrease in SAS activity and NE concentration [3]. Subsequently, the sensitivity of ß-AR cardiomyocytes is restored [5].

Indeed, the expression and function of ß-AR cardiomyocytes in HF are in a dynamic process, which is influenced by hemodynamic status and treatment effects [3]. ß-ARs are paired transmembrane proteins. To date, three subtypes of ß-AR ($ß_1$-, $ß_2$- and $ß_3$-AR) have been well studied. It is believed that these receptors are found on almost all cells of the body. $ß_1$- and $ß_2$-AR are widely represented on the membranes of cardiomyocytes. Catecholamines realize their positive ino-, chrono-, dromo-, bathmo-

tropic effects mainly through β_1-AR. In HF, the sensitivity and number of β_1-AR decreases, while the expression of β_2-AR remains relatively stable. However, the functional interaction of β_2-AR with G-proteins is reduced in HF [6]. It is known that the decrease in β_1-AR sensitivity caused by high levels of NE can be partially compensated by increased expression of G-protein (mediator between β-AR and cAMP) [7]. Over time, the expression of this compensatory mechanism is exhausted. However, the decrease in the sensitivity of β-AR cardiomyocytes under conditions of chronic hypercatecholemia is insufficient. The issue of drug influence on these processes remains unresolved.

Two common nonsynonymous SNPs were found in nucleotides 145 (A/G), which leads to the coding of amino acids Ser (basic allele) or Gly in 49 extracellular sequence of β_1-AR, and at the polymorphism in nucleotide 1165 (G/C), there is a coding of either amino acid Arg (basic allele) or Gly in 389 sequence of the intracellular part of the receptor. The Gly amino acid at position 389 was the first to be found in the cloning of human β_1-AR. This allele is called "wild", but it is less common in the population. However, among African Americans, Gly is approximately as common as the Arg allele. That is why, in modern literature, they usually refrain from using the term «wild type» for any variant, and designate them as β_1Arg389 or β_1Gly389 [3].

The Gly/Arg amino-acid variation at position 389 is located within the fourth intracellular loop formed by 12 amino acids. It is proved that by analogy with other G-protein-coupled receptors, the polymorphism of this allele is also manifested in the activity of β_1-AR [3]. In the competitiveness studies performed on partially purified cell membranes of Chinese hamster fibroblasts (CHW cells), a higher activity of β_1-AR at Arg389 polymorphism was demonstrated compared to β_1Gly389 [8].

Similar results were obtained by another group of researchers who studied the relevant processes in the Chinese hamster ovary cell model. They demonstrated that with the Arg389 polymorphism, β_1-ARs have a greater affinity for the Gs-type protein than with Gly389 [6]. It was in the presence of Arg389 allele of β_1-AR that the authors found a 30-fold increase in cAMP synthesis upon stimulation of β_1-AR with isoproterenol, in contrast to the model with β_1Gly389 polymorphism [6].

When using β-AB, in particular metoprolol, bisoprolol and propranolol, no differences in β_1-AR sensitivity were found neither at Gly nor at Arg polymorphism [9]. But when carvedilol was used, the sensitivity of β_1Arg389 was greater compared to β_1Gly389 [9]. These data are difficult to interpret, but they suggest that there are specific compounds/phenotypes for the $\beta_1$389 position [10].

Rathz D. A. et al. (2003) demonstrated that the β_1Arg389 polymorphism has a faster (50 %) decrease in receptor sensitivity under chronic stimulation than the Gly389 polymorphism [11]. However, in studies on CHW models and human embryonic kidney cells, these scientists found no differences in the agonist-stimulated interaction of β_1-AR with adenylate cyclase in the presence of another polymorphism (β_1Ser49 and β_1Gly49) [11]. At the same time, another group of researchers reported an increase in basal and stimulated cAMP activity in the Gly49 polymorphism, which was found in a model of human embryonic kidney cells [12]. This polymorphism of β_1-AR is localized on the extracellular site of the receptor. According to the data of polyacrylamide gel electrophoresis, it was found that the β_1Ser49 receptor has altered glycosylation, in contrast to receptors with Gly49 polymorphism [3]. Since glycosylation affects receptor drift, these data may explain the differences between their sensitivity [3]. β_1Gly49 alters the phenotype of the heart in HF due to an increased ability to down-regulate in response to stimulation (decreased sensitivity) [12].

The study by Gerald W. et al. (2009) demonstrated that in transgenic mice at the age of 3 months, basal and maximal dobutamine-stimulated cardiac contractility was higher in the β_1Arg389 polymorphism, in contrast to that in the group with the β_1Gly389 polymorphism [3]. The authors also noted that at the age of 6 months, mice with the β_1Arg389 polymorphism retained increased basal cardiac contractility, but there was no response to dobutamine stimulation [3]. This desensitization in the sixth month of mice life was caused by a decrease in the sensitivity of the receptor conjugated to the «S» form of G-protein. This led to

a decrease in myocardial systolic function up to 9 months. The authors called this phenomenon $ß_1$AR-mediated cardiomyopathy [3]. But, in people with end-stage HF, no significant differences in myocardial contractility depending on the genotype (Arg or Gly) were found [3].

After additional experiments with transgenic mice, the first evidence was obtained that there may be a differential response to the use of ß-AB, depending on the genotype [13]. Under conditions of acute infusion of propranolol into the heart in an ex vivo model, a dose-dependent decrease in myocardial contractility was demonstrated in the $ß_1$Arg389 genotype. At the same time, in the $ß_1$Gly389 polymorphism, a decrease in inotropic function was observed only when using the maximum concentration of propranolol. In in vivo studies, when propranolol was added to the drinking water of mice for 1 month, a decrease in heart rate was observed only in the presence of the Arg389 genotype [13]. In order to further evaluate the significance of alleles at position 389 in the context of HF in humans, a number of studies with physiological endpoints were conducted with the participation of a relatively small number of patients. In one of these studies, stepwise exercise tolerance testing was performed in 263 patients with NYHA III/IV HF. The main result was the determination of the maximum oxygen consumption rate (VO_2) [14]. A significant difference in VO_2 was found between Arg389 and Gly389 homozygotes (17.7 ± 0.4 vs. 14.5 ± 0.6 mL/kg/min, p = 0.006). The VO_2 value in heterozygotes (Arg389Gly) corresponded to the average values of homozygous patients (16.9 ± 0.6 mL/kg/min) [14].

Further stratification of patients by polymorphism at position 49 ($ß_1$Ser49Gly) showed that homozygous patients (Ser49) had higher VO_2 values compared to Gly49 carriers (homozygotes and heterozygotes). The authors suggested that this difference was probably caused by the $ß_1$Arg389 polymorphism due to high linkage disequilibrium between 49 and 389 alleles [14]. This study demonstrated a «hyperdynamic» type of hemodynamics at $ß_1$Arg389 polymorphism in humans [14]. These results of the response to exercise were reproduced by another group of authors in a clinical study involving patients with HF [15]. However, it was not possible to establish similar results in the study of healthy people (without HF) [16]. However, when analyzing the changes in cardiac function in response to dobutamine infusion in healthy volunteers, a greater increase in heart rate and myocardial contractility was found, and it was also found that dobutamine-stimulated plasma renin activity was significantly higher in the $ß_1$Arg389 genotype compared to homozygotes for the Gly389 allele [17].

The influence of this polymorphism on $ß_1$-AR activity in the kidneys has been demonstrated [17]. Bisoprolol was found to reduce the dobutamine-stimulated cardiac response and renin levels in patients with $ß_1$Arg389 genotype, unlike those with Gly389 [17]. Another study evaluated the effect of carvedilol in 224 patients with HF on the increase in left ventricular ejection fraction (EF LV) during 6 months of treatment [13]. After titration, the dose of carvedilol was the same in patients with Arg389 and Gly389 genotypes. Homozygotes for Arg389 allele had a greater increase in EF LV compared to Gly389 homozygotes. Heterozygotes showed an improvement similar to Arg389 homozygotes (7.02±1.5 %) [13].

The results of comprehensive studies on the cell membranes of transgenic mice, ex vivo in the human heart, as well as analysis of the physical condition of patients with HF and healthy volunteers, demonstrated that the $ß_1$Arg389 genotype has a higher signaling potential compared to $ß_1$Gly389 and provides a more pronounced response to the use of $ß_1$-AB [3]. This difference may have important physiological and pharmacological significance in the implementation of various effects on ß-AR in patients with HF [3]. This version was tested in multicenter studies. Within the framework of the Blocker Evaluation of Survival Trial (BEST) project, genotyping for $ß_1$Arg389 polymorphism was performed [18]. However, the study was terminated early because there were no significant differences between the groups of patients treated with bucindolol or placebo [18]. At the same time, there are important results of this study. In particular, patients with HF who were homozygous for the $ß_1$Arg389 genotype and received bucindolol had better survival compared to patients with this polymorphism, but without the use of bucindolol [18].

In contrast, carriers of the ß$_1$Gly389 genotype had the same mortality regardless of receiving placebo or the drug [18]. It is suggested that there were several problems in the BEST study. The first is a small but significant difference in the frequency of the Gly allele among African Americans compared to Caucasian patients. Mortality in the bucindolol cohort was higher in African Americans. It is assumed that in these patient's mortality was associated with the presence of some other African gene rather than ß$_1$Gly389 [3]. The second drawback of the study is the pharmacological properties of bucindolol itself. The drug has a fairly strong sympatholytic property (reduction of norepinephrine level), which is similar in expression to the effect of the central imidazoline receptor agonist — moxonidine [19]. In addition, in experiments on human heart preparations, it was demonstrated that bucindolol acts as an inverse agonist in the presence of ß$_1$Arg389 genotype, in contrast to ß$_1$Gly389 [20].

In the genetic sub-study of the MERIT-HF trial, the effect of ß$_1$AR (Arg389Gly) polymorphism in HF was studied [21]. The data analysis showed that in patients with HF and ß$_1$Gly389 genotype the use of metoprolol had no effect on the course of the disease [21].

ß$_2$-AR is expressed in many tissues, including vascular, bronchial, renal, cardiac, thyroid, and liver smooth muscle cells [22]. The gene encoding ß$_2$-AR does not contain introns, is located on chromosome 5q31-32 and has several polymorphic sites: at least 51 variants have already been identified [23]. Five of them are nonsynonymous single nucleotide substitutions in the region encoding ß$_2$-AR and are found at positions 46 (extracellular amino terminus; Gly16Arg), 79 (extracellular amino terminus; Gln27Glu), 100 (1st transmembrane domain; Val34Met), 491 (4th domain; Thr164Ile) 659 (5th domain; Ser220Cys). Single nucleotide polymorphisms at position 46 (Gly16Arg) and 79 (Gln27Glu) are the most common, with allele frequencies in the white population of approximately 0.4 % (Arg16, Glu27), while Thr164Ile, Val34Met and Ser220Cys are very rare [23].

These polymorphisms are highly unevenly linked, probably because the human species is relatively young [24].

To study the functional consequences of the ß$_2$Gln27Glu polymorphism, an in vitro study in recombinant systems was conducted [25]. It was found that neither agonist binding nor G-protein blockade, which leads to changes in adenylate cyclase activity, did not depend on the presence of ß$_2$Gln27Glu polymorphism. Replacement of glutamic acid with glutamine at position 27 (Glu27) is associated with resistance to desensitization [26].

The main effect of ß2-AR in blood vessels is vasodilation [26]. After ß$_2$-AR activation, the cAMP-mediated mechanism of smooth myocyte relaxation is activated [26]. It is also known that ß$_2$-AR stimulation is accompanied by the release of nitric oxide (NO) from the vascular endothelium. It is assumed that this mechanism enhances (by ~ 30–50 %) the dilator response to ß$_2$-agonist infusion, as well as to functional load [27]. More pronounced arterial dilatation was found in the presence of ß$_2$Glu27 genotype compared to Gln27 [28]. The ß$_1$Glu27 variant is considered as a gain-of-function mutation [26].

In vivo studies using ß$_2$ agonists demonstrated that subjects homozygous for the Glu27 allele showed slower desensitization than those homozygous for Arg16 + Gln27 [29]. These results are generally consistent with other studies in which the ß$_2$Glu27 variant is associated with resistance to desensitization [26].

In a study involving patients with hypertension, it was demonstrated that the greatest increase in mean arterial pressure, with an increase in salt intake, occurs in the presence of ß$_2$Arg16 and ß$_2$Gln27 genotypes (separately and in combination) [51]. At the same time, the presence of a combination of ß$_2$Arg16 + ß$_2$Gln27 genotypes was associated with low-renin form of hypertension, higher plasma aldosterone levels and lower potassium levels [51].

There is much evidence that the variability of the ß$_2$-AR gene significantly affects the clinical course of CVD [26]. In the CHS study, data from 4441 Caucasian patients and 808 African Americans were evaluated during a 10-year follow-up period. It was found that regardless of race, carriers of the ß$_2$Glu27 genotype had a lower risk of coronary events compared to Gln27 [31]. Further analysis of CHS data demonstrated a greater risk of sudden car-

diac death in homozygotes (Gln27) [32]. Similar results were demonstrated by researchers of another trail — CABS, which is also presented in this publication [32]. In the second study, eight polymorphisms of genes of the sympathetic nervous and renin-angiotensin systems were evaluated in 227 patients with HF. Of these, the $ß_2$Arg16+Gln27 diplotype was the only genetic marker of increased risk of death or heart transplantation [33].

Genetic variability of $ß_2$-AR may have an impact on the effectiveness of therapeutic regimens [34]. In eighty genotyped patients with HF treated with carvedilol, those homozygous for the $ß_2$Gln27 genotype had a significantly lower proportion of so-called «good" responders (improvement of LV function) than those homozygous or heterozygous for the Glu27 polymorphism [35].

Catecholamines exert their action through ß-AR. Activation of intracellular processes occurs with the participation of cytosolic G-protein — a heterotrimer consisting of three subunits: α, ß and γ. It is known that G-proteins are expressed in all cells of the human body. The most common polymorphism C825T of the $ß_3$-subunit gene (GNB3) is associated with increased activity of signaling pathways. At the systemic level, the presence of this polymorphism primarily determines vascular reactivity and cardiomyocyte function [36]. In vivo studies have demonstrated that GNB3 825T genotype carriers have increased vascular wall reactivity upon coronary $α_2$-AR stimulation [37]. Similarly, neutrophils of GNB3 825T genotype carriers show an increased chemotactic response [38].

The T allele is more common among blacks than Caucasians [39]. Approximately 50 % of Africans are homozygous for the GNB3 TT genotype. The prevalence of «mutated» T-allele among Europeans is 38 % [40]. In the AHeFT genetic study, it was found that homozygotes for the T allele (GNB3 TT) have the most unfavorable course of HF and at the same time benefit the most from therapy [39].

Despite the fact that the T polymorphism is functionally inactive, its presence leads to alternative splicing of exon 9 (GNB3) and eventually to a «truncated» $ß_3$-subunit of G-protein. This subunit increases α-adrenergic activation. Often this mutation is the cause of early manifestation (from the age of 17 years) of low-renin variant of hypertension in African Americans [41].

Another study demonstrated that the T-allele of GNB3 may be associated with an increase in arrhythmic events in patients with HF [11]. Schmitz B. et al. (2014) showed that GNB3 gene mutation is associated with reverse remodeling after implantation of resynchronizing device in patients with HF [43]. Chemello D. et al. (2010) demonstrated that the genetic polymorphism T825 of the G-protein $ß_3$ subunit gene is associated with a higher discharge rate in patients with HF who were implanted with a cardioverter-defibrillator for ventricular tachycardia [42].

Polymorphisms of the $ß_1$-, ß-AR genes and $ß_3$-subunit of G-protein probably play an important role in the development and progression of heart failure and the response to ß-blocker therapy, possibly in the functioning of the thyroid gland, as well as in the realization of the effects of thyroid hormones on CVD. It is known that the effect of catecholamines, through ß-AR, determines the nature of structural and functional changes in the thyroid gland [42], as well as the activity of peripheral DD in the liver and adipose tissue [44].

Assumptions about the associations of ß-AR gene polymorphisms and cardiovascular function are based on pre- and clinical studies. It is likely that each of these series of studies at different levels: cellular, organ in experiments with transgenic mice, ex-vivo human heart, have their limitations [3]. However, when conducted in a comprehensive analysis, they can become arguments in favor of the causal relationship between polymorphism and phenotype of pharmacotherapy [3].

Genetic variation is the basis of human phenotypic variability and is of great importance for explaining differences in individuals prone to multifactorial diseases [45]. Identification of genetic predictors that determine the features of the course and prognosis of HF is one of the key areas of modern medicine [46]. Study of gene polymorphisms of the system ß-AR in HF are considered promising, as activation of the sympatho-adrenal system is an important link in the pathogenesis of the disease [45].

Our previous study did not demonstrate the association of ß-AR gene polymorphisms with the development of HF: there was no significant difference in the distribution of alleles and genotypes of ß-AR gene polymorphisms between a group of healthy volunteers and patients with HF [47].

Along with this, it was found that the course of heart failure, which has already developed, may be associated with polymorphisms of $ß_1$- and $ß_2$-AR genes [48]. Thus, in patients with HF, the presence of the A allele (A/G-A/A) of the Ser49Gly polymorphism of the $ß_1$-AR gene is associated with a reduced risk of the combined endpoint (CEP) (OR = 0.52 (0.28–0.96), p = 0.032, dominant heritability model). The data on the reduced risk of CEP in patients with HF in the presence of allele A of the Ser49Gly polymorphism of the $ß_1$-AR gene are confirmed in the log-additive model of heredity (OR = 0.51 (0.28–0.92), p = 0.02). Further calculations showed that the G allele (C/G-G/G) of the Gln27Glu polymorphism of the $ß_2$-AR gene increases the risk of the combined endpoint in patients with HF for 2 years (OR = 1.76 (1.04–2.96), p = 0.032, dominant heredity model and OR = 1.75 (1.06–2.90), p = 0.029 in the over-dominant model) [48].

Among HF patients who had a combined endpoint, the frequency of allele A of the Ser49Gly (c.145A>G) polymorphic locus of the $ß_1$-AR gene is lower (9.1 %) compared to the control group (19.6 %) (6.442; p = 0.011). Patients with CEP are characterized by a lower frequency of heterozygous genotype (G/A) of the polymorphic locus Ser49Gly (c.145A>G) of the $ß_1$-AR gene compared to the control group (by 53.4 %, 5.29, p = 0.021; OR = 0.35 (0.14-0.85). Carriage of the A allele (A/G-A/A) of the Ser49Gly polymorphism of the $ß_1$-AR gene was associated with a decrease in the rate of rehospitalization (RH) (OR = 0.50 [0.26-0.95], p = 0.028, dominant heredity model and OR = 0.49 (0.26-0.92), p = 0.019 in the log-additive model). Among patients with heart failure who had RH, the frequency of allele A of the Ser49Gly polymorphic locus (c.145A>G) of the $ß_1$-AR gene was 56.10 % lower compared to the control group (4.938, p = 0.026). Patients with RH have a lower frequency of heterozygous genotype (G/A) of the Ser49Gly (c.145A>G) polymorphic locus of the $ß_1$-AR gene compared to the control group (by 55.9 %, 5.65, p = 0.018; OR = 0.32 (0.12-0.84)) [48].

Further analysis of heredity models using the SNPstats on-line calculator demonstrated that the risk of reduced LV EF in patients with HF is lowest in carriers of the A allele of the Ser49Gly polymorphic locus (p.145A > G) of the $ß_1$-AR gene (OR = 0.52 (0.30–0.92), p = 0.022 in the dominant model of inheritance and OR = 0.53 (0.30–0.93), p = 0.024 in the over-dominant model). Patients with EF LV < 40 % have a lower (49.5 %) frequency of allele A of the polymorphic locus Ser49Gly (c.145A > G) of the $ß_1$-AR gene compared to the group of healthy volunteers 4,136; p = 0,042). Patients in this category also have a lower (by 53.7 %) frequency of the G/A genotype of the Ser49Gly polymorphic locus (c.145A > G) of the $ß_1$-AR gene compared to the control group (6.015; p = 0.049) [48].

The $ß_1$-AR gene is localized in chromosome 10q24-26. There are two known clinically significant polymorphisms associated with single nucleotide substitutions: at position 49 (extracellular N-terminal site), associated with the replacement of the amino acid serine (Ser) with glycine (Gly) and at position 389 (intracellular carboxy-terminal site) — with the replacement of arginine (Arg) with glycine [49]. The frequency of the Gly allele in the European population is 0.23 [49]. It is assumed that these variants $ß_1$-AR play an important role in the clinical course of HF.

To study the Arg389Gly polymorphism, cell culture studies were performed using directed mutagenesis [50]. It was found that in cardiomyocytes of mice with the Arg389 allele, compared with Gly389Gly carriers, a significantly higher basal level of adenylate cyclase activity was observed, which increased threefold upon stimulation with isoproterenol. The Arg389 allele is associated with improved receptor function and high contractility of myocardium in young mice. However, in 6-month-old mice with Arg389 allele there was a decrease in the inotropic effect of dobutamine, a decrease in $ß_1$-AR signal and a decrease in myocardial contractility [50]. Myocardial fibrosis and abnormal expression of fetal and hypertrophic genes were observed in mice carrying the Arg389 allele.

The hemodynamic effect of propranolol was stronger in the Arg389Arg genotype [50]. In another study, to investigate the association of β_1-AR polymorphism with the recovery of myocardial contractility in conditions of short-term ischemia followed by reperfusion, studies were conducted in mice with the human β_1-AR gene [51]. The researchers noted that 6-month-old mice with the Arg389 allele had a better ability to restore myocardial contractile function compared to Gly389Gly carrier mice, that is, the Arg389 allele provided a cardioprotective effect after myocardial ischemia and reperfusion injury [51].

In a study conducted on isolated trabeculae of right ventricular biopsies of patients with terminal HF, the negative inotropic effect of bucindolol was registered only in carriers of Arg389 allele, but not Gly389 Gly. The effect of carvedilol on trabecular contractility did not depend on the Arg389Gly β_1-adrenoceptor polymorphism [3].

There is evidence from a clinical trial of a longer hospital stay in patients carrying the Gly389 allele of the Arg389Gly polymorphism who underwent cardiac surgery. There were expectations that carriers of the Arg389Arg genotype (CC) would have a lower risk of CVD than people with the «wild» genotype (GG). Meanwhile, the assessment of its impact on the course of heart disease gave much more modest results. Significant differences were only in heart rate and diastolic blood pressure in carriers of different genotypes [42], while other studies have shown that people with the Arg389Arg genotype had only a non-significant increase in the risk of left ventricular hypertrophy [52].

Another frequent polymorphism of the β_1-AR gene is the replacement of the amino acid serine (allele A) with glycine (allele G) at the 49th position (Ser49Gly). The frequency of the Gly allele is 0.14 in the European population [53]. In vitro studies have shown that Ser homozygotes (AA genotype) have lower functional adenylate cyclase activity compared to G allele carriers, but are more sensitive to adrenaline stimulation [12]. In another study, no differences in basal adenylate cyclase activity were found, but high sensitivity to prolonged exposure to agonists was confirmed [54]. High sensitivity to prolonged stimulation by catecholamines is manifested in a decrease in the number of receptors and in the weakening of their response. Therefore, the β_1-AR GG gene polymorphism was called «cardioprotective» in these works. In clinical studies of homozygous patients for Gly, a lower resting heart rate was demonstrated [55].

There is evidence that the maximum oxygen consumption (VO_2) is reduced in recipients who underwent heart transplantation from a donor carrying the Gly49 allele of the Ser49Gly polymorphism of the β_1-AR gene [56]. According to the authors, patients whose donors were carriers of this genotype of Ser49Gly polymorphism require treatment with high doses of β-AB [56]. Another study searched for associations between genotypes of Arg389Gly and Ser49Gly polymorphisms of the β_1-AR gene and survival of patients with HF. 375 patients with dilated cardiomyopathy and 492 healthy controls were examined. In patients receiving lower doses of atenolol (50 % of the average therapeutic dose and below), survival was not associated with the presence of certain genotypes of the studied β_1-AR polymorphisms. Among patients taking high doses of β-AB, the five-year mortality rate was lower in carriers of the Gly49 allele compared to Ser49 ($p = 0.020$) of the Ser49Gly polymorphism [52]. It was concluded that patients with Ser49Ser genotype need higher doses of the drug to achieve therapeutic effect. In a study of patients with dilated cardiomyopathy, it was shown that carriers of the Gly allele had a lower risk of death. The authors attributed this fact to the effect on arrhythmogenesis [56].

The β_2-AR gene is localized in chromosome 5q31_32. While β_1-AR only activate G-protein (Gs), β_2-ARs can also inhibit it (Gi) by reducing cAMP production [57]. Significant mutations are Gly16Arg, Gln27Glu, Val34Met and Thr164Ile. Gly16Arg and Gln27Glu are located in the extracellular part of the receptor, while Thr164Ile is located in the transmembrane domain, and Val34Met is a rare mutation in the first transmembrane portal domain. The proportion of small β_2-AR polymorphisms in the population is as follows: Arg16, Glu27, Ile164 — 39 %, 43 % and less than 5 %, respectively, with a rare proportion of Met34 [57]. Interethnic

variability in allele frequency was shown for some polymorphisms: Gln27Glu in Europeans occurs with a frequency of 35 %, in African Americans — 21 %, in Chinese — 7 %. A single nucleotide substitution of cytosine (C) to guanine (G) at position 79 of the $ß_2$-AR gene leads to the replacement of glutamine (Gln) with glutamic acid (Glu) at codon 27 (rs1042714) [57]. The C allele is called the «wild type» allele because it is most common in the population, and the glutamic acid allele is less common, therefore it is called «mutant». The allelic frequencies of C and G in the general population are 0.55/0.45 respectively [57]. Studies have shown that this polymorphism is closely related to the sensitivity of this receptor to down-regulation. It is assumed that the Glu27 allele is more resistant to down-regulation than the wild type allele, as it causes changes in the conformation of $ß_2$-AR. According to the literature, the association of Gln27Glu $ß_2$-AR polymorphism with the clinical course of HF is rather ambiguous. Thus, in the study of exercise tolerance in patients with compensated HF and found that patients with Arg16/Glu27 had greater endurance compared to the group with Gli16/Gln27 polymorphism. They also noted that a decrease in exercise tolerance always precedes the decompensation of HF. The researchers studied the polymorphism of $ß_2$-AR and $ß_2$-AR 5' LC Arg19Cys in patients with idiopathic dilated cardiomyopathy. The analysis revealed that $ß_2$-AR Arg16 and Gln27 polymorphisms may be associated with a low risk of developing HF. At the same time, other scientists in 2004 studied 256 cases of HF, paying attention to the polymorphisms of $ß_1$-AR Arg389Gly, $ß_2$-AR Arg16Gly and Gln27Glu, but did not find a significant correlation with HF [49]. Two studies investigated the influence of $ß_2$-AR gene polymorphisms on the risk of HF development and progression. The Italian study included 236 patients with HF and 230 healthy volunteers. No associations were found between Arg16Gly, Gln27Glu polymorphisms and the course of HF [49]. Another group of researchers reported the results of a randomized study including patients with ischemic and idiopathic cardiomyopathy. There was no effect of $ß_2$-AR gene polymorphism 16 and 27 on the risk of development and features of HF [58].

In our study, for the Gln27Glu polymorphism of the $ß_2$-AR gene, there was a deviation from the Hardy-Weinberg equilibrium in the group of patients without a combined endpoint ($p = 0.026$) due to the lack of heterozygotes (38.02 % in patients without CEP, versus 51.6 % in the group with adverse HF). In the group of patients with HF with CEP and in the cohort of all patients, no deviation from Hardy-Weinberg equilibrium was observed [48].

The condition for the Hardy-Weinberg law is: the randomness of crossing in the population. It means the same probability of interbreeding between all individuals in the population. Its violation in humans may be associated with consanguineous marriages. In this case, the number of homozygotes in the population increases. Another reason for violation of the Hardy-Weinberg law is the so-called assortativity of marriages, which is associated with the non-randomness of the choice of a marriage partner. For example, there is a certain correlation between spouses in terms of intelligence. Assortativity can be positive or negative and, accordingly, increase variability in the population or reduce it. Assortativity affects not the allele frequencies, but the frequencies of homo- and heterozygotes. The conditions for the fulfillment of the Hardy-Weinberg law are also: the absence of mutations and migrations both in and out of the population; there should be no natural selection; the population should have a sufficiently large size, otherwise, even if other conditions are met, purely random fluctuations in gene frequencies (the so-called gene drift) will be observed. In our opinion, the probable reasons for the deviation of the Hardy-Weinberg equilibrium for the $ß_2$-AR gene polymorphism in the group of patients with HF without CEP Gln27Glu are its small size and large migration of the population in the region where the patients were recruited [59].

Our results also allow us to conclude that genetic differences in ß-adrenoceptor pathways may be associated with the development of low triiodothyronine syndrome (LT3S) in patients with HF [54]. Thus, in the group of patients with HF, the C/G genotype of the Gln27Glu polymorphism of the $ß_2$-AR gene is associated with a decreased risk of LT3S (OR = 0.54 [0.30–0.98], p = 0.037, over-dominant heredity

model) (Table 1). The risk of LT3S increases with the homozygous G/G genotype of this gene (OR = 2.21 [1.05–4.28], p = 0.037, recessive model). A tendency to increase the risk of LT3S was found in the presence of the C/T genotype of the Ser275 polymorphism of the GNB3 gene (OR = 1.75 [0.99–3.07], p = 0.054, over-dominant model of heredity) [60]. When taking into account the presence of LT3S, the risk of recurrent RH increases with the C/G polymorphism of Gln27Glu of the $ß_2$-AR gene (OR = 1.90 [1.08–3.34], p = 0.025, over-dominant inheritance model) (Table 2) [60].

It should also be noted that the risk of LT3S has genetic associations with concomitant TP [54]. It was found that the risk of LT3S in patients with HF with concomitant non-toxic goiter increases in homozygotes (G/G) for the Ser49Gly (c,145A > G) polymorphism of the $ß_1$-AR gene (OR = 20.54 (7.52–56.12), p = 0.0073). There was a tendency to increase the risk of developing this syndrome in heterozygotes (G/C) for the Gly389Arg (c,1165G > C) polymorphism of the $ß_1$-AR gene (OR = 15.57 (1.190–127.80), p = 0.086). In total, in patients with HF with concomitant TP, the risk of LT3S increases in homozygotes (G/G) for the Ser49Gly (c,145A > G) polymorphism of the $ß_1$-AR gene (OR = 9.19 (3.69–22.90), p = 0.044) [61].

The high levels of catecholamines inherent in HF exert their effects through the ß-adrenoceptor system. ß-ARs are found on cells throughout the body, including not only cardiomyocytes, but also vascular smooth muscle cells and extravascular cells of parenchymal organs, including the thyroid gland and liver [62]. Catecholamines through ß-AR regulate the function of the thyroid gland [62] and the activity of deiodinases, both in the gland itself and in the liver and adipose tissue [44]. $ß_1$- and $ß_2$-AR implement the stimulation of catecholamines on intracellular processes through the cytosolic G-protein – a heterotrimer consisting of three subunits: α, ß and γ. $ß_1$-AR only activate G-protein (Gs). $ß_2$-AR, along with this, can also inhibit it (Gi), reducing cAMP production, which can reduce the activity of deiodinases [63, 5, 64]. Evidence that catecholamines increase the activity of deiodinases is a decrease in the concentration of T3 in the blood serum with the use of ß-AB [62]. The inhibitory effect of ß-AB on deiodinase activity is manifested in liver homogenates, it is less pronounced in renal tubular cells [62]. Probably these data can explain the association of $ß_2$-AB gene polymorphism with the risk of LT3S in patients with HF.

Eight studies [65, 52, 20, 66, 67, 13, 68, 69] evaluated the effect of ß-adrenoceptor gene polymorphisms on the effectiveness of ß-AB. Two of them included patients with HF from East Asia, 3 studies — with the involvement of Europeans and 3 studies were mixed (held in North America, mainly consisting of African Americans and former Europeans). Intracardiac hemodynamics (echocardiography and radionuclide ventriculography) were used to evaluate the efficacy of ß-AB therapy administered for at least 3 months. ß-AB types were different, both selective (metoprolol and bisoprolol) and non-selective (carvedilol, bucindolol). The dose of ß-AB was target or maximally tolerated. There was no significant difference in heart rate reduction between Arg389 homozygotes and Gly389 carriers (OR = 20.47 (21.65–0.71), p = 0.43). Even after adjusting for ethnicity, the reduction in HR with ß-AB treatment did not differ between Arg389 and Gly389 homozygotes. Compared to Gly389 carriers, a significant improvement in intracardiac hemodynamic parameters was found in Arg389 homozygotes (OR = 1.83 (0.72–2.94), p = 0.01). Another meta-analysis, which included 4 studies [65, 67, 69] and 477 patients, showed that the improvement of LV parameters was trending in homozygotes for Arg389 compared to Gly389 allele carriers (OR = 20.16 (20.35–0.02), at p = 0.07). In another subgroup analysis, the increase in ejection fraction in Arg389 homozygous patients was significantly greater than in Gly389 carriers (OR = 2.08 (0.94–3.22), p = 0.01) only when treated with selective $ß_1$-ABs, as opposed to patients taking non-selective ß-ABs (OR = 1.90 (20.46–4.26), p = 0.11) [70]. In 10 studies, the influence of $ß_1$-AR polymorphism on the course of HF was evaluated (death and/or CEP were taken into account). Patients were predominantly Caucasian. The etiology of HF was different (CHF, dilated cardiomyopathy, hypertension). No significant difference was found between Arg389 homozygotes and

Table 1

Relationship of β-ARs gene polymorphisms and LT_3S in patients with heart failure

Model of inheritance	Genotype	Without LT_3S (n = 265)	With LT_3S (n = 89)	OR (95% CI)	p	AIC	HWE
1	2	3	4	5	6	7	8
SNP Gly389A of b							
Codominant	G/G	116 (53.7 %)	38 (62.3 %)	1.00	0.47	296.5	0.22
	G/C	80 (37 %)	19 (31.1 %)	0.72 (0.39–1.35)			
	C/C	20 (9.3 %)	4 (6.6 %)	0.61 (0.20–1.90)			
Dominant	G/G	116 (53.7 %)	38 (62.3 %)	1.00	0.23	294.6	
	G/C-C/C	100 (46.3 %)	23 (37.7 %)	0.70 (0.39–1.26)			
Recessive	G/G-G/C	196 (90.7 %)	57 (93.4 %)	1.00	0.5	295.6	
	C/C	20 (9.3 %)	4 (6.6 %)	0.69 (0.23–2.09)			
Overdominant	G/G-C/C	136 (63 %)	42 (68.8 %)	1.00	0.39	295.3	
	G/C	80 (37 %)	19 (31.1 %)	0.77 (0.42–1.41)			
Log-additive	-	-	-	0.76 (0.48–1.20)	0.22	294.6	
SNP Ser49Gly of b							
Codominant	G/G	157 (71.7 %)	52 (82.5 %)	1.00	0.12	301.4	0.44
	A/G	59 (26.9 %)	11 (17.5 %)	0.56 (0.28–1.15)			
	A/A	3 (1.4 %)	0 (0 %)	0.00 (0.00–NA)			
Dominant	G/G	157 (71.7 %)	52 (82.5 %)	1.00	0.074	300.4	
	A/G-A/A	62 (28.3 %)	11 (17.5 %)	0.54 (0.26–1.09)			
Recessive	G/G-A/G	216 (98.6 %)	63 (100 %)	1.00	0.22	302.1	
	A/A	3 (1.4 %)	0 (0 %)	0.00 (0.00–NA)			
Overdominant	G/G-A/A	160 (73.1 %)	52 (82.5 %)	1.00	0.11	301.1	0.44
	A/G	59 (26.9 %)	11 (17.5 %)	0.57 (0.28–1.17)			
Log-additive	-	-	-	0.53 (0.26–1.06)	0.057	300	

Continuation of table 1.

Model of inheritance	Genotype	Without LT_3S (n = 265)	With 3 LT_3S (n = 89)	OR (95% CI)	p	AIC	HWE
1	2	3	4	5	6	7	8
Codominant	C/C	89 (40.8 %)	28 (44.4 %)	1.00	0.045	298.9	0.16
	C/G	101 (46.3 %)	20 (31.8 %)	0.63 (0.33–1.19)			
	G/G	28 (12.8 %)	15 (23.8 %)	1.70 (0.80–3.63)			
Dominant	C/C	89 (40.8 %)	28 (44.4 %)	1.00	0.61	302.8	
	C/G-G/G	129 (59.2 %)	35 (55.6 %)	0.86 (0.49–1.52)			
Recessive	C/C-C/G	190 (87.2 %)	48 (76.2 %)	1.00	0.041	298.9	
	G/G	28 (12.8 %)	15 (23.8 %)	2.12 (1.05–4.28)			
Overdominant	C/C-G/G	117 (53.7 %)	43 (68.2 %)	1.00	0.037	298.7	
	C/G	101 (46.3 %)	20 (31.8 %)	0.54 (0.30–0.98)			
Log-additive	-	-	-	1.16 (0.78–1.71)	0.47	302.6	
SNP Ser275 of GNb							
Codominant	C/C	117 (53.7 %)	29 (46 %)	1.00	0.066	299.6	1
	C/T	81 (37.2 %)	32 (50.8 %)	1.59 (0.90–2.84)			
	T/T	20 (9.2 %)	2 (3.2 %)	0.40 (0.09–1.82)			
Dominant	C/C	117 (53.7 %)	29 (46 %)	1.00	0.29	301.9	
	C/T-T/T	101 (46.3 %)	34 (54 %)	1.36 (0.77–2.38)			
Recessive	C/C-C/T	198 (90.8 %)	61 (96.8 %)	1.00	0.088	300.2	1
	T/T	20 (9.2 %)	2 (3.2 %)	0.32 (0.07–1.43)			
Overdominant	C/C-T/T	137 (62.8 %)	31 (49.2 %)	1.00	0.054	299.4	
	C/T	81 (37.2 %)	32 (50.8 %)	1.75 (0.99–3.07)			
Log-additive	-	-	-	1.04 (0.67–1.62)	0.86	303	

AIC – Akaike information criterion,
HWE – Hardy-Weinberg equilibrium.
The same at table 2.

Table 2

Relationship of gene polymorphisms of the β-AR system with the frequency of re-hospitalization of patients with heart failure taking into account the presence of LT3S

Model of inheritance	Genotype	Without rehospitalization	With rehospitalization	OR (95% CI)	p	AIC	HWE
SNP Ser49Gly of b							
Codominant	G/G	143 (70.8 %)	66 (82.5 %)	1.00	0.16	316.4	0.44
	A/G	56 (27.7 %)	14 (17.5 %)	0.60 (0.31–1.19)			
	A/A	3 (1.5 %)	0	0.00 (0.00–NA)			
Dominant	G/G	143 (70.8 %)	66 (82.5 %)	1.00	0.1	315.4	
	A/G-A/A	59 (29.2 %)	14 (17.5 %)	0.58 (0.29–1.14)			
Recessive	G/G-A/G	199 (98.5 %)	80 (100 %)	1.00	0.23	316.7	
	A/A	3 (1.5 %)	0	0.00 (0.00–NA)			
Overdominant	G/G-A/A	146 (72.3 %)	66 (82.5 %)	1.00	0.15	316	
	A/G	56 (27.7 %)	14 (17.5 %)	0.61 (0.31–1.21)			
Log-additive	-	-	-	0.57 (0.30–1.10)	0.081	315	
SNP Gln27Glu of b							
Codominant	C/C	90 (44.8 %)	27 (33.8 %)	1.00	0.072	314.3	0.33
	C/G	81 (40.3 %)	40 (50 %)	2.01 (1.09–3.72)			
	G/G	30 (14.9 %)	13 (16.2 %)	1.23 (0.53–2.83)			
Dominant	C/C	90 (44.8 %)	27 (33.8 %)	1.00	0.05	313.8	
	C/G-G/G	111 (55.2 %)	532(66.7 %)	1.76 (0.99–3.11)			
Recessive	C/C-C/G	171 (85.1 %)	67 (83.8 %)	1.00	0.7	317.5	
	G/G	30 (14.7 %)	13 (16.2 %)	0.86 (0.40–1.84)			
Overdominant	C/C-G/G	120 (59.7 %)	40 (50 %)	1.00	0.025	312.6	0.33
	C/G	81 (40.3 %)	40 (50 %)	1.90 (1.08–3.34)			
Log-additive	-	-	-	1.25 (0.85–1.82)	0.26	316.3	

Gly389 carriers in overall mortality (OR = 1.07 (0.94–1.21), p = 0.29) or CEP (OR = 1.05 (0.95–16.16), p = 0.37) [70].

We failed to find a significant association between the efficacy of bisoprolol (in general and in different dose regimens) and the Gly389Arg (c.1165G > C) polymorphism of the β_1-AR gene, in terms of reducing the risk of RH, CEP and mortality [71].

Regarding the data on the influence of the Ser49Gly polymorphism of the β_1-AR gene on the course of HF, studies have found that the Gly49 allele significantly increased the risk of developing HF (OR = 1.22 (1.04–1.43), p = 0.02) compared to Ser49 [43]. In the ethnic aspect, Gly49 allele significantly increased the risk of HF compared to Ser49 (OR = 1.18 (1.06–1.31), p = 0.01) in East Asians, but the data were contradictory in different studies [70]. Cumulative mortality among patients with HF homozygous for Ser49 allele did not differ significantly from that in the group of Gly49-carriers (OR = 1.36 (0.93–2.01), p = 0.12), and the same was true for CEP (OR = 0.94 (0.61–1.44), p = 0.76) [70].

The multicenter MERIT-HF study investigated the association of the Gly49Ser polymorphic marker with the efficacy of metoprolol in patients with HF. The polymorphic marker Gly49Ser was not associated with the development of this pathology. The 49Ser allele is associated with a relatively higher need for concomitant medications during the initial phase of metoprolol titration, but it did not affect the maximum tolerated dose of metoprolol, the results of the 6-minute test or quality of life. Against the background of long-term metoprolol administration, a more pronounced decrease in LV end-diastolic volume was found in patients with the 49Gly allele [72]. However, no association of the polymorphism with changes in ejection fraction during treatment with β-AB (metoprolol, carvedilol and bisoprolol) was observed. Hospitalization and five-year mortality rates were significantly lower for patients who had the 49Ser allele in their genotype and took β-AB, while patients with the wild-type allele who did not receive β-AB had the worst prognosis. The 49Ser allele was also associated with improved five-year survival in patients with idiopathic dilated cardiomyopathy who received β-AB [73].

Our study demonstrated that treatment of patients with bisoprolol at a dose of > 5 mg leads to a decrease in the risk of CEP in the presence of G/A — Ser49Gly (c.145A > G) polymorphism of the β_1-AR gene (OR = 0.18 (0.04–0.84), at p = 0.014) [71].

Covolo L. et al. (2004) suggested that perhaps the Gln27Glu polymorphism of the β_2-AR gene does not affect the risk of developing HF, but it probably affects the course of the disease that has already developed [49]. It was not possible to find publications on the relationship of this polymorphism with the effectiveness of selective β_1-AB. There is only a study indicating that the use of non-selective β-AB carvedilol in patients with HF who are carriers of the C-allele of the Gln27Glu polymorphism of the β_2-AR gene in combination with the homozygous (Arg389) genotype of the Gly389Arg polymorphism of the β_1-AR gene leads to a twofold reduction in mortality [74].

According to the results of our study, the use of bisoprolol at a dose of > 5 mg leads to a decrease in the risk of RH and CEP in the presence of a homozygous C/C genotype of the Gln27Glu (c.79C > G) polymorphism of the β_2-AR gene (OR = 0.09 (0.02–0.46), at p = 0.018 and OR = 0.14 (0.04–0.58), at p = 0.006, respectively) [71].

The explanation for this result may be the beneficial effect of bisoprolol at the maximum dose in this polymorphism in terms of preventing the development of ventricular ectopic activity. Thus, a number of studies have demonstrated the association of β_2-AR gene polymorphism with the risk of ventricular arrhythmias. Thus, in a preclinical study in a model of transgenic mice, the role of the Gln27 genotype of the β_2-AR gene in the occurrence of ventricular tachycardia was shown [75]. In a clinical study it was demonstrated that the haplotype Gly16/Gln27 is a risk factor for drug-induced ventricular torsades de pointes [66]. Later, other scientists have demonstrated that the homozygous β_2-AR Gln27 genotype is associated with a high risk of sudden cardiac death and a high incidence of arrhythmogenic death among patients with acute coronary syndrome who stopped taking β-AB [25, 32]. The risk of sudden death in the group of Gln27 homozygotes reached 64 % [32].

CONCLUSIONS

We can conclude that the study of associations of ß-adrenoreceptors system genes polymorphisms with the clinical outcome of heart failure and the effectiveness of ß-adrenoblockers has been continued. It has been demonstrated that carrier state of the A allele of the Ser49Gly (c.145A > G) polymorphism of the $ß_1$-AR gene leads to a decrease in combined endpoint. At the same time, the carrier state of the G allele of the Gln27Glu (c.79C > G) polymorphism of the $ß_2$-AR gene increases the risk of combined endpoint.

Administration of bisoprolol at a dose of > 5 mg leads to a reduction of the risk of the combined endpoint, provided the G/A genotype of the Ser49Gly (c.145A > G) polymorphism of the $ß_1$-AR gene is present. The use of bisoprolol at this dose also reduces the risk of re-hospitalisation and combined endpoint, provided the homozygous genotype (C/C) of the Gln27Glu (c.79C > G) polymorphism of the $ß_2$-AR gene is present.

The probability of LT_3S increases with the homozygous G/G genotype of the Gln27Glu polymorphism of the $ß_2$-AR gene and in the presence of the C/T polymorphism of the Ser275 GNB3 gene. The genotype C/G of the Gln27Glu polymorphism of the $ß_2$-AR gene is associated with a decreased risk of low triiodothyronine syndrome.

In conclusion, it should be said that the final chapter in the history of the studies of associations of ß-adrenoreceptors genes polymorphisms with the course of heart failure and low triiodothyronine syndrome has not yet been written. Further studies are needed.

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THE ASSOCIATIONS OF β-ADRENORECEPTORS GENES POLYMORPHISMS WITH THE COURSE OF HEART FAILURE AND WITH THE LOW TRIIODOTHYRONINE SYNDROME (literature review and own observations)

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The systematization of literature data on the associations of ß-adrenoreceptors (ß-AR) genes polymorphisms with the course of heart failure and with the development of low triiodothyronine syndrome, and the results of our own study were presented. The study of associations of ß-AR system genes polymorphisms with the clinical outcome of heart failure and the effectiveness of ß-adrenoblockers has been continued. It has been demonstrated that carrier state of the A allele of the Ser49Gly (c.145A > G) polymorphism of the b_1-AR gene leads to a decrease in the risk of combined endpoint. At the same time, the carrier state of the G allele of the Gln27Glu (c.79C > G) polymorphism of the b_2-AR gene increases the risk of combined endpoint. Administration of bisoprolol at a dose of > 5 mg leads to a reduction of the risk of the combined endpoint, provided the G/A genotype of the Ser49Gly (c.145A > G) polymorphism of the $ß_1$-AR gene is present. The use of bisoprolol at this dose also reduces the risk of re-hospitalisation and combined endpoint, provided the homozygous genotype (C/C) of the Gln27Glu (c.79C > G) polymorphism of the $ß_2$-AR gene is present. The probability of the low triiodothyronine syndrome increases with the homozygous G/G genotype of the Gln27Glu polymorphism of the $ß_2$-AR gene and in the presence of the C/T genotype of the Ser275 polymorphism of the GNB3 gene. The genotype C/G of the Gln27Glu polymorphism of the $ß_2$-AR gene is associated with a decreased risk of low triiodothyronine syndrome.

Keywords: beta-adrenoreceptor, beta-blocker, heart failure, gene, low triiodothyronine syndrome, polymorphism, treatment, review.

АСОЦІАЦІЇ ПОЛІМОРФІЗМУ ГЕНІВ β-АДРЕНОРЕЦЕПТОРІВ ІЗ ПЕРЕБІГОМ СЕРЦЕВОЇ НЕДОСТАТНОСТІ ТА СИНДРОМОМ НИЗЬКОГО ТРИЙОДТИРОНІНУ (огляд літератури та власні спостереження)

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Наведено систематизацію літературних даних, щодо зв'язку поліморфізму генів β-адренорецепторів (β-AR) з перебігом серцевої недостатності та розвитком синдрому низького трийодтиронінового ряду, а також результати власного дослідження. Продовжено вивчення зв'язків поліморфізму генів системи β-аденорецепції з клінічним перебігом серцевої недостатності та ефективністю β-адреноблокаторів. Продемонстровано, що носійство алеля А поліморфізму Ser49Gly (c.145A > G) гена β_1-AR призводить до зниження ризику комбінованої кінцевої точки (ККТ). У той же час носійство алеля G поліморфізму Gln27Glu (c.79C > G) гена β_2-AR підвищує ризик досягнення ККТ. Застосування бісопрололу в дозі > 5 мг призводить до зниження ризику ККТ за умови наявності генотипу G/A поліморфізму Ser49Gly (c.145A > G) гена β_1-AR. Застосування бісопрололу в цій дозі також знижує ризик повторної госпіталізації та ККТ за умови наявності гомозиготного генотипу (C/C) поліморфізму Gln27Glu (c.79C > G) гена β_2-AR. Вірогідність розвитку синдрому низького трийодтиронінового ряду зростає при гомозиготному генотипі G/G поліморфізму Gln27Glu гена β_2-AR й при наявності генотипу C/T поліморфізму Ser275 гена GNB3. Генотип C/G поліморфізму Gln27Glu гена β_2-AR асоціюється зі зниженим ризиком розвитку синдрому низького трийодтиронінового ряду.

Ключові слова: бета-адренорецептор, бета-адреноблокатор, серцева недостатність, ген, синдром низького трийодтироніну, поліморфізм, лікування, огляд.