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COVID-19 and cardiovascular diseases

The new direction in medical management of chronic heart failure with reduced ejection fraction

Prospects and clinical effectiveness of remote blood pressure monitoring

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Contents

Editor's Welcome

Dear colleagues!

In the 27th issue of the International Heart and Vascular Disease Journal, there are the leading article, original and review articles.

The leading article section presents the review prepared by professor Yavelov I.S. on the issue of increasing concern — the association between coronavirus infection and cardiovascular diseases. It has been established that coronavirus infection can cause cardiac and vascular lesions and, therefore, aggravate the course of cardiovascular diseases. Presented article highlights the main strategies for the management of patients with viral infection and cardiovascular diseases.

Three articles are published in the "Original articles" section. The first article presents a 15-year overview of changes in attitude towards disease prevention. Over 15 years, young and middle-aged Tyumen men developed more positive attitudes towards the need of cardiovascular disease prevention, which creates favorable conditions for the work of preventive health care services. The second study aimed to assess the clinical effectiveness and prospects of remote ambulatory blood pressure monitoring in patients with arterial hypertension. The study enrolled 100 patients. Over the 6-month observation period target blood pressure levels of 135/85 mmHg were achieved in 70% of patients. In most cases antihypertensive therapy was corrected by changing the drug dosing or increasing the number of medications. The third original article studied the dynamics of lipid panel in patients with coronary artery disease, obesity and residual dyslipidemia, who receive optimal statin therapy and follow standard low-calorie diet with additional lipid-lowering product with direct hypolipidemic action. Low-calorie diet for the correction of residual dyslipidemia during the standard statin therapy was superior to statin therapy potentiation and was associated with lower drug-loading.

The "Review articles" section includes two manuscripts. The first article presents the results of randomized clinical trials on the use of hypoglycemic agents in patients with cardiovascular diseases. The article reveals the mechanism of action of sodium glucose cotransporter-2 inhibitors, the pathogenetic validity and evidence base of their use in patients with chronic heart failure, both with and without type 2 diabetes mellitus. The second article is dedicated to medical procedures and electromagnetic interference safety in patients with implanted pacemakers. Authors discuss electromagnetic interference causes, types of pacemaker malfunction and possible precautions, and the need of pacemaker settings control and correction after the procedures. Magnetic Resonance Imaging, radiation therapy, catheter radiofrequency ablation and some types of physiotherapy are thoroughly analyzed.

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

Rafael G. Oganov
Editor-in-Chief
President of the "Cardioprogress" Foundation

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LEADING ARTICLE

COVID-19 and cardiovascular diseases

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Abstract

The new infectious disease caused bySARS-CoV-2 virus (COVID-19) is commonly seen in patients with cardiovascular risk factors and cardiovascular diseases (CVDs) that can affect the course of infectious process. At the same time, the virus can cause additional damage of heart and vessels, lead to cardiovascular complications and aggravate the course of CVDs. This review article presents the main findings on interaction between these pathologies as well as recommendations for the management of patients with COVID-19 and cardiovascular diseases.

Key words: *COVID-19, cardiovascular diseases.*

Conflict of Interests: None declared.

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Covid-19 and cardiovascular diseases: statistics

According to the available data, the incidence of cardiovascular risk factors and cardiovascular diseases (CVDs) is high in patients with COVID-19.The most common concomitant CVD is arterial hypertension (AH) (Table 1). However, it is obvious that the results of the studies highly depend on the region, selection approaches of patients for hospitalization, as well as their average age. Obtained data requires further systematization, and, therefore, current findings on the frequency of various cardiovascular risk factors and CVDs in patients with COVID-19 will be refined and adjusted in future.

COVID-19 and cardiovascular diseases: interaction features

Many studies claim that COVID-19 in patients with CVD is characterized by more severe course and has worse prognosis.

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Table 1. **The frequency of cardiovascular risk factors and CVDs in patients diagnosed with COVID-19 and admitted to the hospital**

	Inciardi R.M. et al. [1]	Goyal P. et al. [2]	Cummings M.J. et al. [3]	Myers L.C. et al. [4]	Guo T. etal. [5]	Shi S. et al. [6]	Guan W. et al. [7]
Number of patients	99	393	257 with acute hypoxemic respiratory failure	377	187	671 with severe COVID-19	1099
Patient's selection procedure	Consecutive admissions with pneumonia, retrospective analysis	Consecutive admissions, retrospective analysis	Prospective cohort study	Retrospective cohort study	Retrospective analysis of electronic records	Retrospective analysis of electronic records	Retrospective analysis of electronic records
Hospitals	1 hospital inBrescia (Italy)	1 hospital in New York (USA)	2 hospitals in New York (USA)	47 hospitals in California	1 hospital in Yuhan (China)	1 hospital in Yuhan (China)	552 hospitals in 30 regions of China
Period of data collection	4–25 of March, 2020	3–27 of March, 2020	March 2nd — April 1st, 2020	1–31 of March, 2020	January 23 — February 23d, 2020	January 1st— February 23, 2020	December 11th — January 29th, 2020
Cardiovascular risk factors (according to the anamnesis)							
Age (years)	Mean 67,0	Median 62,2	Median 62,0	Mean 61,0	Mean 58,5	Median 63	Median 47,0
Smokers	20%	5.1%	13% (including patients who quitted smoking)		9.6%		12.6%
Dyslipidemia	30%						
Diabetes mellitus (DM)	31%	25.2%	36%	31.3%	15.0%	14.5%	7.4%
Obesity	23%	35.8%					
Chronickidneydisease (CKD)	15%		14%	12.7%	3.2%	4.2%	0.7%
AH	64%	50.1%	63%	43.5%	32.6%	29.7%	15%
Chronic heart failure (CHF)	21%		19%	5.8%		3.3%	
Coronary artery disease (CAD)	16%	13.7%			11.2%	8.9%	2.5%
Atrial fibrillation (AF)	19%					1.0%	

Retrospective analysis of the data collected from 99 consecutively admitted patients with COVID-19 and pneumonia with known outcomes during the first 14 days after admission to one of the hospitals in Brescia (Northern Italy) showed that 53 patients with CVDs (CHF, AF or CAD) had higher levels of creatinine, NT-proBNP, high-sensitive cardiac troponin, and procalcitonin [1]. At the same time,these patients initially much more often received blockers of the renin-angiotensin-aldosterone system (RAAS), anticoagulants and statins. As a result, patients with concomitant CVDs had higher rates of mortality and septic shock (36% versus 15%, p=0.02 and 11% versus 0, p=0.02, respectively), and also showed tendency for more frequent occurrence of respiratory distress syndrome, as well as venous and arterial thrombosis. Mortality increased with age and also was significantly higher in patients with CHF, CAD, DM, CKD and with higher level of NT-proBNP, but not with the history of RAAS blockers and anticoagulants treatment.

Retrospective analysis of the data from 187 patients at the University Hospital of Wuhan (China) showed13.3% hospital mortality rate in patients without CVD and normal cardiac troponin level and 37.5% — in patients with CVD and normal cardiac troponin level, 69.4% — in patients with combination of CVD and increased cardiac troponin level [5]. At the same time, the level of cardiac troponin more often increased in the elderly patients and patients with CVDs (54.5% versus 13.2%) and correlated with the level of C-reactive protein (CRP) and NT-proBNP. Patients with elevated cardiac troponin levels more frequently had malignant ventricular arrhythmias and required mechanical ventilation (MV)

According to the retrospective analysis of the data from 671 patients admitted with severe COVID-19 to the University Hospital in Wuhan (China), increased level of cardiac troponin I was independently associated with: age, the presence of AH, CAD, CHF and increased level of CRP [6]. At the same time, increased cardiac troponin I, as well as increased level of the MB fraction of creatine phosphokinase and NT-proBNP, were independent predictors of hospital mortality. In addition, CAD and chronic heart

diseases were independent predictors of mortality according to multivariable regression analysis.

The analysis of the data from 5257 patients with acute hypoxemic respiratory failure in New York, revealed the following independent predictors of hospital mortality: age, CAD or CHF [3].

The results of all these researches indicate that more severe course of the disease, including myocardial damage and dysfunction in patients with COVID-19 and CVDs, can be explained by combination of reasons.

1. Cardiovascular system damage in patients with COVID-19.

It was found that endotheliocytes of lungs, small intestine, kidneys, heart, liver is frequently damaged in patients with COVID-19 due to direct exposure to the virus, systemic immune / inflammatory response and so-called "cytokine storm", as well as due to general infectious pathological changes [8–13]. Since endothelial dysfunction plays important role in the pathogenesis of CVDs, we can expect aggravation of its clinical manifestations and / or the occurrence of complications in such patients. COVID-19 is also characterized by inflammatory changes in the myocardium with corresponding complications (heart failure, cardiac arrhythmias and conduction disorders) [14]. In addition, cardiovascular system can be damaged due to the progression of existing CVDs, as well as severe dysfunction of other organs (lungs, kidneys, liver).

Thrombus formation is activated during COVID-19 that in most severe cases can lead to consumptive coagulopathy and consumptive thrombohemorrhagic disorder. [15–18]. These processes contribute to the appearance of thrombotic / thromboembolic complications (mainly venous) [19]. In addition, microangiopathy with inflammation and thrombosis without thromboembolism has been described in patients with COVID-19that may be associated not only with the activation of thrombus formation processes, but also with the possible direct endothelium damage by SARS-CoV-2 virus, as well as severe immune inflammation that triggers "immunothrombosis" [8–10]. It is believed that such changes contribute to progressive lung damage during COVID-19. These data also confirm the hypothesis of atherosclerotic plaques destabilization and increased risk of "typical" atherothrombotic complications in patients with COVID-19.

The data on incidence of thrombotic / thrombo-embolic complications in admitted patients with COVID-19 are presented in Table 2. The true incidence

Table 2. **Thrombotic / thromboembolic complications in admitted patients with COVID-19**

Patient contingent	Thrombosis prevention, heparin dose	Total number of thrombotic/ thromboembolic complications	Deep vein thrombosis (DVT) in the lower extremities / pulmonary embolism (PE)	Other thrombosis
388 (362closed cases), 16 % Transferred to intensive care unit (ICU). Doppler ultrasound (DU)/ Computer tomography (CT) due to clinical manifestations [20]	In 75 % not from ICU In 100 % of patients from ICU (intermediate doses 21 %, therapeutic doses 23 %)	7.7 %: in 6.6 %, not from ICU, in 27.6 % from ICU. Half during the first 24 hours after admission.	DVT 4.4 % PE 2.8 %	Ischemic stroke 2.5 % Acute coronary syndrome (ACS) 1.1 %
184 patients with pneumonia in ICU. DU/CT due to clinical manifestations [21]	In all patients (doses were elevated from preventive to intermediate during treatment)	16.8 %	DVT 1.6 % PE 13.6 %	Ischemic stroke, Myocardial infarction (MI) or arterial thromboembolism 1.6 %
198 patients, 37 % in ICUrequiring MV. DU/CT due to clinical manifestations [22]	In all patients (doses close to intermediate)	17 %: 3.2 % in patients not from ICU; 39 % in patients from ICU	DVT11 %: 1.6 % not in ICU, 27 % in ICU PE 5.6 %: 1.6 % not in ICU, 12 % in ICU	
81 patients with severe pneumonia in ICU. DU in all patients [23]	No		25 %	
143 patients, 74.2 % with severe disease course DU in all patients [24]	37.1 %		DVT 46.1 % (34.8 % proximal) — 34.0 % with prevention, 63.3 % without prevention	
452 patients, CT due to clinical manifestations [25]	Not known; 79.3 % of patients with confirmed pulmonary embolism received preventive doses of low-molecular-weight heparin		PE 6.4 %	

of such complications, as well as the effectiveness of different approaches for its prevention, is currently difficult to assess due to significant differences between conducted studies — mainly retrospective studies (databases, medical records analysis), different disease severity in included patients, different approaches for preventionand diagnosis of thrombosis / thromboembolism (usually studies include only patients with clinical manifestations). However, it is obvious that the risk of venous thromboembolic complications increases with disease severity and additional risk factors accumulation.

2. Modification of CVD treatment in patients with COVID-19.

Discontinuation or significant reduction in doses of CVD treatment in patients with COVID-19 has potentially adverse consequences and increases the risk of CVD complications. Such medications include: RAAS inhibitors and beta-blockers in patients with CHF with reduced left ventricular ejection fraction, myocardial ischemia control agents, including antiarrhythmic therapy to prevent life-threatening or severe heart rhythm disturbances in patients with the history of myocardial infarction, antihypertensive treatment in patients with arterial hypertension.

3. Cardiotoxicity of medications used for COVID-19 prevention and treatment.

4. The impact of COVID-19 on health services and lack of resources for timely CVD treatment.

In addition to the lack of resources for the treatment of non-communicable diseases during COVID-19 pandemic, modern (especially invasive) methods for CVD diagnosis and treatment are limited, that is associated with anti-epidemic measures, reduction of contacts with potentially infected patients and limited examinations due to increased risk of contamination. For example, experts from the European Society of Cardiology proposed to increase the amount of time before primary percutaneous coronary intervention in patients with ACS with persistent ST-segment elevation to 60 minutes that will potentially increase mortality, especially in the first hours after the MI onset [14].

5. Psychological consequences of the COVID-19 pandemic associated with quarantine, increased stress level and the fear of hospitals due to possible COVID-19 contamination (including patients with acute CVD manifestations).

The number of hospitalizations for MI significantly decreased in Northern California from January 1 to April 14, 2019 compared with 2020 and correlated with the number of COVID-19 cases [26]. A similar pattern of MI hospitalizations was noted in northern Italy [27]. In one of the regions of Italy the number of percutaneous coronary interventions for acute coronary syndromes (per 100,000 inhabitants) decreased by 32 % during the COVID-19 outbreak compared with 4 weeks before the beginning of the epidemic and decreased by 50 % in the last 2 weeks of the observation period (when the number of diagnosed COVID-19 cases increased) [28]. This decrease was especially pronounced in patients aged over 55 years old.

According to multicenter national registry of patients who were admitted to intensive care units in Italy, from March 12 to 19 during the COVID-19 pandemic the number of hospitalizations for MI significantly decreased by 48 % compared with the same week in 2019 (MI with ST segment elevation on the electrocardiography (ECG) — by 26.5 %, MI without ST segment elevation on the ECG — by 65.1 %), and this pattern was observed in all regions of the country (northern, central and southern) [29]. At the same time mortality rate (relative risk (RR) 3.3; p <0.001) and the frequency of most severe complications — cardiogenic shock, life-threatening arrhythmias, myocardial rupture and severe mitral regurgitation, significantly increased (RR 1.8; p=0.009). However, mortality rate in patients with MI with ST segment elevation on ECG did not increase, when severe complications occurred more frequently (RR 2.1; p=0.037). The frequency of coronary angiography did not decrease (94.9 and 94.5 %, respectively). The number of hospitalizations for heart failure (by — 46.8 %) and AF (by — 53.4 %) significantly decreased.

The reasons for this phenomenon are being analyzed and include both lack of health care system resources and the fear of patients to stay at the hospital and, therefore, the admission of patients with worst prognosis. The rate of hospitalization refusal and their outcomes are worth further investigation.

6. Possible prehospital sudden death rate increase.

The analysis showed that the frequency of cardiac death increased by 52 % outside the hospital in 4 provinces of Italy in the Lombardy region from February 21 to April 20, 2020 compared with the same period in 2019 [30]. At the same time, emergency medical teams arrived later in 2020 (15 minutes versus 12 minutes in 2019; p <0.001) and less often restored spontaneous circulation (8.6 versus 19.8 % in 2019; p <0.001). Proven or possible COVID-19 disease was reported in 74 % of prehospital circulatory arrest cas-

es. During the COVID-19 epidemic the frequency of visits for medical care increased by 94.1 %, while the number of visits due to MI with ST segment elevation decreased by 40.2 %. This may be the consequence of COVID-19 severe clinical manifestations (including in combination with CVD).

Features of cardiovascular diseases diagnosis during COVID-19 pandemic

The approaches to CVD diagnosis during COVID-19 pandemic remain the same. At the same time, scheduled diagnostic procedures may be postponed until pandemic's end in order to reduce the risk of infection transmission and protect healthcare workers.

Patients with severe course of COVID-19 may need additional differentiation of infectious disease progression from the onset of CVD or its complications. For example, D-dimer blood concentration increases in patients with COVID-19 that indicates disease progression and poor prognosis, but not always thrombotic / thromboembolic complications [31,32].

Differential diagnosis of increased cardiac troponin blood level that indicates cardiomyocytes damage is another issue of special concern [11,12]. It can be explained by the occurrence of ischemic myocardial necrosis due to atherothrombosis that lead to myocardial infarction, or myocardium oxygenation imbalance due to hypoxia, hypotension, tachyarrhythmia, etc. (that lead to type 2 MI). In addition, patients with COVID-19 showed other, non-ischemic causes of myocardial damage (necrosis) — myocarditis, microangiopathy with inflammation and thrombosis, takotsubo /stress cardiomyopathy, general infectious process consequences (for example, myocardial damage in patients with sepsis), massive pulmonary embolism. The detection of the cause is essential for the choice of patient treatment strategy (for example, the dual antiplatelet therapy in patients with acute coronary syndrome and additional anticoagulant in patients without type 1 myocardial infarction may be excessive). Obviously, myocardial damage with various manifestations / complications is associated with more severe course of COVID-19.

Features of CVD prevention and treatment during the COVID-19 pandemic

Patients with COVID-19 need to follow standard (recommended) approaches for prevention and treatment of CVD. This is especially important during the COVID-19 pandemic, since an infectious disease contributes to additional cardiovascular system damage and aggravates the course of existing CVDs. However, it was recommended to limit instrumental investigations (especially invasive) and treatment of CVD in patients with less severe cases, when it will not lead to clinical course and prognosis deterioration, in order to reduce the spread of infection and to protect healthcare workers [14]. At the same time, hospitals should attempt to distinguish patients with suspicious or diagnosed COVID-19 and documented absence of the disease [14]. However, the data revealed that existing COVID-19diagnostic methods are limited, especially on early stages. As a result, all admitted patients should be considered potential carriers of the SARS-CoV-2 virus until proven otherwise. Unfortunately, this can be time-consuming, while the treatment of the CVDs cannot be postponed.

When treating patients with CVD and COVID-19, drug interactions should be considered. Such information is published by the group on drug interactions of the University of Liverpool [33], as well as presented in documents prepared by other expert groups [14,16].

It is not clear yet if CVD treatment can affect the incidence and severity of COVID-19. Thus, a wide discussion on the possible role of ACE inhibitors/ angiotensin receptor blockers did not reveal any unambiguous answer: on the one hand, according to pathophysiology, patients who receive ACE inhibitors/ angiotensin receptor blockers should have more severe course of COVID-19, on the other hand, there are clinical evidences of neutral and even positive effect of this group of medications on the course of the disease [1, 5, 29, 34–42]. Some studies also showed lower hospital mortality rate in patients with COVID-19 who received statins [29, 43]. At the same time, it should be noted that these data were obtained from retrospective analysis and are not reliable enough from the perspective of evidence-based medicine.

According to available data on the COVID-19 pathogenesis, it is recommended to use heparin (preferably low molecular weight) in all admitted patients for deep vein thrombosis prevention, with the possibility intermediate dose titration (aboveusual preventive, but below therapeutic) or even therapeutic, in patients with low risk of bleeding [16, 44–46]. There is no consensus on the optimal dose of anticoagulants in patients with COVID-19, but many specialists recommend higher (at least intermediate) doses in patients with severe disease course, when expected frequency of thrombosis / thromboembolism is high, and microvascular thrombosis can be suspected.

However, high doses of anticoagulants can cause hemorrhage into the lung tissue with hemorrhagic pneumonitis in patients on mechanical ventilation [47, 48]. Verified thrombotic / thromboembolic complication is an indication for therapeutic doses of anticoagulants, however, in clinical practice, they can be used in patients with suspicious clinical symptoms when instrumental examination is not available or is postponed [16, 44–46]. One of the arguments for heparin administration in patients with COVID-19 is its pleiotropic and anti-inflammatory effect [49].

Antithrombotic treatment discontinuation due to drug interactions or thrombohemorrhagic syndrome development with consumption coagulopathy can lead to adverse consequences. In particular, is not recommended to use antiplatelet agents in patients with low platelet count [15, 16]. Due to significant change of antithrombotic activity of clopidogrel (decrease) and ticagrelor (increase), they are not recommended to be prescribed together with lopinavir / ritonavir [16].

Some medications that are used to treat COVID-19 can have adverse cardiovascular effects, especially in patients with CVD. For example, chloroquine / hydroxychloroquine can prolong the QT interval and contribute to the occurrence of ventricular arrhythmias, as well as, heart blocks [14]. The length of QT can increase even more when chloroquine / hydroxychloroquine is used together with azithromycin [50].

Before administration of medications that prolong QT interval, experts of the European Society of Cardiology recommend to assess the presence of other risk factors (congenital long QT syndrome, other medications that prolong the QT interval, female gender, age over 65 years, the presence of structural heart disease — reduced left ventricular contractility and myocardial hypertrophy, bradycardia with heart rate below 50 beats per minute, the presence of chronic renal failure, hepatic failure, as well as electrolyte disorders — hypokalemia, hypomagnesemia, hypocalcemia) [14]. All reversible risk of QT interval prolongation and ventricular arrhythmias should be eliminated before the beginning of the treatment. It is also necessary to monitor the ECG with the assessment of the corrected QT interval that should not exceed 500 m/s (or ⩾550 m/s with QRS complex width over 120 m/s) and should not lengthen by over 60 m/s during treatment [14]. It is also recommended to pay particular attention to patients with clinical manifestations of the arrhythmia's onset, as well as patients with vomiting, diarrhea, signs of heart or respiratory failure, and other organs dysfunction.

It is essential to timely suspect the occurrence of CVD aggravation and adjust treatment strategy in patients with COVID-19. After the recovery from COVID-19, it is important to assess its consequences for the cardiovascular system and adjust the treatment, focusing on existing approaches for the management and prevention of various CVDs (there are no specific interventions for patients with COVID-19).

Conclusion

Thus, the COVID-19 adversely affects the course of CVD and vice versa. Therefore, on the one hand, it is essential to maintain effective approaches for the prevention and treatment of cardiovascular complications, on the other hand, to be prepared for more severe course of COVID-19 in such patients. It is necessary to involve the most experienced healthcare professionals for their treatment, who can prevent, recognize and treat not only the new infectious disease and its complications, but also cardiovascular pathology.

Conflict of interests: None declared.

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A 15-year overview of changes in attitude towards disease prevention among men in an open urban population

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Abstract

Objective

To evaluate the changes in the attitude towards disease prevention among men aged 25–64 years over a 15-year observation period.

Materials and methods

We conducted cross-sectional epidemiological studies among working-age men (25–64 years) in 1996 and 2010. As a part of cardiovascular disease screening program, the participants completed the WHO questionnaires "Knowledge and Attitude towards Health" under the interviewer's supervision.

Results

During a 15-year observation period we identified an increase in positive attitude towards disease prevention in working-age men of the open population in a moderately urbanized Siberian city. Positive attitude trends were observed among young and middle-aged men. Over 15 years, young and middle-aged Tyumen men developed more positive attitudes towards the need of cardiovascular disease prevention, which creates favorable conditions for the work of preventive health care services.

Conclusion

The results of our study indicate that strictly standardized methodology and database that we used should be utilized for further monitoring and research of urban population health in order to plan and organize regional prevention programs.

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Keywords*: epidemiological study, population monitoring, open population, attitude towards prevention.*

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Introduction

The reduction in cardiovascular disease mortality can be successfully reached only if people are ready to take action in order to improve their health. It is well recognized that good medical knowledge, positive attitude towards disease prevention and readiness for behavioral changes are the major factors that support population health [1–3]. At the same time, poor social environment and culture can get in the way of disease prevention [4–6].

Motivation to change health behavior can be characterized by multiple parameters that include not only knowledge about cardiovascular disease (CVD) and its risk factors (RF), the ability to prevent and treat it and self-assessment of health status but also the attitude towards disease prevention. These parameters have been studied as the part of the WHO MONICA-psychosocial program [1]. It is extremely important to study these parameters as currently existing preventive measure are not effective enough as they were developed only as a part of a biomedical model of health and healthcare [7]. Studies have shown that the best results in changing health behaviors were reached when information provided was tailored for the needs of specific population groups depending on their education and social status, age, gender and etc. [1, 3, 8, 9].

As for today, both in Russia and worldwide the differences in parameters that characterize the attitude towards health and disease prevention are attributed to gender, ecological and demographic factors, family status and socioeconomical status [1.9–11]. Due to radical socioeconomic changes that took place in the Russian Federation since the "perestroika" period in the 1980s, a great need to study the epidemiology of non-infectious diseases and attitude towards its prevention among Russian population has emerged [12, 13]. The analysis of this information will provide the basis for prognosing the reaction to various preventive programs among population as well as the ability for preliminary evaluation of the amount of preventive measures that need to be taken, the financial costs and the potential effectiveness of preventive programs [7]. Therefore, we consider the analysis and further exploration of the provided data to be much needed and relevant.

Objective

To evaluate the changes in the attitude towards disease prevention among men aged 25–64 years over a 15-year population monitoring period.

Materials and methods

This cross-sectional epidemiological study included working-age men from the Central district of Tyumen city and was carried out from 1996 to 2010. The representative samples were formed form the electoral lists that included men aged 25–64 years using the random number generation method. The samples consisted of 1000 individuals (250 for 25–34, 35–44, 45–54, 55–64 years). The response rate was 79.5 % in 1996 and 85.0 % in 2010.

We used the WHO questionnaires "Knowledge and Attitude towards Health" that were completed under the interviewer's supervision as a part of cardiovascular disease screening program. The study was conducted in accordance with the Good Clinical Practice

Standards and Helsinki Declaration principles. The study protocol was approved by the local Ethics committee. Written informed consent was obtained from all individual participants included in the study.

Statistical analysis was performed using the IBM SPSS Statistics 21.0 software. We performed age adjustment by direct standardization based on the age structure of Russian Federation urban population aged 25–64 years. We used Pearson's chi-squared test (χ^2) to determine if the groups were significantly different from each other. A p-value less than 0.05 was considered statistically significant.

Results

Changes in attitude towards disease prevention among men aged 25–64 years in an open population are presented in Table 1.

The first question in the questionnaire explored general issues of attitude towards disease prevention. We asked if people found disease screening beneficial for their health. Data from the first and

Table 1. **A 20-year overview of changes in attitude towards CVD prevention among men aged 25–64 in an open population**

Question/attitude	Age groups										
	25–34		35–44		45–54		55–64		25–64		Age adjusted value
	Absolute number	%	Absolute number	%	Absolute number	%	Absolute number	%	Absolute number	%	%
1. Do you think that preventive health screenings are good for you?											
1.1. Yes, it's good	147/104	67.4/85.2***	152/184	71.7/88.5***	166/136	74.8/85.5*	194/183	73.5/85.1**	659/607	71.9/86.2***	71.2/86.1
1.2. Probably, yes	68/18	31.2/14.8***	60/24	28.3/11.5***	53/23	23.9/14.5*	67/30	25.4/14.0**	248/95	27.1/13.8***	27.9/13.7
1.3. Probably, no	3/0	1.4/0	- /0	- /0	3/0	1.4/0	3/2	1.1/0.9	9/2	0.9/0	1.0/0.2
2. "Can a healthy man of your age avoid some severe diseases by taking early preventive measures?"											
2.1. Yes, of course	128/71	58.7/58.2	106/150	50.0/72.1***	108/93	48.6/58.5	129/152	48.9/70.7***	471/466	51.4/66.2***	52.5/64.3
2.2. Probably, yes	87/51	39.9/41.8	93/56	43.9/26.9***	93/62	41.9/39	124/62	47.0/28.8***	397/231	43.4/32.8***	42.6/34.8
2.3. Definitely, not	3/0	1.4/0	13/2	6.2/1.0**	21/4	9.5/2.5**	11/1	4.2/0.5**	48/7	5.2/1.0***	4.9/0.9

Note: * statistically significant differences between the first and second screenings;
* $p<0.05$;
** $p<0.01$;
*** $p<0.001$.

second screening programs showed that the changes in attitude towards disease prevention were mostly positive (73.5 % versus 85.1 % respectively). The percentage of men with positive attitude towards disease prevention has steadily improved over the 20-year observation period and changed from 71.2 to 86.1 % respectively, $p < 0.001$ (age adjusted rate). This figure went upin all four age groups. We identified statistically significant differences in the number of positive responses in the surveys conducted before and after the 15-year observation period: "Yes, it is beneficial" in men aged 25–34 years (67.4–85.2 %, $p < 0.001$), 35–44 years (71.7–88.5 %, $p < 0.001$), 45–54 years (74.8–85.5 %, $p < 0.05$), 55–64 years (73.9–88.6 %, $p < 0.01$). The rate of ambiguous answers such as "Probably, yes" or "Probably, no" declined over the 15-year observation period (the decrease in the number of "Probably, yes" answers was statistically significant). The percentage of respondents who were uncertain if disease prevention measures were beneficial for their health dropped from 28.9 % to 13.9 % (age adjusted values). In the second screening less respondents from each age group answered "Probably, yes"(see Table 1).

The first screening showed that half of those surveyed answered positively to the question "Can a healthy man of your age avoid some severe diseases by taking early preventive measures?" (52.5 %). At the second screening the number of respondents who answered positively increased to 64.3 %. Such changes were noted not only in the younger age groups (35–44 years, 50–72.1 %, $p < 0.001$), but also in the older ones (55–64 years, 48.9–70.7 %, $p < 0.001$). The percentage of those who were unsure about the importance of the preventive measures decreased both in the younger and older age groups as well as in the general population over the 15-year observation period (42.6–34.8 %, $p < 0.001$). Moreover, the percentage of respondents who didn't believe that preventive measures were effective at all decreased from 4.9 % to the minimal number of 0.9 % over the 15-year observation period ($p < 0.001$). Such a significant reduction occurred in all four described age groups and in the youngest age group thisfigure fell to zero (see Table 1).

Discussion

We evaluated changes in the attitude towards cardiovascular disease prevention that occurred during a long-term observation period and identified specific tendencies that reflect a growing need for preventive measures among urban working-age population. It is well known that the studied parameters are reliable indicators of population health and accepted general measure of population health that is also a prognostic factor of disease incidence and mortality [4, 7].

Previous research has established that the low level of cardiological health among Russian population is due to high prevalence of unconventional risk factors including psychosocial risk factors. Therefore, when forming the modern morbidity and mortality structure in Russia biopsychosocial model of disease control should take into account the changes that occurred at the second epidemiological transition [12].

According to the conception which was the basis of attitude towards health and disease prevention research, successful understanding of the main determinants of objective and subjective health indicators will allow to identify objective indicators of population health that are extremely costly and difficult to study [1].

When planning prevention programs, it is crucial to consider attitude towards disease prevention and health among population. The majority of men who were involved in our study agreed that preventive health screenings were good for them and the prevalence of such opinion significantly increased compared with the last decade of the twentieth century [3]. As such, our findings show that the majority of men in an open population not only have developed more positive attitude towards the idea of disease prevention but are also ready to implement these ideas. Such results seem optimistic enough and are probably due to changes in the political situation and introduction of social and political reforms since the 'perestroika' times during which the first screening was conducted in the Tyumen population. Both of these factors led to the major changes in Russian society. At the same time, according to the results of the previous study of Tyumen population, the tendency to care more about health was identified only after the coronary artery disease was already diagnosed [14]. This situation is, probably, the main reason of the existing problems in preventive cardiology as people are usually quite reluctant to change their opinion about the importance of preventive measures [2, 13]. Positive attitude trends towards the need of cardiovascular disease prevention were observed among young and middle-aged Tyumen men, which creates favorable conditions for the work of preventive health care services.

Conclusion

The results of our study indicate that strictly standardized methodology and the formed database that we used should be utilized for further monitoring and research of urban population health in order to plan and organize regional prevention programs.

We can make several conclusions from our study:

1. During a 15-year observation period we identified a rise in the positive attitude towards disease prevention in working-age men of the open population in a moderately urbanized Siberian city.

2. Positive attitude trends towards the need of cardiovascular disease prevention were observed among young and middle-aged Tyumen men.

Conflict of interests: None declared.

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Prospects and clinical effectiveness of remote blood pressure monitoring

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Objective

To assess the clinical effectiveness and prospects of remote ambulatory blood pressure (BP) monitoring in patients with hypertension (HTN).

Materials and methods

The study enrolled 100 patients with uncontrolled HTN who performed self-measured blood pressure monitoring twice daily using the devices with the option of transmitting measurements to the remote monitoring center via a GSM channel. The information was processed and then transmitted to the physician's personal account in order to assist clinical decisions.

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Results

Over the 6-month observation period target blood pressure levels of 135/85 mmHg were achieved in 70% of patients. In most cases antihypertensive therapy was corrected by changing the drug dosing or increasing the number of medications.

Conclusion

Remote blood pressure monitoring is an effective and reliable way to control blood pressure.

Keywords*: arterial hypertension, blood pressure, telemedicine, remote monitoring.*

Conflict of interests: None declared.

Blood pressure monitors with GSM communication were provided by LLC 'Remote medicine' free of charge.

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Introduction

Hypertension (HTN) is the leading risk factor (RF) of premature death and the main cause of disability worldwide. The prevalence of HTN rises with age and is especially high in older age groups, where HTN coexists with other comorbidities. Uncontrolled HTN is associated with the development of cardiovascular events such as cerebrovascular events, myocardial infarction and sudden cardiac death [1, 2].

At the same time, according to the results of some epidemiological studies, traditional management of patients with HTN is still insufficient to reach target blood pressure level. According to the study of epidemiology of cardiovascular disease and its risk factors in various regions of Russia (ESSE-RF), only 1/3 of women and 14,4% of men reach target blood pressure level [3]. Data from the outpatient registry of cardiovascular disease in Ryazan Oblast showed that in only 25,6% of patients blood pressure <140/90 mmHg was reached [4]. The similar tendency was noted in other studies [2].

Obviously, the common methods of outpatient HTN management are not effective enough. The reasons of insufficient HTN treatment effectiveness include poor treatment adherence and blood pressure control, irrational utilization of healthcare resources and incomplete outpatient management [5–7]. Today, incorporation of telemedicine technologies in the general medical practice seems like a perspective method of improving the effectiveness of patient management [7, 8]. We suppose that use of the devices with the option of transmitting blood pressure measurements to the remote monitoring center via a GSM channel (tonometers) will improve blood pressure control and reduce the load on medical professionals.

Materials and methods

The study was conducted according to the principles laid down in the Helsinki declaration and Good Clinical Practice standards in Ryazan City Clinical Hospital № 11and Ryazan State Medical University.

Study protocol was approved by the Ethics Committee of Ryazan State Medical University. Remote blood pressure monitoring was performed according to the protocols accepted by the Ministry of Health of Russian Federation: "The Protocol of Incorporating Remote Blood Pressure Monitoring in Patients with Hypertension in Compulsory Medical Insurance" [9] as well as the guidelines "Outpatient care in chronic non-communicable diseases and in patients with a high risk of its development. Methodology of remote outpatient care" [10].

Telemedical monitoring of patients with HTN was performed with the assistance of LLC "Remote medicine", on site of which the Remote Monitoring Center (RMC) was organized. In the RMC we formed an automated system of telemedical monitoring that included the software-hardware complex. The RMC performed remote monitoring of patients that consisted of blood pressure control, collection, storage and processing of the collected figures, provided round-the-clock informational support of the patients and medical workers as well as online access to the remote telemedical monitoring program for physicians.

Our study included 100 patients with HTN whom LLC "Remote medicine" provided with the blood pressure monitors with GSM communication free of charge. The leading coordinators of the outpatient monitoring were the physician and the RMC operator. The operator worked in the RMC for 24 hours and provided continuous informational phone support for patients and physicians. The physician organized re-

mote monitoring, adjusted the program according to the assigned criteria and then, based on the collected data, decided whether to make any changes in the patient management.

The physician and the operator registered in the RMC Web-interface and gained access to the personal account and a planning tool (planner) before the monitoring started. The planner collected, processed and interpreted any 'events' received form the remote monitors. The events included any medical or non-medical episode that required specific actions determined by the protocol. Medical episodes included any clinically significant events that required actions from the medical workers. Non-medical events included the absence of blood pressure readings. Information about the absence of blood pressure readingы was transmitted to the RMC operator's planner and the operator immediately called the patient and recommended resuming blood pressure monitoring.

All medical episodes were divided into three categories based on their urgency. Episodes were assigned to the first category if the blood pressure level increased over 179/109 mmHg or decreased below 80/50 mmHg. If the operator registered such episodes, he contacted the patient and advised him to take the medications that were recommended by the physician or to call the ambulance. The physician, in turn, made decisions concerning the patient's management during the next two days. Target blood levels were from 134/84 mmHg to 110/70 mmHg. Readings between 135/85 mmHg to 179/109 mmHg or from 111/71 mmHg to 80/50 mmHg were considered to be in the "grey zone".

The inclusion criteria were:

(1) Age 25–75 y.o.;

(2) Assignment to the Ryazan City Clinical Hospital № 11 provided by the Compulsory Medical Insurance;

(3) Office blood pressure readings > 134/84 mmHg;

(4) The ability to perform blood pressure measurements using the remote monitors;

(5) Residence in the area with good GSM signal.

The exclusion criteria were:

(1) Inability to perform blood pressure measurements due to forms and/or features of the co-existent diseases;

(2) Absence of blood pressure measurements or contact with the patient;

(3) Non-compliance to the recommendations given by the physician or operator during telemedical monitoring.

At the first visit all the participants signed informed consent, blood pressure monitor use agreement and consent to the processing of personal data. The physician explained the need to perform the remote telemedical monitoring, the goals, objectives and expected results of the study in an easily understood form. At the first visit the physician also stated the diagnosis based on the physical exam results, medical history and available medical documents that the patient provided. The antihypertensive therapy was then recommended or corrected. The diagnosis, age and gender were registered in the special form in the physician's personal account using the Web interface. Prior to beginning the study all physicians received detailed instructions on how to use the tonometers with an option of transmitting measurements to the remote monitoring center via a GSM channel.

During the telemedical monitoring all the participants performed three blood pressure measurements twice a day using the provided monitors. Then, all measurements were automatically transmitted to the physician's and operator's planners via the GSM channel.

The patients visited office once in two months. They could also contact their provider any time if they had any complains or questions. Antihypertensive therapy could be corrected both during the office visits and via phone calls. However, medication regimen could be corrected via phone only if the dosages that were corrected were previously prescribed on an in-person visit. Remote blood pressure monitoring was performed for 6 months.

The statistical analysis was performed using the Statsoft Statistica 10.0. Numerical and categorical variables were presented as absolute and relative figures [n (%)], and the relative variables were presented as mean and standard deviation (M±m). The Shapiro–Wilk test was used for evaluating whether the observations deviated from the normal curve. We used Student's t-test to determine if the means were significantly different from each other. Two unrelated groups of categorical variables were compared using Pearson's χ^2 test and Fisher's exact test. A p-value less than 0.05 was considered statistically significant.

Results

Our study included 100 patients (77 women and 23 men). All patients had hypertension and did not reach the target blood pressure levels with the traditional outpatient management. The mean age was 59,5±7,8 years.

The analysis of risk factors and associated clinical conditions showed that 17% (n=17) of the included individuals had objective signs of end-organ damage,

but no symptoms or associated loss of function; 83% (n=83) had both signs and symptoms of end-organ damage. Of all the patients 33% (n=33) had stage 1 hypertension and 54% (n=54%) had stage 3 hypertension. Stage 3 hypertension was diagnosed only in 3% (n=3) of the patients included in the study; 10% (n=10) patients had prehypertension (high normal blood pressure) on the first office visit. We stratified all the patients by the cardiovascular risk and found that the majority of patients had high (32%; n=32) or very high (65%; n=65) cardiovascular risk. Three patients (3%) had moderate risk.

During our study period no monitor defects or malfunctions were observed. All patients completed the study.

After 6 months of remote monitoring target blood levels were reached in 70% (n=70) of patients. By the end of the study the number of patients with high normal blood pressure increased from 10% (n=10) to 19% (n=19); p=0,7; the number of patients with stage 1 and stage 2 decreased from 33% (n=33) to 7% (n=7); p <0,001 and from 54% (n=54) to 3% (n=3); p<0,001 respectively. The number of patients with stage 3 hypertension decreased from 3% (n=3) to 1% (n=1); p=0,6 (Figure 1).

During the remote monitoring we corrected antihypertensive pharmacological therapy mainly by increasing the number of medications as well as recommending fixed-dose combination. Of note is that this strategy seemed clinically justified. Compared with just increasing the dose of one drug, the use of fixed-dose combination of several antihypertensive medications from the different pharmacological classes decreases adverse effects of each drug in a combination and results in a tighter control of blood pressure. Moreover, the use of combination drugs significantly improves adherence to therapy and that, in turn, leads to better effectiveness of treatment [2].

After the period of remote monitoring was completed, all patients were offered to continue antihypertensive therapy. The comparison of the number of medications prescribed is presented in Table 1.

Table 1. **The number of prescribed medications before and after remote monitoring**

Number of antihypertensive drugs	First visit	+ 6 months	p
No medications	7	-	-
1 medication	23	8	0,006
2 medications	45	30	0,03
3 medications	17	38	0,001
4 and more medications	8	24	0,003

As can be seen from Table1, the number of patients who received 3 and 4 and more medications increased over the 6 months of observation. At the same time, the number of patients receiving 1 or 2 medications decreased.

The pattern of antihypertensive drugs prescriptions is presented in the Table 2.

Table 2. **The pattern of antihypertensive drugs prescriptions**

Antihypertensive drugs	First visit	+ 6 months	p
Angiotensin-converting-enzyme inhibitors	53	53	1,0
Angiotensin II receptor blockers	35	33	0,8
Diuretics	38	59	0,001
Calcium channel blockers	36	52	0,001
Beta-blockers	28	53	0,001
Other classes	10	14	0,9

As can be seen from Table 1, after the 6-month monitoring period was completed, the number of patients receiving angiotensin-converting-enzyme in-

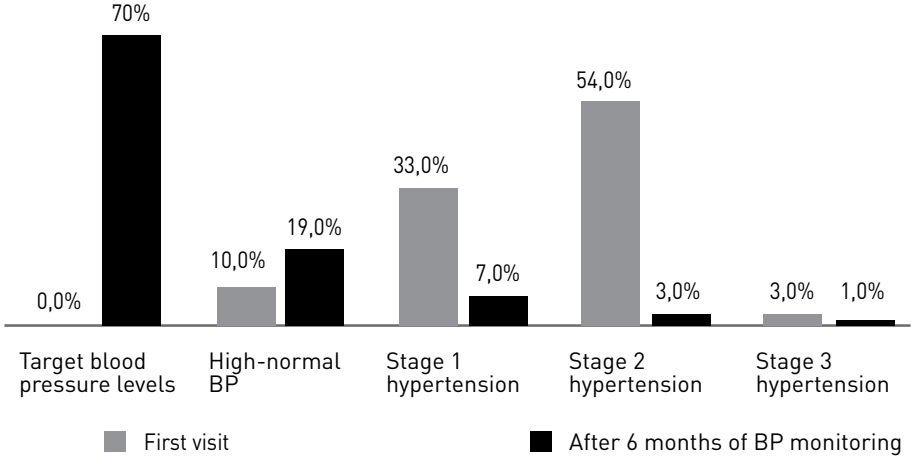

Figure 1. Blood pressure levels at the first office visit and after 6 months of monitoring

hibitors and angiotensin II receptor blockers stayed the same but more patients were prescribed diuretics, calcium channel blockers and beta-blockers.

At 6 months of remote monitoring the number of patients receiving fixed-dose combinations significantly increased from 19% (n=19) to 33% (n=33), p=0,02.

Of all the patients, 30% (n=30) didn't reach target blood pressure levels. Adverse effects occurred in 13% (n=13) and included dizziness and hypotension. We decided to change target levels to high normal blood pressure in these patients with the plans to reach normal blood pressure in the future. In 17% of patients target bloos pressure levels were not reached despite the use of three or more drugs. Considering that these patients were fully compliant and followed all recommendations given by their provider, they can have refractory hypertension.

Discussion

After a 6-month period of remote blood pressure monitoring 70% (n=70) of patients reached target blood pressure levels (<135/85 mmHg). The use of telemedical technologies offered the opportunity to correct antihypertensive therapy according to the latest clinical guidelines and resulted in better blood pressure control. Also, over the monitoring period, the number of antihypertensives prescribed (both separate medications and fixed-dose combinations) markedly increased.

There are some earlier studies of telemedical blood pressure control in the Russian Federation. In one study, the patients sent their blood pressure readings via text messages that were further processed by a special software [11, 12]. In other studies, the patients sent their blood pressure readings via e-mails or text messages for a year [13].

The method of remote blood pressure monitoring that we used in our study uses the device that sends blood pressure figures automatically and doesn't require the patients to know how to write and send e-mails or text messages. That alleviates all the inconveniences for the patient and is crucial for effective management of older patients. Moreover, according to the conditions of the current study, an operator who controlled blood pressure changes, managed the complete absence of blood pressure readings and contacted the patients by phone also took part in the remote monitoring. This allowed to decrease the load on physicians who only had to make decisions concerning any changes in the patient's management. The operator also contacted the patients if he identified high blood pressure levels and recommended to take the prescribed medications or to call for an ambulance. Together it all helped to avoid disturbing the physician when he/she was off work but at the same time the patients were provided with medical help.

One specific feature of telemedical monitoring is that the patient doesn't need to decide to contact the physician himself/herself, but the physician chooses how and when to contact the patient based on the objective monitoring results. As such, the tactics for decision making concerning the 'physician-patient' contacts changes significantly. Usually the patient himself determines whether he/she needs to see the doctor, and the remote monitoring made it possible for the physician to determine the need of the visit and that, in turn, helps to provide more effective blood pressure control. Obviously, the incorporation of telemedical monitoring will offer the opportunity to decrease the cardiovascular disease prevalence and mortality and help reduce the load on medical workers.

Conclusion

Remote blood pressure monitoring in patients with hypertension for a 6-month period helped to reach target blood pressure levels in 70% of patients. This method of remote blood pressure monitoring using the blood pressure monitors with GSM communication is easy to use both for patients and physicians.

Conflict of interest: Blood pressure monitors with GSM communication were provided by LLC 'Remote medicine' free of charge.

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The new possibilities of dietary correction of residual lipid metabolism disorders in patients with coronary artery disease and obesity

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Objective

To estimate the dynamics of lipid panel in patients with coronary artery disease (CAD), obesity and residual dyslipidemia, who receive optimal statin therapy and follow standard low-calorie diet with additional lipid-lowering product (LLP).

Materials and methods

This study included 40 patients with severe coronary atherosclerosis manifestations, who were selected for surgical revascularization of myocardium due to multiple vascular lesions and / or stenosis of proximal segments of

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the coronary arteries and with non-target atherogenic lipoproteins levels during optimal statin therapy. We also estimated additional effect of standard low-calorie diet (LCD) and LLP on the lipid panel.

Results

The results showed that 30-days follow-up of LCD could significantly decrease total cholesterol (TC) level by 15,7% (p=0,0003) and low-density lipoproteins (LDL) by 19,1% (p=0,0024), and the additional intake of LLP increased the efficiency of LCD and contributed to the achievement of reliable reduction of TC by 32.9% (p<0.0001), LDL by 38.1% (p<0.0001), very low density lipoproteins (VLDL) by 44, 5% (p= 0.013) and atherogenic coefficient of 35.2% (p= 0.003).

Conclusion

Based on the obtained results we can conclude that low-calorie diet for the correction of residual dyslipidemia during the standard statin therapy was superior to statin therapy potentiation and was associated with lower drug-loading.

Key words: *coronary artery disease, lipid metabolism, diet, obesity.*

Conflict of interests: None declared.

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Introduction

Coronary artery disease (CAD) is the major cause of death and disability in developed countries [1]. It should be emphasized that Russia is the leading country by the matter of CAD morbidity and mortality — the prevalence is 13,5% [2,3].

Modern approach to the pathogenesis of coronary artery disease is based on the idea of progressive occlusion of coronary arteries that develops over decades in response to the biological effects of various risk factors [4–6]. Hydroxymethylglutaryl-CoA reductase inhibitors (statins) are the basic modern treatment of atherosclerosis with powerful evidence base for their effectiveness for both primary and secondary prevention of the clinical manifestations of atherosclerosis [7,8]. At the same time, the indications fordrug treatmentare constantly expanding in evidence-based medicine, and decreasing fornon-drug approaches at the same time. However, there are still many issues on the treatment of CAD. Therefore, non-drug therapy is very promisingwhen used together with traditional statin therapy. The search for evidence of the efficacy of such approaches is extremely relevant nowadays.

The residual risk of cardiovascular complications in patients receiving optimal statin therapy is an issue of increasing concern. These patients cannot to achieve target values of atherogenic lipoproteins, including low density lipoproteins (LDL), despite receiving therapeutic doses of statins. Most often, high residual dyslipidemia occurs in patients with obesity, and, therefore, is associated not only with the presence of severe metabolic disorders, but also with factors limiting the use of high statins doses, such as non-alcoholic fatty liver disease and steatohepatitis [9].

These patients are in need for new approaches that potentiate the effect of basic lipid-lowering therapy. Such approaches include both pharmacological and non-pharmacological treatment strategies. Pharmacological strategies include, for example, ezetimibe, bile acid sequestrants and some other drugs. However, these approaches are associated with high drug loading and have very limited effectiveness. Many cardiologists see hopes in the new class of targeted drugs, such as evalocumab, that consists of monoclonal antibodies to PCSK9 that decreases the number of LDL receptors [10,11]. The major disadvantage is their high cost.

Dietotherapy (DT) is the most effective and leading non-pharmacological treatment method. At the same time DT cannot be considered as an alternative for statins therapy thath as proven its effectiveness in many studies. However, it has been proven that adequate DT can significantly decrease the level of atherogenic lipids, and in some cases even reduce the dosage of statins [12].

A modern approach to DT is the use of lipid-lowering products (LLP) with known chemical composition enriched with lipotropic components.

Based on the analysis of published data, it is interesting to confirm the effect of new LLP in clinical

practice as an independent nutritional factor for the correction of blood lipid profile disorders in patients with CAD receiving optimal statin therapy.

The objective of this study was to estimate the dynamics of lipid panel characteristics in patients with CAD, obesity and residual dyslipidemia, who receive optimal statin therapy and follow standard low-calorie diet with additional lipid-lowering product.

Materials and methods

An open prospective observational study was carried out on the basis of the Department of Cardiovascular Pathology of Federal State Scientific Institution "Federal Research Centre of Nutrition, Biotechnology and Food Safety" from October 15, 2016 to March 15, 2017.

Characteristics of patients. The study included patients with severe manifestations of coronary atherosclerosis, selected for surgical myocardial revascularization due to multiple vascular lesions and/or stenosis of proximal segments of the coronary arteries. Inclusion criteria were non-target LDL values (over 1.5 mmol / L) during optimal statin therapy (rosuvastatin over 20 mg / day, atorvastatin and simvastatin over 80 mg/day), body mass index (BMI)> 30 kg/m^2.

Given the non-interventional nature of this study, it was governed by the approval of the Ethics Committee of the Federal Research Centre of Nutrition, Biotechnology and Food Safety. All patients were informed of the purpose and nature of the observation and signed informed consent prior to the study. Patients were randomized into two groups by the method of nutritional treatment.

The study included 40 patients meeting the inclusion criteria. Age characteristics and clinical status of all participants are presented in Table 1. Most patients had severe cardiac status: 45–50 % of patients had class III angina, 85–90 % patients revealed arterial hypertension (AH), 35–50 % had clinical manifestations of chronic heart failure (CHF); 35–45 % of patients had non-alcoholic fatty liver disease (NAFLD).

The study follow-up was 30 days and included 3 observation points.

Point 1 (Day 1). On the day of admission, in accordance with the study protocol, patients underwent physical examination, anthropometric, body composition studies, a 6-minute walk test, a study of energy expenditure and fats oxidation rates, proteins and carbohydrates metabolism, and blood sampling.

Point 2 (Day 15). A blood sampling was performed to analyze the blood lipid profile.

Table 1. **Characteristic of studied groups**

Parameters	Studied groups (M±m)	
	Main group	Control group
Number of patients	20	20
Gender, anatomical and age characteristics		
Average age, years	63.08±4.69	61.1±9.9
Men	9	10
Women	11	10
BMI, kg/m^2	39.9±4.4	36.7±5.0
Class of angina		
I (% of patients)	3 (15 %)	2 (10 %)
II (% of patients)	7 (35 %)	9 (45 %)
III (% of patients)	10 (50 %)	9 (45 %)
IV (% of patients)	0	0
Comorbidities		
I–III grade arterial hypertension	18 (90 %)	17 (85 %)
Clinical manifestations of Chronic Heart Failure with over 2ndFunctional Class (% of patients)	10 (50 %)	7 (35 %)
Type 2 diabetes mellitus	13 (65 %)	15 (75 %)
NAFLD (% of patients)	7 (35 %)	9 (45 %)

Point 3 (Day 30) On the day of discharge. Patients underwent anthropometric studies, a study of body composition, basal metabolism, and blood sampling.

Patients from the main group (MG) (N=20) received a standard low-calorie diet (LCD) for 30 days with the additional LLP of 36 g / day (174.6 kcal/day).

Patients from the control group (CG) (N=20) — received LCD only for 30 days.

LCD is a diet with significant reduction of fats and easily digestible carbohydrates, normal protein and complex carbohydrates with increased amount of dietary fiber. Salt is usually limited (3–5 g/day). Dishes should be steamed, stewed, baked, mashed or not mashed. Food temperature — from 15 ° to 60–65 °C. Fluid consumption — 0.8–1.5 liters per day. Fractional nutrition — 4–6 times a day. Chemical composition: proteins — 70–80 g, including animal proteins — 40 g; general fats — 60–70 g, including vegetable — 25 g; total carbohydrates — 130–150 g, dietary fiber —30 g. Energy value: 1350–1550 kcal.

LLP "Dietary Oil" ("SOYUZ-M") is a fat product with the additional skimmed milk powder, with a mass fraction of fat of 53 %. The fatty acid (FA) composition of the LLP "Dietary oil" is presented in table 2.

Chemical composition of both group's diets are presented in table 3.

Biochemical studies were performed using «Konelab 30i» analyzer (ThermoClinicalLabsystems, Finland). Biochemical markers of lipid metabolism were total cholesterol (TC), (⩽ 5.0 mmol/L), triglycerides (TG), (⩽ 1.7 mmol/L), high density lipoprotein cholesterol (HDL) (⩽ 1.0 mmol/L). Very low-density

Table 2. **The fatty acid composition of the LLP "Dietary oil"**

FA name	FA index	FA composition, %
Caprylic	8:0	0.15
Capric	10:0	0.14
Lauric	12:0	2.29
Myristic	14:0	1.57
Palmitic	16:0	35.74
Hexadecenoic	16:1	0.04
Palmitoleic	16:1 7-cys	0.14
Margaric	17:0	0.10
Heptadecene	17:1	0.04
Stearic	18:0	4.44
Elaidic	18:1 9-trans	1.83
Oleic	18:1 9-cys	36.05
Vaccenic	18:1 11-trans	0.89
Iso-octadecanoic	18:2i	0.11
Linoleic	18:2	14.13
γ-linolenic	18:3 ω-6	0.09
α-linolenic	18:3 ω-3	0.90
Arachidonic	20:0	0.48
Gondoic	20:1	0.18
Eicosapentaenoic	20:5	0.23
Docosapentaenoic	22:5	0.07
Docosahexaenoic	22:6	0.35

Table3. **The comparison of the chemical composition of LCD and a modified diet with additional LLP**

Diet composition parameters	LCD	LCD+LLP
Energyvalue, kcal / day	1350–1550	1524,6–1724,6
Proteins, g/day	70–80	70,2–80,2
Fats, g/day	60–70	79–89
Carbohydrates, g/day	130–150	130,3–150,3

lipoprotein cholesterol (VLDL) was determined by dividing the number of TG by 2.2 (l⩽ 0.77 mmol / L); low density lipoprotein cholesterol (LDL) by subtracting the summary of HDL and VLDL from the amount of TC (⩽ 2.8 mmol/l). The atherogenic coefficient (AC) was calculated by the formula of A.N. Klimova (⩽ 3.5 mmol/l).

Statistical analysis was performed using the STATISTICA 10.0 software. When analyzing the main characteristics of patients, parametric criteria were used, and the data are presented as mean± standard deviation or % of the total number of patients. The significance level was set as p<0.05.

Results and discussion

The results of the analysis of blood lipid spectrum dynamics are presented in table 4. Initially, both groups had average lipid profile parameters levels within the reference (but not target) values. Atherogenic lipid fractions were comparable between groups: the level of TC in patients from the MG was 5.47± 0.85 mmol / l, from the CG — 5.71± 1.13 mmol/l (p= 0.463); the level of LDL in MG was 3.62± 0.69 mmol/l, in CG — 3.56± 1.03 mmol / l (p= 0.823), the level of VLDL in the MG was 0.83± 0.57 mmol/l, in CG — 0.81± 0.35 mmol / l (p= 0.89), that allowed to analyze its dynamics. At the same time, the HDL and TG levels between groups were not comparable (HDL: in the MG — 1.05± 0.28 mmol / l, in the CG — 1.49± 0.33 mmol / l, p= 0077) (TG: in the MG= 3.03± 0.80 mmol/l., in the CG= 1.42± 0.49 mmol/l, p<0.01), and, therefore, these indicators were not included in the subsequent analysis.

The analysis of TC level revealed its significant decrease in patients with low-calorie diet (Fig. 1, 2). At the same time, additional inclusion of LLP into the diet allowed to obtain an additional reduction of TC: in patients from the MG the level of TC decreased by 1.13± 0.56 mmol / L (–20.3%, p<0.0001) in 2 weeks, and by 1.80± 1.09 (–32.9%, p<0.0001) in 4 weeks, while in patients from the CG its level only had insignificant tendency to decrease by 0.15± 0.46 mmol/l (p= 0.16) in 2 weeks of treatment and significantly decreased by 0.90± 0.93 mmol/L (–15.7%, p= 0.0003) in 4 weeks.

The intergroup statistical analysis found that the differences were highly significant at the second and third observation points: after 2 weeks the level of total cholesterol in the MG was 4.34± 0.58 mmol/l, in CG — 5.56± 0.79 mmol / l (p<0.0001), after 4 weeks: in

Table 4. **The comparison of blood lipid spectrum parameters during treatment**

Blood lipid spectrum parameters	Initially			After 2 weeks			After 4 weeks		
	MG	CG	p	MG	CG	p	MG	CG	p
TC, mmol/l	5.47±0.85	5.71±1.13	0.463	4.34±0.58	5.56±0.79	<0.0001	3.67±0.73	4.80±0.64	<0.0001
LDL, mmol/l	3.62±0.69	3.56±1.03	0.823	2.68±0.51	3.25±0.71	0.006	2.24±0.72	2.88±0.59	0.003
HDL, mmol/l	1.05±0.28	1.49±0.33	0.007	0.98±,25	1.37±0.31	0.0008	0.99±0.18	1.20±0.31	0.015
VLDL, mmol/l	0.83±0.57	0.81±0.35	0.88	0.59±0.21	0.79±0.34	0.029	0.45±0.22	0.71±0.35	0.009
TG, mmol/l	3.03±0.80	1.42±0.49	<0.01	2.22±0.37	1.49±0.50	<0.0001	1.86±0.60	1.51±0.80	0.124
AC, kg/m^2	2.21±0.81	2.04±0.85	0.52	1.77±0.57	1.95±0.74	0.4	1.42±0.72	1.94±0.90	0.05

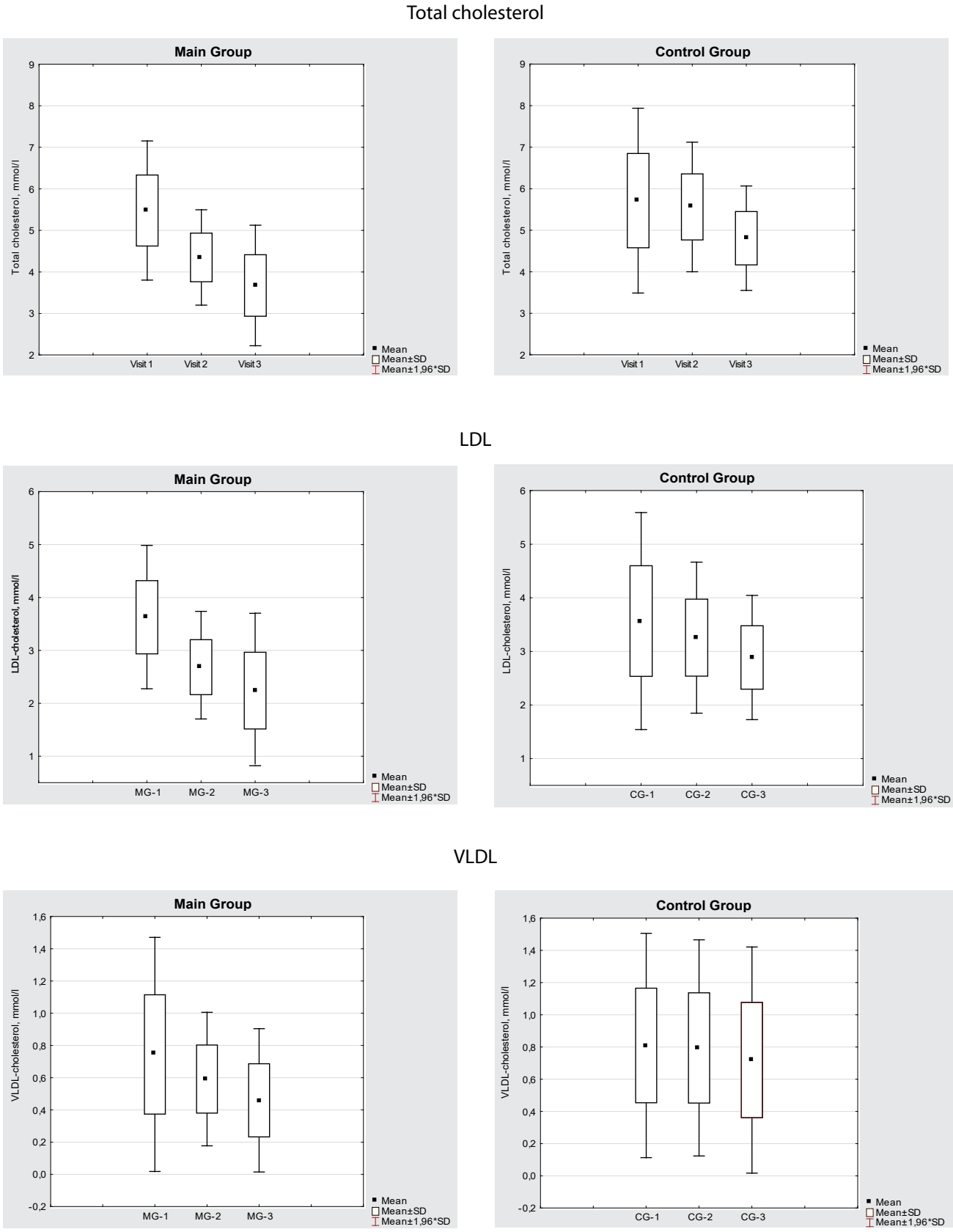
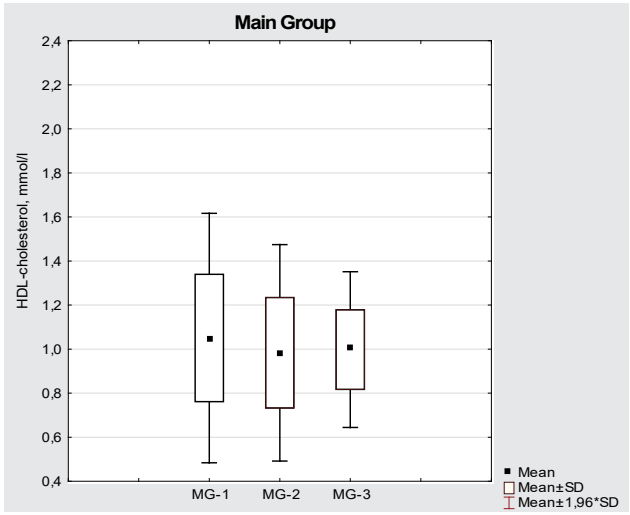
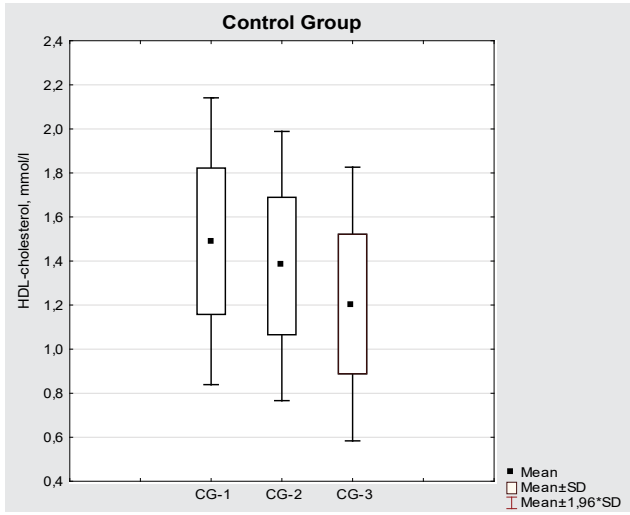


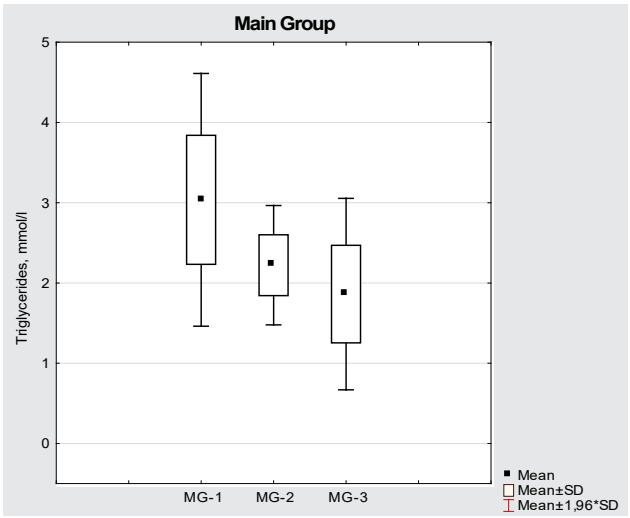
Figure 1. Diagrams of lipid spectrum parameters in patients during treatment

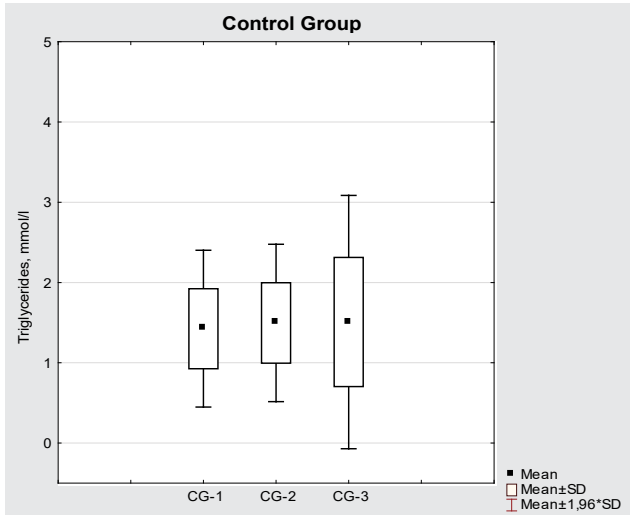
HDL



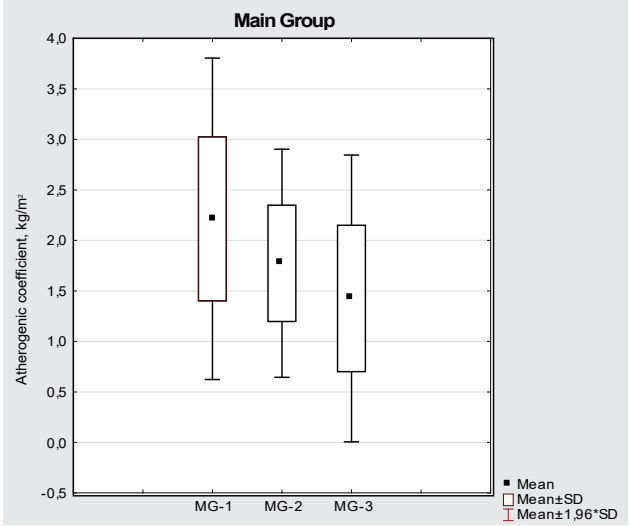


TG





AC



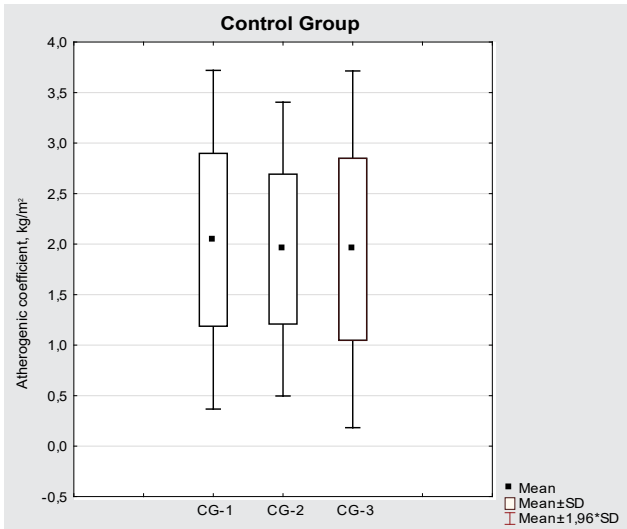


Figure 2. (continuation) Diagrams of lipid spectrum parameters in patients during treatment

MG — 3.67± 0.73 mmol / l, in CG — 4.80± 0.64 mmol/l (p<0.0001).

Average LDL values, despite the ongoing DT, were higher than the target values during the entire observation period, thus, it was not possible to achieve the main goal of diet therapy during this study. At the same time, different nutritional approaches have shown different levels of efficacy. Standard LKD revealed the decrease of LDL by 0.31± 0.43 mmol/L (8.7 %, p= 0.0046) in 2 weeks andin 4 weeks — by 0.68± 0.87 mmol / L (19.1 %, p= 0.0024). The additional LLP intake showed even more pronounced reduction of LDL level — by 0.94± 0.48 mmol / L (–25.9 %, p<0.0001) in 2 weeks and by 1, 38±0.96 (–38.1 %, p<0.0001) in 4 weeks.

Intergroup statistical analysis revealed significant differences during the dynamic observation: at the second observation point the values were 2.68± 0.51 and 3.25± 0.71 mmol / L in the MG and CG, respectively (p= 0.006), at the third point — 2, 24±0.72 and 2.88± 0.59 mmol / L, with p= 0.003.

The dynamics of VLDL level were similar to LDL. VLDL level decreased in both groups during treatment: in the MG it decreased in 2 weeks by 0.24± 0.40 (–28.9 %, p= 0.015) mmol / L and amounted to 0.59± 0. 21 mmol / L, and in 4 weeks — by 0.37± 0.61 mmol/L (–44.5 %, p=0.013) and amounted to 0.45± 0.22 mmol / L. In the CG, the level of VLDL did not change significantly during the entire observation period — there was only tendency to decrease in 2 weeks by 0.015± 0.1 mmol / L (p= 0.5), and in 4 weeks — by 0.09± 0.2 mmol / l (p= 0.058).

Intergroup statistical analysis revealed significant differences in VLDL level, after 2 (at p= 0.029), and 4 (p= 0.009) weeks of treatment.

The analysis of the AC dynamics showed its significant decrease in the MG, as well as the presence of a strong tendency (but unreliable) to decrease in the CG. In the MG, it decreased after 2 weeks from 2.21± 0.81 kg / m^2 to 1.77± 0.57 kg / m^2 — by 0.44± 0.58 kg / m^2 (–19.9 %, p= 0.003), and after 4 weeks — up to 1.42± 0.72 kg / m^2 (–35.2 %, p= 0.003). In the CG, the AC value decreased insignificantly by 0.09± 1.1 kg / m^2 (p= 0.3) and did not change by the end of the observation.

Conclusion

The results obtained in this study allow us to conclude that it should be recommended to use the possibilities of both low-calorie diet and LLP with anti-atherogenic effect in patients with coronary artery disease, obesity, and non-target atherogenic lipoproteins level during standard statin therapy. This approach allows achieving an additional decrease in LDL by more than 44 % without increasing the drug load that is potentially more effective than using other lipid-lowering medications — cholesterol absorption inhibitors or sources of highly purified polyunsaturated fatty acids of the omega-3 family.

Conflict of interests: None declared.

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The new direction in medical management of chronic heart failure with reduced ejection fraction

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Summary

The review article presents the results of randomized clinical trials on the use of hypoglycemic agents in patients with cardiovascular diseases. The article reveals the mechanism of action of sodium glucose cotransporter-2 inhibitors (SGLT2), the pathogenetic validity and evidence base of their use in patients with chronic heart failure, both with and without type 2 diabetes mellitus.

Key words: *chronic heart failure, diabetes mellitus, sodium glucose cotransporter-2 inhibitor.*

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Introduction

Despite the achievements in the managements of chronic heart failure (CHF) over the last years, the prognosis of such patients remains unfavorable. The prevalence of clinically expressed CHF is 4.5% in Russian Federation (RF), and the mortality rate reaches 12% [1, 2]. An increasing number of patients with CHF in RF directly correlates with increased incidence of cardiovascular pathology and cardiovascular disease (CVD) risk factors. Thus, the global number of patients with diabetes mellitus (DM) is growing steadily, and has doubled over the past decade. Our country is no exception. In 2018, over 4.5 million people (3.1% of the population) were diagnosed with DM, and over 4.2 million — with type 2 DM [3]. The results of the NATION study showed that the actual number of patients is twice as large as the official statistics [4]. It has been established that DM is as significant as heart attack in CHF development and progression. In addition, the presence of insulin resistance and related metabolic disorders, including diabetes, aggravates the course of existing cardiovascular pathology and increases the risk of heart failure (HF) decompensation, as well as the frequency of hospitalizations for heart failure [5,6]. An integrated approach for the management of such patients should have a protective effect on the course of concomitant pathology and improve the prognosis. Modern treatment of CHF is based on the inhibition of the renin-angiotensin-aldosterone system (RAAS), and the main groups of medications include: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNi), beta-adrenergic blockers (BAB) and mineralocorticoid receptor antagonists (MRAs). In 2019, foreign and domestic recommendations on CHF included another drugs group that until recently have been used only for the treatment of patients with type 2 DM [2.7]. Initiation of the researchesin this field is associated not only with high prevalence of DM among patients with CHF, but also with similar pathogenesisof these pathologies.

8 classes of sugar-lowering medications are used for the management of patients with DM [3]. However, many of them have limitations in comorbid patients, including patients with CHF. The negative experience of rosiglitazone treatment forced pharmacological companies to provide evidence of cardiovascular safety of newly registered hypoglycemic agents (US Food and Drug Administration Safety (FDA) in 2008 and European Medicines Agency (EMA) in 2012) [8–10]. Subsequently, this lead not only to improvement of the treatment of patients with DM, but also positively affected the prognosis of patients with CHF without DM. The following studies have shown cardiovascular safety of the number of medications. The dipeptidyl peptidase-4 inhibitor saxagliptin did not increase the risk of cardiovascular complications (CC). The combined endpoint included cardiac death (CD), myocardial infarction (MI) and stroke. Obtained results were comparable to placebo (relative risk (RR) 1.0; 95% confidence interval (CI) from 0.89 to 1.12; p= 0.99). At the same time, the saxagliptin increased the risk of hospitalization for HF (RR 1.2; 95% CI from 1.07 to 1.51; p= 0.007) [11]. Other drugs from the same group, such as alogliptin and sitagliptin, did not increase the risk of CD as well as the number of hospitalizations for HF-(RR 1.19; 95% CI from 0.90 to 1.58; p= 0.22) and (RR 1.0; 95% CI from 0.83 to 1.20; p= 0.88), respectively [12,13]. Glucagon-like peptide type 1 agonists showed high efficacy. Liraglutide significantly reduced the risk of combined primary endpoint (CD, nonfatal MI and stroke) compared with placebo (RR 0.87; 95% CI from 0.78 to 0.97; p= 0.01); significantly reduced the risk of CD by 22% (RR 0.78; 95% CI from 0.66 to 0.93; p= 0.007) and all-cause mortality (RR 0.85; 95% CI from 0.74 to 0.97; p= 0.02). The effect on the frequency of hospitalizations for HF (RR 0.87; 95% CI from 0.73 to 1.05; p= 0.14) and unstable angina (RR 0.98; 95% CI from 0.76 to 1, 26; p= 0.87) was comparable with the control group [14]. Semaglutide also significantly reduced the risk of CD (RR 0.74; 95% CI from 0.58 to 0.95; p= 0.02), stroke incidence by 39% (RR 0.61; 95% CI from 0.38 to 0.99; p= 0.04) that most significantly contributed to positive dynamics of combined endpoint. The rates of CD (RR 0.98; 95% CI from 0.65 to 1.48; p= 0.92), nonfatal MI (RR 0.74; 95% CI from 0.51 to 1.08; p= 0, 12) and hospitalizations for HF (RR 1.11; 95% CI from 0.77 to 1.61; p= 0.57) did not differ between studied groups [15]. Lixisenatide and exenatide showed placebo-comparable effect on the risk of CVC and hospitalizations for HF [16, 17].

Sodium-glucose Cotransporter-2 (SGLT2) inhibitors or gliflozins is relatively new group of medications with insulin-independent mechanism of action that already occupies a special place among hypoglycemic agents. This is the only class of medications that improved the prognosis of patients with CHF, including patients without DM [18]. The main mechanism of action of gliflozins is the blockage of renal proximal tubules glucose reabsorption. Normally, glucose glo-

merular filtration rate is approximately 180 g per day. Then the glucose is completely reabsorbed in renal proximal tubules and is not determined in urine analysis. In case the level of blood glucose reaches 10–11 mmol / L (180–200 mg / dL) and exceeds the renal reabsorption potential, it is excreted in the urine [19]. Animal models showed increased expression of renal glucose transporters (SGLT) in mice with diabetes. Most (up to 90 %) of filtered glucose is reabsorbed in the Slproximal nephron segment with the sodium-dependent glucose transporter SGLT2. Remained glucose is reabsorbed in the S2 and S3 segments with sodium glucose transporters 1 (SGLT1). Molecules of SGLT1 and SGLT2 differ by many parameters, including localization, glucose affinity, and specificity. SGLT1 has high affinity with low ability to transport glucose trough the cell membrane. SGLT1 is mainly presented in the cells of small intestine, cardiac, skeletal muscle, trachea, lungs, and to a lesser extent in the renal cells. SGLT1 mutations lead to glucose and galactose malabsorption. SGLT2 is located in the epithelial cells lining the nephron proximal tubule and is the main glucose reabsorption transporter. SGLT2 has low affinity and high glucose transport activity [20].

First SGLT2 inhibitor was isolated from the bark of the apple tree in 1930. The hypoglycemic effect of phorizinwas discovered later in diabetes models in mice. The clinical use of phorizin was limited by non-selective SGLT blockage and rapid beta-glucosidase degradation [21]. Researches in recent decades have focused on the development of selective, breakdown resistant medications. This has led to the appearance of the number of agents with selective SGLT2 inhibition. Its usage disruptsglucose reverse reabsorption in the proximal tubules, followed by glycosuria and blood glucose decrease without hypoglycemia risk. Daily loss of 70–80 g of glucose leads to body weight decrease by 2–4 kg. The drugs also act as osmotic diuretic due to sodium reabsorption impairment, followed by a decrease of circulating blood volume (CBV) and total peripheral resistance (TPR). Thus, blood pressure (BP), intrarenal pressure and urine albumin level decreases and, therefore, fluid retention manifestations control improves in patients with CHF [22–26] (Figure 1).

An additional mechanism of natriuresis of SGLT2 inhibitors is associated with the blockage of 1st (NHE1) and 3rd (NHE3) isoforms of Na+/H+ exchanger. NHE is a membrane glycoprotein involved the maintenance

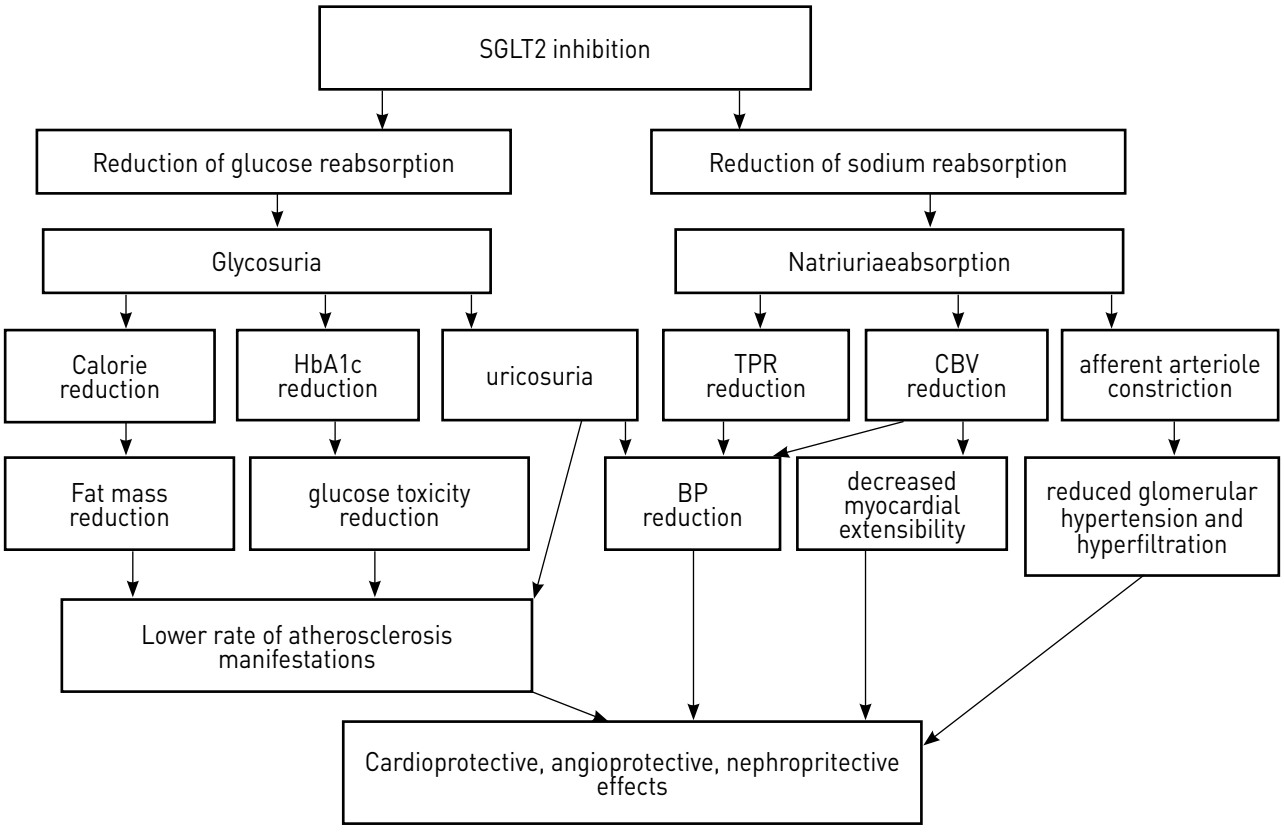

Figure 1. The main sodium-glucose co-transporter 2 inhibition manifestations

of intracellular pH and Na+ concentration. NHE activation due to Na+ / Ca2+ exchange leads to calcium metabolism impartment and, therefore, contributes to the pathogenesis of many CVDs, including HF. It was found that patients with HF have increased NHE3 expression in the proximal tubular epithelial cells and increased sodium reabsorption. Therefore, SGLT2 inhibitors enhance natriuresis in patients with HF through NHE3. Its cardioprotective effect is also associated with NHE1 inhibition and decreasedconcentration of sodium and calcium in the cytoplasm and increased amount of calcium in myocardial mitochondria. Gliflozins also reduces the activity of the sympathoadrenal system that plays one of the main roles in HF pathogenesis [27,28].

In our country, 3 medications from this group are available: dapagliflozin, empagliflozin and canagliflozin. The cardiovascular safety of these drugs has been proven in clinical studies.

The Phase III trial of EMPA-REG Outcome study was randomized, double-blind, placebo-controlled study that involved 590 clinical centers from 42 countries [29]. The inclusion criteria were: type 2 diabetes, age≥ 18 years old, body mass index (BMI)≤ 45 kg/m^2, glycated hemoglobin (HbA1c) 7–10% (average HbA1c 8.1%), with estimated glomerular filtration rate (eGFR)≥30 ml / min / 1.73 m^2 calculated using the MDRD (Modification of Diet in Renal Disease) formula and confirmed CVD (coronary heart disease, arterial hypertension, myocardial infarction or stroke history, peripheral artery disease). The study was performed from September 2010 to April 2013 and included 7028 patients. The average follow-up was 3.1 years. The analysis involved data from 7020 patients. All patients were randomized into three observation groups: the placebo group (n= 2333), the empagliflozin 10 mg per day group (n= 2345), and the empagliflozin 25 mg per day group (n=2342). Participants received basic CVD therapy that included ACE inhibitors or ARBs in 81% of patients, BAB in 65% of patients, diuretics in 43%, and MRAs in 6%. The primary endpoint included: CD, nonfatal MI or stroke. The secondary endpoint included primary endpoints and hospitalizations for unstable angina. In addition, the following were evaluated: hospitalizations for HF, the total hospitalization rate for CHF or CVD, with the exception of fatal strokes. Compared with placebo group, empagliflozin significantly decreased CD by 38%, all-cause mortality by 32%, and hospitalizations for HF by 35%. Decreased CD and all-cause mortality was observed at early stage of the study and persisted throughout all observation period. Groups did not differ significantly by the secondary endpoint. The main results of the EMPA-REG Outcome study are presented in Table 1 [29].

Patients from empagliflozin group less frequently needed additional prescription of loop diuretics. Empagliflozin significantly reduced the frequency of combined events: hospitalizations for HF or loop diuretics prescription (RR 0.63; 95% CI from 0.54 to 0.73; p<0.001); hospitalizations for HF, CD or loop diuretics prescription (RR 0.64; 95% CI from 0.56 to 0.73; p<0.001). Subanalysis of the study results showed that empagliflozin was superior to placebo in patients without initial HF by the following parameters: "hospitalization for HF or CD", "hospitalization for HF", "CD", "all-cause mortality." However, patients with initial HF showed changes comparable

Table 1. **Main results of the EMPA-REG OUTCOME trial: primary and secondary endpoints**

Events	Placebo, n=2333, (%)	Empagliflozin, n=4687, (%)	RR (95% CI)	p
CD, nonfatal MI and stroke	282 (12.1)	490 (10.5)	0.86 (0.74–0.99)	0.04
CD, nonfatal MI and stroke or hospitalization for unstable angina	333 (14.3)	599 (12.8)	0.89 (0.78–1.01)	0.08
All-cause mortality	194 (8.3)	269 (5.7)	0.68 (0.57–0.82)	<0.001
Cardiovascular mortality	137 (5.9)	172 (3.7)	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal MI excluding painless myocardial infarction	126 (5.4)	223 (4.8)	0.87 (0.70–1.09)	0.23
Nonfatal MI excluding painless myocardial infarction	121 (5.2)	213 (4.5)	0.87 (0.70–1.09)	0.22
Myocardial revascularization	186 (8.0)	329 (7.0)	0.86 (0.72–1.04)	0.11
Fatal and nonfatal stroke	69 (3.0)	164 (3.5)	1.18 (0.89–1.56)	0.26
Hospitalization for HF	95 (4.1)	126 (2.7)	0.65 (0.50–0.85)	0.002
Hospitalization for HF or cardiovascular death excluding fatal stroke	198 (8.5)	265 (5.7)	0.66 (0.55–0.79)	<0.001

to placebo by the same parameters. Patients with initial HF were older and more frequently had history of MI or atrial fibrillation, higher BMI, and decreased GFR<60 ml / min / 1.73 m^2 [30]. Empagliflozin also reduced body weight by 2.5 kg on average, waist circumference, blood uric acid levels, both systolic (SBP) and diastolic blood pressure (DBP) and did not increase heart rate at the same time. Medication insignificantly increased low- and high-density lipoproteins. Many patients did not reach glycemic control targets (average HbA1c values in the empagliflozin and placebo groups were 7.81% and 8.16%, respectively). Obtained data confirmed that empagliflozin reduced the risk of CVC not only due to hypoglycemic effect, but also due to cardio-, nephro-, angioprotective effects. The effectiveness of different empagliflozin doses (10 mg and 25 mg) was comparable, despite moderate dose-dependent effect on metabolic parameters. Epmagliflozin showed favorable tolerance profile. The incidence of hypoglycemia, diabetic ketoacidosis, thromboembolic complications, bone fractures, and events associated with decreased blood volume did not differ significantly between groups. Empagliflozin significantly increased the risk of genital infections (p<0.001) and urinary tract infections in women (p<0.05) compared with placebo. In general, the incidence of total adverse effects, severe adverse effects and adverse effects that required medication discontinuation was comparable between empagliflozin and placebo groups. All patients with initial HF (from both placebo and empagliflozin group) had higher incidence of adverse events (AE), including requiring medication discontinuation, compared with patients without initial HF. At the same time, patients from empagliflozin group showed lower frequency of total AEs, severe AEs and AEs requiring medication discontinuation compared with placebo group. Empagliflozin was safe for the function of kidneys. The number of patients with acute renal failure was lower in the empagliflozin group compared with placebo (p<0.01). Empagliflozin also showed significant nephroprotective effect. Medication significantly decreased the risk of doubling of serum creatinine level by 44% (p<0.001) and also decreased the frequency of renal replacement therapy (RRT) by 55% (p= 0.04). The combined "renal point" that included both mentioned above parameters decreased by 46% (p<0.001). By the end of 20th week of observation, the empagliflozin group showed decreased GFR (according to the CKD-EPI equation) [31]. Other studies confirmed nephroprotective effect of empagliflozin. Its administration for 52 weeks decreased the rate albuminuria in patients with type 2 DM and chronic kidney disease (CKD). 25 mg/day of empagliflozin in patients with stage 3 CKD decreased the amount of patients with albuminuria progression from normalbuminuria to microalbuminuria (12.2% of patients in the empagliflozin group; 22.2% of patients in the placebo group) and from microalbuminuria to proteinuria (2% of patients in the empagliflozin group; 11.4% of patients in the placebo group) and increased the amount of patients with reverse changes (macroalbuminuria → microalbuminuria: 32.6% in the empagliflozin group; 8.6% in the placebo group; microalbuminuria → normoalbuminuria: 27.5% in the empagliflozin group; 21.4% in the placebo group) [32]. The study of 851 patients with type 2 DM showed that empagliflozin compared with placebo significantly decreased the urine albumin to creatinine ratio (ACR) in patients with initial microalbuminuria by 32% (p<0.001), in patients with initial proteinuria by 41% (p<0.001). The degree of ACR reduction did not depend on HbA1c, SBP, and body weight [33]. These results confirm that cardio- and nephroprotective metabolic effects of empagliflozin is not directly associated with its hypoglycemic effect.

In June 2017, the results of the CANVAS and CANVAS-Renal studies (CANVAS-R) were published. These studies assessed the effectiveness of another medication from SGLT2 inhibitors — canagliflozin. Canagliflozin has been studied in one of the largest cardiovascular outcome programs among all SGLT2 inhibitors. The CANVAS cardiovascular risk assessment study included 4,330 patients, and CANVAS-R trial with the study of renal outcomes included 5,812 patients. All patients had type 2 DM with HbA1c level of 7–10.5%, CVD or high risk of CVC development. All CANVAS study participants were randomized into 3 groups: two groups received 100 and 300 mg per day of canagliflozin, the third group received placebo. The average duration of drug administration was 4.3 years with following observation of about 5.7 years. Patients from CANVAS-R study were randomly assigned to once-daily placebo or canagliflozin 100 mg (with optional up titration to 300 mg) and placebo. Planned average of drug administration was approximately 1.8 years with the following observation for 2.5 years. The analysis of CANVAS and CANVAS-R studies showed that canagliflozin was superior to placebo and reduced combined primary endpoint by 14% (RR 0.86; 95% CI from 0.75 to 0.97; p= 0.02). At the same time, CVD risk decreased by 13% (RR: 0.87;

95% CI from 0.72 to 1.06), nonfatal MI risk by 15% (RR: 0.85; 95% CI from 0.69 up to 1.05) and the risk of nonfatal stroke by 10% (RR: 0.90; 95% CI from 0.71 to 1.15). Unfortunately, the assessment of the secondary endpoint, including all-cause mortality (RR 0.87; 95% CI from 0.74 to 1.01; p= 0.24), was not performed due to the lack canagliflozin benefits. The medication affected carbohydrate metabolism by reducing HbA1c by 0.58% (95% CI from –0.61 to –0.56; p<0.001) compared with placebo. Therefore, the need for additional hypoglycemic medications decreased by 9.3% (95% CI from –11.0 to –7.6). Canagliflozin also led to body weight decrease by 1.60 kg on average (95% CI from –1.70 to –1.51; p<0.001) and SBP regression by 3.93 mm Hg on average (95% CI, from –4.30 to –3.56; p<0.001), and DBP by 1.39 mm Hg (95% CI –1.61 to –1.17; p<0.001) compared with placebo. It is also remarkable that canagliflozin reduced the risk of hospitalization for heart failure by 33% (RR: 0.67; 95% CI from 0.52 to 0.87). The medication also showed significant nephroprotective effect. Patient taking canagliflozin, showed not only the slowdown in albuminuria progression (RR 0.73; 95% CI from 0.67 to 0.79), but also the regression of albuminuria severity compared with placebo group (293.4 versus 187.5 patients with albuminuria regression per 1000 patient-years; RR 1.70; 95% CI from 1.51 to 1.91). The combined endpoint for renal outcomes, consisting of 40% eGFR reduction, the need for RRT, or death from renal causes, was less common in the study group compared with placebo (5.5 versus 9.0 participants per 1000 patient-years, RR 0.60; 95% CI 0.47 to 0.77) [34]. Serious AEs occurred less frequent in patients from canagliflozin group compared with placebo group (104.3 versus 120.0 patients per 1000 patient-years; RR 0.93; 95% CI from 0.87 to 1.00; p= 0.04). There were no significant differences between the groups on AE leading to medication discontinuation (35.5 versus 32.8 per 1000 patient-years; RR 1.13; 95% CI from 0.99 to 1.28; p= 0.07). However, unanticipated increase in the risk of lower-limb amputation, predominantly at the level of the toe or metatarsal, was observed with canagliflozin (6.3 versus 3.4 per 1000 patient-years RR 1.97; 95% CI 1.41–2.75; p<0.001). Patients who already had amputation or had peripheral vascular disease had higher risk of amputation. Patients taking canagliflozin significantly more often reported male genital infection (34.9 versus 10.8 per 1000 patient-years, p<0.001), osmotic diuresis-related adverse events (34.5 versus 13.3; p<0.001), female genital mycotic infections (68.8 vs 17.5; p<0.001). Patients from canagliflozin group showed higher incidence of all fractures compared with placebo group (15.4 versus 11.9 per 1000 patient-years; RR 1.26; 95% CI from 1.04 to 1.52) [34, 35].

The DECLARE-TIMI 58 study investigated the efficacy of 10 mg per day dapagliflozin in 17160 patients with diabetes and CVD (40% of participants) or cardiovascular risk factors (CVR) (60% of participants). The median follow-up was 4.2 years. Medication did not decrease primary outcome rate defined as cardiovascular death, myocardial infarction, or ischemic stroke (8.8% versus 9.4%; RR 0.93; CI from 0.84 to 1.03; p= 0.17). In patients with history of MI (3584 patients), dapagliflozin significantly reduced the safety outcome by 16% (RR 0.84; 95% CI from 0.72 to 0.99; p=0.039). Dapagliflozin showed significant superiority over placebo by the primary efficacy outcomes defined as composite of cardiovascular death or hospitalization for heart failure (4.9% versus 5.8%; RR 0.83; 95% CI from 0.73 to 0 95; p= 0.005). These results can be explained by major reduction of hospitalization for heart failure decompensation by 27% (RR 0.73; 95% CI from 0.61 to 0.88). Serious adverse events were more often observed in the placebo group (2925 cases versus 3100 in the placebo group; 95% CI 0.91 from 0.87 to 0.96; p<0.001). However, adverse events leading to discontinuation of the drug prevailed in the dapagliflozin group (693 cases versus 592; 95% CI 1.15 from 1.03 to 1.28; p= 0.01). Episodes of hypoglycemia and acute renal damage were less common in the dapagliflozin group (58 versus 83 cases in the placebo group; 95% CI 0.68 from 0.49 to 0.95; p= 0.02) and (125 against 175 cases; 95% CI 0.69 from 0.55 to 0.87; p= 0.002). Dapagliflozin compared with placebo increased the risk of genital infection (76 versus 9 cases; 95% CI 8.36 from 4.19 to 16.68; p<0.001) and diabetic ketoacidosis (27 versus 12 cases; 95% CI 2, 18 from 1.10 to 4.30; p=0.02). It is remarkable that lower rate of bladder cancer with dapagliflozin than with placebo was observed (26 vs. 45 cases; 95% CI 0.57 from 0.35 to 0.93; p= 0.02). The rates of amputation, fracture, volume depletion, and hypersensitivity were balanced between the groups [36].

The CVD-REAL study, published in March 2017, evaluated the risk of hospitalization for heart failure and death from any cause in patients with type 2 DM treated with SGLT-2 inhibitors. The study included over 300,000 patients from 6 countries, who predominantly (87%) had no history of CVD. The results of the study showed that patients with type 2 DM taking SGLT-2 inhibitors such as dapagliflozin,

canagliflozin, empagliflozin for 4 years hadreduced hospitalization rate for heart failure by 39 % (p<0.001) and all-cause mortality by 51 % (p<0.001) compared with other sugar-lowering drugs. The frequency of events of the combined endpoint including hospitalizations for heart failure and death from any cause decreased by 46 % (p<0.001). Similar unidirectional results of the EMPA-REG OUTCOME and CVD-REAL studies indicate the reproduction of the positive effects of taking drugs from the SGLT-2 group in real clinical practice and their high efficiency not only in patients with type 2 DM and a high risk of CVC, but also in patients with lower CVR. Given the absence of significant differences between the efficacy of different SGLT-2representatives, researchers suggested the presence of class-specific cardioprotective effect of SGLT-2 inhibitors [37]. Similar results were obtained in 2019 in meta-analysis that included participants from the EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 studies. The effect of this group of medications was more pronounced in patients with atherosclerosis, that led to 11 % decrease of CVD risk (RR 0.89; 95 % CI from 0.83 to 0.96; p=0.001). The nephroprotective effect of medications was reflected in the decrease of combined "renal" endpoint events, including episodes of decreased renal function, terminal renal failure, and "renal" death by 45 % (RR 0.55; 95 % CI from 0.48 to 0.64; p<0.0001). Significant reduction in the risk of HF decompensation and related hospitalizations by 31 % (RR 0.69; 95 % CI from 0.61 to 0.79; p<0.0001) makes SGLT-2 inhibitors the only group of hypoglycemic medications with positive influence on the course of heart failure [38].

The results of presented studies show not only cardiovascular safety, but also the effectiveness of SGLT-2 inhibitors in patients with heart failure, including patients without DM. In 2019 the results of a randomized, placebo-controlled parallel DAPA-HF study were announced and influenced clinical guidelines for the management of patients with heart failure with reduced ejection fraction (HFrEF), regardless of the presence of DM. The study included 4744 patients with HF of II functional class (FC) and higher, left ventricular ejection fraction (LVEF)⩽40 % and a moderate increase of N-terminal pro–B-type natriuretic peptide ((NT-proBNP)⩾600 pg / ml (⩾400 pg / ml for patients with hospitalization for heart failure over the past 12 months;⩾900 pg / ml for patients with atrial fibrillation / flutter). The study did not include patients with SBP less than 95 mm Hg, type 1 DM, eGFR less than 30 ml / min / 1.73 m^2. The analysis of the results was carried out between four age subgroups: 636 patients (13.4 %) — under 55 years of age; 1242 patients (26.2 %) — aged 55 to 64 years; 1717 patients (36.2 %) — aged 64 to 74 years and 1149 (24.2 %) patients — 75 years and older. Great number of patients had HF of FC II according to NYHA; 1983 patients (41.8 %) had type 2 DM. In addition to optimal medication therapy for heart failure, including ACE inhibitors in 2661 patients (56.1 %); ARB — in 1307 patients (27.6 %); ARNI — in 508 patients (10.7 %); BAB — in 4558 patients (96 %); MRAs — in 3370 patients (71 %); diuretics — 4433 patients (93.4 %), patients received 10 mg per day of dapagliflozin or placebo. The primary outcome was composite of hospitalization for heart failure or CD. The additional secondary outcomes analyzed re-hospitalizations due to HF or CD, the change from baseline to 8 months in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), a composite of worsening renal function, which was defined as a sustained decline in the eGFR of 50 % or greater, end-stage renal disease (defined as a sustained [⩾28 days] eGFR of<15 ml per minute per 1.73 m^2, sustained dialysis, or renal transplantation), or renal death; and death from any cause. The effect of dapagliflozin compared with placebo did not dependon age. The dynamics of the analyzed outcomes was comparable between all subgroups. The primary outcome occurred in 16.3 % of cases in dapagliflozin group compared with 21.2 % in the placebo group (p<0.001). The primary outcome did not depend on the presence of DM (RR 0.75; 95 % CI from 0.63 to 0.90; absence of DM: RR 0.73; 95 % CI from 0.60 to 0.88; p= 0.80). The main results of the study are presented in table 2 [18].

A more significant decrease in the primary outcome compared with placebo was observed in patients aged 75 years and older (RR 0.68; 95 % CI from 0.53 to 0.88; p= 0.003) mainly due to decreased risk of hospitalization for HF: the dynamics of this parameter was more significant in the subgroups of 55–64 and 75 years and older (RR 0.56; 95 % CI from 0.40 to 0.78; p= 0.001 and RR 0.64; 95 % CI from 0, 47 to 0.88; p= 0.006). The same subgroups also showed significant regression of the secondary outcome (CD / re-hospitalizations for HF) by 32 % (RR of 0.68; 95 % CI from 0.51 to 0.91; p=0, 01)) and by 30 % (PP 0.70; 95 % CI from 0.53 to 0.94; p=0.016), respectively. The effect of dapagliflozin in the subgroup of patients 55 years and younger was comparable to placebo. In general, CD was recorded in 9.6 % of cases in the dapagliflozin group and in 11.5 % in the placebo group; hospital-

Table 2. **The main results of DAPA-HF study**

Results	Prespecifiedsubgroups							
	Age< 55 years (n=636)		Age 55–64 years (n=1242)		Age 65–74 years (n=1717)		Age≥ 75 years (n=1149)	
	Placebo n=296	Dapagliflozin n=340	Placebo n=630	Dapagliflozin n=612	Placebo n=887	Dapagliflozin n=830	Placebo n=558	Dapagliflozin n=592
CD or hospitalization for HF/ urgent visit for HF								
n (%)	53 (17.9)	52 (15.3)	131 (20.8)	96 (15.7)	184 (20.7)	135 (16.3)	134 (24.0)	103 (17.4)
RR (95% CI), p	0.87 (0.60–1.28), 0.49		0.71 (0.55–0.93), 0.012		0.76 (0.61–0.95), 0.015		0.68 (0.53–0.88), 0.003	
CD								
n (%)	29 (9.8)	28 (8.2)	70 (11.1)	60 (9.8)	107 (12.1)	79 (9.5)	67 (12.0)	60 (10.2)
RR (95% CI), p	0.85 (0.51–1.43), 0.54		0.87 (0.62–1.23), 0.45		0.78 (0.58–1.04), 0.089		0.83 (0.58–1.17), 0.29	
Hospitalization for HF/ urgent visit for HF								
n (%)	29 (9.8)	34 (10.0)	90 (14.3)	52 (8.5)	117 (13.2)	86 (10.4)	90 (16.1)	65 (11.0)
RR (95% CI), p	1.05 (0.64–1.72), 0.85		0.56 (0.40–0.78), 0.001		0.76 (0.58–1.01), 0.056		0.64 (0.47–0.88), 0.006	

izations for HF in dapagliflozin group — 9.7% versus 13.4% compared with placebo. The number of patients from dapagliflozin group with more than 5 points according to KCCQ questionnaire increased that significantly increased the total KCCQ score by 2.3 between baseline and month 8 compared with placebo (p<0.0001). The number of AEs after medication discontinuation increased with age in the placebo group. Renal function impairment was observed in 1.2% of patients from dapagliflozin group versus 1.6% of patients from placebo group (p= 0.17). Renal AEs were more frequent in the first two age subgroups (<55 and from 55 to 64 years old) with dapagliflozin, however, a greater increase in the number of serious renal adverse effects was recorded in placebo. Since the majority of patients received concomitant diuretic therapy, the comparable frequency of volume depletion is of particular importance [18]. The researchers concluded that dapagliflozin is highly effective in patients with HFrEF. The medication reduced the risk of CD and HF decompensation, improved quality of life with comparable tolerance with placebo in wide age range of patients including 75 years and older. Therefore, nowadays, dapagliflozin is recommended for patients with HFrEF with symptoms of HF despite treatment with ACE inhibitors, BAB and MRAs in order to reduce the risk of CD hospitalization for HF [2].

In the near future, we expect the results of the studies that assess the effect of empagliflozin on the HF progression — EMPERIAL and EMPEROR. The EMPERIAL study included patients with confirmed HF with preserved or reduced EF with and without type 2 DM [39–42].

The studies on the new medications with different mechanisms of action contribute the improvement of the prognosis in patients with HF. Only about 10% of patients took ARNI in the DAPA-HF study. Therefore, the effectiveness of the combination of ARNI and SGLT-2 inhibitors require further investigation.

Conclusion

The review of the studies presented in this article clearly demonstrates the clinical efficacy of SGLT-2 inhibitors in the treatment of patients with cardiovascular diseases. The results concluded that dapagliflozin may be recommended in patients with heart failure with reduced ejection fraction and symptoms of HFwho already take angiotensin-converting enzyme inhibitors, BAB and mineralocorticoid-receptor antagonists to reduce the risk of cardiovascular death and hospitalization for heart failure.

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Medical procedures and electromagnetic interference safety in patients with implanted pacemakers

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The number of patients with implanted pacemakers is steadily rising throughout the world. At the same time, a great variety of modern medical procedures that are routinely used in clinical practice can potentially cause changes in pacemaker settings and even lead to the total dysfunction of the device, which can also be referred to as electromagnetic interference (EMI). Therefore, specific therapeutic and diagnostic methods should be used rationally in patients with pacemakers and potential EMI must be considered. In the current review we discuss EMI causes, types of pacemaker malfunction and possible precautions, and the need of pacemaker settings control and correction after the procedures. Magnetic Resonance Imaging (MRI), therapeutic radiation, catheter radiofrequency ablation and some types of physiotherapy are thoroughly analyzed. We also discuss the importance of avoiding the irrational use of procedures that can be potentially dangerous for patients with implanted pacemakers.

Keywords: *pacemaker, electrical stimulation of the heart, electromagnetic interference, physiotherapy*

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Introduction

The number of patients with implanted devices for treatment of cardiac arrhythmias is steadily rising throughout the world due to the widespread use of pacemakers, implantable cardioverter-defibrillators (ICD) and cardiac re-synchronization therapy (CRT), and the increasing global life expectancy [1-3]. Over forty thousand pacemakers and two thousand ICDs are implanted in Russia annually. Moreover, more than one thousand CRT are performed each year [4]. Despite the fact that the number of pacemaker implantations in Russia is rising by 8-10%there are still 350-400 per 1 million people requiring pacemakers [3, 4].

Modern pacemakers are 'demand' pacemakers as they are able to sense intrinsic cardiac and extrinsic electrical activity and deliver electrical stimulus only when needed. Demand pacemakers can work in inhibitory and/or synchronized electrostimulation (ES) modes [5-7]. Moreover, most recent pacemakers can be characterized as complex programmable devices that have a variety of therapeutic and diagnostic functions and, therefore, require regular preventive maintenance and programming if necessary[1, 6-8].

Physiologic pacing with multifocal and frequency-adaptive pacemakers are used in more than 50% of cases in the western countries [5, 7, 9] and in 33,7% cases in the Russian Federation [4]. Multisensory systems development provided a reliable frequency adaptation of contemporary pacemakers and widened the range of their therapeutic options [2, 6, 9].

Technical characteristics of pacemakers and the risks of EMI

Apart from external electromagnetic waves sources, pacemaker electrical characteristics are also among the potential causes of EMI development [9, 10]. The typical range of the pacing impulse in modern pacemakers is 2,0-5,0 V and the amplitude of the recorded cardiac signals is 1,5-3,5 V [10, 11]. Demand pacemakers are known to be more susceptible to electromagnetic fields compared with asynchronous pacemakers [3, 7, 13]. In patients with frequency-adaptive pacemakers the external electrical signals can provoke pacemaker-mediated tachycardia [1, 13, 14]. In isolated atrial and atrial-ventricular pacing problems with sensing and/or atrial channel impulse capture may occur [5, 12].

Unipolar pacing with the anode-electrode is known to be more susceptible to EMI compared with bipolar pacing [15-16]. Floating atrial bipolar electrodes used in the VAT and VDD modes have been developed to minimize the risk of EMI and hypersensing [1, 5, 7]. When the devices with one atrial electrode (single-chamber pacemakers) are utilized, the lowest pacemaker sensitivity can be used and, therefore, the pacemaker becomes less susceptible to external electromagnetic signals [17]. In the bipolar pacing ST segment elevation and T wave amplitude are 40% less compared with the unipolar pacing that reduces the risk of EMI and pacemaker suppression [16].

In DDD mode atrial channel hypersensing caused by EMI can lead to automatic switch to VVI-stimulation or DDI pacing modes which are asynchronous [13, 16, 18]. The development of a high frequency ventricular electrostimulation due to atrial channel hypersensing to high frequency extracardial signals can be another negative effect of EMI in DDD mode. Interference of electromagnetic field and pacemaker ventricular channel can lead to total pacemaker inhibition and pronounced bradycardia and even asystole especially in "pacemaker-dependent" patients [19].

Magnetic Resonance Imaging (MRI) is a nuclear magnetic resonance-based imaging technique used to produce images of the organs and tissues and is also a source of a strong electromagnetic radiation [20, 21]. Studies have shown that 50-75% patients with implanted pacemakers may need to undergo MRI during the long-lasting period of constant pacing [22]. Clinical guidelines state that MRI is a relative contraindication in patients with pacemakers. MRI can be performed only after all risks and benefits have been evaluated [6].

A systemic review by Zikria et al. [2011] based on the metanalysis of 30 publications that studied the safety of a 1.5 Tesla (T) MRI in 1419 patients with implanted pacemakers showed no significant changes in the devices [21]. MRI was used to evaluate different parts of the body including the chest and the heart. The application of a magnetic field resulted in automatic switch of a pacemaker to an asynchronous mode and increased frequency of impulse production.

Prospective clinical studies showed that in 80-90% case patients with pacemakers undergoing MRI didn't have any serious adverse effects [24]. At the same time, some clinical reports identified various pacemaker dysfunctions that spontaneously resolved after MRI or were managed with programming [11, 23, 25]. These dysfunctions were caused by automatic asynchronous mode activation in the biologically controlled pacemakers, increased pacing threshold, system reset that brought the device to its factory settings and reduction in battery charge. The *in vitro* analysis of 1,5T MRI effects on implanted pacemaker revealed a significant overheating of an electrode [10].

Specific safety measures should be taken in patients who don't have MRI-conditional pacemakers and still require to undergo MRI examination [6, 26] Before the imaging the pacemaker-dependency should be evaluated and pacemaker settings should be carefully checked before and after the imaging. Non-pacemaker-dependent patients should be programmed to the 000 mode (turned off) and the biologically controlled modes should be switched to asynchronous mode. Low power MRI (0,5T) should be preferably used. During the MRI examination the patient should be under the care of a specialist.

The following pacemaker requirements have been developed in order to conduct imaging safely [22]: additional control when switching to the magnetic imaging mode; improved protection from electromagnetic interference that can cause power reset; utilization of electrodes that do not get overheated; elimination or minimization of ferromagnetic components. Since 2011 MRI-conditional implanted devices have been available. They have the SureScan™ function that can be activated before the imaging and makes the examination totally safe for the device [21].

Electrical defibrillation/cardioversion

For a long time, electricalcardioversion in patients with implanted pacemakershas been considered unsafe due to its possible negative effects on the generator and/or the electrode [26]. However, recently developed devices that have bipolar leads are better protected from the external electromagnetic waves [6, 7, 22]. Besides, the development of cardioverters/defibrillators with biphasic impulses increased effectiveness of this method, reduced energy consumption and decreased the risk of pacemaker damage [10].

Among the problems caused by electrical cardioversion/defibrillation in patients with implanted pacemakers were protection mode activation, short-term threshold increase, capture failure, pacemaker generator and electrical circuit dysfunction [10, 16]. Patients with unipolar pacemakers implanted in the right infraclavicular region developed capture failure in 50% of cases due to the increased threshold caused by the relatively high cumulative energy of electroconvulsive therapy [9]. Undersensing and total dysfunction of the pulse generator that required pacemaker reimplantation were also noted. However, no cases of total electrode dysfunction were reported.

The analysis of the "runaway pacemaker" syndrome causes revealed that in most cases it was associated with previous electrical defibrillation [27]. It is a phenomenon in which pacemaker causes sudden high-frequency ventricular electrical stimulation ("pacemaker tachycardia") with constantly increasing impulse frequency over 150 impulses per minute that may lead to ventricular fibrillation. Supposedly, it is caused by the pacemaker electrical circuit dysfunction due effects of cardioversion/defibrillation, when the pacemaker generates electrical impulses of various frequencies and amplitudes. An emergent pacemaker reimplantation is necessary in this case.

Most pacemaker manufacturers recommend using V00/A00 modes when performing electrical cardioversion to disable incoming signal amplifier in order to avoid pacemaker inhibition [17, 25]. Moreover, the time between two successive discharges should not exceed 5 minutes to allow the electrodes to cool down. After cardioversion/defibrillation the pacemaker has to be tested. In case of electrostimulation threshold increase the stimulating impulse voltage has to be also increased. In case of any changes in sensitivity threshold pacemaker has to be reprogrammed.

In patients with implanted pacemakers the lowest possible effective energy of cardioversion has to be used. Prior to the procedure the pacemaker should be programmed to the maximal impulse voltage [10]. Pacemaker dysfunction can be avoided if defibrillator electrodes are placed at least 15 cm from the pacemaker or anterior-posterior position can be used. In that case the electrical field is perpendicular, and not parallel, to the intra-cardial electrode.

Catheter radiofrequency ablation (RFA)

RFA ablation employs electric current in the radiofrequency range (450–500 kHz) [27]. Most implanted pacemakers in patients who underwent catheter RFA proved to be well protected from interference produced by the radiofrequency waves [10]. No cases of pacemaker inhibition or insufficient or excessive sen-

sitivity to cardiac signals (hypo- and hypersensing) were reported [28]. At the same time, patients with mostly monopolar electrodes included in another clinical study, were reported to have sensitivity (detection) and electrostimulation dysfunction [29].

For safe electrostimulation in patients requiring catheter RFA it is necessary to determine if the patient is pacemaker-dependent. In pacemaker-dependent patients temporary pacing should be provided [3, 27] Besides, prior to RFA, the frequency adaptation function of a pacemaker should be disabled. Radiofrequency exposition should be as short as possible, and the area of exposition has to be as far away from the pacemaker as possible. In non-pacemaker-dependent patients 000 mode can be used, which means turning the pacemaker off, or VVI mode with a frequency of stimulation lower than the heart rate [10]. In pacemaker-dependent patients asynchronous V00 mode has to be used. In patients with leadless pacing fewer pacemaker dysfunctions and/or electrode dysfunction during RFA of atrioventricular junction were observed compared with transvenous electrode implantation [29]. Therefore, it is important to test the pacemaker function after the RFA procedure.

Therapeutic radiation. High-energy radiation can have some various negative effects on the pacemaker such as direct circuit damage or intermittent EMI. New implanted pacemakers employ complementary metal oxide semiconductors (CMOS) that are very safe, energy efficient, and don't need much space [1, 7, 11]. Radiation was shown to cause some damage to the thin oxide layers and transistors due to the positive charge accumulation inside the pacemaker circuit that can cause battery dysfunction [10, 30]. The extent of damage depends on the radiation type, cumulative dose and pacemaker location. Various dysfunctions of the signal detection, telemetry, frequency adaptation and total inhibition can also occur [30, 31].

Salerno F. et al. [2016] tested the pacemaker activity during radiation therapy. The revealed problems were as follows [30]: temporary mode switch that continued during the radiation period; pacemaker damage and loss of impulse generation that lasted for the continuous period of time. Therefore, patients undergoing radiation therapy should always be closely monitored during the whole period of radiation treatment and for several weeks after it ends.

In case of absolute indications for radiation therapy some precautions have to be taken in patients with pacemakers [10, 31]. Before the radiation session begins it is important to determine if the patient is pacemaker dependent. Beam angle should be selected to minimize the radiation exposure of the pacemaker. A total limit of radiation cumulative dose shouldn't extend 2 Rad and should be controlled by the dosimeters. Besides, additional pacemaker shielding (1 cm) should be used. Direct radiation should be avoided and, if possible, the pacemaker should be moved to another suitable side. Patients have to be closely monitored all the time and temporary pacing should be available.

Electrocoagulation is one of the most widespread and cost-effective techniques used to cut or coagulate tissues [32]. The high-frequency alternating current can cause pacemaker inhibition or high-frequency ventricular stimulation initiation, which is especially common in patients with dual chamber atrial-ventricular pacing and frequency-adaptive pacing because of the coagulation signals detection that imitate atrial potentials [16]. Moreover, current, which is generated by the electrocoagulator, can cause thermal myocardial damage due to the high current concentration in the "electrode-tissue" contact zone and that can result in the pacemaker threshold increase [10]. Electrocoagulation near the pacemaker can lead to the pacemaker switching to the asynchronous mode or its inhibition because of the hypersensing [13]. As such, electrocoagulation has to be bipolar and shouldn't be performed close to the pulse generator (<15 cm). Current should be perpendicular to the electrode and each coagulation episode shouldn't last longer than several seconds. Pacemaker should be programmed to the asynchronous V00 mode and/or additional endocardial electrode for temporary electrostimulation should be implanted [26]. It was shown that the use of ultrasound scalpel in the electrocoagulation zone decreases the risk of EMI [10]. Also, the minimal energy power should be used for coagulation.

Smart devices used for heart rate monitoring

Interactive telecommunication technologies are lately becoming more widely used for various medical needs such as at home monitoring of patients with implanted antiarrhythmic devices with Home Monitoring function [33-35]. According to the clinical guidelines, it is important to provide telemonitoring of all patients with ICDs, cardiosynchronizing therapy and in pacemaker-dependent patients who make up to 20% of all patients with pacemakers [6].

New telemedical technology make it possible to perform remote monitoring of the implanted devic-

es for treatment of cardiac arrhythmias functioning and allow to register adverse cardiovascular events in time to alleviate their negative effects [34]. As such, safety and compatibility of telemonitoring systems in patients with pacemakers is of great interest. Wireless electrical devices should also be studied more closely in patients with pacemakers due to the high magnetic field strength. However, the unlimited use of this technology in patients with implanted pacemakers can't be recommended yet [6].

Abudan A.A. et al. [2019] studied the safety of a smart device "AliveCor Kardia" (USA) in 251 patients with pacemakers [36]. During the ECG recording no adverse effects or changes in the work of the pacemakers were registered. ECG was correctly interpreted in 90% of patients with pacing and in 94,7% patients with spontaneous heart rhythm. It was shown that "AliveCor Kardia" has a perfect safety profile, doesn't interfere with pacemakers and can be used for remote heart rate monitoring.

Physiotherapy safety

For many years the established clinical practice and the lack of clinical studies on the physiotherapy safety in patients with pacemakers led to the development of quite a pessimistic attitude in cardiologists, physiotherapists and surgeons towards the use of physiotherapeutic methods in patients with pacing [37]. This, in turn, is associated with a potential risk of pacemaker dysfunction and unpredictable patient reaction during physiotherapy that induces electromagnetic fields. Modern physiotherapy guidelines that discuss indications and contraindications to different types of physiotherapy in patients with pacemakers are based not on the clinical studies but on the expert consensus opinion [6, 11, 38].

Indications and contraindications to physiotherapy in patients with pacemakers are known to depend on the specific physiotherapeutic method [10, 18, 37, 38]. Most guidelines state that among the physiotherapeutic methods that can safely be used in patients with pacemakers are [38]: manual therapy/stretching, acupuncture (except for electroacupuncture), magnetic therapy, pulse radiotherapy; laser therapy, ultrasound therapy, hyperbaric oxygen therapy, phototherapy. Interference electrotherapy, microcurrent therapy, transcutaneous electrical nerve/muscle stimulation, electroanalgesia and diathermia are contraindicated in patients with implanted pacemakers.

As most guidelines on physiotherapy in patients with pacemakers are based on separate clinical observations and small sample studies, most pacemaker manufacturers don't recommend the use of diathermy, transcutaneous electrical nerve/muscle stimulation and interference electrotherapy in this category of patients [12, 13, 38]. Some papers report on adverse effects of these types of physiotherapy on pacemaker function such as: pacemaker inhibition, decrease and increase in pacemaker sensitivity; automatic pacemaker switch to asynchronous mode; increase in impulse frequency (external magnet effect); decrease in impulse amplitude and etc. [10, 16, 33, 37]. EMI can sometimes cause generator and electrical circuit dysfunction that require a total device reimplantation [38].

The analysis of EMI causes showed that the risk of pacemaker system changes depends on electric current strength, the distance between the pacemaker and the body part that undergoes physiotherapy; the pacemaker and the stimulating electrodes location and the pacemaker functional parameters [38]. These changes are often temporary and disappear after the procedure is over, but still the pacemaker parameters have to be checked after each session and if necessary, the pacemaker has to be reprogrammed.

Techniques and preventive measures that improve the pacemaker interference resistance

Current pacemakers employ various techniques that improve their interference resistance [2, 5, 11]. An important technology is shielding of the pacemaker electric circuit, i.e. placing it inside a hermetically sealed titanium or stainless-steel case that makes the pacemaker relatively immune to the EMI [39]. Apart from that, special band pass filters are commonly used that protect the pacemakers from the high-frequency fields and, therefore, prevent the external signals detection and EMI development [11]. Devices that automatically switch biologically controlled pacemakers to the synchronous mode in the presence of strong interference are also used [5, 6]. Among the most recent technologies is the development of implanted leadless pacemakers that are less susceptible to EMI due to the absence of leads, small size and intra-cardial location of the device itself [29, 40]. EMI development can also be avoided if all precautions associated with the specific diagnostic or therapeutic procedure are taken.

The pacemaker that are manufactured in the Russian Federation should meet the set of specific technical standards known as GOST and, specifi-

cally, GOST 31212-2003 "Implantable pacemakers. General technical requirements and testing methods" (01.01.2015). The implanted pacemakers have a combined isolation system that is provided by the sealed case made of metal and is covered with special isolation material [11]. According to the GOST, there should be no pacemaker dysfunction after defibrillation and they also should be resistant to EMI. However, the electromagnetic requirements are still in the middle of development.

Temporary pacemaker reprogramming is recommended prior to the diagnostic or therapeutic procedure to minimize the EMI risk [12, 13, 16, 17, 38]: 1) Program the pacemaker to bipolar mode; 2) Evaluate the need of asynchronous pacing using the external magnet; 3) Program the pacemaker to the minimal sensitivity if it doesn't cause competitiveness between the spontaneous and artificial pacemakers; 4) program the impulse current to the maximum strength; 5) In patients with frequency-adaptive pacemakers turn off the frequency adaptation function; 6) Test the pacemaker before and after the procedure and preprogram it if necessary; 7) Use portable heart simulators to evaluate the risk of EMI in each specific case.

Conclusion

In the everyday life patients with implanted pacemakers are vulnerable to unfavorable effects of many sources of electromagnetic fields. The clinicians who are treating the patients with implanted pacemakers should be aware of these potential problems and take care of the safety measures in order to prevent the EMI. To fully understand the indications and contraindications of various medical procedures and to perform them safely in is crucial to understand the principles of their functioning and the pacemaker modes. Naturally, the patients with implanted pacemakers have to be fully evaluated prior to any diagnostic or therapeutic procedures in order to avoid any complications. In case of any uncertainties about the safety of a medical procedure the patient is strongly advised consult the specialist.

Taking into the account the absence and/or the inconsistency of the guidelines on the use of various diagnostic or therapeutic procedures that may interfere with pacemakers, further clinical studies have to be conducted in order to create the evidence-based guidelines.

Conflict of interest: None declared. This study was not sponsored.

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Author Guidelines

MANUSCRIPT PUBLICATION RULES IN THE INTERNATIONAL HEART AND VASCULAR DISEASE JOURNAL

Disclaimer: Edition of rules come into force since November, 2018. The rules describe the conditions of publication of manuscripts (articles) through the site http://www.heart-vdj.com. The editorial Board is ready to answer questions and help authors by e-mail: submissions.ihvdj@gmail.com.

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

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

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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.

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

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

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

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

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tient with chronic heart failure and complete left bundle branch block. Russ J Cardiol. 2011;6:4–8. Russian. Барт Б. Я., Ларина В. Н., Бродский М. С., и др. Ремоделирование сердца и прогноз больных с хронической сердечной недостаточностью при наличии полной блокады левой ножки пучка Гиса. Российский кардиологический журнал. 2011;6:4–8. doi:10.15829/1560-4071-2011-6-4-8.

Book:

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Webpage:

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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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XIV. Journal subscription

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