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Heart failure patients with mid-range ejection fraction: clinical features and prognosis

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Abstract

Aim. To analyze clinical and echocardiographic characteristics and prognosis in patients with heart failure mid-range ejection fraction.

Methods. The study included 76 patients with stable heart failure I–IV functional class, with a mean age of 66.1±10.4 years. All patients were divided into 3 subgroups based on the left ventricular ejection fraction: the first group — heart failure patients with reduced ejection fraction (below 40%), 21.1%; the second group — patients with mid-range ejection fraction (from 40 to 49%), 23.7%; the third group — patients with preserved ejection fraction (>50%), 55.3%. The clinical characteristics of all groups were compared. The quality of life was assessed by the Minnesota Satisfaction Questionnaire (MSQ), the clinical condition was determined by using the clinical condition assessment scale (Russian "Shocks"). The prognosis was studied according to the onset of cardiovascular events one year after enrollment in the study. The endpoints were cardiovascular mortality, myocardial infarction (MI), stroke, hospitalization for acutely decompensated heart failure, thrombotic complications. Statistical analysis was performed by using IBM SPSS Statistics 20 software. Normal distribution of the data was determined by the Shapiro–Wilk test, nominal indicators were compared between groups by using chi-square tests, normally distributed quantitative indicators — by ANOVA. The Kruskal–Wallis test was performed to comparing data with non-normal distribution.

Results. Analysis showed that the most of clinical characteristics (etiological structure, age, gender, quality of life, results on the clinical condition assessment scale for patients with chronic heart failure and a 6-minute walk test, distribution by functional classes of heart failure) in patients with mid-range ejection fraction (HFmrEF) were similar to those in patients with reduced ejection fraction (HFrEF). At the same time, they significantly differed from the characteristics of patients with preserved ejection fraction (HFpEF). Echocardiographic data from patients with mid-range ejection fraction ranks in the middle compared to patients with reduced and preserved ejection fraction. In heart failure patients with mid-range ejection fraction, the incidence of adverse outcomes during the 1st year also was intermediate between heart failure patients with preserved ejection fraction and patients with reduced ejection fraction: for all cardiovascular events in the absence of significant differences (17.6; 10.8 and 18.8%, respectively), myocardial infarction (5,9; 0 and 6.2%), thrombotic complications (5.9; 5.4 and 6.2%). Heart failure patients with mid-range ejection fraction in comparison to patients with preserved ejection fraction and reduced ejection fraction had significantly lower cardiovascular mortality (0; 2.7 and 12.5%, $p > 0.05$) and the number of hospitalization for acutely decompensated heart failure (0; 2,7 and 6.2%).

Conclusion. Clinical characteristics of heart failure patients with mid-range and heart failure patients with reduced ejection fraction are similar but significantly different from those in the group of patients with preserved ejection fraction; echocardiographic data in heart failure patients with mid-range ejection fraction is intermediate between those in patients with reduced ejection fraction and patients with preserved ejection fraction; the prognosis for all cardiovascular events did not differ significantly in the groups depending on the left ventricular ejection fraction.

Keywords: chronic heart failure, left ventricular ejection fraction, cardiovascular outcomes.

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Background. The category of patients with a mid-range left ventricular ejection fraction (LVEF; 40–49%) was identified for the first time in the 2016 European guidelines for the management of patients with heart failure (HF); however, since then, there has been a continuing debate on the extent of practicability of introducing a new category of patients with chronic heart failure (CHF) and whether significant differences exist in clinical manifestations and prognosis.

The fundamental terminology used to describe HF is based on the value of LVEF. According to 2012 recommendations, the normal LVEF level was defined as 50% or higher, and the reduced level was lower than 35%–40%. Patients with EF of 40%–49% could be assigned to both groups 1 and 2. Previous clinical studies, namely, CHARM, TOPCAT, VALLIANT, and PEP-CHF, presented data on CHF with an LVEF range of 40%–49%, which, according to the 2016 ESC classification, can be interpreted as CHF with mid-range LVEF (HFmrEF) [1].

To date, accumulating data attempted to clarify the clinical characteristics and survival rate of patients with HFmrEF. In 2016, Tsao et al. examined 10,270 patients around aged 60 years. Of these patients, more than 55% was recognized as normal LVEF, while 50%–55% was the mid-range LVEF. In that study, the survival rate of patients with LVEF of 50%–55% was worse than that in patients with LVEF of >55% [2].

As a rule, HF is stratified based on a number of key criteria, namely, etiology, demography, LVEF, presence of comorbid pathology, and characteristics of the response to drug therapy. Analysis of the efficiency of drug therapy in patients with CHF should take into account the LVEF range, which, apparently, is currently used as the basis for a number of clinical studies and will expand significantly possible reasons of the effective use of various therapeutic methods and drugs in patients with this pathology [3, 4].

The study aimed to analyze the clinical and echocardiographic characteristics as well as prognosis in patients with HFmrEF.

Materials and methods of research. The study included 76 patients with a stable course of CHF grade I–IV (no CHF decompensation within 1 month), aged 66.1 ± 10.4 years, and had an average CHF duration of 8.5 years. The inclusion criteria were having signed an informed consent form, age ≥18 years, and presence of stable CHF. The exclusion criteria were refusal to sign an informed consent form for participation in the study and presence of cognitive impairment, malignant tumors, renal artery stenosis, and myocardial infarction that occurred less than 30 days.

HF was verified according to the clinical guidelines of the Russian Cardiological Society, Society of Heart Failure Specialists, and Russian national medical society of physicians "Heart failure: chronic (CHF) and acute decompensated (ADHF)."

The quality of life of all patients was assessed according to the Minnesota Patient Questionnaire. Clinical condition was assessed according to a special scale for assessing the clinical condition of a patient with CHF (SACC), and electrocardiography and echocardiography were performed.

Echocardiography was performed to analyze left atrial dimension, end-systolic dimension, end-diastolic dimension, right ventricular dimension, pulmonary artery systolic pressure, left ventricular myocardium mass index, left ventricular myocardium mass, left ventricular posterior wall thickness, and interventricular septum thickness.

Levels of hemoglobin, bilirubin, creatinine, and blood glucose and glomerular filtration rate were assessed. To evaluate the prognosis, a telephone survey of all patients was performed 1 year after inclusion in the study. Follow-up endpoints were cardiovascular mortality, myocardial infarction, cerebral stroke, acute decompensation of CHF, and thrombotic complications.

All patients were distributed into groups of CHF with preserved LVEF (HFpEF), HFmrEF, and CHF with reduced LVEF (HFrEF).

Statistical data processing was performed using parametric and nonparametric analysis in the IBM SPSS Statistics 20 software. Data were analyzed after testing the sample for normal distribution using the Shapiro–Wilk test, as well as kurtosis and asymmetry indices. In quantitative indicators with normal distribution, the arithmetic mean values and standard deviations ($M \pm \sigma$) were calculated. Aggregates of quantitative indicators with non-normal distribution were presented as median with lower and upper quartiles (Me [Q_1; Q_3]). Kruskal–Wallis test with the Dunn post-hoc test was performed for comparison. Indicators measured in the nominal scale were compared using the Pearson χ^2 test: Yates correction was used in less than 10 cases, and Fisher's exact test was in less than 5 cases. The critical level of significance corresponded to $p = 0.05$.

The study protocol was approved by the local ethics committee of the Kazan State Medical University of the Ministry of Health of the Russian Federation (Protocol No. 10 of 12/23/2014, b No. 1 with addition of 01/25/2017).

The study was performed as an open-label, prospective, randomized, controlled, and comparative study.

Results. The main etiology of HF in most patients was ischemic heart disease, while others also

Table 1. Clinical characteristics of patients with chronic heart failure (CHF) according to the value of the left ventricular ejection fraction (EF)

Parameters	CHF			p
	with reduced EF (n = 16)	with mid-range EF (n = 18)	with preserved EF (n = 42)	
Ischemic heart disease, %	6.25	5.55	45.2	$p_{1–2}$=0.727 $p_{2–3}$=0.0026 $p_{1–3}$=0.0053
Arterial hypertension, %	6.25	5.55	14.3	$p_{1–2}$=0.727 $p_{2–3}$=0.663 $p_{1–3}$=0.660
Ischemic heart disease + arterial hypertension, %	87.5	88.9	40.5	$p_{1–2}$=0.652 $p_{2–3}$=0.0006 $p_{1–3}$=0.0025
Men/women,%	62.5/37.5	61.1/38.9	47.6/52.4	$p_{1–2}$=0.786 $p_{2–3}$=0.734 $p_{1–3}$=0.691
Age (M ± σ), years	70.4±11.1	70.0±11.7	62.7±8.4	$p_{1–2}$=0.992 $p_{2–3}$=0.040 $p_{1–3}$=0.036
CHF grade I–II, %	12.5	22.2	59.5	$p_{1–2}$=0.386 $p_{2–3}$=0.007 $p_{1–3}$<0.001
CHF grade III–IV	87.5	77.8	40.5	$p_{1–2}$=0.386 $p_{2–3}$=0.007 $p_{1–3}$<0.001
Walk test (Me [Q_1; Q_3]), m	132.5 [105; 176]	182.5 [110; 272]	350 [250; 400]	$p_{1–2}$=0.162 $p_{2–3}$<0.001 $p_{1–3}$<0.001
SACC (M±σ), points	7.7±2.8	7.2±2.19	5.4±2.8	$p_{1–2}$=0.863 $p_{2–3}$=0.089 $p_{1–3}$=0.023
Quality of life (M±σ), points	47.0±19.2	40.0±20.5	31.2±19.4	$p_{1–2}$=0.59 $p_{2–3}$=0.309 $p_{1–3}$=0.029
CHF duration (M±σ), years	11.8±5.7	9.83±6.1	6.5±3.6	$p_{1–2}$=0.488 $p_{2–3}$=0.06 $p_{1–3}$=0.002

Note: *$p_{1–2}$, comparison of patients with reduced EF and mid-range EF; $p_{2–3,}$ comparison of patients with mid-range EF and preserved EF; $p_{1–3,}$ comparison of patients with reduced EF and preserved EF; SACC, scale for assessing the clinical condition of a patient with chronic heart failure.

had arterial hypertension (61.8% of cases). Arterial hypertension and ischemic heart disease caused CHF in 10.5% and 27.7% of the cases, respectively. When all patients with CHF were distributed into groups according to the LVEF value, differences in etiology were found between the HFmrEF group and HFpEF group (p = 0.0026), as well as between HFrEF and HFpEF groups (p = 0.0053; Table 1).

The ratio of men and women in all three groups was not different. Differences in age were found between the HFmrEF group and HFpEF group, which patients were significantly younger. The structure of the groups according to the CHF grade was comparable in the HFrEF and HFmrEF groups when compared with the HFpEF group that had the same ratio of patients having grades I–II and III–IV. Data were confirmed by the results of the walking test in the HFmrEF and HFrEF groups, which were significantly different from the parameters in the HFpEF group.

Using the SACC, symptoms and signs of HF were more severe in the HFrEF group than in the HFpEF group, similar to the results on HF duration. In a detailed analysis of symptoms and signs of HF, dyspnea was registered in 50% of the cases in the HFmrEF and HFpEF groups (Table 2).

In the HFmrEF group, 66.7%, 22.2%, and 27.8% of the patients were found to have lower-limb

Table 2. Symptoms/signs of patients with chronic heart failure using SACC (%)

Symptoms/signs	Left ventricular ejection fraction			p
	Reduced (n = 16)	Mid-range (n = 18)	Preserved (n = 42)	
Dyspnea	75.0	50.0	50.0	$p_{1–2}$=0.252 $p_{2–3}$=0.778 $p_{1–3}$=0.155
Lower limb edema/swelling	100	66.7	50.0	$p_{1–2}$=0.019 $p_{2–3}$=0.364 $p_{1–3}$=0.0002
Moist rales in the lungs	100	22.2	28.6	$p_{1–2}$=0.0001 $p_{2–3}$=0.456 $p_{1–3}$=0.0001
Raised cephalic pole	50.0	27.8	11.9	$p_{1–2}$=0.328 $p_{2–3}$=0.256 $p_{1–3}$=0.005
Change in body weight	75.0	27.8	14.3	$p_{1–2}$=0.014 $p_{2–3}$=0.357 $p_{1–3}$=0.0001
Cervical vein swelling	12.5	0	0	$p_{1–2}$=0.039 $p_{1–3}$=0.039
Cantering rhythm	75.0	16.7	11.9	$p_{1–2}$=0.0014 $p_{2–3}$=0.686 $p_{1–3}$=0.0001
Hepatomegaly	50.0	27.8	14.3	$p_{1–2}$=0.328 $p_{2–3}$=0.382 $p_{1–3}$=0.012
Systolic blood pressure <100 mmHg	0	0	0	—
Interruptions in the cardiac function	12.5	50	23.8	$p_{1–2}$=0.029 $p_{2–3}$=0.089 $p_{1–3}$=0.484

Note: $p_{1–2}$, comparison of patients with reduced ejection fraction (EF) and mid-range EF; $p_{2–3}$, comparison of patients with mid-range EF and preserved EF; $p_{1–3}$, comparison of patients with reduced EF and preserved EF; SACC, scale for assessing the clinical condition of a patient with chronic heart failure.

edema, rales in the lower parts of the lungs during auscultation, and a forced position with a raised cephalic pole, respectively. None of the patients with HFmrEF or HFpEF showed cervical vein swelling. If a triple heart rate (cantering rhythm) was heard in 75% of the patients with HFrEF, then in HFmrEF, as in HFpEF, it was significantly less common (16.7% and 11.9%, respectively).

Hepatomegaly was found in half of the HFrEF group, in 27.8% of the HFmrEF group, and in 14.3% of the HFpEF group.

Since HF was stable beyond decompensation in all patients during study enrollment, no low systolic blood pressure was recorded. Interruptions in the cardiac function were registered more often in the HFmrEF group than in the other groups (50%).

Echocardiography with the analysis of the main indicators was performed to all patients to verify CHF (Table 3).

Most echocardiographic parameters (end-systolic dimension, end-diastolic dimension, left atrial dimension, and LVEF) were significantly different among the groups depending on the range of LVEF. In the HFrEF group, the end-systolic dimension, end-diastolic dimension, and left atrial dimension were significantly higher, while the LVEF was lower. In the HFmrEF group, the results were an average between the results of the HFpEF and HFrEF groups. The right ventricular dimension was significantly different between the HFrEF group and HFpEF group ($p < 0.001$), as well as between the HFmrEF group and HFrEF group ($p = 0.003$). The systolic pressure in the pulmonary artery was significantly different between groups 1 and 2, as well as between groups 1 and 3.

The left ventricular myocardial mass index in male patients with HFrEF and HFmrEF was higher than that in male patients with HFpEF. The left ventricular myocardial mass index in female patients with CHF was also higher in those with HFrEF and HFmrEF than in those with HFpEF.

Table 3. Echocardiographic findings in patients with chronic heart failure

Parameters	Reference values	Left ventricular ejection fraction			p
		Reduced (n = 16)	Mid-range (n = 18)	Preserved (n = 42)	
Left atrial dimension, cm	2.3–3.7	4.49±0.52	4.09±0.29	3.67±0.38	p_{1-2}=0.019 p_{2-3}=0.002 p_{1-3} <0.001
Right ventricular dimension, cm	2.5–3.0	3.24±0.81	2.69±0.21	2.56±0.26	p_{1-2}=0.003 p_{2-3}=0.555 p_{1-3} <0.001
End-systolic dimension, cm	2.3–3.6	5.26±0.99	4.01±0.69	3.28±0.47	p_{1-2} <0.001 p_{2-3}=0.002 p_{1-3} <0.001
End-diastolic dimension, cm	3.7–5.6	6.11±0.99	5.22±0.69	4.72±0.55	p_{1-2}=0.002 p_{2-3}=0.059 p_{1-3} <0.001
Pulmonary artery systolic pressure, mm Hg	23–26	58.44±22.53	36.81±14.13	26.50±12.40	p_{1-2}=0.001 p_{2-3}=0.083 p_{1-3} <0.001
Left ventricular EF, %	50–70	28.75±7.32	46.00±2.93	57.93±3.92	p_{1-2} <0.001 p_{2-3} <0.001 p_{1-3} <0.001
Left ventricular posterior wall thickness, cm	0.60–1.10	1.19±0.19	1.13±0.13	1.06±0.18	p_{1-2}=0.65 p_{2-3}=0.342 p_{1-3}=0.04
Interventricular septum thickness, cm	0.60–1.10	1.26±0.25	1.18±0.23	1.15±0.22	p_{1-2}=0.673 p_{2-3}=0.435 p_{1-3}=0.123
Left ventricular myocardium mass, g/m^2	67–224	406.06±116.65	302.00±66.4	235.38±77.04	p_{1-2}=0.004 p_{2-3}=0.034 p_{1-3} <0.001
Left ventricular myocardium mass index, men, g/m^2	71–94	213.10±61.92	157.90±26.67	145.25±40.39	p_{1-2}=0.029 p_{2-3}=0.761 p_{1-3}=0.001
Left ventricular myocardium mass index, women, g/m^2	71–89	215.67±65.24	162.67±47.75	104.05±28.16	p_{1-2}=0.087 p_{2-3}=0.012 p_{1-3} <0.001

Note: p_{1-2}, comparison of patients with reduced ejection fraction (EF) and mid-range EF; p_{2-3}, comparison of patients with mid-range EF and preserved EF; p_{1-3}, comparison of patients with reduced EF and preserved EF.

The prognosis of patients with CHF was assessed according to the frequency of cardiovascular events by telephone interviews at 1 year after inclusion in the study. Data were available for 70 (92.1%) of 76 patients. In the comparison using the Fisher test (small number of cases), a decrease in EF in CHF is accompanied by a tendency to an increase in the frequency of achieving the endpoints (Table 4).

The combined endpoint was determined, which indicated all cardiovascular events, including non-fatal ones (i.e., myocardial infarction, stroke, acute decompensation of CHF, and thrombotic complications). The combined endpoint (all cardiovascular events, including non-fatal events) was achieved by 14.3% of all patients with CHF. HFmrEF is the intermediate between HFpEF and HFrEF in terms of the frequency of all cardiovascular events (17.6%, 10.8%, and 18.8%, respectively), nonfatal myocardial infarction (5.9%, 0%, and 6.2%, respectively), and thrombotic complications (5.9%, 5.4%, and 6.2%, respectively). Cardiovascular mortality in HFmrEF was lower than that in HFpEF and HFrEF groups (0%, 2.7%, and 12.5%, respectively), as was the frequency of acute decompensation of HF (0%, 2.7%, and 6.2%, respectively).

Discussion. HFmrEF was found in 23.7% of all patients with HF, which corresponds to the data reported by Solomon and Lam (2014), according to which HFmrEF is registered in 10%–20% of patients with HF [5]. Moreover, more patients with HFrEF (21.1%) were identified in the present study

Table 4. Frequency of reaching the endpoints depending on the left ventricular ejection fraction (%)

Events	Left ventricular ejection fraction			p
	Reduced (n = 16)	Mid-range (n = 17)	Preserved (n = 37)	
Cardiovascular mortality, including non-fatal events	12.5	0.0	2.7	p_{1-2}=0.227 p_{2-3}=0.690 p_{1-3}=0.206
Myocardial infarction	6.2	5.9	0.0	p_{1-2}=0.740 p_{2-3}=0.314 p_{1-3}=0.301
Cerebral stroke	0.0	5.9	2.7	p_{1-2}=0.515 p_{2-3}=0.534 p_{1-3}=0.698
Acute decompensation of heart failure	6.2	0.0	2.7	p_{1-2}=0.484 p_{2-3}=0.685 p_{1-3}=0.516
Thrombotic complications	6.2	5.9	5.4	p_{1-2}=0.742 p_{2-3}=0.686 p_{1-3}=0.668
All cardiovascular events (fatal and non-fatal)	18.8	17.6	10.8	p_{1-2}=0.641 p_{2-3}=0.665 p_{1-3}=0.352

Note: p_{1-2}, comparison of patients with reduced ejection fraction (EF) and mid-range EF; p_{2-3}, comparison of patients with mid-range EF and preserved EF; p_{1-3}, comparison of patients with reduced EF and preserved EF.

than in the study by Kapoor et al. (2016) in which 49% of the patients had HFrEF. The main reason is the inclusion of patients with stable CHF in the present study [6].

The results reveal that patients with HFmrEF and HFrEF have more common clinical presentations than patients with HFpEF, including gender distribution, age, CHF grade, testing by SACC, and HF duration. The same data were obtained in the CHARM study [7]. The TIME-CHF study revealed that patients with HFmrEF represent an intermediate position in terms of age, proportion of women, dyspnea, peripheral edema, and rales in the lungs. Hepatomegaly and asthenia were detected least often in the HFmrEF group [8]. In the CHART-2 Register, patients with HFmrEF had intermediate position between patients with HFrEF and HFpEF in terms of clinical characteristics [9].

As regards echocardiographic parameters, the main parameters (end diastolic dimension, end systolic dimension, left atrium dimension, right ventricular dimension, systolic pressure in the pulmonary artery, left ventricular myocardial mass, and left ventricular myocardial mass index) were significantly different between patients with HFmrEF and patients with HFrEF and HFpEF, ranking intermediate. Saikhan et al. analyzed 110 patients with HFpEF and 61 patients with HFmrEF and noted that left atrial function was more impaired in patients with HFmrEF, which is consistent with the data of the present study [10].

Patients with different ranges of LVEF have distinctive traits in terms of the onset of cardiovascular events within the first year. Our findings that events such as cardiovascular mortality and primary endpoints occur more often in patients with reduced LVEF do not contradict the data of Solomon et al. who revealed that the incidence of cardiovascular mortality increases in patients with reduced LVEF. In CHF with LVEF < 50%, the rate of cardiovascular mortality was 4.1%. However, according to this study, the frequency (4.9%) of CHF decompensation was higher in patients with LVEF >60% [11].

Our data confirm the results of previous studies that the frequency of cardiovascular events in HFmrEF is higher than that in HFpEF. There is a trend towards an increase in overall mortality among patients with HFmrEF compared with patients with HFpEF (p = 0.02) [12].

The SAVE study found a pattern of increase in mortality with a decrease in glomerular filtration rate [13]. Patients with reduced LVEF were considered at high risk of repeated hospitalizations due to CHF decompensation according to the GWTG register after 5 years of follow-up [14].

HFrEF, HFmrEF, and HFpEF are considered different phenotypes of the same syndrome, which is eventually accompanied by a decrease in cardiac output and appearance of congestive signs, with a poor prognosis for cardiovascular events and hospitalizations due to decompensation of CHF [15].

The proposed selection of a group of patients with HFmrEF enables to consider them from the standpoint of a single pathophysiological content and suggest some special aspects in the efficiency of drug therapy and prognosis, as noted in the present study.

Study limitation. The authors acknowledge that data interpretation may have been influenced by the small sample size when patients were grouped according to the LVEF range. Thus, the cardiovascular mortality of patients with HFmrEF was lower to some extent than that of patients with HFpEF and HFrEF, which somewhat contradicts the data of a number of randomized clinical studies.

CONCLUSIONS

1. The clinical characteristics of patients with HFmrEF, such as etiological structure, age, gender, quality of life according to the Minnesota questionnaire, SACC, 6-minute walk test, as well as distribution by CHF grades, were not different from those in patients with HFrEF, but were significantly different from those in patients with HFpEF.

2. Symptoms and signs of CHF (i.e., presence of edema and change in body weight) in patients with HFmrEF were not different from those in patients with a reduced LVEF.

3. Echocardiographic findings from patients with HFmrEF are in the middle position when compared with patients with HFrEF and HFpEF.

4. The prognosis in patients with HFmrEF is not significantly different from those in other groups, being in an intermediate position in the frequency of achieving the combined endpoint.

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REFERENCES

1. Mareev V.Yu., Fomin I.V., Ageev F.T., Arutyunov G.P., Begrambekova Yu.L., Belenkov Yu.N., Vasyuk Yu.A., Galyavich A.S., Garganeeva A.A., Gendlin G.E., Gilyarevsky S.R., Glezer M.G., Drapkina O.M., Duplyakov D.V., Kobalava Zh.D., Koziolova N.A., Lopatin Yu.M., Mareev Yu.V., Moiseev V.S., Nedoshivin A.O., Perepech N.B., Sitnikova M.Yu., Skibitsky V.V., Tarlovskaya E.N, Chestnikova A.I., Shlyakhto E.V. Chronic heart failure (CHF). *Zhurnal serdechnaya nedostatochnost'*. 2017; 18 (1): 3–40. (In Russ.) DOI: 10.18087/rhfj.2017.1.2346.

2. Tsao C.W., Lyass A., Larson M.G., Cheng S., Lam C.S., Aragam J.R., Benjamin E.J., Vasan R.S. Prognosis of adults with borderline left ventricular ejection fraction. *JACC Heart Fail*. 2016; 4 (6): 502–510. DOI: 10.1016/j.jchf.2016.03.003.

3. Filippatos G., Khan S.S., Ambrosy A.P., Cleland G.F., Collins S.P., Lam S.P., Angermann C.E., Ertl G., Dahlstrom U., Hu D., Dickstein K., Perrone S.V., Ghadanfar M., Bermann G., Noe A., Schweizer A., Maier T., Gheorghiade M. International REgistry to assess medical Practice with Ongitudinal obseRvation for Treatment of Heart Failure (REPORT-HF): rationale for and design of a global registry. *Eur. J. Heart Fail*. 2015; 17: 527–533. DOI: 10.1002/ejhf.262.

4. Solomon S.D., Anavekar N., Skali H., McMurray J.V., Swedberg K., Yusuf S., Granger C.B., Michelson E.L., Wang D., Pocock S., Pfeffer M.A. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation*. 2005; 112: 3738–3744. DOI: 10.1161/CIRCULATIONAHA.105.561423.

5. Lam C.S., Solomon S.D. The middle child in heart failure: heart failure with mid-range ejection fraction (40–50%). *Eur. J. Heart Fail*. 2014; 16: 1049–1055. DOI: 10.1002/ejhf.159.

6. Kapoor J.R., Kapoor R., Ju C., Heidenreich P.A., Heidenreich P.A., Eapen Z.J., Hernandez A.F., Butler J., Yancy C.W., Fonarow C.C. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. *JACC Heart Fail*. 2016; 4: 464–472. DOI: 10.1016/j.jchf.2016.02.017.

7. Lund L.H., Claggett B., Liu J. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum *Eur. J. Heart Fail*. 2018; 20: 1230–1239. DOI: 10.1002/ejhf.1149.

8. Rickenbacher P., Kaufmann B.A., Maeder M.T., Bernheim A., Goetschalckx K., Pfister O., Pfisterer M., Brunner-La Rocca H.P. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the trial of intensified versus standard medical therapy in elderly patients with congestive heart failure (TIME-CHF). *Eur. J. Heart Fail*. 2017; 19 (12): 1586–1596. DOI: 10.1002/ejhf.798.

9. Tsuji K., Sakata Y., Nochioka K., Takeshi Yamauchi M.M., Takeo Onose, Abe R., Oikawa T., Kasahara S., Sato M., Shiroto T., Takahashi J., Miyata S., Shimokawa H. Characterization of heart failure patients with mid-range left ventricular ejection fraction — a report from the CHART-2 study. *Eur. J. Heart Fail*. 2017; 19 (10): 1258–1269. DOI: 10.1002/ejhf.807.

10. Saikhan L.A., Hughes A.D., Chung W.S., Alsharqi M., Nihoyannopoulos P. Left atrial function in heart failure with mid-range ejection fraction differs from that of heart failure with preserved ejection fraction: a 2D speckle-tracking echocardiographic study. *Eur. Heart J. Cardiovasc. Imaging.* 2019; 20: 279–290. DOI: 10.1093/ehjci/jey171.

11. Solomon S.D., Claggett B., Lewis E.F., Desai A., Anand I., Sweitzer N.K., O'Meara E., Shah S.J., McKinlay S., Fleg J.L., Sopko G., Pitt B., Pfeffer M.A. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur. Heart J.* 2016; 37 (5): 455–462. DOI: 10.1093/eurheartj/ehv464.

12. Bhambhani V., Kizer J.R., Lima A.C., van der Harst P., Bahrami H., Nayor M., de Filippi C.R., Enserro D., Blaha M.J., Cushman M., Wang T.J., Gansevoort R.T., Fox C.S., Gaggin H.K., Kop W.J., Liu K., Vasan R.S., Psaty B.M., Lee D.S., Brouwers F.P., Hillege H.L., Bartz T.M., Benjamin E.J., Chan C., Allison M., Gardin J.M., Januzzi J.L.Jr., Levy D., Herrington D.M., van Gilst W.H,

Bertoni A.G., Larson M.G., de Boer R.A., Gottdiener J.S., Shah S.J., Ho J.E. Predictors and outcomes of heart failure with mid-range ejection fraction. *Eur. J. Heart Fail.* 2018; 20 (4): 651–659. DOI: 10.1002/ejhf.1091.

13. Tokmakova M.P., Skali H., Kenchaiah S., Braunwald E., Rouleau J.L., Packer M., Chertow G.M., Moyé L.A., Pfeffer M.A., Solomon S.D. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: the survival and ventricular enlargement (SAVE) stud. *Circulation*. 2004; 110: 3667–3673. DOI: 10.1161/01.CIR.0000149806.01354.

14. Shah K.S., Xu H., Matsouaka R.A., Bhatt D.L., Heidenreich P.A., Hernandez A.F., Devore A.D., Yancy C.W., Fonarow C.C. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J. Am. Coll. Cardiol.* 2017; 70 (20): 2476–2486. DOI: 10.1016/j.jacc.2017.08.074.

15. Shavarova E.K., Babaeva L.A., Padaryan S.S., Lukina O.I., Milto A.S., Soseliya N.N. Chronic heart failure: clinical guidelines and real clinical practice. *Rational pharmacotherapy in cardiology.* 2016; 12 (6): 631–637. (In Russ.) DOI: 10.20996/1819-6446-2016-12-6-631-637.