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A systematic approach to the diagnosis of hereditary arrhythmias: current trends and practical recommendations

Hypertensive disorders in pregnancy: diagnosis, target blood pressure levels and pharmacotherapy

Risk of cardiovascular complications in patients with type 1 diabetes mellitus: focus on dyslipidemia and hyperglycemia

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International Heart and Vascular Disease Journal

Journal of the «Cardioprogress» Foundation

Volume 12, № 44, December 2024

Contents

Editor's Welcome

Dear colleagues!

We present to your attention the next, forty-four issue of the International Heart and Vascular Disease Journal that includes the leading, original, review articles.

The "Leading Article" section features a review article dedicated to current aspects of diagnosing hereditary cardiac arrhythmias, established clinical practices, potential challenges, and medical errors in identifying and managing patients with suspected primary electrical heart diseases (channelopathies).

The "Original Articles" section includes two studies. The first article analyzes the role of past COVID-19 infection and gene polymorphisms encoding the renin-angiotensin-aldosterone system in patients with uncontrolled hypertension. A clinical examination was conducted on 116 patients with stage 2 hypertension and uncontrolled arterial hypertension, 96 of whom had experienced mild to moderate COVID-19. According to the authors, identifying the association of blood pressure with AGT gene polymorphism in post-COVID syndrome could enable the initiation of personalized treatment and prevention strategies. The second article examines factors associated with the onset of newly diagnosed atrial fibrillation in a group of patients with non-ST-elevation acute coronary syndrome. The study included 769 patients and demonstrated that those with atrial fibrillation were older, more likely to have comorbidities (stroke, chronic kidney disease), higher GRACE scores, lower SYNTAX scores, and more significant laboratory changes (lower glomerular filtration rate, higher concentrations of lipids and glucose).

The "Review Articles" section features three studies. The first article, dedicated to hypertensive disorders during pregnancy, presents data on clinically justified approaches, improved outcomes, and prevention of complications for both the mother and the fetus. Special attention is given to the treatment of severe arterial hypertension, preeclampsia, including severe preeclampsia, and key approaches to diagnosing and managing pre-existing secondary arterial hypertension during pregnancy. The second article analyzes the risk of cardiovascular complications in patients with type 1 diabetes mellitus (T1DM). Optimal glycemic control without significant hypoglycemia is essential for reducing cardiovascular risk in T1DM patients. While hyperglycemia plays a major role, the risk remains high even in well-controlled T1DM patients, suggesting that other risk factors may also be involved. The third article focuses on the connection between heart failure (HF) and type 2 diabetes mellitus (T2DM), as well as challenges in its diagnosis. The presence of HF leads to more pronounced clinical symptoms, increased hospitalizations, and worsened quality of life and prognosis. In T2DM, HF with preserved ejection fraction is more common, making its diagnosis particularly challenging. Special attention is given to left ventricular diastolic dysfunction, which is an important prognostic factor for HF in T2DM patients.

We invite everybody to collaborate with the journal. Our team is 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

Scientists from the United States assessed the effectiveness of the new oral drug muvalaplin in reducing lipoprotein(a) [Lp(a)] levels in patients at high risk of cardiovascular events. According to standard analysis, muvalaplin led to a 47.6% reduction in Lp(a) concentration compared to placebo at a dose of 10 mg/day and an 81.7% reduction at 60 mg/day. At a dose of 240 mg/day, Lp(a) levels decreased by 85.8%.

The data were analyzed for 233 adult patients with Lp(a) levels above 175 nmol/L. They were randomized into groups taking one of three daily doses of muvalaplin (10, 60, or 240 mg) or placebo for 12 weeks.

According to the JAMA

Scientists from Southern California studied the duration of elevated cardiovascular risk following COVID-19 and whether this risk decreased after recovery.

The analysis revealed that during three years of follow-up, the risk of heart attack, stroke, and death was at least twice as high among adults who had COVID-19, and nearly four times higher among those hospitalized for the virus, compared to those without a history of the disease.

The study included data from 10,005 UK Biobank participants who either tested positive for COVID-19 or were hospitalized due to the infection. The authors concluded that the increased risk of heart attack, stroke, and death should be considered not only as a severe form COVID-19 but also as an additional cardiovascular risk factor.

According to the Arteriosclerosis, Thrombosis, and Vascular Biology journal

Researchers from the Heart Institute of Central America assessed the impact of sodium zirconium cyclosilicate on optimizing spironolactone use in participants with heart failure with reduced ejection fraction (HFrEF) and hyperkalemia.

The analysis showed that 71% of patients taking sodium zirconium cyclosilicate achieved normokalemia while on at least 25 mg/day of spironolactone without emergency hyperkalemia therapy, compared to 36% of patients on placebo.

The authors concluded that in patients with HFrEF and hyperkalemia, sodium zirconium cyclosilicate led to a higher rate of normokalemia at optimal spironolactone doses, reduced the risk of hyperkalemia, and minimized the need to lower the dose/discontinue spironolactone.

According to the JACC

Scientists from Novosibirsk State Technical University developed a method for diagnosing the risk of coronary heart disease (CHD) in young people.

The method evaluates CHD risk based on inflammatory, oxidative, and lipid biomarkers in 200 patients.

As part of the project, researchers proposed a convenient system for visualizing results, allowing different markers and their deviations from the "normal-pathological" threshold to be displayed. The visual representation makes it possible to determine which subsystems of the body contribute to the CHD risk.

According to the Press Service of Novosibirsk State Technical University

Scientists created the AIRE platform, based on artificial intelligence (AI), which integrates eight risk models to predict the likelihood of cardiovascular death.

Using a single electrocardiogram analysis, AIRE generates patient-specific survival curves and predicts the time to death. The platform predicts all-cause mortality with a concordance index (C-index) of 0.775, outperforming assessments based on demographic data and traditional risk factors.

In addition to mortality, the platform can predict the risk of developing atherosclerotic cardiovascular disease, ventricular arrhythmia, and heart failure in patients without such conditions in their medical history.

According to the Lance journal

Researchers reported the ability of protein "signatures" to predict the onset of 67 diseases, including multiple myeloma, non-Hodgkin lymphoma, motor neuron diseases, pulmonary fibrosis, and dilated cardiomyopathy. They evaluated the concentrations of approximately 3,000 plasma proteins to create models predicting the ten-year incidence of 218 common and rare diseases.

The analysis demonstrated that measuring the concentration of five proteins alone, without additional information, was equivalent to clinical models for predicting 163 diseases and significantly outperformed them for 30 conditions

According to the Nature journal

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A systematic approach to the diagnosis of hereditary arrhythmias: current trends and practical recommendations

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This review article discusses the current aspects of diagnosis of hereditary cardiac arrhythmias, current clinical practice, potential difficulties and medical errors in the detection and management of patients with presumed primary electrical heart disease (channelopathies). It should be noted that in the available literature there are single reports devoted to a detailed analysis of the possible causes of delayed or erroneous diagnosis of channelopathies in real clinical practice. Given the high risk of sudden arrhythmic death, which is often the early and first manifestation of hereditary arrhythmia syndromes, their timely diagnosis, implementation of therapeutic and preventive measures in the proband and family members of the first degree of kinship are the most important tasks of the preventive strategy of high cardiovascular risk. These circumstances emphasize the clinical significance of a systematic diagnostic approach in the diagnosis/suspicion of hereditary arrhythmias and compliance with clinical guidelines for the diagnosis and prevention of sudden cardiac death in clinical practice.

Keywords: sudden cardiac death, channelopathies, hereditary arrhythmias, genetic testing, long QT syndrome, Brugada syndrome

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Introduction

Hereditary arrhythmias account for more than half of all initially unexplained cases of sudden cardiac death (SCD) in young adults [1, 2]. Hereditary arrhythmias are primary in 70% of cases (channelopathy) and caused by structural heart disease in 30% of cases [3, 4]. Early diagnosis of hereditary arrhythmias can significantly reduce the risk of SCD because in about 30% of cases, SCD is the first and early symptom of these diseases [1, 5]. The detectability of hereditary arrhythmias, and consequently, the effectiveness of control of sudden arrhythmic death (SAD) is also determined by the complex theoretical knowledge and practical skills of general practitioners [6]. Perhaps this explains the dissonance between the declared frequency of hereditary cardiac arrhythmias and the current real practice, which is usually reduced to the description of notable and isolated clinical episodes.

It should be noted that the wide variability of information on the prevalence of hereditary arrhythmias relies on data obtained in individual epidemiologic studies or extrapolation of their results to the general population [5, 7]. In clinical practice, as a rule, syndromal hereditary arrhythmias (Brugada, Jervell and Lange-Nielsen, Timothy, Andersen-Tawil syndromes) characterized by both cardiac and extracardiac phenotype are identified [8, 9]. However, in most cases, hereditary arrhythmias manifest non-specific signs (syncope, palpitations, seizures), and thus remain without proper attention of specialists [10]. The reason for this may be the functional risk alleles common in the population and conditionally pathogenic or weakly penetrant genetic variants, the phenotypic expression of which requires the presence of additional risk factors (RF) (medications, electrolyte disorders, fever, etc.) [11].

Hereditary arrhythmias can be caused either solely by abnormalities of cardiomyocyte ion channels (channelopathies) or they are an early manifestation of primary (idiopathic) structural heart disease [12, 13]. In addition to life-threatening ventricular tachyarrhythmias, hereditary rhythm and conduction disorders include atrial fibrillation, Wolff-Parkinson-White syndrome, sinoatrial or atrioventricular block, etc.

It should be noted that over the last 20 years, the availability of high-tech medical care for patients with cardiovascular diseases in the Russian Federation has significantly improved. As a result, the frequency of implantation of cardioverter-defibrillators and pacemakers, as well as ablation therapy has increased significantly [13]. This dictates the importance of organizing a coordinated structure of specialized medical and genetic care for the population, including patients with potential hereditary arrhythmias.

In view of the above, it is of particular interest to highlight the following topical aspects of hereditary arrhythmias:

- recognizing the signs and RF that should raise suspicion of hereditary arrhythmia syndrome;
- outlining the reasons for erroneous or delayed diagnosis of hereditary arrhythmias;
- listing the difficulties and limitations of interpreting genetic studies.

It should be noted that a detailed analysis of the difficulties in the diagnosis of hereditary arrhythmias associated with known limitations or erroneous interpretation of the results of studies will improve the efficiency of medical and genetic care for patients with suspected channelopathies. Information was searched in international databases such as PubMed, Scopus, Web of Science and Cochrane Library, as well as in Russian databases, including eLibrary.

Prevalence of hereditary arrhythmias in the population

It should be noted that the data on the prevalence of individual cardiac channelopathies in the general population are the results of international multicenter registry studies, based on which electronic information databases are created that take into account ethnic, racial, and geographical specifics of the distribution of individual variants of hereditary arrhythmias [1, 5, 11]. For example, in European and

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North American populations, Brugada syndrome (BrS,) occurs from 0.012 % to 0.26 %, whereas in endemic areas of southeast Asia (Japan, Thailand, Laos, Philippines) it is much higher and ranges from 0.7 % to 1.0 % [14, 15]. The prevalence of Jervell and Lange-Nielsen syndrome worldwide ranges from 1 to 6 per 1 million population, and in Scandinavian countries it is 1 per 200,000 population [16, 17].

The dispersion in the detection of cardiac channelopathies can also be explained by the wide genetic heterogeneity of individual populations and the influence of external factors [11]. Thus, it was shown that the prevalence of short QT syndrome (SQTS) with a QTc interval ⩽300 ms had the highest frequency per 100,000 people in African Americans (5.8), followed by Caucasians (3.2), Hispanics (1.8), and Asian and Pacific Islanders (1.6) [5].

The heterogeneity of access to genetic testing in different countries also affects the diagnosis of cardiac channelopathies [10, 18]. Careful collection of family history (preferably three generations) is essential to identify patients and affected family members. The absence of clinical manifestation of an underlying hereditary disease (asymptomatic course) tends to reduce the real population frequency of hereditary arrhythmias. The prevalence of cardiac channelopathies is also affected by incomplete penetrance of mutations of the gene responsible for the development of the disease [11]. For example, in 40% of genotyped cases of long QT syndrome (LQTS), QT intervals are within normal limits [19, 20]. Therefore, most experts believe that the estimated prevalence of hereditary arrhythmias in the population may be higher than the existing statistics [5, 11]. According to epidemiologic studies, the prevalence of LQTS, BrS, and catecholaminergic polymorphic VT (CPVT, catecholaminergic polymorphic ventricular tachycardia) individually is about 1:2000. The rarest inherited arrhythmia is SQTS, with an incidence ranging from 1:1000 to 1:10,000 in the population [21].

The prevalence of LQTS and SQTS in the population, along with other factors, is influenced by methodologic errors associated with QT interval measurement on standard ECG [20, 22]. For this purpose, manual QT interval measurement is considered the optimal method. Determination of diagnostic thresholds for shortening or lengthening of the QT interval is an important ECG pattern of LQTS and SQTS, as in BrS the presence of ECG pattern type 1 [9, 20, 23]. On the other hand, the widespread use of pharmacologic provocation with sodium channel blockers in suspected BrS (BrS ECG patterns type 2 or 3) caused drug-induced electrocardiographic "brugadophobia". In this regard, it was reported that in Europe, 70% of asymptomatic patients with BrS were "diagnosed" after a positive ajmalin test [15].

Clinical approach to the diagnosis of cardiac channelopathies

The key components in establishing the diagnosis of channelopathies are a careful evaluation of presenting symptoms, a systematic search for relevant anamnestic data, and an informed approach to diagnostic procedures [2, 12]. Because affected patients may first consult their family physicians, pediatricians, or neurologists, it is critical that all physicians, not just cardiologists, are aware of and able to identify the signs of hereditary arrhythmias [6, 10]. A detailed pedigree of at least three generations should be compiled. History of syncope, arrhythmias, pacemaker implantation, indication of seizures, presence of repeated abortions and early unexplained sudden death or any other cardiac disease should be identified in all family members of the first degree of consanguinity [4, 24].

Systematic collection of medical history, along with other factors, is an important condition for timely diagnosis of hereditary arrhythmias. Manifestation of the disease, manifested by clinical symptoms and the presence of complaints, contributes to the detection of symptomatic patients more often and earlier than asymptomatic patients [2, 13]. The most frequent and formidable manifestations of hereditary arrhythmias are syncope, seizures and sudden death due to certain triggers. Syncope is considered one of the most difficult dilemmas for the clinician because, on the one hand, it can be as innocent as vasovagal syncope and, on the other hand, as fatal as syncope associated with polymorphic VT or VF [25]. Syncope is such an integral part of neurological and cardiological practice that specialized clinics often establish syncope units to comprehensively examine patients and identify possible causes of syncope.

In some channelopathies, arrhythmogenesis can be manifested by different types of ventricular arrhythmias, which have differential diagnostic value. For example, LQTS is most characterized by polymorphic VT of the torsades de pointes (pirouette) type; in

BrS it is polymorphic VT [26, 27]. In CPVT, bidirectional VT characterized by alternating polarity of leading QRS [28] is observed, and in arrhythmogenic cardiomyopathy (CMP) of the right ventricle, monomorphic VT of the left bundle branch block type is observed. These arrhythmias often resolve spontaneously, but can transform into VF. During an arrhythmia attack, patients often experience generalized symptoms such as palpitations, dizziness, paroxysmal dyspnea, chest pain and abrupt weakness, as well as fear or panic.

Importantly, syndromal variants of hereditary arrhythmias reveal extracardiac, multisystem lesions in addition to the cardiac phenotype, which can both aid in the correct diagnosis of the genetic disease and lead to inappropriate patient management. For example, a prolonged QT interval and congenital bilateral sensorineural deafness are characteristic of Jervell and Lange-Nielsen syndrome [9, 17], and facial dysmorphism and syndactyly are characteristic of Andersen-Tawil syndrome [29].

Analysis of possible triggers for arrhythmias often provides a basis for suspicion of underlying pathology in many channelopathies. Triggers often differ depending on the variant of inherited arrhythmia and can aid diagnosis [2, 12]. For example, an arrhythmic event occurring during physical exertion, especially swimming, suggests LQT1 type, while arrhythmic syncope associated with sudden loud auditory stimuli is more characteristic of LQT2 type. Since physical and emotional stimuli are physiologically associated with increased release of catecholamines into the blood, the occurrence of syncope in such situations is characteristic of CPVT [13, 28]. Arrhythmic events occurring during sleep or rest, as well as against the background of fever, indicate LQT3 or BrS type [14, 16].

It should also be noted that almost all hereditary arrhythmias have incomplete penetrance (less than 100% of cases), and therefore, even if the genotype is identical, the phenotype of the disease may differ within a family [11]. Penetrance for individual channelopathies depends on biological sex. For example, the diagnosis of SQTS or BrS based on clinical symptoms is established predominantly in male patients [22, 23]. In addition, carriers of SQTS mutations showed shorter QTc intervals compared to non-carriers. This allows differentiating between shortened QT interval (so-called "benign" variant) and SQTS [14, 21]. Gene penetrance, both gene expression and genotype-phenotype correlation differ between proband and relatives carrying a mutation of the same gene [11]. Thus, the probability of diagnosis of cardiac channelopathies also depends on the variability of expression and penetrance of the disease.

Alternative diagnoses requiring differential diagnosis in hereditary arrhythmias

Difficulties in clinical diagnosis of hereditary arrhythmias are due to non-specific symptomatology, in some cases the absence of ECG pattern and the prevalence of latent (asymptomatic) forms [17, 30]. Given that symptomatic patients with hereditary arrhythmias often have recurrent syncope due to VT or VF, they can be observed for a long time with the diagnosis of "epilepsy" and receive anticonvulsant therapy without effect, remaining in the high-risk group of SCD [2, 25]. At the same time, diagnosis is possible only by genetic test [18].

The most common alternative diagnoses for hereditary arrhythmias are seizure disorder, atypical febrile seizures, and sudden infant death syndrome in children with undiagnosed channelopathy [3, 7, 25]. Therefore, a detailed family history and ECG analysis are mandatory in all patients with an electroencephalographically negative seizure disorder, in young children with atypical seizures during fever, and in family members of first-degree relatives of cases of sudden infant death.

It should be noted that arrhythmogenic syncope often has to be distinguished from an epileptic seizure. An epileptic seizure is usually prodromal, with precursors (auras) of syncope, whereas arrhythmogenic syncope is non-prodromal [13]. In addition, in cases of interrupted cardiac arrest, syncope does not last long, seizures rarely occur, and the person usually feels relatively satisfactory after syncope. However, in most cases of epilepsy, prolonged and generalized tonic-clonic seizures are observed, and after the seizure, patients report abrupt weakness, collapse, and possible tongue biting [25].

It has been retrospectively shown that epilepsy-like seizures triggered by cardiac arrhythmias are the most common cause of late diagnosis of channelopathies and may be misinterpreted as epilepsy [1, 9]. For example, in a cohort of patients with LQTS, abnormal electroencephalograms were detected in 71%

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of cases compared to 13% of controls (p<0.01) [16]. Careful examination of these patients did not reveal any other possible cause other than mutation of the KCNQ1 gene responsible for LQT1. The KCNQ1 gene encoding the potassium channel is known to be expressed not only in the heart but also in the forebrain and brainstem [11, 20].

Life-threatening cardiac arrhythmias are known to occur in a significant proportion of generalized seizure attacks and represent a possible pathophysiological mechanism for the association of unexplained sudden death and epilepsy [25]. Consequently, individual patients diagnosed with epilepsy may have concomitant hereditary arrhythmias and be at particularly high risk of fatal arrhythmias associated with an epileptic seizure [25]. Therefore, information about sudden death in the family of a patient with an unusual convulsive seizure should prompt a thorough cardiologic evaluation.

In pediatric practice, observed primary periodic paralysis or neuromuscular channelopathies also merit attention with respect to cardiac channelopathies [7]. For example, in patients with Andersen-Tawil syndrome (classic type LQT7), hypokalemic periodic paralysis is almost always seen, and often occurs against a background of prolonged generalized weakness and proceeds without myotonic manifestations [29]. Episodes of muscle weakness manifest usually before the age of 10 years or during adolescence. During the time between attacks, such children do not present any complaints.

ECG patterns of hereditary arrhythmias

It should be noted that frequent manifestations of the cardiac phenotype of channelopathies are ECG changes, including various rhythm and conduction disorders. ECG patterns specific for certain types of hereditary arrhythmias play an important role in the diagnosis of these conditions [2, 7]. Therefore, resting 12-lead ECG recording is an integral part of the evaluation of a suspected case of channelopathy. A systematic analysis of all aspects of the ECG should be performed, as atrial and/or ventricular depolarization and repolarization abnormalities may coexist [26].

The basis for the diagnosis of LQTS with a high probability, according to the LQTS diagnostic scoring scale, is a QTc interval ≥500 ms on repeated standard ECGs and in the absence of secondary causes of QT interval prolongation [17, 20]. A similar requirement for the diagnosis of SQTS is a QTc interval ≤330 ms [21], and for the diagnosis of BrS is the registration of a spontaneous ECG pattern type 1 in leads V1-V3 [23]. However, they represent extreme deviations of QTc intervals, which may lead to hypodiagnosis of LQTS and SQTS in more moderate cases.

Abnormal changes in the standard resting ECG with no other explanation may be suspicious for cardiac channelopathies:

- prolonged/shortened QT/QTc interval;
- ventricular extrasystoles occurring during an exercise stress test;
- oblique descending or saddle-shaped ST-segment elevation in leads V1-V3;
- alternation of the T-wave (negative or abnormal T-wave);
- slowing of cardiac conduction (sinoatrial, atrioventricular, and intraventricular block);
- registration of epsilon wave on ECG in leads V1–V3;
- pronounced U-wave, prolonging the QT-U interval, in the precardiac leads;
- pronounced J-wave manifested with or without ST segment elevation, especially in posterior or posterolateral leads of the ECG;
- isolated prolongation of PR interval;
- depression of the PQ (PR) segment in the lower leads of the ECG.

It should be noted that certain types of LQTS have characteristic ECG patterns of the T-wave. For example, LQT1 is characterized by a broadened T, while in LQT2 the T is usually bifurcated and low-amplitude. In LQT3, QT interval prolongation is explained by ST segment prolongation, and the T-wave has a normal configuration [31]. Taking into account personal and family history, this may help in determining the indications for genetic testing [27].

Limitations of interpreting a standard resting ECG

Despite the availability and sufficient informativity of standard resting ECG, this method has limitations in almost all types of channelopathies. For example, there are difficulties with accurate measurement of the QT interval, which negatively affects the frequency of detection and timeliness of diagnosis of LQTS and SQTS [20]. The reasons for this are abnormalities of

ST-T morphology (biphasic, low-amplitude or inverted T-wave) caused by bundle branch block, electrolyte imbalance (hyper- and hypokalemia), ventricular hypertrophy, digitalis effect, etc. [8].

The optimal way to determine the QT interval is its manual measurement in the II lead of a standard ECG at rest and at a heart rate (HR) of 60 to 100 beats per minute [17, 20]. In this case, the tangential method is the most accurate, when the end of the T-wave is determined by the intersection of a tangent line drawn from the steepest point of the T-wave slope with the isoelectric line. To level the influence of HR on the QT interval, it is corrected for HR (QTc) using mathematical formulas, of which the most commonly used is the Bazett formula. It has been shown that even experts measure the QT interval during LQTS with an error of 10 to 70 ms [20]. A study of the prevalence of SQTS based on the analysis of more than 6.3 million ECG recordings in 1.7 million people [22], automatic ECG analysis revealed 1086 cases with a QTc interval ⩽300 ms, while manual QT interval measurement confirmed QTc ⩽300 ms in only 45 episodes.

It has been shown that registration of pronounced U-wave in precordial leads of ECG in Andersen-Tawil and ankyrin-B syndromes mimics QT-U interval prolongation, and exclusion of U-wave from QT interval calculation almost always shows normal or borderline QT intervals [9, 29]. Therefore, there is still debate as to whether ankyrin-B and Andersen-Tawil syndromes are "typical" forms of LQTS [17].

Grounds for suspicion of channelopathies

Based on the results of the initial patient examinations, it is determined whether there are grounds for suspicion of various hereditary arrhythmias if structural causes have been ruled out.

Grounds for suspicion of LQTS:

- prolonged QT interval - in men QT ⩾440 ms and in women QT ⩾460 ms;
- standardized extensive family history positive for syncope, seizures, SCD;
- abnormalities of the T-wave (jagged, dilated, biphasic, negative);
- ECG-documented episode of pirouette-type VT;
- history of an index patient, i.e., a proband whose illness was the basis for collecting a family history for syncope, seizures, and palpitations;
- a pathologically prolonged QTc interval during stress or exercise;
- presence of arrhythmias in the context of specific triggers (e.g., swimming, loud noises, medication, hyperthermia).

Basis for suspicion of CPVT:

- index patient history (occurrence of syncope, seizures, and palpitations in response to adrenergic stimulation);
- normal resting ECG or may have marked bradycardia, atrial arrhythmias including multifocal atrial tachycardia;
- the presence of a family history of syncope, seizures, and SCD;
- the occurrence of frequent polymorphic ventricular extrasystoles during a stress test.

Grounds for suspicion of BrS:

- ECG patterns of BrS type 1, 2, or 3;
- family history positive for syncope, seizures, and SCD;
- index patient history: presence of syncope, seizures and palpitations;
- arrhythmias due to specific triggers (hyperthermia, heavy meals, alcohol consumption).

Additional methods of investigation

If clinical evaluation results suggest that a specific channelopathy is suspected, further investigations, including genetic testing for confirmation, should be performed (Figure 1). Thus, cases of sudden death at a young age in relatives, syncope, documented arrhythmias, or atypical epilepsy in the context of specific triggers should prompt further investigation.

Exercise stress test

In patients with symptoms suggestive of channelopathies and an apparently normal resting ECG, an exercise stress ECG may be performed. Given that about 40% of LQTS cases have a normal QT interval on resting ECG, it is suggested that the QT/QTc interval response to exercise should be evaluated [8, 16]. Whereas, in LQT2 and LQT3 types, the QTc interval is physiologically shortened, patients with LQT1 type have a paradoxical prolongation of the QTc interval [32]. In patients with LQTS, the lie-to-stand test or low-dose adrenaline infusion test is also recommended, although they are inferior to the stress stress test [9]. The appearance of mono- or polymorphic VT during the stress test, which disappears during the recovery phase, is a classic sign of CPVT [28]. It is important to achieve the necessary level of stress, i.e., a rapid

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increase in HR during exercise is more likely to cause VT [13]. It is not uncommon to observe ventricular allorrhythmia during exercise against the background of relatively low HR (100-110 per min), which can turn into VT [28].

hereditary arrhythmias [2, 13]. It is also necessary to identify various triggers of arrhythmic events. It should be noted that the spontaneous BrS ECG pattern can be intermittent or non-permanent. Thus, it has been shown that the reproducibility of BrS type 1

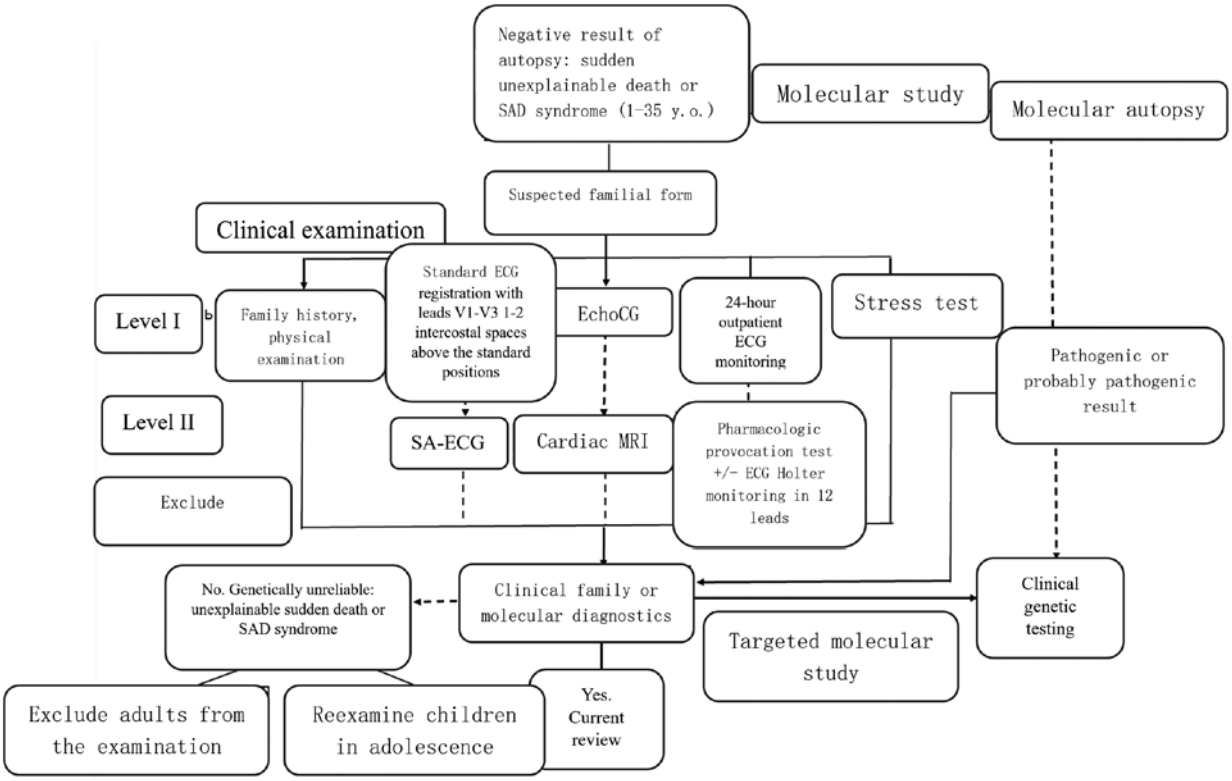

Fig. 1. The scheme of two-stage examination of probands and their family members with suspected hereditary arrhythmias

Registration of high right precordial ECG leads.

It has been shown that registration of leads V1–V3 1–2 intercostal spaces above the standard positions in case of saddle-shaped ST-segment elevation can reveal the hidden BrS ECG pattern type 1 [23]. Echocardiographic determination of registration levels of leads V1-V3, corresponding to the anatomical localization of the right ventricular outflow tract, increases the frequency of registration of diagnostic ECG pattern BrS type 1 in comparison with the standard technique: 100% vs. 43% ($p<0.001$) [15]. Additional criteria for ECG pattern BrS, such as Corrado index for ECG pattern type 1 and ß angle measurement for type 2, are also recommended [26].

Holter ECG monitoring

Is important to detect underlying cardiac rhythm and conduction abnormalities in patients with suspected ECG pattern in repeated ECG recordings is only 25% [15]. Therefore, ECG Holter monitoring can help to detect the dynamic ECG pattern of BrS type I, and thus eliminate the need for pharmacologic provocation. In cases of suspected arrhythmic syncope, implantation of a cardiac monitor is sometimes used, allowing ECG monitoring for 6 months to two years to detect heart rhythm disturbances or potential causes of syncope [13].

Electrophysiologic study (EPS)

In most cases of channelopathies, the use of cardiac EPS to induce VT has no proven benefit and, therefore, is currently not a standard diagnostic method [2]. It has been shown that the prognostic value of a positive result of EPS is 37-50%, and that of a negative result - 46-97% [13]. The possibility of VT induction during EPS using a less aggressive mode of electrical stimulation (one or two extrastimuli) in-

creases the prognostic value of the method. Cardiac EPS is mainly recommended to stratify the risk of arrhythmic events, to determine the indications for implantation of a cardioverter-defibrillator in asymptomatic patients, and to assess the efficacy of drug or ablation therapy [32]. It should be noted that failure to induce VT does not necessarily indicate a low risk of arrhythmia, especially in patients with clinical signs of high risk.

Pharmacologic provocation test

If no other diagnosis is established and the characteristics of SCD can match BrS, provocation tests with class I antiarrhythmic drugs (ajmaline, flecainide, procainamide) in first-degree relatives with structurally normal hearts are recommended [26]. Different prescribing protocols are used for each drug. After intravenous administration of the drug, a standard ECG recording or 12-lead ECG Holter monitoring with high precordial leads V1-V3 is performed to evaluate the BrS type 1 ECG pattern. Ajmaline has been shown to produce significantly more positive results than procainamide or flecainide [23]. Despite its high sensitivity, the ajmaline assay is less specific. For example, in patients with LQT3 type, arrhythmogenic right ventricular cardiomyopathy and r'-ST complexes in leads V1–V3, BrS type 1 ECG pattern may be induced, which has no prognostic value [17, 30]. Therefore, a positive ajmaline test does not provide any useful information about the risk of arrhythmic events in asymptomatic individuals with a non-diagnostic BrS type 2 or 3 ECG pattern [26].

Cardiac imaging

If structural heart disease is suspected, echocardiography or MRI may provide additional information. In these cases, cardiac disease with arrhythmias may be involved, particularly hypertrophic or dilated CMP or arrhythmogenic right ventricular CMP [2]. In this case, cardiac MRI with gadolinium contrast and follow-up of any evolution of the phenotype is recommended.

Diagnostic scoring scales for hereditary arrhythmias

In clinical practice, diagnostic scoring scales are used to verify the diagnosis of some types of hereditary arrhythmias, which take into account the combined value of clinical criteria: ECG characteristics, the nature of symptoms, family history and genetic test results. The validity of the scoring scale depends on the reliability of the criteria themselves. The interpretation of standard resting ECG is of great importance, in particular, the determination of QT interval duration in suspected LQTS and SQTS, differentiation of ECG pattern characteristic of BrS, as well as the analysis of QRS-T complex configuration in J-wave syndromes [17, 30].

It should be noted that the probability of diagnosis and the prevalence of LQTS and SQTS in the population depend not only on the correctness of QT interval measurement, but also on the accepted diagnostic criteria for the duration of QT intervals. For example, the threshold QT intervals for suspicion/diagnosis of SQTS vary widely from 220 to 360 ms: there is a "gray zone" for QTc between 370 and 330 ms [21, 22]. These difficulties are addressed by the LQTS and SQTS diagnostic scales, in which different QT interval values are assigned different scores depending on the suspision/probability of the diagnosis. For example, the modified SQTS diagnostic scoring scale assigns 1 point for a QT interval <370 ms, 2 points for a QT interval <350 ms, and 3 points for a QT interval <330 ms [21]. Evaluation of the proposed diagnostic criteria for SQTS showed that 95% of cases would receive a diagnostic score indicating a high probability of SQTS [22].

It should be noted that diagnostic scales are used to determine the gradations of probability of a particular hereditary arrhythmia syndrome and, if necessary, genetic testing is used. For example, the Schwartz P.J. et al. scale is used in the initial evaluation of patients with LQTS, according to which if the sum of scores is ⩽1, it indicates a low probability of LQTS, at 1.5-3 points the intermediate probability of LQTS is determined, and at ⩾3.5 points — a high probability of LQTS [17].

The HRS/EHRA/APHRS expert consensus document is used to diagnose BrS, and the Shanghai point scale is used only in cases of drug-induced ECG pattern of BrS. In addition to the ECG pattern, one of the following criteria is required to confirm the diagnosis: documented PV/polymorphic VT, syncope, SCD in a family of individuals younger than 45 years of age with a negative autopsy report, BrS type 1 ECG pattern in family members, or nocturnal agonal breathing [23]. Although the diagnostic scale criteria provide a systematic approach to the verification of hereditary arrhythmias, in cases of suspected channelopathies

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in proband family members, the value of the assessment scale will not be highly sensitive due to incomplete penetrance.

Diagnostic genetic testing

General principles of genetic testing

Modern next generation sequencing technologies allow us to study a panel of cardiac rhythm disorders including 40 genes and their mutations associated with the development of channelopathies [2, 11]. For genetic testing, it is crucial to confirm the association of the identified genetic alterations with the clinical phenotype. Therefore, the probability of a positive genetic test is highest in individuals with the highest phenotypic penetrance.

In the HRS/EHRA/APHRS (2022) expert consensus on the diagnosis and management of hereditary arrhythmia syndromes, genetic testing was recommended for probands with a clinical diagnosis and for all family members of a successfully genotyped proband (class I recommendation) (Table) [11]. Genetic tests play an important role in identifying "pre-symptomatic" or "low-symptomatic" young individuals with a genetic phenotype associated with the risk of developing SCD, allowing timely preventive interventions [19]. The strongest evidence in support of variant pathogenicity is segregation by phenotype in several family members [2].

Table. **The value of genetic testing for proband in cardiac channelopathies**

Disease	Diagnostic	Prognostic	Therapeutic
LQTS	+++	+++	+++
CPVT	+++	+	+
BrS	+	+	+
Progressive cardiac conduction defect	+	+	+
SQTS	+	+	+
Familial SSS	–	+	–
Familial AF	–	+	–
Early repolarization syndrome	–	–	–

Note. +++ recommended/indicated or useful; ++ may be recommended/may be useful; + may be considered/may be useful; – not recommended/not indicated or useful.

For all suspected diagnoses associated with cardiac channelopathies, the indications for genetic testing need to be justified. Depending on the level of evidence available, a genetic variant can be characterized as: benign; probably benign; variant of uncertain significance; probably pathogenic; pathogenic [11]. A pathogenic result confirms the clinical diagnosis and may serve as a prognostic or therapeutic landmark, as well as being important for subsequent screening of family members. With few exceptions, the variant of uncertain significance cannot be used for proband management or prognostic evaluation of asymptomatic family members [11].

The EHRA/HRS/APHRS/LAHRS expert consensus document outlines the important concept of "key genes" according to ClinGen (Clinical Genome Resource), i.e. genes that for each variant should be included in the "ideal" screening to enhance the achievement of clinically useful results [11]. The sensitivity of tests proposed for routine genetic testing for all types of LQTS and CPVT averages 65% and 60%, respectively, with SQTS averaging 40% and BrS averaging 25-30% [11, 18].

Family predicting (prognostic) genetic testing

Medical genetics continues to utilize the clinical and genealogical method. A positive genetic test in a proband provides an opportunity for cascade testing of first-degree relatives for a variant associated with the "culprit gene" in the proband [11, 13]. In general, cascade screening is recommended when the results will affect clinical management. Family members in whom a pathogenic variant is found should be clinically screened at regular intervals. If the patient's family members have not undergone genetic testing or are negative, they should also undergo regular clinical screening because there is significant phenotypic heterogeneity in the age of disease manifestation in members of the same family.

Postmortem genetic testing (molecular autopsy)

It is known that the annual incidence of SCD in the age group from 1 to 35 years is estimated from 1.3 to 2.8 per 100,000 population [53], and in 30–40% of cases autopsy does not reveal the cause of sudden death despite toxicologic and histopathologic analyses [33]. It is assumed that some of them died from SAD caused by channelopathies (e.g., LQTS, BrS, and CPVT).

According to guidelines, genetic testing of autopsy material (blood, thymus, spleen, liver) is indicated in all cases of SCD when inherited diseases are

suspected [11], and cascade (mutation/pathogenic variant-specific) genetic testing in first-degree family members is recommended if a pathogenic or likely pathogenic variant is identified [34]. This is particularly relevant given that most inherited diseases are inherited in an autosomal dominant pattern, meaning a 50% chance of surviving family members inheriting the same disease substrate [12]. A standard molecular autopsy panel typically includes 4 major genes that account for the majority of previously unexplained SCD cases, including KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3 / BrS1), and RYR2 (CPVT1) [11].

Molecular autopsy results were reported in 113 cases of unexplained sudden death, and pathogenic variants were identified in 27% of cases [33]. Lahrouchi N. et al. [34] studied the diagnostic value of molecular autopsy and clinical genetic study in 302 members from 82 families. They showed that the combination of molecular autopsy and clinical evaluation of surviving relatives increased the probability of detecting a pathogenic variant from 28% to 49%, and the additional independent result of molecular autopsy was 13%.

Problems of interpreting genetic test results

Selection of a panel of genetic tests and interpretation of genotyping results require a high level of specialized knowledge and a multidisciplinary approach [11]. The identification of a pathogenic variant increases the risk of a phenotype but does not equate to a clinical diagnosis. Also, a negative genetic test result never excludes a valid clinical diagnosis. If the result is positive, its plausibility must be verified, as it may turn out that the identified mutation is not the cause or the sole cause of the disease.

Choosing the right test for genotyping can be difficult due to the repetition of phenotypes and genetic heterogeneity, whereby a similar phenotype may be caused by mutations in different genes (overlap syndrome) [11]. On the other hand, the same mutation can lead to different phenotypes even in the same family (variable expressivity): for example, family members with the same *SCN5A* gene mutation may have different phenotypes, such as BrS, LQTS, and cardiac conduction abnormalities [18].

Without a presumptive diagnosis, it does not make sense to perform a general genetic test to screen every known gene associated with SCD. Such screening often detects variants/mutations that were not the cause of the disease in a particular case and can easily lead to misdiagnosis. Even with a presumptive diagnosis, sometimes the results cannot be correctly interpreted without genetic and clinical investigation of relatives. The identification of a large number of minor genes responsible for multiple variants increases the uncertainty of interpretation.

Difficulties in interpreting the results are also associated with the identification of a frequent genetic variant (polymorphism) that mostly corresponds well to the phenotype but does not explain the severity of the disease [11]. Therefore, several years later it may turn out that the identified mutation was in fact an irrelevant polymorphism. It should be noted that genetic variants in sudden death in the young often remain as variants of uncertain significance for many years, making their management difficult. However, some of them may rapidly convert to likely pathogenic variants after careful screening. Because of the age-related penetrance of a number of hereditary arrhythmias, it is recommended that children be reexamined in adolescence or early adulthood.

Conclusion

Thus, these data indicate the absence of systematic diagnostic strategies in patients with hereditary arrhythmias in real clinical practice, as well as the low level of knowledge of general practitioners on the management of these patients. A comprehensive approach to solving these problems includes the implementation of educational programs on hereditary arrhythmias for physicians of different specialties, combining the efforts of various medical institutions to create an information database of patients, as well as the creation of additional specialized centers and/or cardiogenetics departments that coordinate the work to provide high-tech medical care to affected patients and their families. Strict adherence to current clinical recommendations by physicians of specialized specialties, ensuring an interdisciplinary approach to the management of patients with hereditary arrhythmias, and stimulating the promotion of medical and social knowledge on hereditary diseases and sudden death also play an important role.

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Uncontrolled arterial hypertension: role of suffered COVID-19 infection and polymorphisms of genes encoding the renin-agiotensin-aldosterone system

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The aim of the study was to determine the role of polymorphisms of genes encoding components of the renin-angiotensin-aldosterone system (RAAS) and suffered COVID-19 infection in patients with uncontrolled hypertension.

Methods. Clinical examination of 116 patients with stage 2 uncontrolled arterial hypertension was performed. 96 of them had mild to moderate form of coronavirus infection (COVID-19). Clinical examination, studies of polymorphism of genes encoding RAAS components were performed.

Results. Patients in the ongoing symptomatic COVID-19 phase were found to have higher systolic blood pressure (SBP) levels (p1-2=0.03659; p1-3=<0.00001) than in the postcovid syndrome group. We found that diastolic blood pressure (DBP) remained elevated in patients after COVID-19 (p1-3<0.00001; p2-3<0.00001). In the ongoing symptomatic COVID-19 phase, carriage of the homozygous TT genotype of the AGT 704 T>C gene, rs699, was less frequent (p=0.005) than in the control group. There was a weak negative association of TT genotype AGT704 with body mass index with (r=–0.30, p=0.001), SBP (r=-0.42, p=0.0001) and DBP (r=–0.36, p=0.0001).

Conclusion. Uncontrolled AH was a long-term effect of mild to moderate COVID-19. Analysis of time aspects revealed the greatest persistence of destabilization with regard to DBP. The association of BP elevation with the C allele of the AGT gene polymorphism (T704C) was found in patients who had suffered coronavirus infection in the period up to 12 weeks. Identification of the association

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of BP with the AGT gene polymorphism in postvoid syndrome will provide an opportunity to initiate personalized treatment and develop prevention strategies.

Keywords: postcovid syndrome, arterial hypertension, renin-angiotensin-aldosterone system, gene polymorphism, AGT 704 genotype.

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Introduction

A significant proportion of patients recovering from coronavirus infection (COVID-19) report various clinical symptoms of a physical, psychological and cognitive nature despite the ending of SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) replication four weeks after initial infection [1]. The term "postcovid syndrome" (PCS) is now internationally recognized and is widely used to describe these symptoms [2]. The prolonged course of COVID-19 implies many unfavorable outcomes, among which cardiovascular diseases are often noted [3, 4].

Further study of the impact of COVID-19 in patients with arterial hypertension (AH) is required in order to determine the optimal therapeutic and diagnostic measures for this category of individuals [3]. Currently, it is relevant to determine possible markers to identify patients with adverse effects of COVID-19 [3]. The involvement of the renin-angiotensin-aldosterone system (RAAS) in the pathogenesis of COVID-19 suggests the study of polymorphism of genes encoding RAAS components as a possible factor in the occurrence of uncontrolled AH [4].

The aim of the study was to determine the role of polymorphisms of genes encoding components of the renin-angiotensin-aldosterone system (RAAS) and suffered COVID-19 infection in patients with uncontrolled hypertension.

Methods. 116 patients hospitalized in cardiology department No.1 of the Saratov City Clinical Hospital No.8 for the destabilization of AH were examined. 96 patients had confirmed COVID-19 of mild and moderately severe form more than 4 weeks before admission. Inclusion criteria: patients aged 44–60 years with stage 2 AH and confirmed suffered COVID-19 of mild and moderate form at the outpatient stage more than 4 weeks before the examination. Exclusion criteria: symptomatic AH, other diseases of cardiovascular system, neoplasia, somatic diseases in decompensation stage. Control group: 20 patients with destabilized AH stage 2, who did not have COVID-19. Patients were divided into two groups: up to 12 weeks and more than 12 weeks after the COVID-19 (Table 1).

Clinical study. All patients were evaluated, including clinical examination, general blood count, blood chemistry, electrocardiography, echocardiography (EchoCG), and daily BP monitoring ("Valenta", St. Petersburg). EchoCG was performed on ultrasound scanner HITACHI ALOKA Alpha 7 (Japan). Genes encoding RAAS components (angiotensinogen (AGT: 704 T>C, AGT: 521 C>T), angiotensin II type 1 receptor (AGTR 1: 1166 A>C), angiotensin II type 2 receptor (AGTR 2: 1675 G>A), aldosteron synthase (CYP11B 2: –344 C>T)) were determined using RNS-2 amplifier ("Techne", UK). Patients received complex hypotensive therapy (angiotensin-converting enzyme inhibitors (perindopril 8 mg/day or enalapril 10–20 mg/day), calcium channels antagonist (amlodipine 5–10 mg/day), drugs with central mechanism of action (moxonidine 0.2–0.4 per day).

Table 1. **Characterization of examined patients by groups**

Group and number of patients, n	Mean age, years (M±m)	Amount of males/females, abs. (%)	Period after COVID-19, weeks	Mean number of weeks after COVID-19, weeks (M±m)
Control group (n=20)	54.2±3.6	9(45%)/11(55%)	-	-
Group 1 (n=51)	54.2±4.4	22(43%) /29(57%)	4-12	7.6±2.1
Group 2 (n=45)	52.3±5.3	21(47%) /(53%)	More than 12	19.4±4.5

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Statistical analysis

The data were processed using Microsoft Excel 2016, R-Studio Version 1.1.383. Identification of the nature of data distribution was performed using the Shapiro-Wilk test. The arithmetic mean (M) and standard deviation (m) were determined for descriptive statistics of data with normal distribution. Median, first and third quantiles (Me [1st Qu; 3st Qu]) were determined for non-normal distribution. The Kruskal-Wallis test was used to compare three groups of unrelated continuous variables followed by application of the two-sample Wilcoxon rank-sum test. Pearson's x-square test (χ^2), Fisher's exact test (F) were used to compare groups of independent nominal variables. The established level of statistical significance was $p<0.05$.

Ethical review. The study protocol was approved by the Ethical Committee of the Saratov State Medical University named after V. I. Razumovsky.

Results

A survey of patients who had suffered COVID-19 revealed complaints of increased fatigue, decreased tolerance to physical activity that persisted after the infection. Examination of patients revealed no differences in groups by sex and age (Table 2).

Physical examination (Table 3) revealed greater values of body mass index (BMI) and waist circum-

Table 2. **Age and sex characteristics of patients examined with AH**

Characteristics of the surveyed patients	Control group n = 20	Group 1 n = 51	Group 2 n = 45	P
Age, years	54.2±4.59	55[48.5; 63]	53[43;62]	p1-2=0.325 p1-3= 0.663 p2-3= 0.346
Gender, males/females	9 (45%) /11(55%)	22(43.1%)/ 29(56.9%)	21 (46.7%)/ 24(53.3%)	Comparison of 3 groups (Fisher's test). p = 0.9414 Pairwise comparison of groups p1-2 = 0.887 p1-3 =1 p2-3 = 1

Note. * — parameters have statistically significant differences with the control group; ** — there are statistically significant differences between the first and second groups.

Table 3. **Results of clinical examination of the groups with AH**

Parameters	Group 1 n = 51	Group 2 n = 45	Control group n = 20	p
BMI, kg/m^2	29.21±4.49	29.26±4.85	24.89±3.59*.**	p1-2= 0.959 p1-3= 0.0001 p2-3= 0.001
Waist circumference, cm	94.37±9.84	95.84±11.1	87.37±8.28*	p1-2= 0.496 p1-3= 0.004 p2-3= 0.366
HR, bpm	79.53±8.17	74.51±9.40*	72.7±6.31*.**	p1-2 = 0.022 p1-3<0.00001 p2-3=0.0004
SBP, mmHg	139.6±13.0	131[121;145]*	119.3±15.47*	p1-2=0.036 p1-3= <0.00001 p2-3=0.433
DBP, mmHg	84.45±10.13	81.29±11.24	71.1±5.53*.**	p1-2= 0.153 p1-3<0.00001 p2-3<0.00001
Creatinine, μmol/L	84.82±6.22	80.98±8.47*	79±8.82	p1-2= 0.014 p1-3= 0.076 p2-3= 0.404
Low-density lipoproteins, mmol/l	2.3[1.8; 3.0]	2.1[1.7; 2.6]	2.02±0.28	p1-2= 0.466 p1-3= 0.132 p2-3= 0.336
Uric acid, μmol/l	360.9±86.97	334[313;390]	314.6±48.71	p1-2= 0.223 p1-3= 0.062 p2-3= 0.116
Glucose, mmol/l	5.4[4.95; 5.9]	5.2[4.9; 5.3]	5.12±0.54	p1-2= 0.129 p1-3= 0.054 p2-3= 0.988

Table 3 continuation

Parameters	Group 1 n = 51	Group 2 n = 45	Control group n = 20	p
Left ventricle (LV) myocardial mass index, g/m^2	99.81±11.90	97.07±15.43	98.27±12.56	p1-2= 0.338 p1-3= 0.163 p2-3= 0.320
LV end-diastolic dimension, mm	4.93±0.33	4.85±0.31	4.83±0.29	p1-2= 0.218 p1-3= 0.173 p2-3= 0.129
Left atrium size, mm	4[3.71; 4.14]	3.97±0.26	3.89±0.32	p1-2= 0.874 p1-3= 0.743 p2-3= 0.692

Note. *— parameters have statistically significant differences with group 1; ** — parameters have statistically significant differences with group 2.

ference in patients with COVID-19 than in the control group. Obesity was also more frequent in these groups (p = 0.032; χ^2= 6.857; p1-2 = 0.719; p1-3 = 0.029; p2-3 = 0.013).

Heart rate (HR) in the COVID-19 survivor groups was higher than in the control group. HR was highest in patients during the period of ongoing symptomatic COVID-19 (p1-3 <0.00001). Systolic blood pressure (SBP) in this group also exceeded values in control and second groups (p1-2=0.036; p1-3= <0.00001). Diastolic blood pressure (DBP) in the COVID-19 groups exceeded the control values (p1-3<0.00001; p2-3<0.00001).

Laboratory examination revealed a slightly elevated creatinine level in group 1. EchoCG parameters in the compared groups did not differ significantly.

Table 4. **Results of the study of polymorphism of genes encoding RAAS components**

Gene name	Genotypes	Group 1 n = 51	Group 2 n = 45	Control group n = 20	P		
		Abs. number/%	Abs. number /%	Abs. number /%	Pairwise comparison by genotype	Pairwise comparison of groups	A 3-group analysis
AGT704	TT	23*/45.1	25/55.6	15*/75	p1-2 = 0.413 p1-3 = 0.033 p2-3 = 0.173	P1-2 = 0.434 p1-3 = 0.064 p2-3 = 0.401	0,194
	TC	16/31.4	14/31.1	4/20	p1-2 = 1 p1-3 = 0.394 p2-3 = 0.549		
	CC	12/23.5	6/13.3	1/5	p1-2 = 0.295 p1-3 = 0.092 p2-3 = 0.422		
AGT521	CC	38/74.5	26/57.8	10/50	p1-2 = 0.189 p1-3 = 0.055 p2-3 = 0.588	p1-2 = 0.471 p1-3 = 0.020 p2-3 = 0.102	0,059
	CT	13/25.5	18/40.0	9/45	p1-2 = 0.192 p1-3 = 0.065 p2-3 = 0.788		
	TT	0/0	1/2.2	1/5	p1-2 = 0.468 p1-3= 0.5621 p2-3 = 0.436		
AGTR1	AA	37/72.5	35/77.8	17/85	p1-2 = 0.639 p1-3 = 0.361 p2-3 = 0.738	p1-2 = 0.737 p1-3 = 0.185 p2-3 = 0.121	0,3253
	AC	11/21.6	9/20	1/5	p1-2 = 1 p1-3 = 0.158 p2-3 = 0.156		
	CC	3/5.9	1/2.2	2/10	p1-2 = 0.620 p1-3 =1 p2-3 = 0.524		
AGTR2	AA	20/39.2	20/44.4	9/45	p1-2 = 0.680 p1-3 = 0.789 p2-3 =1	p1-2 = 0.114 p1-3 = 0.858 p2-3 = 0.428	0,29
	GA	26/51.0	25/55.6	10/50	p1-2 = 0.686 p1-3 =1 p2-3 = 0.789		

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Table 4 continuation

Gene name	Genotypes	Group 1 n = 51	Group 2 n = 45	Control group n = 20	P		
		Abs. number/%	Abs. number /%	Abs. number /%	Pairwise comparison by genotype	Pairwise comparison of groups	A 3-group analysis
	GG	5/9.8	0/0	1/5	p1-2 = 0.058 p1-3 = 0.668 p2-3 = 0.077		
CYP11B2	CC	23/46.1	27/60	10/50	p1-2= 0.681 p1-3= 0.794 p2-3 = 0.588	p1-2= 0.307 p1-3 = 0.741 p2-3 = 0.601	0,549
	CT	25/49.0	17/37.8	10/50	p1-2 = 0.306 p1-3 =1 p2-3 = 0.419		
	TT	3/5.9	1/2.2	0/0	p1-2 = 0.620 p1-3 = 0.553 p2-3 = 1		

Note. *— parameters have statistically significant differences with group 1; ** — parameters have statistically significant differences with group 2.

The results of the study of genes polymorphism encoding RAAS components are presented in Table 4.

Significant differences were obtained when comparing AGT 704 gene genotypes in COVID-19 and non-COVID-19 subjects (p1-3 = 0.033). Carriage of the homozygous TT genotype was less frequent in COVID-19 survivors (p=0.005). There was a weak negative association of BMI with TT genotype AGT704 (r=–0.30; p=0.001), SBP (r=–0.42; p=0.0001) and DBP (r=–0.36; p=0.0001). There was a weak correlation of glomerular filtration rate (r=0.42; p=0.0001) with this genotype.

Discussion

Lack of BP control is associated with adverse cardiovascular events in the short term [1]. To date, the specific impact of severe COVID-19 on BP during and after the acute phase of infection has been established [5–7]. In our data, even 12 weeks after moderate to mild COVID-19, BP destabilization persisted in patients with pre-existing hypertension.

A population-based Hamburg Health Study including 432 patients after mild COVID-19 with at least 4 months of follow-up after COVID-19 found a significant increase in DBP in this category (+4.7 mmHg, 95 % CI 3.97–5.7, p<0.001) [5]. For SBP, a trend toward higher values was found (+1.4 mmHg, 95 % CI 0.4–3.2, p= 0.120).

A retrospective cohort study of patients after COVID-19 who were admitted to the Washington University Cardiology Clinic with cardiovascular symptoms found elevations in both SBP and DBP [8]. However, the time factor after COVID-19 was not taken into account when examining the patients. Based on the results of our study, we found that even 12 weeks after COVID-19, patients still had elevated DBP levels (p1-3<0.00001; p2-3<0.00001). Elevated SBP was recorded only in the ongoing COVID-19 group (p1-2=0.036; p1-3=<0.00001). Maximum HR values were noted in the same group (p1-3<0.00001).

A search for risk factors for PCS has revealed a higher prevalence of its occurrence in women [9–11]. However, our study showed no differences in groups by gender. According to a study that included medical records of more than 1 million COVID-19 patients, obese, overweight patients had a higher risk of developing PCS [9, 10]. In our study, abdominal obesity was also detected more frequently in COVID-19 survivors compared to non-infected patients (p = 0.032, χ^2= 6.857).

BP elevation after COVID-19 is presumably associated with tissue RAAS activation. Disruption of ACE upregulation by the introduction of SARS-CoV-2, causes vasoconstriction, inflammation and cellular damage [12]. There is growing evidence supporting the persistence of endothelial dysfunction after COVID-19 [14, 15] as a possible mechanism for the occurrence of the "cardiovascular" phenotype of PCS [8]. However, the etiology of PCS remains unknown to date [13].

In 2023, a new paradigm of PCS was proposed with the inclusion of biological, psychological, and social factors integrated in complex relationships [14]. In this regard, the study of gene dysregulation as part of the biological component of the syndrome is of particular importance. On the other hand, the genetic architecture of BP includes monogenic mutations and genetic polymorphisms that contribute to the occurrence of AH [15]. Considering the fact of involvement of RAAS components in COVID-19, we can assume an association of the occurrence of uncon-

trolled AH in PCS with polymorphisms of genes of the above system. Studies confirm the association of AGT level with the severity of COVID-19 [16].

Information on the role of polymorphisms of genes encoding AGT in the development of PCS is currently lacking. We identified an association of BP level with the C allele of the AGT gene (T704C) in patients with the ongoing symptomatic COVID-19. In the phase of ongoing symptomatic COVID-19, carrying the homozygous TT genotype of the AGT gene 704T>C, rs699 was less frequent (p=0.005) than in the control group. There was also a weak negative association of TT genotype AGT704 with BMI (r=–0.30, p=0.001), SBP (r=–0.42, p=0.0001) and DBP (r=–0.36, p=0.0001).

Conclusion

To date, the association between COVID-19 and AH remains poorly understood. According to the results of our study, uncontrolled AH was a long-term effect of mild to moderate COVID-19. Analysis of time aspects revealed the greatest persistence of destabilization in DBP values. Identification of the association of BP with AGT gene polymorphism in PCS will provide an opportunity to initiate personalized treatment and develop prevention strategies.

Conflict of interests: none declared.

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Predictive markers for new-onset atrial fibrillation in patients with non-ST-elevation acute coronary syndrome

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The aim of the study is to identify markers associated with the occurrence of new-onset atrial fibrillation (AF) in a group of patients with non-ST-elevation acute coronary syndrome (NSTE-ACS).

Methods. A total of 769 patients with NSTE-ACS participated in the observational case-control study while undergoing inpatient treatment at SSMU clinics from January 1, 2019, to January 1, 2020. The results of clinical, standard laboratory, and instrumental diagnostic methods were assessed.

Results. Patients with AF were older (73.5 [66.0; 80.0] years vs. 66.0 [59.0; 73.0] years, p<0.001), had a higher incidence of prior stroke (20 [21.3%] vs. 67 [9.9%] patients, p=0.001), and chronic kidney disease (CKD) (79 [84.0%] vs. 445 [65.9%] patients, p<0.001). They also exhibited a higher heart rate (HR) (86.0 [74.0; 120.0] bpm vs. 76.0 [70.0; 86.0] bpm, p<0.001) and GRACE score (151.5 [143.0; 161.0] vs. 144.0 [134.0; 153.0], p<0.001), but a lower SYNTAX score (10.0 [4.0; 41.0] vs. 40.0 [24.0; 55.0], p=0.029). Patients with AF also had higher levels of creatinine (94.0 [80.0; 113.0] μmol/l vs. 86.0 [72.0; 103.0] μmol/l, p=0.001) and glucose (8.0 [6.0; 11.0] mmol/l vs. 6.0 [6.0; 8.0] mmol/l, p=0.001), along with lower estimated glomerular filtration rate (eGFR, CKD-EPI) (58.0 [46.0; 73.0] ml/min/1.73 m² vs. 73.0 [56.0; 87.0] ml/min/1.73 m², p<0.001), total cholesterol (4.70 [3.45; 5.11] mmol/l vs. 5.00 [4.29; 6.00] mmol/l, p=0.005), and low-density lipoprotein cholesterol (2.74 [2.00; 3.30] mmol/l vs. 3.04 [2.45; 3.79] mmol/l, p=0.023).

According to the echocardiographic findings, no statistically significant differences were identified. Multivariate regression analysis revealed that age (odds ratio [OR] 1.057; 95% confidence interval [CI] 1.010–1.105, p=0.016) and HR (OR 1.057; 95% CI 1.036–1.078, p<0.001) were di-

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rectly associated with the occurrence of AF. The area under the ROC curve for the risk stratification of AF prognosis based on logistic regression values was 0.687 (0.028) with a 95% CI of 0.631–0.742 (p<0.001).

Conclusion. This study demonstrates that patients with AF were older, more likely to have comorbid conditions (stroke, CKD), higher HR, higher GRACE score, lower SYNTAX score, and more pronounced changes in laboratory parameters (lower eGFR, higher lipid spectrum concentrations, and glucose levels). The analysis identified age and HR as predictors of new-onset AF in patients with NSTE-ACS.

Keywords: atrial fibrillation, acute coronary syndrome, myocardial infarction, chronic kidney disease, risk factors.

Conflict of interests: none declared.

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Introduction

New-onset atrial fibrillation (AF) often complicates the course of acute coronary syndrome (ACS), leading to unfavorable short-term and long-term outcomes. The prevalence of AF in patients hospitalized for ACS varies between 2% and 37%. Several factors influencing prognosis are mentioned in the literature, but they remain a topic of discussion [1, 2]. A critical aspect is the management of this patient category, as AF is associated with worsening of the underlying condition, an increased risk of thromboembolic complications, the occurrence and decompensation of heart failure. The presence of comorbid conditions acts as an additional factor determining the poor prognosis of patients with AF in the context of ACS development [3].

The aim of the study is to identify markers associated with the occurrence of new-onset AF in a group of patients with non-ST-elevation acute coronary syndrome (NSTE-ACS).

Methods

An observational "case-control" study included 769 patients with NSTE-ACS who were hospitalized in the SSMU clinics from 01.01.2019 to 01.01.2020. The diagnosis of NSTE-ACS was established based on current guidelines [4].

Inclusion criteria: All patients signed informed consent to participate in the trial. The time from the onset of NSTE-ACS to hospitalization was 2.0 (1.0; 3.0) hours: 38% of patients were admitted within 2 hours, 36% within 1 hour, 23% within 3 hours, and 3% more than 3 hours after the onset.

Exclusion criteria: ACS with ST-segment elevation, other cardiovascular diseases (pericarditis, myocarditis, cardiomyopathies, pulmonary embolism), decompensated comorbid conditions (liver, kidney, or blood diseases, diabetes mellitus, malignant neoplasms). The study protocol was approved by the SSMU Ethics Committee.

Two groups were identified: the group with AF (94 patients, 45 (47.9%) men, median age 73.5 (66.0; 80.0) years) and the group without AF (675 patients, 367 (54.4%) men, median age 66.0 (59.0; 73.0) years). The results of clinical, standard laboratory, and instrumental diagnostic methods were assessed.

Statistical analysis

Data analysis was performed using the SPSS software package, version 26 (USA). Non-parametric statistical methods were applied to process the results, as the distribution of quantitative data did not follow a normal distribution (presented as the median (Me) with the 25th and 75th percentiles). Qualitative parameters were expressed in absolute numbers and percentages (%).

For the analysis of independent samples, non-parametric statistical methods such as the Mann–Whitney U-test were used. Differences in qualitative variables were assessed using contingency tables: if the number of observations in any cell of the table was 10 or more, the chi-square test was applied; if the number of observations ranged from 5 to 9, Yates' continuity correction was used; and if the number of observations was <5, Fisher's exact test was applied.

To calculate sensitivity, specificity, predictive value, and diagnostic significance of parameters, ROC analysis was performed. Binary logistic regression was used to calculate the odds ratio (OR).

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Differences were considered statistically significant at p<0.05.

Results

During the study, a detailed analysis of clinical markers, laboratory parameters, and echocardiographic findings was conducted. The results of the assessment of pharmacological therapy showed that the prescription of antiplatelet therapy (acetylsalicylic acid, P2Y12 receptor blockers), anticoagulants, HMG-CoA reductase inhibitors, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists, beta-blockers, calcium antagonists, and nitrates were comparable between the groups.

In some cases, AF was spontaneously resolved (in 48 (51.1%) patients) within 5–30 minutes. For symptomatic patients, administration of class III antiarrhythmic drugs (amiodarone) was required (in 31 (33.0%) patients). In other cases, due to the absence of clinical symptoms associated with AF, ongoing baseline therapy contributed to the resolution of arrhythmia.

The clinical characteristics of the patients are presented in Table 1.

SYNTAX score calculations were performed in 90 (11.7%) patients due to multivessel coronary artery disease. As shown in the table, statistically significant differences were identified in terms of age, history of stroke, chronic kidney disease (CKD), heart rate (HR), GRACE risk score, and SYNTAX score. Patients with AF were older, had a higher prevalence of prior stroke, CKD, and elevated HR (evaluated in the AF group outside the arrhythmia episode), as well as higher GRACE scores but lower SYNTAX scores.

Echocardiographic studies revealed changes in the following localizations (areas of hypokinesia): the anterior wall in 163 (21.2%) patients, the posterior wall in 174 (22.6%), the lateral wall in 103 (13.4%), the anterolateral wall in 82 (10.7%), the posterolateral wall in 120 (15.6%), and unspecified localization in 40 (5.2%) patients.

Coronary angiography was performed in 265 (34.5%) patients. The findings showed atherosclerotic involvement in the following coronary arteries: the left anterior descending artery in 261 (33.9%), the circumflex artery in 139 (18.1%), the right coronary artery in 160 (20.8%), the intermediate artery in 6 (0.8%), the diagonal artery in 17 (2.2%), the obtuse marginal branch in 22 (2.9%), and the posterior interventricular artery in 8 (1.0%) patients.

Table 1. **The clinical characteristics of the patients**

Parameter	Absence of AF (n=675)	Presence of AF (n=94)	p
Age, years	66.0(59.0;73.0)	73.5(66.0;80.0)	<0.001
Sex (m/f), n (%)	367 (54.4 %) / 308 (45.6 %)	45 (47.9 %) / 49 (52.1 %)	0.237
History of MI, n (%)	313 (46.4 %)	59 (53.2 %)	0.215
History of stroke, n (%)	67 (9.9 %)	20 (21.3 %)	0.001
Peripheral arterial disease, n (%)	202 (29.9 %)	31 (33.0 %)	0.546
History of percutaneous coronary intervention (PCI), n (%)	112 (16.6 %)	21 (22.3%)	0.167
History of coronary artery bypass grafting (CABG), n (%)	31 (4.6 %)	8 (8.5 %)	0.127
Chronic kidney disease (CKD), n (%)	445 (65.9 %)	79 (84.0 %)	<0.001
GFR by CKD-EPI, ≥60 ml/min/1,73 m2	267 (60.0 %)	39 (49.4 %)	0.003
C3a	105 (15.6 %)	23 (24.4 %)	
C3b	56 (8.3 %)	15 (16.0 %)	
C4	11 (1.6 %)	1 (1.1 %)	
C4	6 (0.9 %)	1 (1.1 %)	
Diabetes mellitus, n (%)	232 (34.4 %)	41 (43.6 %)	0.079
Arterial hypertension, n (%)	86 (52.4 %)	10 (43.5 %)	0.421
Smoking, n (%)	5 (0.7 %)	0.0 (0.0 %)	1.000
HR/min	76.0 (70.0;86.0)	86.0 (74.0;120.0)	<0.001
Systolic BP, mmHg	140.0(120.0; 160.0)	137.5 (120.0;150.0)	0.144
GRACE, score	144.0 (134.0; 153.0)	151.5 (143.0;161.0)	<0.001
SYNTAX score	40.0 (24.0;55.0)	10.0 (4.0;41.0)	0.029

Single-vessel stenting was performed in 222 (28.9%) patients, two-vessel stenting in 79 (10.3%) patients, and three-vessel stenting in 1 (0.1%) patient. Complications during the hospital stage were noted in 1 (0.1%) patient due to artery dissection and in 1 (0.1%) patient due to re-occlusion of a previously stented artery.

The distribution of coronary artery lesions by groups is presented in Table 2.

Table 2. **Coronary angiography parameters in individuals with CHD**

Parameter	Absence of AF (n=675)	Presence of AF (n=94)	p
Lesion of the left anterior descending artery, n (%)	236.0 (35.0%)	25.0 (26.6%)	0.108
Lesion of the circumflex artery, n (%)	115.0 (17.0%)	24.0 (25.5%)	0.045
Lesion of the right coronary artery, n (%)	138.0 (20.4%)	22.0 (23.4%)	0.508
Lesion of the intermediate artery, n (%)	5.0 (0.7%)	1.0 (1.1%)	0.544
Lesion of the diagonal artery, n (%)	17.0 (2.5%)	0.0 (0.0%)	0.249
Lesion of the obtuse marginal branch, n (%)	22 (3.3%)	0.0 (0.0%)	0.096
Lesion the posterior interventricular artery, n (%)	6 (0.9%)	2 (2.1%)	0.255

Thus, statistically significant differences between the groups were demonstrated regarding the involvement of the circumflex artery (p=0.045).

The laboratory findings are presented in Table 3.

Table 3. **Laboratory parameters**

Parameter	Absence of AF (n=675)	Presence of AF (n=94)	p
Creatinine, μmol/l	86.0 (72.0;103.0)	94.0 (80.0; 113.0)	0.001
GFR by CKD-EPI, ml/min/1,73 m2	73.0 (56.0; 87.0)	58.0 (46.0; 73.0)	<0.001
Glucose, mmol/l	6.0 (6.0; 8.0)	8.0 (6.0; 11.0)	0.001
Hemoglobin, g/l	136.0 (123.0; 146.0)	132.0 (119.0; 142.0)	0.083
Total cholesterol (TC), mmol/l	5.00 (4.29; 6.00)	4.70 (3.45; 5.11)	0.005
Low-density lipoprotein cholesterol (LDL-C), mmol/l	3.04 (2.45; 3.79)	2.74 (2.00; 3.30)	0.023
High-density lipoprotein cholesterol (HDL-C), mmol/l	1.06 (1.00; 1.40)	1.00 (0.95; 1.41)	0.543
Troponin T, ng/l	43.95 (15.0; 412.5)	75.0 (21.0; 343.5)	0.228

According to the data in the table, patients with AF had higher levels of creatinine and glucose, as well as lower levels of GFR by CKD-EPI, total cholesterol (TC), and LDL cholesterol (LDL-C).

The echocardiographic findings are presented in Table 4, with no statistically significant differences observed in the studied parameters.

The groups differed in terms of the number of hospital days: in the AF group, the median was 11.0 (8.0; 14.0) hospital days, while in the non-AF group, it was 10.0 (8.0; 13.0) hospital days (p=0.004).

Table 4. **Echocardiographic parameters**

Parameter	Absence of AF (n=675)	Presence of AF (n=94)	p
End-systolic dimension (ESD), mm	31.0(27.0; 35.0)	29.0(27.0;36.5)	0.847
End-diastolic dimension (EDD), mm	47.0(43.0;52.0)	47.0(44.0;52.0)	0.680
End-systolic volume (ESV), ml	38.0(31.0;50.0)	40.0(30.0;56.0)	0.765
End-diastolic volume (EDV), ml	97.0(80.0;120.0)	98.0(80.0;113.0)	0.680
Left atrium (LA), area, mm^2	38.0(35.0;42.0)	40.0(36.0;44.0)	0.013
Left ventricular mass index (LVMI), g/m^2	103.0(87.0;121.0)	106.5(95.5;123.5)	0.208
Left ventricular ejection fraction (LVEF), %	58.0(51.0;62.0)	56.0(50.0;60.0)	0.053

A risk prediction model for the development of new cases of AF based on clinical and instrumental factors was prepared using binary logistic regression. The created multifactorial regression model is statistically significant (p<0.001). Considering the value of the Nagelkerke R^2, 28.9% of the variance in AF risk is determined by the factors included in the model.

According to the regression coefficients, age and HR (evaluated outside the AF episode in the AF group) showed a direct relationship with the risk of AF development. The characteristics of each factor are presented in Table 5.

Table 5. **Characteristics of the relationship between predictors and the probability of developing new cases of AF in patients with NSTE-ACS**

Predictors	Univariate analysis		Multivariate analysis	
	Raw OR; 95% CI	p	Adjusted OR; 95% CI	p
Age	1.071; 1.046-1.096	<0.001	1.057; 1010-1.105	0.016
HR	1.046; 1.034-1.058	<0.001	1.057; 1.036-1.078	<0.001

For the logistic function, the Youden's index (J) was 18.48%. At P⩾18.48%, a high risk of developing AF was predicted, while P<18.48% indicated a low risk of developing AF. The sensitivity was 85.7%, specificity was 52.9%, positive predictive value was 60.0%, negative predictive value was 91.0%, and diagnostic accuracy was 80.7%.

The area under the ROC curve, which determines the risk stratification of AF prognosis and the values of the logistic regression function (Figure 1), was 0.687 (0.028) with a 95% CI of 0.631–0.742. The resulting model was statistically significant (p<0.001).

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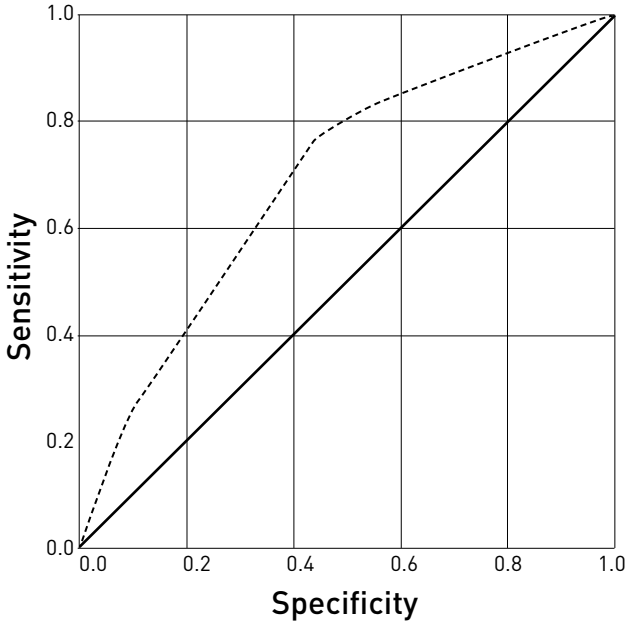

Fig. 1. The ROC curve for the logistic regression function and the risk of developing AF

Discussion

AF is one of the most common cardiovascular diseases (CVD) that impacts the quality and longevity of life for adults in various countries around the world. Its molecular, cellular, neurohumoral, and hemodynamic pathophysiological mechanisms are complex, and there is growing understanding that a wide range of comorbidities may contribute to atrial remodeling, which promotes the development of AF. Furthermore, recent studies have shown that HR is not constant, and temporary changes in comorbid conditions complicate the dynamics of AF.

In this study, the incidence of newly developed AF was 12.2%, which is consistent with the literature sources [5].

Our data demonstrate that age is a risk factor (RF) for the development of AF in NSTE-ACS patients, which aligns with the results of other studies. For example, Ben Halima M et al. (2022) showed that in multivariate analysis, age over 62 years (p = 0.04; adjusted OR = 4.83; 95% CI: 1.07-21.77) was an independent predictor for the development of AF during acute coronary syndrome, along with chronic heart failure (CHF), prior stroke, and hyperuricemia [1].

The results of this study indicate that a high HR is a significant predictor of new-onset AF development in patients with NSTE-ACS.

It is well known that an increased HR induces myocardial ischemia in patients with coronary heart disease (CHD), and reducing HR is a widely accepted strategy to prevent ischemic episodes [6]. Additionally, clinical data suggest that slowing the HR alleviates symptoms of angina by improving microcirculation and coronary blood flow [7]. Elevated HR is an established risk factor for cardiovascular complications in patients with CHD and CHF [8]. Therefore, reducing HR improves prognosis in patients with heart failure, as demonstrated in the SHIFT study. HR is also an important factor determining arrhythmias; low HR may be associated with AF, while high HR after physical exertion may be associated with sudden cardiac death. Moreover, patients with AF are at higher risk for cardiovascular complications [9–12].

It has been shown that resting HR is a potential risk factor for the development of AF [13]. However, the results of this analysis have been contradictory, and the relationship between HR and AF has not been established [14, 15]. In a subsequent meta-analysis, a search in the Cochrane Library, PubMed, and Embase databases, including 10 studies, presented a total of 18,630 cases of AF in 431,432 participants [16]. The dose-effect analysis showed a non-linear relationship between resting HR and the risk of developing AF (non-linearity, p<0.0001), indicating a significant J-shaped relationship between these two factors. Both low and high resting HR were associated with an increased risk of developing AF compared to the average HR (68–80 beats per minute).

The results of the present study partially align with the literature data. For example, in the study by Ben Halima M et al. (2022), multivariate regression analysis revealed, alongside age over 62 years (p=0.04; adjusted OR = 4.83; 95% CI 1.07-21.77), chronic kidney failure (p=0.043; adjusted OR = 6.61; 95% CI 1.06-35.80), a history of stroke (p=0.002; adjusted OR = 44.51; 95% CI 3.97-498.10), and hyperuricemia ⩾62 mg/l (p=0.04; adjusted OR = 4.4; 95% CI 1.06–18.15) as independent predictors for AF development in patients with ACS [1].

Similar data are demonstrated in the study by Biccirè FG et al. (2023), where patients with AF were older (p<0.001), more often suffered from arterial hypertension (p = 0.012), chronic obstructive pulmonary disease (p < 0.001), and hyperthyroidism (p = 0.018) [2].

As shown in our study, echocardiographic parameters were not included in the predictive model, which may be related to the mechanisms of AF devel-

opment in NSTE-ACS. Specifically, ischemia caused by the acute form of CHD can lead to disturbances in the electrical activity of the myocardium, promoting the development of AF. Left atrial stretch: increased pressure in the left atrium, associated with heart failure or other conditions, may predispose to AF. Inflammatory processes: ACS is accompanied by systemic inflammation, which can affect the electrical conductivity and automaticity of the atria. Stress and sympathetic nervous system activation: the acute stress reaction to sudden myocardial ischemia can lead to increased sympathetic activity, which also increases the risk of AF. Comorbidities: the presence of chronic diseases, such as hypertension or heart failure, can raise the risk of AF in patients with ACS [17–19]. These mechanisms may act independently or in combination, increasing the likelihood of AF in ACS patients. Therefore, preventive measures to correct risk factors, pharmacological treatment of comorbidities, or timely treatment of ACS, including coronary angiography if necessary, can reduce the likelihood of newly diagnosed AF.

Thus, factors associated with the risk of newly occurring AF in NSTE-ACS require careful assessment upon patient admission to the hospital.

Conclusion

This study demonstrates that patients with AF were older, more likely to have comorbid conditions (stroke, CKD), higher HR, higher GRACE score, lower SYNTAX score, and more pronounced changes in laboratory parameters (lower eGFR, higher lipid spectrum concentrations, and glucose levels). The analysis identified age and HR as predictors of new-onset AF in patients with NSTE-ACS.

Conflict of interests: none declared.

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Hypertensive disorders in pregnancy: diagnosis, target blood pressure levels and pharmacotherapy

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This review article discusses current and controversial data related to questions about the prevalence, diagnosis, and treatment of hypertensive disorders of pregnancy (HDP). Current data on the definition, classification, and pathophysiology of HDP, including the pathophysiology of uterine and placental pre-eclampsia, are presented. The issues of stratification and risk prediction of pre-eclampsia development using modern laboratory and instrumental examination methods are discussed. Much attention is paid to modern, clinically based approaches to HDP, improvement of outcomes and prevention of maternal and fetal complications in HDP. Special attention is paid to the management of severe arterial hypertension (AH), pre-eclampsia, including pre-eclampsia with severe manifestations. Data on the pathophysiology of development, treatment of postpartum AH, including breastfeeding, are presented. The main approaches to the diagnosis and treatment of pre-existing secondary AH in pregnancy are also presented.

Keywords: hypertensive disorders of pregnancy, gestational arterial hypertension, pre-eclampsia, risk stratification.

Conflict of interests: none declared.

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Introduction

The prevalence of hypertensive disorders of pregnancy (HDP) is nearly 10% worldwide and is a major cause of maternal, fetal or neonatal morbidity and mortality [1]. On the maternal side, elevated blood pressure (BP) leads to increased risks of acute cerebral circulatory failure, pulmonary edema, placental abruption, disseminated intravascular coagulation

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and thromboembolic complications, as well as to the multiple organ failure. On the fetal side, HDP leads to the development of antenatal mortality, prematurity, delayed development, increased risks of preterm labor, and low birth weight [2]. The prevalence of HDP continues to increase due to the increasing incidence of obesity and other cardiometabolic factors in pregnant women, as well as the increasing age of pregnant women [3].

Definition and classification of hypertensive disorders in pregnancy

Most guidelines worldwide define the arterial hypertension (AH) during pregnancy as BP ⩾140/90 mmHg and classify AH as mild (140-159/90-109 mmHg) or severe (⩾160 mmHg/110 mmHg) [2, 4], in contrast to the commonly accepted three-stage classification of AH outside pregnancy.

The thresholds for diagnosis and treatment of AH for the general population have changed over the years. The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines lowered the threshold for diagnosis of AH to 130/80 mmHg from 140/90 mmHg [5] based on observational studies and clinical trials demonstrating a reduced incidence of cardiovascular events when treated to lower BP levels.

Elevated systolic blood pressure (SBP) throughout pregnancy, even below the diagnostic threshold for AH, is associated with an increased risk of preterm labor, prematurity for gestational age, and low birth weight [6]. A cohort study including 137,389 pregnancies estimated the prevalence of AH among pregnant women using the lower ACC/AHA diagnostic threshold (SBP⩾130 mmHg or diastolic blood pressure (DBP) ⩾80 mmHg) instead of the American College of Obstetricians and Gynecologists (AGOG) threshold (SBP⩾160 mmHg or DBP ⩾105 mmHg). At the same time, the prevalence of AH increased from 10.3% to 28.1%, resulting in a net reclassification index of 20.8% for the detection of future preeclampsia and 3.8% for fetal/neonatal adverse events [7].

HDP are classified according to the timing of their occurrence during the pregnancy. The definition and classification of HDP [8] are summarized in Table 1.

BP measurements at the beginning of the second trimester in women who have not previously measured BP should be interpreted with caution because of the physiologic drop in BP in the second trimester. Women with hypertensive level of BP after 20 weeks and unknown BP before 20 weeks should be managed as women with gestational AH. In these women with unclassifiable pre-pregnancy AH, reassessment of BP 6 weeks after delivery will help distinguish pre-existing hypertension from gestational AH.

Among women with pre-existing hypertension, nearly 25% will develop pre-eclampsia [9]. This is usually associated with an abrupt or progressive

Table 1. **Classification of arterial hypertension in pregnancy**

<table>
<tr><td colspan="4">A. Pre-existing (chronic) AH.
AH that precedes pregnancy or develops before 20 weeks' gestation, usually persists for more than 42 days after delivery, and may be associated with proteinuria.</td></tr>
<tr><td>1. Primary AH</td><td>2. Secondary AH</td><td>White coat AH (elevated office BP and normal BP outside the office)</td><td>Masked AH (normal office and elevated out-of-office BP).</td></tr>
<tr><td colspan="4">B. Gestational AH.
AH develops after 20 weeks of pregnancy and usually resolves within 42 days of the delivery</td></tr>
<tr><td colspan="2">1. Transient gestational AH is detected in the clinic but then resolves with repeated BP measurements taken within a few hours, is associated with a 40% risk of developing true gestational AH or pre-eclampsia in the remainder of pregnancy</td><td colspan="2">2. Pre-eclampsia is gestational AH accompanied by one or more of the following conditions first occurring at or after 20 weeks of gestation:
- proteinuria (24-hour urinary albumin excretion >300 mg/day or albumin/creatinine ratio in a random urine sample >30 mg/g)
- acute kidney injury (serum creatinine ⩾90 μmol/l)
- liver damage (elevated alanine aminotransferase or aspartate aminotransferase levels >40 IU/l with or without right subcostal or epigastric pain)
- neurologic complications (e.g., eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomas)
- hematologic complications (platelet count <150,000*109, disseminated intravascular coagulation syndrome, hemolysis)
- uteroplacental dysfunction (fetal growth retardation, abnormal umbilical artery Doppler analysis or stillbirth)</td></tr>
<tr><td colspan="4">C. Preexisting AH + pre-eclampsia.
Preexisting AH associated with any of the above-mentioned maternal organ dysfunction consistent with pre-eclampsia, or further BP elevation with first-onset proteinuria.</td></tr>
<tr><td colspan="4">D. Antenatally unclassifiable AH.
If elevated BP is first recorded after 20 weeks of gestation and AH is diagnosed, the reassessment 42 days after delivery is necessary. If AH resolves, it should be reclassified as gestational AH, whereas if AH persists, it should be reclassified as pre-existing AH.</td></tr>
</table>

increase in BP. Clinicians should always consider pre-eclampsia as a serious disease with rather unpredictable consequences.

Measuring blood pressure during pregnancy

Manual auscultatory blood pressure measurement remains the gold standard, as automated devices tend to underestimate BP and are unreliable in severe preeclampsia. For clinical purposes, two BP elevations four hours apart are required to detect AH during pregnancy. Only devices approved specifically for pregnant women should be used [10]. 24-hour blood pressure monitoring (24HBPM) is superior to office BP measurement for predicting pregnancy outcome. 24HBPM helps to avoid unnecessary treatment in white coat AH.

Non-sustained arterial hypertension

White coat AH occurs in 25% of non-pregnant adults, its prevalence during pregnancy is less known and varies from 4% to 30% according to different data [11]. Based on 24-hour BP measurement, the white coat AH was diagnosed in 32% of women with AH [12]. A meta-analysis of studies on white coat AH showed an increased risk of pre-eclampsia and adverse fetal outcomes compared to women with normotension, but the risks were lower compared to women with sustained chronic or gestational AH [13]. Any category of non-sustained BP elevation during pregnancy can progress to persistent AH.

Pathophysiology of hypertensive disorders in pregnancy

During normal pregnancy, systemic vascular resistance decreases and plasma volume and cardiac output increase [15]. In women with pre-eclampsia, some studies have shown that plasma volume may decrease [16]. Renal blood flow and glomerular filtration rate (GFR) are increased by 50% in normal pregnancy, but about 30% lower in women with pre-eclampsia. Numerous studies in women with pre-eclampsia have shown suppression of plasma renin activity, high BP, decreased GFR, and frequent edema [9].

Cardiometabolic changes are more prominent in women who develop pre-eclampsia and include increased insulin resistance, total cholesterol, triglycerides, and low-density lipoprotein cholesterol [17]. Hypercoagulability, a feature of normal pregnancy, may be excessive in pre-eclampsia and is caused by increased thrombin formation, fibrinogen and activated protein C resistance, as well as due to decreased protein S and fibrinolysis [18].

Pathogenesis of placental and maternal pre-eclampsia syndrome

During normal pregnancy, the diameter of uterine spiral arteries increases significantly due to remodeling of the endothelium and vascular smooth muscle stimulated by the release of proteases from endovascular trophoblast and uterine natural killer cells. Failure to remodel the spiral artery (i.e., smooth muscle preservation) is a hallmark of pre-eclampsia and results in decreased uteroplacental perfusion, as demonstrated by non-invasive blood flow and perfusion studies using Doppler ultrasound (US) or magnetic resonance imaging (MRI) [19].

Placental pathology due to rheologic abnormalities includes changes in the architecture of the villi due to turbulent jets penetrating the intervillous space at a velocity of 1-2 m/s (10-20 times higher than normal), causing rupture of the entrapped villi and formation of echogenic cystic lesions visible during ultrasound [20]. In addition, preservation of vascular smooth muscle retains the ability to spontaneous vasoconstriction and leads to ischemia-reperfusion injury.

Abnormal placentation in early pregnancy leads to an increase in an antiangiogenic factor of placental origin: circulating soluble fms-like tyrosine kinase 1 (sFlt1), and a consequent neutralization and decrease in proangiogenic factors: placental growth factor (PlGF) and vascular endothelial growth factor, which contributes to glomerulopathy and increased BP [19]. Measurements of sFlt1, PlGF and their ratios have been included in risk stratification in several therapeutic trials for the prevention of pre-eclampsia, but are not commonly used to guide clinical care in most of the countries

An elevated sFlt1/PlGF ratio may be particularly prominent in women with early (less than 34 weeks' gestation) severe pre-eclampsia, which some refer to as placental pre-eclampsia because of the association between placental ischemia and adverse fetal outcomes [21].

Pre-eclampsia occurring later in pregnancy is associated with maternal vascular dysfunction prior to pregnancy (secondary to AH, diabetes mellitus, or

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obesity), less severe placental pathology, and fewer fetal complications [21]. The molecular and pathophysiologic mechanisms of pre-eclampsia are still not completely clear, but the etiology is likely a combination and interaction of both placental and maternal pathways. Regardless of the variant of pre-eclampsia, the diagnosis and treatment of HDP remains the basis for prevention of immediate maternal complications as well as of seizures treatment with magnesium sulfate.

Additional tests in pregnancy

In HDP, basic laboratory tests are recommended, including a general blood count, urinalysis, biochemical testing for liver enzymes, creatinine, and uric acid. Hyperuricemia in HDP is associated with an increased risk of adverse maternal and fetal outcomes [22].

Examination for 24-hour albuminuria, albumin-creatinine ratio can detect pre-existing renal disease in early pregnancy and pre-eclampsia in the second half of pregnancy. Proteinuria may also be a precursor to subsequent BP elevation in the natural course of pre-eclampsia, and the presence of proteinuria is no longer a necessary criterion for the diagnosis of pre-eclampsia [23].

Several laboratory markers have been tested for predicting pre-eclampsia in early pregnancy:

- Angiogenic factors [endoglin, PlGF, sFlt-1 and sFlt-1/PIGF ratio];
- Pregnancy-related plasma protein A in combination with clinical (e.g., BP, maternal risk factors - FR) and ultrasound characteristics (e.g., uterine artery Doppler) [24].

However, additional studies are desirable to clarify the role of the above-mentioned markers alone or in combination with clinical characteristics in predicting pre-eclampsia (24, 25).

If serum creatinine or any parameters in urinalysis are abnormal, renal ultrasound and uterine and umbilical artery duplex scanning (performed after 20 weeks of gestation) should be considered to identify those at higher risk of gestational AH, pre-eclampsia and fetal development delay.

Prevention of pre-eclampsia and adverse maternal and fetal outcomes

A meta-analysis of 44 randomized controlled trials demonstrated that diet correction reduces maternal weight gain during pregnancy and improves pregnancy outcomes [26].

In addition, in women with low calcium intake (i.e., < 600 mg/day), calcium supplementation at a dose of at least 1 g/day has been recommended to reduce the risk of pre-eclampsia [27]. Although there are no recommendations for salt restriction, it is important for women with pre-existing AH to continue on a sodium-restricted diet.

Physical exercise can reduce the risk of gestational AH and pre-eclampsia by about 30% and 40%, respectively [28]. The first Canadian guideline on physical activity during pregnancy, published in 2019, recommends physical activity for all women without contraindications [29]. If there are no contraindications, aerobic exercise (3–4 times a week for 30–60 minutes before delivery) should be recommended.

Drug therapy

Low-dose aspirin starting at 12-16 weeks of gestation reduces the risk of pre-eclampsia and related adverse outcomes by 10–20% in high-risk women. The classification of pre-eclampsia risk as high and moderate is based on the ACOG recommendations for aspirin therapy to prevent pre-eclampsia. Therapy is indicated in the presence of ⩾1 high or ⩾ 2 moderate risk factors [30].

The high risk of pre-eclampsia includes:

- Previous pre-eclampsia;
- Chronic AH (BP ⩾140/90 mmHg);
- Pre-gestational diabetes;
- Chronic kidney disease (CKD);
- Multiple pregnancy;
- Autoimmune diseases such as systemic lupus erythematosus or antiphospholipid syndrome.

The moderate risk of pre-eclampsia includes:

- History of adverse pregnancy outcomes (stillbirth, placental abruption);
- Age 35 years or older;
- Body mass index (BMI) of 30 kg/m^2 or more at the first visit;
- Aggravated family history (first degree relatives);
- Low socioeconomic status;
- Race (Negroid).

Other risk factors (RF) of pre-eclampsia development also include: chronic AH (BP 130-139/80-89 mmHg), white coat AH, BMI more than 25 kg/m2, ges-

tational diabetes, insulin resistance, history of acute kidney injury, hyperthyroidism, fetal trisomy-13, genetic predisposition, assisted reproductive technologies, oocyte donation, pregnancy interval more than 4 years.

If the risk of pre-eclampsia is high or moderate, 100–150 mg of acetylsalicylic acid is recommended from week 11 to 14 until the 36th week of pregnancy [31].

Antihypertensive therapy during pregnancy

The treatment of HDP includes the question of the benefit of treatment and normalization of BP in pregnant women combined with concerns about fetal well-being due to decreased uteroplacental perfusion and intrauterine exposure to antihypertensive drugs.

Mild pre-existing essential arterial hypertension

The decision about antihypertensive therapy use in the first and early second trimester may be individualized, based on pre-pregnancy BP levels in the absence of treatment, BP values in the first trimester, the presence of target organ damage, and BP values after possible short-term withdrawal of antihypertensive treatment in individual cases. It should be decided on a case-by-case basis whether the benefit of drug treatment during fetal organogenesis (up to week 16) exceeds the risk of fetal exposure, as any drug can be potentially harmful in the first trimester, including alpha-methyldopa [32].

All renin-angiotensin system (RAAS) blockers should be discontinued during the first trimester. In a large meta-analysis including 19 studies and 4,163,753 pregnant women, 13 studies reported an increased risk of at least one adverse pregnancy outcome in women who were exposed to RAAS blockers [33].

In the first trimester in women with office BP < 130/80 mmHg, antihypertensive therapy may be discontinued or de-escalated under careful BP monitoring until week 16. If BP rises >140/90 mmHg, antihypertensive therapy should be resumed at any gestational age.

It should be remembered that there may be a physiologic decrease in BP at the beginning of the second trimester, and that even mild antihypertensive therapy during this period can potentially lead to excessive BP reduction, which increases the risk of miscarriage.

In the large randomized multicenter CHIPS (The Control of Hypertension in Pregnancy Study) study [34], which included 987 women with HDP, of whom 74.6% had a history of AH, BP was 138.8 ± 0.5 mmHg among women in the less strictly controlled group versus 133.1 ± 0.5 mmHg in the strictly controlled group. Among women receiving antihypertensive therapy, labetalol was the most commonly used drug (68.9% and 68.8% in the two groups, respectively), with the remainder receiving methyldopa or nifedipine. In another large randomized CHAP (Chronic Hypertension and Pregnancy) study [35], which included 2806 women with chronic AH with less than 23 weeks' gestation, were assigned to receive antihypertensive drugs (labetalol or prolonged-acting nifedipine or other drugs such as amlodipine or methyldopa (active treatment group), or receive no treatment unless severe AH developed (control group).

Studies have shown that compared with placebo, strict and less strict BP control on antihypertensive therapy were more beneficial and not harmful. In the CHIPS study [34], the effect of BP lowering was favorable for the primary outcome, i.e. severe pre-eclampsia, preterm delivery at less than 35 weeks of gestation, placental abruption or development of neonatal fetal death.

The BP values observed in the CHIPS (133/85 mmHg) and CHAP (129/79 mmHg) studies reduced pregnancy-related complications by 35% and 18%, respectively; both studies achieved a reduction in pre-eclampsia, including severe pre-eclampsia.

However, in the CHIPS study, there was a gestational age-insignificant increase in the incidence of adverse neonatal outcomes, while this was not found in the CHAP study, keeping the issue of excessive BP lowering and the associated risk of fetal hypoperfusion relevant.

Current epidemiologic and demographic trends indicate an increase in age at first pregnancy. In addition, fertility treatments facilitate pregnancy in women who have conditions associated with increased cardiovascular risk (e.g. diabetes mellitus, CKD, polycystic ovary syndrome). In high-income countries, chronic kidney and heart diseases are seen in 3% and 1–4% of pregnancies, respectively [36, 37], with more intensive treatment recommended for these women.

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It is widely accepted that initial antihypertensive therapy is monotherapy with a recognized first-line drug: methyldopa or labetalol. Some [38, 39] but not all scientific societies support the use of nifedipine as initial therapy. In countries where labetalol is not available (e.g. Germany), alternative beta-blockers such as metoprolol or oxprenolol can be considered. These therapeutic options are based on small individual studies and are supported by national and international clinical practice guidelines.

Based on a systematic review of randomized trials for all types of AH in pregnant women considered together, for all antihypertensive drugs considered together, or for beta-blockers (including labetalol) considered separately, there is no clear evidence that one drug is preferable to another [40].

However, in a separate network meta-analysis specifically focused on the treatment of chronic AH, atenolol was associated with fetal growth retardation [41], especially in long-term use.

Mild gestational arterial hypertension

Although the CHIPS study [34] included a limited number of women with gestational AH (25.4%), secondary analysis showed no differences in outcomes between women with gestational and pre-existing AH for both primary and secondary outcomes. Initiating treatment at BP values ≥140/90 mmHg seems reasonable, whereas lowering DBP to <80 mmHg is not recommended. The same medications recommended for pre-existing AH can be used in women with gestational AH.

Pre-eclampsia

Antihypertensive therapy for pre-eclampsia with mild or severe AH is not different from treatment of AH without pre-eclampsia, although evidence is limited. AH control can be achieved with labetalol (unless contraindicated) alone or with a combination of labetalol, prolonged-acting nifedipine, and/or alpha-methyldopa.

In pre-eclampsia with severe manifestations (AH of any degree with cardiovascular, neurological, hematologic complications, liver or renal dysfunction, severe AH), treatment with magnesium sulfate infusion is necessary to prevent eclampsia and remains also the method of choice for eclamptic seizures. Magnesium sulfate infusion is recommended within 24 hours after delivery and for prophylactic purposes [43].

Severe arterial hypertension

In severe AH, hospitalization is mandatory to ensure a gradual decrease in BP to <160/105 mmHg and to exclude pre-eclampsia. Continuous cardiotocographic monitoring is also mandatory [42]. The choice of antihypertensive drugs and route of administration depends on the initial diagnosis, expected time of labor and the presence/absence of pre-eclampsia, as well as the preferences and experience of the treating physicians.

A recent comprehensive network meta-analysis including 29 studies and 2521 women showed that nifedipine can be recommended as a BP control strategy in pregnant women with severe AH, while labetalol and hydralazine actually showed limited efficacy [44]. However, in cases of pre-eclampsia with severe manifestations, persistent severe AH, or recurrent severe AH despite oral medication, intravenous labetalol or urapidil should be used before, during, and often after delivery. In pre-eclampsia without severe manifestations or severe AH without pre-eclampsia, an effective and gradually escalating multidrug regimen should be used to lower BP to target levels [34], with hydralazine avoided before delivery because of its association with more adverse perinatal outcomes.

Hydralazine should be administered when labetalol or urapidil is unavailable, insufficient BP reduction, presence of grade II or III atrioventricular block, severe heart failure, asthma, bradycardia or severe postpartum AH.

If pre-eclampsia is accompanied by pulmonary edema, the drug of choice is nitroglycerin administered intravenously at a dose of 5 mg/min with gradual increases every 3–5 minutes to a maximum dose of 100 mg/min with careful BP control.

Sodium nitroprusside is recommended as a reserve drug in the treatment of severe AH because of the increased risk of fetal cyanide poisoning with prolonged use [45].

Pregnant women with severe AH living far away from the maternity hospital may be given 10 mg of short-acting nifedipine orally, and a second dose should be administered 1 hour later if severe AH persists. Short-acting nifedipine sublingually is contraindicated. Successful treatment of severe AH with oral preparations of labetalol, intermediate-acting nifedipine, and methyldopa has been clinically confirmed in resource-limited countries [46].

An additional drug that may be considered for resistant AH is furosemide [47]. It is noteworthy that diuretics, the mainstay of treatment for AH in non-pregnant women, are infrequently used in pregnant women. It is now recognized that in women with salt-sensitive, hyporeninemic forms of chronic AH or CKD and reduced GFR, diuretics can be safely used, although possibly at lower doses [48]. Recent studies suggest that they may be particularly effective in postpartum AH [49].

Pre-existing secondary arterial hypertension

The majority (about 90%) of women with chronic AH have primary AH. Secondary AH may occur in a small proportion of women and is associated with poorer maternal and fetal prognosis. Secondary AH should be excluded if AH is severe or persistent, there is no family history of AH, in the presence of hypokalemia, decreased GFR, or albuminuria in early pregnancy, and maternal age <35 years.

Table 2 summarizes the major causes of AH in pregnancy, diagnostic features, outcomes, and management options.

Women with pre-existing AH should receive counseling before conception, including exclusion of secondary causes of AH. Ultrasound renal Doppler ultrasonography should be performed in all women with AH planning pregnancy. In women diagnosed with fibromuscular dysplasia, further evaluation of other vascular basins, especially the cerebral basin, should be performed before pregnancy to rule out any additional arterial damage. Achieving optimal BP control and, if indicated, renal artery revascularization are recommended before conception [50].

In women with known hyperaldosteronism before conception or with clinical suspicion of this condition early in pregnancy, careful laboratory evaluation should be performed. After the second trimester of pregnancy, eplerenone in addition to conventional BP-lowering treatment may be considered for uncontrolled AH with or without hypokalemia. The fall in progesterone levels after delivery due to its competitive antagonism with aldosterone may increase BP and exacerbate hypokalemia [51].

For the purpose of management of women with kidney disease before pregnancy, it is important to know the degree of CKD, the level of estimated GFR, or the degree of proteinuria rather than the underlying cause. Women without significant proteinuria, normal BP in early pregnancy, and mild renal failure usually have an uncomplicated pregnancy. Women with moderate or more severe CKD are at increased risk for both fetal and maternal complications and worsening of already impaired renal function. Women with a GFR less than 40 ml/min/1.73 m^2 and protein-

Table 2. **Secondary causes of arterial hypertension in pregnancy**

Name	Clinical fetures	Laboratory investigations	Pregnancy outcomes	Treatment/management
CKD	Edema Nicturia	Proteinuria Hematuria Decrease in estimated GFR	Pre-eclampsia Preterm labor Delayed fetal development	Antihypertensive drugs Low-dose aspirin
Primary hyperaldosteronism	Exacerbation of postpartum AH, muscle cramps and weakness, frequent urination, thirst.	Suppression of hypokalemia by aldosterone antagonists Increase in aldosterone-renin ratio	Increased risk of pre-eclampsia	Calcium channel blockers Labetalol Thiazide diuretics Potassium supplements
Renovascular hypertension	Persistent AH. Murmur when auscultating the renal arteries.	Increased plasma renin activity level	Pre-eclampsia Preterm labor	Antihypertensive drugs Angioplasty in the second trimester
Pheochromocytoma	Persistent BP elevation, hypertensive crises, rhythm disturbances, increased nervousness	Elevated levels of metanephrines or catecholamines in plasma/urine.	Severe AH Fetal + maternal mortality	MRI without gadolinium contrast Alpha-blockers Calcium channel blockers Surgery in the second trimester
Cushing's disease	Gestational diabetes Abdominal striae	Free cortisol in urine Cortisol in saliva late at night High dose dexamethasone suppression test	Pre-eclampsia Preterm labor Delayed fetal development Fetal mortality	Metyrapone surgery
Obstructive sleep apnea	Apnea Fatigue Headaches Depression	Polysomnography abnormalities. Desaturation Increased level of glycated hemoglobin Elevated erythropoietin levels	Pre-eclampsia Preterm labor	Mandibular repositioning devices (CPAP therapy)

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uria greater than 1 g/day should be considered at very high risk for pregnancy and renal outcomes, including the need for renal replacement therapy [52, 53].

Pheochromocytoma in pregnancy is a disease that is very rare with a frequency of 0.002% of all pregnancies, while it is one of the most life-threatening conditions for mother and fetus [54]. The dominant sign is AH, the rest of the signs and symptoms are highly variable and unspecific. If pheochromocytoma is not detected, maternal and fetal mortality is about 50%. Timely detection and adequate therapy during pregnancy reduce maternal and neonatal mortality to < 5 and <15%, respectively. For biochemical diagnosis, the tests of choice are the determination of metanephrines in plasma or urine. For reliable diagnosis of pheochromocytoma localization, MRI is the most appropriate method with a sensitivity of more than 90%.

If pheochromocytoma is diagnosed during pregnancy, laparoscopic adrenalectomy should be performed in 10-14 days after preliminary medical preparation (alpha-adrenergic receptor blockade combined with beta-adrenergic receptor blockade) [54]. When pheochromocytoma is diagnosed in the third trimester, using the same treatment regimen as surgical preparation, the patient should preferably be managed until the fetus is viable. Since natural childbirth is associated with a higher mortality rate, cesarean section with tumor removal in one session or at a later stage is preferred (54).

Blood pressure in the postpartum period

The prevalence of postpartum AH can be as high as 8% in women without preterm AH (48 hours after delivery and up to 6 weeks after delivery) and up to 50% in women with a history of pre-eclampsia 6-12 weeks after delivery [55]. About 80% of maternal mortality occurs in the first week after delivery, and HDP remains one of its leading causes.

Women with normotensive pregnancies may have an increase in BP in the first day after delivery, which is attributed to the use of vasoactive drugs to promote uterine contraction, blood transfusion, intravenous fluid administration, use of nonsteroidal anti-inflammatory drugs for postpartum analgesia, physiologic uterine "autotransfusion phenomenon" or excessive fluid intake, and mobilization of extravascular fluid. Women with pre-eclampsia have a decreased diuresis within 12-36 hours after delivery due to delayed fluid redistribution associated with a greater drop in colloid osmotic pressure compared with normal pregnancy [56].

The distinction between postpartum exacerbation of prenatal AH and de novo postpartum pre-eclampsia is unclear. The duration of AH varies from a few days to 3 months, which may lead to the development of both metabolic abnormalities in the mother, such as insulin resistance and weight gain, and serious complications, such as stroke, seizures, and cardiomyopathy. Further studies addressing the underlying mechanisms of such pathology are needed to improve outcomes [55].

The rate of increase in the prenatal sFlt1/PlGF ratio is an independent predictor of AH persisting after delivery [57]. In addition, it has been shown that pre-eclampsia-related endothelial dysfunction and altered cerebrovascular autoregulation persist in the postpartum period and may increase the risk of postpartum AH.

A recent randomized controlled clinical trial showed that postpartum use of furosemide in women with AH was associated with a 60% reduction in the incidence of persistent AH on day 7 of postpartum period [49].

Another unusual phenotype of postpartum AH is the so-called "late postpartum AH" phenotype, which appears 6 months after delivery and subsides within a few months. The pathogenesis of this condition is unknown, but one possibility is that the resumption of postpartum menstruation increases BP by redistribution of excess progesterone and activation of mineralocorticoid receptors [9].

All antihypertensive agents used during pregnancy can be used in the postpartum period to achieve BP control. However, the use of angiotensin-converting enzyme inhibitors in the postpartum period should be allowed in women with concomitant cardiorenal diseases [4].

Postpartum hypertension and breastfeeding

Antihypertensive drugs are excreted into breast milk mainly in very low concentrations. Nifedipine and verapamil are considered compatible with breastfeeding. Although diuretics are not contraindicated, they may lead to decreased milk production. Similarly, alpha-methyldopa is compatible with breastfeeding, although it is not the drug of first choice in the post-

partum period because it increases the risk of postpartum depression. Angiotensin-converting enzyme inhibitors are compatible with breastfeeding and can be used in women with concomitant cardiovascular diseases or CKD. Angiotensin II receptor blockers are not currently recommended in lactation due to limited safety evidence [4].

Long-term cardiovascular consequences of hypertensive disorders during pregnancy

Several registries have demonstrated that pregnant women with HDP are at increased cardiovascular risk, which also includes the risk of developing persistent AH in the future. A meta-analysis of cohort studies showed that pre-eclampsia with more severe manifestations was associated with a higher prevalence of future morbidity compared to pre-eclampsia with less severe manifestations [58]. A genome-wide genetic association study using Mendelian randomization provided evidence supporting an association between HDP and a higher risk of coronary heart disease and stroke, which is only partially mediated by cardiometabolic factors [59]. Lifestyle modification is indicated in women with HDP to reduce the risk of complications in subsequent pregnancies, as well as to reduce the risk of CVD in general.

Conclusion

To date, the superiority of any of the commonly used antihypertensive agents in the treatment of HDP has not been demonstrated. A personalized approach based on the nature of the AH, its degree, results of daily and ambulatory BP monitoring, heart rate, presence and nature of associated conditions, age, race, and patient preferences appears to be more effective in better controlling BP, protecting women from AH complications and possible CVD after pregnancy.

Evidence-based consensus is needed on diagnostic and treatment thresholds, BP targets, and long-term CVD risk assessment. Future guidelines should avoid integrating historical, unsubstantiated viewpoints that impede the improvement of women's health during pregnancy and the postpartum period.

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Risk of cardiovascular complications in patients with type 1 diabetes mellitus: focus on dyslipidemia and hyperglycemia

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Type 1 diabetes mellitus (type 1 DM) is a polygenic multifactorial disease based on immune-mediated or idiopathic destruction of pancreatic ß-cells leading to absolute insulin deficiency. In 2021, there were approximately 8.4 million people with type 1 DM worldwide. By 2040, the total number of cases is estimated to increase to 13.5-17.4 million. In Russia, according to the study in 2021, there are about 336 thousand patients with type 1 DM, by 2040 the number of patients is expected to increase 2.5-fold. People with type 1 DM have a 4-8 times higher risk of cardiovascular diseases (CVD) than the rest of the population. The underlying mechanisms of CVD development in type 1 DM are poorly understood. Optimal glycemic control without significant hypoglycemia is mandatory to reduce CVD in patients with type 1 DM. Although hyperglycemia plays an important role, CVD risk remains high even in well-compensated patients with type 1 DM, suggesting that other cardiovascular risk factors may be involved. Further studies are needed to research the factors involved in the premature development of CVD in patients with type 1 DM.

Keywords: type 1 diabetes mellitus, risk, cardiovascular diseases, atherosclerosis, complications.

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Type 1 diabetes mellitus: definition and epidemiology

Type 1 diabetes mellitus (type 1 DM) is a polygenic multifactorial disease based on immune-mediated or idiopathic destruction of pancreatic ß-cells leading to absolute insulin deficiency. Type 1 DM develops in the presence of genetic predisposition, which requires environmental factors that act as a trigger of autoimmune damage of pancreatic ß-cells. Both infectious and non-infectious factors can act as triggers [1].

In most individuals, changes in insulin secretion and glucose tolerance occur within 1 to 3 months after islet antibodies are detected. After a critical mass (it is not known exactly which one) of ß-cells is destroyed, disease manifestation occurs with the need for administration of exogenous insulin. Manifestation occurs after a "latent phase" that lasts from several months to many years, which in individuals with a genetic predisposition and several types of antibodies can be considered as asymptomatic type 1 DM.

The main mechanisms of trigger factors action are: activation of polyclonal lymphocytes (e.g., by infectious agents); molecular mimicry, i.e., the identity of protein sequence regions of an infectious or chemical agent and autoantigens; and increased immunogenicity, which induces an immune response. These mechanisms eventually trigger the development of autoimmune processes and lead to the production of various autoantibodies, the most significant of which are autoantibodies to insulin (IAA), glutamate decarboxylase (GADA), islet cells (ICA), tyrosine phosphatase-like protein (IA-2A), zinc transporter (Zn-T8A) [1].

In 2021, there were approximately 8.4 million people with type 1 DM worldwide: of these, 18% were younger than 20 years of age, 64% were aged 20–59 years, and 19% were aged 60 years or older. It is estimated that one in five deaths from type 1 DM occurred in people younger than 25 years of age due to hypodiagnosis. Traditionally, type 1 DM has been considered a disease that begins at an early age. However, the findings will demonstrate that numerically more adults than children are diagnosed each year (316,000 vs. 194,000 new cases worldwide in 2021), with a median age at diagnosis of 32 years. About 35,000 patients with undiagnosed type 1 DM died within 12 months of symptom onset. One fifth (1.8 million) of people with type 1 DM lived in low-income and lower-middle-income countries. In Russia, according to the study in 2021, there are about 336 thousand patients with type 1 DM. By 2040, the authors project an increase in the total number of cases to 13.5–17.4 million (60–107% more than in 2021), with the greatest relative increase in low- and lower-middle-income countries. It is expected that by 2040, the number of people with type 1 DM will increase 2.5-fold [2].

Type 1 diabetes mellitus and risk of cardiovascular diseases

Individuals with type 1 DM have a 4–8 times higher risk of cardiovascular diseases (CVD) than the general population [3,4]. The pathophysiology of type 1 DM is characterized by rapid and early autoimmune destruction of pancreatic β-cells, which leads to hyperglycemia and the need for lifelong insulin replacement therapy. Hyperglycemia is one of the most important cardiovascular factors; The highest all-cause mortality in people with diabetes was at HbA1c levels above 9.0% (HR=1.69; 95% CI 1.09 to 2.66) and in people without diabetes was at HbA1c levels above 6.0% (HR=1.74; 95% CI 1.38 to 2.20). However, both diabetic and non-diabetic populations with lower HbA1c levels (below 6.0% HR=1.57; 95% CI 1.14 to 2.17 and below 5.0% HR=1.19; 95% CI 1.04 to 1.36, respectively) had higher all-cause mortality [5]. Consequently, it can be argued that individuals with type 1 DM have a high risk of CVD, which remains the leading cause of death for this patient group. Despite improved control of some classic risk factors (RF), including effective glycemic control, cardiovascular morbidity and mortality are

still significantly higher than in the general population. In routine clinical practice, estimation of cardiovascular risk (CVR) in individuals with type 1 DM using scales or equations is often inaccurate because much of the evidence comes from pooled samples of people with type 2 and type 1 DM or from extrapolation of studies conducted on patients with type 2 DM. Given that type 1 DM occurs at a young age, long-term exposure to the disease and its consequences (e.g., hyperglycemia, changes in lipid metabolism, or inflammation) have a detrimental impact on cardiovascular health. It is therefore crucial to have tools that allow early identification of individuals at higher risk of CVD and thus be able to make the most appropriate management decisions on a case-by-case basis.

Atherosclerosis is known to be responsible for the majority of cardiovascular events (CVE). Individuals with diabetes have pathophysiologic changes that contribute to the development of atherosclerosis and may imply greater vulnerability to atheromatous plaques. Carotid atherosclerosis in type 1 DM is associated with many pathologies and changes associated with a higher risk of CVD. These include; high systolic blood pressure (SBP) [6], pre-eclampsia [7, 8], retinopathy [9, 10], insulin resistance [11, 12], excessive body weight [13], increased left ventricular mass [14], cerebral microhemorrhages [15], cognitive impairment [16], inflammation and endothelial dysfunction [17, 18].

Screening of subclinical atherosclerosis using various methods, mainly imaging, has proven valuable for predicting cardiovascular events. Its use allows the determination of CVD risk category and, therefore, the individualization of therapeutic treatment. However, the available data on individuals with type 1 DM are insufficient to reevaluate CVR. In a cross-sectional study involving 289 adults with type 1 DM without symptoms of peripheral arterial disease (PAD), an ankle-brachial index (ABI) level < 0.9 was determined in 6% and ABI > 1.2 in 26%. In 15% of patients with abnormal ABI, carotid atherosclerosis was detected by ultrasound, and 40% had asymptomatic PAD confirmed by ultrasound Doppler ultrasonography of lower limb arteries and/or ankle brachial index [19].

One meta-analysis showed that patients with type 1 DM had significantly greater carotid intima-media thickness (standardized mean difference (SMD): 0.89; 95% confidence interval (CI) 0.69 to 1.09; P < 0.001)), lower endothelium-dependent vasodilation (SMD: –1.45%; 95% CI -1.74 to -1.17; P < 0.001), increased carotid pulse wave velocity (SMD: 0.57; 95% CI 0.03-1.11; P < 0.001), and decreased glyceryl trinitrate-mediated carotid dilatation (SMD: -1.11; 95% CI -1.55 to –0.66; P < 0.001) compared with a control group of patients without DM [20].

International studies on cardiovascular diseases in type 1 diabetes mellitus

Analysis of data from clinical trials investigating the association of type 1 DM and CVD reveals some patterns. In a study using data from the Swedish and Scottish registers, 4070 and 3429 (men and women) with type 1 diabetes in Scotland and 4014 and 3956 (men and women) in Sweden aged 65 years and older had a 100% risk of developing CVD ≥10% in the next 10 years [21]. Also, when determining the 5-year model of CVR from data of the Swedish National Registry in patients with type 1 DM, the adjusted risk ratios for fatal/non-fatal CVD were 2.76 (2.21–3.44) for duration of diabetes; 1.47 (1.21–1.78) for patient age at onset of CVD; 1.26 (1.09–1.45) for the logarithm of the ratio of total cholesterol to high-density lipoprotein cholesterol; 1.19 (1.03–1.38) for the logarithm of HbA1c; 1.76 (1.27-2.46) for tobacco smoking; 1.52 (1.10–2.10) for macroalbuminuria (> 200 μg/min); 3.51 (2.54–4.84) for prior CVD, with a C-index of 0.83, with sensitivity and specificity of 72% and 77%, respectively, for the upper quartile of predicted risk [22].

27,195 people with type 1 diabetes and 135,178 controls without diabetes participated in another study based on the Swedish National Registry. During the follow-up period, 959 people with type 1 diabetes and 1501 controls died (median follow-up was 10 years). The corresponding risk ratios for individuals who developed type 1 DM at age 26-30 years were 2.83 — of which 3.64 were for all-cause mortality: 2.78 (2.29–3.38) — cardiovascular mortality; 3.85 (3.05–4.87) — for non-cardiovascular mortality. For CVD: 6.08 — for coronary heart disease, 5.77 — for acute myocardial infarction (MI), 3.22 — for stroke, 5.07 — for heart failure, and 1.18 (0.79–1.77) — for atrial fibrillation. And excess risk differed up to fivefold between age groups. The highest overall incidence rate observed for all-cause mortality was 1.9 (95% CI 1.71–2.11) per 100,000 person-years for people with type 1 DM [23].

Experts from the Steno Diabetes Center in Gentofte, Denmark, also proposed a CVR model based on data from 4996 adult patients with type 1 DM from 2001

to 2013. The final CVD prediction model was validated on another population of 2119 patients with type 1 DM. Over a median follow-up period of 6.8 years (interquartile range 2.9–10.9), 793 (18.4%) patients developed CVD. For the 5-year risk of developing CVD, the discriminatory C-index was 0.826 (95% CI 0.807-0.845) for the primary study and a C-index of 0.803 (95% CI 0.767–0.839) for the follow-up data. The Hosmer-Lemeshow test showed good calibration (P >0.05) in both cohorts [24]. The Epidemiology of Diabetic Complications (EDC) prospective cohort study conducted in Pittsburgh, USA included patients at age 27 years with type 1 DM which started in childhood (aged <17 years) and a mean duration of diabetes of 19 years/median of 18 years. Major atherosclerotic CVE (CVD death, MI or stroke) were associated with diabetes duration, albumin excretion rate, baseline SBP, smoking and mean HbA1c [25].

Glycemic control and cardiovascular outcomes in type 1 diabetes mellitus

Data from the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study provided evidence-based conclusions about the beneficial effects of better glycemic control on cardiovascular events in patients with type 1 DM. In the DCCT study, the incidence of cardiovascular events was very low in patients receiving intensive therapy and fewer cardiovascular events were observed than in the conventionally treated group, although without statistically significant differences. After completion of DCCT, 93% of patients agreed to participate in the EDIC follow-up study. Age-adjusted higher levels of mean HbA 1c levels estimated by the Cox proportional hazards model were associated with an increased risk of cardiovascular death (hazard ratio (HR)=5.19), acute MI (HR = 4.98), stroke (HR = 3.07), congestive heart failure (HR = 4.82), transcatheter coronary angioplasty/aortocoronary artery bypass grafting (HR = 5.40), and angina pectoris (HR = 4.75), but not with asymptomatic myocardial infarction (HR = 1.12) during 29 years of follow-up. Compared with conventional therapy, intensive treatment reduced the risk of any CVE by 51%; the risk of non-fatal MI, stroke, or death from CVD by 34%. [26]. In the DCCT/EDIC study, higher HbA1c levels were strongly associated with age and arterial hypertension in relation to CVD risk (HR = 3.94), [27]. According to the results of a meta-analysis, intensive glycemic control maintains the long-term incidence of serious CVD, especially in patients with diabetes duration <10 years at baseline, without increasing their prevalence of CVD during follow-up > 10 years [28].

Correction of lipid metabolism disorders in type 1 diabetes mellitus

Although lipid and lipoprotein levels are often within the normal range in patients with type 1 DM, low-density lipoprotein cholesterol (LDL-C) levels are a significant predictor of CVE and mortality in patients with type 1 DM, especially those with early onset type 1 DM (aged ⩽10 years) and a duration of DM >20 years [29–31]. It is known that even type 1 DM patients with good glycemic control have some changes in lipoprotein composition and functionality, which may be important for CVD risk in type 1 DM patients. In a Korean study, it was shown that statin therapy, during a mean follow-up period of 9.9 ± 3.7 years in 931 patients with type 1 DM (8.5%) was associated with a reduced risk of ischemic stroke and MI (adjusted HR 0.76; 95% CI 0.66–0.88; p < 0.001) [32], at the same time, ezetimibe was more effective in lowering LDL-C in patients with type 1 DM compared with patients with type 2 DM, and in the group with type 1 DM, ezetimibe lowered LDL-C more than statins [33]. PCSK9 concentration is known to be increased in young people with type 1 DM [34], and PCSK9 inhibitors reduce LDL-C levels by 47.8% compared to placebo in patients with type 1 DM [35].

Conclusion

Type 1 DM is associated with a higher mortality rate from CVD than the general population. CVD are a major cause of this mortality, but the underlying mechanisms are poorly understood. Lifestyle interventions and optimal glycemic control without significant hypoglycemia are mandatory to reduce CVD in patients with type 1 DM. Although hyperglycemia plays an important role, CVD risk remains high even in well-controlled patients with type 1 DM, suggesting that other factors of CVR may be involved. Further studies are needed to research the factors involved in the premature development of CVD in patients with type 1 DM to better predict and stratify CVD risk, and to clarify the age at which treatment with modern cardiovascular drugs should be initiated in young patients with type 1 DM. Potential targets for new therapeutic approaches to prevent the development and progression of sub-

clinical atherosclerosis in patients with type 1 DM should be identified.

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Causes of formation of heart failure and difficulties in its diagnosing in patients with type 2 diabetes mellitus

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Diabetes mellitus (DM) is one of the fastest growing diseases worldwide, with prevalence reaching global pandemic proportions in recent decades. The significant increase in diabetes increases morbidity and mortality from cardiovascular complications, with heart failure (HF) being the most prominent one. In patients with DM, the presence of HF leads to a greater severity of clinical symptoms, increased hospitalization rates, poorer quality of life and poorer prognosis. HF with preserved ejection fraction is more common in type 2 DM, and its diagnosis is not an easy task. Special attention is paid to left ventricular diastolic dysfunction, which is an important prognostic factor of HF in the group of type 2 DM patients. This review article is devoted to the problem of interrelation and diagnosis of HF in patients with type 2 diabetes mellitus.

Keywords: Diabetes mellitus, heart failure, diastolic left ventricular dysfunction, diabetic cardiomyopathy, cardiovascular diseases.

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Introduction

According to the International Diabetes Federation, 643 million people will suffer from diabetes mellitus (DM) by 2030 and 783 million by 2045, of whom type 2 DM will account for 90% of cases, while the situation in developing countries is projected to be even more severe [1–3]. In the Russian Federation, as in most countries of the world, there is a trend of not only a continuous increase in the prevalence of diabetes, but also a significant expansion of morbidity — a shift in the debut of type 2 DM in the young age group with a steady increase in life expectancy with diabetes [4].

The commonality of risk factors (RF) for the development of diabetes and atherosclerotic cardiovascular diseases (ACVD), confirmed by studies based on Mendeleev randomization [5], determines the observed increase in the incidence of ACVD, accompanying the increase in the incidence of diabetes. At the same time, an increased risk of ACVD begins to form already at the stage of pre-diabetic hyperglycemia [6].

Over the last decades, a number of population studies (Sweden, Korea, USA, Canada, UK) have shown a dynamic decrease in the incidence of ACVD, cardiovascular and total mortality in DM, which demonstrates the fundamental possibility of influencing the prognosis of patients [7–9]. Undoubtedly, this positive trend is a consequence of many factors: better control of CVD RF due to active lifestyle changes or targeted drug therapy, including the use of drugs with cardioprotective effects, individualization of glycemic targets and wider prescription of sugar-lowering drugs with a low risk of hypoglycemia, multidisciplinary approach to patients with DM [10]. A recent systematic review of 57 articles with a total number of participants of about 4 million patients with DM demonstrated that the overall prevalence of ACVD is 32.2% [6, 11].

Thus, ACVD have been, are and will be the main pathology determining the prognosis of life in patients with diabetes. Reduced mortality due to acute cardiovascular events, increased years of life with diabetes, a steady trend of population aging, changing the spectrum of comorbid pathology in diabetes, contribute to the maintenance of a significant prevalence of the end stage of the cardiovascular continuum — heart failure (HF).

Heart failure in patients with type 2 diabetes mellitus: epidemiology and causes of formation

HF, as an inevitable final outcome of almost all CVD, is a growing epidemic, occupies leading positions in the structure of total mortality and permanent disability of patients, including those of working age. Regardless of HF phenotype among patients, the prevalence of type 2 DM significantly exceeds the population average (Table 1) [12]. According to the Russian EPOCH-CHF study (representative sample of the European part of the Russian Federation), the frequency of DM in the group of patients with HF was 16.6%, which is slightly lower than the corresponding number in most foreign studies [13]

Table 1. **Prevalence of type 2 DM in HF studies**

Study	Prevalence of type 2 DM
EPOCH-CHF [15]	16.6 %
HFrEF [12]	
PARADIGM-HF	35 %
SHIFT	30 %
EchoCRT	41 %
HF-ACTION	32 %
SENIORS	26 %
SOLVD	15 %
MERIT-HF	25 %
CHARM-Added	29 %
DIG-REF	28 %
HFpEF [12]	
I-Preserve	27 %
PEP-CHF	21 %
DIG-PEF	29 %
CHARM-Preserved	28 %
TOPCAT	33 %

Type 2 DM is associated with worse clinical status and increased cardiovascular and total mortality in both patients with HF with reduced (HFrEF) and HF with preserved ejection fraction (HFpEF) compared with HF patients without type 2 DM. HF is an independent predictor of fatal and non-fatal events in patients with type 2 DM [12]. Once HF is diagnosed in patients with type 2 DM over 65 years of age, the risk of mortality increases tenfold, and the 5-year survival rate decreases to 12.5% [14, 15].

By the age of over 40 years, 40-50% of patients with diabetes develop at least one CVD — unstable angina pectoris, myocardial infarction (MI), life-threatening heart rhythm disorders, with chronic heart failure (CHF) developing the fastest [16]. Type 2 DM

patients have a high incidence of silent forms of coronary heart disease (CHD) and myocardial infarction (MI) in combination with dyslipidemia, arterial hypertension (AH), smoking, aggravated family history of CVD, micro- or macroalbuminuria [17]. CHD and MI are associated with irreversible changes in the heart and represent a permanent substrate for the development and progression of HF [18]. Approximately 2/3 of deaths in patients with DM are related to ACVD: of these, 40% are due to CHD, about 10% to stroke, and 15% to other CVD, mainly HF. Among patients with diabetes, an increased risk of death from ACVD is observed in younger individuals with a long history of hyperglycemia and significant renal complications [19].

The leading factors of ACVD are considered to be diabetes and AH, which are regarded as unfavorable mutually aggravating diseases due to the common pathogenesis and causal relationships. AH is found in up to 80% of patients with type 2 DM [20]. The combination of DM and AH has a negative impact on left ventricular (LV) structure, myocardial dysfunction and arterial stiffness. AH and DM have been shown to be independently associated with impaired LV diastolic function (LVDF), with their coexistence leading to the most severe impact on LV diastolic mechanics and associated with higher filling pressures than in patients with either disease alone [21]. AH and DM are the main links of the cardiometabolic process, the outcome of which is ACVD.

Nevertheless, numerous population-based studies suggest a significantly increased risk of HF in patients with type 2 DM, unexplained by traditional risk factors such as obesity, AH, age, CHD, dyslipidemia, and heart valve disease. Even after adjusting for these factors, the relative risk of developing HF in patients with DM is 2-fold higher than the general population, which may be explained by the development of diabetic cardiomyopathy, most commonly associated with LV diastolic dysfunction (LVDD) and the development of HFpEF [3]. One study reported that optimal management of CVD RF in type 2 DM cannot neutralize the excess risk of HF, which remains high compared to patients without type 2 DM. These data suggest that HF preventive interventions are particularly challenging in type 2 DM [14].

In 2013, the American College of Cardiology, the American Heart Association, and the European Society of Cardiology (ESC), in collaboration with the European Association for the Study of Diabetes, defined diabetic cardiomyopathy (DCMP) as a clinical condition of ventricular dysfunction occurring in the absence of coronary atherosclerosis, AH, and heart valve pathology in patients with DM [22]. The term itself emphasizes the special etiology of cardiomyopathy, which distinguishes it from other forms. According to one of the largest foreign population studies, the prevalence of DCMP is 16.9% [23]. According to Russian researchers, the prevalence of DCMP is 18.7% [24].

The following are considered as the main factors of DCMP pathogenesis: direct effect of hyperglycemia, insulin resistance, mild inflammation, endothelial dysfunction, fibrosis, lipotoxicity and steatosis of myocardium, loss of myocardial "metabolic plasticity" [22, 25, 26]. The staged course of DCMP is characterized by progression from early stages with insignificant pathophysiological changes in the myocardium, normal LV myocardial mass to late manifestations with impaired diastolic and systolic function, symptoms/signs of HF [22, 27, 28]. At present, there are no reliable specific histologic signs, biochemical markers or clinical manifestations of early stages of DCMP [22]. The earliest objectively reported functional manifestation of DCMP is LVDD, which includes prolonged and delayed LV filling and relaxation in the absence of concomitant impairment of LV systolic function [29]. It is noteworthy that the existence of isolated LVDD as an indicator of DCMP has been disputed until recently, because patients in the early stages of DM were not subjected to routine careful assessment of diastolic function [30].

Many studies report that DCMP does not have any overt clinical manifestations and is more characterized by known symptoms/signs of HF with progression to late stage. Despite the rapid increase in the number of preclinical and clinical studies of DCMP in recent decades, the course of DCMP is still unclear. However, the feasibility of a multifactorial strategy in DCMP, as in HF, is implied [31]. It should be noted that DCMP is one of the most controversial aspects of cardiovascular manifestations of DM. The very existence of this phenomenon is not recognized by all expert communities in the field of cardiology [32]. Nevertheless, the possibility of DCMP development determines the necessity of HF screening in all patients with diabetes, regardless of the presence of CHD or AH.

Problems of diagnosing heart failure in patients with type 2 diabetes mellitus

It is known that HF is one of the most common initial manifestations of CVD in patients with type 2 DM and can manifest as HFpEF, HF with moderately reduced ejection fraction (HFmrEF) or HFrEF [32]. HFpEF has become the dominant form of HF worldwide in association with population aging and increasing prevalence of obesity, diabetes, and AH [33].

It has been shown that in the general population of patients with HF, the HFpEF phenotype is characterized by a slightly higher frequency of AH, obesity, and diabetes [34]. In particular, more than 40% of patients with HFpEF have type 2 DM, while in patients with type 2 DM, according to some data, HFpEF is more common [29]. In a Korean study, 64%, 14.4%, and 21.6% of patients with type 2 DM have HFpEF, HFmrEF, and HFrEF, respectively [35]. It is likely that the associations of DM and HFpEF objectively exist, but are not sufficiently accurate, primarily due to the difficulties in verifying HFpEF.

Among patients with DM, regular systematic screening at each visit for symptoms or signs of HF is recommended [32]. As in the general population of patients undergoing HF screening, the most problematic group is patients with diabetes and HFpEF. Currently, the following criteria must be met to make the diagnosis of HFpEF according to the recommendations of the European Society of Cardiology for the Diagnosis and Treatment of HF [36].

1. Presence of symptoms and signs of HF.
2. Preserved EF (≥50 %).
3. Elevated levels of natriuretic peptides (NUP).
4. Presence of heart LVDD.

The main problem in diagnosing HFpEF is its asymptomatic course in the early stages, and the similarity of symptoms between HF and other diseases (obesity, chronic obstructive pulmonary disease) further increases the risk of both hypo- and overdiagnosis of HF [29]. HFpEF is characterized by clinical manifestations similar to those of patients suffering from HFrEF [37]. The development of HF clinic in conditions of preserved LV ejection fraction (LVEF) can be explained only by one thing — difficulty of LV diastolic filling and compensatory increase of LV filling pressure [18].

The most widely used markers of myocardial stress for the diagnosis and prognosis of HF in everyday clinical practice are: brain natriuretic peptide (BNP) and N-terminal fragment of brain natriuretic propeptide (NT-proBNP) in blood. NT-proBNP and BNP below 125 pg/ml and 35 pg/ml, respectively, indicate the absence of HF [37]. The difficulty in identifying concentrations with positive diagnostic value is due to various clinical conditions that lead to elevated BNP regardless of the presence of HF (e.g., renal failure, atrial fibrillation (AF), hyperthyroidism, sacubitril/valsartan drug administration, acute coronary syndrome, mitral regurgitation, pulmonary disease, as well as older age, female gender) [38–40].

The most significant limitations of NUP sensitivity are that the established threshold values used for HF diagnosis are not applicable to overweight/obese people, which naturally characterizes the clinical status of patients with type 2 DM [41]. It has been demonstrated that an increase for each unit of body mass index is associated with a 9 pg/mL decrease in NUP [41, 42]. Nevertheless, potentially NUP have valuable prognostic value for both short-term and long-term cardiovascular events in individuals with DM [25]. The SAVOR-TIMI 53 study reported that individuals with diabetes without known CVD but with elevated NT-proBNP levels had a 3-fold higher risk of developing HF than those with known CVD and normal NT-proBNP levels [43]. Similarly, the ADVANCE study showed that NT-proBNP predicts the risk of HF, total mortality and CVD mortality in people with type 2 DM [44].

In view of the accumulated data, the updated European Society of Cardiology guidelines on CVD management in DM (2023) indicate that in patients with DM with one or more symptoms/signs of HF, NUP determination is one of the screening procedures, as in the general population. In general, NUP determination in patients with diabetes is recommended to exclude, but not to diagnose HF [25].

LVDD is defined by impaired relaxation and increased stiffness of heart chambers, which are manifested by increased filling pressure at rest or during exercise [45]. The independent prognostic value of LVDD, which is accompanied by a significant increase in the risk of death from CVD, regardless of LV size and systolic function, has been proved [18]. In the group of patients with type 2 DM, as in the general population, LVDD is an important prognostic factor of HF. About a quarter of asymptomatic patients with DM may have LVDD, and this group is found to have twice the risk of developing HF (37% vs. 17%) after 5

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Table 2. **LVDF assessment parameters in patients with preserved EF (ASE/EACVI, 2016)**

Parameter	Threshold value
E/e' mean	>14
e' septal/lateral	<7 cm/s/<10 cm/s
tricuspid regurgitation velocity	>2,8 m/s
LAVI	>34 ml/m^2

Note. E — LV early diastolic filling velocity, e' — early diastolic velocity of the mitral annulus fibrosus, LAVI — left atrium volume index.

years of follow-up. Echocardiography (EchoCG) is the most widely used imaging modality to assess cardiac function and cardiac morphology due to its non-invasive assessment of LV filling parameters, availability, and relatively low cost [46].

In accordance with the current guidelines of the American Society of Echocardiography and the European Society of Cardiovascular Imaging, LVDF assessment is based on a comprehensive analysis of a number of parameters obtained using two-dimensional and Doppler scanning modes (Table 2). Depending on the number of detected signs, LVDF can be defined as normal (in the presence of one sign), impaired (in the presence of three or more signs), or uncertain (in the presence of two signs) [47].

The limitations of the ASE/EACVI algorithm are related to the fact that it does not allow to assess LVDF in a number of clinical situations (AF, marked mitral regurgitation, marked calcification of the mitral valve, etc.), as well as due to technical and methodological limitations of EchoCG. The low diagnostic accuracy of the ASE/EACVI algorithm has been shown in a number of studies [48–50].

In 2019, the Association of Heart Failure Specialists proposed a new step-by-step algorithm for the diagnosis of HFpEF — HFA-PEFF, which is based on the identification of "major" and "minor" criteria defined according to their sensitivity and specificity [51] (Table 3). According to the ESC recommendations, a set of parameters is also used to confirm diastolic dysfunction (DD), highlighting the greater importance of determining the E/e' ratio as the best non-invasive way to assess LV filling pressure [36].

According to European and Russian guidelines for the diagnosis of HFpEF, diastolic stress test is an essential component of the diagnostic algorithm

Table 3. **Comparative characterization of echocardiographic criteria for the diagnosis of HFpEF in the ESC guidelines for the diagnosis and treatment of acute and chronic HF**

Echocardiographic criteria for HFpEF of the HFA-PEFF algorithm (2019) [52]			HFpEF criteria in the ESC guidelines (2021) [36]
	Functional	Morphological	Normal LVEF
Major	— e´sept. <7 cm/s or e´ lat. <10 cm/s (age <75 years)/ e´ sept. <5 cm/s or e´ lat. <7 cm/s (age ⩾ 75 years) or — E/e´ ⩾15 or — TV velocity >2,8 m/s (PASP>35 mmHg)	— LAVI >34 ml/m^2 (sinus rhythm)/ >40 ml/m^2 (AF); or — LVMMI ⩾149 g/m^2 (males) and ⩾ 122 g/m^2 (females) at RTI >0,42	Objective examination of heart function and structure: Main structural changes: LAVI >34 ml/m^2 and (or) LVMMI for males 115g/m^2, for females 95g/m^2 Main functional changes: ratio of peak early diastolic blood flow at the mitral valve to the mean value of mitral valve annulus velocity in early diastole of the interventricular septum and lateral wall (E/e') >9, mean value of mitral valve annulus velocity in early diastole of the interventricular septum and lateral wall (e')<9 cm/s In uncertain cases, perform stress test or invasive measurement of LV filling pressure
Minor	— E/e´ 9-14; or — GLS <16%;	— LAVI 29-34 ml/m^2 (sinus rhythm) и 34-40 ml/m^2 (AF) or — LVMMI ⩾115 g/m^2 (males) и ⩾ 95 g/m^2 (females) or — RTI >0,42 or — LV wall thickness ⩾12 mm.	
Each major criterion is worth 2 points and minor criteria is worth 1 point. Score ⩾5: HFpEF is considered confirmed Score 0-1: diagnosis of HFpEF is unlikely. Score 2-4: perform diastolic stress test or invasive assessment of hemodynamic parameters of LV filling.			

Notes. e´sept. — velocity of the early diastolic motion of the septal part of the mitral fibrous ring, e´lat. — velocity of early diastolic motion of the lateral part of the mitral fibrous ring, E — velocity of the early diastolic component of transmitral blood flow, RTI — relative thickness index, PASP — pulmonary artery systolic pressure.

for HFpEF [36, 37]. Diastolic stress test can be performed with the help of EchoCG, usually using a loading protocol on a semi-recumbent bicycle ergometer. When evaluating the results, such parameters as E/e' and tricuspid regurgitation velocity have the greatest diagnostic value.

Since the diagnosis of HFpEF based on echocardiographic data and NUP levels has limited sensitivity, algorithms with a scoring system have recently been proposed [33]. In particular, the H2FPEF scale (H2 FPEF score; **H**eavy, **H**ypertensive (H2); atrial **F**ibrillation; **P**ulmonary hypertesion; **E**lder; **F**illing pressure) consists of six variables evaluated dichotomously (if a sign is present, the corresponding score is counted):

— H2 (Body mass index >30 kg/m^2 = 2 points; use of ≥2 antihypertensive medications = 1 point);

— F (AF = 3 points);

— P (systolic pulmonary artery pressure> 35 mmHg = 1 point);

— E (age> 60 years = 1 point);

— F (E/e >9 = 1 point).

The points range from 0 to 9, and with a score of ≥ 6, HFpEF is detected with a probability of ≥90% [33].

The algorithm proposed by the ESC HF Study Association (HFA-PEFF score) consists of the following steps:

(1) Preliminary assessment

(2) EchoCG diagnostic examination (parameters include: e', E/e', left atrial volume index (LAVI), LVMMI, relative LV wall thickness, tricuspid regurgitation velocity, global longitudinal LV deformation and NUP.

(3) Extensive examination with functional testing in case of uncertainty (echocardiographic or invasive techniques).

(4) HF etiology determination.

When calculating HPA-HEFF, 2 points are given for each major criterion met, and 1 point is given for each minor criterion. A score of ≥5 points in step 2 allows the diagnosis of HFpEF, a score of ≤1 makes the diagnosis of HFpEF highly unlikely, and a score of 2–4 points requires proceeding to step 3 [52].

Thus, the accurate non-invasive diagnosis of LVDD remains a challenge, which leads to problems in the diagnosis of HFpEF. The search for examination methods that improve the diagnosis of HF in type 2 DM continues. A promising direction in LVDD diagnosis seems to be the use of three-dimensional EchoCG, as well as the assessment of LV myocardial longitudinal deformation by two-dimensional tracking of "gray scale" spots. The number of works confirming the possibility of LVDF assessment using these methods is constantly growing, but the number of them is still insufficient for them to be recommended for use in routine practice, which may well be explained by the need for special equipment, complex and expensive software. New biomarkers in addition to NUP (troponins, secreted proteins as markers of myocardial fibrosis [secreted Frizzled proteins], metabolites of intestinal microbiota [trimethylamine-N-oxide]) are actively investigated as a component of HFpEF diagnostic panel [25, 35]. Early diagnosis of HF in patients with type 2 DM is all the more important because with a new view on the mechanisms of development of cardioprotective effect of modern means of treatment of type 2 DM and HF (first of all, sodium glucose co-transporter type 2 inhibitors) the prospects of maximum early intervention for better treatment of this very serious complication of type 2 DM open up [52].

Conclusion

HF remains an important clinical problem for physicians managing patients with type 2 DM. Patients with HF and DM have a worse prognosis than patients without DM. AH and CHD are the main causes of HF in type 2 DM. Despite the growing interest in the study of DCMP, including the study of the role of DCMP in the development of HF, to date, there is no clear understanding of this pathological condition. The problem of the relationship between HF and type 2 DM is multifaceted and requires further continued research. The importance of HF screening in diabetes can hardly be overestimated, as the CVD continuum starts with such RF as diabetes, progresses to vasculopathy and myocardial dysfunction, and finally ends with cardiovascular death. HF screening is a must in the management of patients with type 2 DM. Diagnosis of HF in type 2 DM is performed according to generally accepted principles. Accurate non-invasive diagnosis of LVDD remains a challenge, which leads to problems in the diagnosis of HFpEF, one of the leading phenotypes of HF in patients with diabetes. We are actively searching for an optimal algorithm for diagnosing HF in patients with diabetes in the direction of improving echocardiographic criteria and searching for additional biomarkers of structural and functional changes of the heart.

Conflict of interests: none declared.

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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).

I. The International heart and vascular disease journal accepts the following manuscripts:

1) *Original papers* present the results of clinical studies. The word limit is 3.000 (including references, tables, and figure legends). The maximal number of references is 15. The structured abstract should contain 5 sections (**Aim, Material and Methods, Results, Conclusion**, and **Key words**), and be no longer than 300 words.

2) *Lectures*, or clinically oriented reviews, are written by experts in broader areas of medicine. Lectures could be focused on epidemiology, pathophysiology, diagnostics, treatment, and prevention. The word limit is 5.000 (including references, tables, and figure legends). The maximal reference number is 80. The unstructured abstract is no longer than 150 words.

3) *Literature reviews* are focused on more specific topics, compared to lectures. The word limit is 4.500 (including references, tables, and figure legends). The maximal reference number is 50. The unstructured abstract is up to 150 words.

4) *Clinical case* is a brief report on a complex diagnostic problem and its solution, or a description of

a rare clinical observation. The word limit is 600 (including references, tables, and figure legends). The maximal number of references is 5. No abstract is required.

5) *Clinical opinion* informs the readers on the topics of cardiovascular medicine and related disciplines. The word limit is 2.500 (including references, tables, and figure legends). The maximal number of references is 15.

The journal accepts for publication original phase 2, 3 and 4 clinical studies. Literature reviews should be based on sources not older than 5 years.

II. Information about the article, which includes the following sections, is combined into a single file "letter (cover)":

1) the manuscript is not under consideration in another edition has not been previously published contains a full disclosure of the conflict of interest all authors meet the criteria of authorship, it was read and approved the author (s) are responsible for the power of attorney submitted in the manuscript materials. 6) all contact information of the author responsible for correspondence information about previous publications of the authors on the same topic or pre-publication.

If the manuscript is a part of the thesis, it is necessary **to specify** the estimated terms of thesis defense.

The "letter of direction (accompanying)" should be made out on one or two sheets. Using the form of the official institution-at the choice of the author's team. In the address: "to The chief editor of the Russian cardiology journal, academician of RAS, Professor Oganov R. G.". The signatures of **all authors** should be placed at the bottom.

"Directional (cover) letter" is scanned. File format. jpeg attached as an additional file of the manuscript.

The absence of a letter or incomplete text of the letter (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

III. Registration on the Website and information about the authors.

Any of the authors can submit an article to the journal. Usually it is the one who then conducts correspondence with the editorial office and to whose mail notification letters come (when submitting a manuscript through the site, you can choose to send notifications to all authors).

The author registers on the site, entering his full name. In the form to be filled in when submitting an article, all authors and all additional information (places of work, positions, academic titles, institutions, ORCID – all authors) are indicated.

If the author has several places of work, it is written: 1. "The name of the institution..." 2. "Name of institution."... The name of the institution is written in abbreviated form, for example, Moscow state University, Moscow. Brackets are not put.

How to fill in the article metadata: all data that is entered in the "article metadata" must exactly match the data specified in the text of the article!

Authors ' names (you can not write in full, the format of the journal provides for the publication of names and initials. Therefore, in the "Windows", where the name and patronymic of the authors are written in capital letters with a dot (example: A.).

Names of institutions (write the official name. At the same time – there is a reduction of Federal, STATE, etc.; the quotation marks are placed; Ministry of health of Russia, a city without the letter G.

Positions and titles (using traditional abbreviations: PhD, senior researcher, leading researcher, PhD, C.b.N., MD), head reduces to the head., then write the full name of the laboratory/Department / Department; Director, head, Professor – is not reduced.

The order of the authors. Authors ' priority should be entered into the system in accordance with the order of the article. The movements are made by small arrows "top" / "bottom", which are located under the data of each of the authors. The data of the author responsible for the correspondence, put a dot in a circle denoting this information. Other authors point do not put.

Summary. Sections of the abstract should exactly match the sections prescribed In the rules for authors. If the sections are not correct, the Editors will ask to correct them. What the authors are currently publishing on the site will then be included in all systems after the final publication. Be careful!

Making literary references. Submitted article will not be reviewed until the correction of literary references in accordance with the rules for authors is made. The authors "forget" and somewhere to remove point (such inconsistencies can be corrected in the Revision), but if the design literature is radically different from what is required or present hyperlinks,

the Editors will not start with the article to eliminate errors.

Keyword. They are written with a small letter, separated by a semicolon. At the end put a point. In the text of the article the keywords are written separated by commas.

A file is prepared separately in Word, which is then sent as an additional file. The file must contain:

Title page of the manuscript. The title of the manuscript is written in capital letters, without hyphenation, in bold. Initials and surnames of authors-Ivanov I. I., Petrov P. p. the full name of organization (s) from which (s) there was a manuscript, the city, the country is Given. Footnotes are in Arabic numerals after the authors ' names and before the names of institutions.

Example of design:

THE PREVALENCE OF RISK FACTORS OF NONCOMMUNICABLE DISEASES IN THE RUSSIAN POPULATION IN 2012–2013. THE RESEARCH RESULTS OF THE ESSE-RF

Muromtseva G.A.[1], Kontsevaya A.V.[1], Konstantinov V.V. [1], Artamonova G.V. [2], Galaganova T.M. [3],...

[1] FGBU State research center of preventive medicine of the Ministry of health of Russia, Moscow;

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

[3] RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

Information about the authors, where indicated: full name, place of work of all authors, their positions, ORCID; full contact information is required for one (or more) of the author and includes e-mail, available phone number.

All members of the group of authors should meet all four criteria of authorship set forth in the ICMJE recommendations: 1) concept and design development or data analysis and interpretation, and 2) manuscript justification or verification of critical intellectual content, and 3) final approval for publication of the manuscript, and 4) consent to be responsible for all aspects of the work, and assume that issues relating to the thoroughness and diligent execution of any part of the study submitted are duly investigated and resolved. This information should also be contained in the document.

If the submitted material has authors who do not meet the criteria of authorship, but have made some contribution to the work, they should be listed in this document and at the end of the article in the section of Acknowledgements.

Information on conflict of interest / funding.

The section contains the disclosure by all authors of possible relations with industrial and financial organizations that may lead to a conflict of interest in connection with the material presented in the manuscript. It is desirable to list the sources of funding for the work. If there is no conflict of interest, it is written: "Conflict of interest is not declared." Information on the existence of a conflict of interest should also be reflected in the Conflict of interest section at the end of the article.

Information about grants. Should be mentioned at the end of the article in the section Acknowledgements and at the end of the section Material and methods – with a full description of the role of the source of funding in the performance of work (design, information collection, analysis, data interpretation, etc.).

Information and ethics in the study.

Example of design:

The study was carried out in accordance with the standards of good clinical Practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The study Protocol was approved by the Ethical committees of all participating clinical centers. Prior to being included in the study, written informed consent was obtained from all participants.

This information should also be reflected in the Material and methods section of the article.

All additional information (permits, questionnaires, etc.) can be requested from the authors in addition to the preparation of the work for printing.

Information on overlapping publications (if available).

Copyright. The use of any material (tables, figures) marked with a copyright icon in the article should be confirmed by a special permission from the author or publisher.

Information about the obtained consent in patients for the study.

Obtaining consent from patients for the study should also be reflected in the Material and methods.

For all clinical trials: information about the registration and placement of data on the study in any public register of clinical trials. The term "clinical study" refers to any research project that affects people (or groups of subjects) with/or without a comparative control group, studies the interaction between inter-

ventions to improve health or the results obtained. The world health organization offers the primary register: International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/network/primary/en/index.html). The clinical study is considered to be reliable in a group of more than 20 patients.

The number of words in the article (excluding summaries, sources of literature, figure captions and tables), the number of tables and figures.

The absence of an information file or incomplete text (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

IV. Manusctipt submision check-list

Since the main file of the manuscript is automatically sent to the reviewer for» blind review», it should not contain the names of the authors and institutions. The file contains only the following sections:

Article title
Summary with key words
List of abbreviations
Text
Acknowledgements (if any)
List of references
Tables, figures (if they can be embedded in the text of Word format).

The article title is written in capital letters (PREVALENCE of RISK FACTORS...), the end point is not needed. The title should clearly reflect the purpose of the work.

Summary with key words-sections are drawn up each with a separate line, highlighted in bold. The abstract should contain only those sections that are described in the rules for authors. For example, there is no section "Relevance" in the summary. The authors prescribe the relevance of their work in the introductory section of the manuscript.

List of abbreviations – when compiling a list of abbreviations to the article, including text, tables and figures, only those used by the author 3 or more times are included. Usually shrink often used in manuscripts of the terms (e.g., hypertension, CHF FC) and title of clinical trials (SOLVD, TIMI, HOPE).

The first reference to an abbreviation is always accompanied by the full spelling of the abbreviated concept, and the abbreviation is indicated in brackets. For example, blood pressure (BP); heart rate (HR). Capital letters are more often used to denote abbreviations. If abbreviations are used only in tables and figures, and are not used in the text, they should not be included in the list of abbreviations, but should be given a transcript in the note to the table or figure. The summary of the article, as a separate document, is subject to the same rules as the article (abbreviations are made when they are used 3 or more times).

Abbreviations should be generally accepted and understandable to the reader, in accordance with the generally accepted norms in the scientific literature. Undesirable abbreviations that coincide in writing with others that have a different meaning.

Abbreviations in the list of abbreviations are written in alphabetical order, separated by commas, in solid text, using "dash". **Example of design:** BP-blood pressure, HR-heart rate.

Text – the text of the manuscript of the original works should be structured: Introduction, Material and methods, Results, Discussion and Conclusion. The text of reviews and lectures can be unstructured.

Text is printed on A4 sheet, font size – 12 pt, line spacing – 1.5, margins 2 cm on all sides. The system of SI units is used for processing the material, the% sign is put through a space from the number, the value of p is written with a semicolon: $p < 0.0001$; the value of n is written with a small letter (n=20); signs >, <, ±, =, +, – when numerical values are written without a space; the value of "year" or "year" is issued – 2014 or 2002 – 2014.

The article should be carefully verified by the author (s). The authors are responsible for the correctness of citation, doses and other factual materials.

Introduction – it is necessary to describe the context and prerequisites of the work (what is the essence of the problem and its significance). It sets certain goals or describes the object of the study, or a hypothesis that needs to be tested by comparison or observation. Only those sources that directly indicate the problem are cited.

Statistics – all published materials are reviewed by an expert in statistics and must meet "Uniform requirements for manuscripts submitted to biomedical journals" (Uniform Requirements for Manuscripts Submitted to Biomedical Journals, Ann Intern Med 1997, 126: 36 – 47). In the preparation of the statistical part of the work it is recommended to use special guidelines, for example, the European journal of cardiology: www.oxfordjournals.org/our_journals/eurheartj/for_authors/stat_guide.html

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.

Making graphs, diagrams and drawings – tables and figures should provide the reader with visual information, be interesting and educational. They should be placed after the text of the article, as the reviewer and editor look at the manuscript as a whole. However, to print in the journal (at the stage of creating a layout) graphics, diagrams and drawings are required in electronic form in the formats "MS Excel", "Adobe Illustrator", "Corel Draw", "MS PowerPoint", photos with a resolution of at least 300 dpi.

The names of the graphs and figures, as well as notes to them should be placed under the figure/graph or placed at the end of the article.

These files are referred to as additional files. Figures should not repeat the materials of the tables.

Tables should contain the compressed, necessary data. Each table is placed at the end of the text (after the list of references) with the number, name and explanation (note, abbreviations).

The tables should clearly indicate the dimension of the indicators and the form of data (M±m; M±SD; Me; Mo; percentiles, etc.). All figures, totals and percentages should be carefully verified, and also correspond to the mention in the text. The explanatory notes are given below the table, if necessary. The footnotes must be in the following order: *, †, §, ||, ¶, #, **, †† etc.

Abbreviations should be listed in a footnote below the table in alphabetical order (for tables its list of abbreviations!).

Each first mention of a figure or table in the text is highlighted with a yellow marker. If a reference to a figure or table is included in the sentence, the full spelling of the word «figure 1», «table 1» is used; if the words are enclosed in brackets, the abbreviation is used (Fig. 1), (table. 1).

Providing the main file of the manuscript with the names of the authors or institutions is the basis for refusal to accept the manuscript for consideration.

V. The list of references.

In the form to fill in when submitting the article provides a list of cited literature (section – Literature).

Literary references are listed in the order of citation in the manuscript. The text refers to the serial number of the cited work in square brackets [1] or [1, 2]. Each link in the list is on a new line. All documents referred to in the text should be included in the list of references.

References to works that are not in the list of references and Vice versa, references to unpublished works, as well as to works of many years ago (>10 years) are not allowed. The only exceptions are rare highly informative works. Especially close attention to this item, please pay to those authors who submit "literature Review".

The bibliographic description contains the names of the authors up to three, after which, for domestic publications should indicate "et al.", for foreign – "et al." When citing articles from journals indicate in the following order the output: the name and initials of the authors, the name of the source, year, volume, number, pages (from and to). When citing articles from the collections indicate the output: name, initials, title, title of the collection, place of publication, year of publication, page (from and to).

If you want to make a quotation of the authors ' names in the text, you must specify the name of the first author with the initials, the year of work. Example design: Smith AA, et al. (2018).

With the purpose of increase of citation in the journal is the transliteration of Russian sources with the use of the official languages in the following order: the authors and the journal title is transliterated in the Latin alphabet, and the name of the article is semantic transliteration (translation into English). The name of the source where the work is published is transliterated in Latin if the source (journal) does not have an official name in English).

All Russian-language sources of literature should be presented in the transliterated version of the model given below.

The author (s) are responsible for the correctness of the data given in the references.

The list of references should correspond to the format recommended by the American National organization For information standards (national Information Standards organization – NISO), adopted by the National Library of Medicine (NLM) for databases (Library's MEDLINE/PubMed database) NLM: http://www.nlm.nih.gov/citingmedicine Oh? The names of periodicals may be abbreviated. Usually this

form of writing is accepted by the publisher; it can be found on the website of the publisher, or in the list of abbreviations Index Medicus.

Mandatory all articles DOI specified, all books ISBN. References to dissertations, patents, theses and any collections without output and ISBN are not accepted.

Examples of link design:

Article citation:

Smith A, Jones B, Clements S. Clinical translation of tissue-engineered airway. Lancet. 2008;372:1201–09. DOI:10.00000/0000-0000-.

Russian-language sources with transliteration:

Bart BYa, Larina VN, Brodskyi MS, et al. Cardiac remodelling and clinical prognosis in patient with chronic heart failure and complete left bundle branch block. Russ J Cardiol. 2011;6:4–8. Russian. Барт Б. Я., Ларина В. Н., Бродский М. С., и др. Ремоделирование сердца и прогноз больных с хронической сердечной недостаточностью при наличии полной блокады левой ножки пучка Гиса. Российский кардиологический журнал. 2011;6:4–8. DOI:10.15829/1560-4071-2011-6-4-8.

Book:

Shlyakhto EV, Konradi AO, Tsyrlin VA. The autonomic nervous system and hypertension. SPb.: Meditsinskoe izdatel'stvo; 2008. Russian. Шляхто Е. В., Конради А. О., Цырлин В. А. Вегетативная нервная система и артериальная гипертензия. СПб.: Медицинское издательство; 2008. ISBN 0000–0000.

Chapter:

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.

Russian chapter:

Diagnostics and treatment of chronic heart failure. In. National clinical guidelines 4th ed. Moscow: Silicea-Polygraf; 2011. pp.203–93. Russian Диагностика и лечение хронической сердечной недостаточности. В кн: Национальные клинические рекомендации. 4-е издание. М.: Силицея-Полиграф; 2011.сс.203–96. ISBN 0000–0000.

Webpage:

Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

All sources of literature are checked for correctness through the system of the Russian electronic library. Significant errors in citation or duplication of the source are the reason for the return of the manuscript to the authors for revision.

VI. Preparation of manuscript.

The author prepares the following documents to upload the manuscript to the site:

The main file Is the text of the article (the system renames it after loading, so it does not matter how it is called).

Additional files-Directional (accompanying) letter, Information file with the Title page, information about the authors and disclosure of conflicts of interest, files with pictures.

For more information on placing articles on the website you can read http://cardiovascular.elpub.ru/jour/announcement

VII. Copyright and publishing policy.

This section regulates the relationship between the editorial Office (Publisher) of *International heart and vascular disease journal* (the "editorial Office") and the author or group of authors who submitted their manuscript for publication in the *International heart and vascular disease journal* (the "Author").

The author, by sending the article to the Editor, agrees that the editorial Board of the journal shall be transferred to the exclusive property rights to use the manuscript (transferred to the Editorial Board of the journal material, including such protected objects of copyright as photos of the author, drawings, diagrams, tables, etc.), including the reproduction in print and on the Internet; distribution; translation into any languages of the peoples of the world; export and import of copies of the journal with the article of the Author for distribution, to bring to the public.

The editorial Board reserves the right to reduce and edit the materials of the manuscript, to carry out scientific editing, to reduce and correct articles, to change the design of graphs, drawings and tables to bring into line with the design of the journal, without changing the meaning of the information provided.

When using the article, the editors have the right to supply it with any illustrated material, advertising and allow third parties to do so.

The editorial Board has the right to assign the rights received from the Author to third parties and has the right to prohibit third parties from any use of materials published in the journal for commercial purposes.

The author guarantees that he has exclusive rights to use the submitted material. In case of violation of this guarantee and the presentation of claims to the editorial Board, the Author independently and at his own expense undertakes to settle all claims. The editorial Board is not responsible to third parties for violation of the Author's guarantees.

The Author retains the right to use the published material, its fragments and parts for personal, including scientific and teaching purposes.

The Author transfers the above rights to the Editors without limitation of their validity period, in the territory of all countries of the world without limitation, including the territory of the Russian Federation.

The rights to the manuscript are considered to be transferred By the author of the editorial Office from the moment of sending an information letter about the acceptance of the manuscript to the press.

Reprinting of materials published in the journal by other individuals and legal entities is possible only with the written permission of the editorial Board, with the obligatory indication of the journal name, number and year of publication.

The editors are not responsible for the accuracy of the information provided by the Author.

The author, sending the manuscript to the Editor, gives permission to use and process personal data.

The editorial Board reserves the right to reduce and correct the articles, to change the design of graphs, figures and tables to comply with the standard of the journal, without changing the meaning of the information provided. In case of untimely response of the author (s) to the request of the editorial Board, the editorial Board may at its discretion make changes to the article or refuse to publish.

Sending to the editor of works that have already been sent to other publications or printed in them is absolutely not allowed. The editors are not responsible for the accuracy of the information provided by the authors. Articles sent in violation of the rules of registration are not accepted by the editorial Board for consideration.

VIII. The procedure for rewiewing manuscripts

The manuscript should be sent in electronic form to the Editor through the website – http://www.heart-vdj.com. The manuscript should be drawn up in accordance with these requirements for scientific articles submitted for publication in the journal.

The author is sent a notification letter of receipt of the manuscript with the number (ID), which will be used in subsequent correspondence. The author can track the stages of work on his manuscript through the site. Since the process of bringing the manuscript to the necessary standards takes enough expert time, the payment for the initial review of the article was introduced, which the author (s) are required to carry out after the article is posted on the site.

The manuscript must pass the primary selection: the Editorial Board has the right to refuse publication or send comments to the article, which must be corrected by the Author before reviewing.

– checking the completeness of the manuscript: if you do not comply with the requirements of the Rules for the authors to complete the manuscript or its design, the Editors have the right to refuse to publish or in writing to require to send the missing materials or to correct the version already downloaded to the site.

– Manuscripts are checked in the "Antiplagiat" system. The originality of the manuscript should be at least 75 %. We expect manuscripts submitted for publication to be written in an original style that involves new thinking without the use of previously published text. Manuscript with originality below 75 % shall not be admissible.

All manuscripts submitted to the journal are sent to one of the permanent reviewers or an independent expert according to the profile of the research.

The review process is anonymous both for the Author and for the reviewers. The manuscript is sent to the reviewer without the names of the authors and the name of the institution.

The editorial Board informs the Author of the results of the review by e-mail.

If the reviewer makes a conclusion about the possibility of publication of the article and does not make significant corrections, the article is given to the expert on statistics and after a positive report is accepted for further work.

If the reviewer makes a conclusion about the possibility of publication of the article and gives instructions on the need for its correction, the Editorial Board sends the review to the Author with a proposal to take into account the recommendations of the reviewer in the preparation of a new version of the ar-

ticle or to refute them. In this case, the Author needs to make changes to the last version of the article file, which is located on the site (download file from the site, make changes and place the corrected article again, after removing the primary (uncorrected) version). The revised article is re-sent for review, and the conclusion is given that all the recommendations of the reviewer were taken into account. After receiving a positive response of the reviewer, the article is given to the expert on statistics and after a positive report is accepted for further work.

If the reviewer makes a conclusion about the impossibility of publication of the article. The author of the reviewed work is given the opportunity to read the text of the review, if he does not agree with the conclusions of the reviewer. In case of disagreement with the opinion of the reviewer, the Author has the right to provide a reasoned response to the Editor. The article can be sent for re-review or for approval to the editorial Board. The editorial Board or its authorized editor shall send its response to the Author.

All manuscripts that have been reviewed and evaluated by an expert in statistics are submitted to the editorial Board, which decides on the publication. After the decision on the admission of article for publication, the Editorial office inserts the publication of the article in terms of publications. Information about the annual (thematic) plan of publications is placed on the website of the journal.

The decision to publish a manuscript is made solely on the basis of its significance, originality, clarity of presentation and compliance of the research topic with the direction of the journal. Reports on studies in which negative results are obtained or the provisions of previously published articles are challenged are considered on General grounds.

Original reviews are kept in the Editorial office for 5 years from the date of publication.

In case of a decision to refuse to publish an article, its archive copy remains in the electronic system of the editorial Board, but access to it by editors or reviewers is closed.

IX. The manner of publication of manuscripts

According to the requirements of the Higher attestation Commission, the journal provides priority for post-graduate and doctoral works, the period of their publication depends on the expected date of protection, which the authors must specify in the primary documents attached to the manuscript.

Each issue of the journal is formed by a separate Executive editor appointed by the editor-in-Chief and/or editorial Board. It is the responsibility of the editor-in-charge to select high-quality articles for publication, and he can be guided by both thematic principles and a separate scientific direction.

All selected articles are submitted to the scientific editor and proofreader. After creating the layout of the article and editing it, the article will be available to the Author through the site. At this stage, it will be possible to send comments on the text of the article. The author is obliged to send his / her consent to the publication or his / her comments within the established time specified in the cover letter.

The editorial office does not send the author's copy by mail or PDF of the article by e-mail, access to the published numbers is open.

Subscription to the printed version is carried out by half a year (through subscription agencies).

X. After the publication in the journal

Information on publication is distributed in the following scientific citation databases: Russian science citation index, CYBERLENINKA and others. The article is assigned a DOI index and the full text is publicly available on the journal's website.

Information about the publication of the issue is distributed by mailing of The Cardioprogress Foundation and in social networks.

We expect the authors of the articles to actively make efforts to bring the results of their research to the public, namely: to have a personal page on the Internet (personal page), to monitor and update your profile ORCID and RecsearcherID, to involve colleagues in their work through social networks.

XI. Revocation or correction of articles

The full text of the journal's policy on Revocation and correction of articles is available in the information section on the website. The editors follow COPE Recommendations issued by the Committee on publishing ethics (COPE) – http://www.publicationethics.org.uk. in cases:

Editors of journals should consider the opinion of the publication, if:

they have clear evidence of the unreliability of the information published, either as a result of conscious actions (for example, falsification of data), or due to good faith errors (for example, errors in calculations or experiments); the findings have been previously published in another publication and there is no proper reference, authorization and justification for re-publication (i.e. duplicate publication).); it is plagiarism; describes unethical research.

Editors of journals should consider the concerns, if:

they received information about the authors ' inappropriate actions, but there is no clear evidence of such behavior; there are arguments that the results of the work are unreliable, and the institution in which the authors work is not going to find out the truth; they believe that the investigation into the alleged violations committed by the authors in connection with the publication has either not been or will not be fair, impartial and convincing; the authors ' violations are being investigated, but the results are not expected soon enough.

Journal editors should consider making amendments if:

a small part of the rest of the high-quality publication is unreliable (especially because of conscientious errors); the list of authors / sponsors contains errors (i.e., it does not contain someone who is worthy to be an author, or a person who does not meet the authorship criteria).

In most cases, a review is not appropriate if:

authorship needs to be changed, but there is no reason to doubt the validity of the findings.

XII. Position E-log backup (if journal is no longer published)

The purpose of backup is to prevent loss of information in case of hardware, software, critical and crisis situations, etc.

Information of the following main categories is subject to backup: – personal information of authors (personal directories on file servers); – pdf of published articles; – information about literary links to the article in the DOI system.

All this information is publicly available in The system of the Russian citation index on the website of the Electronic library www.elibrary.ru

XIII. Journal subscription

Information on subscriptions is available on the journal website in the section "Subscription":

XIV. Journal subscription

The name of the journal in English is International heart and vascular disease journal.

Official sites where information about the journal is placed:

http://www.heart-vdj.com

On the reception of the articles, making decisions about publication, reviews – mmamedov@mail.ru

On organizational issues (working with the site, subscription) – editor.ihvdj@gmail.com

Editorial office:

Room 213, Building 2, Prospect Gostinichny 6, Moscow 127106, Russia

e-mail: editor.ihvdj@gmail.com

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

The manuscripts are accepted if has not been published or submitted for publication elsewhere.

The file of the submitted article is in the format of a Microsoft Word document. It does not contain the names of the authors and institutions.

Files with a letter of transmittal and General information have been prepared for upload to the site.

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