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Dynamics of heart failure markers and cardiac reverse remodeling in patients receiving cardiac contractility modulation therapy

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Aim. To assess the clinical course and cardiac reverse remodeling in patients with heart failure (HF) with reduced ejection fraction (HFrEF) receiving cardiac contractility modulation (CCM) therapy.

Material and methods. Fifty-five patients (mean age, 53±11 years, 46 males) with NYHA class II-III HFrEF (ischemic etiology in 73% of patients), sinus rhythm, QRS<130 ms or QRS<150 ms of non-LBBB morphology receiving optimal medical therapy were enrolled into the study. CCM devices were implanted to all patients between October 2016 and September 2017. We assessed the following parameters: hospitalizations and mortality due to decompensated HF; changes in HF class, NTproBNP concentration, peak oxygen consumption, six-minute walk test, left ventricular end-systolic and end-diastolic volumes and ejection fraction (EF), atrial and ventricular arrhythmias. A comparative analysis of the studied parameters was carried out depending on the pacing with one and two ventricular leads, on LVEF value (⩾25% and <25%) and HF etiology.

Results. CCM therapy was associated with a decrease in HF class (p<0,00004001), HF-related hospitalization rate (p<0,0001001), blood NTproBNP concentration (p⩽0,018), an increase in peak oxygen consumption during the first year (p<0,006011), as well as a decrease in LV volumes and a LVEF increase (p<0,0001001). The direction of these changes did not depend on the number of ventricular leads and LVEF. The presence of ischemic cardiomyopathy and old myocardial infarction did not affect the disease prognosis, but was associated with a lower change in LV volumes and NTproBNP during 24 months of CCM therapy. LVEF values were significantly higher in the group of patients with HFrEF not associated with coronary artery disease after 12 and 24 months of follow-up.

Conclusion. In the group of patients with class II-III HFrEF, CCM therapy in most patients was associated with improved clinical and hemodynamic status, increased exercise tolerance, decreased HF-related hospitalization rate, positive echocardiographic and NTproBNP changes.

Key words: cardiac contractility modulation, heart failure, reduced ejection fraction.

Relationships and Activities: none.

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Cardiac contractility modulation is a new treatment method for patients with moderate and severe chronic heart failure (CHF) with a low left ventricular ejection fraction (EF), narrow QRS <130 ms or QRS <150 ms of the type of non-specific intraventricular block, which are not indicated for cardiac resynchronization therapy, and the CHF symptoms persist and/or progress, despite taking optimal drug therapy. The principle of cardiac contractility modulation (CCM) is to stimulate the interventricular septum (IVS) with pulses of high amplitude and duration during the absolute refractory period. These impulses do not cause electrical activation of the myocardium, do not affect the heart rate, but increase the strength and duration of the action potential of cardiomyocytes, which contributes to the improvement of myocardium contractile function and the reverse remodeling in long-term period. In recent decades, the CCM influence on the clinical CHF course and LV myocardial remodeling has been of considerable interest [1]. However, there is currently insufficient data on the positive CCM effect, published randomized studies [2, 3] include a limited follow-up period, and despite receiving approval from the US Food and Drug Administration (FDA), CCM is not included in the recommendations for the treatment of patients with HFrEF.

Goal of the study: to evaluate the clinical course dynamics and the possibility of inversion of myocardial remodeling in patients with HFrEF associated with CCM.

Material and methods

In the period from October 2016 to September 2017, within the framework of the CCM clinical testing for the treatment of CHF at the Federal State Budgetary Institution "Almazov National Medical Research Centre" of the Ministry of Health of Russia, 55 patients were implanted with CCM devices (50 Optimizer Generation IV and 5 Optimizer Smart, Impulse Dynamics, Germany), endocardial electrodes for active fixation St. Jude Medical Tendril STS 2088TC.

The conditions for participation in the project, the criteria for clinical testing enrollment and exclusion were described in detail in the previous publication [4]. The main criteria for enrollment in the protocol were: HFrEF of functional class (FC) II and III (NYHA), sinus rhythm, QRS <130 ms or QRS <150 ms in the presence of non-specific intraventricular block, optimal and stable CHF drug therapy for at least 3 months.

Method of CCM system implantation. Implantation of CCM devices was carried out in the X-ray operating room; incision was performed in the right subclavian region under local anesthesia with an anesthetic solution; puncture of subclavian vein and/or venesection of the brachiocephalic vein, electrode insertion: atrial electrode was placed in the area of right atrial auricle, ventricular electrodes (VEs) — in basal and median parts of IVS at a distance of >2 cm from each other. In animal studies, it has been shown that stimulation of basal and median IVS parts is preferred [5], which is associated with the location of β1-adrenoreceptors in these zones [6], the stimulation of which leads to the activation of slow calcium channels and the launch of calcium-mediated intracellular mechanisms that lead to improved myocardial contractility. In 15 patients, VEs were implanted in the middle and basal parts of IVF, in 33 in the middle part, and only in 7 patients with ischemic HFrEF, one of the VEs was implanted in the lower third of the IVF, which was associated with a large area of post-infarction scar changes and the inability to achieve optimal parameters of stimulation and sensitivity. The external analyzer was used to test the electrodes resistance, the sensitivity to atrial and ventricular signals, and the stimulation thresholds. With satisfactory test results, the electrodes were connected to corresponding ports of stimulating device, and the patient's sensations during the application of CCM stimuli were evaluated. Separately, a bed for the electrodes and the device under subcutaneous adipose tissue was formed. The wound was sutured in layers.

Follow-up. After devices implantation, all patients were monitored by a case manager of patients with implanted electronic devices and specialists in heart failure (HF) treatment. Scheduled visits to the clinic were conducted every 3 months during the first year and every 6 months during the second year of follow-up. During each visit, the clinical status was assessed: patients were examined and current therapy was corrected, CHF FC was determined, a 6-minute walk test (6MWT), electrocardiography (ECG), daily ECG monitoring, monitoring of CCM work and setting up were carried out. The concentration of N-terminal pro B type natriuretic peptide (NT-proBNP) in blood serum was assessed every 6 months for one and a half years, and a cardiorespiratory test was performed for one year (tradmil, Ohusop Rgo model, Jaeger, Germany). Echocardiography (EchoCG) according to the standard method by one operator on the device VIVID 9 (GE, USA), was performed for 2 years. For each patient, the number of hospitalizations for 6 months was assessed before implantation; the average number of hospitalizations for each control point was calculated over the previous 6-month time interval.

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

The study assessed the dynamics of the following indicators: CHF FC, NT-proBNP, peak oxygen

Table 1

Clinical characteristics of patients

General data	
Gender (men), n (%)	46 (84%)
Age, years, M±SD	53±11
Resting heart rate, beats/min, M±SD	62±9
Underlying disease	
CHD, proportion of patients with PICS, n (%)	40 (73%), 37 (92,5%)
Myocardial revascularization, n (%)	30 (55%)
Dilated cardiomyopathy, n (%)	15 (27%)
ICD, n (%)	12 (22%)
Paroxysmal atrial fibrillation, n (%)	8 (14%)
Diabetes mellitus, n (%)	8 (14%)
Hospitalizations	
Number of patients hospitalized for 6 months before implantation, n (%)	38 (69%)
Number of hospitalizations for 6 months before implantation, Me [Q1; Q3]	1 [0; 1]
Minimum/maximum number of hospitalizations	0-4
Examination data	
Functional class of CHF (NYHA), Me [Q1; Q3]	2 [2; 3]
6MWT, m, M±SD	383±98
VO2peak, ml/kg/min, M±SD	16,2±5
LV EF, %, M±SD	26±6
LV EDV, ml, M±SD	257±58
LV ESV, ml, M±SD	187±54
Width of QRS complex, MS, M±SD	112±16
Laboratory data	
NT-proBNP, pg/ml, Me [Q1; Q3]	1094 [569; 1749]
Drug therapy	
β-AB, n (%)	55 (100%)
ACE inhibitors/ARA, n (%)	52 (96%)
Mineralocorticoid receptor antagonists, n (%)	51 (93%)
Diuretics: loop, n (%)	53 (96%)
Amiodarone, n (%)	7 (13%)

Notes: the data is presented: 1) n — absolute number of patients (%); 2) Me [Q1; Q3] — median and quartiles; 3) M±SD — mean ± standard deviation.

Abbreviations: AIIRA — angiotensin II receptor blocker, CHD — coronary heart disease, ACE inhibitors — angiotensin-converting enzyme inhibitors, ICD — implanted cardioverter defibrillators, EDV — end-diastolic volume, CSR — end-systolic volume, LV — left ventricle, PICS — postinfarction cardiosclerosis, 6MWT — 6-minute walk test, EF — ejection fraction, CHF — chronic heart failure, ECG — electrocardiography, EchoCG — echocardiography, β-AB — β-adrenergic blocker, NT-proBNP — N-terminal pro brain natriuretic peptide.

consumption (peakVO_2), walking distance during 6MWT, end-systolic and end-diastolic LV (ESV and EDV, respectively) volumes, LV EF measured by the Simpson method, atrial and ventricular arrhythmias according to the results of daily ECG monitoring and statistics of implanted cardioverter defibrillators (ICD), hospitalizations and deaths due to CHF decompensation, cases of heart transplantation.

Statistical data processing. Statistical analysis was carried out using the software pack IBM SPSS 23 and STATISTICA 10. The categorical indicators are represented by the frequencies and percentages of the total number of observations. Quantitative indicators were checked for normality using the Kolmogorov-Smirnov test. The data is described as the mean value ± standard deviation (M±SD) in case of normal distribution; the median of 25% and

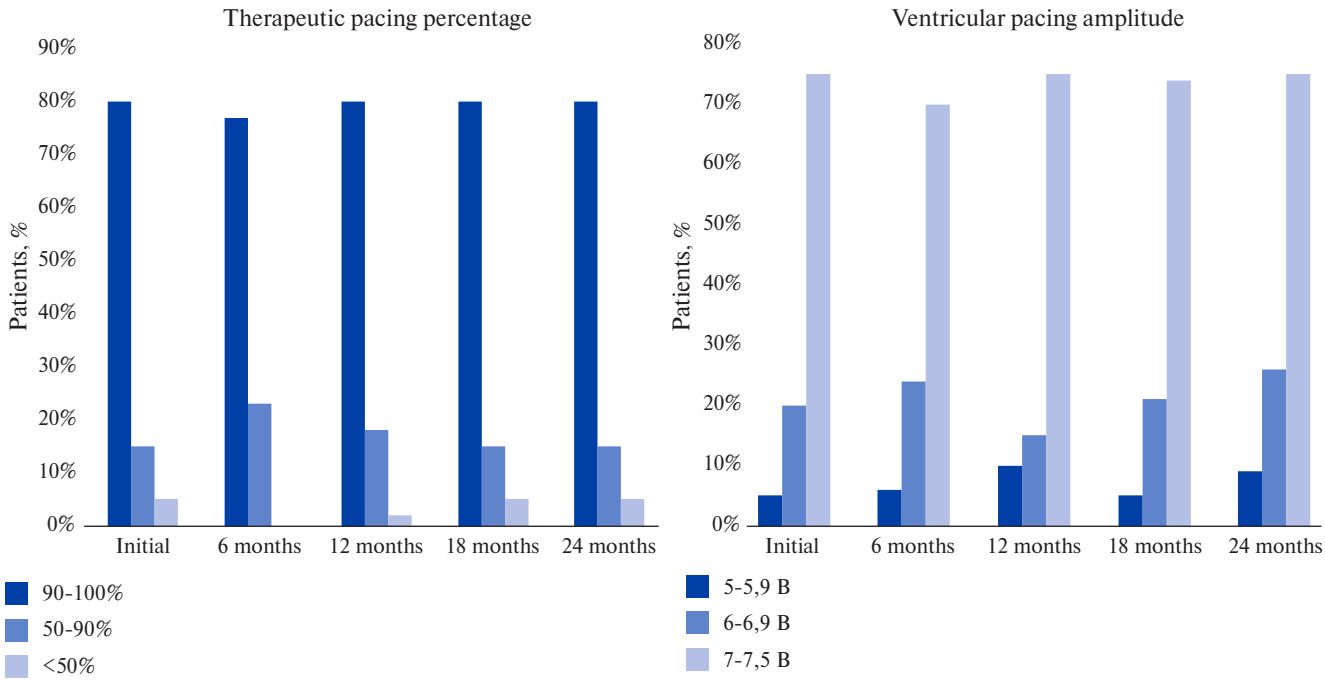

Figure 1. The percentage of therapeutic stimulation (left panel) and the amplitude of ventricular stimulation (right panel) in patients with implanted CCM devices.

75% quartiles in case of abnormal distribution; the minimum and maximum values. The Wilcoxon's test (2 time points) and the Friedman's test (3 or more time points) were used to assess the dynamics of indicators with distribution other than normal. The CHF FC indicators and the number of hospitalizations due to CHF decompensation had an abnormal distribution, but due to the fact that their median values did not change from 6-24 months of follow-up, graphs were plotted using the mean values to visually display the indicator dynamics. The variance analysis for dependent samples ANOVA Repeated was used to analyze the quantitative repeat indicators with normal distribution. At $p<0,05$, the differences were considered significant.

The study was carried out in accordance with the Good Clinical Practice standards and the principles of the Helsinki Declaration. The study protocol was approved by the Ethics Committees of all participating clinical centers. All participants received written informed consent before enrollment.

Results

There were no intraoperative complications. In the early postoperative period, one patient was found to have suppuration of the CCM bed and its reimplantation was performed for 6 days.

The survival rate for the 2-year follow-up period was 80% (44 patients): 2 cases of sudden cardiac death (SCD) and 1 fatal case due to CHF decompensation during the first year of follow-up; 2 cases of SCD and 4 fatal cases due to CHF decompensation, 1 heart transplant, 1 fatal case due to cancer progression after device implantation during the second year of follow-up. Detailed data on the outcomes were presented earlier [4].

Electrophysiological parameters of stimulation. CCM devices were programmed immediately after implantation, before patients were discharged for 3-4 days, every 3 months for 1 year, and every 6 months for 2 years of follow-up. The necessary recommendations were followed during programming: achieving the maximum percentage of therapeutic stimulation (>90%) and setting the maximum tolerable amplitude of ventricular stimulation (7-7,5 V for both VEs). The recommended amplitude and duration of ventricular stimulation in CCM are 5-7,5 V and 5,14 ms, respectively. In cases of insufficient therapeutic stimulation (<90%), the device operating time increased from 7 to 9-10 hours per day. As a result, the majority of patients within 2 years achieved and maintained the required percentage of therapeutic stimulation during the day (>90%) and established the maximum tolerable amplitude of ventricular stimulation (7-7,5 V for both VEs) (Figure 1).

3 months after implantation, unpredictable adverse events were detected in the form of stimulation of the CCM bed associated with violation of VEs isolation. Within 2 years, 48% of patients had to disconnect a single VE [4]. After VEs disconnection, the maximum stimulation amplitude was

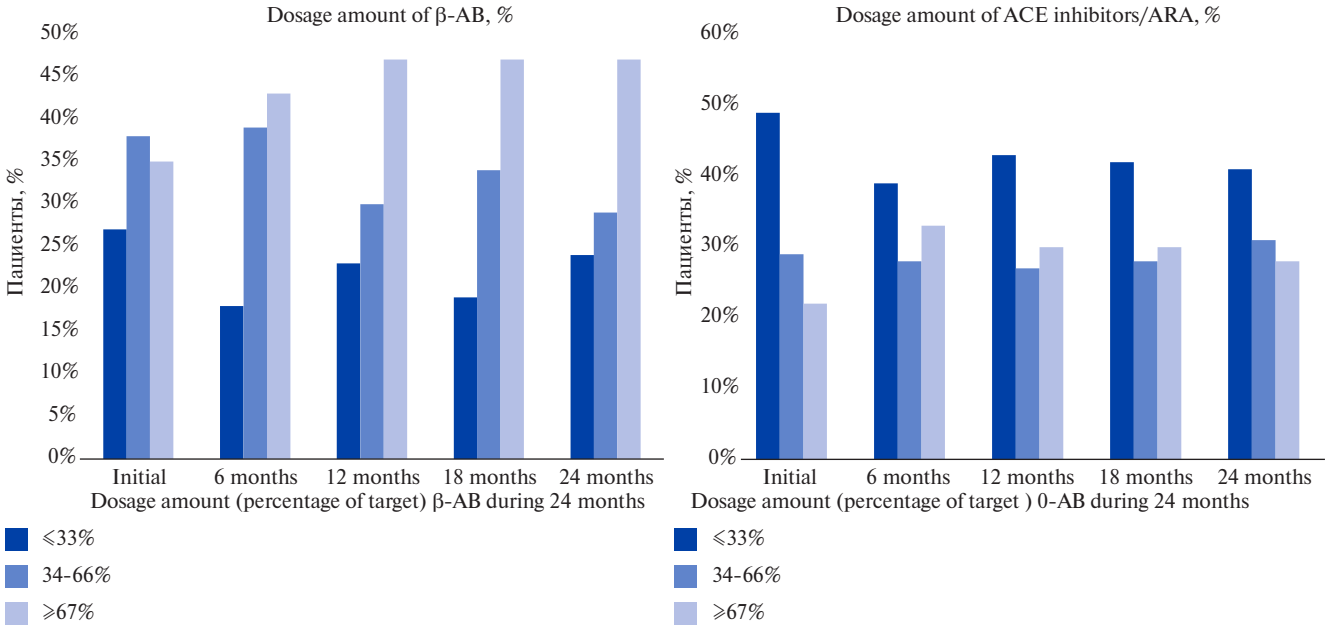

Figure 2. Dosage amount (percentage of recommended target) of β-AB (left panel), ACE inhibitors/ARA (right panel) during 24 months of follow-up.
Abbreviations: AIIRA — angiotensin II receptor blocker, ACE inhibitors — angiotensin-converting enzyme inhibitors, β-AB — β-adrenergic blocker.

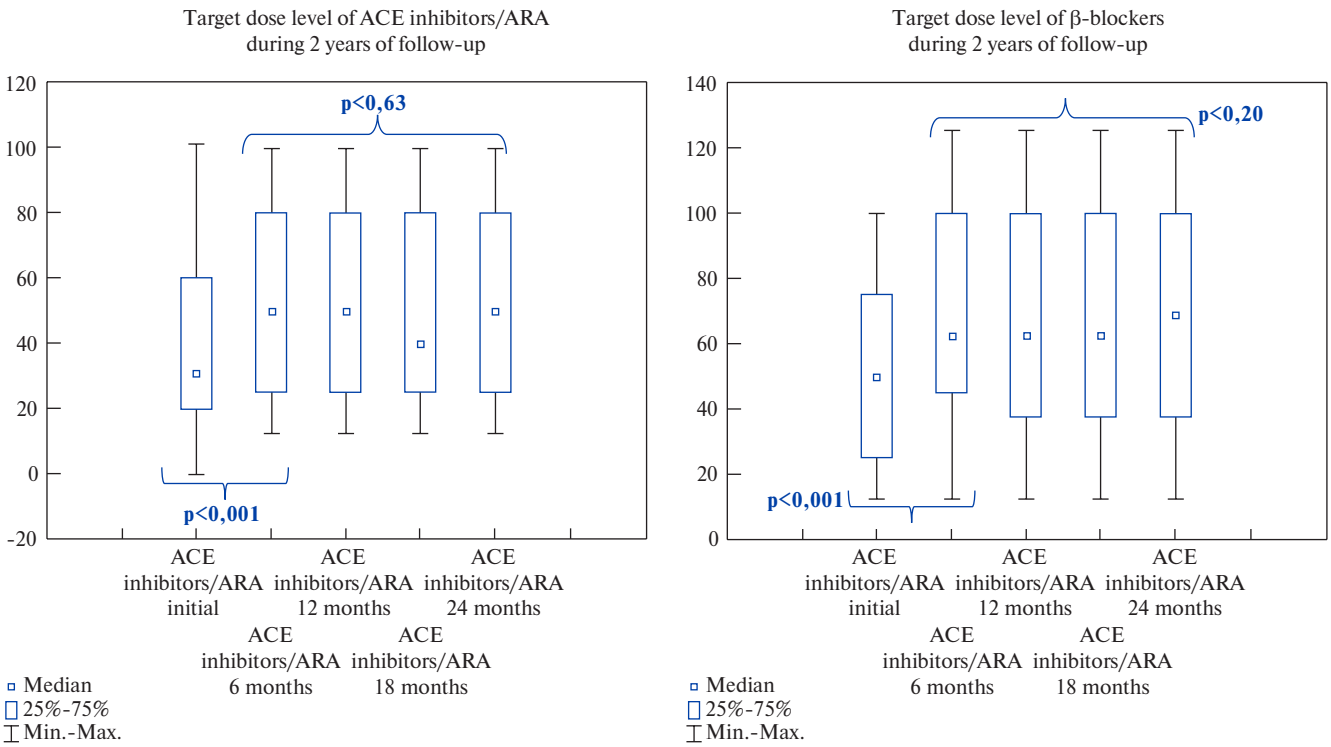

Figure 3. Dynamics of the dose of ACE inhibitors/ARA (left panel) and β-AB (right panel) during 24 months of follow-up.
Abbreviations: AIIRA — angiotensin II receptor blocker, ACE inhibitors — angiotensin-converting enzyme inhibitors, β-AB — β-adrenergic blocker.

set from a single VE and the stimulation duration was increased to 9-10 hours per day. CCM system audit and replacement of both VEs was carried out in 10 patients over 2 years. In all patients, the audit revealed violations of VEs insulation in several places and carbonisation in the area of insulation defects.

To assess the effect of disconnecting one VE on the studied parameters, patients were divided into

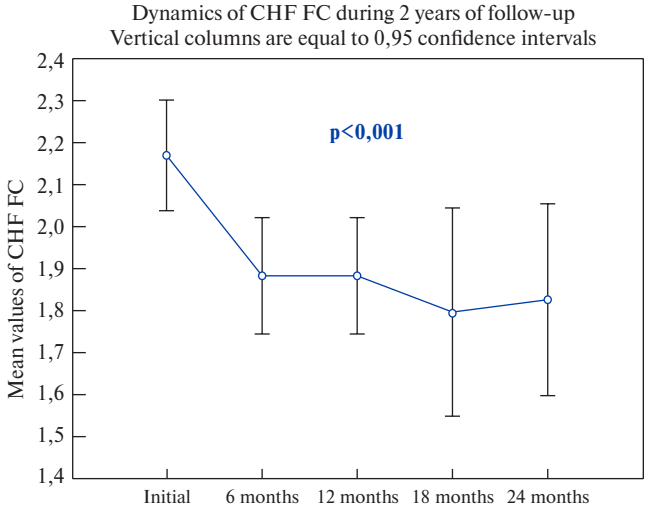

Figure 4. Dynamics of mean values of CHF FC during 2 years of follow-up.
Abbreviations: CI — confidence interval, FC — functional class, CHF — chronic heart failure.

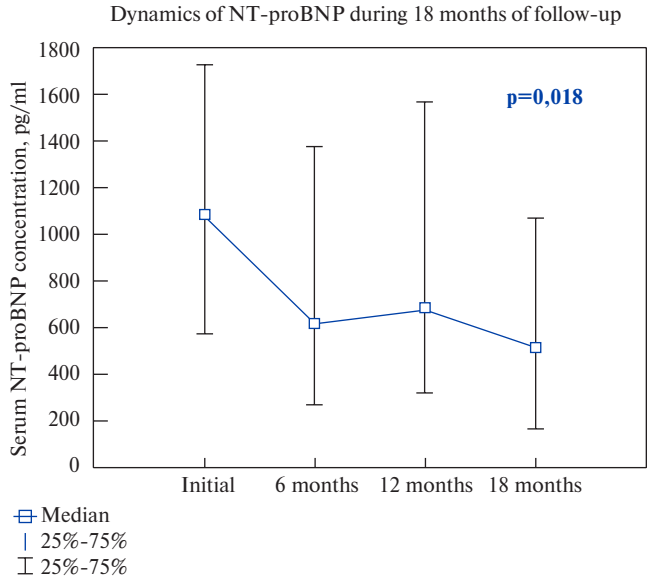

Figure 5. Dynamics of NT-proBNP during 18 months of follow-up.
Abbreviation: NT-proBNP — N-terminal pro brain natriuretic peptide.

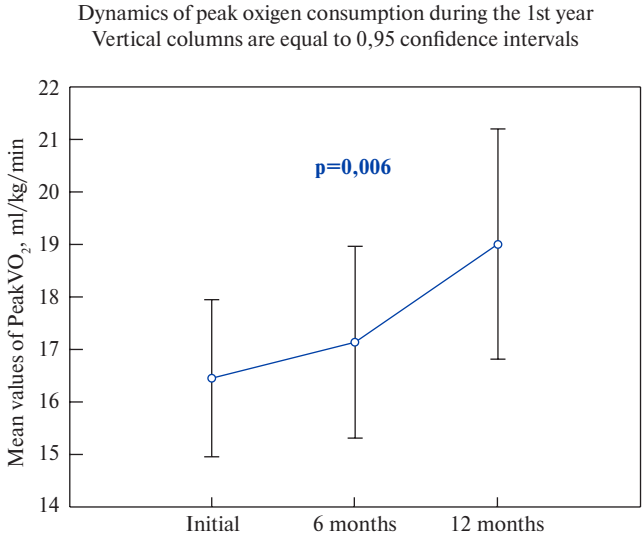

Figure 6. The dynamics of peakVO_2 during 1 year.
Abbreviations: CI — confidence interval, peakVO_2 — peak oxygen consumption.

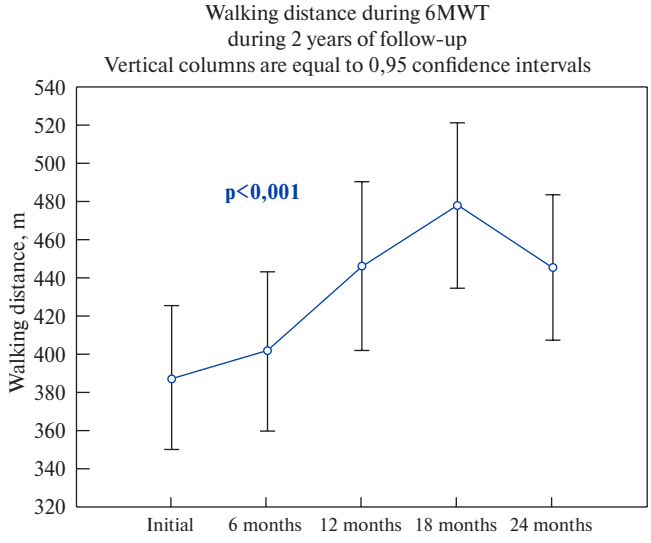

Figure 7. Dynamics of the 6MWT distance during 2 years of observation.
Abbreviations: CI — confidence interval, 6MWT — 6-minute walk test.

groups with one and two operating VEs. The first year of follow-up and 2 years of follow-up were analyzed separately; the patients were divided into those who did not have insulation violations during the entire follow-up period, and those who had 1 electrode disconnected or both VEs replaced.

Analysis of HFrEF drug therapy. The dosage amount (percentage of recommended target) of β-adrenergic blockers (β-AB) and angiotensin-converting enzyme inhibitors (ACE inhibitors)/angiotensin I receptor blocker (AIRA) and dose titration of these drugs are shown in Figure 2.

The analysis of drug therapy showed a significant increase in the dose of ACE inhibitors and ARA during the first 6 months ($p<0,001$) after CCM implantation and the lack of drug dose dynamics during further follow-up ($p<0,63$). β-AB doses were also significantly increased in the first 6 months after implantation ($p<0,0001$) and did not change during the subsequent follow-up period

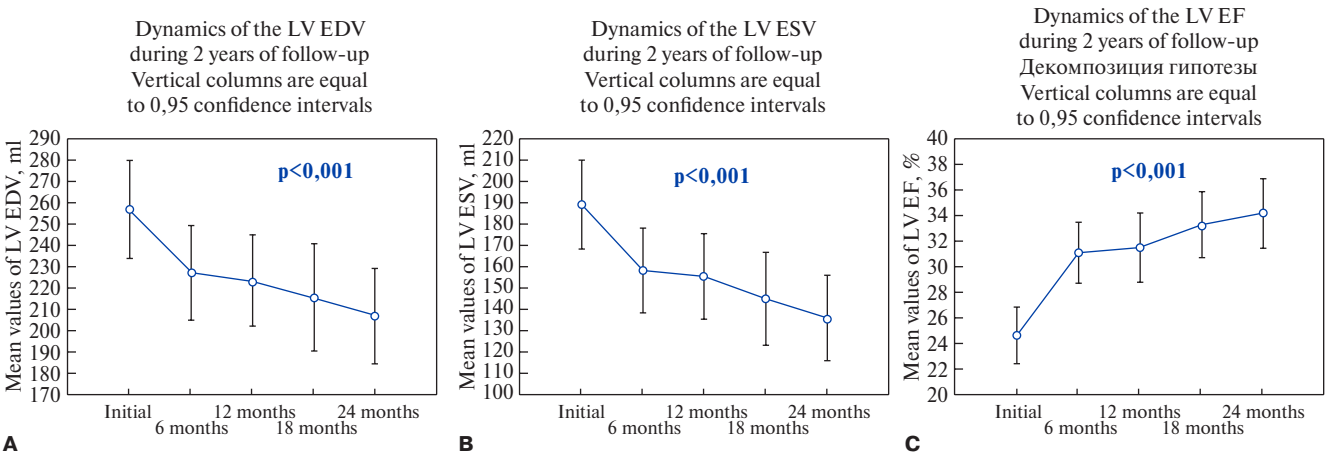

Figure 8. Dynamics of LV EDV (**A**), LV ESV (**B**), and LV EF (**C**) during 2 years of follow-up.
Abbreviations: CI — confidence interval, LV EDV — left ventricular end-diastolic volume, LV ESV — left ventricular end-systolic volume, LV EF — left ventricular ejection fraction.

Table 2

Dynamics of studied parameters in patients with stimulation of one and two VEs

Period	Without electrodes disconnection	Electrodes disconnection
Functional class of CHF, Me [Q1, Q3]		
Initial	2 [2; 3]	2 [2; 2]
12 months	2 [2; 2]	2 [2; 2]
24 months	2 [2; 2]	2 [1; 2]
NT-proBNP concentration, pg/ml, Me [Q1, Q3]		
Initial	1137 [542; 1749]	1066 [728; 1452]
12 months	446 [317; 1326]	748 [438; 1571]
18 months	551 [268; 1653]	478 [136; 800]
VO_2peak, ml/kg/min, M±SD		
Initial	16,9 [12,4; 18,2]	16,5 [13,4; 21,4]
12 months	17,2 [14,6; 22,9]	20,7 [15,9; 24,3]
End-diastolic volume, ml, M±SD		
Initial	264±19	253±14
12 months	239±17	215±13
24 months	223±18	198±14
End-systolic volume, ml, M±SD		
Initial	193±17	188±13
12 months	167±16	150±12
24 months	153±16	127±12
Ejection fraction, %, M±SD		
Initial	23±2	25±1
12 months	31±2	32±2
24 months	31±2	36±2
Number of hospitalizations due to CHF decompensation, Me [Q1, Q3]		
Initial	1 [0; 1]	1 [0; 2]
12 months	0 [0; 0]	0 [0; 0]
24 months	0 [0; 0]	0 [0; 0]

Note: Me [Q1, Q3] — median, 25% and 75% quartiles, M±SD — the mean±standard deviation. For all parameters in subgroups comparison p>0,05.
Abbreviations: CHF — chronic heart failure, NT-proBNP — N-terminal pro brain natriuretic peptide.

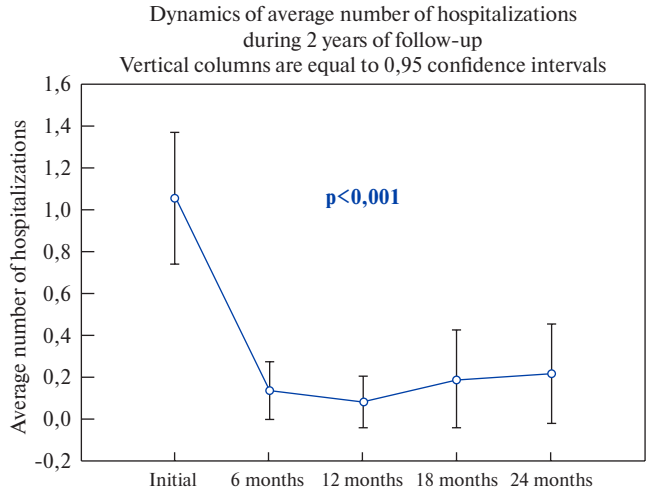

Figure 9. Dynamics of hospitalizations due to CHF decompensation during 2 years of follow-up.
Abbreviation: CI — confidence interval.

(p<0,20). The dynamics of drug doses is shown in Figure 3.

The loop diuretic dose in 15 patients (27%) during 24 months of follow-up decreased by 25-50%.

Dynamics of studied indicators

CHF FC. Within 2 years, there was a significant decrease in CHF FC (p<0,001, n=44). Pronounced dynamics were observed after 6 months compared to the initial values of FC, p<0,001 (n=53), 12 months (p<0,001, n=51), 18 months (p=0,003, n=49), 24 months (p<0,001, n=44). No significant dynamics of CHF FC from 6 to 24 months of follow-up was revealed, p=0,43 (Figure 4).

A decrease in CHF FC within 2 years was observed in 15 patients (27%), an increase in CHF FC was observed in 6 patients (11%), of which 3 patients had a decrease in CHF FC within 1 year and an increase in CHF FC with pronounced CHF

Table 3

Differences in NT-proBNP levels in patients with and without CHD anamnesis (Mann-Whitney test)

Value	n no CHD	n CHD	NT-proBNP no CHD	NT-proBNP CHD	p-value
NT-proBNP initial	15	40	1029 [316; 1446]	1049 [686,5; 1908]	p=0,712
NT-proBNP 6 months	13	35	278 [117; 543]	916 [396; 2222]	p=0,008
NT-proBNP 12 months	14	36	299,0 [93,9; 689]	845,8 [442; 1804,5]	p=0,006
NT-proBNP 18 months	7	13	136,2 [59; 268]	793 [478;1318]	p=0,007
Dynamics of NT-proBNP over 12 months, p-value (Friedman test)			p=0,02	p=0,01	

Abbreviations: CHD — ischaemic heart disease, NT-proBNP — concentration of N-terminal pro brain natriuretic peptide.

Table 4

Differences in peakVO_2 levels in patients with and without CHD anamnesis (Mann-Whitney test)

Value, Me [Q1; Q3]	n no CHD	n CHD	PeakVO_2, ml/kg/min no CHD	PeakVO_2, ml/kg/min CHD	p-value
PeakVO_2 original	15	39	20,8 [13,0; 21,8]	16,0 [12,4; 18,2]	p=0,007
PeakVO_2 6 months	12	31	21,2 [14,5; 23,8]	16,2 [12,3; 19,1]	p=0,05
PeakVO_2 12 months	15	37	18,1 [15,9; 28,2]	17,3 [14,5; 22,5]	p=0,24
Dynamics of peakVO_2 for 1 year, p-value (Friedman criterion)			p=0,56	p=0,03	

Abbreviations: CHD — coronary heart disease, peakVO_2 — peak oxygen consumption.

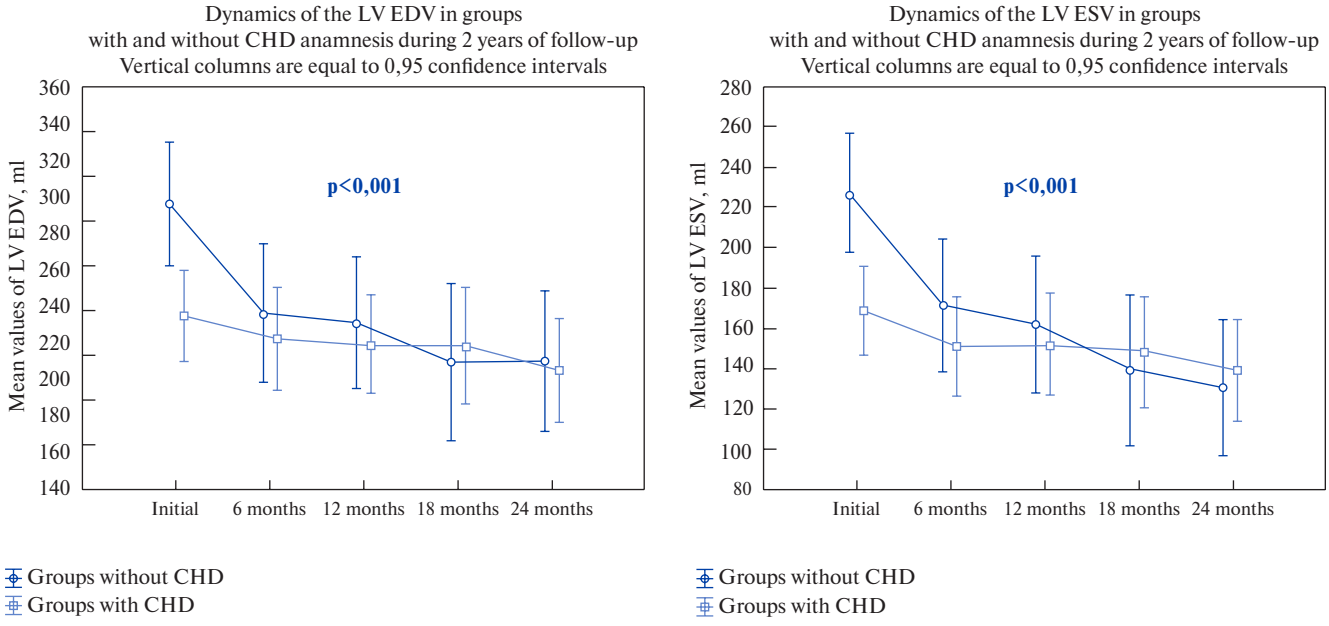

Figure 10. Dynamics of the LV EDV and LV ESV for 2 years in the group with CHD and without CHD.
Abbreviations: CI — confidence interval, CHD — coronary heart disease, LV EDV — left ventricle end-diastolic volume, LV ESV — left ventricle end-systolic volume.

decompensation up to fatal case by the end of 2 years of follow-up. 3 patients (5%) had an increase in FC by the end of the 1st year and a decrease in FC in the second year of follow-up. FC did not change in 31 (56%) patients.

Concentration of NT-proBNP in the blood. The level of NT-proBNP was studied in the first 18 months of follow-up. There was a positive trend over the entire follow-up period, p=0,018, n=20 (Figure 5). A decrease in the NT-proBNP level

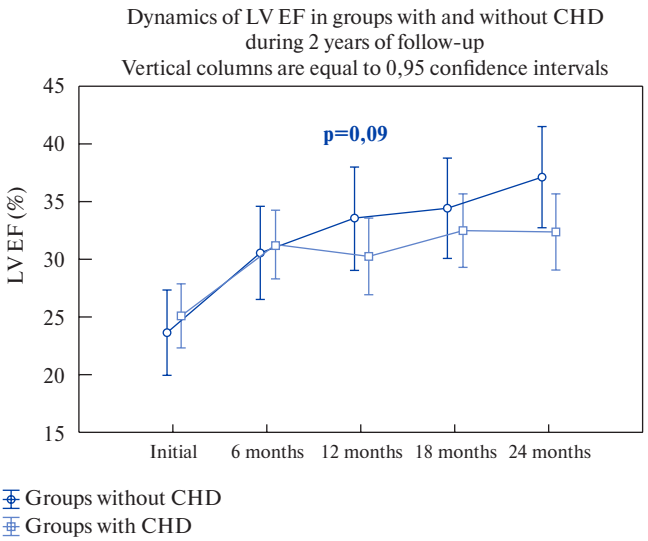

Figure 11. Dynamics of LV EF in groups with and without CHD during 2 years of follow-up.
Abbreviations: CI — confidence interval, CHD — coronary heart disease, LV EF — left ventricular ejection fraction.

compared to the initial value was observed after 6 months (p<0,001, n=48), 12 months (p=0,018, n=50) and 18 months (p=0,027, n=20).

A decrease in the NT-proBNP level within 1 year was observed in 30 (55%) patients, an increase — in 11 (20%) patients, without changes — in 13 (24%). After 18 months after CCM device implantation, the NT-proBNP level was studied in 20 patients. The decrease in NT-proBNP compared to the initial value was in 14 (70%), the increase — in 5 (25%), without changes in 1 (5%) patient.

PeakVO_2. The PeakVO_2 value increased during the first year by an average of 21±31% in 35 (64%) patients, p=0.006. The peakVO_2 dynamics at three time points is shown in Figure 6.

6MWT. The 6MWT analysis on average for the group showed a positive trend one year later (p<0,001, n=35) and 2 years later (p<0,001, n=34) after CCM implantation. Individual indicators, compared with the initial, improved in 27 patients by 12 months, and in 29 patients by 24 months. The 6MWT dynamics is shown in Figure 7.

EchoCG data. 6 months after the CCM device implantation, a 10% decrease in LV ESV compared to the initial was detected in 27 of 55 patients (49,1%), 12 months later — in 22 of 52 patients (42%), 24 months later — in 29 of 44 patients (66%). An increase in LV EF by more than 10% compared to the initial was detected in 26 of 54 patients (48%) after 6 months, in 25 of 52 (48%) — after 12 months and in 34 of 44 patients (77%) — 24 months after CCM implantation.

The dynamics of mean values of these indicators is shown in the figures (Figure 8 A, B, C).

Hospitalizations due to CHF decompensation. The number of hospitalizations due to CHF decompensation, compared with the indicator for 6 months before surgery decreased by 6 months after CCM device implantation (p<0,0001), this effect persisted for 2 years of follow-up (Figure 9).

Dynamics analysis of the studied parameters in patients with one and two VEs. The dynamics of all the studied parameters did not differ in the groups of patients with and without disconnecting one of the VEs at all control points, p>0,05 (Table 2).

Dynamics of the studied parameters depending on HFrEF etiology. Dynamics of CHF FC in groups of patients with coronary heart disease (CHD) (92,5% of patients with post-infarction cardiosclerosis (PIC)) and without CHD did not differ during the first year, 2 [2; 2] and 2 [1; 2], respectively, p=0.22, and the second year of follow-up, 2 [2; 2] and 2 [1; 2], respectively, p=0,25. There were also no differences in the dynamics of number of hospitalizations due to CHF decompensation (minimum-maximum number of hospitalizations 0-1 and 0-3 during the first and second years, respectively, for patients without CHD, 0-2 and 0-3 during the first and second years, respectively, for patients with CHD), p>0,05 at all-time points.

The dynamics analysis of the NT-proBNP level in the groups with CHD and without CHD showed that the initial NT-proBNPlevel did not differ in both groups (Table 3). However, at 6, 12, and 18 months after implantation, the NT-proBNP level was significantly higher in patients with CHD (Table 3). There was a significant positive dynamic of the indicator within each group during 1 year of follow-up (Table 3).

The peakVO_2 values was at baseline and 6 months after CCM implantation was lower in the group of patients with CHD (Table 4).

The EchoCG parameters dynamics of LV EDV and LV ESV differed in the groups of patients with ischemic and non-coronary cardiomyopathy during 1 year and 2 years of follow-up, p=0,036 and p=0,0003 for LV EDV and p=0,007 and p<0,001 for LV ESV, respectively, due to the initial values of LV EDV and LV ESV (Figure 10). When excluding the starting point, the dynamics in the two groups was not significant, p=0,39 for LV EDV and p=0,25 for LV ESV. The decrease in volume parameters was more expressed in the group of patients with non-coronary cardiomyopathy.

The analysis of LV EF absolute values showed significant differences in the two groups at 12 and 24 months after CCM therapy, p=0,03 and p=0,01, respectively. However, the indicator dynamics in

Table 5

Differences in NT-proBNP index in groups with baseline of LV EF ⩾25% and LV EF ⩽25% during 18 months of follow-up (Mann-Whitney test)

Value	n	n	NT-proBNP	NT-proBNP	p-value
	EF ⩾25%	EF <25%	EF ⩾25%	EF <25%	
NT-proBNP исходно	29	26	866 [511; 1094]	1300 [1137; 1777]	p=0,006
NT-proBNP 6 мес.	25	23	547 [205; 942]	936 [416; 2230]	p=0,07
NT-proBNP 12 мес.	27	23	533,4 [221,9; 849]	1099 [374,9; 2152]	p=0,06
NT-proBNP 18 мес.	10	10	763 [190,1; 1318]	407,3 [136,2; 823,5]	p=0,5
Dynamics of NT-proBNP over 12 months, p-value (Friedman test)			p=0,07	p=0,005	

Abbreviations: EF — ejection fraction, NT-proBNP — N-terminal pro brain natriuretic peptide.

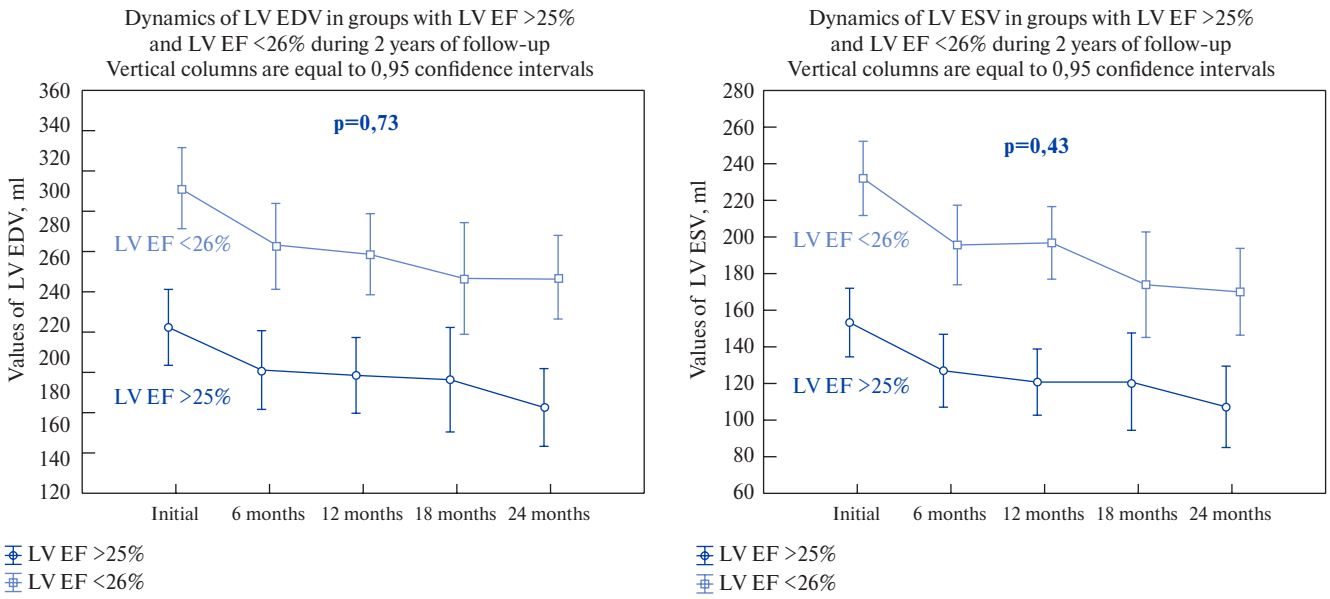

Figure 12. Dynamics of LV EDV and LV ESV in groups with initial value of LV EF > and <25% during 2 years of follow-up.
Abbreviations: CI — confidence interval, LV EDV — left ventricular end-diastolic volume, LV ESV — left ventricular end-systolic volume, LV EF — left ventricular ejection fraction.

both groups did not differ significantly, p=0,09 (Figure 11).

Dynamics of studied parameters in patients in the groups with the initial value of LV EF ⩾25% and LV EF <25%. The dynamics of CHF FC, the number of hospitalizations due to CHF decompensation, and peakVO_2 did not differ in the LV EF groups ⩾25% and LV EF <25% during 2 years of follow-up.

The absolute NT-proBNP values were initially higher in the group with LV EF <25%. At further follow-up, there were no significant differences in NT-proBNP in the groups (Table 5).

The analysis of EchoCG parameters revealed regular significant differences in LV volumes in the groups with LV EF ⩾25% and LV EF <25%. With that, the volume dynamics in both groups was identical (Figure 12).

Cardiac arrhythmias analysis and indications for ICD implantation. In accordance with the European Recommendations of 2016 and the recommendations of the All-Russian Scientific Society of Arrhythmologists, 2017, the presence of HFrEF with LV EF ⩽35% in the absence of reversible causes is an indication for the SCC primary prevention [7, 8]. Prior to the CCM device implantation, 11 (22%) patients had ICD for the primary SCC prevention. The remaining patients were scheduled for ICD implantation after CCM implantation. During the 1 and 2 years of follow-up, ICDs were implanted in 21 (38%) and 3 (4%) patients, respectively. There were no ICD triggers with regards to paroxysmal ventricular arrhythmias. 2 patients refused ICD implantation, and two died suddenly during the first 6 months before ICD implantation. Within 2 years, 10 patients

(18%) were removed from the ICD waiting list due to achievement of LV EF >35% (LV EF was 38% in 2 patients and >40% — in 8 patients), of which 1 patient died suddenly at the age of 18 months (his initial LV EF was 35%, and at the 12-month visit it reached 43%).

Cessation of CCM therapy occurred in one patient after 18 months after device implantation due to transition of atrial fibrillation to a permanent form. Electro-pulse therapy with sinus rhythm withholding for no more than 1 month was carried out twice. Arrhythmia catheter ablation was not carried out due to the predicted low efficiency.

Discussion

Our study shows a clear positive trend of current HFrEF associated with CCM within a two-year follow-up period: reduction of CHF FC hospitalizations because of CHF decompensation, decrease the concentration of NT-proBNP in the blood, an increase in peakVO_2 in the first year of follow-up as well as the decrease and increase in LV EF volumes.

Violations of the VEs isolation were detected in half of the patients during the follow-up, which required the disconnection of one VE. Subjectively, when VEs disconnecting, patients noted a feeling unwell, a decrease in tolerance to physical activity, discomfort with the appearance of muscle stimulation and inconvenience due to the need for additional visits to the clinic. However, the dynamics of objective indicators and EchoCG parameters for 2 years did not differ in the groups with one and two VEs. Our data correlate with Röger S, et al. [9], who compared 2 groups of patients with one and two VEs (23 and 25 patients in each group, respectively) and assessed peakVO_2, CHF FC, quality of life, and also did not receive any differences. The obtained results may be important in the future when optimizing CCM devices. The currently recommended parameters of stimulation, as well as the need for implantation of two VEs, are based on data obtained in the study on CCM therapy in animal models [10].

The curation feature of the studied group of patients had involvement of a HF cardiologist expert that provided their management in accordance with the current recommendations from the patients formation position and the dose selection of modern drugs [8, 11]. A significant increase in the dose of β-AB and ACE inhibitors/ARA was observed during the first 6 months, then the doses of these drugs did not significantly change. It should be noted that 27% of patients managed to reduce the dose of loop diuretics by 25-50%, which confirms a significant improvement in their status. There were no changes in drug doses of the main groups for CHF treatment in the period from 6-24 months of the follow-up, while the positive dynamics of HF severity, the improvement of laboratory and echocardiographic parameters continued, makes it highly likely that we were dealing not only with the drug therapy contribution, but also CCM to the positive dynamics of the patients' status.

When analyzing the studied parameters, depending on CHF etiology, it was shown that patients with ischemic HFrEF had significantly higher NT-proBNP values after 6, 12 and 18 months, and lower peakVO_2 values at baseline and 6 months after CCM implantation. The positive dynamics of EchoCG parameters was observed in both groups, but the curve of LV volume reduction was significantly more expressed in the group of patients with non-coronarogenic HFrEF. Initially, higher values of LV EDV and ESV in this group significantly decreased in the first 6 months after implantation, with a further decrease by the end of the 2-year follow-up, while patients with ischemic HFrEF had initially lower values of LV volumes, and the volume dynamics curve was flatter. LV EF significantly increased in both groups within 2 years, but its absolute values were significantly higher in the group of patients with HFrEF of non-coronary etiology after 12 and 24 months of follow-up. It is important to note that despite the differences in the clinical response to CCM in patients with CHF of different etiologies, the presence of CHD, PIX did not have a significant negative effect on CHF outcomes (mortality and hospitalization due to CHF decompensation) [4].

Randomized clinical studies (HF-FIX-5, HF-FIX-5 subgroup with LV EF 25-45%, HF-FIX-5C) showed a better response to CCM in patients with LV EF 25-45% [2, 3]. In 2019, an analysis of the economic CCM applicability in patients with HFrEF [12] was conducted, that showed the advantage of implanting CCM devices in this group compared to traditional drug therapy. However, extension study is needed to confirm this data. The cohort of patients presented in the study did not include persons with LV EF >35%. All patients were divided into groups with LV EF ⩾25% and <25%. There were no significant differences in the number of hospitalizations due to CHF decompensation, the dynamics of CHF FC, peakVO_2, and NT-proBNP. The dynamics of echocardiographic parameters did not differ in the groups. Lower values of LV volumes were observed in patients with LV EF more than 25%. There were no differences in the HFrEF course outcomes with LVEF value of more or less than 25% for 2 years [4].

The experience obtained in the study showed the need to implant ICDs in patients before implanting CCM devices, as required by national and European recommendations [7, 8]. In 18% of patients, during a two-year follow-up period, LV EF ranged from

35-40%, which turned out to be an obstacle to ICD implantation, resulting in SCC. The encouraging results of the CCM use in the majority of HFrEF patients with sinus rhythm should stimulate the search for predictors of a positive response to this type of electrophysiological treatment, which will help to personalize the electrotherapy type when choosing tactics to improve the prognosis.

Study limitations. The presented data were obtained in the course of follow-up study, which was conducted within the protocol of clinical testing of the Ministry of Health of the Russian Federation 2016-19-16 and did not have a control group. The sample of patients included mainly men, which did not allow to assess the gender characteristics of the CCM use.

Conclusion

In the group of patients with HFrEF of FC II-III, the CCM use in most patients was associated with improvement or stabilization of clinical and hemodynamic state, increase in exercise tolerance, decrease in number of hospitalizations due to HF decompensation, positive dynamics of functional and geometric parameters of LV and marker of myocardial NT-proBNP stress.

The positive trend of changes in the indicators of CHF severity markers and prognosis was not affected by disease causation, but the presence of CHD, PICS was associated with a lower dynamics of the volume EchoCG parameters of reverse myocardial remodeling and NT-proBNP associated with CCM.

When using CCM, an individual approach to the implantation technique, the choice of consumables and constant dynamic monitoring with the participation of a cardiologist-a specialist in heart failure is required.

Relationships and Activities: none.

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Prognostic value of atrial fibrillation in patients with heart failure and different left ventricular ejection fraction: results of the multicenter RIF-CHF register

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Heart failure (HF) and atrial fibrillation (AF) are the most common cardiovascular conditions in clinical practice and frequently coexist. The number of patients with HF and AF is increasing every year.

Aim. To analyze the effect of clinical course and management of HF and AF on the outcomes.

Material and methods. The data of 1003 patients from the first Russian register of patients with HF and AF (RIF-CHF) were analyzed. The endpoints included hospitalization due to decompensated HF, cardiovascular mortality, thromboembolic events, and major bleeding. Predictors of unfavorable outcomes were analyzed separately for patients with HF with preserved ejection fraction (AF+HFpEF), mid-range ejection fraction (AF+HFmrEF), and reduced ejection fraction (AF+HFrEF).

Results. Among all patients with HF, 39% had HFpEF, 15% — HFmrEF, and 46% — HFrEF. A total of 57,2% of patients were rehospitalized due to decompensated HF within one year. Hospitalization risk was the highest for HFmrEF patients (66%, p=0,017). Reduced ejection fraction was associated with the increased risk of cardiovascular mortality (15,5% vs 5,4% in other groups, p<0,001) but not ischemic stroke (2,4% vs 3%, p=0,776). Patients with HFpEF had lower risk to achieve the composite endpoint (stroke+MI+cardiovascular death) as compared to patients with HFmrEF and HFrEF (12,7% vs 22% and 25,5%, p<0,001). Regression logistic analysis revealed that factors such as demographic characteristics, disease severity, and selected therapy had different effects on the risk of unfavorable outcomes depending on ejection fraction group.

Conclusion. Each group of patients with different ejection fractions is characterized by its own pattern of factors associated with unfavorable outcomes. The demographic and clinical characteristics of patients with mid-range ejection fraction demonstrate that these patients need to be studied as a separate cohort.

Key words: heart failure, atrial fibrillation, left ventricular ejection fraction, treatment.

Relationships and Activities: none.

Trial ID: ClinicalTrials.gov ID: NCT02790801.

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The incidence of heart failure (HF) and atrial fibrillation (AF) in the world has the pandemic character [1]. This is largely due to population ageing and improvement in survival rate of patients with cardiovascular diseases [2]. According to epidemiological studies, >37 million people worldwide suffer from AF [3]. According to the Framingham study, the risk of developing AF in people over 55 years of age is 37% [4]. AF not only reduces the quality of life, but also worsens the prognosis. The 10-year survival rate among people with AF aged 55 to 74 years is 42,4% and 38,5% for women and men, compared to 79,1% and 70% for women and men without AF [5].

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Worldwide, >64 million people suffer from chronic HF (CHF) [3]. Population-based studies show that the CHF incidence is higher among men than among women, and increases dramatically with age [6]. The CHF prevalence among the population of developed countries is 1-3%, increasing to 10% and 30% in the age groups over 70 and 85 years, respectively [7]. In comparison with the increase in the AF incidence over the past few decades, the number of new cases of HF during this period was stable. The increase in the number of patients with CHF is largely associated with improved survival rate [8, 9].

CHF and AF are often combined with each other. This can be partly explained by the presence of common risk factors (RF), such as age, hypertension, coronary heart disease, diabetes mellitus, obesity, obstructive sleep apnea syndrome, valvular disease, kidney disease, smoking [10, 11]. HF develops in two-thirds of people with AF, and AF, in turn, complicates the HF course in one-third of patients [12, 13]. The combination of CHF and AF increases the stroke risk, admission due to CHF decompensation and overall mortality rate [14]. According to the Framingham study, mortality rates (per 1000 patient-years) in patients with HF and the development of new AF were 257 and 302 for patients with HF with preserved ejection fraction (EF) (HFpEF) and HF with reduced EF (HFrEF), respectively, compared with 120 in patients without HF. Mortality rate (per 1000 patient-years) in patients with a new diagnosis of HF and previous AF was 290 compared to 244 in people without AF [12]. As the RE-LY study analysis has shown, HF is an independent predictor of overall mortality rate and has the highest predictive significance for cardiovascular mortality in patients with AF [15]. An additional point is that unlike patients with sinus rhythm, patients with HFrEF and concomitant AF have no effect from beta-blocker therapy from viewpoint of overall mortality rate, mortality rate from cardiovascular diseases, or hospitalization [16]. This highlights the importance of analyzing the outcomes of patients with CHF in AF, rather than extrapolating data from patients with sinus rhythm.

According to the European Guidelines for HF management (2016), HF is divided into 3 clinical subtypes: HFpEF: EF ⩾50%, HF with midrange EF (HFmrEF): 40⩽ EF <49% and HFrEF: EF <40% [17]. These groups of patients have major differences in a number of parameters, ranging from epidemiology, etiology and pathogenesis to diagnosis, therapeutic strategy and prognosis. Many questions on the therapeutic strategy remain to be resolved. One reason is that our HFpEF and HFmrEF knowledge is limited to data from retrospective studies or subanalyses of randomized trials [17, 18].

Our study was aimed at analyzing the features of the CHF course in combination with AF, collecting data on diagnosis, treatment and level of compliance with clinical recommendations for CHF and AF treatment in the Russian Federation.

Material and methods

The study design was described earlier [19]. A multicenter prospective observational study from February 2015 to January 2016 enrolled 1003 patients with CHF in combination with AF. The patients were enrolled in 30 medical centers from 21 regions of the Russian Federation. All patients had a confirmed diagnosis of CHF and AF, in accordance with the current European guidelines for HF treatment dated 2012 [20] and the European guidelines for AF treatment dated 2012 [21].

Endpoints. The primary endpoint of the study was hospitalization due to HF worsening. Secondary endpoints were cardiovascular mortality, any thromboembolic complications (TEC) and major bleeding as defined by the International Society on Thrombosis and Hemostasis (ISTH) [22].

The study was conducted in accordance with the principles of Good Clinical Practice (GCP), which protect the rights of study participants, rules for ensuring their safety and compliance with the requirements on study validity. The study was approved by the Committee on Ethics in Clinical

Table 1

Demographic parameters, anamnesis data

Parameters	All patients (n=1003)	AF-HFpEF (n=387)	AF-HFmrEF (n=150)	AF-HFrEF (n=466)	Significance, p
Demographic parameters					
Age, years	68 (60;76)	72 (63;78)	67 (58;75)	66 (58;75)	<0,001
Age ⩾65 years, %	589 (58,7%)	270 (69,8%)	82 (54,7%)	237 (50,9%)	<0,001
Age ⩾75 years, %	310 (30,9%)	157 (40,6%)	38 (25,3%)	115 (24,7%)	<0,001
Female, %	437 (43,6%)	253 (65,4%)	64 (42,7%)	120 (25,8%)	<0,001
BMI ⩾30, %	360 (35,9%)	147 (38%)	62 (41,3%)	151 (32,4%)	0,076
Low physical activity, %	570 (56,8%)	191 (49,4%)	96 (64%)	283 (60,7%)	<0,001
Smoking					
Never smoked, %	603 (60,1%)	295 (76,2%)	84 (56%)	224 (48,1%)	<0,001
Gave up smoking, %	216 (21,5%)	53 (13,7%)	38 (25,3%)	125 (26,8%)	
Smoking, %	184 (18,3%)	39 (10,1%)	28 (18,7%)	117 (25,1%)	
Comorbidity					
Hypertension, %	653 (65,1%)	263 (68%)	108 (72%)	282 (60,5%)	0,012
Duration of hypertension, age	14 (10;20)	13 (10;20)	10 (7,5;20)	15 (10;20)	0,916
CHD, %	686 (68,4%)	271 (70%)	107 (71,3%)	308 (66,1%)	0,336
Diabetes mellitus, %	247 (24,6%)	89 (23%)	38 (25,3%)	120 (25,8%)	0,632
Anamnesis of stroke, TIA, %	158 (15,8%)	58 (15%)	22 (14,7%)	78 (16,7%)	0,747
Anamnesis of MI, %	382 (38,1%)	98 (25,3%)	61 (40,7%)	223 (47,9%)	<0,001
Peripheral vascular disease, %	502 (50%)	157 (40,6%)	74 (49,3%)	271 (58,2%)	<0,001
Impaired renal function, %	145 (14,5%)	45 (11,6%)	24 (16%)	76 (16,3%)	0,123
Liver function abnormality, %	101 (10,1%)	12 (3,1%)	20 (13,3%)	69 (14,8%)	<0,001
Family anamnesis					
Family history of early development of CHD	230 (22,9%)	78 (20,2%)	43 (28,7%)	109 (23,4%)	0,106
Hypertension in relatives	516 (51,4%)	231 (59,7%)	84 (56%)	201 (43,1%)	<0,001

Abbreviations: CHD — coronary heart disease, MI — myocardial infarction, BMI — body mass index, HFrEF — heart failure with reduced left ventricular ejection fraction, HFmrEF — heart failure with midrange left ventricular ejection fraction, HFpEF — heart failure with preserved left ventricular ejection fraction, TIA — transient ischemic attack, AF — atrial fibrillation.

Cardiology of the Federal State Budgetary Institution "National Medical Research Center of Cardiology" of the Ministry of Health of the Russian Federation and registered on clinicaltrials.gov (NCT02790801).

Statistical data analysis. Descriptive statistics were described in absolute frequencies or as a median and interquartile interval. Depending on variables type, the Mann-Whitney test, Pearson's chi-square, Fisher's exact test, and the nonparametric Kruskal-Wallis test by rank and median were used. The Kaplan-Meyer analysis was used to determine the time to the study's endpoints. A two-sided significance criterion of (p) <0,05 was considered statistically significant. Statistical data analysis was performed using STATISTICA 7.0 (StatSoft, USA) and RStudio version 1.0.136 with R packages version 3.3.1.

Results

General characteristics of patients. The register enrolled 1003 patients with HF in combination with AF. Almost half were with reduced left ventricular (LV) EF — 46,4% of patients, 38,6% and 15% of patients had preserved and midrange LV EF, respectively. The clinical characteristics of the patients are shown in Tables 1-3.

Patients with preserved LV EF were older (median age of 72 years (63;78) versus 67 years (58;75) in the HFmrEF group and 66 years (58;75) in the HFrEF group), p<0,001. The percentage of women was highest (65,4%) in the HFpEF group and lowest in the HFrEF group (25,8%), p<0,001. The majority of patients with HFpEF — 76,2%, never smoked, while in the groups of patients with HFmrEF and HFrEF, non-smoking patients, were less, 56% and 48,1%,

Table 2

Clinical characteristics of AF and HF severity

Parameters	All patients (n=1003)	AF-HFpEF (n=387)	AF-HFmrEF (n=150)	AF-HFrEF (n=466)	Significance, p
Duration of HF, months	40 (12;96)	48 (22,5;100)	36 (12;72)	48 (12;96)	0,265
Duration of AF, months	48 (15;96)	50 (24;108)	38 (12;89)	40 (12;96)	0,042
Age of HF onset, years	62,1 (54,7;70,1)	64 (57,5;72,9)	61,65 (54,15;70,3)	60,9 (52,9;67,8)	<0,0001
Age of AF onset, years	62 (54,25;70,7)	64,4 (57,9;72,6)	60,8 (50,88;70,22)	59,9 (51,5;68,55)	<0,0001
AF onset after HF	478 (47,7%)	197 (50,9%)	58 (38,7%)	223 (47,9%)	0,039
AF form					
Paroxysmal	276 (27,5%)	144 (37,2%)	30 (20%)	102 (21,9%)	<0,001
Persistent/ permanent	727 (72,5%)	243 (62,8%)	120 (80%)	364 (78,1%)	
BP					
Systolic BP, mmHg	130 (120;140)	140 (130;150)	130 (120;140)	120 (110;140)	<0,0001
Diastolic BP, mmHg	80 (70;90)	80 (80;90)	80 (70;90)	80 (70;80)	0,01
HR					
HR, beats/min	84 (70;100)	80 (68;90)	85,5 (75,25;90,75)	84 (75;97)	0,226
HR >100, n (%)	327 (32,6%)	103 (26,6%)	56 (37,3%)	168 (36,1%)	0,005
CHA_2DS_2-VASc, median, interquartile interval	4 (3;5)	5 (3;6)	4 (3;5)	4 (2;5)	<0,001
HAS-BLED, median, interquartile interval	3 (2;4)	5 (3;6)	4 (3;5)	4 (2;5)	<0,001
Severity of AF symptoms by EHRA	2 (2;3)	2 (2;2)	2 (2;2)	2 (2;3)	0,083

Abbreviations: BP — blood pressure, HF — heart failure, HFrEF — heart failure with reduced left ventricular ejection fraction, HFmrEF — heart failure with midrange left ventricular ejection fraction, HFpEF — heart failure with preserved left ventricular ejection fraction, AF — atrial fibrillation, HR — heart rate.

Table 3

Data of instrumental and laboratory methods of examination at the time of enrollment

Parameters	All patients (n=1003)	AF-HFpEF (n=387)	AF-HFmrEF (n=150)	AF-HFrEF (n=466)	Significance, p
LV EF, %	40 (35;58)	60 (55;65)	43 (40;46)	34 (29;37)	<0,0001
LV EDD, cm	5,6 (5;6,3)	5 (4,6;5,3)	5,9 (5,3;6,38)	6,2 (5,7;6,91)	<0,0001
LV ESD, cm	4,1 (3,2;5,05)	3,1 (3;3,6)	4,5 (4;5)	5 (4,5;5,7)	<0,0001
CTAR, %	57 (54;62)	56,5 (53;61)	60 (55;63)	57 (55;63)	0,086
Number of VPB/day,	122 (17;775,5)	40 (8;327,25)	79 (13;1163)	277 (78,5;1319)	0,029
BNP, pg/ml	300 (158,25;602,48)	245,5 (152,25;429,75)	317,5 (142,25;507,15)	490,5 (186,52;941,75)	0,008
NT-proBNP, pg/ml	536 (349,5;1085)	562 (425;968)	338 (327;353,5)	1484 (289;2866)	0,01
D-dimer, ug/ml	1,2 (0,35;4,75)	1,38 (0,22;109)	2 (0,24;187)	1,1 (0,49;1,65)	0,048

Abbreviations: VPB — ventricular premature beats, CTAR — cardio-thoracic area ratio, LV EDD — end-diastolic dimension, LV CSR — end-systolic dimension, LV — left ventricle, HFrEF — heart failure with reduced left ventricular ejection fraction, HFmrEF — heart failure with midrange left ventricular ejection fraction, HFpEF — heart failure with preserved left ventricular ejection fraction, EF — ejection fraction, AF — atrial fibrillation, BNP — brain natriuretic peptide, NT-proBNP — N-terminal propeptide of natriuretic hormone (B-type).

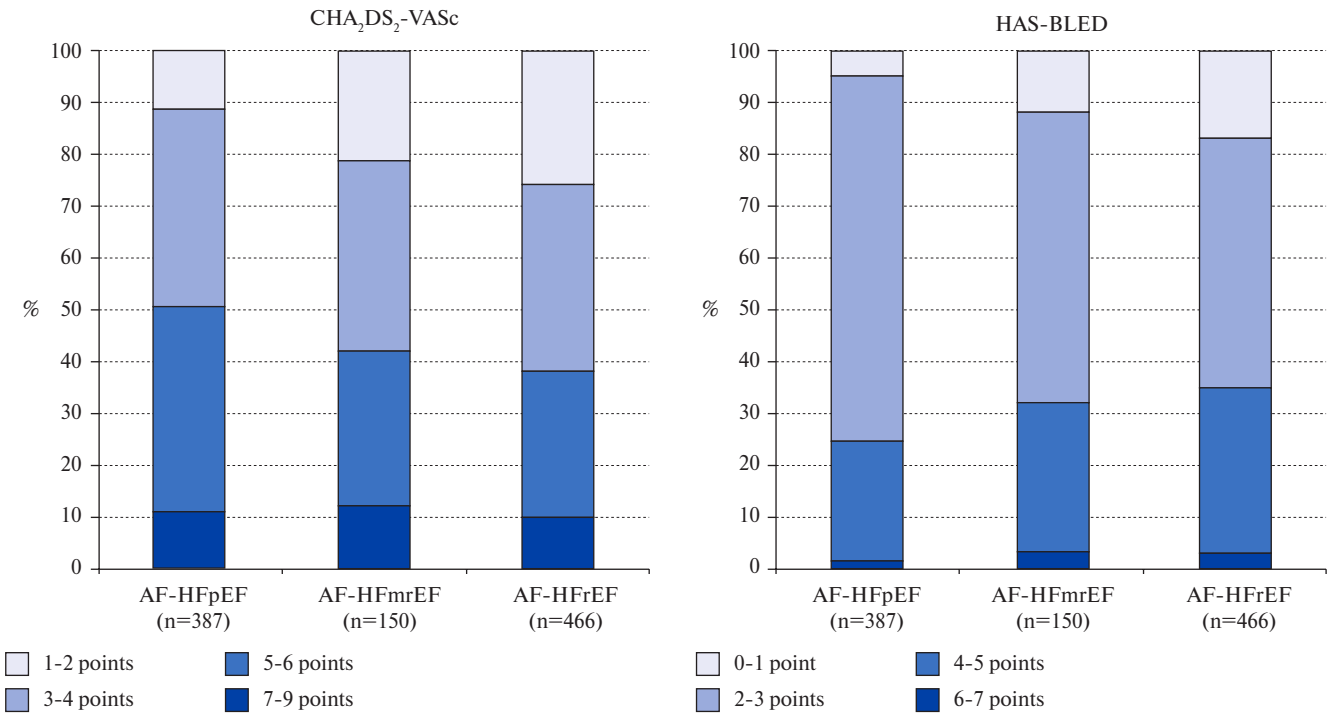

Figure 1. Assessment of TEC and bleeding risk.
Abbreviations: HFrEF — heart failure with reduced left ventricular ejection fraction, HFmrgEF — heart failure with midrange left ventricular ejection fraction, HFpEF — heart failure with preserved left ventricular ejection fraction, AF — atrial fibrillation.

respectively, p<0,001. Perhaps this is due to the fact that there were more women in the HFpEF group as a percentage. The groups of patients were comparable by frequency migrated with anamnesis of stroke or transient ischaemic attack, 15%, 14,7% and 16,7% in HFpEF groups, HFmrEF and HFrEF, respectively, p=0,747. In addition, the groups of patients were comparable by the frequency of occurrence of diabetes mellitus and impaired renal function. Significant differences in the groups were recorded by the frequency of myocardial infarction (MI), 25,3%, 40,7% and 47,9% in the HFpEF, HFmrEF and HFrEF groups, respectively, p<0,001. Also, patients with HFrEF most often suffered from peripheral arterial disease and liver function abnormality.

The patient groups did not differ significantly in the duration of heart failure before enrollment. Anamnesis of AF before enrollment to the register was higher in patients with HFpEF — median is 50 months (24;108), for patients with HFmrEF and HFrEF, the AF median duration before enrollment was 38 (12;89) and 40 (12;96) months, respectively, p=0,042. In groups of patients HFpEF and HFrEF (50,9% and 47,9%, respectively), the highest number of patients had a HF diagnosis before AF onset, and in the HFmrEF group, only in 38,7% of patients HF onset were before establishing the AF diagnosis, p=0,039.

The proportion of patients with paroxysmal AF was almost 2 times higher in the HFpEF group — 37,2% compared to patients from the HFmrEF and HFrEF groups (20% and 21,9%, respectively), p<0,001. In addition, patients with HFpEF had higher blood pressure numbers and a lower heart rate (HR). Only 26,6% of patients with HFpEF had heart rate >100 bpm, while in patients with HFmrEF and HFrEF, heart rate control was worse, heart rate >100 bpm was recorded in 37,3% and 36,1% of patients, respectively, p=0,005.

The study population had a high risk of TEC and bleeding, the median according to the CHA_2DS_2-VASc scale was 4 points (3;5), the median according to the HAS-BLED scale was 3 points (2;4). The groups of patients differed by the risk of TEC and bleeding, patients with HFpEF had higher scores according to both the CHA_2DS_2-VASc and HAS-BLED scales compared to patients with HFmrEF and HFrEF, p<0,001 (Figure 1, Table 2).

The drug therapy of patients in the registry is presented in Table 4. In the group of patients with HFpEF, the rate control strategy (p<0,001) was more often chosen and antiarrhythmic drugs were more often prescribed to these patients (p<0,001). It was noteworthy that only for 45,5% of patients with reduced LV EF the rational HF therapy were selected. For rational therapy in HF with reduced LV

Table 4

Drug therapy

Parameters	All patients (n=1003)	AF-HFpEF (n=387)	AF-HFmrEF (n=150)	AF-HFrEF (n=466)	Significance, p
Strategy of AF therapy					
Rhythm control	339 (33,8%)	157 (40,6%)	52 (34,7%)	130 (27,9%)	<0,001
HR monitoring	664 (66,2%)	230 (59,4%)	98 (65,3%)	336 (72,1%)	
Rational HF therapy	396 (39,5%)	106 (27,4%)	78 (52%)	212 (45,5%)	<0,001
Drugs group					
BB	830 (82,8%)	301 (77,8%)	136 (90,7%)	393 (84,3%)	<0,001
Antiarrhythmic drugs	255 (25,4%)	123 (31,8%)	37 (24,7%)	95 (20,4%)	<0,001
ACE inhibitors	658 (65,6%)	187 (48,3%)	113 (75,3%)	358 (76,8%)	<0,001
ARB	218 (21,7%)	116 (30%)	27 (18%)	75 (16,1%)	<0,001
MCRA	642 (64%)	164 (42,4%)	116 (77,3%)	362 (77,7%)	<0,001
Statins	606 (60,4%)	252 (65,1%)	89 (59,3%)	265 (56,9%)	0,046
Diuretics	883 (88%)	332 (85,8%)	131 (87,3%)	420 (90,1%)	0,137
Digoxin	360 (35,9%)	101 (26,1%)	53 (35,3%)	206 (44,2%)	<0,001
Oral anticoagulants (Warfarin/NOAC)	738 (73,6%)	297 (76,7%)	121 (80,7%)	320 (68,7%)	<0,001
Warfarin	403 (40,2%)	157 (40,6%)	66 (44%)	180 (38,6%)	0,491
NOAC	335 (33,4%)	140 (36,2%)	55 (36,7%)	140 (30%)	0,107
Antiplatelet agents	466 (46,5%)	177 (45,7%)	61 (40,7%)	228 (48,9%)	0,200

Abbreviations: MCRA — mineralocorticoid receptor antagonists, BB — beta-blockers, ARB — angiotensin II receptor blockers, ACE inhibitors — angiotensin-converting enzyme inhibitors, NOAC — novel oral anticoagulant, HF — heart failure, HFrEF — heart failure with reduced left ventricular ejection fraction, HFmrgEF — heart failure with midrange left ventricular ejection fraction, HFpEF — heart failure with preserved left ventricular ejection fraction, AF — atrial fibrillation, HR — heart rate.

Table 5

Outcomes of patients with HF in combination with AF

Endpoints	All patients (n=1003)	AF-HFpEF (n=387)	AF-HFmrEF (n=150)	AF-HFrEF (n=466)	Significance, p
Hospitalization due to HF worsening	574 (57,2%)	204 (52,7%)	99 (66%)	271 (58,2%)	0,017
Cardiovascular mortality	102 (10,2%)	16 (4,1%)	14 (9,3%)	72 (15,5%)	<0,001
Thromboembolic events	34 (3,4%)	14 (3,6%)	7 (4,7%)	13 (2,8%)	0,451
Ischemic stroke	27 (2,7%)	12 (3,1%)	4 (2,7%)	11 (2,4%)	0,776
Myocardial infarction	101 (10,1%)	26 (6,7%)	20 (13,3%)	55 (11,8%)	0,014
Composite point (stroke, MI, cardiovascular mortality)	201 (17%)	49 (12,7%)	33 (22%)	119 (25,5%)	<0,001
Major bleeding	39 (3,9%)	15 (3,9%)	7 (4,7%)	17 (3,6%)	0,815

Abbreviations: MI — myocardial infarction, HF — heart failure, HFrEF — heart failure with reduced left ventricular ejection fraction, HFmrgEF — heart failure with midrange left ventricular ejection fraction, HFpEF — heart failure with preserved left ventricular ejection fraction, AF — atrial fibrillation.

EF, we assumed the presence of angiotensin-converting enzyme inhibitors (ACE inhibitors)/angiotensin II receptor blockers (ARBs), beta-blockers (BBs), mineralocorticoid receptor antagonists (MCRA) in the treatment regimen in doses exceeding 50% of target values, as well as diuretics in the presence of fluid retention symptoms. The frequency of ordering long-term anticoagulant treatment in the study population was 73,6%, 40,2% of patients took Warfarin and 33,4% were under therapy with novel oral anticoagulants (NOAC). The most common anticoagulant treatment was prescribed to patients with HFmrEF — 80,7% of patients, with HFpEF and HFrEF, the frequency of prescribing anticoagulant treatment was lower — 76,7% and 68,7%, respectively, p<0,001.

Results of follow-up of patients in the course of 12 months. In the course of 12 months of follow-up, 57,2% of patients were hospitalized at least once due to HF decompensation. The highest frequency

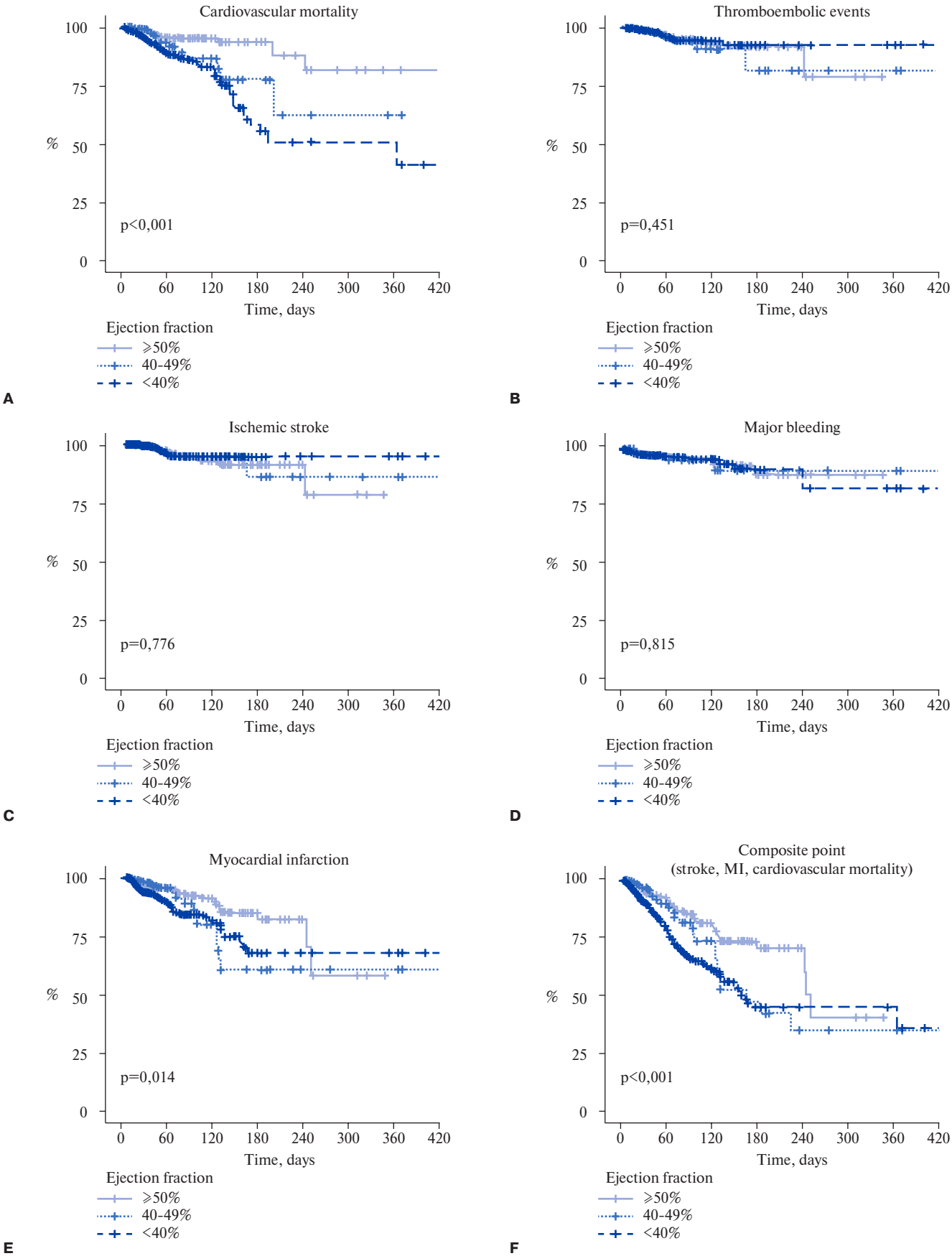

Figure 2. Kaplan-Mayer curves for subgroups by LV EF.

Table 6

Univariate regression logistic analysis of the hospitalization risk due to HF decompensation

Group of factors	Factor	AF-HFpEF		AF-HFmrEF		AF-HFrEF	
		RR (2,5-97,5)	p	RR (2,5-97,5)	p	RR (2,5-97,5)	p
Demographic profile	Age >65 years	2,329 (1,462-3,745)	<0,001			1,736 (1,17-2,584)	0,006
	Female	1,866 (1,198-2,921)	0,006				
Lifestyle, habits	Smoking (ever)	1,852 (1,073-3,236)	0,028				
	Bad habits	2,009 (1,107-3,723)	0,023				
	Alcohol abuse					1,37 (1,038-1,828)	0,028
	Physical activity			0,549 (0,274-1,081)	0,085	0,616 (0,399-0,944)	0,027
Symptoms and syndromes	HF signs	1,482 (1,146-1,946)	0,003				
	Increased venous pressure					2,383 (1,02-5,847)	0,048
	HF symptoms					2,275 (1,1-4,844)	0,028
Concurrent diseases	Diabetes mellitus	1,733 (1,048-2,908)	0,034				
Cardio-vascular system	Arterial hypertension					2,347 (1,524-3,663)	<0,001
	Tricuspid insufficiency	1,408 (1,027-1,949)	0,036				
	Aortic valve insufficiency	1,721 (1,074-2,865)	0,028				
	Insufficiency on pulmonary artery valve	3,69 (1,46-10,87)	0,01				
	Significant coronary artery stenosis					2,166 (1,276-3,8)	0,005
	CTAR, %					1,138 (1,047-1,244)	0,003
	Peripheral vascular diseases	1,73 (1,126-2,673)	0,013				
	Anamnesis of stroke/TIA/ thromboembolism	1,866 (1,198-2,921)	0,006				
Treatment	Antiarrhythmic drugs	0,622 (0,393-0,978)	0,041				
	ACE inhibitors	0,582 (0,371-0,907)	0,017				
	CCB at constant AF	0,505 (0,311-0,812)	0,005				
	ARB	0,466 (0,288-0,745)	0,002			0,587 (0,331-1,01)	0,06
	Anticoagulants					0,389 (0,257-0,587)	<0,001
	BB at continuous AF					0,279 (0,152-0,496)	<0,001
	Rational HF therapy					0,409 (0,271-0,611)	<0,001
	MCRA					0,584 (0,361-0,942)	0,027
	NOAC					0,588 (0,377-0,907)	0,017
	Heart rate control strategy (vs rhythm control)	1,779 (1,156-2,747)	0,009			0,283 (0,125-0,599)	<0,001
AF/HF features	Development of HF after AF onset	2,002 (1,049-3,879)	0,037				
	Duration of AF	1,005 (1,001-1,01)	0,022				
	Duration of HF					1,005 (1,002-1,009)	0,003
	EF					0,958 (0,922-0,995)	0,026
	Persistent form of AF (vs paroxysmal)	0,464 (0,296-0,722)	0,001			2,755 (1,451-5,405)	0,002
Risk of TEC/ bleeding	CHA_2DS_2-VASc	1,393 (1,215-1,608)	<0,001	1,191 (0,981-1,46)	0,083	1,215 (1,089-1,359)	0,001
	HAS-BLED	1,461 (1,174-1,836)	0,001			1,196 (1,014-1,414)	0,035

Abbreviations: MCRA — mineralocorticoid receptor antagonists, BB — beta-blockers, CCB — calcium channel blockers, ARB — angiotensin II receptor blocker, ACE inhibitors — angiotensin-converting enzyme inhibitors, CTAR — cardio-thoracic area ratio, NOAC — novel oral anticoagulant, RR — risk ratio, HF — heart failure, HFrEF — heart failure with reduced fraction left ventricular ejection, HFmrgEF — heart failure with midrange left ventricular ejection fraction, HFpEF — heart failure with preserved left ventricular ejection fraction, TIA — transient ischaemic attack, TEC — thromboembolic complications, AF — atrial fibrillation, Heart Rate — heart rate.

Table 7

Univariate logistic regression analysis of cardiovascular mortality risk

Group of factors	Factor	AF-HFpEF		AF-HFmrEF		AF-HFrEF	
		RR (2,5-97,5)	p	RR (2,5-97,5)	p	RR (2,5-97,5)	p
Laboratory tests	Total cholesterol			0,515 (0,291-0,851)	0,014		
	INR	2,825 (1,353-7,937)	0,013				
Symptoms and syndromes	Anemia	5,618 (1,799-16,667)	0,002	4,219 (1,156-14,286)	0,022		
	HF signs	2,299 (1,441-3,676)	<0,001	1,567 (0,924-2,653)	0,089	1,497 (1,163-1,927)	0,002
	HF symptoms	1,961 (1,335-2,941)	0,001			1,346 (1,121-1,629)	0,002
Concurrent diseases	Erosive and ulcerative lesions of gastrointestinal tract according to endoscopy					2,353 (0,951-5,464)	0,053
	Liver function abnormality			5,291 (1,425-18,519)	0,009		
	Renal disorder	4,184 (1,245-12,5)	0,013				
Cardio-vascular system	Aortic valve insufficiency			2,907 (0,915-10,101)	0,075		
	Arterial hypertension					2 (1,089-3,891)	0,032
	CTAR, %	1,597 (1,133-2,841)	0,036			1,161 (1,053-1,294)	0,004
	Anamnesis of MI and/or stroke	3,521 (1,222-11,494)	0,024				
	Insufficiency on pulmonary artery valve					2,725 (1,269-5,882)	0,009
	Right atrium enlargement					3,546 (1,235-14,925)	0,04
	Tricuspid insufficiency					1,37 (0,983-1,908)	0,061
	Echocardiographic signs of previous MI	3,636 (1,233-10,526)	0,016			1,957 (1,129-3,509)	0,02
	Dilation of pulmonary artery					2,375 (1,224-4,608)	0,01
	Anamnesis of major bleeding	6,494 (2,174-19,231)	0,001	3,891 (1,073-13,158)	0,03		
Treatment	Anticoagulants					0,389 (0,225-0,666)	0,001
	NOAC					0,42 (0,202-0,806)	0,013
	Peripheral vasodilators					4,587 (1,695-11,905)	0,002
	Statins	0,254 (0,083-0,724)	0,011			0,627 (0,366-1,08)	0,089
	ACE inhibitors	0,22 (0,069-0,84)	0,015				
	BB at continuous AF					0,404 (0,213-0,791)	0,006
	CCB at constant AF	0,172 (0,009-0,872)	0,091				
	Rational HF therapy					0,432 (0,238-0,757)	0,004
AF/HF features	Development of HF after AF onset					0,463 (0,209-0,987)	0,05
	Age of AF onset					1,037 (1,011-1,067)	0,007
	HR >100 bpm			4,545 (0,917-33,333)	0,081		
Risk of TEC/ bleeding	CHA_2DS_2-VASc	1,385 (1,029-1,869)	0,031			1,163 (1,01-1,342)	0,037
	HAS-BLED	2,105 (1,305-3,425)	0,002	1,938 (1,238-3,175)	0,005	1,37 (1,098-1,715)	0,006

Abbreviations: BB — beta-blockers, CCB — calcium channel blocker, ACE inhibitors — angiotensin-converting enzyme inhibitors, GIT — gastrointestinal tract, MI — myocardial infarction, CTAR — cardio-thoracic area ratio, INR — international normalized ratio, NOAC — novel oral anticoagulants, RR — risk ratio, HF — heart failure, HFrEF — heart failure with reduced left ventricular ejection fraction, HFmrgEF — heart failure with mid-range left ventricular ejection fraction, HFpEF — heart failure with preserved left ventricular ejection fraction, TEC — thromboembolic complications, AF — atrial fibrillation, HR — heart rate.

Table 8

Univariate regression logistic analysis of MI risk

Group of factors	Factor	AF-HFpEF		AF-HFmrEF		AF-HFrEF	
		RR (2,5-97,5)	p	RR (2,5-97,5)	p	RR (2,5-97,5)	p
Laboratory tests	Triglycerides					1,566 (1,11-2,362)	0,02
Demographics specifications	Age >65 years	3,115 (1,044-13,398)	0,071	3,27 (1,099-12,063)	0,047		
Lifestyle, habits	Physical activity	0,455 (0,173-1,069)	0,086				
	Poor nutrition					4,714 (1,363-29,721)	0,038
Symptoms and syndromes	Signs of AH (loud second heart sound on PA, LVH)	3,242 (1,269-9,964)	0,022	10,108 (1,969-185,253)	0,027		
	Anemia					1,964 (0,84-4,21)	0,097
	HF signs	1,87 (1,256-2,754)	0,002	1,962 (1,237-3,208)	0,005		
Concurrent diseases	Liver function abnormality			4,417 (1,34-13,764)	0,011		
Cardio-vascular system	Aortic valve insufficiency	0,418 (0,148-1,045)	0,082	7,368 (2,457-27,37)	0,001	3,427 (1,565-7,683)	0,002
	Peripheral vascular diseases	8,226 (3,029-28,777)	<0,001				
	Pathological changes on electrocardiogram			10,88 (2,92-70,815)	0,002		
	Anamnesis of MI and/or stroke	9,643 (3,547-33,762)	<0,001				
	Cardiomyopathy	1,591 (0,827-2,635)	0,096	1,68 (0,88-2,999)	0,086	1,528 (0,947-2,371)	0,068
	Family history of early development of CHD			0,256 (0,039-0,972)	0,08	1,911 (1,009-3,569)	0,044
	Significant coronary artery stenosis			3,316 (1,1-9,569)	0,028	2,036 (1,025-3,888)	0,035
	Anamnesis of coronary artery stenting	3,311 (1,131-8,591)	0,019	4,727 (1,528-14,174)	0,006	2,043 (0,99-4,011)	0,044
	Anamnesis of PATE	5,873 (0,809-29,014)	0,041	5,7 (1,041-28,378)	0,032		
	Tricuspid insufficiency					1,601 (1,105-2,323)	0,013
	Venous thrombosis of lower limbs	4,543 (0,966-16,216)	0,03	9 (0,76-127,873)	0,078		
	Echocardiographic signs of previous MI	9,509 (3,986-24,457)	<0,001	10,51 (2,822-68,395)	0,002	4,459 (2,144-10,482)	<0,001
	Dilation of pulmonary artery	4,165 (1,47-11,651)	0,006	9,797 (2,931-39,334)	<0,001	2,727 (1,323-5,652)	0,006
Treatment	Rivaroxaban			0,114 (0,006-0,79)	0,057		
	Digoxin			0,324 (0,072-1,051)	0,088		
	ACE inhibitors			0,407 (0,147-1,158)	0,084		
	Ivabradine					6,313 (1,516-24,687)	0,007
AF/HF features	Development of HF after AF onset	3,154 (1,026-11,799)	0,058			0,471 (0,19-1,101)	0,089
	Age of HF onset	1,051 (1,005-1,101)	0,033	1,045 (0,996-1,102)	0,082		
	Persistent AF form					0,158 (0,009-0,752)	0,071
	Resting HR			0,382 (0,143-0,945)	0,043		
Risk of TEC/ bleeding	CHA_2DS_2-VASc	1,372 (1,077-1,752)	0,01	1,398 (1,069-1,865)	0,017		
	HAS-BLED			1,609 (1,09-2,432)	0,019		

Abbreviations: AH — arterial hypertension, LVH — left ventricular hypertrophy, ACE angiotensin-converting enzyme inhibitors, CHD — coronary heart disease, MI — myocardial infarction, PA — pulmonary artery, RR — risk ratio, HF — heart failure, HFrEF — heart failure with reduced left ventricular ejection fraction, HFmrgEF — heart failure with midrange left ventricular ejection fraction, HFpEF — heart failure with preserved left ventricular ejection fraction, PATE — pulmonary artery thromboembolia, TEC — thromboembolic complications, AF — atrial fibrillation, HR — heart rate.

of hospitalizations was observed in the group with HFmrEF (66%), patients with HFpEF were less often hospitalized (52,7%), p=0,017 (Table 5). In the study, significant differences in cardiovascular death incidence depending on LV EF were noted. Increased mortality rate was associated with reduced LV EF, as a result, cardiovascular mortality in patients with HFpEF was 4,1%, in the HFmrEF and HFrEF groups — 9,3% and 15,5%, respectively, p<0,001 (Table 5, Figure 2 A).

The TEC frequency in the total patient cohort in the course of 12 months was 3,4%, ischemic stroke was suffered by 2,7% of patients, these indicators did not depend on LV EF (Figure 2 B, C). It is worthy of note that several patients (10 patients — 1% of the sample) had 2 different events during the year (for example, ischemic stroke and pulmonary artery thromboembolia (PATE). The study reported 39 major bleeding (3,9%), of whom 13 (1,3%) cases of gastrointestinal bleeding, 6 (0,6%) — pulmonary hemorrhage, 5 (0,5%) — intracranial bleeding and 15 (1,5%) bleeding at other sites (Figure 2 D).

In the course of 12 months of follow-up, 101 (10,1%) new cases of MI were registered in the total patient cohort. In the vast majority of cases, MIs (96 out of 101) were recurrent. Among the enrolled patients who had anamnesis of MI, the frequency of recurrent MI was 25.1%, while the incidence rate of the first MI was low — 0,8%, p<0,001. There were statistically significant differences in the frequency of MI between patients depending on LV EF, the lowest frequency was observed in patients with HFpEF — 6,7%, p=0,014 (Figure 2 E). In addition, in the group of patients with HFpEF, the lowest frequency of reaching the combined endpoint (stroke, MI, cardiovascular mortality), 12,7%, was demonstrated, in the HFmrEF and HFrEF groups the frequency of achieving the composite endpoint was 22% and 25,5%, respectively, p<0,001 (Figure 2 E).

Predictors of unfavorable prognosis. We carried out a search and analysis of factors influencing the achievement of endpoints in the study for the three groups of patients: HFpEF, HFmrEF and HFrEF. The analysis of factors related to outcomes led us to the conclusion that RF of adverse outcomes significantly differ for the groups depending on EF. However, it is important to note that the groups had significant differences in a number of parameters that were described above. Predictors of hospitalization due to HF decompensation in the group of patients with HFpEF were age >65 years, female sex, smoking, diabetes mellitus, peripheral artery atherosclerosis, stroke or transient ischaemic attack in the anamnesis, HF onset after AF development. The predictors of hospitalization for patients with HFrEF due to HF decompensation were age >65 years, arterial hypertension, and hemodynamically significant coronary artery stenosis. Symptoms were more predictive in terms of hospitalization for patients with HFrEF and HF signs — for patients with HFpEF. Persistent AF compared to paroxysmal reduced the hospitalization risk with HFpEF and increased the frequency of hospitalizations in patients with HFrEF. The choice of HR control strategy compared to rhythm control increased the hospitalization risk in patients with HFpEF and reduced it in patients with HFrEF. In patients with HFpEF, the hospitalization risk was reduced with regular administration of antiarrhythmic drugs, calcium antagonists, persistent AF, renin-angiotensin-aldosterone system (RAAS) blockers. For patients with HFrEF, the hospitalization risk was reduced by taking anticoagulants, in particular, taking NOACs, as well as BBs, MCRAs, RAAS blockers and rational therapy of HF, which included BBs, RAAS antagonists, and MCRAs. In addition, patients with high scores according to the CHA_2DS_2-VASc and HAS-BLED scales had a higher hospitalization risk (Table 6).

RF of cardiovascular mortality also had differences by group depending on LV EF. Predictors of cardiovascular mortality in patients with intermediate LV EF were anemia, liver function abnormality, anamnesis of major bleeding, and a high risk of bleeding according to the HAS-BLED scale. HF symptoms and signs, signs of MI according to echocardiography, as well as a high risk of TEC and bleeding according to the CHA_2DS_2-VASc and HAS-BLED scales were common RF of cardiovascular mortality for patients with HFpEF and HFrEF. Significant RF for patients with HFpEF were impaired renal function and anamnesis of major bleeding, and the risk of death was reduced by taking statins and ACE inhibitors. For patients with HFrEF, arterial hypertension, pulmonary artery regurgitation, dilation of pulmonary trunk, right atrium enlargement were predictors of cardiovascular mortality, and the risk of death was reduced by taking anticoagulants, BBs and rational therapy of CHF, in addition, the risk of death was lower if HF developed later than the AF onset (Table 7).

The MI RFs assessment showed that for patients with HFpEF, HFmrEF and HFrEF, the common RFs were anamnesis of stent angioplasty of coronary arteries and zones of impaired local contractility according to echocardiography. In addition, the predictors of MI in patients with HFpEF were HF signs during objective examination, anamnesis of peripheral artery disease, anamnesis of stroke/MI, anamnesis of PATE and a high risk of TEC according to the CHA_2DS_2-VASc scale. MI RF were in patients with HFREF over 65 years of age, signs of HF on physical examination, liver function

abnormality, known stenosis of coronary arteries, a anamnesis of PATE, as well as a high calculated risk of TEC and bleeding. Increased triglyceride levels, known coronary artery stenosis, and a burdened family anamnesis of coronary heart disease were predictors of MI in HFrEF patients (Table 8).

Discussion

The goal of our study was to analyze the features of CHF diagnosis and treatment in patients with AF to assess patient outcomes and degree of compliance with clinical recommendations for CHF and AF treatment in the Russian Federation. The primary study's endpoint was hospitalization due to HF worsening. According to the follow-up results in the course of 12 months, the frequency of hospitalizations due to HF decompensation was 57,2%. The greatest risk of hospitalization were patients with HFmrEF. Cardiovascular mortality, any feasibility studies, and major bleeding were taken as secondary endpoints. It was identified that the risk of cardiovascular death in the study increased in parallel with the LV EF decrease. Despite the fact that patients with HFpEF had a higher estimated TEC risk, the incidence rate of ischemic stroke is not dependent on LV EF. Patients with HFpEF had the lowest risk of reaching the composite endpoint (stroke, MI, cardiovascular mortality) in comparison with patients with HFmrEF and HFrEF.

According to the EPOCHA-CHF's study [23], 56,8% of patients with CHF in Russia have preserved LV EF, in our study, the number of patients with preserved LV EF was lower — 38,6%. This can be ascribed to the fact that the majority of patients were enrolled in inpatient facility, which indicates the disease severity in the studied subgroup. Also worth noting is that our study enrolled patients with proven elevated levels of natriuretic peptides, whereas the EPOCHA-CHF's study used different criteria for establishing the HFpEF diagnosis.

According to our data, CHF rational treatment, as well as long-term anticoagulant treatment, are determining factors in reducing the risk of hospitalization and cardiovascular mortality in patients with HFrEF. In spite of that, the therapy in the studied cohort was suboptimal. In the group of patients with HFrEF, ACE inhibitors was taken by 76,8% of patients, ARBs — 16,1% of patients, BBs — 84,3%, MCRAs — 77,7%. The insufficient level of compliance with clinical recommendations can be found in many observational studies in comparison with data from randomized clinical studies. Thus, in the EORP-AF registry, ACE inhibitors was taken by 48% of patients, ARBs — 21%, BBs — 72,2%, diuretics — 59,2% [24]. In the QUALIFY register (n=7092), the level of compliance with clinical recommendations for the CHF treatment was assessed, the authors analyzed the frequency of prescribing ACE inhibitors, ARBs, BBs, MCRAs and ivabradine. The level of compliance with recommendations was good in 67%, moderate — in 25% and poor — in 8% of patients. The proportion of patients who received the target dose of drugs or ⩾50% of the target dose was low (27,9% and 63,3% for ACE inhibitors, 14,8% and 51,8% for BBs, 6,9% and 39,5% for ARBs, 70,8% and 99,1% for AMCRs, 26,6% and 86,4% for ivabradine, respectively) [25]. The therapy that the patients in our study received had a great impact on the hospitalization frequency. For patients with HFrEF, the most important factor was whether they received anticoagulant treatment and its type. Rational therapy (RAAS antagonist+BB+AMCR) significantly reduced the risk of re-hospitalization. In a prospective multicenter AF-CHF study, the BB use was associated with a reduction in mortality rate, but did not reduce the hospitalization frequency in patients with HFrEF and AF without regard for the AF form or burden [26]. These data differ from the results of the meta-analysis by Kotecha D, et al. [16], according to which BBs in patients with HFrEF and AF did not reduce the mortality rate from all causes, the risk ratio was 0,97 compared to placebo (95% confidence interval (CI) 0,83-1,14) as against patients with sinus rhythm — 0,73 (95% CI 0,67-0,880), p=0,002. In the work of Rienstra M, et al., it was concluded that the effect of beta-blockers in patients with CHF and AF is significantly different from the effect of these drugs in patients with CHF and sinus rhythm, however, they do not have a positive effect on the hospitalization frequency due to CHF decompensation or mortality rate [27].

All patients with AF and HF have strict indications for appointment of anticoagulant treatment. Taking anticoagulants is a proven method to influence the prognosis of patients with CHF in combination with AF [17], but the results of multicenter registries by the AF problem, such as GARFIELD (The Global Anticoagulant Registry in the FIELD) [28] and Euro Heart Survey AF [29], show a significant gap between clinical recommendations for patient management and actual clinical practice. The frequency of prescribing long-term anticoagulant treatment in the population of patients in our study was 73,6%. In the Euro Heart Survey AF registry, 32% of patients did not receive anticoagulant treatment in the absence of contraindications [29]. The GARFIELD's results show that 38% of patients with risk of TEC according to the $CHADS_2$ scale ⩾2 did not receive anticoagulants, while 42,5% of low-risk patients ($CHADS_2$ =0) received anticoagulant treatment [28]. According

to a meta-analysis by Kotecha D, et al. (n=54,587) the frequency of prescribing anticoagulant treatment in patients with CHF in combination with AF is even lower (especially in cohort studies), 49,9% and 54,8% for patients with HFpEF and HFrEF, respectively [30]. A meta-analysis by Savarese G, et al. (n=55011) shows that although patients with HF in combination with AF have a higher mortality rate, if they take anticoagulants, the frequency of TEC and major bleeding in them does not differ from patients without HF [31]. The above once again emphasizes the need for appointment of anticoagulant treatment in patients with CHF in combination with AF.

Congestive HF is an independent RF of stroke in AF [32]. In large observational studies, it was observed that the prevalence of AF was higher in patients with HFpEF. This is thought to be related to the increased left atrial stiffness observed in HFpEF, while HFrEF is connected with eccentric left atrial remodeling [33]. According to the results of ESC-HF Long-Term Registry, the incidence of AF in patients with HFrEF, HFmrEF and HFpEF was 27%, 29% and 39%, respectively [34]. In the Swedish HF registry, patients were older and the incidence of AF was higher — 53%, 60%, and 65% in patients with HFrEF, HFmrEF, and HFpEF, respectively, but, as in the previous study, patients with HFpEF were dominant [35]. According to the analysis of a subgroup of patients with CHF in the PREFER register in AF, patients with HFpEF had a higher risk of TEC according to the CHA_2DS_2-VASc scale compared to patients with HFrEF and HFmrEF (4,7 vs 4,1 and 4,4, respectively). Despite this, the number of strokes in the group of patients with HFpEF was lower compared to the other two groups (0,65% vs 1,71% in HFmrEF; 1,75% in HFrEF; p=0,014). It was found that the risk of stroke increased by 0,054% with a 1% decrease in LV EF (95% CI 0,013-0,096; p=0,031), and in patients taking anticoagulants (90% of cohort), the risk of stroke increased by 0,030% with a 1% decrease in LV EF (95% CI 0,011-0,048; p=0,003). The TEC predictors in patients with AF in combination with HF were reduced LV EF, NYHA class, and age [36]. This is an interesting observation, because despite the lower estimated risk of stroke according to the CHA_2DS_2-VASc scale, a decrease in LV EF was associated with an increase in the frequency of strokes. In addition, it is worth noting that the CHA_2DS_2-VASc scale does not take into account EF in CHF. In our study, patients with HFpEF also had a higher risk of TEC according to the CHA_2DS_2-VASc scale, but we did not find significant differences in the TEC frequency depending on LV EF.

We did not find significant differences between the groups by frequency of major bleeding, the small number of events did not allow us to analyze the RF of bleeding.

The strategy selection for controlling the rhythm or HR in patients with CHF in combination with AF has significant differences depending on LV EF. The effectiveness of two AF therapeutic strategies in patients with HFrEF was compared in the AF-CHF study [26]. There were no significant differences in level of total or cardiovascular mortality, the frequency of stroke and hospitalizations due to HF decompensation between the two groups. Perhaps, the lack of effectiveness of pharmacological rhythm control is explained by shortcomings of modern antiarrhythmic drugs, which do not always provide stable retention of the sinus rhythm and cause adverse effects, in particular, have proarrhythmic effects. Drug-free treatments, such as catheter ablation, can serve as an alternative to antiarrhythmic therapy. Currently, there are data from the CASTLE-AF study, which showed the effect of catheter ablation on rigid endpoints in patients with HFrEF and AF [37]. The evidence base regarding the selection of control strategy of rhythm or HR in patients with AF and HFpEF is limited. Analysis of the GWTG-HF register (n=15682) shows that the selection of control strategy of rhythm has advantages over HR control in patients with HFpEF and AF over 65 years of age. The selection of rhythm control tactics was associated with a decrease in overall mortality during the year of follow-up, risk ratio 0,86; 95% CI 0,75-0,98; p=0,02 [38]. In our study, the selection of control strategy of rhythm and the use of antiarrhythmic drugs reduced the hospitalization frequency in HFpEF patients.

According to the data received, patients with HFrEF had the highest rates of cardiovascular death, in addition, HFrEF was associated with the achievement of composite endpoint (stroke, MI, cardiovascular mortality). The similar data were received in a meta-analysis by Kotecha D, et al. (n=54587), patients with HFrEF and AF had a higher mortality rate compared to patients with HFpEF and AF, 24% vs 18%, respectively, p=0,02 [30]. It is worth noting that, as in our study, the frequency of strokes between the groups did not differ depending on LV EF in this meta-analysis. However, whether AF independently connected with worse prognosis, with HFrEF remains controversial and poorly understood in HFpEF and HFmrEF. According to ESC-HFA HF Long-Term Registry (n=14964), the presence of AF was associated with an increased hospitalization risk due to decompensation of CHF and composite endpoint (hospitalization due to CHF decompensation + overall mortality) in patients with HFpEF and HFmrEF, but not HFrEF in comparison with similar groups of patients with sinus rhythm [34].

Oppositely, the results of Swedish Heart Failure Registry (n=41446) show that AF is connected with an increased risk of death, hospitalization due to decompensation of CHF and stroke in all groups by EF [35].

The group of patients with HFmrEF significantly differed from the other two groups in relation to the achievement of primary endpoint. In this group, the percentage of re-hospitalized patients was significantly higher. We found that each group was characterized by its own factors related to the primary endpoint.

Our study has a number of limitations. Despite the large pool of patients enrolled in it, the compared groups had significant initial differences. Due to the insufficient use of surgical methods for the CHF treatment, data on implantation of a cardioverter-defibrillator, cardiac resynchronization therapy, and catheter ablation were not included in the statistical analysis. Nevertheless, we have accumulated a large amount of data that reflects the real situation in clinical practice for our country and can be associate with works from other countries. Our goal was to study the differences between the groups depending on LV EF and to determine the predictors of adverse outcomes. We investigated how modern clinical practice in Russia meets international recommendations. This study was the first in our country and enrolled patients from 23 regions of Russia.

Conclusion

Each subgroup of patients, depending on LV EF, has specific features of the CHF and AF course, and the risks and predictors of adverse outcomes for these subgroups are different. Low LV EF is associated with an increased risk of death from cardiovascular diseases, but not with the risk of TEO (such as stroke and systemic embolism). Rational treatment of CHF and long-term anticoagulant treatment are key factors that reduce the risk of re-hospitalization and cardiovascular mortality in patients with HFrEF. The heart rate control strategy has some advantages associated with a reduced hospitalization risk due to CHF decompensation in patients with HFrEF, while the rhythm control strategy is more useful for patients with HFpEF.

Relationships and Activities: none.

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Risk of heart failure depending on the structure and subclinical target organ damage in patients with hypertension

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Aim. To determine the risk of heart failure (HF) in patients with hypertension (HTN) depending on the structure of subclinical target organ damage (TOD).

Material and methods. The study included 234 patients with HTN without signs of HF. The mean age was 45,96±8,54 years. The patients underwent echocardiography with an assessment of myocardial mass index, ejection fraction, left ventricular diastolic function. Volumetric sphygmoplethysmography with determination of cardio-ankle vascular index (CAVI1) and carotid-femoral pulse wave velocity (PWVcf). Cystatin C blood concentration with the calculation of the glomerular filtration rate (GFR) was performed. NT-proBNP blood levels was also determined. Patients were divided into 4 groups depending on the presence and structure of subclinical TOD. The first group consisted of 74 (31,6%) patients without documented subclinical TOD; the second group — 99 (42,3%) patients with one subclinical TOD; the third group — 42 (18,0%) patients with two TOD; the fourth group — 19 (8,1%) patients with three TOD.

Results. Patients in the groups differed significantly in blood NT-proBNP concentration (p<0,001). As the amount of TOD increased, NT-proBNP increased above the reference value 125 pg/ml (p=0,010). The odds ratio (OR) and relative risk (RR) of HF, determined by NT-proBNP concentration >125 pg/ml, were significantly associated with the TOD structure compared to the group without confirmed TOD (p=0,035, p=0,21, p=0,044, respectively). Correlation analysis revealed direct relationships between the NT-proBNP level and TOD amount (r=0,56; p<0,005), LVH (r=0,33; p<0,005), cystatin C level (r=0,31; p<0,005), CAVI1 and PWVcf (r=0,23; p<0,005 and r=0,26; p<0,005, respectively).

Conclusion. The risk of HF in patients with hypertension depends on the presence and structure of subclinical TOD. With the involvement of one target organ, OR and RR for HF were 4,23 and 3,74, respectively (95% CI for OR, 1,09-19,19; for RR, 1,08-16,03); with the involvement of two target organs — 5,57 (95% CI, 1,23-28,51) and 4,70 (95% CI, 1,21-21,84), respectively; with the multiple TOD — 6,31 (95% CI, 1,4-40,83) and 5,19 (95% CI, 1,04-27,95), respectively.

Key words: heart failure risk, hypertension, target organs.

Relationships and Activities: none.

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According to international and Russian epidemiological studies, hypertensive disease (HD) is one of the main reasons of the development of chronic heart failure (CHF), which takes the lead along with coronary heart disease in the structure of cardiovascular mortality both in the world practice and in the Russian Federation [1].

The main diagnostic criteria for the presence of CHF are typical clinical symptoms and signs, echocardiographic indicators reflecting structural and functional changes in the left heart, and an increase in concentration of natriuretic peptides (NUP) [1, 2].

One of the controversial issues that has been actively discussed recently is asymptomatic CHF, its criteria and risk factors for transformation into clinically significant form [3, 4]. A number of researchers believe that diastolic dysfunction of left ventricle (LV), structural and functional rearrangement of left heart cannot be objective criteria for the CHF preclinical stage due to the fact that various protocols and methods for their diagnosis are used in routine practice.

In this regard, for the verification of CHF preclinical stages and the risk of its development, NUPs are of crucial importance. Thus, according to Gaborit FS, et al. (2020), in patients 60 years and older with 1 or more risk factors for CHF (HD, diabetes mellitus of type 2, chronic kidney disease, atrial fibrillation, vascular disease) with asymptomatic LV dysfunction an increase in concentration of N-terminal fragment of brain natriuretic peptide precursor (NT-proBNP) was associated with an increase in the risk of developing CHF by 49%, the median fragment of NUP — by 77% [5].

There is some evidence that the NT-proBNP level is also associated with subclinical LV dysfunction, including in asymptomatic individuals [6], and is considered as an independent prognostic predictor [7]. Therefore, its definition was recommended not only for CHF diagnosis, but also for assessing the risk of its development.

The literature describes studies that have shown that in some patients, changes in NUP concentration within the range of normal values can be considered as a risk factor for the development of HD itself. It is believed that the brain NUP (BNP) is delivered by ventricular cardiomyocytes as a result of "spontaneous" and "induced" appearance, where the first is largely under genetic control, and the second is stimulated by mechanical stretching, as well as the direct or indirect effects [8]. However, according to some data, a slight increase in NUP in the blood can also be observed in the general population. At the same time, the mechanisms underlying the increase in NUP in healthy subjects are insufficiently studied and have contradictory character [9]. In this manner, the NUP pathophysiological role in the CHF development associated with HD and the possible mechanisms of its formation are also not fully understood and continue to be actively discussed in scientific communities [8].

It is known that the activation of neurohumoral systems in patients with HD leads to the target organ damage (TOD). In connection with the wider use of various imaging study methods, the detection of TOD is becoming more and more obvious both in patients with HD and in the preclinical stages of CHF [10]. However, while such an approach is effective, it is often time consuming and expensive. Therefore, the search for a universal TOD marker and the associated risk of developing CHF is of great clinical interest. In this regard, the NT-proBNP indicator may be of great diagnostic value, since it correlates with the LV myocardial mass index (LVMMI), is associated with aortic stiffness, and its level increases in patients with nonterminal chronic kidney disease [11, 12].

As can be seen from the above, the search for universal and easily accessible markers for assessing the risk of developing asymptomatic CHF in patients with HD with TOD is an relevant cardiological task.

The study's goal was to determine the risk of developing asymptomatic CHF, estimated by NT-proBNP concentration, in patients with HD, depending on the presence and subclinical TOD structure.

Material and methods

The study was carried out in accordance with the Good Clinical Practice standards and the principles of the Helsinki Declaration. The study protocol was approved by the Ethics Committee. All participants received written informed consent before enrollment.

The study enrolled 234 patients of employable age, suffering from HD, working at one of the enterprises of Perm. The median age was 45,96±8,54 years. The average duration of HD is 4,11 [2;6] years. Among the examined 139 (59,4%) men and 95 (40,6%) women.

The HD diagnosis was verified in accordance with the Russian (2020) and European Recommendations on Arterial Hypertension (2018).

The criteria for enrollment were HD of I-II disease state, any degree of increase in blood pressure without CHF clinical symptoms and signs.

The criteria for non-enrollment were: HD of III disease state, secondary arterial hypertension; symptoms and signs that make it possible to suspect CHF; verified diagnosis of CHF; oncological and other diseases that require specific treatment and monitoring; acute inflammatory and infectious dis-

Table 1

Clinical and anamnestic characteristics of patients depending on NT-proBNP level (n=234)

Indicator	Patients without target organ damage (n=74)	Patients with 1 target organ damage (n=99)	Patients with 2 target organs damage (n=42)	Patients with 3 target organs damage (n=19)	p_{mg}
Gender, abs. m/w	32/42	63/36	27/15	11/8	0,050
Age, years	44,65±7,65	47,95±7,39	45,10±9,85	44,25±9,41	0,047
Smoking, abs./%	17/22,97	23/23,23	10/23,81	6/31,58	1,000
HD duration	3,04 [2,0;4,0]	7,78 [3,0;7,0]	4,57 [2,0;6,0]	4,5 [3,0;5,0]	<0,001
DM, abs./%	3/4,05	9/9,09	5/11,91	3/15,79	0,378
COPD, abs./%	2/2,70	3/3,03	1/2,38	1/5,26	1,000
BMI, kg/m^2	28,08±3,81	28,52±3,96	28,80±5,19	29,47±4,47	0,663
WC, cm	92,22±10,61	95,58±11,09	96,17±13,38	97,81±11,96	0,116
SBD, mmHg	132,76±9,93	138,83±14,27	139,38±14,31	140,09±13,59	0,020
DBP, mmHg	86,91±8,64	91,70±10,98	91,04±12,80	93,47±9,89	0,022
HR, beats/min	68,52±10,66	67,91±9,24	67,00±11,08	68,87±9,77	0,941

Abbreviations: HD — hypertension disease, DBP — diastolic blood pressure, BMI — body mass index, WC — waist circumference, SBD — systolic blood pressure, DM — diabetes mellitus, COPD — chronic obstructive pulmonary disease, HR — heart rate.

Table 2

Characteristics of drug therapy in patients depending on NT-proBNP level (n=234)

Indicator	Patients without target organ damage (n=74)	Patients with 1 target organ damage (n=99)	Patients with 2 target organs damage (n=42)	Patients with 3 target organs damage (n=19)	p_{mg}
ACE inhibitors, abs./%	39/52,70	57/57,58	20/47,62	9/47,37	0,918
AIIRA, abs./%	35/47,30	42/42,42	22/52,38	10/52,63	0,918
BB, abs./%	21/28,38	39/39,40	19/45,24	9/47,37	0,268
Calcium antagonists, abs./%	19/25,68	35/35,35	12/28,57	7/36,84	0,709
Diuretics, abs./%	17/22,97	29/29,29	13/30,95	6/31,58	0,993
Statins, abs./%	45/60,81	51/51,52	22/52,38	11/57,89	0,880
Antiplatelet agents, abs./%	4/5,41	11/11,11	8/19,05	5/26,32	0,041

Abbreviations: ACE inhibitors — angiotensin-converting enzyme inhibitors, AIIRA — angiotensin II receptor blocker, BB — β-adrenergic blockers.

eases; mental illnesses that prevent the signing of informed consent and further adequate contact with the patient during the examination.

To assess the CHF development risk, the NT-proBNP concentration in the blood serum was determined using an enzyme immunoassay using a reagent from the company Vector-Best (Russia) on the analyzer Expert Plus Microplate Reader (Biochrom, UK). The NT-proBNP concentration in the blood serum >125 pg/ml was considered as an indicator corresponding to one of the CHF diagnostic criteria.

To assess the presence of LV hypertrophy (LVH) as a target organ in HD, echocardiography was carried out according to the standard method recommended by the American and European Society of Echocardiography on a Vivid S5 ultrasound scanner (General Electric, USA). LVH was confirmed for overweight and obese patients with LVMMI for men >50 g/m^{2,7}, for women >47 g/m^{2,7}; for patients with normal body weight with LVMMI in men >115 g/m^2, in women >95 g/m^2. To assess the LV functional state, the LV systolic function was determined according to LV ejection fraction, assessed by the Simpson method, LV diastolic function based on the determination of speed indicators of transmitral diastolic flow and tissue visualization of mitral valve annulus fibrosus ring movement.

To verify kidney damage as a target organ in HD, the filtration function was evaluated by determining the serum cystatin level with the enzyme immunoassay method, and the glomerular filtration rate (GFR) was calculated using the formula CKD-EPIcys (Chronic Kidney Disease Epidemio-

Table 3

Structure of target organ damage in groups (n=234)

Indicator	Patients without target organ damage (n=74)	Patients with 1 target organ damage (n=99)	Patients with 2 target organs damage (n=42)	Patients with 3 target organs damage (n=19)	p_{mg}
LVH, abs./%	0/0	65/65,66	37/88,10	19/100,00	p<0,001
LVDD, abs./%	0/0	6/6,06	4/9,52	3/15,79	0,038
LV EF, %	62,13±7,28	61,12±9,21	60,19±8,65	59,99±9,43	0,606
Increase in cystatin C >1000 pg/ml, abs./%	0/0	14/14,14	12/28,57	19/100,00	p<0,001
CAVI1 >9, abs./%	0/0	6/6,06	9/21,43	7/36,84	p<0,001
FSC >10 m/s, abs./%	0/0	14/14,14	26/61,91	12/63,16	p<0,001

Abbreviations: LVH — left ventricular hypertrophy, LVDD — left ventricular diastolic dysfunction, cfPWV — carotid-femoral pulse wave velocity, LV EF — left ventricular ejection fraction, CAVI1 — cardiovascular-ankle-vascular index.

Table 4

NT-proBNP level in patients, depending on TOD (n=234)

Indicator	Patients without target organ damage (n=74)	Patients with 1 target organ damage (n=99)	Patients with 2 target organs damage (n=42)	Patients with 3 target organs damage (n=19)	p_{mg}
Intermediate level NT-proBNP, pg/ml	0,007 [0,004;0,009]	0,009 [0,006;3,640]	31,15 [11,70;75,00]	231,65 [146,35;367,20]	<0,001
Occurrence frequency of elevated NT-proBNP levels >125, pg/ml, abs./%	3/4,05	15/15,15	8/19,05	5/31,58	0,009

Abbreviation: NT-proBNP — N-terminal fragment of brain natriuretic peptide precursor.

logy Collaboration Cystatin-Based). Signs of kidney damage in HD were considered to be an increase in concentration of cystatin C in blood >1000 ng/ml and/or a decrease in GFR according to the formula CKD-EPIcys 60 ml/min/1,73 m^2.

To assess arterial damage, volumetric sphygmoplethysmography was carried out on a VaSeraVS-1000 device (Fucuda Denshi, Japan) with determination of cardio-ankle-vascular index (CAVI1) and pulse wave velocity in carotid-femoral segment (PWVcf). Signs of arterial damage in HD were considered to be an increase in CAVI1 >9 and/or PWVcf >10 m/s.

To determine the relationship between HD and TOD with the risk of developing CHF, patients were divided into 4 groups. The first group consisted of 74 (27,6%) patients without confirmed TOD, the second group enrolled 99 patients with signs of subclinical lesions of one target organ, the third group consisted of 42 patients with lesions of two target organs, the fourth group enrolled 19 patients with confirmed subclinical lesions of three target organs.

Statistical processing of the obtained results was carried out using the program STATISTICA 10.0. For continuous characters, the arithmetic mean (M) ± standard deviation (SD) or the median with the lower and upper quartile (Me [LQ;UQ]) were calculated. For qualitative signs, the absolute frequency of the sign, the sign frequency as a percentage (%) or the 95% confidence interval (CI) were calculated. To test statistical hypotheses about distribution type, the Shapiro-Wilk and Kolmogorov-Smirnov criteria were used. The distribution of most features did not correspond to the law of normal distribution. In the multi-group comparison of quantitative indicators, the Kruskall-Wallis criterion was used, and for qualitative characteristics, the χ^2 criterion was used. Statistically significant when comparing the four independent groups were the differences in indicators at p<0,012. To study the relationship between the indicators reflecting TOD and the concentration of NT-proBNP, 2x2 conjugacy tables were compiled, χ^2 was calculated with the calculation of achieved significance level for them with the Yates correction for continuity, the odds ratio (OR), relative risk (RR) and 95% CI for OR and RR were determined. At p<0,05, the differences were considered statistically significant. The study of relationship between features was carried out on the basis of Spearman's rank correlation coefficients.

The funding was made from the authors' own funds.

All manipulations related to development of study design, obtaining informed consent, collecting biological material, conducting diagnostic tests, interpreting the results and their statistical processing are carried out by the authors themselves.

Results

Patients in the groups did not significantly differ in age, gender, cardiovascular risk factors, structure of concomitant pathology, antihypertensive and other drug therapy, and clinical characteristics (Tables 1, 2). The groups differed in HD duration and TOD frequency (Tables 1, 3).

All patients, according to echocardiography, had a preserved LV ejection fraction without statistically significant differences between the groups. 121 patients (51,71%) had LVH signs (0% of patients — in group 1, 65,66% of patients — in group 2, 88,10% — in group 3 and 100,00% — in group 4). In 5,12% of patients, LV diastolic dysfunction was detected without significant differences between the groups.

When assessing the arterial wall state, it turned out that arterial stiffness, estimated by CAVI1 index, was increased in 22 patients (9,40%), while in patients of group 1 there was no increase in CAVI1 (0%), in group 2 it was observed in 6,06% of patients, in group 3 — in 21,43% of patients, in group 4 — in 36,84% of patients.

PWVcf >10 m/s was detected in 52 patients (22,22%): in group 1, there were no patients with an increase in PWVcf, in group 2, an increase in PWVcf was found in 14,14% of patients, in group 3 — in 61,91% of patients, in group 4 — in 63,16% of patients.

When assessing the kidneys state, it was revealed that impaired renal filtration function with a level of cystatin C >1000 ng/ml was observed in 45 patients (19,23%), while the level of cystatin C was normal in group 1, an increase in the level of cystatin C was observed in 14,14% of patients in group 2, in group 3 — in 28,57% of patients, in group 4 — in all 100% of patients. GFR in all patients was >60 ml/min/1,73 m^2.

Patients in the groups differed significantly in the mean NT-proBNP concentration ($p<0,001$) (Table 4). As the number of TODS increased, NT-proBNP increased significantly ($p<0,001$). Also, as the number of TODS increased, an increase in the frequency of NT-proBNP increases >125 pg/ml ($p=0,010$) was detected. Among patients of group 1 without TOD, the incidence of elevated NT-proBNP was 4,05%, among patients of group 2 — 15,15%, among patients of group 3 — 19,05%, among patients of group 4 — 31,58%.

The correlation analysis revealed the relationship of NT-proBNP level with number of TOD ($r=0,56$; $p<0.005$), LVH ($r=0,33$; $p<0,005$), the concentration of cystatin C in blood ($r=0,31$; $p<0,005$), CAVI1 and PWVcf ($r=0,23$; $p<0,005$ and $r=0,26$; $p<0,005$, respectively).

When assessing the OR and RR of CHF development, the following data were obtained. The OR and RR values were statistically significant ($p=0,035$) and were 4,23 and 3,74, respectively (95% CI for OR =1,09-19,19; for RR =1,08-16,03). The OR of CHF development in damage of two target organs increased more than 5 times in comparison with the group without TOD (OR 5,57, 95% CI 1,23-28,51), and RR of its development was 4.70 (95% CI 1,21-21,84, $p=0,021$). An increase in the NT-proBNP level is also statistically significantly associated with damage to three target organs ($p=0,044$). In the presence of multiple organ damage, the chance of developing CHF increased more than 6 times (OR 6,31, 95% CI 1,04-40,83), and RR of its development was 5,19 (95% CI 1,04-27,95).

Discussion

Our work shows that the CHF risk assessed by increasing the NT-proBNP concentration in patients with CHF depends on the presence and structure of subclinical TOD.

It was shown that as the number of TOD increases in patients with HD, the NT-proBNP concentration increases as a criterion for preclinical CHF stages.

The obtained data can be justified from a physiological point of view. In TOD pathogenesis, activation of renin-angiotensin-aldosterone (RAAS) and sympatho-adrenal systems (SNS) play an important role. In the early stages of HD, BNP functions as a compensating agent that reduces the activity of these systems [6]. With disease progression, the RAAS and SNS activation increases, there is an imbalance of the NUP system and, despite high levels, endogenous NUP become resistant, and are no longer able to compensate for neurohumoral activation. At this stage, an increase in delivery and BNP and NT-proBNP concentration is considered not as a compensatory mechanism, but as a violation of the altered organ function. In addition, the BNP delivery, which is more associated with positive and compensatory effects, is under genetic control, and with an increase in the RAAS and SNS activity, it is stimulated by mechanical stretching of cardiomyocytes — myocardial stress. Therefore, the final NT-proBNP and BNP concentration in serum is determined by the balance between their production, degradation, and renal clearance. Therefore, TOD can affect the BNP concentration in serum, increasing it.

TOD, as well as their various combinations, play an important role both in the progression of CHF itself and in determining the risk of its development.

Thus, there are well-known studies in the literature that have shown that NPS blood concentrations, in particular NT-proBNP and BNP, are directly related to LVH [13]. Increased NUP delivery by cardiac myocytes into the bloodstream may be the result of increased LV wall tension, the development of its hypertrophy or volume overload. There is also evidence that the NT-proBNP level can be an independent and prognostic marker of LVH risk in patients without CHF, since it reflects a subclinical pathological process, including inflammation, myocardial fibrosis, and subsequently heart remodeling [14]. In our study, a correlation was obtained between NT-rroBNP and LVH, and the CHF development risk was shown depending on this parameter. However, the LVH contribution to the CHF development risk has not been assessed separately in the TOD structure and requires further study.

We have shown that the frequency of increased CAVI1 >9 and PWVcf >10 m/s were connected with the risk of asymptomatic CHF development. It is understood that an increase in arterial stiffness leads to a decrease in elasticity of peripheral arteries and a change in reflected wave. With an increase in arterial stiffness, the reflected wave returns to aorta during late systole, which leads to an increase in afterload on heart and a decrease in coronary perfusion. This process may trigger the development of diastolic heart dysfunction and LVH [15]. Having said so, the stretching of cardiomyocytes is an important stimulus for the NUP production [9]. Nah E-H, et al. (2019) suggested that a higher NT-proBNP level may be associated not so much with LV diastolic dysfunction as with initial preclinical structural changes in cardiomyocytes [16].

In our study, the presence of an increase in the cystatin C level in blood was considered as a kidney damage in HD. An increase in cystatin C was observed with an increase in the NT-proBNP level and, accordingly, with an increase in the TOD number. The literature describes the association of NT-proBNP with TOD, in particular, in the kidneys, including in patients with HD without CHF symptoms and signs [11]. Also, according to some studies, an increase in the cystatin C level correlates with concentric LV remodeling [17]. Consequently, in patients with HD in the presence of LV structural rearrangement, the risk of glomerular renal dysfunction increases, which, in turn, leads to a high tension of myocardial stress and an increased CHF development risk. However, the mechanism of increasing the NT-proBNP level in patients with TOD, including chronic kidney disease, is more complex, remains not fully understood and requires further study.

The study limitations are as follows: in patients with HD, the diagnostic criterion for the CHF development risk was considered to be the NT-proBNP concentration >125 pg/ml, while the "gray" area of this indicator was not taken into account; indicators reflecting increased collagen formation and fibrosis were not used to diagnose TOD in patients with HD; the study does not present the rating of each TOD separately in assessing the CHF development risk.

Conclusion

The results indicate that the CHF development risk in patients with HD, determined by the NT-proBNP concentration in blood, depends on the presence and structure of subclinical TOD. As the number of TOD increases, not only the average level of NT-proBNP increases, but also the frequency of occurrence of an increase in NT-proBNP above the diagnostic value of 125 pg/ml increases. In case of one target organ damage, OR and RR of CHF development were 4,23 and 3,74, respectively (95% CI for OR =1,09-19,19; for RR =1,08-16,03), in case of two target organs — 5,57 (95% CI 1,23-28,51) and 4,70 (95% CI 1,21 — 21,84), respectively, in case of multiorgan lesion — 6,31 (95% CI 1,04-40,83) and 5,19 (95% CI 1,04-27,95), respectively.

Relationships and Activities: none.

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An open-label multicenter observational study (registry) of patients recovered from coronavirus disease 2019 (COVID-19) with involvement of the cardiovascular system or with baseline severe cardiovascular diseases: rationale, design, and implications for clinical practice

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The potential impact on cardiovascular morbidity and mortality have become one of the most important issues of the coronavirus disease 2019 (COVID-19) pandemic. COVID-19 may be associated with more frequent development of acute cardiovascular complications, while patients with established cardiovascular diseases are characterized by a higher risk of severe infection and adverse in-hospital outcomes. Due to the spread scale of the pandemic, understanding the long-term cardiovascular consequences of COVID-19 is of no less importance. Inability to extrapolate available international data to the Russian population has led to the initiation of a national multicenter study (registry) of patients recovered from COVID-19 and with concomitant involvement of the cardiovascular system or with baseline severe cardiovascular diseases. The article presents its rationale, design and implications of the results for clinical practice.

Key words: novel CO, COVID-19, SARS-CoV-2, cardiovascular diseases, registry.

Relationships and Activities: none.

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In conjunction with the incidence scale and direct socio-economic losses, the potential effect of novel coronavirus pandemic (COVID-19) on cardiovascular morbidity and mortality gives cause for particular concern. Testify to the fact that from 15% to 70% of COVID-19 fatal case are recorded in patients with a history of cardiovascular diseases (CVD) [1]. Severe course of COVID-19, higher need for stay in intensive care unit, artificial ventilation, vasopressor or mechanical circulatory support is more often observed in patients with risk factors or established CVD. COVID-19 can lead to cardiovascular complications due to hypoxia and systemic pro-inflammatory effects, but also direct injury to the heart and vascular endothelium [10].

According to recent reports, the COVID-19 pandemic, covering ~3,4 million people, claimed >62 thousand human lives in the Russian Federation in 2020 [11]. The data on epidemiology, course features and CVD outcomes in COVID-19 in the Russian Federation are limited. The conclusions obtained on populations in other countries, certainly, differing from the Russian Federation according to clinical and demographic characteristics of the population, CVD epidemiology and cardiovascular care, cannot be extrapolated to the Russian population. Besides they mainly relate to acute events recorded during hospitalization of patients with COVID-19 [9, 12, 13]. Long-term cardiovascular outcomes after hospital discharge remain understudied.

The need to assess and predict potential medical and socio-economic consequences for population health in the Russian Federation, as well as the importance of optimal tactics and justifying the development of specialized follow-up programs for patients with combination of COVID-19 and CVD promoted the initiation of a selective multicenter study (registry) of patients with damage of the cardiovascular system (CVS) or in the course of severe CVS disease.

Goal of the study: to determine the immediate and long-term prognosis in patients who have undergone COVID-19 with CVS damage, and to form an optimal follow-up system for such patients, including follow-up duration, examination frequency and standards.

Material and methods

Study population. The study is conducted in a population of patients who have been hospitalized with COVID-19 and CVS damage or with severe CVS pathology. The enrollment criteria and the groups that are expected to be monitored dynamically under protocol are presented in Table 1.

Study design and data source. The study (register) is openly observationally researched and is aimed at collecting data from general practitioners, therapists and cardiologists about patients discharged from hospital and meeting the enrollment criteria. Sequential patient enrollment and prospective follow-up for at least 12 months after discharge with the possibility of extension based

on preliminary analysis result is expected. In the absence of an opportunity for in presence visit, the data will be collected by phone.

Any organization in the Russian Federation becomes center-participant in the study in case of declared desire and opportunity to include and monitor at least 30 patients during the year. The patient enrollment is possible either at the phase of discharge from hospital (option with prospective enrollment), or at the stage of the first outpatient visit after discharge (option with retrospective enrollment), which allows center-participants to select patients who survived during hospitalization, have confirmed COVID-19 status and verified CVS damage.

A general electronic individual registration card is formed for each patient included in the study, regardless of CVS damage type. For each enrollment criteria, additional anamnesis and examination data are assumed according to Table 2. The data collection is carried out only in electronic form.

Sub-study of biomarkers. As part of the study (register), an additional study of biomarker level in blood plasma and serum samples and genetic testing is carried out in the core laboratory.

Imaging sub-study. As part of the study (register), an additional image sub-study is carried out. Video images are provided with the study participant identification number (without specifying the patient's personal data) to a single image processing center. This allows an independent expert to perform an in-depth analysis of imaging data (heart structure and function, coronary artery damage to coronary arteries, lung parenchyma, and pulmonary vascular flow).

Confidentiality and informed consent. All data entered in the online form register, as well as video images and biological samples, are marked in a strictly depersonalized form. Patients included in the study sign an informed consent to participate in the study, take, storage and transfer to third parties video images and biological samples without indicating their personal data. The study protocol and the consent form are approved by the ethics committee(s) of appropriate centers prior to start of patient enrollment.

Study organizer. The study (register) organizer is the Russian Society of Cardiology (RSC). On September 17, 2020, the RSC official website published an advertise for the study (register) initiation and the protocol [14]. Additionally, RSC members were

notified by email. The initial collection, processing and further analysis of biological samples and video images will be carried out on the basis of the Federal State Budgetary Institution "Almazov National Medical Research Centre" of the Ministry of Health of the Russian Federation. The study was approved by the Ethics Committee of the Federal State Budgetary Institution "Almazov National Medical Research Centre" of the Ministry of Health of the Russian Federation (Protocol No. 09-20-01C dated September 11, 2020). The enrollment of new center-participants and communication with researchers is carried out by the coordination group.

Statistical analysis. In statistical processing, the patient clinical and demographic characteristics, COVID-19 severity, CVS damage frequency, quality of life of the enrolled patients, follow-up trajectory of cardiovascular damage course, outcomes (construction of Kaplan-Meier survival curves in subgroups) will be assessed, if the prognostic effect is confirmed, the construction of multivariate Cox regression models will be also assessed.

Discussion

Increasing public awareness and medical aid appealability, maintaining its availability and quality, but also assessing the possible obvious and non-obvious residue of infection, including long-term ones, in convalescents, is of particular significance in patient with COVID-19 and CVD population. The organization of systematic patient follow-up, standardized and coordinated data collection at the domestic level and their timely analysis can have a decisive importance in strategic planning and cardiology service transformation in the present epidemiological conditions. The supplied study (register) will provide information on the spectrum of cardiovascular consequences in the short and long term in hospitalized patients who have come through COVID-19.

The importance of studying the relationship between COVID-19 and CVD is not limited to the high and growing incidence and appalling socio-economic losses that have become a challenge for the health system during the COVID-19 dissemination and have been a persistent problem over the decades in the fight against the burden of chronic non-communicable diseases [15]. The COVID-19 and CVD progression and adverse effects share common pathophysiological mechanisms — inflammation, activation of the sympathetic and renin-angiotensin-aldosterone systems, damage to target organs, their dysfunction and failure [16, 17]. Such general characteristics as elderly age of patients, risk factors (smoking, obesity, arterial hypertension), and high frequency of comorbid conditions emphasize the need to study the features of the COVID-19 and CVD combination. In the study of frequency and outcomes in severe COVID-19 compared with acute respiratory distress syndrome of other etiologies, it was shown that age, gender, and kidney function correcting factor reduces the presumed higher risk of myocardial damage in COVID-19, and additional inclusion of multiple organ dysfunction in a multifactorial model reduces the fatal case associated with myocardial injury [18].

The interpretation of myocardial damage in COVID-19 is ambiguous. In its genesis, along with destabilization of atheromas and development of acute coronary events, damage to microvasculature, appearance or aggravation of an imbalance between oxygen demand and delivery in conditions of acute systemic inflammation and cytokine storm, development of tako-tsubo syndrome, and thrombotic complications may play a role [10]. The design of an algorithm for decision-making tactics (incl. solution to an issue on percutaneous coronary intervention) in each specific situation requires the collection of extensive data and their competent analysis. The importance of examination and careful long-term

Table 1

Criteria for enrollment and list of groups expected to be monitored dynamically within the study (register) framework

1. Hospitalization with COVID-19 with U07.1 or U07.2 code according to the International Classification of Diseases, 10th Edition.
2. CVS damage, defined as*: 1) proven myocarditis or suspected myocarditis; 2) presence of chronic heart failure of grade II or more grade before disease or appearance of heart failure signs associated with COVID-19; 3) combination with acute coronary syndrome or development of acute coronary syndrome associated with infection, including performed endovascular procedures; 4) proven pulmonary artery thromboembolia; 5) hemodynamically relevant arrhythmias (atrial fibrillation, high-grade ventricular extrasystole, paroxysmal ventricular arrhythmias), including associated with prolongation of the QT interval.

Note: * — patient can be enrolled according to one or more criteria of CVS damage.

Table 2

Schedule of visits (telephone contacts) and list of necessary examinations

	Enrollment	1 month* ± 1 week	3 months ± 1 week	6 months ± 2 weeks	12 months ± 2 weeks
Detailed analysis of documentation and CRF filling	+				
Structured complaints analysis	+	+*	+	+	+
Objective data	+	+*	+	+	+
Informed consent	+ during prospective enrollment		+ during retrospective enrollment		
EchoCG	+[&]	+*	+*[#]	+	+
Biochemical examination data (special examination by subgroups)	+		+ (during in presence visit)	+	+
Blood collection for biobanking, including genetic analysis	+ during prospective enrollment		+ during retrospective enrollment	+ (except for genetics)	+ (except for genetics)
Analysis of therapy	+		+	+	+
Analysis of hospitalization			+	+	+
Endpoint analysis			+	+	+
Quality of life questionnaire (KCCQ)	+ (when check-out)		+	+	+
Contrast-enhanced cardiac MRI*	+		+		
Endomyocardial biopsy*	+		+		
Daily ECG monitoring*		+	+		
MSCT pulmonary angiography[#]	+[#]		+ (if control study was performed)[#]		
CA results[&]	+ (if performed)				

Note: * — only for the criterion "proven myocarditis or suspected myocarditis", additional visit of 1 month — only in case of severe course; [#] — only for the criterion "proven pulmonary artery thromboembolia"; [&] — only for the criterion "combination with acute coronary syndrome or development of acute coronary syndrome associated with COVID-19", all EchoCG protocols performed during hospitalization are downloaded.

Acronyms and abbreviations: CRF — clinical report form, CA — coronary angiography, MRI — magnetic resonance imaging, MSCT — multispiral computed tomography, ECG — electrocardiography, EchoCG — echocardiography, KCCQ (Kansas City Cardiomyopathy Questionnaire) — Kansas questionnaire for patients with cardiomyopathy.

follow-up of patients with myocardial damage associated with COVID-19 is emphasized by described clinical cases of myocarditis and identification of SARS-CoV-2 virus particles in cardiomyocytes by electron microscopy [19-21]. The study of the results of magnetic resonance imaging of the heart, showing signs of distant changes in the myocardium in patients coming through COVID-19 stirs particular control [22]. Whether these changes are the consequence of background risk factors and comorbid conditions, or a direct result of COVID-19, remains to be determined in the prospective follow-up of patients enrolled upon the criteria for confirmed myocarditis or suspected myocarditis, with subsequent image interpretation by an independent expert.

A separate group for enrollment is patients with hemodynamically significant heart rhythm disorders. Along with the increased risk of arrhythmias associated with infectious process (irrespective of the presence of structural and functional changes in myocardium), the interest in these complications comes from the potential cardiotoxicity of drugs that are widely used empirically as COVID-19 therapy. With insufficient scientifically grounded data on the management of patients, most approaches rely on the experts' opinion. This also applies to the choice of drug and the dosage regimen of anticoagulants in patients hospitalized with COVID-19. The study of routine clinical practice will allow to assess the frequency of thrombotic and thromboembolic complications, primarily pulmonary artery thromboembolia, as well as their outcomes, including the risk of hemorrhagic complications, depending on the chosen therapeutic strategy.

Since dispensary observation of patients who have undergone COVID-19 is not yet regulated by

orders and procedures for providing assistance, and rehabilitation programs mainly expect rehabilitation after pneumonia, it is critically important to collect data on recovery time, possible separated risks in patients with clinically significant CVS damage associated with COVID-19, as well as to assess the prognosis of patients who initially had serious heart damage, chronic heart failure, in whom the transferred infection could affect its further course. The detected changes in the biomarker level may contribute to understanding the COVID-19 pathogenesis, as well as be additional factors that can be used in stratifying patients by the CVD damage risk or adverse outcomes.

Study limitations. In a situation of continuing tense epidemiological situation, participation in the study (register) may be an additional workload on medical organizations' staff. A greater readiness to participate in patient enrollment from research centers and clinics at institutes, rather than urban hospitals that are restructured to provide assistance to patients with COVID-19 can be expected, which potentially limits the sample representativeness. However, data from more than 30 centers of different regions that are currently registered as participants can provide a picture that is more corresponded to actual practice than data obtained from a single institution.

The study design retains the limitations inherent in observational studies, and to obtain more solid evidence, it may be necessary to use the results of registers and observational studies performed in the Russian Federation before COVID-19 pandemic development.

Conclusion

By the aid of the join forces of specialists-participants in studies from different cities of the Russian Federation, it is expected that the data obtained on features of clinical manifestations of the COVID-19 and CVD combination, management in real clinical practice and outcomes in the future will justify approaches to the prevention of complications, the introduction of new treatment methods and determine optimal management for such patients.

Relationships and Activities: none.

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Impact of the first wave of coronavirus disease 2019 (COVID-19) pandemic on the diagnosis of heart disease in the Russian Federation: results from the Russian segment of the IAEA INCAPS COVID study

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Aim. To assess the impact of the first wave of coronavirus disease 2019 (COVID-19) pandemic on the diagnosis of heart disease in the Russian Federation.

Material and methods. Fifteen Russian medical centers from 5 cities took part in an online survey organized by the Division of Human Health of the International Atomic Energy Agency (IAEA), containing questions regarding alterations in cardiovascular procedure volumes resulting from COVID-19 in March-April 2020.

Results. A number of outpatients undergoing cardiac diagnostic procedures was noted in 80% of clinics. Cardiovascular procedure volumes in the period from March 2019 to March 2020 in general decreased by 9,5%, and from March 2019 to April 2020, by 56,5%. Stress electrocardiography decreased by 38,4%, stress echocardiography by 72,5%, stress single-photon emission computed tomography by 66,9%, computed tomography angiography by 49,7%, magnetic resonance imaging by 42,7%, invasive coronary angiography by 40,7%. The decrease in diagnostic procedure volumes in selected regions (Tomsk Oblast, Kemerovo Oblast, Tatarstan) was not so pronounced compared to Moscow and St. Petersburg (-20,7%, -75,2%, -93,8% in April 2020, respectively, p<0,001).

Conclusion. The first wave of the COVID-19 pandemic caused a sharp decrease in the number of diagnostic cardiac procedures in Russia. This has potential long-term implications for patients with cardiovascular disease. Understanding these implications can help guide diagnostic strategies during the ongoing COVID-19 pandemic and minimize the future losses.

Key words: COVID-19, cardiac diagnostic procedures.

Relationships and Activities: none.

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Over the past year, the pandemic of the new coronavirus infection (COVID-19) has become one of the major global problems affecting all of humanity and having far-reaching socio-economic consequences. However, even during this period, the main cause of death in the population remains cardiovascular diseases (CVD). Between January and September 2020, 1,5 million people worldwide died from COVID-19, while 17 million died from CVD. In Russia, during the period from March to September 2020, 7317 people died from COVID-19 complications, and in another 5825 cases, various diseases in COVID-positive patients were the cause of death. At the same time, over the same period of time, 39985 people died from acute heart attack in Russia, and 220719 people died from coronary heart disease (CHD) in general [1, 2].

In domestic and foreign recommendations for the management of patients with CHD, non-invasive cardiac imaging methods play a leading role in diagnosis, evaluation of the therapy effectiveness and prognosis of patients with CHD. Timely diagnosis of CVD using methods such as echocardiography (EchoCG), computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission tomography (SPECT), and coronary angiography (CA) is crucial for the patient's prognosis, while delaying or refusing to perform diagnostic procedures directly affects the long-term risk of cardiovascular complications and mortality [3]. In this regard, numerous interim recommendations for cardiac imaging during the COVID-19 pandemic have been issued [4-6].

However, the global situation with COVID-19 has led to a serious failure in the provision of many medical services, including regarding the performance of diagnostic studies in cardiology. At the same time, there was a focus shift for the entire field of radiation diagnostics — the volume of chest CT to assess lung damage in COVID-19 increased dramatically [7], while many laboratories and departments, including cardiological imaging, were

temporarily mothballed. In this regard, the Division of Human Health of the International Atomic Energy Agency (IAEA) initiated a major international study INCAPS COVID, which included data from 909 medical centers from 108 countries, to analyze the relationship between the COVID-19 pandemic and the cardiac imaging industry state [8]. This article presents the subanalysis results of the INCAPS COVID study, the purpose of which is to assess the impact of first COVID-19 wave on volume of diagnostic studies of cardiac diseases in the Russian Federation.

Table 1

The provision levels of supplies and protective equipment in institutions at the time of the peak of the first COVID-19 wave

	Available	Currently not available, supplies are planned	Not available, supplies are not planned
Protectants			
Surgical masks	14 (93%)	1 (7%)	0 (0%)
Masks N95/KN95/KF94/FFP2	8 (53%)	4 (27%)	3 (20%)
Gloves	14 (93%)	1 (7%)	0 (0%)
Protective overalls	13 (87%)	1 (7%)	1 (7%)
Glasses/screens	7 (47%)	6 (40%)	2 (13%)
Consumables (isotope laboratories only)			
^{99m}Tc Generators	9/10 (90%)	-	-
^{18}F-FDG	2/2 (100%)	-	-
^{13}N-ammonium	2/2 (100%)	-	-
Technetrile/tetrofosmin kits	10/10 (100%)	-	-

Table 2

Implementation frequency of various measures related to changing the work process in the COVID-19 conditions

	Russian Federation			Europe	
Number of centers	15			236	
	Implemented	Not implemented, planned	Not implemented, not planned	Implemented	p
Changing the work process structure					
Reduction of outpatient admissions	12 (80%)	2 (13%)	1 (7%)	201 (85%)	0,86
Cancellation of admission of all non-emergency outpatients	9 (60%)	1 (7%)	5 (33%)	189 (80%)	0,13
Cancellation of admission of all outpatients	7 (47%)	2 (13%)	6 (40%)	103 (44%)	0,97
Phased resumption of activities after the peak of the pandemic	5 (33%)	10 (67%)	0	141 (60%)	0,08
Increase in working hours after the peak of the pandemic	0	6 (40%)	9 (60%)	50 (21%)	0,10
Increase in weekend hours after the peak of the pandemic	0	3 (20%)	12 (80%)	28 (12%)	0,32
Switching to remote means for patient contact	3 (20%)	3 (20%)	9 (60%)	110 (47%)	0,08
Changing the procedure for patients admission					
Move to remote means for patient registration (questionnaires, informed consents)	3 (20%)	5 (33%)	7 (47%)	100 (42%)	0,15
Changing patient transportation (use of elevators, etc.)	5 (33%)	3 (20%)	7 (47%)	166 (70%)	<0,01
Distancing in waiting rooms	9 (60%)	5 (33%)	1 (7%)	209 (89%)	<0,01
Separate rooms for patients with COVID-19	7 (47%)	6 (40%)	2 (13%)	194 (82%)	<0,01
Reducing the time of stay of patients in waiting rooms	8 (53%)	4 (27%)	3 (20%)	198 (84%)	<0,01

Table 2. Continued

	Russian Federation			Europe	
Number of centers	15			236	
	Implemented	Not implemented, planned	Not implemented, not planned	Implemented	p
Restricting access to persons accompanying patients	8 (53%)	5 (33%)	2 (13%)	223 (94%)	<0,01
Temperature measurement for all patients and visitors	12 (80%)	2 (13%)	1 (7%)	126 (53%)	0,08
Mandatory completion of a questionnaire for COVID-19 symptoms by patients and visitors	9 (60%)	3 (20%)	3 (20%)	162 (69%)	0,68
Test for COVID-19 in all patients before enrollment	1 (7%)	4 (27%)	10 (67%)	22 (9%)	0,91
Mandatory wearing of masks for all patients and visitors	12 (80%)	2 (13%)	1 (7%)	169 (72%)	0,68
Changing the study protocol					
Use of pharmacological load tests instead of physical, if possible	4/13 (31%)	2/13 (15%)	7/13 (54%)	99 (42%)	0,37
Changing the nuclear cardiology protocols (for example, increasing the input activity to reduce the data collection time, use as a first phase with a load test)	3/10 (23%)	2/10 (15%)	5/10 (38%)	42 (18%)	0,89
Changing the heart CT protocols (for example, a decrease in the use frequency of intravenous drugs to reduce HR)	1/13 (8%)	3/13 (23%)	9/13 (69%)	24 (10%)	0,99
Additional time after each study for sanitary disposal of equipment and premises	11 (73%)	3 (20%)	1 (7%)	172 (73%)	0,79
Increasing the distance between staff and patients	10 (67%)	3 (20%)	2 (13%)	198 (84%)	0,17
Mandatory use of personal protective equipment	11 (73%)	3 (20%)	1 (7%)	210 (89%)	0,16
Changing or eliminating the protocols that require long-term contact with patient	5 (33%)	5 (33%)	5 (33%)	133 (56%)	0,14
Changing the personnel process					
Rotation of work shifts	9 (60%)	4 (27%)	2 (13%)	157 (67%)	0,81
Employment freeze/holidays without pay of part of the staff of radiologists/radiologists due to economic crisis on grounds of COVID-19	1 (7%)	0	14 (93%)	19 (8%)	0,76
— for the average staff of diagnostic laboratories	2 (13%)	0	13 (87%)	18 (8%)	0,76
Cut of radiologists'/radiologists' salary	5 (33%)	1 (7%)	9 (60%)	10 (4%)	<0,001
— for the average staff of diagnostic laboratories	5 (33%)	2 (13%)	8 (53%)	10 (4%)	<0,001
Dismissal of part of radiologists/radiologists	1 (7%)	1 (7%)	13 (87%)	4 (2%)	0,70
— for the average staff of diagnostic laboratories	0	1 (7%)	14 (93%)	5 (2%)	0,70

Abbreviations: CT — computed tomography, HR — heart rate, IV — intravenous.

Material and methods

The database for subanalysis was formed as part of the INCAPS COVID study under IAEA auspices. The online questionnaire form was developed by a group of specialists in the field of cardiology and cardiovascular system visualization [8]. The questionnaire included items related to organization of work in medical institutions, staff of diagnostic laboratories and departments, availability of personal protective equipment, and strategic plans after re-opening. Changes in volume of cardiological studies were recorded in connection with the current epidemiological situation (in April 2020) compared to March 2020 (the month preceding the epidemic onset) and the same period of the last year (March 2019), namely, the volume of performed radionuclide studies (SPECT and positron emission tomography (PET)), and CT (including for assessment of coronary calcium and CT-coronarography). Moreover, some data were obtained on the volume dynamics of such studies as EchoCG, heart MRI, heart PET for infectious diseases, as well as invasive CA. The data was collected using a questionnaire form using the IAEA's secure IRIS software plat-

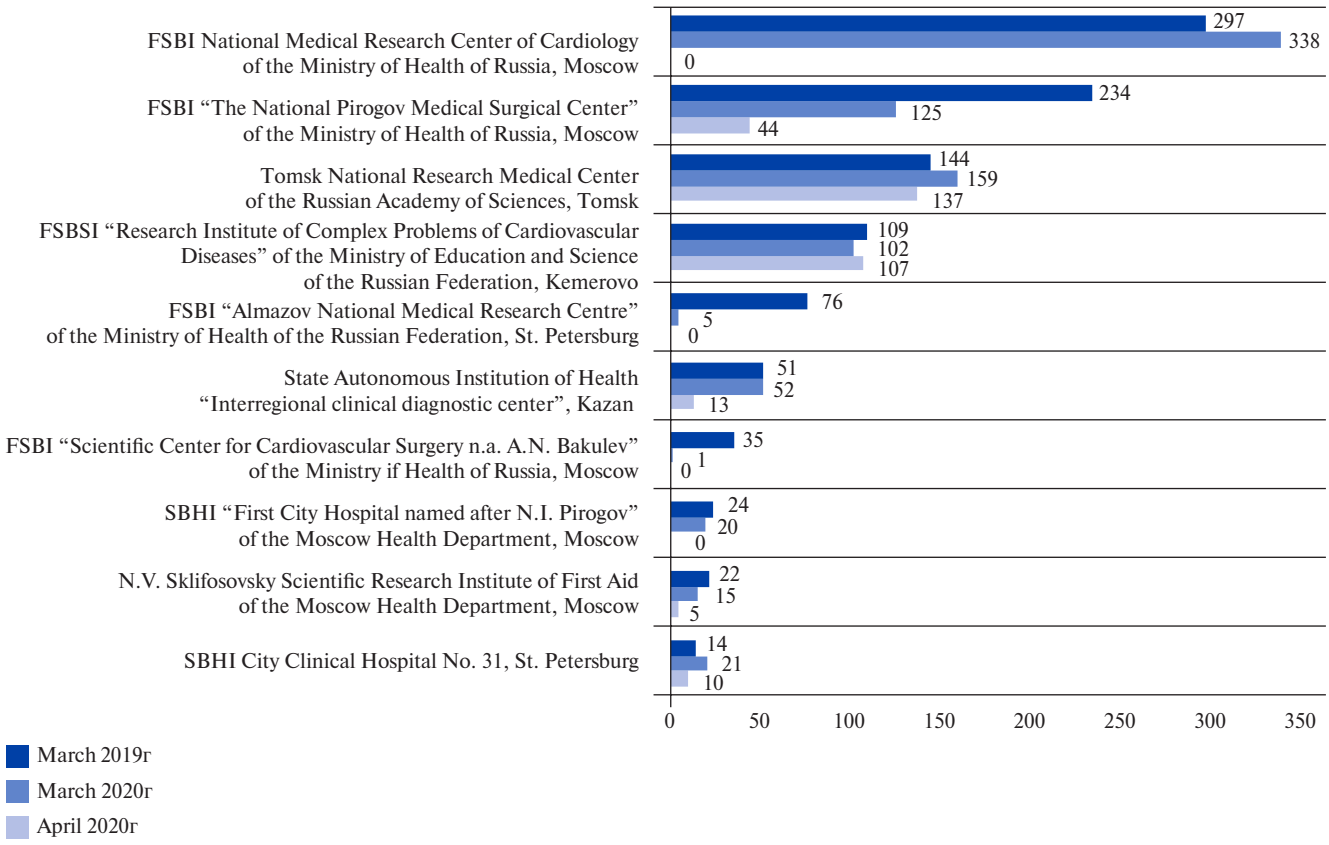

Figure 1. Volume dynamics of radionuclide myocardium studies in various centers of Russia in March and April 2020 in comparison to March 2019.

form (https://iris.iaea.org). Russian centers were invited to participate in the study through invitations from national coordinators with the participation of the Moscow Branch of the Society of Nuclear Medicine and the Russian Society of Radiologists and Radiologists. The participation of investigator sites was voluntary, no personal and confidential data was collected, so the study did not require the ethics committees' opinion.

The statistical analysis was performed using Microsoft Excel 2013 and MedCalc 15.8. The answers to the questionnaire questions are presented in the form of numerical values and percentages. The fractions were compared using the chi-square test with the Yates correction. Since official figures on hospitalizations number of patients with COVID-19 in Russia are only available from April 25, 2020, earlier values are obtained by constructing a trend line with reverse forecast.

Results

For the Russian Federation, the data are provided by questionnaires from 15 medical centers, including 8 — from Moscow, 4 — from St. Petersburg and 1 each — from Tomsk, Kazan and Kemerovo. All the enrolled centers were specialized or multidisciplinary hospitals, 13 of them — with the implementation of educational programs, including 8 federal centers and 7 city health institutions, with a capacity from 165 to 2000 (on average 500 (400-970)) beds. Of the 15 institutions, 10 had an isotope laboratory (including 2 had PET), 13 had CT (including hybrid devices of SPECT/CT or PET/CT), 13 performed exercise tolerance tests on a continuous basis.

The treatment and diagnostic units of the included centers were generally provided with individual protective gear. 90% of isotope laboratories were provided with ^{99m}Tc generators for this period, and radiopharmaceuticals ^{18}F-FDG and ^{13}N-ammonium for studies of myocardial metabolism and perfusion were available in both enrolled PET centers. The provision levels of supplies and protective equipment in institutions at the time of the peak of the first COVID-19 wave (May 2020) are shown in Table 1.

A decrease in outpatient flow of patients in Russian clinics for diagnostic cardiological examinations, as in European ones, was noted in the majority (80% vs 85%, p=0,89) of clinics. In comparison with Europe, Russian clinics less often resorted to various changes in the procedure for receiving patients. In particular, in Russia, they less often switched

Table 3

Dynamics of the cardiological examination volume in Russia in March and April 2020 compared to March 2019

	Russian Federation				Generally	Europe	p
	Moscow	Saint-Petersburg	Regions*	p			
Number of centers	8	4	3	-	15	251	-
Volume dynamics of execution of all studies							
03.2019-03.2020	-14,5%	-67,9%	3,2%	<0,001	-9,5%	-45%	<0,001
03.2019-04.2020	-75,2%	-93,8%	-20,7%	<0,001	-56,5%	-69%	<0,001
Volume dynamics of perfusion SPECT of myocardium							
03.2019-03.2020	-16,6%	-51,9%	3,0%	<0,001	-12,4%	-	-
03.2019-04.2020	-91,8%	-81,5%	-15,5%	<0,001	-66,9%	-79%	<0,001

Note: *regions — Tomsk region, Kemerovo region, Tatarstan.
Abbreviation: SPECT — single photon emission computed tomography.

Table 4

Volume dynamics of other cardiological examinations performed in April 2020 compared to March 2019

	Russian Federation	Europe	p
Stress ECG	-38,4%	-83%	<0,001
Stress EchoCG	-72,5%	-84%	<0,001
Stress PET	-100%	-42%	<0,001
Stress MRI	-14,3%	-68%	<0,001
CT-CS	-54,8%	-78%	<0,001
CTA	-49,7%	-69%	<0,001
EchoCG	-61,6%	-67%	<0,01
TE-EchoCG	-87,4%	-74%	0,002
PET (infections)	-100%	-53%	<0,001
MRI	-42,7%	-72%	<0,001
Invasive CA	-40,7%	-51%	0,006

Abbreviations: CA — coronary angiography, CS — clinical study, CT — computed tomography, CTA — computed tomographic angiography, MRI — magnetic resonance imaging, PET — positron emission tomography, TE-EchoCG — transesophageal echocardiography, ECG — electrocardiography, EchoCG — echocardiography.

to remote communication with patients, and less often modified the principles of transportation and logistics of the patients flow in the premises of diagnostic departments. Changes in work process structure and study protocols were implemented with approximately the same frequency as in European clinics. Summary data on the frequency of implementation of various measures related to changes in work process due to work in the COVID-19 conditions are given in Table 2.

In general, the volume of cardiac diagnostic procedures in the Russian centers enrolled in the period from March 2019 to March 2020 decreased by 9,5% (in European centers — by 45%, p<0,001), from March 2019 to April 2020 — by 56,5% (in Europe — by 69%, p<0,001). At the same time, the decrease in the study volume in the regions, including perfusion myocardium SPECT, was not as expressed as in Moscow and St. Petersburg (all p<0,001) (Table 3). The change in radionuclide studies in absolute values is given in Figure 1. The change in functional studies is given in Figure 2 A, while other cardiological examinations performed at rest are shown in Figure 2 B.

The scope of other cardiac studies has decreased to a lesser extent than in Europe (all p<0,01) by April 2020. At the same time, the number of PET scans in progress (incl. for myocardial blood flow assessment and for infection diagnosis), as well as transesophageal EchoCG has decreased to a greater extent than in Europe (all p<0,01). The data on change in scope of cardiac studies against European data are given in Table 4.

Empirical regularities between the nature of COVID-19 pandemic state and a decrease in scope of cardiac studies in different regions. In this connection, the number of studies in St. Petersburg decreased by 68% in March 2020 compared with March 2019, despite the relatively small number of COVID-19 cases. In April 2020, the number of cases and hospitalizations in Moscow was critical, while the number of cardiological examinations decreased by 75%, while in St. Petersburg and the regions — by 94% and 21%, respectively, with a much lower incidence of infections, hospitalizations and deaths than in Moscow, per 100 thousand populations (Table 5).

Discussion

The COVID-19 pandemic has had a major impact on the healthcare industry worldwide. The

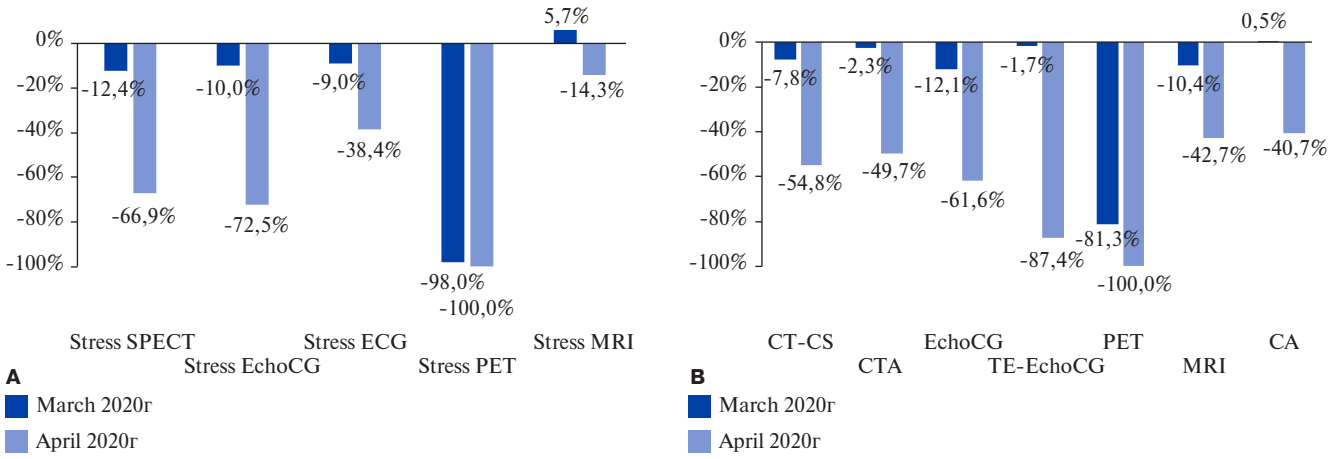

Figure 2. Changing the number of functional (**A**) and other (**B**) cardiological examinations in March and April 2020 in comparison to the same period in 2019.
Abbreviations: CA — coronary angiography, CS — clinical study, CT — computed tomography, CTA — computed tomographic angiography, MRI — magnetic resonance imaging, SPECT — single photon emission computed tomography, PET — positron emission tomography, TE-EchoCG — transesophageal echocardiography, ECG — electrocardiography, EchoCG — echocardiography.

Table 5

Dynamics of infections, hospitalizations, deaths from COVID-19 and volume of cardiac studies in the studied regions in March and April 2020

	Moscow		Saint-Petersburg		Regions	
	March 2020	April 2020	March 2020	March 2020	April 2020	March 2020
Total infections	1613	52126	98	3964	25	1015
Infections per 100 thousand	12,9	416,8	1,8	74,1	0,3	13,2
Total hospitalizations*	1452	35378	88	2656	22	680
Hospitalizations per 100 thousand*	11,6	282,9	1,6	49,6	0,3	8,9
Total deaths	11	600	2	27	0	4
Deaths per 100 thousand	0,1	4,8	0,0	0,5	0,0	0,1
Decrease in the number of cardiac examinations	-14,5%	-75,2%	-67,9%	-93,8%	3,2%	-20,7%

Note: * — the data is based on the interpolation of official reports after April 25 by constructing a trend line with reverse forecast.

results of large international INCAPS COVID study initiated by the IAEA Human Health Division, which included data from 909 medical centers from 108 countries, recorded an unprecedented decrease in the global volume of diagnostic cardiac imaging — by 42% in March 2020 and by 64% in April 2020 compared to data for March 2019 [8]. In Europe, a set of measures related to work in COVID-19 conditions varied significantly, taking into account the situation severity in different countries and regions, but the total number of cardiac examinations also decreased — by 45% in March 2020 and by 69% in April 2020. The reduction of studies and the frequency of restrictive measures from European countries were greatest in the southern regions, where the damage from the pandemic's first wave was most severe. In March 2020, location (Southern Europe) and high mortality from COVID-19 (per 100000 population) were independent predictors of reduced cardiological examinations. In April 2020, such predictors were the location and low level of the country economy (expressed in gross domestic product) [9]. These results stress the significant variability in the public health service response of different countries to the pandemic and its role in further increasing the risk for patients with CVD.

During the first wave of the COVID-19 pandemic, 7 of the 8 enrolled federal centers in Russia were redesignated as COVID-centers, which, together with other changes in the internal regulations related to COVID-19, led to many innovations in work process of diagnostic laboratories. In most centers, the volume of outpatient patients decreased, in 4 centers, the attendance of patients for radionuclide studies was completely stopped (Figure 1), and a number of limit rules were introduced within the

remaining flow. Measures were also taken to modify the protocols for recording studies, minimizing the potential for infection of patients and staff at workplaces. According to our data, the implementation frequency of these changes in Russia sufficiently differs from the European practice. Apparently, this is due to the fact that at the time of filling out the questionnaires (the end of May 2020), a large part of diagnostic laboratories was mothballed, and the new rules were implemented later, as the outpatient flow was gradually resumed. At the same time, in many centers of Russia, the flows of outpatient and hospital patients were subsequently differentiated (by organizing separate entrances, exits and partitions), which was not reflected in the form of the European Questionnaire.

According to our data, the volume of cardiological examinations in Russia in March 2020 compared to March 2019 decreased by 9,5%, and in April 2020 — by 56,5%, while in Europe the decrease was 45% and 69%, respectively ($p<0,001$). The main contribution to decrease in the study volume was made by Moscow and St. Petersburg, while in the enrolled regional centers, the decline in study volume in April was only 20,7%. This can be explained by dynamics of pandemic spread in Russia — in March, the cases in Moscow (which faced COVID-19 earlier than other Russian cities) were still only at the very beginning of an increasing trend, while in many European countries at this time, the peak of morbidity was already approaching. In turn, a sharp increase in the COVID-19 incidence in the regions occurred about another month later. Thus, the first deaths from COVID-19 in Moscow were recorded on March 25, in St. Petersburg — on March 29, in Kemerovo region — on April 18, in Tatarstan — on April 29, in Tomsk — on May 1. For this reason, in March 2020, there was not yet a massive decline in the number of cardiological examinations in the regions, and by April 2020, this decline was still less significant than in Moscow and St. Petersburg, which, in turn, was less significant than in Europe.

By autumn 2020, most of the centers that were converted into COVID centers during the first COVID-19 wave have returned to their main operation, and the diagnostic laboratories are largely disbanded and continue to see patients in the conditions of a full-fledged second wave of the pandemic. All the safety measures that were developed and implemented at the beginning of the first wave (Table 2), but not so carefully observed at that time, have now become de facto mandatory. We are talking primarily about optimizing the working hours of medical and paramedical personnel of radiological and radiological departments, switching to remote means of contact with patients (before and after studies), distancing at all stages of the study, additional sanitary measures, temperature measurement, mandatory wearing of masks, collection of COVID-anamnesis, for hospital patients — stay in observational departments.

Despite the changes in work process of diagnostic departments, special attention should now be paid to eliminating or at least reducing the consequences of the first pandemic wave. Thus, a significant decrease in the number of diagnostic cardiological examinations in the second quarter of 2020 led to the queueing formation for study among those who at that time were refused due to the closure of laboratories. In this regard, it is impossible not to mention another problem related to the state of isotopic laboratories in the country. While in Europe, the INCAPS COVID study enrolled 251 centers with isotope laboratories that are engaged in nuclear cardiology on a consistent basis (i.e., approximately 1 per 2,8 million population), according to the most optimistic estimates, there are currently no more than 15 such laboratories, of which 10 were enrolled in Russia (i.e., 1 per 14,5 million population). At the same time, given that the overwhelming volume of radionuclide cardiological studies in Russia is carried out in 6 centers — Federal State Budgetary Institution (FSBI) "National Medical Research Center of Cardiology" of the Ministry of Health of Russia (Moscow), FSBI "The National Pirogov Medical Surgical Center" of the Ministry of Health of Russia (Moscow), Cardiology Research Institute, Federal State Budgetary Scientific Institution "Tomsk National Research Medical Center of the Russian Academy of Sciences", FSBSI "Research Institute of Complex Problems of Cardiovascular Diseases" of the Ministry of Education and Science of the Russian Federation (Kemerovo), State Autonomous Institution of Health "Interregional clinical diagnostic center" (Kazan) and FSBI "Almazov National Medical Research Centre" of the Ministry of Health of the Russian Federation (St. Petersburg), in Russia, the number of performed cardiac isotope studies per head is at least 10 times less than in Europe. As a result, according to our approximate data, the waiting list for perfusion scintigraphy of myocardium in patients with suspected or established CHD at the end of 2020 (even taking into account the work resumption) in these centers is at least 500-700 people.

It should be emphasized that the heart imaging by radiation diagnostics is central to the diagnostic algorithm for many patients with both acute and chronic conditions. In particular, the imaging of transient myocardial ischemia by perfusion scintigraphy and SPECT is a key point in determining the management of patients with CHD. In particular,

the method is used to select patients for invasive CA and PCI, reducing the number of unpractical interventions. Therefore, the drop in the already low volume of cardiological radionuclide examinations performed in Russia caused by COVID-19 will have serious short-and long-term consequences for all patients with CVD in whom the diagnostic study was canceled or postponed. In addition, it is known that COVID-19 itself is associated with myocardial damage, arrhythmias, venous and arterial thrombosis [10]. These effects will exacerbate the increased risk of adverse outcomes in patients with CVD after COVID-19 infection, combined with the continued decline in the capacity of the cardiology emergency service redirected to receive patients with COVID-19 [11]. Thus, in Europe, the number of hospitalizations in March 2020 with acute myocardial infarction in emergency departments decreased by half, as a result of which there was a proportional increase in out-of-hospital cases of cardiac arrest and an increase in cardiovascular mortality in general [12-15].

According to European data, the retaliatory measures of the governments of various countries had some regularities. In particular, the most significant decrease in the cardiac diagnostics volume was typical not only for countries with highest mortality from COVID-19, but also for countries with a relatively low gross domestic product [9]. It is likely that such attempts to prevent overloading the health care system have a short-term effect, but will have dire consequences in the long term.

Conclusion

A timely solution to the problem of overloading the health system by organizers of domestic health care is extremely important, since at present the end date of the COVID-19 pandemic cannot be set. In turn, at the level of diagnostic departments, it is essential to strictly adhere to the adopted protective measures, logistics modifications and patient examination protocols. This is necessary to maintain the readiness to increase the flow of patients and their safe examination under the conditions of the ongoing COVID-19 pandemic.

Annex

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