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Trends in cardiovascular mortality
in CIS countries between 1990
and 2022

Pre-heart failure in young
men with metabolic
syndrome: clinical
aspects, diagnosis and
management strategies

Modern neuroimaging
and reperfusion therapy
in the management
of wake-up stroke

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Editor's Welcome

Dear colleagues!

We present to your attention the forty-eighth issue of the International Heart and Vascular Disease Journal, which features leading, original, and review articles.

The "Leading Article" section presents a review article analyzing mortality from cardiovascular diseases (CVD) and its trends from 1990 to 2022 in the countries of the Commonwealth of Independent States (CIS). Across all CIS countries, average CVD mortality decreased by 20.4% over the entire observation period, which is

three times lower than in Western European countries, where the reduction reached 60.2%. According to the authors, reducing cardiovascular morbidity and mortality in CIS countries requires the development of effective, innovative, diagnostic, therapeutic, and rehabilitative technologies for prevention and control that are accessible to the majority of the population.

The "Original Articles" section features two studies. The first article examines specific characteristics of physical activity and work capacity among individuals engaged in expedition-based rotational work under Arctic conditions. The study sample consisted of 750 men aged 25–54 years. Less than one fifth of all rotational workers participating in the study regularly engaged in physical exercise, and less than one quarter spent their leisure time passively. Over the past year, age-related trends were identified not only toward a decline in physical activity but also toward an increase in work capacity during the third decade of life. The second article is experimental in nature. It investigates the effects of meldonium on cardiomyocyte reproduction in the setting of hypertrophy and polyploidy, which could potentially expand the range and reliability of cardiac adaptation to overload. The experimental animals were male Wistar rats (total $n = 18$). The authors demonstrated that the use of meldonium during intense physical activity leads to reduced cellular hypertrophy, an increased proportion of binucleated cardiomyocytes, and a decreased number of tetraploid mononuclear cells.

The "Review Articles" section presents three papers. In the first review, the authors analyze current literature data on the pathogenesis, diagnostic approaches, and treatment of wake-up stroke. Management of the hyperacute phase of acute cerebrovascular events has evolved significantly due to improved patient selection methods, advances in instrumental diagnostics, and increased availability of new devices designed for thrombectomy procedures. The second review shows that atrial dysfunction in young men with metabolic syndrome represents a subclinical stage of cardiovascular damage; early diagnosis and timely correction of risk factors can prevent progression to clinically overt heart failure and reduce long-term cardiovascular risk. The third review provides an overview of major clinical trials evaluating the impact of sodium–glucose cotransporter 2 inhibitors on reducing cardiovascular risk and mortality from chronic heart failure, primarily through their beneficial effects on the course of chronic heart failure.

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

Review of international medical news

Experts studied the long-term effects of aspirin in older adults without a history of cardiovascular disease.

Data from 15,668 older individuals were analyzed. At study entry, none had cardiovascular disease, dementia, or physical limitations.

The analysis showed that over the combined follow-up period, including the trial and post-trial phases, aspirin did not provide a significant reduction in the risk of major cardiovascular events compared with placebo. In the post-trial period, aspirin use was associated with an 18% increase in stroke incidence and a 25% increase in myocardial infarction.

According to the European Heart Journal

Scientists studied the effect of daily coffee consumption on the recurrence of atrial fibrillation and atrial flutter after successful cardioversion.

Participants were randomized to daily coffee consumption (at least one cup per day) or complete abstinence from coffee and caffeine for six months. The frequency of clinically confirmed recurrences was assessed.

Participants who consumed coffee experienced fewer recurrences of atrial fibrillation regardless of baseline coffee intake. Researchers noted that moderate coffee consumption did not worsen the disease course or increase the risk of complications.

According to the JAMA journal

Researchers from Japan evaluated the effect of statins on the risk of subarachnoid hemorrhage.

Data from 3,498 patients with newly diagnosed subarachnoid hemorrhage and 14,000 control participants were analyzed.

The analysis showed that statin use was associated with a 19% reduction in the risk of subarachnoid hemorrhage. The effect was particularly pronounced in patients with a history of hypertension or cerebrovascular disease.

The authors concluded that statins are associated with a reduced risk of subarachnoid hemorrhage, especially in patients with hypertension.

According to the Stroke journal

Researchers studied the effect of nighttime and daytime light exposure on the risk of cardiovascular disease.

Data from 88,905 UK Biobank participants (mean age 62 years) were analyzed. Participants wore wrist-based light sensors for one week to record daytime and nighttime light exposure. Over nearly eight years of follow-up, cases of stroke, heart failure, myocardial infarction, coronary heart disease, and arrhythmias were recorded.

The analysis showed that individuals exposed to the brightest nighttime light had a 1.32-fold higher

risk of coronary heart disease, a 1.56-fold higher risk of heart failure, and a 1.32- and 1.28-fold higher risk of atrial fibrillation and stroke, respectively.

According to the JAMA Network Open journal

Researchers evaluated the association between premenstrual disorders and the risk of cardiovascular disease.

Data from 135,000 women with premenstrual disorders were analyzed. All participants had reached menarche but had not yet entered menopause at the time of inclusion.

The analysis showed that women with premenstrual disorders had an 11% higher risk of any cardiovascular disease compared with women without such disorders.

Premenstrual disorders were also associated with hypertension, coronary heart disease, and cerebrovascular disease, and additionally increased the risk of arrhythmia by 1.31-fold and ischemic stroke by 1.27-fold.

According to the Nature journal

Experts presented a report on the impact of nicotine on the cardiovascular system.

The authors stated that nicotine is a potent toxin for the heart and blood vessels regardless of the form of consumption. Harmful effects were observed with the use of e-cigarettes, heated tobacco products, hookahs, cigars, and oral nicotine pouches.

The report also noted that the long-term effects of new nicotine products are insufficiently studied, and the combined use of multiple nicotine forms complicates assessment of each product's contribution to cardiovascular risk.

According to the European Heart Journal

Researchers from Australia studied the relationship between step count, walking speed, and cardiovascular risk in people with hypertension.

Data from 32,192 individuals with high blood pressure from the UK Biobank were analyzed. The mean age was 64 years. All participants wore a wrist accelerometer for seven days to measure step count and speed.

The analysis showed that each additional 1,000 steps per day (up to 10,000) was associated with a 17% reduction in the risk of major adverse cardiovascular events. The risk of heart failure decreased by 22%, myocardial infarction by 9%, and stroke by 24%.

The authors concluded that increasing step count was beneficial for people with hypertension, including those who walked fewer than 10,000 steps per day.

According to the ESC portal

Trends in cardiovascular mortality in CIS countries between 1990 and 2022

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Objective. The aim of this analytical review is to analyze cardiovascular disease (CVD) mortality and its trends from 1990 to 2022 in the countries of the Commonwealth of Independent States (CIS).

Methods. This review analyzes data from CIS countries belonging to the Eastern European and Central Asian regions. The study employed data from the research group of the “Global Burden of Disease” (GBD) project. The GBD generates time series of comprehensive health metrics, including CVD prevalence, cause-specific mortality rates (CSMR), years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life years (DALYs). Based on GBD results, we analyzed CVD mortality from 1990 to 2022 in the Central Asian and Eastern European regions, whose countries joined the CIS in 1991–1994.

Results. In 2022, the age-standardized CVD mortality rates among CIS countries in the Central Asian region ranged from 331.8 to 542.3 per 100,000 population. The 1.6-fold difference between the minimum and maximum rates indicates high variability within the region. From 1990 to 2022, over 32 years, CVD mortality in the Central Asian region decreased by 16.5%.

Among the CIS countries in Eastern Europe in 2022, the age-standardized CVD mortality rates ranged from 215.0 (Estonia) to 553.0 (Ukraine) per 100,000 population; the difference between the minimum and maximum rates was more than 2.6-fold. Over 32 years, CVD mortality in these countries decreased by 24.3%. Eastern European countries ranked first among 21 global regions in terms of age-standardized CVD mortality in both 1990 and 2022.

Across all CIS countries over the entire observation period, CVD mortality decreased on average by 20.4%. This reduction is three times smaller compared to Western European countries, where the decrease amounted to 60.2%.

Conclusion. Over the past decades, a substantial global decline in CVD mortality has been observed. This trend is more pronounced in regions with high levels of economic development compared to countries with lower economic levels, which include the CIS countries of Central Asia and Eastern Europe. To reduce cardiovascular morbidity and mortality in the CIS countries, it is necessary to develop effective, innovative, and widely accessible preventive, diagnostic, therapeutic, and rehabilitative technologies for CVD prevention and control.

Keywords: cardiovascular mortality, trends, risk factors, Eastern Europe, Central Asia.

Conflict of interest: none declared.

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Introduction

Since the second half of the 20th century and into the early 21st century, the leading causes of death worldwide have been chronic non-communicable diseases. Among these, cardiovascular diseases (CVDs) hold the leading position, followed by malignant neoplasms, as well as external causes: injuries, poisonings, and accidents [1, 2]. Up to 20 million people die annually from CVDs, the world's leading cause of death.

Socio-economic problems, population aging, and inadequate management of risk factors (RFs) are among the reasons for this unfavorable epidemiological picture [3]. In countries that were part of the

USSR, CVD morbidity and mortality rates are among the highest in the world. According to experts, the collapse of the USSR, along with political, social, and economic changes, negatively impacted population health indicators and led to increased mortality among adults. The healthcare system also underwent significant changes; previous state-run screening, prevention, and rehabilitation programs for chronic diseases were effectively discontinued. Collectively, this had a detrimental effect on demographic indicators in the post-Soviet countries [1].

Over the past decade, the CVD situation in the Commonwealth of Independent States (CIS) has somewhat stabilized, with a noted decline in cardio-

vascular mortality [2]. However, according to WHO data, cardiovascular morbidity and mortality rates in this region remain among the highest globally.

The aim of this analytical review is to analyze CVD mortality and its trends from 1990 to 2022 in the CIS countries.

Methods

The article analyzes data from CIS countries belonging to the Eastern European and Central Asian regions. According to the definition by an international expert commission, these regions comprise countries and territories that are geographically proximate and epidemiologically similar. The Central Asian region includes Azerbaijan, Armenia, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, and Mongolia (the latter is not a CIS member). The Eastern European region includes Russia, Ukraine, Belarus, Moldova, Lithuania, Latvia, and Estonia.

The article utilizes data from the research group on the Global Burden of Disease, Injuries, and Risk Factors (GBD). For each region, the GBD generates time series of summary health indicators, including CVD prevalence, cause-specific mortality rates (CSMR), years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life years (DALYs). CVD mortality was analyzed across eighteen specific cardiovascular diseases. Each epidemiological measure of interest was estimated for 23 age groups, from birth to 95 years and older, for males, females, and both sexes combined, from 1990 to 2022. Age standardization was performed using the direct method with the world standard population age structure. This standard population is defined using the population structure of all locations with a population >5 million. This involves calculating the proportion of the population in each age group for a specific location. Furthermore, these age proportions are averaged across all such locations [4–8].

Results

Cardiovascular mortality in Central Asia

In 2022, age-standardized CVD mortality rates among countries in this region ranged from 331.8 to 542.3 per 100,000 population. The more than 1.6-fold difference between the minimum and maximum rates indicates high variability in mortality within the region. Over the 32-year period from 1990 to 2022, CVD

mortality in this region decreased by 16.5%. Notably, the region's relative standing was high: in 1990, Central Asia ranked 4th, and in 2022, it ranked 2nd in age-standardized CVD mortality among 21 global regions. Furthermore, in 2022, Central Asia ranked first worldwide in terms of CVD prevalence.

The leading causes of age-standardized disability-adjusted life years (DALYs) were coronary heart disease (CHD) and subtypes of stroke (table 1). High systolic blood pressure (SBP) was associated with the highest number of attributable age-standardized CVD DALYs - 4875.3 per 100,000 population.

The top three countries for age-standardized CHD mortality were Uzbekistan, Turkmenistan, and Azerbaijan. For age-standardized mortality from ischemic stroke, the leading countries were Georgia, Kazakhstan, and Turkmenistan. Regarding the analogous indicator for arterial hypertension (AH), the top countries were Georgia, Tajikistan, and Azerbaijan.

The following are recognized contributors to CVD. In the development of CHD and ischemic stroke, behavioral risk factors such as dietary risks, smoking, and secondhand smoke play a significant role. Among metabolic risk factors for CHD development, systolic hypertension, high LDL cholesterol, kidney dysfunction, high body mass index (BMI), and high fasting plasma glucose are prominent. The contribution of these risk factors to stroke development is less pronounced. Another important factor influencing mortality from CHD and stroke is environmental air pollution.

Cardiovascular mortality in Eastern Europe

According to the analysis, in 2022, age-standardized CVD mortality rates among Eastern European countries ranged from 215.0 (Estonia) to 553.0 (Ukraine) per 100,000 population; the difference between the minimum and maximum rates was more than 2.6-fold. Over 32 years (from 1990 to 2022), CVD mortality in this region decreased by 24.3%. Among 21 global regions, Eastern Europe ranked first in age-standardized CVD mortality both in 1990 and in 2022.

Notably, in the structure of adult mortality, the proportion of alcoholic cardiomyopathy is higher compared to other regions. Following CHD and all stroke subtypes, alcoholic cardiomyopathy had the highest age-standardized disability-adjusted life years (DALYs) in 2022 — 521.2 per 100,000 population (Table 2). Among all risks in Eastern European coun-

Table 1. Cardiovascular disease indicators in the Central Asia region for 2022: counts and age-standardized rates per 100,000 population

Cardiovascular Disease, Type	Prevalence (Count)	Deaths (Count)	Prevalence (Rate)	Mortality (Rate)	Disability-Adjusted Life Years (DALY, Rate)
Rheumatic heart disease	618,471	2,480	624.3	2.8	119.3
CHD	7125,865	182,604	8573.3	268.9	5,135.8
Ischemic stroke	951,108	45,226	1091.5	69.6	1,330.9
Intracerebral hemorrhage	184,547	34,154	194.0	45.2	1,008.4
Subarachnoid hemorrhage	102,912	4,109	109.7	5.2	147.4
AH	71,919	12,724	96.4	19.0	337.4
Non-rheumatic degenerative mitral valve disease	375,266	246	500.0	0.3	14.7
Myocarditis	6,279	303	6.8	0.3	12.0
Other cardiomyopathies	54,216	7,598	60.3	8.7	272.5
Atrial fibrillation and flutter	424,061	1,571	565.6	2.6	79.6
Lower extremity peripheral artery disease	612,533	349	835.5	0.5	13.2
Other cardiovascular diseases	427,924	2,008	497.1	2.6	90.7

Note. The DALY (Disability-Adjusted Life Year) coefficient is a health metric measuring the burden of disease, expressed as the total number of years of healthy life lost due to premature death, disability, or ill health. One DALY equals one lost year of "ideal" healthy life, combining losses from mortality (Years of Life Lost, YLL) and years lived with disability (Years Lived with Disability, YLD).

Table 2. Cardiovascular Disease Indicators in the Eastern Europe Region for 2022: Counts and Age-Standardized Rates per 100,000 Population

Cardiovascular Disease, Type	Prevalence (Count)	Deaths (Count)	Prevalence (Rate)	Mortality (Rate)	Disability-Adjusted Life Years (DALY, Rate)
Rheumatic heart disease	241,126	3,324	73.9	1.0	28.6
CHD	25389,496	914,066	7243.7	254.3	4,882.7
Ischemic stroke	3074,246	348,195	924.7	95.7	1,642.8
Intracerebral hemorrhage	467,843	90,934	159.3	26.4	680.1
Subarachnoid hemorrhage	317,276	16,751	108.9	5.0	154.7
AH	171,771	27,760	46.8	7.7	138.5
Non-rheumatic degenerative mitral valve disease	949,952	832	259.7	0.2	9.6
Myocarditis	17,479	743	7.7	0.2	8.6
Alcoholic cardiomyopathy	177,153	38,801	63.6	13.2	521.2
Other cardiomyopathies	157,875	25,924	76.2	8.9	339.9
Atrial fibrillation and flutter	2384,327	19,282	663.1	5.3	119.9
Lower extremity peripheral artery disease	4018,233	13,208	1,099.9	3.6	66.3
Other cardiovascular diseases	2914,750	16,721	863.9	4.9	164.1

Note. The DALY (Disability-Adjusted Life Year) coefficient is a health metric measuring the burden of disease, expressed as the total number of years of healthy life lost due to premature death, disability, or ill health. One DALY equals one lost year of "ideal" healthy life, combining losses from mortality (Years of Life Lost, YLL) and years lived with disability (Years Lived with Disability, YLD).

tries, high systolic blood pressure (SBP) caused the greatest number of age-standardized CVD DALYs — 4619.4 per 100,000 population.

In this region, the top three countries for age-standardized CHD mortality are Ukraine, Belarus, and Moldova. For age-standardized mortality from ischemic stroke, the leading countries are Russia, Latvia, and Ukraine. Regarding the analogous indicator for hypertensive heart disease, the top countries are Estonia, Moldova, and Latvia.

It is known that in the development of CHD and ischemic stroke, among behavioral risk factors, di-

etary risks and smoking play a significant role, while alcohol use plays a major role in the development of intermittent claudication. Among metabolic risk factors for CHD development, the following are prominent: systolic hypertension, high LDL cholesterol, high body mass index (BMI), kidney dysfunction, and high fasting plasma glucose. The contribution of these risk factors to stroke development is less pronounced. Furthermore, important factors influencing mortality from CHD and stroke are environmental air pollution and cold climate.

Discussion

According to international parameters, CIS countries were divided into two regions based on geographical location: Central Asia and Eastern Europe. In 2022, the maximum CVD mortality rates in these regions were similar, while the minimum mortality rate in Eastern Europe was 1.5 times lower than in Central Asia. In Western Europe, the comparable indicators (ranging from 80.2 to 199.9 per 100,000 population) during the analyzed period were 2.5 times lower than in the CIS countries [3].

Over the 32-year observation period, CVD mortality in the CIS countries decreased by an average of 20.4%, which is three times less than the 60.2% reduction seen in Western Europe. By this measure, Western European countries have one of the best indicators among 21 global regions, ranking 19th in 2022, while both CIS regions ranked the worst, occupying 1st and 2nd place.

In the structure of CVD mortality in CIS countries, CHD is the leading cause, accounting for 30% to 75%, compared to a range of 25% to 55% in Western Europe. In Western Europe, arrhythmias, cardiomyopathies, and valvular heart diseases also contribute to the mortality structure. The primary behavioral risk factors in both the CIS and Western Europe are dietary risks and smoking. Among metabolic risk factors, hypertension and hypercholesterolemia occupy the top two positions, while the negative impact of environmental factors on cardiovascular mortality is more pronounced in CIS countries than in Western Europe. It should be emphasized that Western Europe already had low CVD mortality rates among 21 global regions in 1990, ranking 15th [3].

The economic development level of countries influences the structure and rates of socially significant causes of death, which undoubtedly affects life expectancy. Overall, in economically developed countries over the past three decades, there has been a clear trend of a decreasing proportion of CVDs in the overall mortality structure. One in five deaths is registered before the age of 70. In developing countries, the picture is somewhat different. The trend in CVD mortality changes slowly, with nearly every second death resulting from CVD complications occurring before the age of 70. The less social stratification in a society and the larger the proportion of people belonging to the so-called middle class, the greater the effect of prevention programs. Success in the positive trend of

CVD mortality in Western countries can be attributed to several factors: healthcare funding, effective primary prevention, screening, and the accessibility of high-tech/advanced treatments for CVD. In developing countries, along with social problems, insufficient control and high prevalence of risk factors play a significant role in the rise of morbidity [9, 10].

A large study conducted in Russia in the early 21st century demonstrated a close correlation between cardiovascular mortality and the number of people over working age, as well as the proportion of the population with low economic income. Undoubtedly, changes in the demographic situation also played a role in the increased CVD mortality in the Russian Federation at the turn of the century. Specifically, declining birth rates and an increasing proportion of elderly people, among whom the frequency of CVD is high. Furthermore, improvements in diagnostic methods in recent decades have contributed to better detection of CVD and, consequently, an increase in the proportion of diagnosed patients [11]. We believe that in CIS countries, especially those in the Eastern European region, the problems are similar [12]. However, in CIS countries belonging to the Central Asian region, the situation with high CVD mortality is primarily due to insufficiently effective implementation of primary and secondary CVD prevention [13]. Strengthening the preventive focus within the healthcare systems of CIS regions will help reduce the morbidity and mortality from CVD among the population. On the other hand, in recent years, these countries have also been successfully implementing high-tech diagnostic and treatment methods for a number of CVD. This provides hope for subsequent improvement in the epidemiological situation regarding CVD mortality in both CIS regions.

Conclusion

In recent decades, a substantial global decline in cardiovascular disease CVD mortality has been observed. This trend is more pronounced in regions with high levels of economic development compared to countries with lower economic levels, which include the CIS countries of Central Asia and Eastern Europe.

To reduce cardiovascular morbidity and mortality in the CIS countries, it is essential to develop effective, innovative, and widely accessible preventive, diagnostic, therapeutic, and rehabilitative technologies for CVD prevention and control. The long-term

implementation of a comprehensive set of measures could contribute to lowering mortality among the adult population.

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Physical activity and work capacity among fly-in fly-out workers in the Arctic region

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Objective. The aim of this study was to examine the specific features of physical activity and work capacity among fly-in fly-out workers in the Arctic region, aged 25–54 years.

Methods. The study sample consisted of a random representative selection of male workers aged 25–54, employed on a fly-in fly-out basis by the EURACORE industrial enterprise in the Arctic latitudes of the Tyumen region. Initially, 750 men aged 25–54 were recruited, with a response rate of 82.4%. The final sample included 618 men, divided into age groups: 25–34 years. (n=214), 35–44 years (n=206), and 45–54 years (n=198). Pearson's chi-squared test was used to assess the significance of differences between sample proportions in the two groups. When absolute frequencies were less than 5, Fisher's exact test was applied.

Results. Men aged 45–54 years reported no change in their physical activity significantly more often than men from 25–34 y.o. (85.3–67.7%, $p<0.001$) and 35–44 y.o. (85.3 – 84.4%, $p<0.001$) age groups, as well as the total sample (85.3–79.0%, $p<0.001$). Concurrently, the youngest group (25–34 years) had the highest proportion of men with low physical activity compared to the 35–44 age group (18.7% vs. 4.4%, $p<0.001$), the 45–54 age group (18.7% vs. 6.6%, $p<0.001$), and the total sample (18.7% vs. 10.0%, $p<0.001$).

In the 25–34 age group, work capacity had increased over the past 12 months more often than in the 45–54 age group (14.5% vs. 6.1%, $p=0.0052$). No change in work capacity was reported more frequently in the 45–54 group

compared to the 25–34 group (85.8% vs. 73.4%, $p=0.0017$). A significant decrease in work capacity was also observed in the youngest group compared to the overall sample average (8.0% vs. 3.1%, $p=0.0011$).

Conclusion. Thus, less than one-fifth of the fly-in fly-out workers surveyed engaged in regular physical exercise, while more than one-fifth held the opposite stance on this matter. Less than a quarter of shift workers spent their leisure time passively. More than a quarter of the men rated their physical activity as significantly higher than that of their peers. Over the past year, age-related trends were identified to show not only a decrease in physical activity but also an increase in work capacity during the third decade of life.

Keywords: organized population, work capacity, physical activity, men, fly-in fly-out work, Arctic.

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Introduction

In recent decades, the issue of maintaining high physical activity and efficient work organization among shift workers in the Arctic region has remained relevant. Research confirms that expedition-based rotational work under intense operational loads in the West Siberian oil and gas extraction complex leads to fatigue and a decline in professional performance [1, 2]. An obvious reason may be the specific mobile nature of this work, which creates exclusively male teams, composed of individuals differing in age, cultural, and personal characteristics, who are forced to live and work together — a situation that can, in turn, lead to social and ethical issues [3].

Furthermore, the situation is exacerbated by the harsh natural and climatic conditions in which oil and gas workers operate. Additional negative factors include the remoteness of work sites from base enterprises, constant cyclical long-distance travel

from places of residence to worksites and back [4–6], increased work intensity during the rotation period, longer shifts, reduced rest time between shifts in the absence of days off, modest living conditions, and limited access to medical care [3, 6–8]. The inherent features of expedition-based rotational work: the duration and regularity of exposure, the increasing risk from severe and harmful production factors with longer service records, and the accumulation of pathology, classify this work method as a source of chronic occupational stress with an extreme impact character [8–11].

Consequently, a priority task is to study factors that can enhance physical activity and work capacity among individuals engaged in expedition-based rotational work in the Arctic. An active yet moderate physical lifestyle, along with high disease resistance, improves a person's general condition and well-being, increases social energy and work ca-

capacity, which, in turn, serves as an effective way of preventing health issues after exhausting work periods [12–16]. Physical exercise enhances functional recovery across all components of the musculoskeletal, cardiovascular, and other systems, and helps mitigate other risk factors (RFs) [14–17]. At the same time, working in such a mobile mode leads to constant strain and adaptation in the body's regulatory systems, necessitating the development of socially oriented preventive programs for rotational workers. Therefore, the scientific foundation required for developing such programs can be established by identifying population-based patterns in the prevalence of cardiovascular disease (CVD) risk factors, particularly regarding physical activity and work capacity under northern rotational work conditions.

Objective

The aim of this study was to examine the specific features of physical activity and work capacity among individuals engaged in fly-in fly-out work in the Arctic region, aged 25–54 years.

Methods

The study was conducted from March 2022 to February 2023. The study sample consisted of a random representative selection of male workers aged 25–54, employed on a fly-in fly-out basis at the EURACORE industrial enterprise in the Arctic latitudes of the Tyumen region. The initial sample included 750 men aged 25–54, with a response rate of 82.4%. The final sample comprised 618 men divided into age groups: 25–34 years ($n=214$), 35–44 years ($n=206$), and 45–54 years ($n=198$).

Physical activity (assessed via 4 questions from the provided test) and work capacity (assessed via 1 question from the provided test) were analyzed using the standard WHO MONICA Psychosocial questionnaire “Knowledge and Attitudes to Own Health” [18].

Written informed consent was obtained from each participant for cardiovascular screening, and the Ethics Committee of the Tyumen Cardiology Research Center approved the study protocol.

Statistical analysis

Pearson's chi-squared test was used to assess the significance of differences between sample proportions in two groups. When absolute frequencies were less than 5, Fisher's exact test was applied.

A p-value <0.05 was considered statistically significant. Age-standardization of the studied parameters was performed to extrapolate the data to the entire population and to allow correct comparison with other population-based studies of this profile, in accordance with the latest Russian population census for the 25–54 year-old range and the age structure of the examined subjects in each of the three age groups (Table 1).

Results

The study revealed that among workers engaged in fly-in fly-out work in the Arctic region, less than one-fifth (17.9%) regularly performed physical exercise, while more than one-fifth (20.9%) completely abstained from physical activity. The majority (over 60% of workers) either expressed a desire to exercise or exercised irregularly without significant success. No age-related trends were identified for any of these indicators among the respondents.

Regarding leisure time, no significant differences were observed between age groups either. Over 60% could not clearly define how they spend their free time and gave an indefinite response (“it varies”) concerning their leisure activities. Only 14.5% of individuals working on a rotational expedition basis spent their leisure time actively, while more than 20% preferred passive rest.

For the majority of workers engaged in fly-in fly-out work in the Arctic, physical activity had not changed over the past 12 months. Men aged 45–54 reported “no change” significantly more often than the younger groups: compared to men aged 25–34 (85.3% vs. 67.7%, $p<0.001$) and 35–44 (85.3% vs. 84.4%, $p<0.001$), as well as the total sample (85.3% vs. 79.0%, $p<0.001$). At the same time, the youngest group (25–34 years) showed the highest proportion of men with low physical activity compared to the 35–44 age group (18.7% vs. 4.4%, $p<0.001$), the 45–54 age group (18.7% vs. 6.6%, $p<0.001$), and the overall sample (18.7% vs. 10.0%, $p<0.001$).

Regardless of age, one-tenth of the shift workers considered their physical activity to be more passive or significantly more passive. On the other hand, more than a quarter of workers rated their activity as above average compared to other men of their age.

The majority of shift workers in the Arctic (62.1%) considered their physical activity comparable to that of their peers.

Table 1

Physical activity and work capacity among fly-in fly-out workers across the age range

Question / Attitude	Age groups (years)				ASP %
	25-34 (n=214) %	35-44 (n=206) %	45-54 (n=198) %	25-54 (n=618) %	
Do you do physical exercise (besides work-related)?					
I don't need it	22.9	20.4	19.7	21.0	20.9
I should exercise but I don't	49.9	39.8	40.4	43.5	43.1
I have tried but was unsuccessful	13.1	20.4	19.2	17.5	17.6
I exercise regularly	13.6	19.4	20.7	17.8	17.9
According to doctors, exercise is contraindicated for me	0.5	0	0	0.2	0.1
How do you spend your leisure time?					
Physically active (gardening, sports, walking, cycling, running, etc.)	14.0	14.1	15.7	14.6	14.5
It varies	58.4	61.6	61.5	60.5	60.4
Physically passive (lying down, sitting, watching TV, reading, writing, crafting, etc.)	26.2	18.0	17.7	20.7	20.4
I have no leisure time	1.4	6.3	5.1	4.2	4.3
Has your physical activity (mobility, sports, etc.) changed over the past 12 months?					
Yes, I have become more active	13.6	11.2	8.1	11.0	10.9
Has not changed	67.7	***84.4	***85.3	***79.0	79.1
I have become less active/mobile	18.7	***4.4	***6.6	***10.0	9.7
How do you rate your physical activity compared to other people your age?					
I am significantly more active	7.0	5.8	6.1	6.3	6.3
Somewhat more active	19.6	23.3	20.7	21.2	21.2
About the same as others	57.0	63.6	66.1	62.2	62.1
Somewhat less active	13.6	6.8	7.1	9.2	9.0
Significantly less active/passive	2.8	0.5	0	1.1	1.1
Has your work capacity changed over the past 12 months?					
Has increased	14.5	11.7	**6.1	10.8	10.6
Has not changed	73.4	83.9	**85.8	80.9	80.9
Has decreased	3.7	4.4	7.6	5.2	5.2
Has significantly decreased	8.4	0	0.5	**3.1	2.9

Note. * to the left of a value denotes a statistically significant difference between the 25-34 year age group and other age groups; * to the right denotes a significant difference between the 35-44 year age group and other groups; * to the bottom left denotes a significant difference between the 45-54 year age group and the 25-54 year age group. * — p<0.05; ** — p<0.01; *** — p<0.001; ASR — age-standardized parameter.

Regarding work capacity, an increase was observed in onetenth of individuals working on a rotational expedition basis over the past twelve months. In the 25–34 age group, work capacity had increased over the past 12 months more often than in the 45–54 age group (14.5% vs. 6.1%, $p=0.0052$). No change in work capacity was reported more frequently in the 45–54 group compared to the 25–34 group (85.8% vs. 73.4%, $p=0.0017$). A significant decrease in work capacity was also observed in the youngest group compared to the overall sample average (8.4% vs. 3.1%, $p=0.0011$).

Discussion

This study is part of a project investigating CVDs and their RFs among men engaged in flyin flyout work at the oil extraction complex in Western Siberia. Various aspects of this project have been published in Russian journals [2, 9, 11].

Among rotational expedition workers at the oil and gas extraction complex in the Arctic, physical activity among middleaged men generally prevailed over that among younger men. A similar trend was noted in studies by our colleagues from Novosibirsk concerning men of the same age groups [5].

The present study showed that the majority of young men do not meet their need for regular physical exercise, despite their desire and the necessity to do so. Furthermore, no positive trend towards increased active leisure time is observed among young men, which leads to a decline in physical activity and work capacity even when there is an intention to engage in regular physical exercise. This age group is also characterized by a low level of selfassessment regarding physical activity.

Based on the analysis of this study, it can be stated that approximately equal numbers of shift workers were identified to regularly engage in physical exercise and those with a negative attitude towards it. Correspondingly, an equal number of participants preferred passive leisure activities. Although more than a quarter of those working on a rotational expedition basis consider their level of physical activity

higher than that of their peers, a decrease in physical activity was noted in the young age group.

Consequently, young men with low physical activity are at risk for developing CVDs, as scientific research confirms the link between physical inactivity and increased risk of allcause mortality.

At the same time, this study revealed an increase in work capacity among shift workers during the third decade of life over the past year. However, this is accompanied by a lowered sensitivity threshold, posing a threat to their health when working in the extreme conditions of the Arctic region and on a rotational expedition schedule.

Health risks are exacerbated by limited opportunities for adequate rest after the working day in this age category, likely due to the specifics of the twelvehour work regime, living away from family, and the close quarters of an exclusively male cohort. An additional factor contributing to increased health risks, especially among young men, is hesitancy regarding the early diagnosis and treatment of diseases.

Conclusion

Thus, less than one-fifth of all shift workers who participated in the study regularly engaged in physical exercise, while more than one-fifth held the opposite stance on this matter. Less than one-fourth of the shift workers spent their leisure time passively. More than one-quarter of the men rated their physical activity as significantly higher than that of their peers. Over the past year, age-related trends were identified to show not only a decrease in physical activity but also an increase in work capacity during the third decade of life.

The results of this study can be used for evidence-based planning of preventive measures among workers engaged in fly-in fly-out operations at oil and gas extraction facilities in the Russian Arctic zone. The research data can provide a foundation for developing effective programs aimed at health preservation and well-being enhancement of workers under these conditions.

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Effects of meldonium on cardiomyocyte hypertrophy and myocardial polyploidy in physically exercised rats

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Hypertrophy of cardiomyocytes can be considered an adaptive response that enhances cardiac performance by increasing the myocardial contractility under conditions of physical exercise. However, myocardial hypertrophy can lead to persistent decompensation of cardiac function.

The aim of the study was to determine the effect of meldonium on reproduction of cardiomyocytes against the background of their hypertrophy and polyploidy, which could expand the range and reliability of adaptation to overload.

Methods. The experimental animals were male Wistar rats, weighing 180–210 g, divided into three groups (18 rats in total). The animals swam for 15 minutes (Group 1 — light exercise), 30 minutes (Group 2 — moderate exercise), and 55–59 minutes (Group 3 — heavy ex-

ercise). During the experiment, meldonium was added to the rats' diet at a dose of 100–120 mg/kg of body weight.

Results. Moderate mode of physical exercise was the most beneficial for the rat myocardium. Heavy physical exercise led to structural impairments in the myocardium, its polyploidy, accompanied by persistent cardiomyocyte hypertrophy and a decrease in the proliferative potential of cardiomyocytes. Meldonium significantly altered the morphological parameters of the heart under heavy physical exercise. Its administration led to an increase in the number of binucleated cells, which became polyploid, while simultaneously reducing the number of hypertrophied tetraploid mononucleated cells.

Conclusion. The use of meldonium during heavy physical exercise reduces cell hypertrophy, increases the percent-

age of binucleated cardiomyocytes, and decreases the number of tetraploid mononucleated cells.

Keywords: physical exercise, polyploidy, binucleated cardiomyocytes, tetraploid cells, proliferation, apoptosis, meldonium.

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Introduction

Heavy physical exercise leads to organ alterations [1–3]. According to authors' data, intensive exercise can contribute to the risk of sudden cardiac death (SCA) [4]. Achievement of outstanding and constantly improving sportive results is commonly accompanied with heavy physical exercise, which blurs the line between the normal adaptive mechanisms of the cardiovascular system and pathologic shifts, caused by the dystrophy in cardiomyocytes. Hypertrophy of cardiomyocytes is considered an adaptive reaction of the organism, when muscular fibers thicken and the structure of the heart alters. It leads to enhanced cardiac performance, improving the myocardial contractility during the increased load. However, beyond a certain point, myocardial hypertrophy might lead to persistent decompensation of cardiac function. This is why the identification of the range of the effective hypertrophy and the pharmacologic ways of prevention of decompensation of cardiac function, are of practical interest.

Meldonium is known to modulate myocardial energy metabolism by enhancing aerobic glycolysis and the malate-aspartate shuttle, thereby potentially improving energy balance. Its antiischemic, vasoprotective, antioxidative activity and ability to restrict apoptosis and prevent the alterations of electric activity of the heart is also identified. These mechanisms are the reason for an increased scientific interest towards the study of the effects of meldonium on myocardial hypertrophy in physical exercise.

The aim of the study was to determine the effect of meldonium on reproduction of cardiomyocytes against the background of their hypertrophy and polyploidy, which could expand the range and reliability of adaptation to overload.

Methods

The study was conducted at I. N. Ulianov Chuvash State University. The animals were kept under standard vivarium conditions.

Rats were divided into three groups ($n=6$ per group). Animals in each group underwent a physical exercise regimen (swimming) in water at a comfortable temperature of 32–34 °C for 10 days. Group 1 swam for 15 minutes daily (light exercise), Group 2 for 30 minutes (moderate exercise), and Group 3 swam to exhaustion, defined as the point of drowning (55–59 minutes after the start of the experiment), representing heavy exercise. Throughout the 10-day experiment, meldonium was added to the animals' diet at a daily dose of 100–120 mg/kg of body weight. The experimental rats ($n=18$) were euthanized immediately after the final exercise session, and another cohort ($n=18$) was euthanized 30 days post-exercise. For comparison, three control groups of six rats were subjected to the same graded exercise regimens, but did not receive meldonium in their diet. An additional control group of intact animals ($n=3$ per group), which were not exercised, was used. Upon completion of the experiment, animals were euthanized by decapitation using a guillotine, and the hearts were non-traumatically extracted.

Outcome registration methods

During autopsy, the heart was excised in full and placed in 10% formalin for primary fixation for 24 hours. This was followed by secondary fixation and dehydration. The resulting fragments of the left ventricle (LV) were embedded in paraffin, and 5 μm thick histological sections were prepared using a "Microm" sledge microtome.

The sections were stained with hematoxylin and eosin. The amount of deoxyribonucleic acid in the

cardiomyocyte nuclei was determined using a Biolam-70 microscope equipped for photometry with a MFEL-1 microphoto attachment and a FEU-79A photometer. Measurements were taken in transmitted light with a bandpass filter having a maximum transmittance at a wavelength of 570 nm and an applied voltage of 900 V. Peripheral blood lymphocytes and small lymphocytes from lymph nodes served as the diploid reference. Binucleated cardiomyocytes were counted per 7000 nuclei at a magnification of 900x. To assess the degree of hypertrophy, the diameter of the cardiomyocytes was measured. The data were processed using the SIGMA SCAN PRO software.

Immunohistochemical analysis was performed using the proliferation marker Ki-67 (Santa Cruz Biotechnology) according to a standard protocol. For this, 3 µm thick sections were placed on highly adhesive glass slides coated with L-polylysine and dried at room temperature for 24 hours.

Staining was carried out both manually and automatically using the AUTOSTAINER-360 (THERMO, UK) and Leica BOND-MAX (Germany) automated stainers with the EnVision (Dako, Denmark) and NovoLink™ Polymer (Novocastra, UK) detection systems, respectively. Controls included non-immune rabbit and mouse sera, as well as sections of rat heart tissue from control groups.

The staining results were assessed by counting 200 cardiomyocyte nuclei across six random fields of view at 400x magnification.

Inclusion criteria: Male Wistar rats weighing 180–210 g, with no external defects, injuries, or behavioral abnormalities.

Exclusion criteria: Presence of concomitant pathology in the internal organs or brain of the rats.

Ethical approval

The study was conducted in compliance with the Federal Law of the Russian Federation “On the Protection of Animals from Cruel Treatment” dated January 1, 1997. The study protocol was approved by the Local Ethical Committee of Mari State University, Ministry of Health of Russia (Protocol No. 1, April 28, 2023).

Statistical analysis

Descriptive statistical analysis was performed using Statistica 10 (USA) and Microsoft Excel 2016 (USA). The Kruskal-Wallis test was used to assess the

equality of medians across multiple samples, with results considered significant at $p < 0.05$. Data for each animal group were averaged, and the standard error and standard deviation were calculated.

Results

In control rats of the first two groups, the myocardium macroscopically showed almost no differences from that of the intact animals. In the third group, noticeable flabbiness of the heart and dilation of its chambers were observed.

Histological examination of the left ventricular (LV) myocardium in the first group revealed vascular congestion (Fig. 1a-b); in the second group, hemorrhages (Fig. 1c); and in the third group, marked dystrophic changes in cardiomyocytes and edema. Signs of cytoplasmic homogenization and interstitial edema with vascular congestion were also identified (Fig. 1d).

Histological examination of the LV myocardium in all groups showed varying degrees of cardiomyocyte hypertrophy, ranging from mild in the first group to severe in the third group. The cytoplasm of the enlarged cardiomyocytes was hypereosinophilic with hyperchromatic nuclei. Binucleated cardiomyocytes, as well as diploid and tetraploid cells, were detected in all rat groups. In the first group, diploid cardiomyocytes were the predominant cell type in the myocardium. Against the background of moderate cardiomyocyte hypertrophy, polyploidy developed primarily due to binucleated cells.

The highest level of polyploidy against the background of severe cardiomyocyte hypertrophy was observed in the third group, characterized by an increase in the number of mononucleated tetraploid cells to $32.9 \pm 7.3\%$ and a decrease in diploid cardiomyocytes to $67.1 \pm 8.0\%$. A reduction in the number of binucleated cells to $7.1 \pm 5.0\%$ was also noted (Table 1).

As shown in Table 2, even after 30 days, the morphological parameters in the first and second groups showed only minor differences from those observed immediately after the experiment: nuclear diameter and the number of binucleated cardiomyocytes were close to the levels in intact animals, while the number of tetraploid nuclei was somewhat higher than immediately post-experiment.

In the third group, marked hypertrophy, a reduced number of binucleated cardiomyocytes, and a decreased proportion of diploid cells ($71.7 \pm 6.0\%$) per-

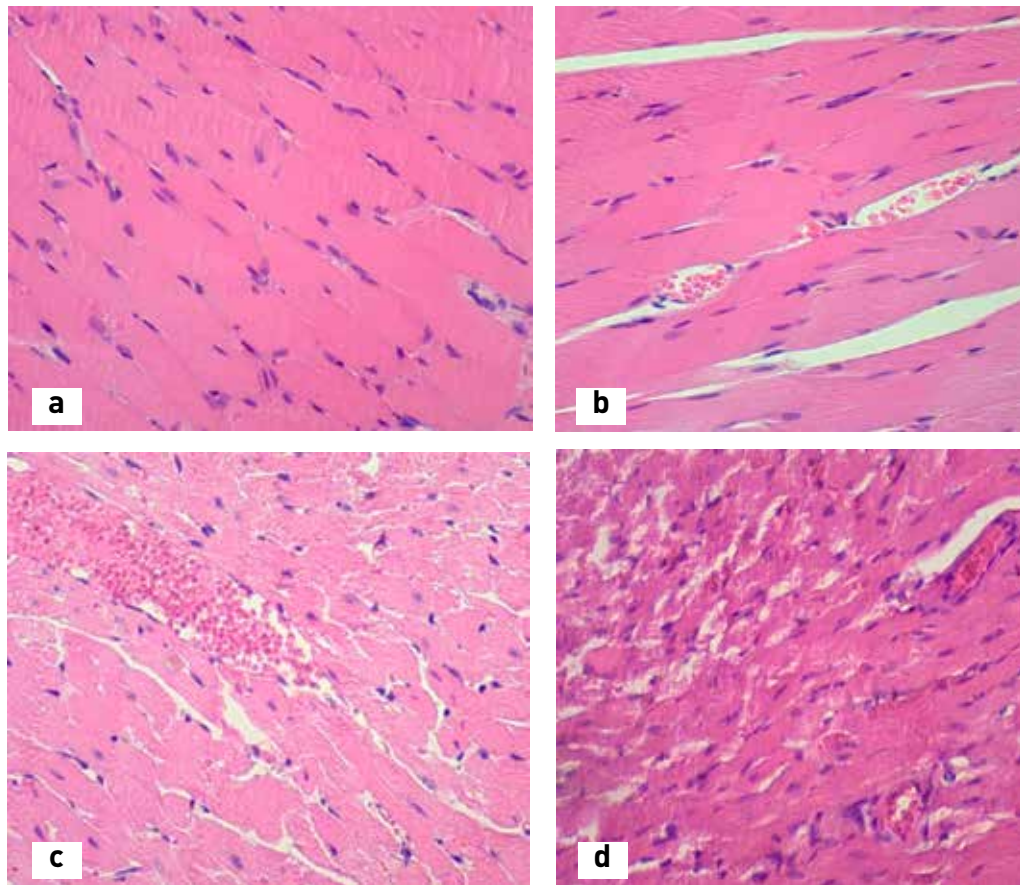


Fig. 1. Microscopic view of the heart: Cardiomyocytes of intact animals (a) and under light physical exercise (b): vascular congestion; c — under moderate physical exercise: edema, hemorrhagic site; d — under heavy physical exercise: cardiomyocytes cytoplasm homogenization, interstitial edema; vascular congestion. Hematoxylin and eosin stain, $\times 400$

Table 1. Comparative morphology of left ventricular cardiomyocytes in intact rats immediately after graded physical exercise

Parameters	Intact animals	Group 1	Group 2	Group 3
Diameter of nuclei of cardiomyocytes, μm	5.2 ± 0.8	5.0 ± 1.6	5.1 ± 0.8	7.2 ± 5.2
Number of binucleated cardiomyocytes, ‰	12.7 ± 1.9	14.2 ± 3.4	10.2 ± 3.4	$7.1 \pm 5.0^*$
Diploid/tetraploid cardiomyocytes nuclei, %	$91.6 \pm 7.4 / 8.2 \pm 6.3$	$90.9 \pm 4.2 / 9.1 \pm 4.2$	$93.8 \pm 3.2 / 6.2 \pm 6.0$	$67.1 \pm 8.0 / 32.9 \pm 7.3^*$
Ki-67 positive nuclei, %	0	0	0	0

Note: * — indicates a statistically significant difference from the intact (control) group, $p < 0.05$.

sisted, due to an increase in tetraploid cells ($28.3 \pm 6.3\%$). Thus, the cardiomyocyte hypertrophy and polyploidization via mononucleated cells, which developed under heavy load, persist for a considerable time.

Tables 3 and 4 present comparative characteristics of cardiomyocytes under physical exercise of varying

Table 2. Morphological parameters of left ventricular cardiomyocytes in rats 30 days after graded exercise

Parameters	Group 1	Group 2	Group 3
Diameter of nuclei of cardiomyocytes, μm	5.1 ± 1.8	5.2 ± 0.8	7.2 ± 6.23
Number of binucleated cardiomyocytes, ‰	12.6 ± 2.7	18.0 ± 3.5	$8.1 \pm 7.0^*$
Diploid/tetraploid cardiomyocytes nuclei, %	$84.4 \pm 3.4 / 15.6 \pm 2.5$	$90.5 \pm 3.1 / 9.5 \pm 2.6$	$71.7 \pm 6.0 / 28.3 \pm 6.3^*$
Ki-67 positive nuclei, %	0	0	0

Note: * — indicates a statistically significant difference from the intact (control) group, $p < 0.05$.

intensity, both immediately after the experiments and 30 days post-experiment, under conditions of meldonium administration.

The microscopic picture of the myocardium in rats subjected to physical exercise with meldonium was consistent across all groups: cardiomyocytes had clear boundaries and well-defined striations. The microscopic changes observed in the myocardium under heavy physical exercise are of particular interest.

Table 3. Comparative morphology of LV cardiomyocytes in control rats immediately after graded exercise (under meldonium treatment)

Parameters	Group 1	Group 2	Group 3
Diameter of nuclei of cardiomyocytes, μm	4.3 \pm 1.7	5.0 \pm 1.9	5.4 \pm 4.3
Number of binucleated cardiomyocytes, ‰	17.0 \pm 2.6	24.3 \pm 3.0*	15.6 \pm 5.3*
Diploid/tetraploid cardiomyocytes nuclei, %	91.9 \pm 3.5/ 8.1 \pm 3.2	94.0 \pm 3.1/ 6.0 \pm 4.2	83.0 \pm 3.6/ 17.0 \pm 3.5*
Ki-67 positive nuclei, %	0	0	0

Note: * — indicates a statistically significant difference from the intact (control) group, $p < 0.05$.

Table 4. Morphological Parameters of LV cardiomyocytes in control rats at 30 days post-exercise (under meldonium treatment)

Parameters	Group 1	Group 2	Group 3
Diameter of nuclei of cardiomyocytes, μm	4.6 \pm 2.0	5.0 \pm 1.6	5.3 \pm 2.6
Number of binucleated cardiomyocytes, ‰	13.2 \pm 1.8	17.1 \pm 2.6	16.2 \pm 3.0
Diploid/tetraploid cardiomyocytes nuclei, %	90.2 \pm 3.5/ 9.8 \pm 4.1	90.7 \pm 3.4/ 9.3 \pm 4.0	82.7 \pm 3.1/ 17.3 \pm 3.*
Ki-67 positive nuclei, %	0	0	0

Note: * — indicates a statistically significant difference from the intact (control) group, $p < 0.05$.

Similar to the rats in the first two groups, the cardiomyocytes had clear boundaries without signs of dystrophic changes. The stroma showed no signs of edema, inflammatory cells, or hemorrhages, and the vessels were moderately congested. The absence of alterative changes in the myocardium of the third group rats can be objectively explained, in our view, by the morphometric parameters of the cardiomyocytes, which indicate that the heart was functioning without signs of overexertion.

In the groups with meldonium administration, the morphological parameters throughout the experiment (from the first to the 30th day) after a single exercise session did not change fundamentally compared to the baseline values; only a slight increase in the number of binucleated cardiomyocytes and diploid cells was observed.

The data from the third group are of particular interest. In contrast to the baseline data, cell hypertrophy was reduced, the number of binucleated cardiomyocytes increased, and the number of tetraploid mononucleated cells decreased.

Discussion

This study establishes that physical exercise induces myocardial polyploidization. Polyploidy can occur in cells of various tissues, including liver parenchyma, cardiac muscle cells, bone marrow megakaryocytes, and placental trophoblasts. This phenomenon is observed during normal organ development [6–11]. Polyploidy is achieved either through nuclear division without cytokinesis, resulting in a binucleated polyploid cell, or through genome duplication within a single nucleus, resulting in a mononucleated cell of higher ploidy. It leads to an increase in cellular size, nuclear size, and the appearance of binucleated cells [8]. Increased functional load on an organ elevates its ploidy level [8]. Furthermore, polyploid cells exhibit higher metabolic activity compared to diploid cells [6, 8]. Consequently, the process of polyploidization results in cell hypertrophy, which constitutes an organ's response to increased functional demand.

In the control groups, myocardial polyploidization in rats of the first and second groups (light and moderate exercise) was achieved in two ways: through the formation of binucleated cardiomyocytes and through the accumulation of nuclear material in the genome, resulting in nuclei of higher ploidy (predominantly tetraploid). Heavy physical exercise (third group), against a background of alterative processes in the myocardium, increased the number of tetraploid cardiomyocytes while decreasing the number of binucleated cells. Under conditions of organ overexertion, such as heavy physical exercise, the process of polyploidy develops primarily through nuclear hypertrophy of cardiomyocytes via the formation of mononucleated polyploid cells.

In the experiment with meldonium administration during physical exercise, an increase in the number of binucleated cells was observed across all groups, with a corresponding decrease in mononucleated tetraploid cells. Notably, myocardial hypertrophy was absent in these cases.

Immunohistochemical analysis for the proliferation marker Ki-67 did not reveal positive nuclei under conditions of meldonium application. The absence of proliferation markers is generally accepted in the literature, however, some researchers have observed Ki-67-positive cardiomyocyte nuclei in the heart following myocardial infarction [7]. Thus, the use of meldonium during swimming exercise led to an increase in binucleated cells and a reduction in the

degree of cellular hypertrophy. This effect is likely attributable to meldonium's ability to reduce carnitine synthesis and the transport of long-chain fatty acids across cell membranes, preventing the accumulation of activated forms of non-oxidized fatty acids — acyl-carnitine and acyl-CoA derivatives. The decreased carnitine concentration promotes the synthesis of gamma-butyrobetaine, which possesses vasodilatory properties. Meldonium restores the balance between oxygen delivery and consumption in cells and prevents the impairment of adenosine triphosphate transport [5].

Conclusion

This study revealed that heavy physical activity induces myocardial polyploidization accompanied by persistent nuclear hypertrophy. Microscopic examina-

tion of the heart showed signs of alterative damage. These changes persisted for up to 30 days after the swimming sessions concluded.

The administration of meldonium in the experiment significantly altered the morphological picture of the myocardium in a positive direction. This was particularly evident in the myocardium of rats subjected to heavy exercise. In these cases, the resulting myocardial polyploidy occurred largely through the formation of binucleated polyploid cells. This process took place concurrently with moderate hypertrophy and the formation of mononucleated polyploid cardiomyocytes. The microscopic architecture of the myocardium was virtually indistinguishable from the normal heart structure.

Conflict of interest: none declared.

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Modern neuroimaging and reperfusion therapy in the management of wake-up stroke

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Wake-up stroke (WUS) remains one of the most challenging medical problems in acute cerebrovascular disease. Until recently, the unknown time of symptom onset made these patients eligible only for limited therapeutic options, thereby diminishing the likelihood of a favorable outcome. However, the development of advanced neuroimaging techniques and the revision of approaches to assessing brain tissue viability, have radically expanded treatment possibilities for this patient category.

A paradigm shift was driven by the introduction of advanced MRI and CT protocols, which enabled not only

differentiation between the ischemic core and penumbra, but also estimation of “biologic time” of the stroke. Such methods as MRI DWI-FLAIR mismatch, perfusion CT, and CT-angiography, present objective criteria for patients in order for reperfusion therapy, despite the unknown time of symptom onset.

Objective. The aim of this review is to summarize current literature on the pathogenesis, risk factors (RFs), diagnosis, and management of WUS.

Methods. This review is based on the analysis of publications by Russian and international authors from print

and online sources over the past 10 years. The following search terms were used: wake-up stroke, computed tomography, magnetic resonance imaging, thrombolysis, and thrombectomy. Studies or articles that did not meet quality standards were excluded.

Results. This review examines current evidence on the pathogenesis, RFs, diagnostic approaches, and treatment strategies for WUS. It describes the role of various MRI sequences in decision-making for reperfusion therapy. Furthermore, it provides an analysis of the literature to define indications for systemic thrombolysis and mechanical thrombectomy in cerebral vessels.

Conclusion. Pharmacological and endovascular treatment in the hyperacute phase of ischemic stroke has evolved considerably over the past two decades. This progress is attributable to improved patient selection cri-

teria, advances in diagnostic imaging, and greater availability of modern thrombectomy devices.

Keywords: wake-up stroke, computed tomography, magnetic resonance imaging, thrombolysis, thrombectomy.

Conflict of interest: none declared.

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Introduction

Wake-up stroke (WUS) is a subtype of ischemic stroke in which no signs of neurological deficit are detected before the patient goes to sleep, but they become apparent immediately after awakening. Approximately 14–25% of patients with acute ischemic cerebrovascular events wake up with symptoms of stroke [1–3]. Management of patients with WUS is complicated by the inability to determine the exact time of stroke onset, which by default places them outside the standard “therapeutic window.”

According to recent studies, thrombolysis or reperfusion therapy may be an effective treatment option for this group of patients, provided that appropriate patient selection is performed [4, 5]. Selection is based on multimodal magnetic resonance imaging

and computed tomography data, which allow visualization of brain regions in which ischemic changes are potentially reversible within a certain time frame.

The aim of this study is to summarize current literature on the pathogenesis, risk factors (RFs), diagnosis, and management of WUS.

Methods

This review is based on the analysis of publications by Russian and international authors from print and online sources over the past 10 years. The following search terms were used: wake-up stroke, computed tomography, magnetic resonance imaging, thrombolysis, and thrombectomy. Studies or articles that did not meet quality standards were excluded.

Results

The pathogenesis and risk factors of wake-up stroke

The pathogenesis of WUS is not yet fully understood. Current research suggests that the underlying mechanisms may involve impaired cerebral perfusion and systemic hemodynamic changes due to nocturnal fluctuations in blood pressure, heart rate, oxygen desaturation, as well as sympathetic nervous system activity, slowed metabolism, and other factors [4–6]. Microvascular pathology is also considered a potential contributor. Although patients with WUS most frequently present with lacunar infarcts, the causal

relationship between cerebral microvascular disease and WUS pathogenesis requires further investigation [6]. Unusual etiologies, such as cervical spondylosis, have also been described among the diverse causes of WUS [7].

The risk factors for WUS are likely similar to those for acute cerebrovascular accidents (ACVA) in general. However, given its unique temporal profile, certain factors are hypothesized to play a more prominent role. These include obstructive sleep apnea (OSA), dyslipidemia, a sedentary lifestyle, diabetes mellitus, as well as race, age, and sex [8–10]. OSA is one of the

most common risk factors for stroke. Severe OSA may increase the likelihood of WUS by inducing hemodynamic shifts, coagulopathies, and autonomic dysfunction [4, 11-14]. Furthermore, OSA impairs the cortical respiratory drive, which may also predispose to WUS. Notably, stroke itself typically exacerbates OSA [14].

Analysis of lipid profiles in WUS patients has shown a tendency toward elevated levels of low-density lipoproteins and cholesterol [9]. A sedentary lifestyle is another widespread risk factor for WUS [3, 5]. Diabetes mellitus also increases WUS risk, highlighting the role of cerebral microvascular injury as a key pathogenetic mechanism [11].

Epidemiological data indicate that WUS is more common among black individuals and younger adults [2]. In younger patients, the presence of a patent foramen ovale and OSA elevates WUS risk [15]. Sex also contributes to the risk profile: a history of OSA is more frequently reported in men with WUS than in women [9], although current evidence in this area remains insufficient.

The therapeutic window in wake-up stroke

The first 3-4.5 hours from symptom onset represent the optimal window for thrombolysis. Although the exact time of "disease onset" is never known in WUS, evidence suggests that most ACVA causing WUS occur within a relatively short period before awakening. The demographic characteristics, clinical presentation, and neuroimaging findings in patients with WUS do not differ from those in patients with a precisely known time of ischemia that falls within the therapeutic window [16].

Barreto A.D. et al. published a multicenter prospective study on thrombolysis outcomes in WUS patients treated within 3 hours of awakening. The results of this work also demonstrated the safety and efficacy of intravenous thrombolysis in this population [17].

Current literature also addresses the treatment of patients with Unwitnessed Stroke (UWS), a broader category encompassing both WUS and daytime strokes with an unknown onset time. This combined category differs somewhat in terms of risk factors, etiology, and clinical presentation, necessitating careful analysis in clinical practice. In diagnosing and treating WUS, the concept of "last known well" (LKW) time, which is the last time the patient was seen without a neurological deficit, has become standard, used as a substitute for the unknown exact time of ischemia. A single-center retrospective study of 206

patients divided into a WUS group and a group with witnessed stroke onset within the previous 8 hours concluded that the outcomes of endovascular therapy were comparable between the groups [18].

WUS patients presenting within 9 hours of the midpoint of sleep were also included in the EXTEND trial, which established that their outcomes could be improved by timely thrombolysis when significant penumbra was present on imaging [19]. These results are promising, as they suggest a potential expansion of the conventional therapeutic window.

Determining the exact time of stroke onset is crucial, as it typically dictates the extent of salvageable brain tissue at risk. Frequently, this very question becomes a major obstacle in defining treatment strategy. Technological advances in MRI and CT have provided a solution. Modern advanced neuroimaging protocols can identify patients with potentially viable ischemic tissue, thereby pushing the boundaries of the standard time-based therapeutic window. Today, the paradigm is shifting from a rigid "time window" to a "tissue window," representing an area of active investigation. A substantial body of evidence confirms that the most justified approach is to base treatment decisions on whether imaging findings meet specific criteria for viability, rather than on elapsed time alone [20].

Thrombolysis in patients with wake-up stroke

Due to the uncertain time of symptom onset, only 8-27% of patients with WUS receive thrombolytic therapy, even though many could be good candidates for this procedure given careful patient selection [21, 22].

Non-contrast CT of the brain remains the preferred initial imaging modality in the routine diagnosis and management of acute stroke to exclude intracranial hemorrhage. However, its use in isolation is not recommended for treatment decisions in WUS. CT perfusion (CTP) imaging, a technique for assessing cerebral blood flow using CT, can provide crucial information on cerebral hemodynamics and enable identification of the ischemic penumbra.

A recent retrospective analysis of 22 WUS patients demonstrated the efficacy of systemic thrombolytic therapy in patients selected for reperfusion treatment based on CTP findings, compared to conservative management, which supports the conclusion that thrombolysis can significantly improve functional outcomes in these patients [23, 24].

Although CT-based technologies are often more practical in the hyperacute phase of stroke, the advent of multimodal MRI has significantly increased the diagnostic value of the method. Studies note that a salvageable penumbra is clearly visualized on MRI in more than half of WUS patients within the first 3 hours of stroke onset. Available data indicate that MRI utilizing sequences such as DWI (Diffusion-Weighted Imaging), FLAIR (Fluid-Attenuated Inversion Recovery), PWI (Perfusion-Weighted Imaging), and SWI (Susceptibility-Weighted Imaging) can not only extend the therapeutic window but also help exclude contraindications for specific treatments and assess the contribution of certain risk factors. Several studies have shown that MRI-guided thrombolytic therapy is safer and more effective compared to treatment decisions based solely on CTP [25].

The DWI-FLAIR Mismatch

The DWI-FLAIR mismatch refers to a discrepancy where an acute ischemic lesion is visible on DWI but appears normal on FLAIR sequences. This finding indirectly suggests that the stroke likely occurred within a relatively short time frame. DWI is highly sensitive to cytotoxic edema, while FLAIR detects vasogenic edema [25].

Data from multicenter studies involving ACVA patients presenting within 4.5 hours of symptom onset show that the DWI-FLAIR mismatch can identify patients within this time window with an accuracy of 0.78 and a positive predictive value (PPV) of 0.83 [26].

A study utilizing artificial intelligence to analyze DWI and FLAIR scans for the presence of this mismatch demonstrated that such technologies can also be applied to the diagnostic workup of WUS patients [27].

In the WAKE-UP trial, the DWI-FLAIR mismatch was used to justify thrombolytic therapy for patients with UWS. Treatment outcomes in the thrombolysis group were significantly better than in the placebo group [28].

The DWI-FLAIR mismatch concept has limitations. For instance, it may overestimate the actual time of stroke onset due to its low sensitivity and negative predictive value (NPV), potentially excluding candidates who could still benefit from reperfusion therapy [29].

In nearly 80% of ACVA patients, a salvageable penumbra is visible within the first 3 hours of ischemia. This represents brain tissue with less severe perfusion reduction than the ischemic core, where neu-

ronal damage remains reversible if effective treatment is initiated promptly. In such patients, DWI-PWI mismatch-based thrombolysis can lead to favorable functional outcomes [25].

It is anticipated that a favorable MRI profile (a DWI-PWI mismatch in the absence of a FLAIR signal hyperintensity) will eventually become a widely accepted screening standard. This approach would allow clinicians to analyze scans more rapidly than waiting for software processing that matches imaging findings to the ASPECTS (Alberta Stroke Program Early CT Score) scale [30]. MRI-ASPECTS could make thrombolytic therapy considerably more effective and safer for WUS patients by substantially reducing diagnostic decision-making time.

Additional MRI-based screening approaches

Several other MRI-based diagnostic methods for ACVA have been proposed. In a retrospective study, Guo et al. utilized a DWI-T2-weighted image mismatch to justify thrombolytic therapy, reporting satisfactory outcomes in WUS patients [31]. Furthermore, a machine learning model has been developed to estimate stroke onset time from MRI data. This method demonstrated superior accuracy compared to the qualitative assessment of DWI-FLAIR mismatch [32].

Legrand L. et al. suggested that a discrepancy between FLAIR vascular hyperintensity (FVH) and DWI lesions could serve as a criterion for selecting patients likely to benefit from thrombolysis. This FVH-DWI mismatch is defined as FVH signals present outside the DWI-delineated lesion area [33]. Whether this mismatch is more suitable than DWI-FLAIR for screening WUS patients requires further investigation. It has been established that quantitative FLAIR analysis can identify patients within 6 to 8 hours of symptom onset [34].

According to research by Cheng B. et al., FLAIR signal intensity correlates with time from symptom onset: greater signal intensity indicates a longer elapsed time since ischemia and is associated with worse clinical outcomes [35].

A discrepancy between findings on Magnetic Resonance Angiography (MRA) and DWI has also been shown to correlate with the extent of the DWI-PWI mismatch and can serve as a patient selection criterion. This mismatch may also indicate the presence of a proximal intracranial internal carotid artery

or M1 segment middle cerebral artery occlusion with a DWI lesion volume of less than 50 ml [36].

Contraindications and risks of thrombolysis in wake-up stroke

The primary contraindication to thrombolysis is intracranial hemorrhage (ICH). While non-contrast head CT was traditionally used for all suspected stroke patients to rule out ICH, the development of multimodal MRI has revealed superior alternatives for this purpose, such as Gradient Echo (GRE) and DWI sequences. SWI also exhibits high sensitivity for intracranial hemorrhages, particularly chronic microbleeds. Additionally, DWI on low-field scanners can visualize acute hemorrhage within infarct zones.

MRI also facilitates bleeding risk assessment. For instance, thrombolysis is not recommended for patients with a DWI lesion volume (VDWI) > 100 ml or a Tmax ≥ 8 sec perfusion lesion volume (VTmax>8s) ≥ 100 ml due to the unacceptably high risk of symptomatic intracranial hemorrhage [25].

Thrombectomy in patients with wake-up stroke

Another treatment option for WUS patients is mechanical thrombectomy. Numerous clinical observations and observational studies have demonstrated that interventions guided by CT and MRI findings are becoming increasingly common [37, 38].

An observational study, using a CTP mismatch (defined as NIHSS ≥ 4 and a TTP/CBF ratio ≥ 2) in combination with large vessel occlusion (LVO) as the primary criterion, recommended endovascular treatment for ten WUS patients. Their outcomes were deemed favorable in 33.3% of cases, with a 3-month modified Rankin Scale (mRS) score of ≤ 2. Thrombectomy based on DWI-PWI mismatch proved effective for treating both WUS and strokes with a known onset time [39].

Another study conducted in Brazil enrolled WUS patients with an ASPECTS > 6 and a last known well time < 24 hours for endovascular therapy, also reporting satisfactory outcomes [40].

Interventions based on ASPECTS score were further analyzed in another retrospective study, whose conclusions also confirm their positive impact on clinical outcomes. The authors of the DAWN trial screened patients for a mismatch between clinical severity and ischemic core volume, assessed using RAPID software [41]. In this trial, patients were stratified into

three cohorts: Cohort A – patients aged ≥80 years with NIHSS ≥10 and core volume <21 mL; Cohort B – patients aged <80 years with NIHSS ≥10 and core volume <31 mL; Cohort C – patients aged <80 years with NIHSS ≥20 and core volume <51 mL. After analyzing 90-day functional outcomes (mRS) and stroke-associated mortality, the authors concluded that thrombectomy combined with standard medical therapy yields better outcomes than medical therapy alone. A post-hoc analysis indicated that baseline non-contrast CT findings and ASPECTS directly influence treatment results in DAWN patients [42].

A clinical-imaging mismatch (defined as NIHSS ≥ 12 and ASPECTS ≥ 7) was established. Santos T. et al. used this criterion in their work, leading them to conclude that thrombectomy is safe and effective in WUS patients [43].

A recent re-analysis of the DAWN trial data demonstrated that endovascular therapy was equally effective regardless of the witnessed nature of the stroke onset [44, 45], reinforcing the importance of basing the decision for endovascular intervention on perfusion imaging findings.

Conclusion

Pharmacological and endovascular treatment of ACVA in the hyperacute phase has evolved considerably over the past two decades. This progress is attributable to improved patient selection methods, advances in diagnostic imaging, and greater availability of modern thrombectomy devices. The presence of a skilled multidisciplinary team, an optimized workflow, rapid diagnostics, and effective treatment strategies enables the delivery of early, targeted therapy. This approach aims to minimize final infarct volume and reduce the likelihood of persistent disability.

Recent evidence indicates that approximately one in five acute ischemic strokes is a wake-up stroke. According to current guidelines, this patient group has traditionally been ineligible for thrombolysis. However, findings from recent studies suggest that advanced MRI (DWI-FLAIR mismatch) and CT perfusion imaging are pivotal in extending the therapeutic window for this stroke subtype. The use of these modalities contributes to improved functional outcomes. Nevertheless, convincing evidence supporting the routine application of this approach specifically in WUS management is still lacking, highlighting the need for further research in this field.

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Pre-heart failure in young men with metabolic syndrome: clinical aspects, diagnosis and management strategies

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The relevance of the topic is underscored by the increasing prevalence of metabolic syndrome (MetS) among young men and its contribution to the early development of left ventricular diastolic dysfunction and pre-heart failure (pre-HF), which are the key predictors of cardiovascular complications and reduced quality of life. This necessitates the development of early diagnostic criteria and timely risk stratification systems.

The aim of this review is to summarize current data on the pathogenesis, clinical presentation, diagnostic criteria, disease course and management of pre-HF in young men with MetS, and to define the role of early identification of

diastolic dysfunction of as a marker of subclinical cardiac impairment in this population.

Methods. An analytical review of recent Russian and international scientific publications addressing pre-HF in the context of MetS was conducted, with a focus on its development, clinical course, and diagnosis in young men. The information search utilized the following databases: Russian Science Citation Index, Best Evidence, PubMed, Clinical Evidence, Cochrane Library.

Results. Pre-HF is an early stage of heart failure, where structural and functional cardiac alterations can be observed without any elicited clinical manifestations. In young

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men with MetS, pre-HF is developed due to the combination of arterial hypertension (AH), insulin resistance (IR), obesity, and dyslipidemia, leading to the chronic cardiac overload and cardiovascular disease progression. Identification of pre-HF in this population demands a combined approach, including echocardiography with diastolic function analysis, assessment of natriuretic peptides, inflammatory marker levels, and insulin resistance. Therapy for pre-HF against the background of MetS is aimed at modifying risk factors, normalizing the metabolic profile, and improving cardiovascular parameters. Early diagnosis and timely intervention for pre-HF in young men with MetS can significantly reduce the risk of disease progression and the development of cardiovascular complications.

Conclusion. Pre-HF in young men with MetS represents a subclinical stage of cardiovascular impairment, caused by the combined effects of IR, AH, obesity, and dyslipidemia. Its early identification with the use of echocardiog-

raphy, biomarkers, and metabolic parameters, as well as the timely correction of risk factors, allows the prevention of the development of clinical heart failure and decreases the long-term cardiovascular risk.

Keywords: arterial hypertension, insulin resistance, obesity, hyperlipidemia, dyslipidemia, heart failure.

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Introduction

Pre-heart failure (pre-HF) is a clinical condition characterized by impaired atrial function that can lead to a range of complications, including hemodynamic disturbances and the development of cardiovascular disease (CVD) [1]. Pre-HF is defined by the absence of current or prior symptoms and signs of chronic heart failure (CHF), combined with evidence of structural and/or functional cardiac abnormalities and/or elevated BNP levels. In recent years, there has been an increase in the incidence of pre-HF among young individuals, particularly men with metabolic syndrome (MetS) [1, 2]. MetS, which includes IR, hyperlipidemia, AH, and obesity, significantly elevates the risk of developing CVD, including pre-HF [2].

The concept of pre-HF, although formally defined only in the 21st century, has deep theoretical roots. In Russian cardiology, the foundations of a prenosological approach to CHF were laid as early as the mid-20th century. F.Z. Meerson, in his works from the 1960s–1980s, developed the concept of pathological myocardial adaptation, emphasizing that hypertrophy and neurohumoral activation in the context of metabolic disorders (obesity, IR) could transform from compensatory into damaging mechanisms, leading to impaired energetics, ionic homeostasis, and progression of fibrosis — long before the onset of clinical symptoms [3]. N.M. Mukharlyamov introduced into clinical practice the concept of “latent”

heart failure, linking it to diastolic dysfunction with preserved systolic function in patients with arterial hypertension and metabolic disorders [4]. Even then, the particular vulnerability of young men with abdominal obesity and hyperinsulinemia was highlighted. The work of E.I. Chazov and his school in the 1980s–1990s complemented this model by establishing the pathogenic link between hyperinsulinemia, endothelial dysfunction, and left ventricular (LV) remodeling—the precursor of a “metabolic” form of pre-HF [5]. On the international level, the concept was formalized within the ACCF/AHA classification (2005, 2013, 2022), where stages A (risk factors without structural changes) and B (structural-functional abnormalities without symptoms) correspond to the modern definition of pre-HF. The ESC guidelines (2016–2021) further refined the criteria: pre-HF is diagnosed by the combination of ≥ 1 risk factor (including MetS) and ≥ 1 objective sign of cardiac remodeling (LV hypertrophy, reduced GLS, fibrosis on MRI, elevated NT-proBNP or hs-cTn) in the absence of typical CHF symptoms [6, 7]. Alongside LV remodeling, a key role in the pathogenesis of pre-HF is played by atrial cardiomyopathy — a complex of structural, functional, and electrophysiological changes that develop in the atrial myocardium long before the clinical symptoms of CHF appear. In young men with MetS, this process is initiated by IR, visceral obesity, and systemic inflammation [8].

Thus, pre-HF is a condition reflecting the transition from physiological compensation to pathological myocardial remodeling. It represents a reversible (with timely intervention) stage in the continuum of CHF, particularly relevant for young men with MetS, in whom hidden, metabolically-mediated impairments of diastolic function and cardiac output reserve predominate.

The aim of this review is to summarize current data on the pathogenesis, clinical presentation, diagnostic criteria, and disease course of pre-HF in young men with MetS, and to define the role of early detectable diastolic dysfunction as a marker of subclinical cardiac impairment in this population.

Methods

This work presents an analytical review of the scientific literature published over the past 10–15 years in Russian and international sources. A search for relevant publications was conducted in the following databases: Russian Science Citation Index (eLIBRARY.ru), PubMed, Cochrane Library, Best Evidence, and Clinical Evidence. Search terms and their combinations in Russian and English included: pre-heart failure, metabolic syndrome, diastolic dysfunction, young men, subclinical myocardial impairment. The analysis included clinical guidelines, systematic reviews, prospective and retrospective cohort studies, as well as original articles relevant to the review topic and possessing a high level of evidence.

Results

Metabolic syndrome and its association with pre-heart failure

Metabolic syndrome is a cluster of conditions that includes IR, hypertension, hyperlipidemia, and obesity. These risk factors significantly increase the likelihood of developing CVD, including pre-heart failure [9]. There is currently a trend of rising MetS incidence among young people, which is associated with lifestyle changes such as low physical activity, poor diet, and increased stress levels [10]. Chronic inflammation, elevated levels of C-reactive protein (CRP), and endothelial dysfunction — all components of MetS — play a key role in the pathogenesis of pre-HF [11]. Cardiac remodeling caused by excess weight and chronic inflammation leads to increased atrial pressure and impaired atrial function, which can subsequently result in heart failure (HF) [12].

In 2024, the Russian Society of Cardiology (RSC) continued to adopt and adapt international guidelines for the diagnosis and management of HF [13]. A significant step was the incorporation of concepts proposed in 2016 by the European Society of Cardiology and the American Heart Association [14]. One of the notable changes in the HF classification has been the identification of a pre-HF stage (Fig. 1). This conceptual innovation aims to facilitate earlier identification of patients at risk of developing HF before overt clinical symptoms appear.

Pre-HF includes patients with risk factors (RFs) such as AH, diabetes, obesity, and other metabolic disorders that could lead to HF, but who do not yet exhibit clear signs of heart disease. It is important to note that this state is not a disease per se, but rather a precursor to the development of more serious CVD.

For patients with MetS, which includes IR, hyperlipidemia, and abdominal obesity, identifying this stage is of particular importance as they are often at elevated risk. In this context, the timely recognition of pre-HF enables cardiologists to implement preventive measures and halt disease progression, thereby improving long-term patient outcomes. Special attention should be paid to young men with MetS. A recent trend shows increasing disease incidence in this group, associated with lifestyle changes, physical inactivity, and poor diet. Studies show that in such patients, pre-HF can develop against the background of chronic inflammation, hypertension, and metabolic disorders, which contributes to increased cardiac load [15–17]. Applying a classification that includes pre-HF allows for closer monitoring of at-risk young individuals and the introduction of preventive therapy before severe clinical symptoms appear.

Since 2024, the RSC has emphasized the importance of the timely diagnosis and correction of risk factors in patients with pre-HF and now recommends using a combined approach. This approach includes managing blood pressure, blood glucose levels, lipid profile, and body weight [2]. To prevent HF, medications that normalize these parameters may be prescribed, along with regular physical exercise and diet therapy. Furthermore, the use of “rapid diagnostics” involving inflammatory markers such as CRP, as well as conducting echocardiographic studies to detect early signs of myocardial dysfunction and other pathologies associated with the initial stage of HF, is recommended [18–20]. This

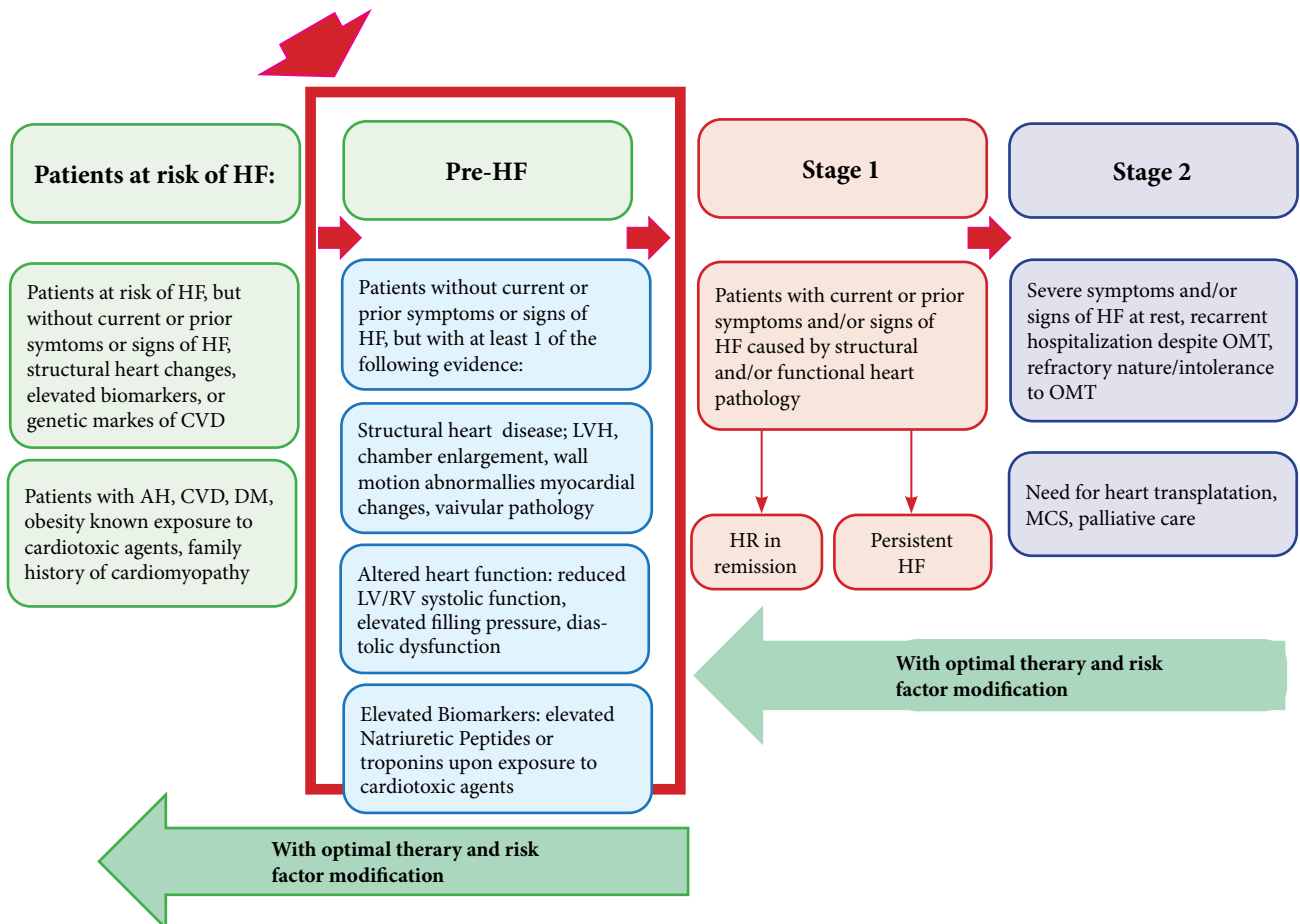


Fig. 1. Modification of the classification by Heidenreich PA, et al. and Bozkurt B [3].

is particularly important for young patients, as early intervention can prevent the development of more serious CVD in the future.

The HF classification that includes a pre-stage, as proposed by the European Society of Cardiology and the American Heart Association, has gained widespread acceptance and has been integrated into clinical practice, including within Russian guidelines [15, 21]. This concept enables more effective identification of individuals at high cardiovascular risk, such as young men with MetS, and facilitates the application of early preventive treatment. Consequently, the timely diagnosis and correction of risk factors can significantly reduce the prevalence of HF and improve long-term patient prognosis.

Pathophysiology of pre-heart failure

Pre-HF in young individuals with MetS develops in several stages [2]. The initial stage involves endothelial dysfunction, which reduces nitric oxide production, leading to vasoconstriction and elevated blood pressure. These vascular changes increase the load

on the heart, particularly the atria, which begin to hypertrophy and lose their efficiency [22].

Furthermore, IR, inherent to MetS, promotes the accumulation of adipose tissue. This, in turn, leads to obesity, increased circulating blood volume, and elevated atrial pressure [23]. These factors contribute to further cardiac remodeling, exacerbating atrial dysfunction and increasing the risk of pre-HF. Chronic inflammation, a hallmark of MetS, also plays a significant role in the development of pre-HF [24]. Elevated blood levels of CRP and interleukins activate immune cells, causing damage to blood vessels and the myocardium, thereby impairing its function [25].

Clinical presentation of pre-heart failure

Young men with MetS may not experience overt symptoms during the pre-HF stage. However, as the condition progresses, symptoms such as shortness of breath, fatigue, swelling in the legs and ankles, and chest heaviness may appear. These manifestations can be nonspecific and similar to other conditions, complicating early diagnosis.

Diagnosing pre-HF in patients with MetS primarily involves echocardiography and analysis of remodeling markers (BNP and NT-proBNP) and inflammatory markers such as CRP (standard CRP, sCRP, and high-sensitivity CRP, hsCRP) and fibrinogen [26]. Echocardiography allows for the assessment of atrial size and function, as well as the detection of signs of hypertrophy and remodeling. Monitoring blood lipid and insulin levels is also crucial, as changes in these parameters indicate the presence of MetS and a predisposition to CVD [27].

Management strategies for pre-heart failure

Pre-HF is characterized by the absence of HF symptoms and signs, yet the patient has risk factors such as AH, diabetes mellitus, obesity, or a history of CVD. According to the updated clinical guidelines of the RSC, approved in 2024 and effective from 2025, treatment at this stage is focused on modifying risk factors and preventing disease progression [3].

Main therapeutic approaches for pre-HF

1. Blood pressure control: Maintaining target blood pressure levels (<130/80 mm Hg) through lifestyle modifications and, if necessary, pharmacotherapy (renin-angiotensin-aldosterone system inhibitors or calcium channel blockers — particularly in the presence of left ventricular remodeling signs; β -blockers should be prescribed with caution and only when clearly indicated, as they may worsen insulin resistance).

2. Lipid profile management: Prescribing lipid-lowering agents in cases of atherogenic dyslipidemia or high cardiovascular risk (statins, ezetimibe, omega-3-acid ethyl esters, bempedoic acid; PCSK9 inhibitors, inclisiran, or pelacarsen may be used if required).

3. Glucose level monitoring and control: Ensuring adequate glycemic control in patients with diabetes mellitus (metformin, empagliflozin, dapagliflozin)

4. Limiting cardiotoxic exposure: Restricting the use of cardiotoxic agents (non-steroidal and steroidal anti-inflammatory drugs — only for strict indications).

5. Avoiding harmful habits: Providing recommendations for smoking cessation and limiting alcohol consumption.

6. Physical activity: Encouraging regular physical exercise tailored to the patient's condition.

7. Dietary recommendations: Reducing intake of salt and saturated fats, increasing consumption of fruits, vegetables, and whole grains, and weight management.

Thus, the modern approach to managing pre-HF in young men with MetS is based on early and aggressive modification of risk factors, the use of organ-protective medications, and regular monitoring of subclinical cardiac impairment markers. This strategy aims to prevent progression to overt clinical HF. It is important to note the typically low treatment adherence in this patient group. Therefore, motivational support and digital tools (software, telemedicine) are necessary.

Prognosis and long-term perspectives

The prognosis for young men with MetS-related pre-HF depends on the timeliness of diagnosis and the effectiveness of treatment [3, 9]. With adequate intervention focused on controlling risk factors and improving cardiac function, many patients can achieve significant improvements in quality of life and avoid disease progression. However, without proper treatment, pre-HF can lead to the development of more serious conditions, including chronic heart failure and atherosclerosis [28, 29].

Conclusion

Pre-HF in young men with MetS is a medical problem, requiring a combined approach for diagnosis and management. Introducing the concept of pre-HF into clinical practice allows the identification of patients at early stages of risk of disease development and its effective prevention. Contemporary treatment strategies, including pharmacologic therapy, lifestyle modification and risk factors control, might significantly improve the prognosis and decrease the prevalence of CVDs in this population.

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Review article

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Effectiveness of sodium-glucose cotransporter 2 inhibitors in the treatment of chronic heart failure

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Chronic heart failure (CHF) is one of the outcomes of cardiovascular diseases (CVDs) that significantly worsens patient prognosis. For this reason, research has been ongoing for decades to find effective drugs that can improve the prognosis for patients with CHF.

Methods. The article was prepared based on a review of literature published in peer-reviewed journals available on PubMed, eLIBRARY.RU, CyberLeninka, and other research platforms over the last 10 years.

Results. Despite significant progress in understanding the pathogenesis and treatment of CHF, the search for effective therapies continues. One of the discoveries of recent years has been drugs from the class of sodium-glucose cotransporter 2 inhibitors (SGLT2i), the efficacy of which in CHF has been demonstrated in a number of major clinical trials.

Conclusion. SGLT2i are antidiabetic drugs that hold an important place in the management of type 2 diabetes mellitus. They have been shown to favorably influence the

course of CHF, thereby reducing cardiovascular risks and mortality from CHF.

Keywords: sodium-glucose cotransporter 2 inhibitors, chronic heart failure, diabetes mellitus, left ventricular ejection fraction, blood volume, cardiovascular diseases.

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Introduction

Chronic heart failure (CHF) is a condition that represents one of the outcomes of cardiovascular disease (CVD). Its global prevalence ranges from 0.3% (India) to 5.3% (Australia) [1]. Mortality from CHF in various forms of coronary heart disease (CHD) in Russia is 35%. The most common causes of CHF development are arterial hypertension and CHD [1]. The overall prognosis for patients with CHF is unfavorable. According to the EPOKHA study, the average life expectancy for patients with CHF of functional class (FC) 1–2 is 8.4 years (95% confidence interval [CI]: 7.8–9.1 years), while for CHF FC 3–4 it is 3.8 years (95% CI: 3.4–4.2 years) [2].

Research has been ongoing for many decades to find effective drugs capable of improving the prognosis for patients with CHF.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have demonstrated a favorable effect on the course and outcomes of CHF based on the results of numerous large studies; however, the extent of this effectiveness remains a subject of debate.

SGLT2i are drugs that inhibit sodium-glucose cotransporter-2 (SGLT2) proteins, located predomi-

Results

Potential mechanisms of action of SGLT2i

As mentioned above, SGLT2i inhibit the reabsorption of glucose in the proximal renal tubules, inducing glucosuria and thereby lowering plasma glucose levels. This occurs when the glucose transport proteins become fully saturated, reaching maximum glucose reabsorption capacity, and the excess glucose begins to be excreted in the urine [3].

Results from clinical studies indicate that SGLT2i reduce body weight by 1 to 4 kg [4]. For instance, according to completed randomized clinical trials (RCTs), monotherapy with ipragliflozin was associated with an average body weight reduction of 2.33 kg ($p < 0.001$) and a waist circumference reduction of 1.61 cm over 16 weeks [5]. Furthermore, the weight loss is attributed to a reduction in visceral fat, not just a decrease in intravascular volume due to reduced blood volume (BV) from increased diuresis [4].

SGLT2i also possess a modest antihypertensive effect, reducing both systolic blood pressure (SBP) and diastolic blood pressure (DBP). This is related to their diuretic, osmotic diuretic, and natriuretic ef-

fects in the epithelial cells of the early proximal tubules of the kidneys. Under normal conditions, these transporters reabsorb glucose and sodium into the bloodstream [3]. Thus, drugs in the SGLT2i group inhibit the reabsorption of glucose and sodium in the proximal renal tubules by blocking the sodium-glucose cotransporters. To date, known representatives of this drug class include canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, and luseogliflozin.

Methods

The materials for this review article were gathered from peer-reviewed publications indexed in PubMed, eLIBRARY.RU, CyberLeninka, and other research platforms over the last 10 years. This timeframe encompasses the publication of pivotal clinical trials relevant to the subject. The literature search employed the following key terms: SGLT2 inhibitors, cardiometabolic disorders, chronic heart failure, cardiovascular complications, and type 2 diabetes mellitus.

Studies or articles that did not meet quality standards were excluded from the analysis.

fects, which lead to a reduction in BV, decrease cardiac preload, and thereby improve cardiac function [3, 6]. Additionally, SGLT2i therapy has been shown to reduce arterial stiffness and BP, i.e., myocardial afterload, which can be explained by their positive effect on endothelial function through increased nitric oxide (NO) production, released in response to reduced oxidative stress [7].

SGLT2i therapy has been associated with increased serum erythropoietin levels. This is because SGLT2i suppress sodium reabsorption, thereby reducing adenosine triphosphate (ATP) consumption by Na^+/K^+ -ATPase. Consequently, hypoxic conditions in epithelial cells improve, potentially leading to the conversion of myofibroblasts into erythropoietin-producing fibroblasts [8].

There is a viewpoint that SGLT2i improve myocardial metabolism by shifting energy substrate utilization to ketone bodies, the levels of which increase during SGLT2i therapy [6, 9].

Various studies have observed that dapagliflozin and empagliflozin can reduce left ventricular myocar-

dial mass [7]. Furthermore, it has been demonstrated that dapagliflozin can attenuate myocardial fibrotic changes by suppressing collagen synthesis through increased macrophage activity and inhibition of myofibroblast differentiation [10–12].

SGLT2i have been found to reduce levels of reactive oxygen species (ROS), which have damage the myocardium, causing electrophysiological and contractile dysfunction of cardiomyocytes, mitochondrial dysfunction, and enhanced myocardial fibrosis. ROS contribute to endothelial dysfunction associated with heart failure (HF) by accelerating NO degradation, converting it into peroxynitrite [13].

It has been demonstrated that SGLT2i lower blood leptin levels and increase the concentration of adiponectin, which has a cardioprotective effect, including reducing myocardial infarct size [14].

Numerous studies have established that these drugs inhibit NHE1 (sodium-hydrogen exchanger type 1), widely expressed in the cell membrane of all tissues, especially in the myocardium. This leads to reduced intracellular sodium and calcium levels, improving mitochondrial function and enhancing cardiomyocyte viability [6]. Inhibition of NHE3 (sodium-hydrogen exchanger type 3) by SGLT2i in the proximal tubules reduces sodium reabsorption [15]. Dysregulation of sodium handling plays a crucial role in the development and progression of CHF, as intracellular sodium concentration in cardiomyocytes is critical for cardiac electromechanical coupling and contractility. In CHF, cytosolic sodium concentration in cardiomyocytes increases due to an imbalance between ion influx and efflux. Sodium-calcium exchange in cardiomyocytes regulates cardiac contractility, and disruption in the homeostasis of these ions contributes to the contractile dysfunction present in CHF [16].

It has been established that empagliflozin can reduce pulse pressure, which may increase with greater vascular wall stiffness. Furthermore, empagliflozin was found to lower markers of arterial stiffness [17]. Empagliflozin treatment is associated with a 14.4% reduction in carotid-femoral pulse wave velocity and a 7.8% reduction in central pulse pressure.

Treatment with SGLT2i leads to a reduction in levels of proinflammatory cytokines, namely CRP, TNF- α , IL-6, and MCP-1. Another mechanism for reducing inflammation is decreasing renal urate reabsorption, thereby lowering blood levels of the proinflammatory

uric acid. Moreover, SGLT2i increase NO bioavailability by suppressing its degradation pathway. Reducing inflammation is significant because enhanced systemic inflammation markedly increases the risk of atherosclerotic cardiovascular disease [18].

Adverse effects of SGLT2i

It has been found that SGLT2i therapy leads to a slight increase in LDL cholesterol and a 10% reduction in 1,25-dihydroxyvitamin D levels [19]. Additionally, frequent occurrences of vulvovaginal candidiasis and lower urinary tract infections have been noted with SGLT2i use [20].

Contraindications for SGLT2i include: type 1 diabetes mellitus, diabetic ketoacidosis, severe liver failure, renal failure with a glomerular filtration rate (GFR) < 45 mL/min/1.73 m², pregnancy, and breastfeeding. SGLT2 inhibitors are also contraindicated in patients undergoing hemodialysis¹.

Evidence base for the efficacy of SGLT2i in CHF treatment

One of the studies that proved the efficacy of SGLT2 inhibitors in treating CHF is the SOLOIST-WHF trial (Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure), conducted from 2018 to 2021. It investigated the effect of sotagliflozin on cardiovascular outcomes in patients with type 2 diabetes following an episode of worsening heart failure. This study included 1,222 patients randomized into two groups (608 received sotagliflozin and 614 received placebo). During the follow-up, it was found that the group receiving sotagliflozin had a significantly lower total number of cardiovascular deaths, hospitalizations, and urgent visits for heart failure compared to the placebo group — 51.0 vs. 76.3 events (relative risk [RR] = 0.67; 95% CI: 0.52–0.85; $p < 0.001$). The rate of cardiovascular death was 10.6 events per 100 patient-years in the sotagliflozin group and 12.5 events per 100 patient-years in the placebo group (RR=0.84; 95% CI: 0.58–1.22) [21].

Another study demonstrating the efficacy of SGLT2i was the EMPEROR-REDUCED trial (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction), conducted in 2020. This trial included 3,730 patients with CHF of NYHA class 2–4 and a left ventricular ejection fraction

¹ Vidal drug database. <https://www.vidal.ru/>

(LVEF) $\leq 40\%$, who received either empagliflozin (10 mg daily) or placebo in addition to recommended therapy. Over 1 year and 4 months, the number of cardiovascular deaths or hospitalizations due to worsening HF was higher in the placebo group (462 (24.7%) out of 1,867 patients), than in the empagliflozin group (361 (19.4%) out of 1,863 patients). The effect of empagliflozin was also found to be similar in patients with and without diabetes [22].

In the DAPA-HF trial, which studied 4,744 patients with CHF of NYHA class 2-4 and LVEF $\leq 40\%$, divided into groups receiving either dapagliflozin (10 mg daily) or placebo in addition to prescribed therapy, it was found that the likelihood of cardiovascular death was lower in the dapagliflozin group (8.2%) compared to the placebo group (9.6%), regardless of the presence of diabetes (95% CI: 0.66–1.04). The risk of hospitalization for heart failure was also reduced in the dapagliflozin group (13.7%) compared to placebo (18.2%) (95% CI: 0.63–0.85) [23].

The EMPEROR-Preserved trial involved 5,988 individuals with heart failure and LVEF $\geq 40\%$. Participants were divided into two groups in a 1:1 ratio, with one group receiving empagliflozin (10 mg daily) and the other receiving placebo. The study results established that empagliflozin reduces the risk of cardiovascular death or hospitalization for heart failure by 21% compared to placebo. Empagliflozin was effective for all types of CHF, regardless of the presence or absence of diabetes [24].

Research has shown that in patients with stable CHF and LVEF, switching from renin-angiotensin-aldosterone system blockers to angiotensin receptor-neprilysin inhibitors and adding SGLT2i reduces the one-year mortality rate from 12.2% to 8.9% [25].

It has been established that dapagliflozin promotes reverse myocardial remodeling and improves cardiac contractility. One study included patients with CHF who were prescribed dapagliflozin and patients with atrial fibrillation who served as a comparison group. During dapagliflozin therapy, a statistically significant increase in LVEF was observed from $29 \pm 6\%$ (27–31) to $37 \pm 9\%$ (33–40), $p < 0.001$, along with a reduction in the volumetric and linear dimensions of the left ventricle and left atrium. Specifically, end-diastolic dimension decreased from 70 (64–73) to 63 (60–70) mm ($p < 0.001$), end-systolic dimension from 55 ± 7 (52–58) to 50 ± 7 (47–52) mm ($p < 0.003$), end-diastolic volume

from 239 ± 50 (220–258) to 207 ± 43 mL/m² (191–223) ($p < 0.001$), end-systolic volume from 170 ± 40 (155–185) to 140 ± 33 mL/m² ($p < 0.001$), left atrial dimension from 48 ± 5 (46–49) to 44 ± 6 (42–46) mm ($p < 0.001$), and left ventricular myocardial mass from 156.5 (130–180) to 109 (98–145) g ($p = 0.001$) [26].

In a clinical study of patients with CHF and iron-deficiency anemia, an increase in hemoglobin concentration and hematocrit was observed after treatment with dapagliflozin — from 13.4 ± 0.3 to 13.9 ± 0.4 g/dL ($p = 0.02$) and from $41.3 \pm 0.9\%$ to $43.5 \pm 1.0\%$ ($p = 0.01$), respectively. The therapy also reduced hepcidin and ferritin concentrations by $24 \pm 3\%$ and $32 \pm 7\%$ respectively, while increasing levels of the hepcidin inhibitor erythroferrone by $71 \pm 22\%$ and causing a transient $21 \pm 7\%$ increase in erythropoietin levels after 6 weeks of treatment. Additionally, dapagliflozin increased plasma transferrin levels by $11 \pm 3\%$ and the expression of transferrin receptors 1 and 2 in blood mononuclear cells by $59 \pm 14\%$, with no changes observed in the expression of the cellular iron exporter ferroportin. Thus, it was shown that dapagliflozin positively influences erythropoietin synthesis in patients with CHF and anemia [27].

It has been established that empagliflozin significantly improves parameters of diastolic function after 6 months. This study included 84 patients with CHF of NYHA class 2–3, LVEF $> 50\%$, signs of diastolic dysfunction, and elevated NT-pro-BNP levels (> 125 pg/mL). They were randomized into two equal groups: one group received empagliflozin (10 mg) in addition to standard therapy, while the other received standard therapy alone. All patients underwent transthoracic echocardiography before the study and after 6 months of therapy to assess standard parameters of systolic and diastolic LV function. Key efficacy parameters included the E/e' ratio (average of septal and lateral positions), left atrial volume index, and left ventricular mass index. In the empagliflozin group, a statistically significant reduction in the E/e' ratio and left atrial volume index was observed. In the control group, no significant changes in these parameters were found. The effect on the left ventricular mass index was statistically insignificant in both groups [28]. To date, there is no data on whether genetic population diversity affects SGLT2i therapy. Thus, it can be concluded that SGLT2i therapy provides the same effect in all patients [29].

Conclusion

Nowadays, clinicians have a wide range of drugs of various classes with different mechanisms of action at their disposal, the efficacy of which has been proven in the treatment of patients with CHF. However, the prognosis for these patients remains unfavorable, which drives the ongoing search for new medications capable of improving life expectancy and slowing the progression of CHF.

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in the International heart and vascular disease journal

Edit from December, 2021

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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,...

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

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

³RD 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.

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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).

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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/ictcp/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. Manuscript submission 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

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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 $>$, $<$, \pm , $=$, $+$, $-$ 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.

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

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

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 ($M \pm m$; $M \pm SD$; 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).

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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.

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

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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.

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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.

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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.

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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 protec-

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X. After the publication in the journal

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

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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:

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XIV. Journal subscription

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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

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Text should be typed with an interval of one line spacing, font Times New Roman, 12 pt; to highlight the accents it is recommended to use italics rather than underlining (except Internet links). All images, graphics and tables are placed within the text according to the meaning of the particular part of text (and not at the end of the document).

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