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Congenital long QT syndrome: genetic architecture, risk stratification and treatment approaches

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Journal of the «Cardioprogress» Foundation

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Contents

Editor's Welcome

Dear colleagues!

We present to your attention the next, forty-second issue of the International Heart and Vascular Disease Journal that includes the leading, original, review articles, as well as the report of the International Congress of the European Society of Cardiology.

The "Leading Article" section presents current and controversial issues related to the diagnosis, risk stratification, and management of patients with congenital long QT syndrome (LQTS). Attention is paid to the description of genotype-phenotype correlations of LSQT and molecular-genetic mechanisms of cardiac transmembrane ion channels disorders leading to arrhythmogenesis. The main methods of treatment of the LQTS patients, especially those with a high risk of cardiac events, are analyzed.

Three papers are presented in the "Original Articles" section. The first article examines the prognostic significance of conventional and novel biomarkers (growth stimulation expressed gene 2 (ST2)) to assess the risk of adverse cardiovascular events in patients with coronavirus infection. A prospective comparative study included 112 patients hospitalized with a confirmed diagnosis of COVID-19. An ST2 level of >36 ng/mL on the day of hospitalization, as well as the presence of AH and obesity, increased the likelihood of cardiovascular events within 1 year of discharge in patients. The second article examined possible associations of galectin-3 with laboratory and instrumental parameters in patients with chronic heart failure (CHF) and osteoarthritis. Elevated galectin-3 levels and their association with parameters reflecting the severity of heart failure progression in the group of patients with CHF and osteoarthritis may indicate more pronounced myocardial fibrosis and a higher risk of adverse outcome compared to patients without osteoarthritis. In the third article, the researchers studied the main high-resolution ECG parameters in 120 elderly patients (81.32±4.2 years) with CHF. The results of the study indicated that the decreased values of high-resolution ECG parameters such as TotQRSF, RMS40, and LAS40, which reflect myocardial electrical heterogeneity, led to an unfavorable prognosis in elderly patients with severe CHF.

The "Review Articles" section contains two works. The first article reviews the causes of hypertriglyceridemia and its association with atherosclerosis. The results of major randomized trials of fibrates, omega-3 polyunsaturated fatty acids, and nicotinic acid are reviewed to assess the efficacy, safety, and impact of treatment on cardiovascular outcomes. The second article analyzes the neurobiology of stress and anxiety and summarizes the conceptual views of panic attacks and their association with cardiovascular diseases to provide a further strategy for clinical research on panic attacks and to optimize preventive interventions.

The journal published the main results of 29 clinical trials presented at the Congress of the European Society of Cardiology (2023). The studies were devoted to the treatment of acute and chronic heart failure, arrhythmias, CHD, non-coronary myocardial diseases.

We invite everybody to collaborate with the journal. We are waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

Mekhman N. Mamedov
Editor-in-Chief
President of the "Cardioprogress" Foundation

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International medical review

Researchers evaluated the effect of fish oil on the progression of cardiovascular diseases (CVD).

The health effects of fish oil were found to depend on the presence of CVD. Among baseline healthy individuals, supplementation increased the risk of atrial fibrillation (AF) by 13% and the risk of stroke by 5%.

However, among participants with pre-existing CVD, regular supplementation was associated with a reduced risk of progression. For example, in the presence of AF, the risk of myocardial infarction was reduced by 15% and the risk of major adverse cardiovascular events was reduced by 8%. In heart failure, the risk of death was reduced by 9% with regular fish oil supplementation.

According to the BMJ journal

Researchers from Beijing evaluated the effects of intensive and standard blood pressure control on the incidence of cardiovascular events in women and men with type 2 diabetes mellitus (T2DM).

The analysis showed that the early onset of hypertension increased the likelihood of cardiovascular events. The risk increased by 11% for each decade earlier the disease was diagnosed. If hypertension was diagnosed before the age of 50, the likelihood of cardiovascular events increased by 47%. No such association was seen in men.

The authors concluded that women with type 2 DM who are diagnosed with hypertension before age 50 may benefit significantly from intensive therapy compared with standard antihypertensive treatment.

According to the Diabetes Care journal

The efficacy and safety of transcatheter aortic valve implantation (TAVI) in patients requiring aortic valve replacement was evaluated by researchers from Germany.

They analyzed data from 1404 patients aged 65 years and older with severe aortic stenosis. Of these, 701 were in the TAVI group and 713 were in the surgical valve replacement group.

The analysis showed that mortality from any cause or stroke was slightly lower one year after TAVI than after surgical valve replacement (5.4% and 10%, respectively).

According to the NEJM journal

Canadian researchers compared the efficacy and safety of edoxaban and apixaban in a group of patients over 80 years old with non-valvular atrial fibrillation.

Edoxaban and apixaban showed similar efficacy in preventing thromboembolism, with adjusted incidence rates of 20.38 cases versus 19.22 cases per 1,000 person-years.

The incidence of thromboembolism was determined to assess efficacy and the incidence of major bleeding was determined to assess safety. In addition, the risk of all-cause mortality and the risk of combined adverse outcomes were assessed.

According to the Stroke journal

Researchers from Italy evaluated the effect of micro- and nanoplastics on the risk of cardiovascular diseases and mortality in patients undergoing carotid endarterectomy for asymptomatic carotid artery disease.

The analysis showed that patients with detectable micro- and nanoplastic particles in atherosclerotic plaques had a 4.5-fold increased risk of myocardial infarction, stroke, or death from any cause after 34 months of follow-up.

Data were analyzed for 304 patients, of whom 257 completed the study.

According to the The New England Journal of Medicine

The child who received the world's first partial heart transplant in the spring of 2022 is doing well. The transplanted valves continue to grow with the patient.

After 14 months of follow-up, the child's EchoCG showed no stenosis or regurgitation in the transplanted valves. The study demonstrated an adaptive growth and an excellent hemodynamic function of the valves after partial heart transplantation.

The researchers reported that although partial heart transplantation allows the use of hearts unsuitable for full transplantation, the major problem is still the shortage of donors.

According to the JAMA Network journal

Congenital long QT syndrome: genetic architecture, risk stratification and treatment approaches

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This review article discusses current and controversial issues related to the diagnosis, risk stratification, and management of patients with congenital long QT syndrome (LQTS). Recent data on the genetic architecture of LQTS are presented, a risk stratification model is analyzed, and new potential cardiovascular prognostic factors are characterized. Much attention is given to the description of genotype-phenotype correlations of LQTS and molecular genetic mechanisms of cardiac transmembrane ion channel abnormalities that are key in the arrhythmogenesis of LQTS. The main methods of management of patients with LQTS, especially those at high risk of cardiac events, including a genotype-specific approach to management, are also presented.

Keywords: Long QT syndrome, risk stratification, sudden cardiac death, cardioverter-defibrillator.

Conflict of interests: none declared.

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Introduction

Congenital long QT syndrome (LQTS) is the most common inherited arrhythmia in the absence of structural heart disease [1–3]. LQTS is characterized by a genetically and phenotypically heterogeneous cardiac repolarization disorder manifested by an increased risk of polymorphic ventricular tachycardia (VT) and sudden cardiac death (SCD) [4, 5].

The prevalence of congenital LQTS in the population is not well known, but is thought to be between 1:2500 and 1:5000 [6]. Considering that it is undetectable in up to ⅔ of patients and 10 % to 35 % of patients have a normal QTc, it is likely that the true prevalence of LQTS is much higher [6, 7]. In general, the clinical penetrance of LQTS for all genetic types ranges from 25 % to 100 %, with an average of about 40 % [8, 9]. However, the penetrance is significantly increased by additional factors, especially by drugs that prolong the QT interval [10].

The molecular/genetic (cellular) mechanism of LQTS is based on ion channel dysfunction caused by mutations in LQTS susceptibility genes, which contributes to a decrease in the currents of inward-rectifier potassium channels (I_{Ks}, I_{Kr}, I_{K1}) and/or an increase in the depolarizing inward sodium or calcium currents (I_{Na} and I_{CaL}), resulting in prolongation of the action potential (AP) and QT interval [2, 4, 11]. In the presence of significant slowing of ventricular repolarization and increased transmural dispersion of repolarization, early postdepolarizations (electrical substrate) occur that act as trigger activity from the Purkinje network and initiate the development of polymorphic VT, especially the pirouette-type *torsades de pointes* (TdP) that is a distinctive feature of LQTS [1, 10, 12].

The aim of this review article is to detail the current genetic architecture of congenital LQTS, describe new potential risk factor (RF) stratification and current therapeutic strategies, including a genotype-specific approach in the management of patients with LQTS.

Current genetic architecture of congenital LQTS

Congenital LQTS is a polygenic disease and currently about 17 LQTS genotypes (referred to as LQT — long QT) and more than 760 mutations have been identified, leading to a revision of the LQTS classification [3, 13]. LQTS is known to be associated with mutations in 6 potassium channel genes (*KCNQ1, KCNH2, KCNE1, KCNE2, KCNJ2, KCNJ5*), 2 sodium channel genes (*SCN5A, SCN4B*), 1 calcium channel gene (*CACNA1C*) and 4 specific binding and assembly protein genes (*AKAP9, ANK9, CAV3, SNTA1*) [13, 14]. The contribution of genes involved in cellular calcium homeostasis, such as calmodulin (*CALM1, CALM2, CALM3*) and triadin (TRDN), which cause malignant variants of LQTS, is also increasingly recognized [1, 3, 13].

It should be noted that 6 LQTS susceptibility genes are classified as "defined" or definitive (*KCNQ1, KCNH2, SCN5A, CALM1, CALM2, CALM3*), 1 gene is *TRDN,* with strong evidence and 1 gene is *CACNA1C* with moderate evidence [8]. Therefore, genetic testing for these genes should be considered in patients with LQTS whose clinical manifestations correspond to a specific phenotypic expression. These extremely rare, pathogenic or probable pathogenic variants that significantly reduce repolarization reserve define the penetrant monogenic variants of congenital LQTS [13].

According to ClinGen, most of the identified LQTS susceptibility genes (*ANK2, KCNE1, KCNE2, KCNJ2, KCNJ5, SNTA1, AKAP9, SCN4B, CAV3*) have controversial or limited evidence [8] and should not be routinely tested in the evaluation of patients and families with LQTS. These genes are associated with potentially proarrhythmic "functional risk alleles" and poorly penetrant functional genetic variants in congenital LQTS [13].

Over the past two decades, the accumulated clinical experience has set the stage for a revision of the genetic architecture of LQTS with a possible downregulation of about 40 % of LQTS susceptibility genes. Taking into account the syndromic approach, a new classification of LQTS has been proposed, distinguishing the following genotype-phenotype correlations 1) non-syndromal variants of LQTS with canonical or "major" genes non-syndromal variants of LQTS with "minor" genes syndromal variants of LQTS with multisystem involvment (in 5–10 % of LQTS cases). Syndromal LQTS (Ankyrin-B, Andersen-Tawil, Timothy, and Jervell and Lange-Nielsen syndromes),

in which QT interval prolongation is possible, are associated with a pathogenic variant in one of the additional minor LQTS susceptibility genes [13, 15].

The 3 most common LQTS genotypes are caused by mutations in canonical genes — *KCNQ1, KCNH2, and SCN5A*, which are designated LQT1, LQT2, and LQT3, respectively (Table 1). These genes account for 85–95 % of all gene-positive LQTS cases [1, 6, 16]. The LQT1 genotype is the most common, occurring in 35–50 % of all LQTS variants and causing the development of Jervell and Lange-Nielsen syndrome in 90 % of cases [2, 17]. The LQT2 genotype is detected in 25–40 % and the LQT3 genotype in 5–10 % of cases. The other LQTS genotypes are found in less than 1.5 % of cases [13].

The *KCNQ1* gene responsible for the development of LQT1 encodes the α-subunit of the potassium channel that regulates slow delayed rectifier potassium currents (I_{Ks}). Loss-of-function mutations in *KCNQ1* cause a decrease in I_{Ks}, contributing to prolonged repolarization and QT interval, particularly during exercise [1, 2, 16]. The LQT2-related *KCNH2* gene encodes the α-subunit of the voltage-gated potassium channel and mediates the fast delayed rectifier potassium current (I_{Kr}) [4]. Loss-of-function mutations of the *KCNH2* gene result in decreased I_{Kr} current and are more likely to be associated with cardiac events. The *SCN5A* gene, responsible for LQT3, encodes a voltage-gated sodium channel (NaV1.5). *SCN5A* gain-of-function mutations result in increased late sodium depolarizing current (I_{NaL}) and AP prolongation [13].

It should be noted that genetic variants of minor LQTS susceptibility genes, the population frequency of which significantly exceeds the prevalence of congenital LQTS with canonical genes, may cause proarrhythmic state in the background of QT prolonging drugs, electrolyte abnormalities, structural heart disease and genetic background with repolarization

Table 1. **Characteristics of LQTS susceptibility genes [13]**

Gene	Locus	Protein	Mutation effect	Frequency (%)
Non-syndromal LQTS with canonical genes				
KCNQ1 (LQT1)	11p15.5	K_V7.1	Decrease of I_{Ks}	30–35
KCNH2 (LQT2)	7q35-36	K_V11.1	Decrease of I_{Kr}	25–30
SCN5A (LQT3)	3p21-p24	Na_V1.5	Increase of I_{Na}	5–10
Non-syndromal LQTS with minor genes				
AKAP9	7q21-q22	Yotiao	Decrease of I_{Ks}	< 1
CACNA1C	12p13.3	Ca_V1.2	Increase of I_{CaL}	~ 1-2
CALM1	14q32.11	Calmodulin-1	Increase of I_{CaL} (Ca^{2+}-dependent inactivation)	~ 1-2
CALM2	2p21.3	Calmodulin-2		~ 1
CALM3	19q13.32	Calmodulin-3		< 1
CAV3	3p25	Caveolin-3	Increase of I_{Na}	< 1
KCNE1	21q22.1	MinK	Decrease of I_{Ks}	< 1
KCNE2	21q22.1	MiRP1	Decrease of I_{Kr}	< 1
KCNJ5	11q24.3	Kir3.4	Decrease of $I_{K, Ach}$	< 1
SCN4B	11q23.3	β4-subunit/ Na_V1.5	Increase of I_{Na}	< 1
SNTA1	20q11.2	α1-syntrophin	Increase of I_{Na}	< 1
Cardiac phenotype of Timothy syndrome (type II)				
CACNA1C	12p13.3	Ca_V1.2	Increase of I_{CaL}	~ 1
Syndromal LQTS with multisystem involvement				
Jervell and Lange-Nielsen syndrome (JLNS).				
KCNQ1 (JLNS 1)	11p15.5	K_V7.1	Decrease of I_{Ks}	Very rare
KCNE1 (JLNS 2)	21q22.1-q22	MinK	Decrease of I_{Ks}	
Ankyrin-B syndrome				
ANKB	4q25-q27	Ankyrin-B	Decrease of Ankyrin-B	< 1
Andersen-Tawil syndrome				
KCNJ2	17q23	Kir2.1	Decrease of I_{K1}	< 1
Timothy syndrome (type I)				
CACNA1C	12p13.33	Ca_V1.2	Increase of I_{CaL}	Very rare
Triadin knockout syndrome				
TRDN	6q22.31	Triadin	Increase of I_{CaL}	~ 2

reserve deficiency [10, 13]. These variants result in a moderate decrease in cardiac repolarization reserve and rarely cause syncope or SCD due to LQTS. Therefore, these variants may serve as major drivers of so-called oligogenic variants of congenital LQTS when present in genetic backgrounds containing other QT-related genetic modifiers, such as common variants in *NOS1AP* [11].

The involvement of calmodulin (*CALM*) and triadin (*TRDN*) genes in LQTS has been linked to their connection to calcium signaling mechanisms, including regulation of cardiac ion channels [3, 13]. Three *CALM1-3* genes located on different chromosomes encode the same calmodulin protein, and their rare genetic variants are associated with *LQT14, LQT15, and LQT16*. The phenotypic features of these variants are manifestation of symptoms in infancy or early childhood, with marked sinus bradycardia or atrioventricular block, prolongation of the QT interval, seizures, and developmental delay. The *TRDN* gene, which encodes L-type calcium channels (triadin protein), has been classified as having strong evidence for causation of atypical LQTS, a triadin knockout syndrome. Atypical features include autosomal recessive inheritance, onset in infancy or early childhood, and negative T-peaks in the precordial leads of the ECG.

Homozygous or compound heterozygous mutations in the *KCNQ1* (type I) and *KCNE1* (type II) genes, which encode the α- and β-subunits of the potassium channel I_{Ks}, respectively, have been shown to be associated with different types of Jervell and Lange-Nielsen syndrome [2, 17]. This syndrome is characterized by bilateral sensorineural deafness, QTc prolongation usually greater than 550 m/s, and the occurrence of VT or ventricular fibrillation (VF) [15]. Cardiac features are most commonly inherited as an autosomal dominant trait, and sensorineural deafness is inherited as an autosomal recessive trait [13]. Pathogenic variants in the *KCNE1* gene have been shown to be relatively benign compared to pathogenic variants in the *KCNQ1* gene. In addition, expression of the *KCNQ1* gene in nervous tissue may contribute to the combination of channelopathy and epilepsy [16].

Loss-of-function variants of ankyrin-B encoded by *ANK2* have been shown to be associated with ankyrin-B syndrome (LQT4, according to the traditional classification), which is manifested by different phenotypes of arrhythmias resulting from impaired cellular calcium homeostasis [13]. The *ANK2* gene has an extremely low mutation frequency and functional features uncharacteristic of LQTS: atrial fibrillation, complete atrioventricular block or sinus node dysfunction.

KCNJ2 gene variants are usually associated with Andersen-Tawil syndrome, which is characterized by a triad of features: 1) hypokalemic periodic paralysis craniofacial and skeletal dysmorphism; and 3) QT interval prolongation with a high risk of polymorphic VT [15]. Mutations in the *KCNJ2* gene (type I), which encodes the Kir2.1 protein of the abnormal potassium rectifier channel (I_{K1} current), an important regulator of resting membrane potential, are detected in 80–90 % of cases. In 10–20 % of cases, Andersen-Tawil syndrome is associated with a mutation in the *KCNJ5* gene (type II), which encodes the G protein-coupled Kir3.4 potassium channels that conduct the $I_{K,Ach}$ current. It should be noted that in Ankyrin-B and Andersen-Tawil syndromes, QT interval prolongation is not a permanent feature of the cardiac phenotype.

Mutations in the *CACNA1C* gene, encoding the L-type calcium channel (CaV1.2), are associated with Timothy syndrome, which has two molecular genetic variants: the "classical" variant (type I) with a multisystem phenotype and the "atypical" variant (type II) — an isolated cardiac phenotype [13, 15]. The "classical" variant (LQT8, according to the traditional classification) is caused by a mutation in exon 8a of the *CACNA1C* gene and polymorphism of clinical manifestations: facial dysmorphism, autism, syndactyly, congenital heart defects, immunodeficiency states and early family history of SCD before the age of 30 years. In addition to possible QT interval prolongation, the ECG shows notable sinus bradycardia, macroalternation of the T-wave, conduction abnormalities, and ventricular arrhythmias, often drug-induced.

Risk stratification for cardiac events in congenital LQTS

Despite its rarity, congenital LQTS is the leading cause of SCD in otherwise healthy young adults, highlighting the importance of robust risk stratification to reduce the burden of SCD [5, 18, 19]. Genetic testing can identify the molecular substrate and thus genotype-specific proarrhythmic conditions [9, 10, 14]. However, the risk of arrhythmia in individual patients varies widely even within families carrying the same variant. This makes individual risk stratification

a challenging task, especially when antiarrhythmic treatment or cardioverter-defibrillator implantation is indicated [20, 21].

The developed system for risk stratification of cardiac events in patients with congenital LQTS under 40 years of age includes such markers as resting QTc interval value, sex, and the 3 main genotypes of the disease — LQT1, LQT2, and LQT3 (Table 2) [16, 18, 21]. Based on these markers, 3 risk levels or groups of patients have been identified: low risk (<30 %), intermediate risk (30–40 %), and high risk (>50 %).

Thus, a baseline QTc ⩾500 m/s at rest is considered definitely abnormal when observed in the absence of QT-prolonging RF. It is an independent predictor of cardiac events and serves as a class I recommendation for genetic testing for LQTS [21]. Of note, numerous prospective studies have demonstrated the high predictive value of prognostic stratification in patients with LQTS [1, 22, 23].

Table 2. **Risk stratification in patients with congenital LQTS [14]**

Risk of cardiac events by the age of 40	Resting QTc	Genotype	Gender
High risk (>50 %)	⩾ 500 m/s	LQT1	male/female
		LQT2	male/female
		LQT3	male
Intermediate risk (30–49 %)	< 500 m/s	LQT2	female
		LQT3	female
		LQT3	male
	⩾ 500 m/s	LQT3	female
Low risk (<30 %)	< 500 m/s	LQT2	male
		LQT1	male/female

Determination of LQTS genotype is a determinant of RF of SCD along with QT interval duration [21, 24]. Women with LQT2 and men with LQT3 who have a QTc interval >500 m/s fall into a higher risk category for SCD independent of other RF [12, 15]. In addition, women with LQT2 are at highest risk for cardiac events in the peripartum period, especially in the first 9 months after delivery [25]. The onset of arrhythmic events in childhood has been shown to be an important predictor of their recurrence in later life [5, 18]. However, in individuals with a positive genotype, a family history of SCD in a first-degree relative is not associated with an increased risk of SCD in LQTS [19].

In recent years, new markers for prognostic stratification in LQTS have been proposed to differentiate risk groups among patients with LQTS. In addition, new risk stratifiers for LQTS have demonstrated a high predictive value in the prediction of cardiac events, superior to the resting QTc interval [26-28]. In particular, the $T_{peak} - T_{end}$ interval has been shown to be an indicator of cardiac proarrhythmic potential due to transmural and local repolarization dispersion in patients with LQTS [27]. It has also been demonstrated that QT interval dispersion (QTd) — the variability of the QT interval between the leads of a standard ECG — reflects the heterogeneity of ventricular repolarization and may therefore serve as a marker of cardiac electrical instability [29].

The assessment of exercise repolarization reserve is of practical interest, although genotype-specific proarrhythmic triggers, particularly QTc response, are not included in risk stratification schemes for patients with LQTS. This is particularly important given that approximately 40 % of patients with genetically confirmed LQTS have a normal resting QTc interval. It is known that the QTc interval is prolonged during exercise in LQT1 (impaired adaptation of QT interval to HR), shortened in LQT2, and significantly shortened in LQT3 [2, 16].

It has also been shown that in LQTS, heterogeneously prolonged ventricular repolarization and impaired regional repolarization lead to changes in myocardial mechanical function, creating an electromechanical substrate capable of causing pathological myocardial excitability and triggers the *re-entry mechanism* [26, 28]. In this context, a new criterion of electromechanical dispersion has been proposed — the "electromechanical window", an indicator determined by tissue Doppler cardiac imaging.

Importantly, these potential markers of cardiac event risk have been shown to be strongly correlated with outcomes of BAB therapy and sympathetic denervation, to have genotypic risk differences, and to allow differentiation between symptomatic and asymptomatic patients with LQTS [27].

In addition, the correct diagnosis of LQTS in patients with a normal resting QTc interval but genetically confirmed LQTS is important for risk stratification. Recently, the use of artificial intelligence in the interpretation of standard ECGs has allowed the identification of patients with electrocardiographically hidden LQTS and provides almost 80 % accurate pretest assessment of LQTS genotype in patients with normal resting QTc interval [30].

Role of genetic risk in the prediction of cardiac events in LQTS

Given that LQTS is the most common channelopathy in which SCD is often the first manifestation of the disease, the clinical importance of genetic type identification is high [12, 18, 21].

The impact of genotype, sex and age on the prognosis of LQTS has been described in detail by the International LQTS Registry study group in patients with LQT1-3 variants [16]. Mortality from cardiac events was highest in men and women with LQT3 (19 % and 18 %, respectively), followed by men with LQT1 and LQT2 (5 % and 6 %, respectively), and finally women (2 % for both types). In addition, affected males have an increased incidence of cardiac events in childhood, but the trend is reversed in adolescence and early adulthood [12]. The risk of cardiac events in childhood has been shown to be significantly higher in men with LQT1 than in women with LQT1 (OR 1.72), whereas there were no significant gender differences in patients with LQT2 and LQT3. In adulthood, women with LQT1 and LQT2 had a higher risk of cardiac events than men. Earlier symptom manifestation was associated with a more severe LQTS outcome.

Goldenberg I. et al. [25] evaluated the individual risk of cardiac events in 767 women with LQT1 and LQT2 types aged 15–60 years based on the developed prognostic model. The risk prediction model included the following variables: genotype/mutation position, specific QTc thresholds, history of syncope, and beta blockers (BAB) therapy. The predicted 10-year cardiac event rate was shown to be 2 % at low risk, 5 % at intermediate risk, and 14 % at high risk. The authors believe that the model developed to estimate prognosis in LQTS may help to improve gender-specific risk stratification and therapeutic decision making.

Carriers of LQTS mutations are shown to have an increased risk of cardiac events even in the absence of QTc prolongation. At the same time, the penetrance of mutations in patients with normal QTc may be reflected in the abnormal shape of the T-wave [16, 19]. Cortez D. et al [31] demonstrated the predictive value of the three-dimensional vector of the T wave as a quantitative indicator of repolarization in *KCNH2* (LQT2) mutation carriers with normal QTc at high risk for cardiac events.

In addition, the prognostic significance of assessing the effect of BAB therapy on the incidence of cardiac events depending on the LQTS genotype has been demonstrated [32]. Thus, in patients younger than 40 years, the incidence of cardiac events during BAB therapy was significantly higher in LQT2 (46 %) and LQT3 (42 %) types than in patients with LQT1 type (30 %) [12]. Arrhythmic events in LQT3 have been shown to be more likely to be fatal.

Mutations that result in amino acid substitutions in specific regions of the ion channel also increase the risk of arrhythmias [12, 23]. For example, in LQT1 type, mutations in the cytoplasmic loops of the *KCNQ1* protein or mutations with dominant negative ion current effects are associated with a worse prognosis, especially when compared to mutations affecting the C-terminal regions of the protein. It is also known that single nucleotide polymorphisms in *NOS1AP* and *KCNQ1* are associated with an increased risk of cardiac events in patients with LQTS and can therefore be used in clinical risk stratification [12, 18].

Treatment tactics for congenital LQTS

When choosing management tactics for patients with LQTS, it should be considered that specific manifestations of the disease are syncope and SCD caused by polymorphic VT or VF, often provoked by acute adrenergic activation. Patients diagnosed with LQTS are advised to make lifestyle changes and refrain from taking drugs that prolong the QT interval (Class I; Level of Evidence B) [21, 33]. It is important to note that the choice of therapeutic tactics should be determined by the phenotype, but knowledge of the LQTS genotype may help in prescribing genotype-specific therapy [1, 14].

Genotype-specific pharmacotherapy for LQTS. Currently BAB, especially nadolol and propranolol remain the main drugs used for the treatment of LQTS [32, 34, 35]. According to clinical guidelines, prescription of BAB is indicated in patients with LQT1 and LQT5 diagnosed by genetic testing (class IIa; level of evidence B). In patients with LQT3, the prevailing opinion for a long time was that there was no effect or contraindication to BAB [32]. However, recent studies have shown that BAB significantly reduce the risk of cardiac events in patients with LQT3, especially in women [25].

From the point of view of genotype-specific treatment of LQTS, not all BAB are equivalent [35]. Four BABs studied — nadolol, metoprolol, propranolol, bisoprolol — showed similar efficacy in preventing arrhythmic events in LQT1, but in LQT2, nadolol proved

to be the only BAB that caused a significant reduction in risk. In pregnant women diagnosed with LQTS, nadolol is also recommended because it is the most effective BAB for LQTS and is well tolerated [25].

For LQT2 and LQT6, additional therapy may include long-term potassium supplements and/or spironolactone (class IIa; level of evidence B), and calcium channel blockers are recommended (class IIb; level of evidence B). Because LQT3 is caused by an excess of I_{Na} sodium current entry, mexiletine, which has antiarrhythmic effects (class IIa; level of evidence B), is recommended [21, 36]. In addition, mexiletine significantly shortened the QTc interval in ⅔ of patients with potassium channel-mediated LQT2 [37]. The drug is effective both as monotherapy and in combination with BAB [37].

Long-term treatment with amiodarone has been shown to prolong the QT interval, but TdP is very rare [1, 21]. This is because amiodarone slows repolarization uniformly in all layers of the cardiac wall and therefore does not cause an increase in transmural dispersion of repolarization, which is a substrate for TdP [1, 4, 9]. In addition, the low risk of developing TdP with amiodarone is related to the drug's additional effect of inhibiting I_{NaL}, which reduces the arrhythmogenic potential.

Ranolazine has also been successfully used to treat ventricular arrhythmias in patients with LQT3. The drug blocks late sodium and fast potassium currents (I_{NaL}, I_{Kr}) and therefore has the effects of class IC and III antiarrhythmic drugs [38]. During long-term therapy with ranolazine, the degree of QT interval prolongation is limited, which is explained by the drug's effect of blocking the I_{NaL} current. In addition, like flecainide, ranolazine counters TdP inducers and can therefore be used in patients with LQT3, especially when flecainide is contraindicated [37]. In Andersen-Tawil syndrome, calcium channel blockers (verapamil) and fast sodium channel blockers (flecainide) are recommended to control ventricular arrhythmias [21, 33].

Non-pharmacologic treatment options for LQTS

Implantation of a cardioverter-defibrillator (ICD) is an integral part of the current therapeutic options for LQTS [33, 39, 40]. This is because the recurrent episodes of sudden cardiac arrest are often observed despite optimal medical therapy. Therefore, the use of ICD is recommended for the primary prevention of SCD in patients diagnosed with LQT3 by molecular genetic testing and for the secondary prevention of SCD in patients diagnosed with LQTS: LQT1, LQT2, LQT5 and LQT6 (Class I, Level of Evidence B). The ICD is also indicated in patients with a clinical diagnosis of LQTS in the presence of significant RF of SCD in the background of BAB administration (Class IIa, Level of Evidence B). The ICD may be recommended in patients with recurrent VT or SCD who have contraindications for BAB [21, 34].

Independent RF that closely correlate with motivated ICD discharges in the setting of adequate BAB therapy have been identified [39, 40]: previous sudden cardiac arrest; long (>500 m/s) or very long QTc interval (>550 m/s); LQT2 genotype and multiple mutations associated with LQTS (mainly patients with Jervell and Lange-Nielsen syndrome).

The artificial cardiac pacemaker (ACP) implantation remains one of the most effective methods of VT prevention in patients with LQTS, especially in those with "pause-dependent" arrhythmias [2, 18]. Indications for ACP are: absence of BAB effect or their intolerance; presence of spontaneous atrioventricular or sinoatrial block; "jagged rhythm" in AF [1, 2, 16]. To optimize the effectiveness of ACP, it is necessary to meet the requirements for programming the electrostimulation parameters: 1) set a sufficiently high lower frequency limit of electrostimulation disable ACP algorithms that allow HR deceleration below the lower frequency limit or can cause pauses (hysteresis function) use the "rhythm frequency smoothing" algorithm to prevent pause-dependent TdP.

The beneficial effects of ACP may be related to the shortening of the QTc interval and the elimination of the pause-dependent TdP trigger. It should be noted that a relatively frequent imposed resting rhythm and/or absence of pauses after extrasystoles (without ACP hysteresis function) prevents TdP. ACP implantation combined with BAB is probably an effective method in patients with LQTS by preventing episodes of TdP and/or reducing the effects of BAB-induced bradycardia [34]. An ICD with integrated anti-bradycardia electrical stimulation function may provide more benefit by preventing bradycardia-dependent TdP and/or managing VT/VF episodes [39, 40].

Cardiac sympathetic denervation (CSD) has been proposed as an effective therapy for LQTS in addition to antiarrhythmic drugs and ICD [21, 39]. Removal of the left stellate ganglion has been shown to elimi-

nate the asymmetric sympathetic innervation of the heart, which is an arrhythmogenic factor, leading to a shortening of the QT interval and the reduced risk of SCD [20]. Current clinical guidelines consider the use of left-sided CSD in patients diagnosed with LQTS who have underlying RF for SCD despite receiving BAB (class IIa recommendation, level of evidence B) [21]. (Complete) surgical removal of the ganglia and bilateral sympathectomy compared to video thoracoscopic (partial) sympathectomy has been shown to significantly shorten the QTc interval and reduce the incidence of cardiac events in patients with LQTS [11].

Dusi V. et al. [41] found in 125 patients with LQTS, including those with ICD, a reduction in the mean annual cardiac event rate of 86 % ($p<0.0001$) after CSD. Patients with QTc ⩾500 m/s had a 50 % chance of achieving a mean QTc shortening of 60 m/s. For primary prevention of SCD, the CSD procedure was effective in 97 % of cases. Thus, there is a compelling evidence for the long-term benefit of left-sided CSD in LQTS complicated by arrhythmic events. At the same time, antiarrhythmic protection depends on the phenotype of LQTS and the degree of QTc shortening after CSD.

Conclusion

As demonstrated, the high frequency of background genetic variability observed in recent years, particularly in minor LQTS susceptibility genes, is changing paradigms about the genetic architecture of congenital LQTS. As a result, a number of minor LQTS susceptibility genes previously thought to be responsible for 5–10 % of non-syndromal LQTS variants may be downgraded to the status of gene with limited or controversial evidence or categorized as oligogenic/polygenic variants.

Given these issues, there is a need for ongoing reassessment (reclassification) of functional risk alleles and poorly penetrant LQTS genetic variants that may contribute to the pathogenesis of LQTS and therefore reflect the true genetic risk of the disease. Despite advances in the management of patients with LQTS, including effective genotype-specific pharmacotherapy and the widespread use of implantable antiarrhythmic devices, congenital LQTS remains a dangerous disease with potentially fatal consequences. Therefore, further large prospective clinical trials are urgently needed, especially to improve risk stratification for cardiac events and early detection of patients and their family members with LQTS.

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Prognostic role of ST2 biomarker in the development of adverse cardiovascular events in patients with new-onset coronavirus infection

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The aim of the study is to determine the prognostic significance of established and novel cardiovascular biomarkers (growth stimulation expressed gene 2 (ST2)) for assessing the risk of adverse cardiovascular events (ACVE) in patients with novel coronavirus infection (COVID-19) during long-term follow-up.

Methods. A non-randomized, prospective comparative study included 112 patients hospitalized with a confirmed diagnosis of COVID-19. In addition to standard laboratory tests, the levels of cardiovascular biomarkers (lactate dehydrogenase (LDH), high-sensitivity troponin I (hsTrI), high-sensitivity troponin T (hsTrT), creatine phosphokinase (CPK), creatine phosphokinase MB fraction (CPK-MB), ST2) were determined on the day of hospital admission. Patients were followed for 366 [365; 380] days.

Results. During the follow-up period, 14 (12.5%) patients developed ACVE, including 4 (3.6%) deaths from cardiovascular causes. The group of patients with developed ACVE had higher admission BMI, IL-6, D-dimer, LDH, CPK, CPK-MB and ST2 concentrations ($p<0.05$ for all parameters). Predictors of the development of ACVE were arterial hypertension (AH) (odds ratio (OR) 2.73, 95% confidence interval (CI) 1.20–6.22, χ^2 =5.3, p=0.021), obesity (OR 2.13, 95% CI 1.15–3.96; χ^2 =5.6, p=0.018), ST2 level > 36 ng/mL (OR 1.23, 95% CI 1.11–1.37; AUC 0.949, sensitivity 92.9%, specificity 33%, p=0.000).

Conclusion. The ST2 level of >36 ng/mL on the day of hospitalization as well as the presence of AH and obesity increased the likelihood of developing ACVE within 1 year of discharge in patients who had a coronavirus infection.

Keywords: ST2, cardiovascular diseases, adverse cardiovascular events, COVID-19.

Conflict of interests: none declared.

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Introduction

Approximately 24 million confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) were recorded during the pandemic of a new coronavirus infection (COVID-19) in the Russian Federation. According to the number of deaths from COVID-19, Russia ranks 4th in the world with 400 thousand deaths, and the mortality rate from COVID-19 per 100 thousand population was 276 [1].

About 80 % of infected patients have no significant symptoms of COVID-19, or the severity of the clinical picture of the disease varies from mild to moderate [2]. The severe course of COVID-19 is characterized by a "cytokine storm", acute respiratory distress syndrome, systemic inflammatory response (SIRS) and the development of multiple organ failure. In patients with severe COVID-19, pre-existing cardiovascular disease (CVD), arterial hypertension (AH) and heart failure increase the risk of poor clinical prognosis and in-hospital mortality [3]. A number of patients without a history of CVD were found to have acute myocardial injury and dysfunction during hospitalization for COVID-19, as determined by elevated high-sensitivity cardiac troponins (hsTr) above the 99th percentile [4, 5]. Considering that COVID-19 in combination with SIRS may have unfavorable effects on the cardiovascular system, biomarkers of cardiac damage such as B-type natriuretic peptide (BNP), hsTr, lactate dehydrogenase (LDH), D-dimer, along with proinflammatory markers (interleukin 6 (IL-6), C-reactive protein (CRP), ferritin) were included in the COVID-19 in-hospital mortality prediction models [3, 5].

Cardiovascular symptoms as part of COVID-19 manifestation [3, 7], destabilization of known or registration of newly detected CVD in the acute phase of the disease [3, 5, 6] are described in the works of a number of authors, however, more recent studies emphasize the importance of long-term follow-up of patients due to the possibility of development of delayed adverse cardiovascular events (ACVE) [7]. In their study, Zagidullin N. et al. found a correlation between the incidence of ACVE during long-term follow-up and the levels of traditional (high-sensitivity troponin I (hsTrI)) and promising (growth stimulation expressed gene 2 (ST2)) biomarkers at admission [7].

ST2 is a receptor protein expressed by immune cells, cardiomyocytes, fibroblasts and endotheliocytes that can exist in two isoforms, soluble (ST2) and transmembrane (ST2L). In myocardial alterations on the background of SIRS, there is a hyperproduction of interleukins, including interleukin-33 (IL-33), which binds to ST2L, realizing the cardioprotective effect of IL-33 [8]. In turn, IL-33 acts as a ligand for ST2. Myocardial stress leads to an increase in ST2 concentration, which interacts with IL-33 and blocks its antiproliferative and antiapoptotic effects [8, 9]. In the study by Pascual-Figal D.A. et al, it was shown that in patients with known heart failure, ST2 was actively produced in alveocytes and increased in cardiogenic pulmonary edema and bronchopneumonia [9]. Zeng Z. et al. found a correlation between the serum concentration of ST2 and the activity of the inflammatory response in COVID-19 [10].

Considering the possible ST2 production in lung tissue [9], activation of ST2 production by immune cells in SIRS [8] and myocardial stress [8, 9], association with inflammation in COVID-19 [10], a more detailed study of the role of plasma ST2 levels in myocardial damage in COVID-19 patients is relevant.

The aim of this study was to determine the prognostic significance of common (LDH, hsTrI, high-sensitivity troponin T (hsTrT), creatine phosphokinase (CPK), creatine phosphokinase MB fraction (CPK-MB)) and novel (ST2) cardiovascular biomarkers for assessing the risk of ACVE in COVID-19 patients during long-term follow-up.

Methods

A non-randomized, prospective comparative study included 112 patients hospitalized with a confirmed diagnosis of COVID-19. A total of 188 patients were consecutively enrolled in the initial screening. Subsequently, 76 patients withdrew from the non-randomized prospective comparative study for various reasons.

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Inclusion criteria for patients were: need for hospitalization due to COVID; positive PCR test for detection of SARS-CoV-2 RNA on admission; lung lesions of 1–4 degrees; voluntary consent of the patient to participate in the study; age 40–70 years. Exclusion criteria were: existing CVD; acute and chronic bronchial and pulmonary diseases of other etiologies; cancer; type 1 and type 2 diabetes mellitus (DM).

On the day of admission to the remodeled COVID-19 hospital, all patients underwent chest computed tomography (CT) and venous blood samples were taken for complete blood count (CBC) and biochemical blood analysis (total protein, albumin, creatinine, AST, ALT, total cholesterol, procalcitonin, LDH, CPK, CPK-MB, hsTrT, hsTrI, D-dimer, CRP, ferritin, IL-6, ST2). ST2 levels were determined using a commercially available Presage® ST2 assay kit (enzyme immunoassay kit for quantitative determination of ST2, "Biokhimmak", Russia), which is designed to quantify ST2 by enzyme-linked immunosorbent assay in 96-well microplates with monoclonal antibody coated on the bottom of the wells. Diluted plasma or serum samples were added to the appropriate wells of the microplate and incubated for the indicated time. The concentration of ST2 was detected by adding a colorimetric reagent. The threshold value of ST2 was set at 35 ng/ml [11].

Patients with COVID-19 at the hospitalization stage received drug therapy as recommended in the current "Temporary guidelines for the prevention, diagnosis, and treatment of novel coronavirus infection" [12].

The sample of 112 patients was followed up for 12 months from the moment of discharge from the hospital, while the cases of developed ACVE (myocardial infarction, pulmonary embolism, acute cerebral circulatory failure, death from cardiovascular causes) were being registered.

Statistical analysis

STATISTICA 8.0 and MedCalc 8.2.0.3 programs were used for statistical processing of the obtained results. The distribution of parameters was checked for conformity to the normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The median, upper and lower quartiles (Me [Q1; Q3]) were indicated to represent signs with non-normal distribution. Differences between groups were analyzed by non-parametric methods using the Mann-Whitney U-test. Differences between categorical variables were analyzed using the χ^2-Pearson test. Correlations between ST2 level and clinical and laboratory parameters were established by calculation of Kendall correlation coefficient (r). Logistic regression analysis with calculation of the natural logarithm of the odds ratio (OR) with 95 % confidence interval (CI) was performed to assess the independent influence of the studied predictors on the occurrence of ACVE. ROC-curve (receiver operating characteristic) was plotted and area under the ROC-curve (AUC, Area under the ROC Curve) was calculated. In the process of ROC-analysis the cut-off point was determined with calculation of sensitivity and specificity of prognostic biomarker levels. Differences at $p<0.05$ were considered statistically significant.

The study protocol was approved by the local ethics committee of the Saratov State Medical University. Before inclusion in the study, all patients signed a voluntary informed consent for further participation.

Results

The clinical characteristics of the patients at the time of hospitalization are shown in Table 1. The majority of patients were women (57.1 %). Smoking was found in less than a quarter of patients (21.4 %), and the most common comorbidities were excess body weight (26.8 %) and dyslipidemia (45.5 %).

Table 2 shows the baseline laboratory values and Table 3 — the cardiovascular markers of the COVID-19 patients at hospital admission. Leukopenia (white blood cell count less than 4×10^9/L) was observed in 16 patients (14.3 %), leukocytosis (white blood cell count greater than 9×10^9/L) in 24 patients (21.4 %), thrombocytopenia (platelet count less than 150×10^9/L) in 22 patients (19.6 %), serum CRP greater than 10 mg/L in 103 patients (91.9 %), and IL-6 greater than 7 pg/mL in 50 patients (44.6 %).

Among cardiovascular parameters, only ST2 (in 51 (45.5 %) hospitalized patients) showed an increase above the threshold values. At the same time, no increase in hsTrT, hsTrI, CPK, CPK-MB, LDH levels was observed in any of the patients studied.

Correlation analysis revealed a direct moderate relationship between ST2 concentration and transition to non-invasive lung ventilation during hospitalization ($r=0.40$, $p<0.05$) and after discharge due to ACVE ($r=0.42$, $p<0.05$). In correlation analysis, weak direct correlations were found between ST2 and

Table 1. **Clinical characteristics of patients at the time of hospitalization**

Parameter	Patients (n=112)
Age, years	58.0 [48.5; 63.5]
Males n (%)	48 (42.9)
Females, n (%)	64 (57.1)
Body mass index, kg/m^2	25.3 [23.3; 29.4]
Hospitalization duration, days	10.0 [8.0; 14.0]
Duration of the disease at the time of hospitalization, days	7.0 [5.5; 10.0]
SpO_2, %	96.0 [94.0; 97.0]
HR, per minute	85.0 [75.0; 95.0]
Systolic BP, mmHg	125 [115.0; 130.0]
Diastolic BP, mmHg	76 [70.0; 83.0]
RR, per minute	17 [16.0; 20.0]
Severity of COVID-19 course: Moderately severe, n (%) Severe, n (%)	 77 (68.8) 35 (31.2)
CT stage at the time of hospitalization: 1, n (%) 2, n (%) 3, n (%) 4, n (%)	 63 (56.3) 31 (27.7) 16 (14.3) 2 (1.8)
Smoking, n (%)	24 (21.4)
AH at the time of hospitalization: 1 grade, n (%) 2 grade, n (%)	 13 (11.6) 6 (5.4)
Dyslipidemia, n (%)	51 (45.5)
Excess body weight, n (%)	30 (26.8)
Alimentary obesity: 1 grade, n (%) 2 grade, n (%)	 7 (6.3) 4 (3.6)

Note. CT stage at the time of hospitalization was established on the basis of the current "Temporary guidelines for prevention, diagnosis and treatment of novev coronavirus infection".

Table 2. **Laboratory parameters of patients at the time of hospitalization (Me [Q25; Q75])**

Parameter	Patients (n=112)
Leukocytes, ×10^9/l	6.7 [4.6; 9.0]
Lymphocytes, %	18 [12.0; 29.0]
Monocytes, %	5 [3; 8]
Thrombocytes, ×10^9/l	198 [150; 264]
Hemoglobin, g/l	138 [128; 151]
Erythrocytes, ×10^{12}/l	4.6 [4.3; 5.1]
Sed rate, mm/h	27 [19; 36]
CRP, mg/l	41 [17; 98]
Ferritin, ng/mL	285 [150; 601]
IL-6, pg/mL	4.1 [0.6; 28.6]
Total cholesterol, mmol/L	4.2 [3.5; 5.0]
Non-HDL-C, mmol/L	3.5 [2.7; 4.1]
Glucose, mmol/L	6.0 [5.4; 7.0]
ALT, units/l	35 [26; 60]
ACT, units/l	37 [28; 53]
D-dimer, μg/mL	0.6 [0.4; 1.0]
GFR, ml/min/m^2	84 [68; 94]

Table 3. **Concentrations of cardiovascular biomarkers in patients hospitalized with COVID-19 (Me [Q25; Q75])**

Biomarker	Patients (n=112)
LDH, units/l	175 [170; 190]
CPK, units/l	61 [57; 69]
CPK-MB, units/l	12 [9; 15]
hsTrT, ng/mL	3.5 [2; 5]
hsTrI, ng/mL	6 [4; 8.5]
ST2, ng/mL	34 [29.4; 42]

Table 4. **Structure of adverse cardiovascular events at 1-year follow-up of patients**

Study endpoints	Patients, n (%)
Adverse cardiovascular events	
MI	9 (8.0)
Stroke	3 (2.7)
PE	2 (1.8)
Deaths due to cardiovascular causes	
MI	3 (2.7)
PE	1 (0.9)

hsTrT (r=0.17, p<0.05) and LDH (r=0.14, p<0.05) levels. No correlations were found between ST2 concentration and the value of other cardiovascular (hsTrI (r=0.05, p>0.05), CPK (r=0.12, p>0.05), CPK-MB (r=0.10, p>0.05)) and inflammatory parameters (CRP (r=0.05, p>0.05), ferritin (r=0.08, p>0.05), IL-6 (r=0.05, p>0.05)).

The incidence of ACVE during the prospective follow-up is summarized in Table 4. ACVE were recorded in 14 (12.5 %) patients, including 4 (3.6 %) deaths from cardiovascular causes.

We compared the clinical and laboratory data in patients who did not reach the endpoints during the long-term follow-up (group 1) and those, who reached them (group 2) (Table 5). Table 5 shows that the patient groups did not differ in sex, age, severity of COVID-19 course, CRP, ferritin, and hsTrI levels. Significant differences were found in BMI, IL-6, D-dimer, LDH, CPK, CPK-MB, and ST2 concentrations at admission (p<0.05 for all parameters).

Using these variables as predictors of ACVE onset, we performed logistic regression analysis with OR calculation for each of the variables. Despite significant differences between the patient groups in several clinical and laboratory parameters, comorbidities were the predictors of ACVE onset: AH (OR 2.73, 95 % CI, 1.20–6.22; χ^2 =5.3, p=0.021), obesity (OR 2.13, 95 %, CI 1.15–3.96; χ^2 =5.6, p=0.018); ST2 levels (OR 1.23, 95 %, CI 1.11–1.37, p=0.000).

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Table 5. **Clinical and laboratory parameters in patients with COVID-19 depending on the development of endpoints at 1-year follow-up**

Parameter	Group 1, n=98	Group 2, n=14	p
Gender Males, n (%) Females, n (%)	 42 (42.9) 56 (57.1)	 6 (42.9) 8 (57.1)	0.563
Age, years	58 [49; 64]	57 [46; 63]	0.933
BMI, kg/m^2	24.9 [22.9; 29.0]	28.8 [25.0; 36.3]	0.018
COVID-19 course: Moderately severe, n (%) Severe, n (%)	 70 (71.4) 28 (28.6)	 7 (50) 7 (50)	0.105
CRP, mg/l	39.2 [17; 99]	72 [51; 128]	0.078
Ferritin, ng/mL	288 [156; 601]	448 [250; 898]	0.130
Total cholesterol, mmol/L	4.1 [3.5; 4.8]	5.2 [4.2; 5.8]	0.014
Non-HDL-C, mmol/L	3.3 [2.7; 4.0]	4.2 [3.5; 5.0]	0.012
D-dimer, μg/mL	0.56 [0.38; 0.92]	1.2 [0.8; 1.9]	0.001
hsTrT, ng/mL	3 [2; 5]	6 [4; 6]	0.003
hsTrI, ng/mL	6 [4; 8]	7 [5; 12]	0.150
IL-6, pg/mL	2.9 [0.6; 29.1]	15.9 [7.8; 58.5]	0.017
LDH, Units/l	175 [170; 180]	210 [195; 210]	0.000
CPK, Units/l	60 [57; 66]	71 [68; 83]	0.000
CPK-MB, Units/l	11 [9; 14]	23 [15; 33]	0.000
ST2, ng/mL	33.3 [28.5; 38]	64 [55; 84.3]	0.000

Note. The p values were obtained from the results of the non-parametric Mann-Whitney test

Based on the results of the ROC analysis, an optimal ST2 concentration of > 36 ng/mL was calculated (AUC =0.949, sensitivity 92.9%, specificity 33%, p=0.000) (Figure 1).

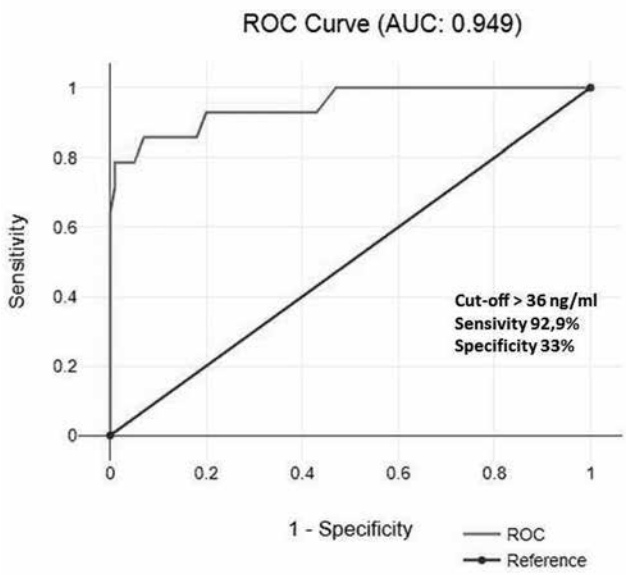

Fig. 1. Sensitivity and specificity of serum ST2 concentration in risk stratification of ACVE development in COVID-19 patients (ROC analysis)

Discussion

During the COVID-19 pandemic, the interpretation of laboratory parameters and the development of prognostic models of adverse outcomes were actively used to identify patients at high risk for adverse clinical outcomes along with chest CT [3, 5]. The most common markers of inflammation (CRP, IL-6, ferritin) and cellular damage (LDH, hsTr) have been included in these prognostic models [2, 5, 13]. These studies investigated the prognosis of various outcomes during hospitalization, and delayed outcomes were not given enough attention.

By reviewing the published works on the evaluation of ACVE development during long-term (1–2 years) follow-up of COVID-19 patients, we selected a list of cardiovascular biomarkers (LDH, hsTrI, hsTrT, CPK, CPK-MB, ST2) that were associated with the onset of ACVE [6, 7, 10]. The performed correlation analysis did not reveal significant relationships between ST2 level and the level of other laboratory parameters (including cardiovascular), which indicates the independence and standalone position of the new cardiovascular biomarker ST2. In other published works, the authors did not determine the correlation strength between ST2 level and clinical/laboratory characteristics of hospitalized patients with COVID-19.

In our study, the incidence of ACVE within 12 months was 12.5%, which is not significantly different from the incidence of ACVE in Zagidullin N. et al. (2023), which was 8.4% [7]. Reliable predictors of ACVE in this study were: hsTrI (HR 1.354, 95% CI 1.073–1.710, p=0.011) and ST2 (HR 1.002, 95% CI 1.000–1.004, p=0.017). The incidence of fatal outcomes (3.6% and 4.1%, respectively) was comparable to that observed by Motloch LJ. et al. (2023) [14]. In this large study, the predictor of mortality in the first year after discharge was the ST2 marker (HR 1.006, 95% CI 1.002–1.009, p<0.001) [14].

In our study, no significant effect of hsTrI concentration on the prognosis of patients after discharge was found, which is consistent with the data of Motloch LJ. et al. (2023) [14], but the results obtained differ from the findings of Fiedler L. et al. (2023) [7], who also analyzed the hsTrI level on the day of hospitalization. The lack of prognostic value of hsTrI may be explained by the time of blood collection from the patients (in our study and in the experiment of Motloch LJ. et al. (2002) [14], blood tests were performed on the first day of admission), and it should take at least 1–2 weeks before the myocardium is damaged by the SARS-CoV2 virus and the hsTrI level

rises [5]. The discrepancy in the results may also be due to the fact that the patients in our study had no history of CVD, and in the work of Zagidullin N. et al. (2023), 4.4 % of patients had coronary heart disease and 2.0 % had chronic heart failure.

With regard to the long-term prognosis of ACVE and mortality, the assessment of ST2 concentration has the greatest value [7, 14], which was determined in our work. We obtained significant differences between patient groups in a number of laboratory parameters (IL-6, D-dimer, LDH, CPK, CPK-MB and ST2 ($p<0.05$ for all parameters)), but only ST2 level increased the chance of ACVE (OR 1.23 [95 % CI 1.11–1.37]; AUC 0.949, sensitivity 92.9 %, specificity 33 %, $p=0.000$). The cut-off point for ST2>36 ng/mL was also determined, which is close to the cut-off points for ST2 obtained by Zhang Q. et al. (2021) [15]. The authors found that ST2 levels ⩾34.2 ng/mL (AUC 0.662, sensitivity 66.7 %, specificity 65.2 %, $p<0.001$) increased the risk of ACVE in patients with acute coronary syndrome without ST-segment elevation (HR = 10.22, 95 % CI 4.05–25.7, $p<0.001$) [15].

Conclusion

Measuring the concentrations of not only traditional but also novel biomarkers may help to stratify the development of long-term adverse events in patients with COVID-19. The study found that elevated ST2 levels in combination with traditional cardiovascular risk factors (AH, obesity) were statistically significantly associated with the development of adverse clinical outcomes in a cohort of COVID-19 patients. The likelihood of ACVE in COVID-19 patients within 1 year of hospital discharge is higher in patients with ST2 levels >36 ng/mL on the day of hospitalization. Therefore, the detection of ST2 >36 ng/mL elevation may help to predict the long-term adverse outcomes in COVID-19 patients.

Study limitations. Our study had several limitations. The study was conducted in a small sample of patients from a single institution. There was no study of cardiovascular biomarker levels in the dynamic, which could expand the list of predictive laboratory parameters.

Conflict of interests: none declared.

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Pathogenetic associations of galectin-3 levels with chronic heart failure severity parameters in patients with osteoarthritis

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Chronic heart failure (CHF) is a disease that negatively affects the prognosis of patients. The presence of aggravating (comorbid) conditions, in particular connective tissue disorders, can aggravate the course of heart failure (HF). Modern immunologic markers can be used for additional assessment of the severity of the CHF course.
The aim of the study was to investigate possible associations of galectin-3 with laboratory and instrumental parameters in patients with CHF and osteoarthritis (OA).
Methods. A one-stage cross-sectional study was performed in 115 patients with CHF who were undergoing outpatient follow-up: 65 patients — the study group with CHF and knee OA and 50 patients — the group with CHF without OA. A comparative analysis of laboratory and instrumental parameters reflecting the severity of OA progression and galectin-3 in both groups was performed, as well as the search for possible associations of galectin-3 with parameters reflecting the severity of CHF. The results of the comparative analysis are presented as median (Me) with first (Q1) and third (Q3) quartiles based on the Mann-Whitney test. The method of linear regression analysis was used to analyze the characteristics of the analyzed associations between several parameters. The critical level of significance of the statistical hypotheses evaluated was $p<0.05$. Comparison of frequency differences in the analyzed groups was performed using the χ^2-Pearson test.
Results. Significant differences in creatinine levels, glomerular filtration rate (GFR), changes in lipidogram parameters were found between the studied groups. Higher rate of left ventricular hypertrophy (LVH), higher values of left ventricular myocardial mass index and ratio of transmitral flow parameters were found in the studied group (CHF and OA) compared to patients with CHF without OA. A statistically significant increased level of galectin-3 was found in the group of patients with CHF and OA compared to patients without OA: 39.4 (30.3 — 68.2) and 19.1 (15.5 — 8.4) ng/mL, respectively. Also in the group of patients with

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CHF and OA, a logistic regression model was constructed with galectin-3 levels and parameters reflecting the severity of the CHF course.

Conclusion. Chronic low-intensity inflammatory process, as exemplified by OA, may significantly worsen the course of CHF. The increased level of galectin-3 and its association with parameters reflecting the severity of the HF course in the group of patients with CHF and OA may indicate more pronounced myocardial fibrosis and a higher risk of adverse outcomes compared to patients without OA.

Keywords: chronic heart failure, osteoarthritis, comorbidity, galectin-3

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Introduction

In recent years, a substantial amount of data has accumulated in the literature regarding the pathogenetic aggravating associations of cardiovascular diseases (CVD) with osteoarthritis (OA). According to meta-analyses including 15 studies with 32,278,744 participants, the prevalence of cardiovascular pathology in patients with OA ranges from 24 % to 39 %. These patients have been reported to have an increased risk of CVD, including coronary heart disease (CHD), arterial hypertension (AH), and chronic heart failure (CHF) [1–3]. The increased risk of CVD development with the background of OA is caused by a number of factors: chronic non-infectious inflammation of low severity, which leads to a progression of endothelial dysfunction and development of atherosclerosis; constant intake of painkillers — non-steroidal anti-inflammatory drugs, leading to deterioration of renal function, fluid retention in the body; decreased physical activity [4]. These factors lead to the development of AH or worsen the course of existing one [5]. The presence of CVD and OA in patients is often associated with the presence of obesity [6].

The study of the progression of CHF in patients with OA is currently trending. The role of chronic inflammation in the development of CHF is actively discussed. According to the available data, proinflammatory cytokines may play a leading role in the development and progression of CHF. Patients with CHF with preserved left ventricular ejection fraction (LVEF) in the setting of pre-existing rheumatic pathology, particularly OA, should be considered as a distinct risk group [7, 8]. Immunologic cytokines, in particular galectin-3, a marker of myocardial fibrosis involved in the regulation of reactions such as cell differentiation, cell cycle and apoptosis, may provide additional information about the severity and prognosis of such patients. The study of its properties in patients with CHF and OA may be valuable for determining additional clinical data and prognosis [9, 10].

The aim of the study was to perform a comparative analysis of laboratory and instrumental parameters of CHF in patients with and without OA, including the myocardial fibrosis marker galectin-3, and its possible associations with CHF severity parameters.

Methods

The study included 65 patients with CHF and OA; 50 patients with CHF and without OA. Examination and enrollment into the study were carried out in the therapeutic and rheumatological departments of the Irkutsk City Clinical Hospital No. 1. When patients were included in the study, individual consultations were conducted in accordance with the ethical principles required by the Declaration of Helsinki of the World Medical Association, revised in 2013. The work was approved by the protocol of the local ethics committee of the above-mentioned hospital, on the basis of structural subdivisions where the inclusion of patients was carried out (protocol dated 05.10.2013). When agreeing to participate in the study, patients signed a voluntary informed consent.

Inclusion criteria for the study were:

— Age between 50 and 70 years;

— presence of CHF confirmed on the basis of current clinical guidelines;

— CHF developed with the background of CHD and/or hypertension;

— presence of OA confirmed on the basis of current clinical guidelines;

Exclusion criteria for the study were:

— severe course of CHF (Functional classes (FC) III and IV CHF according to NYHA);

— non-ischemic etiology of CHF;

— secondary (posttraumatic) knee OA;

— diabetes mellitus;

— GFR less than 30 mL/min/1.73m^2.

The diagnosis of CHF was confirmed based on clinical guidelines [11, 12]. The general characterization of patients is presented in Table 1.

Table 1. **Characteristics of patients**

Parameter	Groups		p	χ^2
	CHF and OA (n=65)	CHF with no OA (n=50)		
Age, years; Me (Q1 — Q3)	58 (52–65)	56 (50–63)	0.07	
CHF course duration, years; Me (Q1 — Q3)	6 (4–8)	5 (5–10)	0.08	
Patients with CHD, n (%)	65 (100%)	50 (100%)	0.1	0.01
Patients with AH and CHD, n (%)	57 (88%)	42 (84%)	0.09	0.05

Comparative analysis of the therapy taken by the patients is presented in Table 2.

Table 2. **Drug therapy taken**

Medications	Groups		p	χ^2
	CHF and OA (n=65)	CHF with no OA (n=50)		
ACE inhibitors	14 (22%)	13 (25%)	0.07	2.1
ARBs	30 (46%)	20 (40%)	0.06	1.9
Beta-blockers	65 (100%)	50 (100%)	0.1	1
MRAs	11 (17%)	10 (21%)	0.09	1.4
Statins	55 (85%)	42 (84%)	0.08	1.3

Standard laboratory and instrumental tests were performed in the study groups. The serum concentration of galectin-3 was analyzed. The obtained data were analyzed using the software STATISTICA 10.0. Evaluation of data distribution characteristics was performed using Shapiro-Wilk test. The results of comparative analysis are presented as medians (Me) with indication of first (Q1) and third (Q3) quartiles on the basis of Mann-Whitney U-test. The method of linear regression analysis was used to assess the associations of several parameters. The critical level of significance of the evaluated statistical hypotheses was $p < 0.05$. Comparison of frequency differences in the analyzed groups was performed using χ^2-Pearson test [13].

Results

The comparative analysis of echocardiographic (EchoCG) parameters showed no significant differences in the parameters compared, except for the increase in left ventricular mass index (LVMI) and the ratio of early to late mitral velocity, which was found in the group of patients with CHF and OA (Table 3).

Table 3. **Comparative analysis of morphologic parameters of myocardium**

Parameter	CHF and OA (n=65)	CHF with no OA (n=50)	p
EDD, cm; Me (Q1 –Q3)	4.44 (4.4–5.8)	4.7 (4.2–5.6)	0.5
ESD, cm; Me (Q1–Q3)	3.3 (2.4–4.2)	3.2 (2.2–4.1)	0.2
LVPW, cm; Me (Q1–Q3)	1.2 (1.1–1.4)	1.15 (1–1.3)	0.6
IVST, cm; Me (Q1–Q3)	1.2 (1.15–1.3)	1.1 (1.12–1.18)	0.2
LVMI, g/m^2, Me (Q1–Q3)	127.4 (107.8–134.3)	118.5 (104.1–125.6)	0.03
LVEF, %, Me (Q1–Q3)	45.05 (42.4–51.7)	44.2 (41.3–52.1)	0.09
E/A, Me (Q1–Q3)	1.1 (0.9–1.2)	0.9 (0.7–1.0)	0.02
LVH, n (%)	61 (95%)	46 (93%)	0.004 (χ^2 = 10.7)

Comparative analysis of the levels of the N-terminal pro–B-type natriuretic peptide (NT-proBNP) showed no statistically significant differences between the groups studied (Fig. 1).

The analysis of laboratory parameters in the studied groups revealed statistically significant differences in erythrocyte sedimentation rate and C-reactive

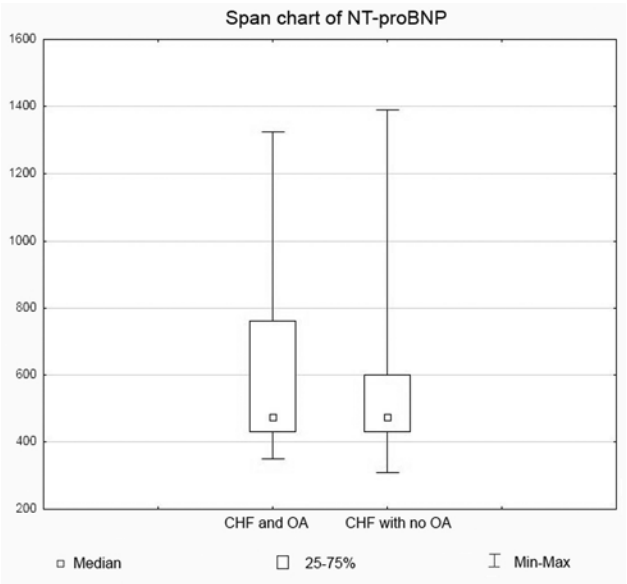

Fig. 1. Comparative analysis of NT-proBNP levels, pg/mL

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Table 4. **Comparative analysis of laboratory parameters**

Parameter	CHF and OA (n=65)	CHF with no OA (n=50)	p
Hemoglobin, g/l	112.1 (95.06 –129.2)	130.9 (119 –139.4)	0.008
Erythrocytes, 10^{12}/L	3.3 (2.05–3.9)	4.4 (3.4–4.9)	0.009
Thrombocytes, 10^{9}/L	385.9 (256.6–456.8)	372.1 (282.3–411.5)	0.07
Erythrocyte sedimentation rate, mm/h	33.6 (14.8–45.8)	7.1 (3.3–10.4)	0.001
Glucose, mmol/L	5.1 (3.7–6.1)	5.6 (4.2–6)	0.3
Glycated hemoglobin, %	5.4 (3.3–6.1)	5.3 (3.9–5.8)	0.2
Total protein, g/L	79.6 (59.01–88.4)	77.6 (56.05–85.6)	0.06
Creatinine, μmol/L	98.3 (72.5–133.2)	74.2 (65.2–111.4)	0.001
GFR, ml/min	63.2 (54.2–80.2)	74.8 (64.5–90.1)	0.004
C-reactive protein, mg/L	34.01 (14.4–54.01)	2.1 (0.3–3.2)	0.06
Potassium, mmol/L	3.9 (3.3–5.2)	4.2 (3.2–5.09)	0.09
Sodium, mmol/L	120.2 (112.9–145.2)	138.5 (114.5–142.8)	0.2
Calcium, mmol/L	2.1 (1.9–2.4)	1.9 (1.5–2.1)	0.05
Aspartate aminotransferase, IU/L	22.9 (15.5–26.5)	20.7 (16.9–28.9)	0.1
Alanine aminotransferase, IU/L	22.1 (13.09–26.3)	21.7 (14.5–25.8)	0.5
Total cholesterol, mmol/L	5.5 (4.1–6.1)	4.2 (3.4–5.1)	0.04
Triglycerides, mmol/L	2.04 (0.9–2.5)	1.5 (0.7–2.1)	0.001
LDL, mmol/L	2.4 (1.1–2.9)	1.9 (0.6–2.1)	0.04
HDL, mmol/L	0.9 (0.3–1.1)	1.3 (0.4–1.5)	0.03
Atherogenicity coefficient	5.2 (4.1–5.6)	3.3 (2.9–4.5)	0.001
Systolic BP	143.5 (132–155)	136.5 (124–149)	0.04
Diastolic BP	90.5 (70–111)	80 (65–95)	0.02

protein levels in the OA group. Significantly increased creatinine level and decreased glomerular filtration rate (GFR) were also found in the OA group. These findings are probably due to the presence of chronic inflammatory process as well as regular intake of non-steroidal anti-inflammatory drugs (NSAIDs). Changes in lipidogram parameters and higher levels of mean blood pressure (BP) were also found in the CHF and OA group (Table 4).

A significant increase in galectin-3 levels was found in the group of patients with CHF and OA compared to patients without OA (Fig. 2).

When building a regression model with the level of galectin-3 and earlier found parameters having statistically significant differences, a statistical association was obtained indicating the deterioration of these indicators with a background of increasing galectin-3 concentration (Table 5, Fig. 3).

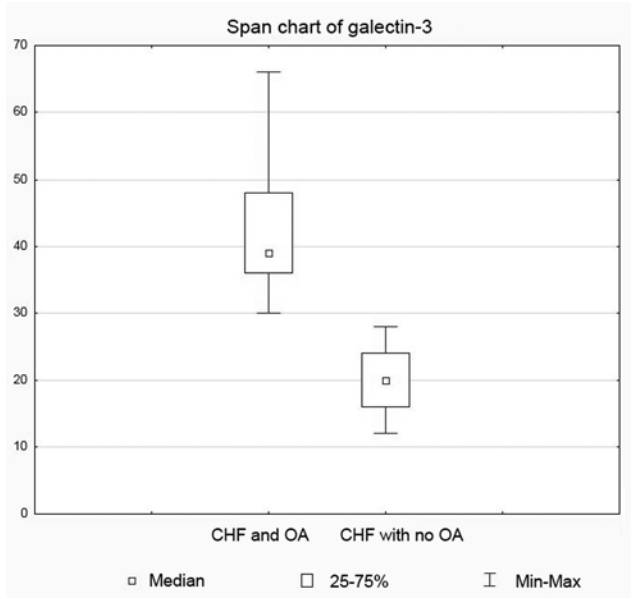

Fig. 2. Galectin-3 levels

Table 5. **Results of linear regression analysis**

Parameters	Galectin-3: Me (Q — Q3) 39.4 (30.3 — 68.2); t=2.14; p=0.043			
	r	r2	beta	p
C-reactive protein, mg/L	0.34	0.24	0.34	0.04
NT-proBNP, pg/l	0.28	0.29	0.35	0.008
Total cholesterol, mmol/L	0.3	0.4	0.44	0.006
LDL, mmol/L	0.41	0.31	0.2	0.001
LVH	0.2	0.3	0.3	0.03
LVMI, g/m^2	0.2	0.25	0.4	0.01

Discussion

Low-level chronic inflammation is thought to be a major factor in the development and progression of CHF [14]. The presence of OA in patients with CHF is a serious aggravating factor. The results of this study are consistent with this hypothesis, namely the statistically significant increased levels of galectin-3, LVMI, E/A and incidence rate of LVH compared to patients without OA. The absence of significant differences in

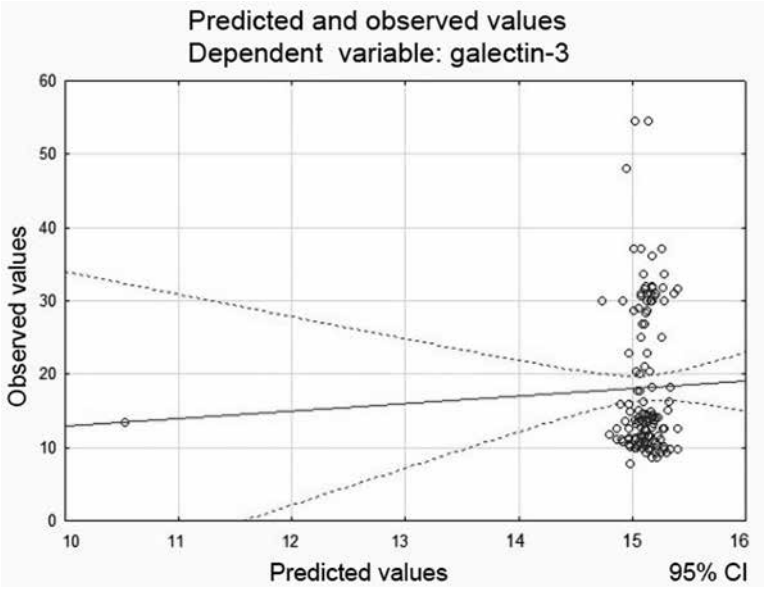

Fig. 3. Linear regression of galectin-3 with the studied parameters

NT-proBNP levels between groups may indicate the absence of clinical manifestations of CHF in the presence of the above changes.

In our opinion, the found statistically significant differences in BP levels are noteworthy. The reasons for such changes may be, on the one hand, sodium retention, constant intake of NSAIDs, as well as changes in the state of the vascular wall with the background of more pronounced changes in lipidogram parameters. This hypothesis is in accordance with the opinion of other authors working in this field. The combination of dyslipidemia, hypertension and chronic low-intensity inflammation is the most important pathogenetic comorbid combination that significantly worsens the prognosis of patients [15, 16].

For CHF patients with preserved and moderately reduced LVEF with OA, determining the prognosis is an important and open question. Given the lack of differences in many echocardiographic parameters and NT-proBNP levels, the use of immunologic markers is likely to be a relevant direction. The obtained regression model of galectin-3 with parameters such as NT-proBNP, LVH, LVMI confirms this hypothesis. However, it should be considered that this study was conducted as a single-stage cross-sectional study. Prospective studies are needed to determine the efficacy of this marker.

Conclusion

In addition to the traditional RFs of CHF decompensation, current data suggest that OA should be considered as an additional one. The presence of chronic, low-intensity, non-infectious inflammation in patients with CHF and OA leads to more pronounced myocardial fibrosis. In the present study, this hypothesis is supported by higher levels of galectin-3, LVMI and LVH. In this group of patients, galectin-3 should be considered as an additional marker for the assessment of CHF progression, according to the authors.

Conflict of interests: none declared.

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High-resolution electrocardiography for chronic heart failure in the elderly

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The aim of the study was to investigate the main parameters of high-resolution electrocardiography (HRECG) in elderly patients suffering from chronic heart failure (CHF).

Methods. The study included 120 patients (87 women (72.5%) and 33 men (27.5%)) of elderly age (mean age 81.32±4.2 years) with CHF. Patients with postinfarction cardiosclerosis (PICS) were divided into groups: 38 patients with CHF IIA and CHF IIB stages; 50 patients with complete bundle branch block (CBBB) with CHF IIA and CHF IIB stages; 32 patients with atrial fibrillation (AF) with CHF I and CHF IIA stages. Patients underwent ECG, Holter monitoring, HRECG.

Statistical processing of the study results was performed using the Stat Soft 13.0 software package.

Results. The highest values in the group of patients with CHF + PICS were recorded for QTc (452.52±3.55 ms), QTp (87.83±1.21 ms) and TotQRSF (103.25±2.97 ms). The highest values in the group of patients with AF were recorded for QTc, TotQRSF and LAS40 (452.65±2.69 ms; 100.04±2.36 ms and 51.64±2.85 μV, respectively). In patients with complete bundle branch block (CBBB), the highest values were recorded for QTc, TotQRSF, LAS40 and PTotal (463.25±3.98 ms; 115.44±3.45 ms; 67.44±4.63 μV and 128.83±8.65 ms, respectively). The highest QTc and TotQRSF values were observed in patients with CHF IIB stage + PICS and CHF IIB stage + CBBB. Linear regression analysis revealed a correlation between ventricular late potential indices (TotQRSF, RMS40, LAS40) and cardiac ECHO parameters such as end diastolic diameter (EDD), end systolic diameter (ESD), interventricular septal thickness (IVST), left ventricle posterior wall thickness (LVPWT).

Conclusion. HRECG analysis can assess myocardial electrical instability and remodeling in CHF. In our study, HRECG indices such as TotQRSF, RMS40, and LAS40, which reflect myocardial electrical heterogeneity, were impaired in elderly patients with severe CHF. This suggests the presence of fragmented electrical activity, which may be associated with structural and functional myocardial changes. HRECG analysis can be used for a comprehensive assessment of the cardiovascular system in this group of patients.

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Keywords: chronic heart failure, high-resolution electrocardiography, postinfarction cardiosclerosis, atrial fibrillation, myocardium.

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Introduction

Chronic heart failure (CHF) is a complex clinical syndrome resulting from functional or structural heart disease that impairs ventricular filling or ejection of blood into the systemic circulation. CHF remains a common disease with high morbidity and mortality [1, 2]. Experts estimate the current prevalence of CHF worldwide to be 64.34 million cases according to the Global Health Data Exchange registry [3].

The most common causes of CHF in the Ryazan region are arterial hypertension — 89.6%, atrial fibrillation (AF) — 63.3%, and coronary heart disease — 64.9% [4]. In the process of aging, the probability of these diseases increases, which emphasizes the need for a comprehensive approach to diagnosis and treatment, and raises questions about individual prevention of this disease from an early age [5]. In older age, the problem of senile asthenia syndrome and the presence of multiple comorbidities worsen prognosis, increase the number and duration of hospitalizations, and reduce the survival rate of patients with CHF [6]. Cardiac remodeling alters the electrical activity of the heart, which can be detected by electrocardiogram recording.

In recent years, the method of high-resolution electrocardiography (HRECG) has become more widespread. The basis of this method is computer amplification, averaging and filtering of different parts of the electrocardiogram with their subsequent mathematical processing [7]. Thus, this method allows the selection and analysis of low amplitude signals, which are inaccessible for analysis by traditional methods of ECG recording and containing important diagnostic information [8].

For example, when comparing deceased and surviving patients with chronic rheumatic heart disease, which is a model of slowly progressing CHF, a deterioration in the dynamics of ventricular late potentials detected by HRECG is noted [9]. In this regard, obtaining the most complete information about the electrical potential of the heart in this cohort of patients is an important diagnostic problem.

The study of the main parameters of HRECG in patients with CHF allows a more detailed assessment of myocardial electrophysiological properties, which in turn may influence the management tactics of these patients.

The aim of the study was to investigate the main parameters of high-resolution electrocardiography (HRECG) in elderly patients suffering from chronic heart failure (CHF).

Methods

The study included 120 patients (87 women (72.5%) and 33 men (27.5%)) of advanced age (mean age 81.32±4.2 years) with CHF who signed an informed consent. Inclusion criteria for the study were: presence of CHF diagnosis in medical records and the life expectancy greater than one year. Exclusion criteria: presence of cancer, signs of acute infection including SARS-CoV-2, severe mental illness, and inability to complete the questionnaires required by the study.

The main clinical characteristics of the study subjects are summarized in Table 1.

While evaluating the physical development, the mean height of the study subjects was 163.09±7.86 cm, the mean body weight was 75.18±13.36 kg, the mean BMI was 28.26±4.76 kg/m^2, and the mean waist circumference was 99.80±11.51 cm.

Patients with postinfarction cardiosclerosis (PICS) were divided into the following groups: 38 patients with CHF IIA and CHF IIB stages; 50 patients with complete bundle branch block (CBBB) with CHF IIA and CHF IIB stages, and 32 CHF I/ IIA stages patients with AF. Patients underwent a comprehensive clinical and instrumental evaluation: 12-channel HRECG

Table 1. **Clinical characteristics of patients in the study groups**

Parameters	Studied patients, (n = 120)	
	Abs.	% of group
Hypertension	113	94%
Obesity	40	33
Type 2 diabetes mellitus	22	18
AF (permanent or paroxysmal)	62	52
History of myocardial infarction	29	24
History of stroke	17	14
Senile asthenia syndrome	40	33
CHF, I stage	12	10
CHF, IIA stage	68	73
CHF, IIB stage	20	17
Reduced ejection fraction (EF)	8	7%
Moderately reduced EF	20	17%
Preserved EF	92	76%

with polyfunctional Holter monitor (Cardiotekhnika-07-AD-3/12P, Incart, Russia); echocardiography on Philips Affiniti 70 device with evaluation of end-diastolic diameter (EDD), end-systolic diameter (ESD), interventricular septal thickness in diastole (IVST), left ventricular posterior wall thickness in diastole (LVPWT).

The following HRECG parameters were evaluated: TO (turbulence onset, %), TS (turbulence slope, ms/RR) QTc (corrected QT interval, ms) QTdis (dispersion of QT interval, ms), QTp (value in absolute units to T-wave peak, ms), JTc (corrected JT interval, ms), JTdis (dispersion of JT interval, ms), $MTWA_{max}$ (maximum microvolt alternation of T-wave, μV), $MTWA_{mean}$ (mean microvolt alternation of T-wave, μV), TotQRSF (duration of the filtered QRS complex, ms), RMS40 (root-mean-square amplitude of the last 40 ms of the QRS complex, μV), LAS40 (duration of the low-amplitude portion of the signal at the end of the QRS, μV), PTotal (duration of the filtered P-wave, ms), RMS20 (root-mean-square amplitude of the last 20 ms of the P-peak, μV).

The study was conducted in accordance with Good Clinical Practice and the tenets of the Declaration of Helsinki. The study was approved by the local ethics committee of the Ryazan State Medical University in October 2021. Voluntary informed consent was obtained from all participants prior to enrollment.

Statistical analysis

Statistical processing of the results of the study was performed using the Stat Soft 13.0 software. The arithmetic mean and standard deviation were calculated for quantitative variables. In the absence of normal distribution, non-parametric Wilcoxon and Mann-Whitney tests were used. One-way analysis of variance was used to compare means, and linear regression analysis was used to assess the possible associations between variables.

Differences between groups were considered statistically significant at $p \leq 0.05$.

Results

The main parameters of HRECG in groups of CHF patients depending on the presence of PICS were compared. The parameters data are shown in Table 2. The presented data show statistically significant differences between groups for such parameters as QTc (p=0.034), QTp (p=0.001), TotQRSF (p=0.005) with the highest values in the group of patients with PICS (452.52±3.55 ms; 87.83±1.21 ms and 103.25±2.97 ms, respectively) and RMS40 (p=0.032) with the lowest value in the group of patients with PICS — 21.22±2.14. Other parameters such as TS, QTdis, JTc, JTdis, $MTWA_{max}$, $MTWA_{mean}$, LAS40, PTotal, RMS20 did not show statistically significant differences between groups.

We analyzed the main HRECG parameters in groups of CHF patients depending on the presence of AF. Detailed results are shown in Table 3. The

Table 2. **Comparative characterization of key HRECG parameters in patients with and without PICS**

HRECG parameters	CHF without PICS (M±m)	CHF + PICS (M±m)	p
TO, %	0.83±0.74	−0.16±0.22	0.488
TS, ms/RR	8.03±1.25	4.55±0.71	0.154
QTc, ms	443.21±2.33	452.52±3.55	0.034*
QTdis, ms	18.25±1.00	21.11±1.74	0.146
QTp, ms	83.32±0.68	87.83±1.21	0.001*
JTc, ms	330.12±3.09	334.14±2.92	0.449
JTdis, ms	18.26±1.01	21.26±1.75	0.128
MTWA max, μV	111.24±47.6	32.33±6.92	0.379
MTWA mean, μV	41.35±21.69	8.67±0.76	0.424
TotQRSF, ms	93.82±1.70	103.25±2.97	0.005*
RMS40, μV	27.24±1.46	21.22±2.14	0.032*
LAS40, μV	45.91±2.04	53.04±3.60	0.079
PTotal, ms	114.45±2.79	115.07±3.85	0.909
RMS20, μV	3.65±0.07	3.49±0.13	0.288

Note. *p<0.05 — statistically significant differences between groups.

Table 3. **Comparative characterization of key HRECG parameters in patients with and without AF**

Parameters	CHF without AF (M±m)	CHF + AF (M±m)	p
TO, %	0.66±0.73	0.44±0.51	0.875
TS, ms/RR	8.69±1.14	2.15±1.52	0.006*
QTc, ms	438.42±2.71	452.65±2.69	0.001*
QTdis, ms	22.33±1.22	15.84±1.17	0.001*
QTp, ms	84.54±0.83	84.61±0.90	0.954
JTc, ms	328.92±4.27	333.39±2.29	0.348
JTdis, ms	22.35±1.22	15.92±1.18	0.001*
MTWA max, μV	24.62±4.15	141.2±62.10	0.124
MTWA mean, μV	7.98±0.50	52.03±28.38	0.202
TotQRSF, ms	92.62±1.73	100.04±2.36	0.010*
RMS40, μV	26.24±1.87	25.20±1.62	0.673
LAS40, μV	43.48±1.98	51.64±2.85	0.022*
PTotal, ms	112.12±2.98	121.73±2.12	0.067
RMS20, μV	3.72±0.07	3.30±0.12	0.005*

Note. *p<0.05 — statistically significant differences between groups.

Table 4. **Comparative characterization of key HRECG parameters in patients with and without CBBB**

Parameters	CHF without CBBB (M±m)	CHF + CBBB (M±m)	p
TO, %	0.57±0.70	0.81±0.82	0.869
TS, ms/RR	7.8±1.21	4.97±0.72	0.269
QTc, ms	439.38±2.03	463.25±3.98	0.001*
QTdis, ms	18.24±0.98	21.36±1.86	0.122
QTp, ms	84.34±0.71	85.21±1.22	0.530
JTc, ms	333.41±2.97	325.36±3.45	0.132
JTdis, ms	18.28±0.98	21.44±1.86	0.118
MTWA max, μV	101.77±51.04	72.73±17.62	0.728
MTWA mean, μV	42.31±23.37	12.70±6.12	0.435
TotQRSF, ms	89.72±1.27	115.44±3.45	0.001*
RMS40, μV	28.86±1.43	16.08±1.87	0.001*
LAS40, μV	41.08±1.47	67.44±4.63	0.001*
PTotal, ms	110.89±1.67	128.83±8.65	0.001*
RMS20, μV	3.68±0.07	3.38±0.14	0.062

Note. *p<0.05 — statistically significant differences between groups.

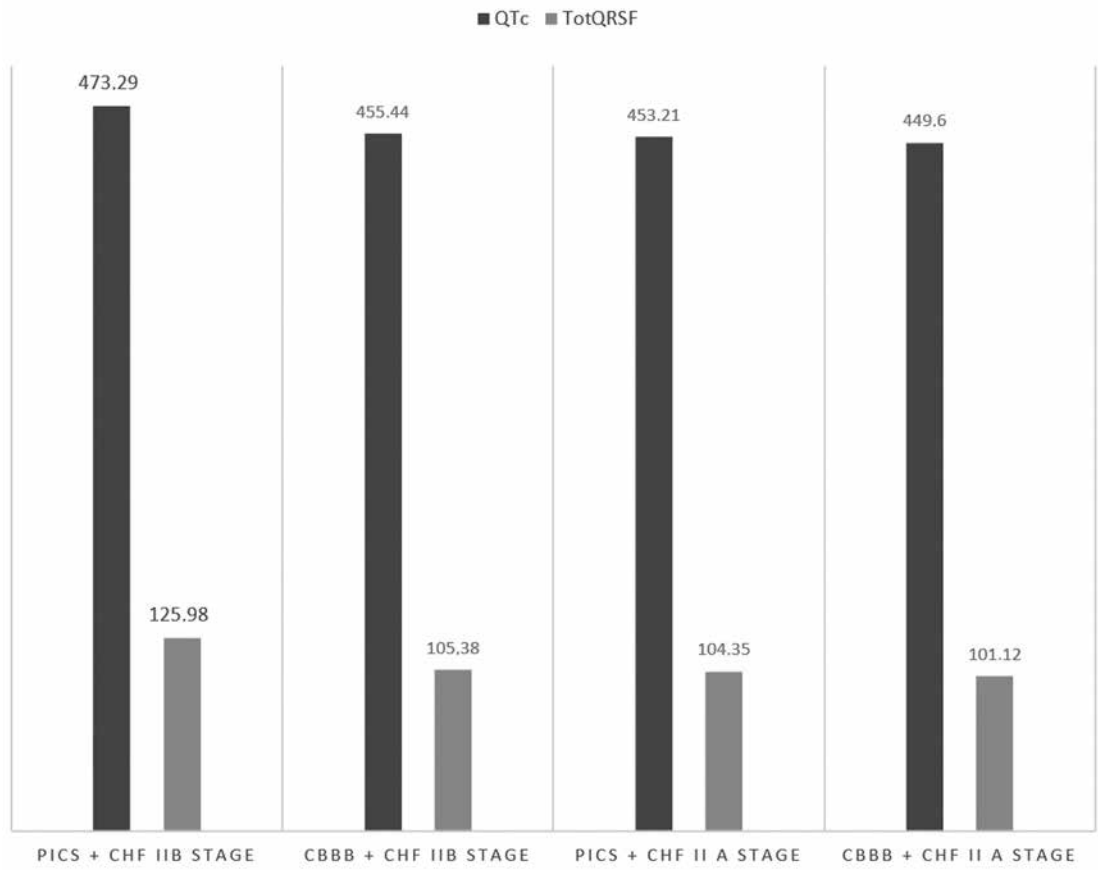

Fig. 1. Comparative characterization of QTc and TotQRSF in patients with CHF + PICS, CHF + CBBB

groups were statistically significantly different in the following parameters: TS (p=0.006), QTc (p=0.001), QTdis (p=0.001), JTdis (p=0.001), TotQRSF (p=0.010), LAS40 (p=0.022) and RMS20 (p=0.005). The highest values for TS, QTdis, JTdis and RMS20 were observed in the group of patients without AF (8.69±1.14%; 22.33±1.22 ms; 22.35±1.22 ms; 22.35±1.22 ms and 3.72±0.07 μV, respectively). The highest values of QTc, TotQRSF and LAS40 were recorded in the group of patients with AF (452.65±2.69 ms; 100.04±2.36 ms

Table 5. **Relationship between cardiac ultrasound parameters (EDD, ESD, IVST, LVPWT) and ventricular late potentials (TotQRSF, RMS40, LAS40)**

Parameters	B	R2	p
EDD and TotQRSF	12.1 (7.95; 16.25)	0.165	0.001*
EDD and RMS40	–6.92 (–10.54; –3.31)	0.079	0.001*
EDD and LAS40	9.93 (4.56;15.30)	0.074	0.001*
ESD and TotQRSF	13.73 (10.07;17.39)	0.248	0.001*
ESD and RMS40	–7.06 (–10.39; –3.73)	0.095	0.001*
ESD and LAS40	11.98 (7.14;16.83)	0.125	0.001*
IVST and TotQRSF	31.80 (11.16; 52.44)	0.053	0.003*
IVST and RMS40	0.94 (–16.64; 18.52)	0.001	0.916
IVST and LAS40	14.07 (–11.87; 40.00)	0.007	0.286
LVPWT and TotQRSF	33.13 (7.67; 58.59)	0.038	0.011*
LVPWT and RMS40	21.20 (–0.08; 42.48)	0.023	0.051
LVPWT and LAS40	2.46 (–29.39; 34.32)	0.001	0.879

Note. *p<0.05 — statistically significant differences between groups.

and 51.64±2.85 μV, respectively). Parameters such as $MTWA_{max}$, $MTWA_{mean}$, RMS40, PTotal, LAS40 showed no statistically significant differences between the groups.

The main characteristics of HRECG in CHF groups depending on the presence of CBBB were evaluated (Table 4). The parameters QTc (p=0.001), TotQRSF (p=0.001), LAS40 (p=0.001), and PTotal (p=0.001) showed statistically significant differences between CHF without CBBB and CHF with CBBB groups, with their highest values in the group of patients with CBBB (463.25±3.98 ms; 115.44±3.45 ms; 67.44±4.63 μV; 128.83±8.65 ms, respectively). The following parameters including TO, TS, QTdis, QTp, JTc, JTdis, $MTWA_{max}$, $MTWA_{mean}$, and RMS20 showed no statistically significant differences between groups.

Linear regression analysis was performed to identify the possible relationship of ventricular late potentials represented by the indices (TotQRSF, RMS40, LAS40) with cardiac ultrasound. The analysis showed that there was indeed a statistically significant relationship between different parameters of the ECG and the cardiac ultrasound. Specifically, the EDD and ESD showed a correlation with the following parameters: TotQRSF, RMS40, LAS40. IVST and LVPWT seemed to correlate with TotQRSF. However, IVST and LVPWT parameters did not show statistically significant relationship with LAS40, RMS40.

The highest values of QTc and TotQRSF were observed in patients with CHF stage IIB + PICS and CHF stage IIB + CBBB (Figure 1).

Tables 2, 3, 4, 5 summarize the results of HRECG.

Discussion

The HRECG method is becoming more and more widespread in clinical practice. The method itself and its individual parameters, which characterize the temporal and amplitude properties of the QRS complex and the P-wave, can be used to assess myocardial electrical instability and the processes of electrophysiological cardiac remodeling observed in patients with CHF and associated with poor long-term prognosis [7]. Thus, more pronounced values of QRS fragmentation (TotQRSF) are observed in deceased patients with chronic rheumatic heart disease, and the increase of this parameter increases the risk of death, as well as the deterioration of ventricular late potentials (TotQRSF, RMS40 and LAS40) at 10-year follow-up [9].

In our study, this parameter was statistically higher in the group of patients with PICS (103.25±2.97 ms), AF (100.04±2.36 ms), and CBBB (115.44±3.45 ms). Increased TotQRSF interval, shortened RMS40 interval in CHF + PICS patients (103.25±2.97 ms and 21.22±2.14 μV, respectively), CHF+CBBB patients (115.44±3.45 ms and 16.08±1.87 μV, respectively), and increased LAS40 in AF and CBBB groups (51, 64±2.85 μV and 67.44±4.63 μV, respectively) may indicate the presence of myocardial zones with inhomogeneous conduction, which represent an anatomic-physiological substrate for the development of arrhythmias.

In the linear regression analysis, TotQRSF, RMS40 and LAS40 correlated with cardiac ultrasound parameters such as EDD, ESD, IVST, LVPWT. This may indicate that these parameters may reflect structural changes in the myocardium. These results show the importance of assessing QRS fragmentation to identify a more "severe" cohort of CHF patients in order to optimize the treatment strategy and evaluate the prognosis of the disease. Thus, the addition of SGLT2 receptor inhibitors leads to a significant improvement in ventricular late potential indices after 6 months [10]. On the other hand, the use of antiarrhythmic drugs from the IC group can lead to a worsening of these parameters [10].

Changes in QT interval duration are associated with a number of cardiovascular diseases. At the same time, the prognostic significance of the parameters and their thresholds are not well understood. A

number of studies have found a reliable association between prolongation of the QT interval and the severity of myocardial damage [11].

In our study, an increased QTc interval was found in patients with CHF + PICS, patients with CHF + AF and patients with CHF + CBBB (452.52±3.55 ms; 452.65±2.69 ms; 463.25±3.98 ms, respectively). The highest values were found in patients with CHF stage IIB + PICS and CHF stage IIB + CBBB. The prolongation of the QT interval in patients with CHF + PICS, as well as in patients with CHF + CBBB, indicates the presence of myocardial electrical instability, which is unfavorable in terms of the development of life-threatening arrhythmias.

Thus, these results highlight not only the relationship of electrocardiographic parameters in the assessment of cardiac function, but also their potential application in clinical practice to improve the diagnosis and management of patients with cardiovascular diseases.

Conclusion

The HRECG method is becoming more and more widespread in clinical practice, allowing to assess myocardial electrical instability and processes of electrophysiological remodeling of the heart in patients with CHF. Our study demonstrated a worsening of the parameters such as TotQRSF, RMS40 and LAS40, reflecting electrical heterogeneity in the myocardium in more severe patients. This suggests the presence of fragmented myocardial electrical activity in elderly patients with CHF, which may be a substrate for the development of life-threatening complications. Changes in these parameters may correlate with anatomic and functional characteristics of the heart determined by ultrasound. These parameters, together with changes in QT interval duration, are associated with structural changes in the myocardium and may serve as indicators of myocardial electrical instability. Thus, this method is useful and promising for a comprehensive assessment of the cardiovascular system and clinical decision making in this group of patients.

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Correction of hypertriglyceridemia and ways to improve the prognosis of patients

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Individuals with high triglyceride levels remain at high risk for premature cardiovascular disease despite reductions in low-density lipoprotein cholesterol levels. This review discusses the causes of hypertriglyceridemia (HTG) and its association with atherosclerosis. Non-pharmacologic and pharmacologic means of correcting HTG are presented. The results of the major randomized trials of fibrates, omega-3 polyunsaturated fatty acids, and nicotinic acid are reviewed to assess the efficacy, safety, and impact of treatment on cardiovascular outcomes. The first data from clinical trials of new drugs for the treatment of HTG are reported.

Keywords: hypertriglyceridemia, cardiovascular complications, statins, fibrates, omega-3 polyunsaturated fatty acids, apolipoprotein C–III inhibitors, angiopoietin-like protein 3 inhibitors.

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Introduction

Currently, low-density lipoprotein (LDL) cholesterol (C) levels are the primary target of most available hypolipidemic therapies because of their established direct association with cardiovascular disease (CVD) risk [1]. In recent years, triglyceride (TG) levels have also become an important focus of researchers and physicans because of their association with the incidence of myocardial infarction (MI), unstable angina, and the need for arterial revascularization [2]. In addition, the risk of premature CVD remains high in individuals with high TG levels despite decreasing LDL–C levels [3].

A fasting TG level <1.7 mmol/L is considered normal, mild/moderately elevated — 1.7–5.6 mmol/L; severe hypertriglyceridemia (HTG) is recognized when the level is ⩾5.7 mmol/L [4]. HTG is associated with a linear increase in the risk of major adverse cardiovascular events (MACE), and severe HTG (especially >10 mmol/L) is associated with the risk of acute pancreatitis (AP) [5, 6]. Mild to moderate HTG is found in 1/3-1/4 of the population, about half of patients with type 2 diabetes mellitus (DM), and requires treatment for primary and secondary prevention [7]. Typically, people with HTG have a combination of genetic causes and modifiable factors, most commonly obesity, insulin resistance, and type 2 DM.

Current beliefs about the role of HTG correction are rather contradictory. On the one hand, the cardiovascular risk assessment system SCORE-2/SCORE2-OR has a parameter "C not related to high-density lipoprotein (HDL)" (the difference between total C and HDL–C), which now takes into account the influence of not only total C (as in SCORE) and LDL–C on clinical outcomes, but also other lipid fractions — very-low-density lipoproteins, intermediate-density lipoproteins, chylomicrons and their remnants, collectively termed "TG-rich lipoproteins" (TGRL), which contain atherogenic apolipoprotein B (apoB) [8]. On the other hand, even in the SCORE2-Diabetes version for type 2 DM patients, HTG is not mentioned among the major cardiovascular risk factors [9]. Meanwhile, experts from the European Society of Cardiology and the European Atherosclerosis Society in 2019 noted that a TG level >2.3 mmol/L is a risk factor for CVD and recommended TG-lowering therapy in such cases [1]. In the Russian guidelines "Dyslipidemia. Clinical Recommendations 2023", the problem of HTG is given sufficient attention and contains similar European principles for the management of such patients [10].

This review discusses the influence of HTG on the development of atherosclerosis and the possibilities of its correction, as well as the influence of available treatment methods on cardiovascular outcomes.

Hypertriglyceridemia and atherosclerosis

The effect of HTG, especially when combined with low HDL–C levels, on the development of atherosclerosis and its complications is realized by several mechanisms. First, HTG reflects elevated concentrations of TGRL in blood, and TGRL, like other apoB-containing lipoproteins, are directly atherogenic, easily penetrating the endothelium due to their small particle size (⩾70 nm) [11]. Second, high plasma TG concentrations contribute to several characteristic changes in the profile of circulating lipoproteins that are associated with enhanced atherogenesis. HTG stimulates the activity of C-transfer protein, which remodels the lipoproteins by exchanging TG for C esters between TGRL and TG-poor lipoproteins. This results in small, dense LDL particles that are more atherogenic than would be expected from their C content alone because there are many apoB molecules for each unit of C [11]. Smaller C-depleted HDL particles are more rapidly excreted by the kidneys, further reducing HDL–C levels. In general, despite often normal LDL–C levels, individuals with HTG tend to have elevated levels of atherogenic non-HDL–C and apoB, reflecting a high risk of atherosclerosis [12]. TGRLs have been shown to be associated with atherosclerosis through increased inflammation, oxidative stress and endothelial dysfunction. TGRLs are taken up by macrophages by phagocytosis, leading to the formation of C-rich foam cells in the arterial intima to form a primary lesion. Smooth muscle cells from the media migrate into this area, eventually forming an unstable atherosclerotic plaque [13]. In addition, by inhibiting fibrinolysis, HTG increases blood viscosity and promotes thrombosis [14].

Elevated TGRL levels are associated with a high risk of MACE in both primary and secondary prevention, even among patients receiving statins [15]. In a large retrospective study, participants in both primary (n=373,389) and secondary prevention groups (n=97,832) with TG levels ⩾1.7 mmol/L on statin therapy had a lower adjusted risk of death but a significantly higher risk of MACE [16]. Many patients with

DM, even those successfully controlling LDL–C levels with statins, still have an increased risk of MACE due to HTG [17].

The causes of hypertriglyceridemia

Mild to moderate HTG is usually due to heredity and modifiable environmental factors. Modern diets high in calories, fat, added sugars, and ultra-processed foods contribute directly to HTG and indirectly to the development of visceral obesity, non-alcoholic fatty liver disease, insulin resistance, and type 2 DM.

Monogenic disorders causing HTG occur in approximately 0.01 % of the general population and in 1–2 % of individuals with the most severe HTG (TG levels >10 mmol/L) [18]. Genetic testing is generally not recommended for the detection or management of HTG because genes that regulate TG levels are often recessive with heterogeneous penetrance [19]. However, when monogenic disorders such as familial chylomicronemia syndrome, familial lipodystrophy, and familial dysbetalipoproteinemia are suspected, genetic testing may influence prognosis, management strategies, and expectations regarding response to lifestyle modifications and pharmacotherapy.

When determining an individualized strategy to reduce TG and cardiovascular risk, potential secondary causes of HTG, including a number of diseases and medications (Table 1), should be evaluated and, if possible, treated [20].

Table 1. **Main causes of secondary hypertriglyceridemia**

Secondary disorders	Medications
Obesity	β-adrenoblockers
Metabolic syndrome	Thiazide diuretics
Diabetes	L-asparaginase
Hypothyroidism	Bile acid sequestrants
Chronic liver disease	Atypical neuroleptics
Chronic kidney disease	Rosiglitazone
Nephrotic syndrome	Sirolimus
Lipodystrophy	Cyclophosphamide
Autoimmune disorders	Isotretinoin
Pregnancy (3rd trimester)	Oral estrogens
Weight gain after weight loss	Tamoxifen
Rheumatoid arthritis	Glucocorticoids
Glycogen storage diseases	Retinoids
Psoriasis	Raloxifene
Sepsis	Cyclosporine
Multiple myeloma	Interferon
Systemic lupus erythematosus	Tacrolimus
Cushing's syndrome	Propofol

Hypertriglyceridemia treatment

Non-pharmacological treatment

Given the strong association of HTG with lifestyle and metabolic syndrome, many of the treatment principles for insulin resistance, type 2 DM, obesity, CVD, and non-alcoholic fatty liver disease can be successfully applied to the management of patients with HTG. Lifestyle modifications that can significantly reduce TG levels include >5 % weight loss (possible ⩾70 % reduction in TG), dietary changes (⩾70 % reduction), and physical activity (⩽30 % reduction) [21, 22].

The main feasible targets for dietary changes include: avoiding foods high in refined carbohydrates; including seafood, especially oily fish; increasing consumption of fiber-rich foods (fruits, vegetables, and whole grains); avoiding excessive alcohol consumption; and replacing saturated animal fats (meat) with monounsaturated and polyunsaturated fats in the form of high-quality vegetable oil. Energy intake should be adjusted to achieve and maintain a healthy body weight [1, 10]. Individuals with severe HTG and hyperchylomicronemia (TG >10 mmol/L) should reduce the total fat content of the diet and use lean seafood [23].

In light of the recent results of the PURE trial, it appears that whole milk products should not be excluded [24]. Interestingly, vegetarian and vegan diets reduce levels of total C, LDL–C and apoB, thereby reducing CVD risk, but do not affect blood TG levels [25].

The prevalence of HTG is significantly higher in regular alcohol drinkers [26]. In individuals with pre-existing HTG, excessive alcohol consumption significantly increases the risk of CVD. Therefore, it is recommended that patients with severe HTG abstain from alcohol altogether.

Aerobic and strength training can significantly reduce TG levels, but their effect depends on the baseline level of the parameter, caloric expenditure, regularity, intensity, and duration of physical activity [27].

Statins

Although statins are best known for their role in lowering LDL–C and reducing the risk of MACE, they also provide a dose-dependent reduction in TG levels of 10–30 % in patients with HTG, and as much as 40 % in severe HTG [28]. Current guidelines suggest that patients with mild-to-moderate HTG may benefit from lifestyle modification and consideration

of statin therapy based on individual cardiovascular risk [10, 29]. In HTG, a significant reduction in MACE risk can be achieved with statin therapy. Therefore, US experts consider a TG level ≥2 mmol/L as a factor that increases cardiovascular risk, favoring the prescription of statin therapy in individuals with a low or borderline 10-year risk of MACE [4]. However, in statin-treated patients with controlled LDL–C levels, elevated TG levels may account for a significant proportion of their residual risk of recurrent cardiovascular events. In a pooled analysis of 10 clinical trials (n=5724) in patients with atherosclerotic cardiovascular disease (ACVD) receiving statins, residual C contained in TGRL significantly correlated with changes in atheroma volume on treatment in multivariate analysis (p<0.001), independent of LDL–C, apoB, CRP, HDL–C levels, and clinical risk factors. Higher residual C levels also correlated with a higher risk of MACE. These data support further studies of interventions to reduce residual C levels in statin-treated patients with residual cardiovascular risk [30].

Fibrates and omega-3 polyunsaturated fatty acids (PUFAs) have been the most studied for their potential to correct HTG with putative effects on cardiovascular outcomes.

Fibrates

Fibrate monotherapy reduces TG levels by 20–50 %, while reducing LDL–C levels by 5–20 %, with a 50 % increase in LDL particle size and a 10–20 % increase in LDL–C levels [10]. A number of clinical trials of fibrates to determine their potential to reduce cardiovascular risk are known: HHS (Helsinki Heart Study), VA-HIT (VA HDL Intervention Trial), ACCORD (Action to Control Cardiovascular Risk in Diabetes), FIELD (Fenofibrate Intervention and Event Lowering in Diabetes), DAIS (Diabetes Atherosclerosis Intervention Study), BIP (Bezafibrate Infarction Prevention). A systematic review and meta-regression analysis of 9 trials of fibrates (n=41,520) showed that these drugs can reduce the risk of MACE by lowering TG-C levels without affecting LDL–C levels. However, the risk of transaminase elevation, myopathy, and rhabdomyolysis should be carefully considered when adding fibrates, especially with gemfibrozil (but not fenofibrate), to statin therapy [31].

A new member of the fibrate class — a selective modulator of the peroxisome proliferator-activated receptor alpha, pemafibrate at a dose of 0.2 mg twice daily was evaluated in the double-blind, randomized, placebo-controlled PROMINENT trial in 10 497 patients with type 2 DM, mild or moderate HTG (TG level 2.3–5.7 mmol/l), HDL–C ⩽1 mmol/l and LDL–C ⩽ 2.6 mmol/l. They were already taking statins. At a median follow-up of 3.4 years, when TG, residual C and apolipoprotein C–III (apoC–III) levels were reduced by 1/4 but apoB by only 4.8 %, the sum of events of the primary efficacy endpoint (non-fatal MI, ischemic stroke, coronary revascularization or death from cardiovascular causes) was observed with equal frequency in the pemafibrate and placebo groups. The overall incidence of serious adverse events was not significantly different between the groups, but the use of pemafibrate was associated with a higher incidence of renal adverse events, venous thromboembolism, and a lower incidence of non-alcoholic fatty liver disease [32].

Retrospective and secondary analyses of fibrate trials have suggested that fibrate-treated patients with HTG and low HDL–C levels may achieve improved cardiovascular outcomes despite overall neutral trial results, which served as the hypothesis for a large prospective project [33]. However, the PROMINENT trial in such a population confirmed that fibrates may reduce the risk of MACE when used as monotherapy, but not when added to statins. TG-lowering therapy is likely to reduce the risk of MACE if it increases TGRL clearance rather than simply converting remnant lipoproteins to LDL. Lowering TG levels without lowering apoB levels is not sufficient to improve cardiovascular outcomes, so fibrates should not be used to reduce the risk of MACE in individuals receiving statins, although they may still be used to reduce the risk of AP associated with severe HTG [34]. Based on these findings, the combination of statin plus fibrate is not recommended by the American Diabetes Association experts for patients with type 2 DM to reduce the risk of adverse atherosclerotic cardiovascular events [35]. A recent meta-analysis confirmed the lack of improvement in cardiovascular outcomes when fibrates are added to statins in patients with type 2 DM [36].

Omega-3 polyunsaturated fatty acids

Omega-3 PUFAs, including the combinations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), purified EPA (icosapent ethyl), reduce high TG levels by 20–45 % without unidirectional effects on LDL–C levels [10]. A number of clinical trials

investigating the role of omega-3 PUFAs in reducing the risk of MACE are well known: GISSI-P (Gruppo Italiano per lo Studio della Sopravvvivenza nell'Infarto miocardico-Prevenzione), JELIS (Japan EPA Lipid Intervention Study), ORIGIN (Outcome Reduction with an Initial Glargine Intervention), ASCEND (A Study of Cardiovascular Events iN Diabetes), REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial), VITAL (the Vitamin D and Omega-3 Trial), STRENGTH (A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia), and OMEMI (Omega-3 Fatty Acids in Elderly Patients With Acute Myocardial Infarction). In a meta-regression analysis including 42 studies of omega-3 PUFAs (n=149,359), administration of 1 g/day of EPA was associated with a 9 % relative risk reduction of MI [37].

In the GISSI-P trial in patients with recent MI (<3 months), EPA/DHA at a dose of 1 g/day reduced the risk of MACE, but only a small subgroup of participants were receiving statins [38]. In the ASCEND, VITAL, and OMEMI trials, low doses of EPA/DHA did not significantly reduce the incidence of MACE during baseline statin treatment [39–41].

The JELIS and REDUCE-IT trials evaluated the effects of EPA alone at moderate and high doses, respectively. In JELIS, 18,645 patients with elevated LDL-C levels treated with statins were randomized to receive 1.8 g/day of EPA or conventional treatment. The mean baseline plasma TG level was normal (1.7 mmol/L), and the overall treatment-related reduction in this parameter was only 9 %. At a mean follow-up of 4.6 years, the EPA group showed a 19 % relative risk reduction in major coronary events (p=0.011) [42], and patients in the EPA treatment group with baseline HTG and low HDL-C levels had a 53 % reduction in the risk of major cardiac events (p=0.043) [43]. In JELIS, participants with high (≥150 μg/L) plasma EPA concentrations had a significantly lower risk of MACE than participants with low (<87 μg/L) concentrations [44].

The aim of the REDUCE-IT project was to confirm the results of JELIS and address its limitations in a double-blind, randomized, placebo-controlled trial in 8179 patients with established CVD or DM and other risk factors on statin therapy using a higher dose (2 g twice daily) of purified EPA. Baseline fasting TG levels were 1.52–5.63 mmol/L and LDL-C levels were 1.06–2.59 mmol/l. At a median follow-up of 4.9 years, EPA was associated with a 25 % reduction in the risk of the primary endpoint (cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization or unstable angina) compared to placebo (p<0.001). At the same time, the risk of CVD death was reduced by 20 %, MI by 31 % and stroke by 28 %. Hospitalizations for atrial fibrillation or flutter were more frequent in the EPA group than in the placebo group (3.1 % vs. 2.1 %, p=0.004) [45]. No association was found between lower TG levels with EPA treatment and a reduced incidence of adverse events. However, higher plasma EPA levels after treatment were strongly associated with a reduced risk of MACE. In this regard, an important role may be attributed to the pleiotropic effect of icosapent ethyl, resulting in slowing the progression of atherosclerotic plaques and altering their structure [46].

In the STRENGTH trial of 13,078 patients at high cardiovascular risk, with HTG and low HDL-C levels, the addition of EPA/DHA at a dose of 4 g/day to statins did not reduce the risk of MACE compared with placebo [47]. Possible explanations for the discrepancy between the results of the REDUCE-IT and STRENGTH trials include 1) differences in the omega-3 PUFA formulations used (EPA and EPA/DHA); 2) follow-up periods (STRENGTH was stopped early due to no perspectives); 3) proportions of patients with established ACVD; and 4) differences in the placebo used (mineral oil vs. corn oil) [29]. The last point is of concern because the use of mineral oil as placebo in REDUCE-IT was associated with adverse effects on lipid and inflammatory biomarkers and reduced statin absorption [48]. However, the 25 % difference in MACE risk between the groups is too large to be explained by the adverse effect of the chosen placebo alone.

Apolipoprotein C–III inhibitors

Individuals with elevated levels of apoC–III, a member of the TGRL, have reduced hepatic uptake of TG-rich particles, resulting in HTG, accelerated development of atherosclerosis, and significantly increased risk of its complications. Therefore, apoC–III is one of the main targets of emerging treatments for severe HTG to reduce the risk of MACE and AP [49]. The first apoC–III inhibitor, volanesorsen, effectively reduced TG levels in 77 % of patients with familial chylomicronemia syndrome, in whom fibrates, omega-3 PUFAs and statins are usually in-

effective, but cause thrombocytopenia in half of the cases [50]. Olesarsen, which targets matrix apoC–III ribonucleic acid in the liver to inhibit apoC–III synthesis, was used subcutaneously for 6–12 months in a randomized, double-blind, placebo-controlled phase 2 study in 114 patients with fasting serum TG levels of 2.26–5.65 mmol/L, with varying degrees of good tolerability [51]. Olesarsen dose-dependently reduced TG levels by 23–60 %, while significant reductions in apoC–III, very-low-density lipoprotein C, non-HDL–C and apoB levels were observed. These data suggest that apoC–III inhibition may reduce TG levels in a population with established ACVD or at high risk of developing it. In addition, the beneficial effects of such therapy on other atherogenic lipoproteins when added to standard therapy may suggest the possibility of reducing the risk of adverse cardiovascular outcomes.

Angiopoietin-like protein inhibitors 3

Angiopoietin-like protein 3 (ALP-3) inhibits both lipoprotein lipase and endothelial lipase in humans, which may lead to elevated plasma TG and C–LDL levels with increased risk of ACVD. In this regard, ALP-3 may be another target for novel lipid-modifying therapies [52]. Vupanorsen, which inhibits ALP-3 synthesis in the liver, was compared to placebo for efficacy and safety in a randomized phase 2 study in 286 patients with non-LDL–C levels ⩾2.6 mmol/L and TG levels 1.7–5.7 mmol/L on statin therapy [53]. The vupanorsen group showed a 22.0–27.7 % reduction in non-HDL–C and a 41.3–56.8 % reduction in TG, but only a 6.0–15.1 % reduction in apoB. Higher doses of vupanorsen resulted in significantly increased levels of alanine aminotransferase or aspartate aminotransferase and increased liver fat fraction, which requires careful evaluation of the safety of this new drug.

Finding new ways to correct monogenic hypertriglyceridemia

Lipoprotein lipase deficiency is a rare monogenic autosomal recessive disease characterized by mutations in the gene for this enzyme, accumulation of chylomicrons in the blood, and HTG. Lipoprotein lipase deficiency has been corrected by replacement gene therapy using adenovirus as a vector. Intramuscular administration of human transgene to mice provided effective gene transfer to skeletal muscle and liver with normalization of plasma TG levels within 6 months [54]. The developers of this therapy now hope to be able to use it in the future not to treat HTG but to reduce LDL–C levels.

Another option for correction of familial chylomicronemia syndrome caused by lipoprotein lipase deficiency is inhibition of diacylglycerol acyltransferase 1, which mediates TG synthesis. Pradigastat, a drug with this mechanism of action, reduced TG levels by 41 % at the 20 mg dose and 70 % at the 40 mg dose after oral administration once daily in 6 patients. Pradigastat caused only mild transient gastrointestinal side effects and may be considered a promising treatment for this rare pathology [55].

European Society of Cardiology guidelines for the management of cardiovascular diseases in patients with diabetes (2023)

Experts from the European Society of Cardiology have identified DM-specific changes in the ratio of individual lipids in the blood, as well as disturbances in lipoprotein structure and function. In patients with DM, statins are recommended as first-line therapy to achieve LDL (or non-HDL-C) target levels determined on the basis of the cardiovascular risk profile (Class I recommendation, Level of Evidence A). In patients with HTG, high-dose EPA (2 g twice daily) in combination with statins may be considered (class of recommendation IIb, level of evidence B). The potential use of fibrates to reduce TG levels is very limited because of the risk of myopathy when administered concomitantly with statins and negligible benefit according to randomized trials [56].

American Diabetes Association's Standards of Diabetes Care (2024)

The American Diabetes Association recommends to evaluate secondary causes of HTG and consider medication to reduce CVD risk in people with fasting TG levels ⩾5.7 mmol/L (level of evidence: C). It is recommended that lifestyle factors (obesity and metabolic syndrome), secondary factors (DM, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase TG levels be considered and corrected in adults with moderate HTG (2.0–5.6 mmol/L fasting or nonfasting, level of evidence C).. In individuals with ACVD or cardiovascular risk factors with statin-controlled LDL–C levels but elevated TG levels (1.5–5.6 mmol/L), supplementation with EPA may be

considered to reduce the cardiovascular risk (level of evidence A) [57].

Conclusion

HTG is commonly found in patients with type 2 DM and other cardiometabolic disorders, contributes to an increased risk of ACVD and CVD, and requires correction, as recognized in current clinical guidelines. Management of patients with HTG includes exclusion or possible elimination of its secondary causes and individualized lifestyle counseling. In severe HTG, TG-lowering pharmacotherapy should be used along with lifestyle modification to reduce the risk of developing AP. In those at high risk of ACVD, statin-based dyslipidemia therapy to reduce LDL–C, non-HDL–C and apoB levels is indicated. Fibrates and low-dose omega-3 PUFAs (<1.5 g/day) do not reduce the risk of MACE in patients taking statins, but may be useful to lower TG levels in patients with severe HTG to reduce the risk of AP. Patients with HTG often have type 2 DM and should receive optimal therapy with proven ability to reduce the risk of cardiovascular complications.

Traditional approaches to treating HTG with available drugs do not address the residual risk of MACE in patients receiving statins. New drugs currently being investigated for the treatment of HTG (apoC–III inhibitors, ALP-3, pradigastat, gene therapy) under the control of the most informative biochemical marker (apoB) may potentially provide an additional reduction in the risk of cardiovascular complications.

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Non-specific adaptive defense reactions of the body in the development of panic attacks and primary prevention of cardiovascular diseases

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Aim of the study. The aim of this review is to explore the neurobiology of stress and fear, to summarize the conceptual views of panic attacks (PA) and their association with cardiovascular diseases (CVD), to provide a further strategy for clinical research on PA, and to optimize prevention and treatment interventions.

Methods. Scientific articles up to and including 2024 were searched in six electronic medical databases ("Web of Science", "Scopus", "MEDLINE/PubMed", "EMBASE", "elibrary.ru", "cyberleninka.ru"). Inclusion criteria were: keywords "anxiety disorders, autonomic disorders, COVID-19, PA, CVD, neurobiology of stress and anxiety, non-specific adaptive defense mechanisms and reactions (NADMR) of the organism, non-specific methods of treatment and prevention", cardiovascular diseases, coronary heart disease; types of scientific papers "original clinical studies"; period of research for the last 5 years. Scientific papers with psycho-organic diseases, severe somatic diseases and/or their complications were excluded. The dialectical and systematic approach was used as the methodological framework to address the objectives. The exploratory method of analysis was applied in the review of titles, abstracts and full texts. The deductive method was used to identify private patterns of different concepts. In case of discrepancies, possible solutions were synthesized.

Results. The analysis of studies devoted to different concepts of PA etiology, neurobiology of fear and evolution of views on the pathogenetic relationship between PA and CVD allowed to identify their relationship with NADMR, in which non-linear "mediator" effect would influence the development of PA and CVD. The analysis and synthesis of data from different PA concepts showed that there is no contradiction between the concepts and proposed a PA concept with a broader spectrum of nonlinear "mediator" mechanism of PA. With these results, the author substantiates the association of NADMR with PA and CVD through a nonlinear "mediator" mechanism.

Conclusion. The study of NADMR is important for the improvement of the general physical and mental health and well-being of the population in the long term, especially in conditions of aggressive environmental factors. It also

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makes it possible to emphasize the need to study complex methods of treatment, including "non-specific", the results of which should be reflected in new standards of treatment of this nosology.

Keywords: non-specific adaptive defense mechanisms and reactions, panic attacks, neurobiology of stress and fear, COVID-19, cardiovascular diseases, coronary heart disease.

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Introduction

Mental and physical distress are a part of human evolution that can enhance mental and physical performance. Depending on the period of human history, the nature and quality of stressors may vary [1].

As humanity progresses, the modern world is filled with new anthropogenic stressors that can not only deteriorate but also ruin human health. For this reason, some researchers point to the impossibility of harmonious human existence in the anthropogenic environment [2].

Depending on a variety of exogenous and endogenous factors, a certain part of the population develops panic attacks (PA), with statistical evidence of a high prevalence among all population groups worldwide [3].

Therefore, further study of the mechanisms of development of psychovegetative disorders will improve the prevention and treatment of PA and reduce the prevalence of cardiovascular diseases (CVD).

Any non-standard situation for a human being is a stress, a biological concept that was proposed by Hans Sellier. He introduced the definition of stress as "a non-specific reaction of the organism to any demand on it" [4]. The definition of stress was based on the "general adaptation syndrome", which includes three stages: initial symptoms, adaptation to stress and manifestation when stress does not end. Some authors previously referred to the unexplored component (mechanism) of stress as "non-specific". Studies in recent years have shown that the "non-specific response" is a non-linear reaction of "mediators", where abnormal activity of one of the "mediators" disturbs and distorts the rest of the network and has a cumulative effect [5].

Therefore, it is now quite acceptable to refer to such mechanisms and reactions as non-specific adaptive defense mechanisms and reactions (NADMR), which Hans Sellier called "adaptive evaluations whose significance is genetically determined". More recent work on stress has used different definitions depending on the stimulus or response to it. This leads to confusion when stress is confused with stressors (triggers/stressors). Therefore, a number of researchers, based on the discoveries of recent years, have proposed the need to define stress as a combination of external factors (stressor) and internal factors (stress perception and emergence) [6].

Hans Sellier distinguished two types of stress: acceptable ("eustress") and negative ("distress"), regardless of the stressor, which are still used today [7]. Later, new data on the effects of stressors on the body made it possible to propose a new definition of stress: "good, bad and very bad stress" [8].

According to "allostatic load" studies, the duration of stress depends on the combination of external and internal factors that determine the positive adaptive and harmful effects of stress. Short-term (acute) stress can last from one minute to two hours [9, 10], and long-term (chronic) stress can last from a few hours a day to weeks or months [11]. Chronic stress determines the ultimate spectrum of adverse effects [6], which depends on the nature of the adaptive responses: adaptive, compensatory, and maladaptive [12].

Chronic stress is also associated with functional strain, which can lead to exhaustion of the organism. Exhaustion leads to NADMR breakdown and maladaptation. The increase or decrease in NADMR depends on the combination of internal and external stressors, which determines the boundary of the stress dichotomy [12].

It can be assumed that the boundary between positive and negative stress will shift towards adaptation

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or maladaptation depending on the functional state of the organism, as a "stress threshold" [13].

In order to increase stress resistance and, as a result, the functional state of the organism, it is recommended to use widely dosed mental and physical exercise for preventive purposes, increasing the resistance and endurance of all body systems [14].

The "stress threshold" is individual for each person, when it is exceeded, there are violations of regulatory systems. The severity of disorders in the functioning of organs and systems of the organism and the time of their occurrence depend on the nature of the stressor and individual constitutional features of a person, which determine the reaction and perception of stressors [15-17].

The "stress and coping theory" has also been proposed [18]. Cognitive interpretation plays a key role in this theory, acting as a mediator between stressor and response. According to this theory, the body is unable to cope with emerging events due to impaired cognitive interpretation. The "stress and coping theory" is reflected in recent work on Gestalt phenomenology [19].

Stressors can lead to anxiety and, in extreme cases, to very severe fear, loss of behavioral control (coping), and even suicide if the person does not receive timely help [20, 21].

A sudden onset of intense fear or discomfort, exacerbated by intense autonomic arousal and peaking within a few minutes, is defined by the DSM as PA. It is accompanied by at least four somatic symptoms with the background of a sense of imminent threat to health or life without apparent cause. It is characterized by an association with physical (non-cognitive) fear and anxiety [19, 22].

In the ICD-10 classification of the Russian Federation, PA is a type of anxiety disorder in the form of spontaneous anxiety attacks not clearly associated with specific situations or objects, accompanied by a sharp increase in the level of anxiety and numerous somatic symptoms.

The prevalence of PA varies from 2% to 25% depending on the country. On average, 100,000 people represent 7-9% of the world's population, according to the WHO. This difference in statistics may be due to cultural differences (such as referral to a specialist or adherence to traditional non-drug treatments). In addition, constitutional features of the psyche and aggressive factors of the human environment differ in different regions [23].

Aggressive environmental factors include phenomena such as the COVID-19 pandemic and military conflicts, the escalation of which worldwide in recent years will contribute to an increase in delayed psychiatric disorders [15], including PA, the treatment of which may become more resistant to pharmacotherapy [20].

A person who has experienced social, personal, or other shocks may require long-term rehabilitation treatment to return to a normal rhythm of life, as conscious stressors may shift to unconscious ones or have delayed effects [21]. Therefore, people affected by severe stressors are particularly in need of long-term rehabilitation.

As a matter of fact, unconscious stressors make anxiety disorders more uncomfortable because the source of danger cannot be identified. In these primary care patients, anxiety may be overlooked during assessment, contributing to the development of chronic anxiety disorders [24].

High risk factors for the development of PA have been identified, despite the lack of obvious causes and a direct link between the level of social stability/protection and bad habits/dependencies (smoking, alcohol and other psychoactive substances). Individuals exposed to these risk factors, according to the study of PA history, show more unstable psychoemotional states in their absence in the body [25].

Persistent attempts to obtain psychoactive substances increase mental arousal. On the one hand, this encourages continued smoking and addiction, and on the other hand, it provokes PA in the absence of these substances in the blood. Managing PA in this population requires a unique treatment approach.

According to the American Psychiatric Association in 2013, PA reflect, but are not limited to, an abrupt autonomic surge of marked discomfort and extreme fear or a sense of impending doom accompanied by a strong urge to escape or fight [26].

As a result, PA may be a risk factor for several forms of psychopathology. These include, major depressive disorder, generalized anxiety disorder, personality disorders, substance use disorders and severe mental illness [27, 28].

Methods

Scientific articles up to and including 2024 were searched in six electronic medical databases ("Web of Science", "Scopus", "MEDLINE/PubMed", "EMBASE",

"elibrary.ru", "cyberleninka.ru"). Inclusion criteria were: keywords "anxiety disorders, autonomic disorders, COVID-19, PA, CVD, neurobiology of stress and anxiety, non-specific adaptive defense mechanisms and reactions (NADMR) of the organism, non-specific methods of treatment and prevention", cardiovascular diseases, coronary heart disease; types of scientific papers "original clinical studies"; period of research for the last 5 years. Scientific papers with psycho-organic diseases, severe somatic diseases and/or their complications were excluded.

The dialectical and systematic approach was used as the methodological framework to address the objectives. The exploratory method of analysis was applied in the review of titles, abstracts and full texts. The deductive method was used to identify private patterns of different concepts. In case of discrepancies, possible solutions were synthesized.

Results

Until the 2000s, there were many different theories, with neuroanatomical ones being the most popular. However, there is still no absolute consensus on the neurobiology of PA.

The study of the pathogenetic mechanisms of PA in a neuroanatomical model revealed the so-called "fear network", the core of which is the amygdala body. The septo-hippocampal system in interaction with the amygdala is involved in the formation of adaptation through emotional memory to stress [29] and neuroplasticity of synapses (remodeling of dendrites) due to cortisol, for which receptors are present in the dentate gyrus of the hippocampus. These results were recorded in the brain as genomic and epigenomic signatures.

In the new definition of "good, tolerant, and toxic" stress, compared to the old "good, bad, and very bad," the researchers replaced the term "bad" with "tolerant" because the end result of this condition is not deterministic and is conditionally pathological. Because "tolerant stress" can be considered a compensatory type of stress response and a borderline state between "good and toxic stress", the end result of which is determined by the totality of the non-linear action of "mediators" as adaptive ("good stress") and maladaptive ("toxic stress").

Not all scientists share this view on the development of PA. An alternative hypothesis for the etiology of PA is related to the panic system, based on the clinical findings of Gestalt phenomenology versus those of affective neuroscience. Researchers propose to consider PA as "an acute attack of loneliness that is not adequately recognized by the patient due to the interference of a dissociative component that makes it impossible to integrate all the neurophysiological responses activated by the panic/dissociation brain system into a coherent emotional sensation" [19].

Meanwhile, Russian scientists talk about the lack of a common neurobiological concept [30, 31]. This may indicate more concepts or a more complex model of PA, which in turn indicates the prospects for further clinical research [32, 33].

In addition, there are other studies that suggest the involvement of cognitive interpretation of external stimuli in the development of pathological anxiety. Normally, fear is an evolutionarily inherited protective emotion. If the perception and cognitive interpretation of this emotion is disturbed, PA may develop [20].

While the etiology of PA remains controversial, it is already clear that there is an association between PA and CVD [34].

Traditionally, scientists considered a panic attack to be a "functional" arousal and identified it only after careful exclusion of "organic" causes. Today, even psychiatrists reject the term "functional disorders" as applied to mental illness. Functional and organic disorders can occur in somatic pathology and psychiatric disorders. In addition, there is a growing body of literature supporting the existence of a clear link between mental and physiological processes [35].

For a long time, researchers denied such a link between psychological and physiological processes. For example, until the 2000s, studies by a group of scientists from the National Heart Foundation of Australia found no direct causal relationship between coronary heart disease (CHD) and anxiety-depressive disorders or PA. The researchers attributed the increased risk of CHD to factors such as smoking, dyslipidemia, alcohol consumption, and arterial hypertension [36].

In the early 2000s, a systematic review of prospective cohort studies found a mixed association between CHD and PA, with no significant established risk of CHD in PA. Preliminary evidence links PA to myocardial ischemia through two pathophysiological mechanisms: reduced heart rate variability and myocardial ischemia. Therefore, researchers have suggested further prospective studies to prove the association between PA and CHD [37].

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In another systematic review and meta-analysis of recent years, researchers concluded that there is no risk of developing CHD with the background of PA. They explained the etiologic relationship between them by the fact that PA precedes CHD, but in reality CHD could be misdiagnosed and interpreted as PA. However, due to several "limitations" at the time of the systematic review, including the small number of original studies, the results cannot exclude the association of PA with CHD and the increased risk of developing the latter [38]. They may serve to refine the design of further original studies.

Indeed, in 2012, the first study of myocardial perfusion in PA without established CHD was conducted, showing an association of PA with myocardial ischemia.

Another original study from the Baker Institute's Human Neurotransmitter Laboratory in Melbourne found that mental stress triggers cardiovascular events. Due to the fact that PA have "forms of sympathetic nervous system amplification", they increase the risk of CVD. It is noteworthy that the authors of this article emphasize the lack of specific prevention of cardiovascular triggers, one of which is PA [38]. Therefore, the study of NADMR may be a promising area of clinical research in the prevention of PA.

The combination of CVD risk factors such as alcohol, tobacco, psychoactive substances, etc. together with PA will accumulate a pathogenetic effect. Such a cumulative effect even increases the risk of acute coronary syndrome, which also mimics the clinical picture of PA and leads to a more severe course of it [39].

Consequently, the treatment of PA can be considered as primary prevention of CVD [38].

General treatment protocols for mental disorders favor a holistic biopsychosocial approach, excluding acute CVD. The National Institute for Health and Clinical Excellence (NICE 2017) treatment protocols recommend the following modular treatment regimen in descending order of evidence of greatest effectiveness: psychotherapy, pharmacological intervention, and non- pharmacological intervention [40].

Cognitive-behavioral therapy is the method of choice for PA in psychotherapy. However, in the long-term course of PA, psychotherapy and pharmacotherapy can be supplemented with physiotherapy, acupuncture, organic preparations to restore the neurotransmitter deficit due to long-term depletion of the chronic course of the pathological process, correction of the psychoemotional background, Ericksonian hypnosis, and the use of a new method of metacognitive therapy [41-43].

At the moment of an acute anxiety attack, which can provoke PA, relaxation techniques of concentration on breathing and relaxation of involuntarily tensed muscles will help to control it [44].

According to the 2017 NICE guidelines, anxiolytics, neuroleptics or benzodiazepines are recommended for the treatment of PA. Depending on the severity of the course of PA, anxiolytics or selective serotonin reuptake inhibitors (SSRIs) may be the first line of treatment for anxiety. Tetracyclic antidepressants may sometimes be more effective. Benzodiazepines are used for generalized anxiety disorder [20].

Discussion

Perhaps there is no contradiction between the described theories of the origin of PA, and the problem is not only the dissociative component that interferes with the formation of a "coherent emotional feeling". It is possible that the link in these views is the septo-hippocampal gyrus, where a false emotion is formed after activation by an acute stressor or sensitization by a chronic stressor of the fear brain network. One of the triggers would be separation/loneliness. The separation/loneliness would then transform into an anxiety attack, and the constructs of emotional memory in childhood may not contradict the example of Parkinson's disease in old age on which the findings of Gestalt phenomenology are based.

Thus, the example described above may also support the author's view that the problem is not just a matter of cognitive interpretation of the single emotion of loneliness. Rather, it is more likely that the cognitive interpretation of various/single emotions triggers a non-linear cascade of "mediators", the end result of which determines NADMR.

Such seemingly conflicting scientific evidence on the etiology of PA may be different parts of the same whole, pointing to a much more complex and non-linear neurobiology of NADMR stress tolerance than a disruption in an individual brain's fear network or a faulty cognitive interpretation of external stimuli. The establishment of an interdisciplinary panel would help advance the study of PA.

In 2019, an interdisciplinary commission addressed the issue of stress resilience, the results of which,

after editing and harmonization, were published in August 2020. The proposed definitions of stress resilience were all different. However, the commission unanimously affirmed that stress resilience is a multilevel process, from the neurobiological level to the level of social structure. This takes the study of stress resilience to a new level and suggests a non-linear response of NADMR "mediators" in the formation of stress tolerance [45].

Despite the differentiated approach to the treatment of anxiety-depressive disorders, there are still emerging forms resistant to pharmacotherapy that are still poorly understood [46]. It is possible that with prolonged use of SSRIs and persistence of a psychotraumatic factor, endogenous serotonin is depleted. As a result, non-selective tetracyclic antidepressants and benzodiazepines show better results than SSRIs in generalized anxiety disorder.

In the future, a possible solution to the problem of imperfect drug therapy in the form of the emergence of drug-resistant forms of anxiety-depressive disorders will be further study of the role of neuropeptides. They are involved in neuromodulation of behavioral disorders: corticotropin-releasing factor, galanin, oxytocin, vasopressin, neuropeptide Y and orexins[47]. Neuropeptides can be used as markers in clinical trials of new or complex PA treatments.

Specific and non-specific rehabilitation methods are recommended as prophylaxis for universal (no risk group), selective (high risk group) and indicative (minimal risk group) groups [48].

Specificity consists of excluding or limiting PA-provoking factors. Specific prophylaxis is short-term and effective when used episodically. Non-specific methods of prevention are increasing and strengthening the mental and physical functional capabilities of the organism, normalization of biorhythms, avoidance of bad habits, proper nutrition, audiotherapy with sounds of nature, pleasant music, meditative recordings, helpful relaxation and other methods of recovery [49, 50].

Conclusion

Since mental disorders may contribute to impaired autonomic function, which creates favorable conditions for the development of CVD, early diagnosis and treatment of PA would be a prevention of CVD, and increasing stress tolerance would be a prevention of PA. Therefore, further study of NADMR will contribute to a better understanding of the mechanism of "non-linear mediator" effects in the development of PA and its causal relationship with CVD.

Thus, the presented results summarizing the different concepts of PA and their relationship with CVD, the results of research on the neurobiology of stress and anxiety in the long term may have implications for improving the overall physical and mental health and well-being of the nation in the long term. Especially by integrated therapies in the face of aggressive environmental factors. The results of the NADMR studies will allow the design of subsequent clinical trials on PA, CVD and "non-specific" methods of treatment of these diseases in order to increase the functional activity of the organism and improve adaptive capabilities.

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The most important clinical trials presented at the HOT LINE sessions of the European Society of Cardiology Congress 2023

At the 9 scientific sessions of the HOT LINE Congress of the European Society of Cardiology 2023, the results of 29 randomized clinical trials were presented for the first time. The studies were devoted to various areas of cardiology, including the treatment of acute and chronic heart failure, cardiac arrhythmias, coronary heart disease, non-coronary myocardial diseases, the search for optimal diagnostic strategies, anticoagulant therapy, and treatment of COVID-19.

Keywords: clinical trials, cardiovascular diseases, treatment, diagnostics.

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STEP-HFpEF. Heart failure with preserved ejection fraction (HFpEF) is an increasingly common condition with particularly severe symptoms and functional impairment in obese individuals. In 529 patients with HFpEF and obesity, the results of semaglutide at a dose of 2.4 mg subcutaneously once weekly compared with placebo were observed for 52 weeks after randomization. The semaglutide group showed significant improvements according to Kansas City Cardiomyopathy Questionnaire quality of life (by 7.8 points; $p<0.001$), decreased body weight (by 10.7 %; $p<0.001$), increased 6-minute walk distance (by 20.3 m; $p<0.001$) and decreased C-reactive protein levels compared to placebo. Serious adverse events were reported in 13.3 % of participants in the semaglutide group and 26.7 % in the placebo group [1].

NOAH-AFNET 6. It is unclear whether episodes of frequent atrial pacing detected by an implanted device in the absence of atrial fibrillation (AF) require the initiation of anticoagulant therapy. Elderly patients with episodes (at least 6 minutes, mean 2.8 hours) of rapid (≥170 beats per minute) atrial rhythm detected by implantable devices and at least one risk factor for stroke were assigned to standard treatment with edoxaban (n=1270) or placebo (n=1266). The study was stopped early due to safety concerns at a mean follow-up of 21 months. The incidence of stroke was approximately 1 % per patient-year in both groups. There was no significant reduction in the incidence of cardiovascular death, stroke or systemic embolism with edoxaban compared to placebo ($p=0.15$), but a significant increase in the incidence of death from any

cause or major bleeding (p=0.03). In the study cohort, 18.2 % of patients developed electrocardiographically diagnosed atrial fibrillation during follow-up [2].

COP-AF. The perioperative risk of AF is thought to be related to inflammation, suggesting a potential benefit of anti-inflammatory drugs. Patients undergoing major non-cardiac thoracic surgery (lung lobe resection and others) received colchicine 0.5 mg (n=1608) or placebo (n=1601) 4 hours before surgery and twice daily for 10 days. During the 14-day follow-up, clinically significant perioperative atrial fibrillation was observed in 6.4 % and 7.5 % of cases (p=0.22), and myocardial damage in 18.3 % and 20.3 % (p=0.16) of patients receiving colchicine and placebo, respectively. Sepsis or infection was reported in 6.4 % of patients in the colchicine group and 5.2 % in the placebo group (p=0.14). Colchicine administration was significantly more associated with the development of non-infectious diarrhea (8.3 % vs. 2.4 % with placebo; p<0.001) [3].

QUEST. The 4 capsules of traditional Chinese medicine combination herbal medicine qiliqiangxin 3 times daily or placebo was added to standard therapy in 3110 patients with chronic heart failure (CHF) with reduced left ventricular ejection fraction (LV EF) (≤40 %). During a median follow-up of 18.3 months, the primary endpoint (rehospitalization for worsening HF or cardiovascular death) was observed in 25.02 % of patients in the qiliqiangxin group versus 30.03 % in the placebo group (p<0.001), and there was a significant reduction in the risk of each of the two endpoint components in the more active treatment group. No significant differences were observed between the matched groups in the incidence of all-cause mortality (14.21 % vs. 16.85 %) and the development of adverse events, including gastrointestinal symptoms, worsening renal function and increased liver enzyme levels [4].

BUDAPEST-CRT Upgrade. *De novo* implantation of a defibrillator-enabled cardiac resynchronization therapy device reduces the risk of morbidity and mortality in patients with left bundle branch block, HF, and reduced EF. However, the benefit of switching patients with HF and reduced EF from right ventricular pacing to cardiac resynchronization therapy with defibrillation capability is unclear. The study included 360 patients with an implantable cardioverter-defibrillator and intermittent or continuous right ventricular pacing with a stimulated QRS complex duration of at least 150 m/s. The placement of an additional left ventricular stimulation lead implanted in the lateral branch of the coronary sinus (n=215) was associated with a lower risk of the primary endpoint. That included: hospitalization for heart failure, all-cause mortlity, or no reverse myocardial remodeling (32.4 % vs. 78.9 %; p<0.001) and HF hospitalization or all-cause mortality (10 % vs. 32 %; p<0.001) compared to the continued right ventricular pacing with defibrillation option group (n=145) over 12 months of follow-up. The incidence of procedure- or device-related complications was similar in both groups [5].

HEART-FID. Iron carboxymaltosate therapy has previously been shown to reduce symptoms and improve quality of life in HF patients with reduced LV EF and iron deficiency, but the effect of such treatment on outcomes required additional study. Intravenous iron carboxymaltosate (n=1532) every 6 months (as needed based on iron and hemoglobin levels) or placebo (n=1533) was added to the treatment regimen for chronic HF with reduced (≤40 %) LV EF in iron-deficient patients. At 12 months, there were no significant differences in all-cause mortality (8.6 % vs. 10.3 % of cases) and hospitalization for HF (13.3 % vs. 14.8 %) in the iron carboxymaltosate and placebo groups, respectively, although the 6-minute walk distance increased by 8 m in the iron group and by 4 m in the placebo group at 6 months (p=0.02). The incidence of serious adverse events during the treatment period was not significantly different between the two groups (27.0 % vs. 26.2 % of cases, respectively) [6].

FIRE. The benefit of complete coronary revascularization in elderly patients with myocardial infarction (MI) and multivessel stenoses remains unclear. Patients with MI and multivessel coronary artery stenoses (mean age 80 years) underwent percutaneous coronary intervention (PCI) with stenting of all arteries with hemodynamically significant stenosis (n=720) or only the culprit artery (n=725). The combined primary endpoint of death, myocardial infarction, stroke, or any revascularization procedure at 1 year was less frequent in the complete revascularization group (15.7 % vs. 21.0 % in the culprit artery stenting group; p=0.01), and the safety of the intervention (composite of stroke, bleeding, or acute kidney injury associated with the administration of radiopaque contrast) was comparable (p=0.37) [7].

ECLS-SHOCK. Extracorporeal membrane oxygenation is increasingly used in the treatment of cardio-

genic shock in patients with MI without evidence of its effect on mortality. Patients with MI, experiencing the cardiogenic shock, who were scheduled for early revascularization were treated with venoarterial extracorporeal membrane oxygenation plus conventional medical therapy (n=209) or conventional medical therapy alone (control group; n=208). The primary efficacy endpoint, death from any cause at 30 days, was observed in 47.8 % versus 49.0 % of patients in the full extracorporeal support group and the control group, respectively (p=0.81). In the first group, moderate or major bleeding was 2.44 times more frequent and peripheral vascular complications requiring intervention were 2.86 times more frequent [8].

STOPDAPT-3. Patients with acute coronary syndromes (75 %) or at high risk of bleeding were treated with prasugrel 20 mg once prior to PCI and, after randomization, continued to receive prasugrel monotherapy at a dose of 3.75 mg/day (n=2984) or a combination of prasugrel (3.75 mg/day) with aspirin (81-100 mg/day; n=2982) for 1 month. The antiplatelet monotherapy and dual therapy groups did not differ significantly in the frequency of Academic Research Consortium bleeding type 3 or 5 (4.47 % vs. 4.71 %; p=0.66 for superiority) and the cumulative incidence of cardiovascular death, MI, definite stent thrombosis, or stroke (4.12 % vs. 3.69 %; p=0.01 for non-inferiority) at 30 days. Antiplatelet monotherapy with prasugrel increased the risk of subacute definite or probable stent thrombosis by 3.4-fold and the risk of unplanned coronary revascularization by 83 %. The aspirin-free strategy with low-dose prasugrel showed no superiority over dual antiplatelet therapy with respect to major bleeding at 1 month after PCI, but no inferiority in regard to the risk of cardiovascular events. In addition, the aspirin-free strategy was associated with an excess of coronary events [9].

ILUMIEN IV. Limited data were available on clinical outcomes after PCI in complex coronary artery lesions with optical coherence tomography versus standard coronary angiography. There was a significant difference in the minimum stent area (5.72±2.04 mm^2 vs. 5.36±1.87 mm^2; p<0. 001) with similar cumulative incidence of adverse outcomes — death from cardiac causes, MI or revascularization due to ischemia in the target artery area at 2 years (7.4 % and 8.2 % of cases; p=0.45), and stent thrombosis within 2 years (0.5 % vs. 1.4 % of cases; p=0.02) in the optical coherence tomography (n=1233) and angiography groups (n=1254), respectively [10].

OCTOBER. Patients with clinical indications for PCI and complex bifurcation lesions underwent myocardial revascularization using optical coherence tomography (n=600) or conventional coronary angiography (n=601). At a median follow-up of 2 years, the composite of primary endpoint events — cardiac death, MI, or target artery revascularization due to ischemia — was reported significantly less frequently in the optical coherence tomography-guided intervention group (10.1 % of patients) than in the conventional coronary angiography group (14.1 %; p=0.035). Procedure-related complications occurred at similar rates in the two groups (6.8 % and 5.7 % of cases, respectively) [11].

OCTIVUS. PCI was performed while using optical coherence tomography (n=1005) or intravascular ultrasound (n=1003) in patients with significant coronary artery lesions. After one year of follow-up, the incidence of the primary endpoint — death from cardiac causes, MI, or revascularization due to ischemia in the target artery area — was 2.5 % in the optical coherence tomography group and 3.1 % in the intravascular ultrasound group (p<0.001 for no less effective). The risk of contrast-induced nephropathy was similar in the two groups (p=0.85), and major procedural complications were lower in the optical coherence tomography group than in the intravascular ultrasound group (p=0.047), although no imaging procedure-related complications were observed [12].

ATTRibute-CM. A total of 421 elderly patients with transthyretin amyloid cardiomyopathy were prescribed akoramidis 800 mg twice daily (n=421) or placebo twice daily (n=211) for 30 months, with additional open-label use of tafamidis allowed at the discretion of the physician after 12 months. 14.5 % of patients receiving akoramidis and 21.8 % of patients receiving placebo were prescribed with tafamidis, which has previously been shown to be effective in this setting. The akoramidis group showed a statistically significant superiority in the risk of the primary combined endpoint with a hazard ratio of 1.772 (p<0.0001) in a hierarchical analysis that prioritized the endpoints in the following order: all-cause mortality, followed by the incidence of cardiovascular-related hospitalizations, subsequent change from baseline in the level of the N-terminal precursor of brain natriuretic peptide, subsequent change from baseline in the

6-minute walk distance. In addition, acoramidis was associated with a 50 % reduction in the relative risk of cardiovascular hospitalization (p<0.0001) [13].

ARREST. Patients with spontaneous circulatory recovery after out-of-hospital cardiac arrest without ST-segment elevation were transported by London Ambulance Service staff to one of 7 cardiac arrest centers (n=431) or to the geographically nearest emergency department (n=431) of 32 London hospitals. The primary endpoint (30-day all-cause mortality) was 63 % in the cardiac arrest center group and 63 % in the standard of care group (unadjusted hazard ratio 1.00; p=0.96). Only 2 % of patients in the cardiac arrest center group and 1 % in the standard of care group experienced serious adverse events, none of which were considered treatment-related. Thus, in patients without ST-segment elevation after successful out-of-hospital resuscitation, transfer to a specialized cardiac arrest center does not reduce mortality [14].

ADVENT. The comparative efficacy and safety of pulsed field ablation-based pulmonary vein isolation and conventional thermoablation in patients with paroxysmal AF have not been evaluated. Patients with paroxysmal AF refractory to antiarrhythmic drugs underwent pulsed-field catheter ablation (n=305) or conventional radiofrequency or cryoballoon (thermal) catheter ablation (n=302) to isolate the pulmonary vein orifices. At 1 year follow-up, the primary efficacy endpoint of freedom from primary procedure ineffectiveness, documented atrial tachyarrhythmia after a 3-month blinded period, antiarrhythmic drug use, cardioversion, or repeat ablation was reported in 73.3 % versus 71.3 % of cases in the pulsed-field and thermal ablation groups, respectively (p>0.999 for no less efficacy). The primary safety endpoint (acute and chronic serious device and procedure-related adverse events) was reported at the same rate in the matched groups (p>0.999 for no less safety) [15].

MULTISTARS AMI. In patients with ST-segment elevation MI (STEMI) and multivessel coronary stenoses, the optimal timing of complete revascularization remained unknown. Hemodynamically stable patients with STEMI and multivessel coronary heart disease (CHD) underwent immediate multivessel PCI (emergency group; n=418) or first intervention on the "culprit" artery followed by staged multivessel intervention on the "non-culprit" arteries within 19 to 45 days after the index procedure (staged group; n=422). During 1-year follow-up, the sum of events for the primary end point-death from any cause, non-fatal MI, stroke, unplanned revascularization due to ischemia, or hospitalization for HF was 8.5 % in the immediate treatment group compared with 16.3 % in the staged group (p<0.001 for not less effective and p<0.001 for superiority). The risk of death from any cause, stroke, and hospitalization for HF was similar in the matched groups. Serious adverse events were observed in 104 patients in the emergency group and 145 in the stage group [16].

CASTLE HTx. The prognostic role of catheter ablation in patients with symptomatic AF and end-stage HF remained unknown. In a single-center study, patients with symptomatic AF and New York Heart Association functional class II-III HF with EF ⩽35 % received catheter ablation to restore sinus rhythm and medical therapy (n=97) or medical therapy alone (n=97). At a median follow-up of 18 months, the primary endpoint of death from any cause, left ventricular assist device implantation or urgent heart transplantation occurred in 8 % and 30 % of patients, respectively (p<0.001), and death from any cause occurred in 6 % and 20 % of patients in the ablation and medical therapy groups, respectively. Procedure-related complications were observed in 3 patients in the ablation group and 1 patient in the medical therapy group [17].

FRAIL-AF. In frail patients with atrial fibrillation receiving vitamin K antagonists, the appropriateness of switching to direct oral anticoagulants remains unclear. Patients with non-valvular AF and frailty aged ⩾75 years (mean age 83 years) with a glomerular filtration rate ⩾30 ml/min/1.73 m^2 were switched to direct oral anticoagulants (n=662) or continued on vitamin K antagonists (n=661). After 12 months of follow-up, major and clinically significant bleeding (primary endpoint) occurred in 15.3 % vs. 9.4 % of cases (p=0.00112), and the incidence of thromboembolic complications was 2.4 % vs. 2.0 % in the direct oral anticoagulant and vitamin K antagonist groups, respectively. In frail elderly patients with AF, switching from adequate vitamin K antagonist therapy to direct oral anticoagulant therapy should not be considered in the absence of obvious indications [18].

OPT-BIRISK. Patients undergoing PCI for acute coronary syndromes (ACS) at high bleeding risk and high ischemic risk received dual antiplatelet therapy (clopidogrel plus aspirin) for 9 to 12 months,

followed by 9 months of clopidogrel plus aspirin (n=3850) or clopidogrel plus placebo (n=3850), followed by 3 months of aspirin alone. The risk of type 2, 3, or 5 bleeding according to the Bleeding Academic Research Consortium classification was lower in the aspirin-free group (2.5 % vs. 3.3 %; p=0.03) over 9 months of treatment. The cumulative risk of all-cause mortality, MI, stroke or clinically driven revascularization was also lower in the aspirin-free group (2.6 % vs. 3.5 %; p=0.02), and all-cause mortality was 0.3 % vs. 0.5 % of cases (p>0.05) [19].

ARAMIS. Hospitalized patients with symptomatic acute myocarditis and elevated cardiac troponin levels on standard therapy were compared to subcutaneous administration of the interleukin-1 receptor antagonist anakinra 100 mg once daily (n=57) or placebo (n=60) during hospitalization. The primary efficacy endpoint, the number of days free of myocarditis complications after hospital discharge, averaged 30 days in the anakinra group and 31 days in the placebo group. The safety endpoint, the number of serious adverse events within 28 days of discharge, was observed in 12.1 % of patients receiving anakinra and 10.2 % of patients receiving placebo, also with no significant differences between groups [20].

DANPACE II. Patients with sick sinus syndrome (n=539) were initially implanted with pacemakers programmed to a base rate of 60 beats per minute (bpm) with rate-adaptive pacing or a base rate of 40 bpm without rate-adaptive pacing. At 2 years, remote monitoring showed no differences between groups in the number of AF episodes lasting longer than 6 minutes (46 % each), longer than 6 hours or longer than 24 hours, frequency of progression to persistent or permanent AF, cardioversion for AF, or death from any cause. In addition, quality of life and 6-minute walk test scores at 12 months were similar in both groups. Significantly more patients in the 40 bpm pacing group experienced syncope or presyncope (22 %) compared to the 60 bpm pacing group (13 %). For this reason, or because of chronotropic incompetence, 23 % of patients required pacing reprogramming to a higher rate [21].

RED-CVD. In 650 patients with chronic obstructive pulmonary disease (COPD) and/or type 2 diabetes mellitus (DM) in primary care, a diagnostic intervention consisting of three steps was assessed: 1) symptom assessment using a questionnaire; 2) physical examination, determination of N-terminal brain natriuretic peptide precursor levels, and electrocardiogram recording; and 3) at the discretion of the primary care physician, referral to a cardiologist if abnormalities were detected (n=624) or usual care (n=592). Patients progressed to the next stage if they accumulated a number of points above a certain threshold. At one year, the rates of new diagnoses of cardiovascular disease (8.0 % vs. 3.0 %), HF (4.5 % vs. 1.5 %), AF (2.1 % vs. 0.8 %), and CHD (2.6 % vs. 1.4 %) were higher in the intervention group than in the usual care group. An easy-to-use active diagnostic strategy more than doubled the number of newly-found cases of CH, AF, and CHD in patients with COPD and/or type 2 DM in primary care compared with usual care, which may facilitate timely initiation of treatment for emerging cardiovascular conditions [22].

NITRATE CIN. Contrast-induced nephropathy (CIN) during coronary angiography and/or PCI is a long-standing problem. Researchers have searched for years for a method other than hydration to prevent such renal injury, and one after another these attempts have failed (examples include intravenous sodium bicarbonate and oral N-acetylcysteine). In patients with ACS without ST-segment elevation referred for invasive coronary angiography and at risk for CIN (more than half of patients had chronic kidney disease at baseline and 45 % had DM), the efficacy of potassium nitrate at a dose of 12 mmol (n=319) and potassium chloride (placebo; n=321) in capsules once daily for 5 days was compared. In the inorganic nitrate group, compared with placebo, there was a significant reduction in the risk of CIN (creatinine elevation ≥26.5 μmol/L within 48 hours or ≥1.5 times within a week) of 9.1 % vs. 30.5 %, (p<0.0001), procedural MI (2.7 % vs. 12.5 %; p=0.003) and major cardiovascular complications within a year (9.1 % vs. 18.1 % of cases; p=0.001) [23].

DICTATE-AHF. Patients with type 2 DM and an estimated glomerular filtration rate (eGFR) of at least 25 mL/min/1.73 m^2 hospitalized for acute decompensated HF with hypervolemia and receiving intravenous loop diuretics were treated with dapagliflozin at a dose of 10 mg/day for the first 24 hours (n=119) or standard therapy (n=119). After 5 days or up to the day of hospital discharge, there was no advantage of dapagliflozin in influencing the ratio of weight change in kg/dose of loop diuretic in mg. However, dapagliflozin significantly increased 24-hour natriuresis (p=0.025) and 24-hour diuresis (p=0.005), shortened

time to cessation of intravenous diuretic therapy (p=0.006) and time to hospital discharge (p=0.007). Early initiation of dapagliflozin was safe in regard to all DM and cardiovascular outcomes, and there were no between-group differences in change in eGFR from baseline to study end, incidence of adverse events, in-hospital mortality, symptomatic hypotension, hypoglycemia, genitourinary infections, or severe hypokalemia [24].

PUSH-AHF. Treatment of acute HF with natriuresis control in patients 2, 6, 12, 18, 24, and 36 hours after initiation of intravenous loop diuretics with possible dose adjustment (n=150) was compared with standard therapy (n=160). During the first 24 hours, natriuresis was significantly higher by an average of 63 mmol/L in the natriuresis-controlled group (p=0.0061), but the risk of all-cause death or hospitalization for heart failure at 180 days was the same as in the conventional treatment group (31 % in both groups; p=0.698). There were no significant differences between the two groups in terms of length of hospital stay, risk of electrolyte disturbances or worsening of renal function [25].

RIGHT. Patients undergoing primary PCI for STEMI with bivalirudin received postprocedural anticoagulant therapy within 4 hours of the procedure (n=1494): 1) unfractionated heparin at 10 U/kg/hour intravenously with dose adjustment to maintain an activated clotting time of 150-220 s or 2) enoxaparin at a dose of 40 mg once daily subcutaneously or 3) bivalirudin 0.2 mg/kg/hour intravenously or placebo (ie, no anticoagulant therapy; n=1495) for ≥48 hours. At 30 days, there was no difference in the cumulative incidence of the primary efficacy endpoint (all-cause death, non-fatal MI, non-fatal stroke, definite stent thrombosis, or urgent revascularization of any artery at 30 days) between the anticoagulation and placebo groups (p=0.988). However, there was a significant interaction between the primary efficacy endpoint and the type of anticoagulant used (p=0.015 for interaction). Enoxaparin reduced the risk of adverse events by 54 % compared to placebo, while unfractionated heparin increased the risk by 3.71-fold and bivalirudin by 1.24-fold. The incidence of the primary safety endpoint (major bleeding type 3-5 according to the Bleeding Academic Research Consortium within 30 days) did not differ between the two groups compared (p=0.511), and there was no significant interaction between the three anticoagulants (p=0.679 for interaction) [26].

ONCO DVT. The optimal duration of anticoagulant therapy for isolated distal deep vein thrombosis in cancer patients remained undetermined because such treatment may increase the risk of bleeding in addition to its presumed benefit. Active cancer patients with isolated distal deep vein thrombosis were treated with edoxaban (60 mg once daily or 30 mg once daily if creatinine clearance was 30-50 mL per minute or body weight ≤60 kg or in those receiving concomitant treatment with potent P-glycoprotein inhibitors) for 12 months (n=296) or 3 months (n=305). After one year, the primary endpoint, a composite of symptomatic recurrent venous thromboembolism or related death, was reported in 1.0 % vs. 7.2 % of cases (p<0.001), and major bleeding according to International Society on Thrombosis and Hemostasis criteria in 9.5 % vs. 7.2 % of cases in the 12-month and 3-month therapy groups, respectively [27].

The meta-analysis of the **DARE-19**, **RECOVERY**, and **ACTIV-4A** studies. Participants in the three trials who were hospitalized for COVID-19 received either additional sodium-glucose cotransporter type 2 inhibitors (n=3025) or conventional treatment/placebo alone (n=3071) after randomization. The primary endpoint of all-cause mortality within 28 days occurred in 11.7 % and 12.4 % of patients in the sodium-glucose cotransporter type 2 inhibitor and conventional treatment or placebo groups, respectively (p=0.33). There were also no significant differences in the risk of progression of acute kidney injury, need for dialysis, conversion to invasive mechanical ventilation, extracorporeal membrane oxygenation within 28 days, in-hospital mortality (p=0.37), or 90-day mortality (p=0.18). These results do not support the use of type 2 sodium-glucose cotransporter inhibitors as standard of care in this clinical setting, but also do not seem to justify the routine withdrawal of these drugs prescribed for other indications (HF, chronic kidney disease or type 2 DM) during COVID-19.

Conflict of interests: none declared.

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Author Guidelines

Manuscript publication rules
in the International heart and vascular disease journal

Edit from December, 2021

Disclaimer: The rules came into effect from December 2021. The rules describe the conditions of publication of manuscripts (articles) through the site http://www.heart-vdj.com. The editorial Board is ready to answer questions and help authors by e-mail: submissions.ihvdj@gmail.com.

The *International heart and vascular disease journal* has been published since 2013. It is official journal of the Cardioprogress Foundation. The target audience of this peer-reviewed journal is cardiologists and internal disease specialists. The journal is primarily focused on questions of epidemiology, prevention, and cardiac pharmacotherapy. It also publishes lectures and literature reviews on various problems of modern cardiology, reports on new diagnostic methods, and other information which is important for the practitioners.

The General criteria for the publication of articles in the International heart and vascular disease journal are the relevance, novelty of the material and its value in theoretical and/or applied aspects.

The languages of publications are Russian and English. Journal is peer-reviewed, with multistage editing. Editorial board is presented by the leading cardiologists from different countries and Russia.

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All clinical trials should be performed and described in full accordance with the CONSORT standards (http://www.consort-statement.org), observational research – STROBE (http://www.strobe-statement.org), systematic reviews and meta-analyses – PRISMA (http://www.prisma-statement.org), diagnostic accuracy – STAR (http://www.stard-statement.org).

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[2] FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

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Statistical methods are described in detail in the Material and methods section.

Acknowledgements – all participants who do not meet the authorship criteria should be listed in the Acknowledgements section, which is located at the end of the article before the Literature section.

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Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London/Melbourne/Auckland: Lea and Febiger; 1990. p.398–420. ISBN 0000–0000.

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Webpage:

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