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Two-year follow-up of patients with heart failure with reduced ejection fraction receiving cardiac contractility modulation

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Aim. To assess the 2-year prognosis of patients with heart failure with reduced ejection fraction (HFrEF) receiving cardiac contractility modulation (CCM).

Methods. This single-center observational study included 55 patients (46 men, mean age 53±11 years) with NYHA class II-III HFrEF receiving optimal medical therapy, with sinus rhythm, QRS <130 ms or QRS <150 ms with nonspecific intraventricular conduction delay. NYHA class II and III were established in 76% and 24% of patients, respectively. All patients were implanted with CCM devices between October 2016 and September 2017. Follow-up visits were carried out every 3 months during the 1st year and every 6 months during the 2nd year of observation. The primary composite endpoint was mortality and heart transplantation. Secondary composite endpoints included death, heart transplantation, paroxysmal ventricular tachycardia/ventricular fibrillation, hospitalizations due decompensated HF.

Results. The one-year and two-year survival rate was 95% and 80%, respectively. Primary endpoint was observed in 20% of patients. NYHA class III and higher levels of N-terminal pro-brain natriuretic peptide (NTproBNP) were associated with unfavorable prognosis (p=0,014 and p=0,026, respectively). NTproBNP was an independent predictor of survival (p=0,018). CCM contributed to a significant decrease in hospitalizations due to decompensated HF (p<0,0001). The secondary endpoint was observed in 18 (33%) of patients during the 1st year. The predictor for the secondary composite endpoint was NTproBNP (p=0,047).

Conclusion. CCM is associated with a significant decrease in hospitalization rate due to decompensated HF. The 2-year survival rate of patients with NYHA class II-III HF receiving CCM was 80%. The NTproBNP level was an independent predictor of survival in patients receiving CMM for 2 years. Further longer-term studies of the CCM efficacy are required.

Key words: cardiac contractility modulation, heart failure, reduced ejection fraction, long-term results, prognosis.

Relationships and Activities: none.

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Over the past decades, new electrophysiological methods of treating patients with heart failure with reduced ejection fraction (HFrEF) have been actively developed and introduced into clinical practice. Previous studies have proven the effectiveness of cardiac resynchronization therapy (CRT) in the management of patients with HFrEF and electrical desynchrony in presence of complete left bundle branch block with QRS >130 ms and patients with nonspecific intraventricular block with QRS >150 ms. However, most patients with HFrEF have QRS ⩽130 ms and cannot be considered CRT candidates. In addition, in patients with complete right bundle branch block and nonspecific intraventricular block with QRS <150 ms, a positive response to CRT is questionable [1]. In this regard, a new method for management of HFrEF, cardiac contractility modulation (CCM), is of great interest [2]. In CCM, the application of high-amplitude electrical impulses occurs during the absolute refractory period. These impulses do not cause myocardial contraction, do not change the sequence of cardiomyocyte contraction during ventricular systole, but increase the strength and duration of cardiomyocyte action potential, which in some cases leads to reverse remodeling and improvement of the heart's pumping function [3, 4]. The implantation of the CCM system is similar to conventional permanent pacemakers, but with CCM, two ventricular leads are placed in the middle third of interventricular septum at a distance of >2 cm from each other. From these leads, during the absolute refractory period, electrical impulses of high amplitude (>7,5 V) and duration (5,14 ms) are simultaneously applied. Randomized clinical trials demonstrate the safety and the positive effect of CCM on exercise tolerance and quality of life in patients with HFrEF [5, 6]. Data on long-term efficacy and prognosis in patients receiving CCM are limited and continue to be studied [7-9]. The aim of our study was to assess the 2-year prognosis of patients with HFrEF receiving CCM.

Material and methods

From October 2016 to September 2017 at the Almazov National Medical Research Center, 55 patients were implanted with 50 CCM Optimizer IVs systems and 5 Optimizer Smart systems (Impulse Dynamics, Germany). The inclusion criteria were NYHA class II and III HFrEF, sinus rhythm, QRS <130 ms or nonspecific intraventricular block with QRS <150 ms, optimal medication therapy for heart failure (HF) for at least 3 months, signed informed consent. The exclusion criteria were a permanent atrial fibrillation, high-grade premature ventricular contractions; acute myocardial infarction or major heart surgery, percutaneous coronary intervention, valvuloplasty within 12 months and hospitalization due to decompensated HF within 3 months prior to inclusion in the study. The ethics committee of Almazov National Medical Research Center approved this study.

Initially, all patients underwent a physical examination, six-minute walk test, routine blood tests, determination of serum N-terminal pro-brain natriuretic peptide (NTproBNP), electrocardiography, 24-hour Holter monitoring, treadmill cardiopulmonary exercise test (Ochuson Pro, Jaeger, Germany). Echocardiography was performed by one researcher using a VIVID 9 ultrasound system (GE, USA). At the inclusion, the projected survival was assessed in all patients using the Seattle Heart Failure Model (SHFM).

The technique of CCM device implantation and settings were described in earlier publications [2, 4].

After implantation of the CCM system, patients were followed up by specialists in management of HF and patients with implanted devices. Follow-up visits for examination and programming of the CCM were carried out every 3 months during the first year and every 6 months during the second year of observation. The total number and average number of hospitalizations for each control point were assessed over the previous 6-month time interval.

Mortality and heart transplantation (HT) were considered as the primary composite endpoint (CEP). The secondary endpoint included a combination of the following events: death, HT, actuation of implantable cardioverter-defibrillator (ICD) due to paroxysmal ventricular tachycardia/ventricular fibrillation, hospitalization due to decompensated HF.

Changes in HF class and echocardiography parameters in this part of the study was not assessed.

Statistical analysis. The database included >200 parameters. All primary indicators were analyzed using the software packages IBM SPSS Statistic 23 and STASTICA 10. Categorical data were presented by frequencies and percentages of the total number. The contingency tables and Fisher's exact test were used for the analysis. Normally distributed data are presented as mean ± standard deviation (M±SD); medians (Me), 25% and 75% quartiles; minimum and maximum values. To compare the deceased and the survivors according to quantitative data, independent-samples Student's t-test (normally distributed data) or the nonparametric Mann-Whitney test were used. Nonnormally distributed data was assessed using the Wilcoxon test (2 time points) and the Friedman test (3 or more time points). Survival analysis was performed using the Kaplan-Meier estimator. For comparative analysis of individual factors that could potentially affect survival

and death time, we used the log-rank test and regression models. The likelihood of a secondary CEP was assessed by the binary logistic regression. The predictive assessment was performed using ROC analysis. The differences were considered significant at p<0,05.

Clinical characteristics of patients. The study group consist of 46 men (84%) and 9 women (16%) aged 27-73 years. Their clinical characteristics are presented in Table 1. Left ventricle ejection fraction (LVEF) was 14-38%. Class II and III HF were diagnosed in 76% and 24% of cases, respectively. In the group of patients with coronary artery disease, 30% had class II angina, 55% had previously undergone myocardial revascularization. Initially, ICD was recorded in 22% of patients. Other patients were assessed for indications for ICD insertion for primary prevention of sudden cardiac death (SCD). All patients received standard HF therapy: 96% — angiotensin-converting enzyme inhibitors or angiotensin type 1 receptor antagonists, 100% — β-blockers, 93% — mineralocorticoid receptor antagonists, 100% — diuretics. Angiotensin receptor neprilysin inhibitors were not used in this group of patients. Low values of the cardiopulmonary exercise test (peakVO_2 <13 ml/kg/min) were found in 15% of patients with class III HF, but due to age and comorbidities, they were not considered HT candidates. ICD insertion for the primary prevention of SCD was performed in 21 (38%) patients during the first year and in 3 (4%) patients during the second year of follow-up. The target percentage of therapeutic stimulation at baseline and during the two-year follow-up period was 92-94%.

Results

Adverse events associated with device implantation

There were no intraoperative complications during CCM insertion. In the early postoperative period, 1 patient pocket infection of device, which required explantation on the 6th day. By 3 months after implantation, CCM pocket stimulation due to ventricular lead insulation failure. In the period from 12 to 18 months, the need to cut off one of the ventricular leads was in 48% of patients. In 11 (20%) patients, revision and replacement of both ventricular leads were performed.

Endpoint analysis

Two-year follow-up revealed that 44 (80%) patients survived. Primary CEP (death and HT) were noted in 11 (20%) patients (91% — men): 5 (9,1%) deaths were recorded due to decompensated HF, 4 (7,3%) — due to SCD (patients without an implanted ICD); 1 (1,8%) patient underwent HT, 1 (1,8%) patient died due to cancer detected 6 months after implantation of the CCM device (Figure 1).

Significant factors effecting mortality were the class III HF in comparison with class II HF (p=0,014) and NTproBNP value (p=0,026). The distribution of groups depending on HF class and NTproBNP is presented in Table 2.

Survival analysis using the log-rank test revealed that patients differed depending on the initial HF class (p=0,007). Patients with class IIICHF had the worst prognosis. During 2 years, in patients with initial class II and III HF, mortality rate was 12% and 46%, respectively (Figure 2, Table 3).

To analyze the predictive value of HF class and NTproBNP values, ROC analysis was performed (Figure 3). The area under the curve was 0,69 (sensitivity — 55%; specificity — 84%) and 0,73 (sensitivity — 91%; specificity — 50%) for models based on HF class and NTproBNP, respectively, which indicates fair and good quality of models [10].

To assess the relationship between survival and predictors, which showed their significance in univariate analysis (p<0,001 for NTproBNP and p=0,009 for HF class), Cox multivariate regression was used (Table 4).

It was shown that the baseline concentration of NTproBNP was a significant independent predictor of survival, and with an increase in baseline NTproBNP by an additional 100 units, the risk of death in HFrEF patients receiving CCM increased by 2% within 2 years (p=0,018).

The prognosis of an unfavorable outcome in patients receiving CCM did not depend on such parameters as sex (p=0,67), age (p=0,14), causation of disease (p=0,25), LVEF (p=0,91). Thus, the survival rate did not differ in the subgroups of patients who had LVEF >25% and LVEF ⩽25% (p=0,99). Cut-off of one of the ventricular leads also did not affect mortality and/or hospitalizations during the two-year follow-up period (p=0,31 and p=0,44, 12 and 24 months, respectively).

Secondary CEP during 24-month follow-up reached 18 (33%) patients. Hospitalizations due to decompensated HF in the first 6 months after device implantation were registered in 5 (9%) patients compared with 38 (69%) patients before implantation (p<0,0001). This effect was maintained during 2 years of follow up. Each subsequent 6 months the number of hospitalized patients due to decompensated HF did not increase and amounted to 8%, 10% and 9% for the period of 12, 18 and 24 months, respectively (Figure 4, Table 5).

Ventricular arrhythmias were not recorded during 2 years of follow-up.

To assess the likelihood of secondary CEP, the stepwise binary logistic regression was used. NTproBNP concentration was associated with secondary CEP. Chi-square distribution with 1

Table 1

Clinical characteristics of patients before device implantation

Parameter	
Sex (men/women), n (%)	46/9 (84/16%)
Age, years, Me [Q1; Q3]	55 [45;61]
Minimum/maximum, years	27-73
Body mass index, kg/m^2, Me [Q1; Q3]	29 [25;32]
Office systolic blood pressure, mm Hg, Me [Q1; Q3]	110 [105;120]
Orthostatic systolic blood pressure, mm Hg, Me [Q1; Q3]	110 [100;120]
Resting heart rate, bpm, Me [Q1; Q3]	67 [61;73]
Coronary artery disease, old myocardial infarction, n (%)	40 (73%)
Myocardial revascularization, n (%)	30 (55%)
Nonischemic cardiomyopathy, n (%)	15 (27%)
Diabetes, n (%)	8 (14%)
Implanted cardioverter-defibrillator at baseline, n (%)	12 (22%)
Paroxysmal atrial fibrillation, n (%)	8 (14%)
Chronic obstructive pulmonary disease, n (%)	5 (9%)
Smoking, n (%)	12 (22%)
Number of patients hospitalized 6 months before implantation, n (%)	38 (69%)
Number of hospitalizations 6 months before implantation, Me [Q1; Q3]	1 [0;1]
Minimum/maximum number of hospitalizations, n	0-4
NYHA class of HF, Me [Q1; Q3]	2 [2;3]
Six-minute walk test, m, Me [Q1; Q3]	385,00 [346,00;450,00]
Glomerular filtration rate (MDRD), ml/min/1,73 m^2, Me [Q1; Q3]	79 [62;92]
Hemoglobin, g/l, Me [Q1; Q3]	149 [135;154]
Sodium, mol/l, Me [Q1; Q3]	140 [138;142]
Maximal oxygen uptake, ml/kg/min, Me [Q1; Q3]	16,5 [12,4;18,4]
NTproBNP, pg/ml, Me [Q1; Q3]	1094 [569;1749]
LVEF, %, Me [Q1; Q3]	26,00 [21,00;31,00]
LV end-diastolic volume, ml, Me [Q1; Q3]	249,00 [206,00;315,00]
LV end-systolic volume, ml, Me [Q1; Q3]	185,00 [136,00;230,00]
QRS, ms, Me [Q1; Q3]	106 [100;121]
Target therapeutic stimulation, initially, after 6, 12, 18, 24 months of follow-up, %, M±SD	92±13,9, 94±9, 94±10, 91±14,5, 92±11
Beta blockers, n (%)	55 (100%)
ACE inhibitors/ARBs, n (%)	52 (96%)
Mineralocorticoid receptor antagonists, n (%)	51 (93%)
Loop diuretics, n (%)	53 (96%)
Amiodarone, n (%)	7 (13%)

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

Abbreviations: ACE — angiotensin-converting enzyme, ARBs — angiotensin II receptor blockers.

degree of freedom was 7,3 (p=0,007), which means that the predictor is associated with secondary CEP. Odds ratio of 1,001 means that the risk of secondary CEP increases by 0,1% with an increase in NTproBNP by 1 unit (Table 6).

To assess the predictive value of NTproBNP and find the optimal classification threshold, a ROC analysis was performed. The area under the curve was 0,716, which is defined as good on the AUC expert scale (Figure 5). ROC-curve revealed the optimal

Table 2

HF class and NTproBNP values in the groups of survivors and deceased HF patients receiving CCM: 2-year follow-up

Parameter	Survivors n=44 (80%)	Deceased n=11 (20%)
NYHA class II	37 (84,09%)	5 (45,45%)
NYHA class III	7 (15,91%)	6 (54,55%)
p=0,014		
NTproBNP, пг/мл M±SD Me [Q1;Q3]	 1184,35±927,36 987,90 [526,75;1449,00]	 3576,45±4213,27 1200,00 [1094,00;4670,00]
p=0,026		

Note: n — absolute number of patients.
Abbreviations: NTproBNP — N-terminal pro-brain natriuretic peptide, NYHA — New York Heart Association.

Table 3

Number of patients with a risk of primary endpoint

Follow-up period Patient group	Days of follow-up								
	100	200	300	400	500	600	700	800	900
NYHA class II (n)	42	42	41	41	41	40	39	37	37
NYHA class III (n)	13	11	11	10	10	8	7	6	6

Abbreviation: NYHA — New York Heart Association.

Table 4

Multivariate survival analysis

Parameter	B value	P value	RR	95% CI	
NTproBNP	0,0002	0,018	1,0002	1,000037	1,00040
HF class	1,11	0,11	3,03	0,78	11,78

Abbreviations: CI — confidence interval, RR — relative risk, HF — heart failure, NTproBNP — N-terminal pro-brain natriuretic peptide.

classification threshold (p=0,302), at which the sensitivity was 73,7% and the specificity was 65,7%.

Prior to CCM implantation, the prognosis of survival was assessed in all patients using the SHFM. The mean 1-year and 2-year survival rates were 97,7±1,2% and 93,8±11,9%, respectively. The actual — year and 2-year survival was 94,5% and 80%, respectively (with the exclusion of the patient who died due to cancer). The SHFM overestimated survival rates by 3,2% and 13,8%, respectively.

Logistic regression with factors included in SHFM (sex; age; weight; HF class; causation of disease; initial LVEF; systolic blood pressure; taking angiotensin-converting enzyme inhibitors, angiotensin type 1 receptor antagonists, β-blockers, mineralocorticoid receptor antagonists, statins, allopurinol, diuretics; presence of ICD; levels of hemoglobin, lymphocytes, uric acid, total cholesterol, serum sodium) provided a significant predictive model (p<0,001, specificity — 95,5%, sensitivity — 81,8%). Four factors associated with an unfavorable outcome were identified: male sex (p=0,045), HF class (p=0,002), orthostatic systolic blood pressure (p=0,017), serum cholesterol (p=0,010). Separately, only HF class was significantly associated with a poor prognosis (p=0,012).

Discussion

The survival rate of patients with class II-III HFrEF, sinus rhythm and implanted CMM devices

Table 5

Hospitalizations due to decompensated HF depending on HF class at baseline: 2-year follow-up

Parameter \ Follow-up period	Before implantation	Follow-up			
	(-) 6 months	6 months	12 months	18 months	24 months
NYHA class II					
Number of hospitalizations, n	32	4	2	2	5
Number of hospitalized patients, % (n)	64% (27)	7% (3)	5% (2)	5% (2)	8% (3)
NYHA class III					
Number of hospitalizations, n	19	2	2	7	3
Number of hospitalized patients, % (n)	100% (11)	18% (2)	20% (2)	38% (3)	16% (1)

Abbreviation: NYHA — New York Heart Association.

Table 6

Relationship between the secondary CEP and the initial data

Parameter	Multiple regression coefficient	p	Odds ratio	CI (95%)
LV ESV	0,017	0,019	1,017	1,001-1,034
NTproBNP	0,00049	0,046	1,0005	1,000-1,001

Abbreviations: LV ESV — left ventricular end-systolic volume, NTproBNP — N-terminal pro-brain natriuretic peptide.

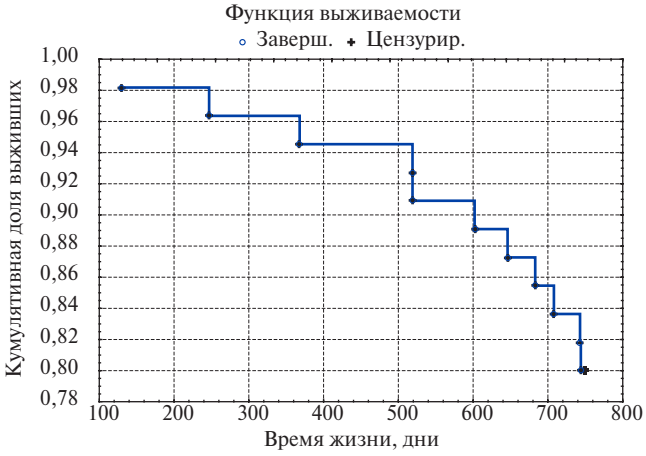


Figure 1. Kaplan-Meier survival curve for all-cause mortality and HT in all patients.

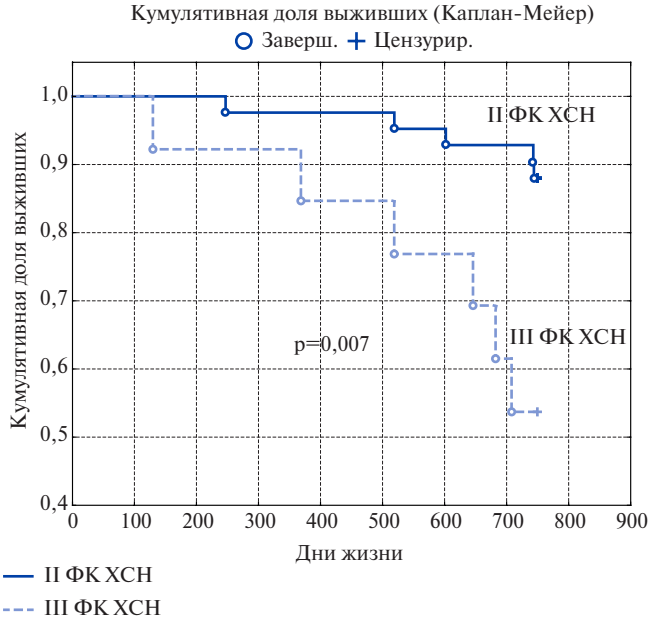
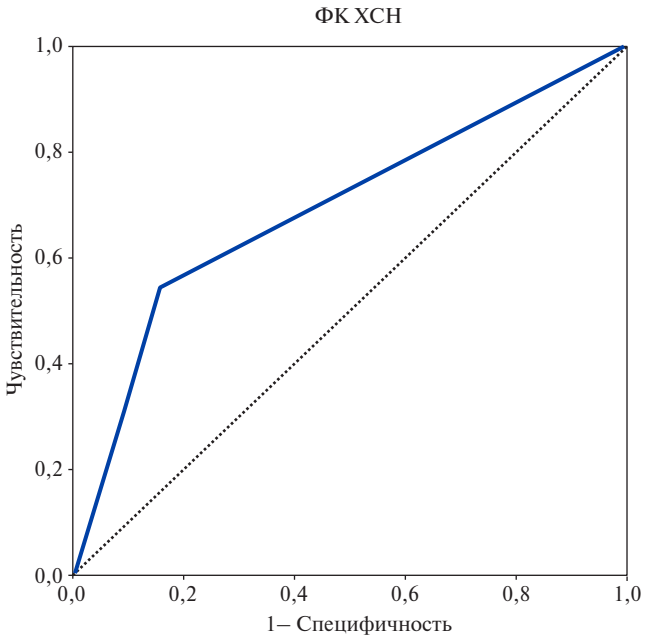


Figure 2. Kaplan-Meier survival curves for all-cause mortality and HT depending on HF class before implantation.

in the presented single-center prospective nonrandomized observational study for the first and second years was 95% and 80%, respectively. Third of patients reached secondary CEP in 2 years. With CCM, from the 6th month, there was a significant decrease in the number of hospitalizations and no life-threatening ventricular arrhythmias were detected.

Randomized and register studies demonstrate a positive effect of CCM on quality of life and exercise tolerance, assessed by ventilatory threshold and/or maximal oxygen uptake. At the same time, the data



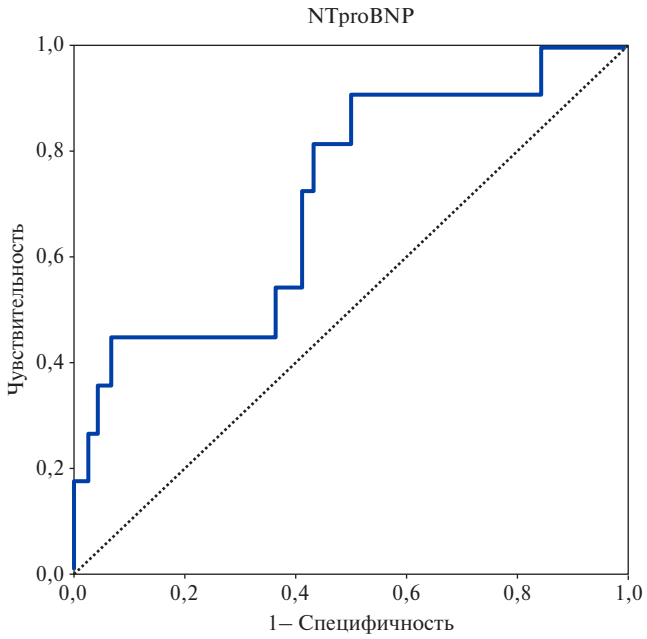


Figure 3. ROC curves for HF class and NTproBNP.

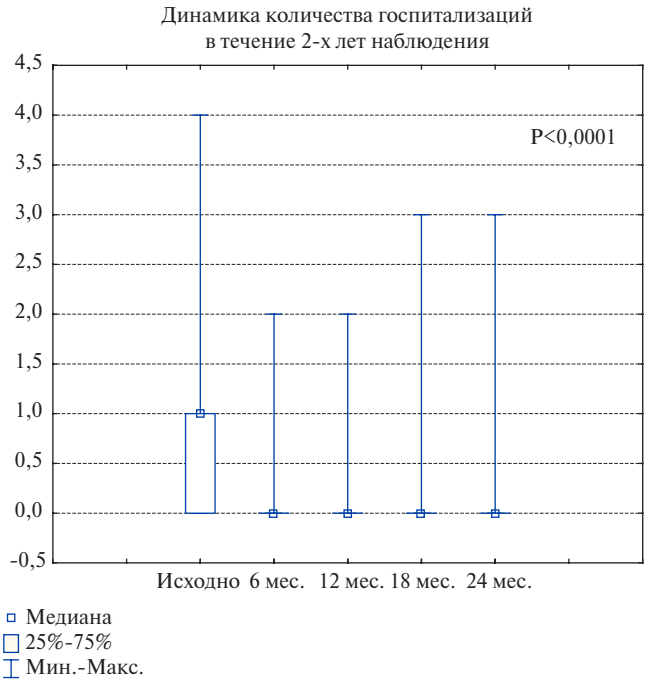


Figure 4. Changes in hospitalization rate during the 2-year follow-up.

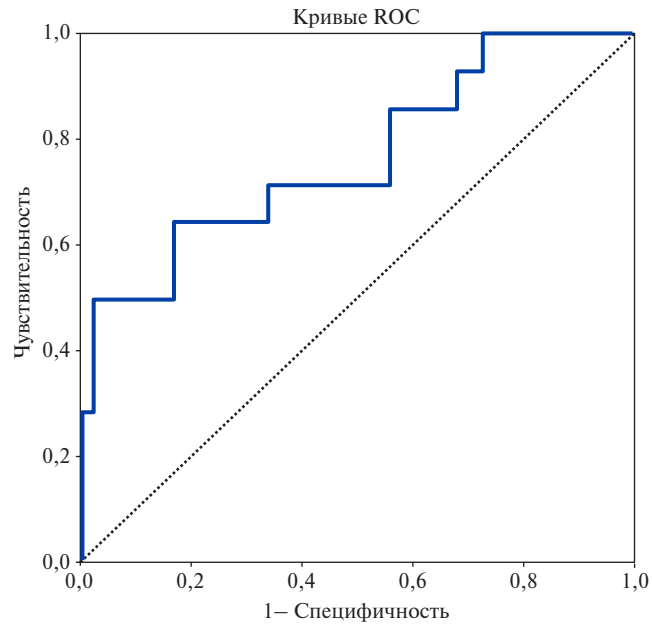


Figure 5. ROC-curve for the CEP risk.

on the effect of CCM on hard endpoint is ambiguous. It should be noted that the FIX-HF randomized clinical trials were limited to short follow-up periods of 3 to 12 months [5, 6]. In the FIX-FH-5C study, the composite endpoint (cardiovascular mortality and hospitalizations due to HF) by 24 weeks of follow-up was significantly lower in the group of CCM and optimal drug therapy compared with patients receiving only HF medication therapy: 2,9% vs 10,8%, respectively (p=0,048) [6]. Similar data were obtained in the European CCM-REG registry, which included 140 patients with class III-IV HF and LVEF of 25-45% [11]. Within 24 months, the all-cause hospitalization rate and due to HF significantly decreased both in the entire group and in the subgroup of patients with LVEF of 25-34% (n=83). The

survival rate for 1, 2 and 3 years in this subgroup was 89,6%, 82% and 79,4%, respectively, and did not differ significantly from the predicted survival rate according to the SHFM (91,8%, 84,6% and 78%, respectively). In the CCM-REG subgroup with LVEF of 35-45%, 3-year mortality was significantly less than predicted, amounting to 94,5% and 91,7% and 88,0%. Moreover, as in our study, the causation of disease and LVEF in the CCM-REG registry did not affect the prognosis of patients, and the SHFM overestimated the survival rate in the group of patients with LVEF <35%, without reaching the significance level. No influence of ischemic HF on outcomes during a two-year follow-up period is probably due to the high percentage of revascularization and the lack of indications for this procedure at the time of CCM implantation. According to Kloppe A, et al. (2016), the SHFM significantly underestimated the survival rate in patients with class II-III HFrEF [9]. The SHFM was developed with the American population and is based on simple clinical, laboratory and therapeutic characteristics for use in outpatients. In our protocol, the NTproBNP level was an important independent predictor influencing the prognosis. Along with this indicator, the severity of HF significantly affected the actual and predicted survival in the study group. Thus, it was previously shown that the most unfavorable prognosis is for patients with class III HF [12]. Obviously, such patients require closer observation and timely referral to other types of high-tech medical care, including HT.

In a meta-analysis of 4 FIX-HF randomized clinical trials, Mando R, et al. (2019) did not find a significant difference in hospitalization and mortality rates between the groups of HFrEF patients receiving and not receiving CCM [13]. It should be noted that there were no differences in arrhythmias between the comparison groups, including ventricular arrhythmias requiring intervention. In our study cohort, there was more than 7% of SCD cases in patients without ICD and previous decompensated HF, which justifies the use of ICD in combination with CCM in this category of patients.

NTproBNP was independently associated with secondary CEP within 2 years in patients receiving CCM. Interestingly, the cut-off of one of the leads did not affect mortality and hospitalization. This is consistent with the study by Röger S, et al. (2017), where single-lead stimulation did not have a significant effect on HF class, maximal oxygen uptake and 6-month mortality, compared to stimulation with 2 leads [14].

Study limitations. This study was observational and did not have a comparison group. In some patients, ICD was not implanted, and in cases of out-hospital death, the contribution of cardiac arrhythmias is not excluded. The drug therapy of HF for 2 years underwent changes in accordance with status of patients and the analysis of its effect on the endpoints was not carried out.

Conclusion

CCM is associated with a significant decrease in the number of hospitalizations due to decompensated HF. In patients with class II and III HF, the one- and two-year survival rate was 95% and 80%, respectively. The predictors of an unfavorable prognosis within 2 years (death/HT) were NYHA class III HF and a higher level of NTproBNP before CCM. The only independent predictor of survival, as well as the of the secondary CEP within 2-year follow-up, was the NTproBNP level.

Relationships and Activities: none.

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