GENDER AND AGE ASPECTS OF CHRONIC HEART FAILURE: CLINICAL AND GENETIC STUDY

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Abstract. Increase in the life expectancy of the population is associated with a tendency of aging in patients with chronic heart failure (CHF). Gender, age and genetic differences of the individual risk factors are still discussed in the aspect of influence on the heart failure clinical phenotype. The study aimed to identify the gender and age differences of chronic heart failure clinical characteristics in terms of the ZBTB17 gene (rs10927875) polymorphism. Materials and methods. A total of 351 patients with CHF of ischemic etiology of both genders were examined. The average age of men was 65.3 ± 9.9, women − 69.7 ± 9.61 years. Results and conclusions: CHF of ischemic etiology in the absence of differences in the burdened family history, previous myocardial infarction (MI) observed mainly in middle-aged and elderly men and elderly and senile women. Significant gender differences in comorbidities were revealed: in 40% of men, CHF was associated with chronic obstructive pulmonary disease (COPD), in 47.3% of women – with chronic kidney disease (CKD) and in 32.2% – with diabetes mellitus (DM). The distribution of rs10927875 polymorphism ZBTB17 genotypes were corresponded to the Hardy-Weinberg equilibrium ($\chi^2 = 0.272$, $p = 0.873$). CC genotype in men was associated with reduced left ventricular ejection fraction (LVEF). CT genotype in women associated with CHF FC III and IV due to the frequent indications in the past on myocardial infarction, concomitant DM, obesity and hypercholesterolemia. The CT genotype rs10927875 was characterized by a frequent combination of CHF with COPD in men and CKD and DM in women.

Keywords: chronic heart failure, rs10927875 polymorphism of the ZBTB17 gene.

List of Abbreviations

CHF – chronic heart failure
MI – diabetes mellitus
CKD – chronic kidney disease
COPD – chronic obstructive pulmonary disease
LVEF – left ventricular ejection fraction
FC – functional class
CHD – coronary heart disease
6MTH – 6-minute walk test
GFR – glomerular filtration rate
CAS – clinical assessment scale
FEV1 – forced expiratory volume in 1 second
FVC – functional vital capacity

Introduction

The prevalence of chronic heart failure (CHF) in Russia is steadily increasing and is closely associated with demographic changes, including the aging of the population. In the Russian Federation, 65.5% of CHF cases are registered at the age of 6–79 years (Mareev *et al.*, 2018). It was shown in I-PRESERVE Study that the proportion of women among all patients with CHF was about 21% (Lam *et al.*, 2012). It is well known that after age 65 years the female/male ratio approaches 3: 1, in other words is noted the tendency of increasing women amount after 65 years (Belenkov, 2006; Bui *et al.*, 2011). The past 20 years showed gender differences in the rate of increase in the incidence of CHF: in women – 9%, in men – 6%. F. Rodriguez et al. showed a high rate of CHF decompensation hospitalizations in women in comparison with men (Rodriguez *et al.*, 2013). Patient gender and age were recognized as important determinants in the development of cardiomyocyte hypertrophy and apoptosis (Patrizio & Marano, 2016). L. Kiczak (2015) demonstrated the slow development of cardiomyocyte apoptosis and left ventricular (LV) remodeling in women compared with men (Kiczak *et al.*, 2015). An increase in the size and decrease in the number of cardiomyocytes

in men with aging (age-related cardiomyopathy) was reported in the absence of such changes in women due to the protective effect of estrogens (Keller & Howlett, 2016; Lista *et al.*, 2011).

The search for genetic markers of heart failure remains one of the promising areas of modern cardiology and focuses on genes encoding components of the renin-angiotensin-aldosterone system, β-adrenergic receptors. Analysis of GWAS (genome-wide association study) results indicated the rs10927875 polymorphism ZBTB17 gene's association with heart failure, mainly due to cardiomyopathy. It is known that the main function of the ZBTB17 gene is to protect cardiomyocytes from apoptosis by modulating the pathways of myocardial hypertrophy (Buyandelger *et al.*, 2015; Knöll *et al.*, 2011). Genome analysis in CHF patients (n = 488010) of the British Biobank revealed association rs10927875 polymorphism of the ZBTB17 gene with systolic (OR = 0.20; $p = 1.12 \times 10^{-5}$) and diastolic blood pressure (OR = 0.09; $p = 5.58 \times 10^{-4}$) and arterial hypertension (OR = 1.02; $p = 1.02 \times 10^{-4}$). The authors demonstrated, that this polymorphism often observed in cases of decreased left ventricular ejection fraction (OR = –0.42%; $p = 1.08 \times 10^{-3}$) and increased LV end-systolic volume (OR = 1.31 ml; $p = 6.49 \times 10^{-4}$). These relationships characterized people without severe clinical CHF manifestations (Aragam *et al.*, 2019).

Thus, recent studies demonstrated gender differences in the CHF clinical picture, risk factors, and prognosis (Lam, 2012). It seems promising to study the rs10927875 polymorphism of the ZBTB17 gene, which expresses in cardiomyocytes and is involved in apoptosis in patients with ischemic heart failure of both genders.

The aim of this study was to identify gender and age characteristics of chronic heart failure clinical phenotypes in terms of ZBTB17 gene polymorphism (rs10927875).

Materials and Methods

The study group (n = 351) included patients with stable heart failure of both genders. Males accounted for 57% (n = 202), age – 65.3 ± ± 9.9 years; female – 43% (n = 149), age – 69.7 ± 9.61 years. All patients had coronary heart disease (CHD), in combination with arterial hypertension 77.3% of men and 70.7 % of women. Male and female patients were comparable in CHF FC: 34% of men and 32.2% of women belonged to FC I-II, 66% and 67.8% − to FC III-I. There was no difference between men and women in the results of the 6-minute walk test (6MTH) according to tolerance to physical activity (237.0 ± 109.0 m and 239.0 ± ± 113.0 m, respectively).

The local ethics committee of the Kazan State Medical University approved the study. Our study was performed according to the Good clinical practice standard. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Heart failure was verified in accordance with the Russian clinical guidelines for heart failure (2018) (Mareev *et al.*, 2018). Testing was carried out by clinical assessment scale (CAS). Echocardiography: glomerular filtration rate (GFR) was determined by CKD-EPI formula, chronic kidney disease (CKD) by national guidelines (2013) (Smirnov *et al.*, 2012). In COPD, obstructive disorders were diagnosed with FEV1 < 80%, FEV1/FVC < 70%, according to the Federal Clinical Guidelines (Chuchalin *et al.*, 2014). Genotyping the rs10927875 polymorphism ZBTB17 gene was done by real-time polymerase chain reaction; whole blood was the material for the isolation of deoxyribonucleic acid.

In statistical analyses, we used the standard Jamovi software package (Version 1.2.2, 2020). Descriptive statistics were presented depending on the type of distribution in the form of mean M and standard deviation SD or median (Me), 25–75‰. The Mann-Whitney U test was used to test for differences between the two compared paired samples. Qualitative indicators were assessed according to the $\chi 2$ test and Fisher's exact test (with the number of observations less than 5). To assess the associations, the odds ratio (OR) was calculated with the determina-

tion of the 95% confidence interval (CI). Differences between groups were considered statistically significant at $p < 0.05$.

Results

In the initial stage, a comparison of men and women with CHF clinical characteristics without considering the genotype was made. The distribution of males and females by age showed differences: in the middle-aged group (under 60 patients), there were more males than females (31.9% and 16%). The elderly group (60–75 years) we did not find gender differences (51.5% and 52%); in the group over 75, there were more women than men (16.7% and 32%), ($\chi^2 = 17, 4$, p <0.001).

Male and female patients were comparable in terms of family history of cardiovascular diseases (40.3% and 44%, p = 0.484); the frequency of myocardial infarction in the past (41.2% and 45.5%, p = 0.097); the presence of atrial fibrillation (AF), (14.1% and 12%, $p = 0.567$). Among men were more often observed smoking (31.1% and 5.3%, $\chi^2 = 35.6$, $p = 0.001$), combination of CHF with COPD (41.7% and 23.3%, $p = 0.0017$, OR = 2.079, CI = 1.309 - 3.302). In women, CHF were often combination with diabetes mellitus (25.9% and 16%, $\chi^2 = 21.1$, $p < 0.001$) and CKD (27.2% and 47.3%, $p = 0.0001$, OR = 0, 4214, CI = 0.27 – – 0.6577). The mean value of LVEF in women exceeded that in men (54.5 ± 8.18% and 50.1 ± ± 11.3%, $p = 0.001$). Heart failure with preserved LVEF (CHFpEF) was detected in 63.3% of men and 76.8% of women; CHF with midrange LVEF (CHFmEF) – in 21.1% and 16%, CHF with low EF - in 15.7% and 7.2% ($\chi^2 = 5.7$, $p = 0.016$, OR = 2.356, CI = 1.164 – – 5.038).

The distribution by genotypes of the rs10927875 polymorphism did not reveal differences between men and women: CC – 42.9% and 42.2%, CT – 45.8% and 46.1%, TT – 11.3% and 11.7%, which is consistent with the Hardy – Weiberg law ($\chi^2 = 0.272$, $p = 0.873$).

At the next study stage, the clinical characteristics were assessed depending on the gender of patients with CC-, CT- and TT-genotypes. A comparison of CC genotype in men and women is presented in Table 1. Men of this genotype were characterized by a younger age in comparison with women (65.1 ± 9.19 years and 69.4 ± 10.3 years, $p = 0.02$). The following differences were obtained: 35% of men and only 11.9% of women of the CC-genotype were under 60 years old; in the group over 75, there were 2.8 times more women than men ($\chi^2 = 16.1$, $p < 0.001$). Men had a higher smoking frequency (25.3% and 9.3%, $\chi^2 = 21.7$, $p = 0.021$) and a lower total blood cholesterol level (5.25 ± 1.45 and 5.73 ± 1.56 mmol / l, $p = 0.024$). The comparison of CKD and COPD prevalence in patients of the CC-genotype did not reveal gender differences. There were no gender differences in belonging to CHF FC. However, LVEF in men did not exceed on average 50.1 ± 10.5%, while in women it was 54.8 ± 8.26% ($p = 0.016$).

Gender differences in CT genotype patients were more different (Table 2). Men of the CT genotype were younger than women (65.0 ± ± 10.3 years and 71.1 ± 9.37 years, $p < 0.001$): in the middle-aged group (< 60 years) more men than women (35 % and 11.9%), no gender differences in the 60–75 age group (51.2% and 49.2%), over 75 years – more women than men (39% and 13.8%, $\chi^2 = 16.1$, $p < 0.001$). In men CT genotype MI was observed less often than in women (31.6% and 54.4%, $\chi^2 = 6.4$, $p = 0.011$). Heart failure of III-IV FC was detected in 76.3% of women and 63.8% of men ($p = 0.033$). The assessment of clinical symptoms revealed higher values in women – 7.0 ± ± 2.46, than in men – 5.77 ± 2.62 points, ($p = 0.004$). The body mass index of women exceeded that of men (30.4 ± 5.96 kg/m^2 and 27.8 ± 5.17 kg/m^2, $p = 0.007$). Along with concomitant CHF pathologies, a frequent combination with COPD was revealed in men – 37.5%, in women - 13.6% ($\chi^2 = 9.798$, $p = 0.001$, OR = = 3.79, CI = 1.618 – 9.59), which could be associated with a higher smoking frequency in men – 33.8% and 1.7% in women ($\chi^2 = 21.7$, $p < 0.001$). Women with CHF more likely to have chronic kidney disease ($\chi^2 = 17.89$, $p = 0.00002$, OR = 0.21, CI = 0.1015 – 0.4486) and diabetes mellitus ($\chi^2 = 17.6$, $p = 0.001$ OR = = 0.1489, CI = 0.05104 – 0.3887). The average

Table 1

Clinical features in CHF patients CC-genotype

Parameter	Men *n* = 75	Women *n* = 54	*P/p*
Age, M± SD	65,1±9,19	69,4±10,3	*P* = 0,02
< 60 years old, %	35%	11,9%	*P* = 0,001
60–75 years old, %	51,2%	49,2%	
> 75 years old, %	13,8%	39%	
COPD, %	36%	25,9%	*P* = 0,322
CKD, %	42,7%	42,6%	
Diabetes mellitus, %	16%	25,9%	*P* = 0,166
Myocardial infarction, %	50,7%	43,4%	*p* = 0,417
Atrial fibrillation, %	17,3%	13%	*p* = 0,499
Glucose level, mmol/l	6,23±1,49	6,95±2,91	*p* = 0,262
GFR, ml/min/1,73м^2	57,7±18,5	60,4±20,4	*p* = 0,423
Cardiovascular anamnesis, %	45,3%	42,6%	*p* = 0,757
Smoking, %	25,3%	9,3%	*P* = 0,021
Systolic BP, mm Hg	145±22,5	143±24,6	*p* = 0,350
Diastolic BP, mm Hg	87±12,6	85,6±11,5	*p* = 0,264
Pulse rate, beats per min	78,9±12,4	79,3±11,2	*p* = 0,998
6 minute walking test, m.	239±107	248±113	*p* = 0,633
Body mass index, kg/m^2	29,4±5,18	28,8±5,66	*p* = 0,353
I-II functional class CHF, %	33,8%	35,2%	*p* = 0,803
III-IV functional class CHF, %	66,2%	64,8%	
Total cholesterol, mmol/l	5,25±1,56	5,73±1,45	*p* = 0,024
triglicerids, mmol/l	1,82±1,31	1,98±1,06	*P* = 0,194
high density lipoproteins, mmol/l	1,17±0,388	1,24±0,354	*p* = 0,241
Ejection fraction, %	50,1±10,5	54,8±8,26	*p* = 0,016
Clinical assessment scale, grade	6,09±2,05	6,19±2,45	*p* = 0,739
Quality of life, grade	43,7±19,3	40,4±16,0	*p* = 0,466
HF preserved Ejection fraction (EF ≥ 50%), %	78,3%	62,1%	*p* = 0,190
HF mid-range ejection fraction (EF 40–49%), %	21,2%	13%	
HF low ejection fraction (EF < 40%), %	16,7%	8,7%	

level of glucose and triglycerides in the blood of women exceeded that of men (6.78 ± 2.18 mmol/L and 5.89 ± 1.33 mmol / L, p = 0.027; 2.01 ± ± 1.17 mmol/L and 1, 39 ± 0.90 mmol/L, $p < 0.001$).

In patients with TT genotype (Suppl. Table 1), some differences were found in the occurrence of risk factors and clinical characteristics, depending on the age period. The average age (< 60 years) was predominantly males (39.1%) than females (8.7%). In the 60–75 age group women predominated (65.2%) in comparison with men (26.1%); over 75 years there were more men than women (34.8% and 26.1%, χ^2 = = 8.6, $p = 0.014$). The phenotypic features of CHF patients TT were characterized by an increased level of total blood cholesterol compared to men (5.65 ± 1.26 mmol / L and 4.87 ± 1.06 mmol/L, $p = 0.048$). About a third of the men smoked, while there were no women with the TT genotype who smoked ($p = 0.002$). In 37.5% of men CHF was combined with COPD ($p = 0.01$).

Table 2

Clinical features in CHF patients CT-genotype

Parameter	Men *n* = 80	Women *n* = 59	*P*/*p*
Age, M± SD	65 ± 10,3	71,1 ± 9,37	*P* < 0,001
< 60 years old, %	35%	11,9%	*P* < 0,001
60–75 years old, %	51,5%	49,2%	
> 75 years old, %	13,8%	39%	
COPD, %	37,5%	13,6%	*P* = 0,001
CKD, %	22,5%	57,6%	*P* = 0,00002
Diabetes mellitus, %	7,5%	36,2%	*P* = 0,001
Myocardial infarction, %	31,6%	54,4%	*p* = 0,008
Atrial fibrillation, %	11,3%	13,6%	*p* = 0,681
Glucose level, mmol/l	5,89 ± 1,33	6,87 ± 2,18	*p* = 0,027
GFR, ml/min/1,73м^2	63,9 ± 19,5	61,7 ± 18,3	*p* = 0,869
Cardiovascular anamnesis, %	35%	47,5%	*p* = 0,139
Smoking, %	33,8%	1,7%	*P* < 0,001
Systolic BP, mm Hg	145 ± 22,7	150 ± 27,2	*p* = 0,181
Diastolic BP, mm Hg	86,1 ± 13,3	88,2 ± 13,3	*p* = 0,105
Pulse rate, beats per min	78,7 ± 11,5	80,0 ± 11,5	*p* = 0,791
6 minute walking test, m.	245 ± 109	227 ± 110	*p* = 0,290
Body mass index, kg/m^2	27,8 ± 5,17	30,4 ± 5,96	*p* = 0,007
I-II functional class CHF, %	36,2%	23,7%	*p* = 0,033
III-IV functional class CHF, %	63,8%	76,3%	
Total cholesterol, mmol/l	5,01 ± 1,32	5,43 ± 1,43	*p* = 0,099
triglicerids, mmol/l	1,39 ± 0,901	2,01 ± 1,17	*P* < 0,001
high density lipoproteins, mmol/l	1,24 ± 0,59	1,2 ± 0,462	*p* = 0,661
Ejection fraction, %	49,2 ± 13,3	53 ± 8,57	*p* = 0,122
Clinical assessment scale, grade	5,77 ± 2,62	7,0 ± 2,46	*p* = 0,004
Quality of life, grade	40,3 ± 19,5	41,6 ± 16,2	*p* = 0,608
HF preserved Ejection fraction (EF ≥ 50%), %	62,5%	78,4%	*p* = 0,136
HF mid-range ejection fraction (EF 40–49%), %	21,9%	15,7%	
HF low ejection fraction (EF <40%), %	15,6%	5,9%	

Discussion

Chronic heart failure is one of the most important problems of modern cardiology and geriatrics. The incidence of this pathology increases in older age groups, in proportion to the prevalence of ischemic heart disease and arterial hypertension as the most common causes of heart failure. This work investigated the gender aspects of CHF of ischemic etiology. It was found that in the absence of differences in the burdened cardiovascular family history, the frequency of myocardial infarction, CHF is detected mainly in middle-aged and elderly men, in elderly and senile women, which is consistent with previous studies of CHF of both ischemic and other etiology. This study proved the gender contrast in the prevalence of heart failure in people under 60 years of age: in men much more often than in women, which is possibly associated with the onset of ischemic heart disease and arterial hypertension in men at a younger age (Fomin, 2016; Rodriguez *et al.*, 2013). In women, CHF develops at a later age, which some authors explain by the development of isolated systolic hypertension in them due to a decrease in estrogen production and a

weakening of their cardioprotective effect (Keller & Howlett, 2016; Sandberg & Ji, 2012). In the age period 60–80 years, the incidence of CHF in women was 2.6 times higher than in men (72% versus 28%) against the background of a shorter life expectancy. In the age group over 80 years old, gender differences in the incidence of CHF are not described (Ageev *et al.*, 2006; Belenkov *et al.*, 2006). The above age-related tendencies were found in persons with CC- and CT-genotypes of the rs10927875 polymorphism ZBTB17 gene: to a greater extent heart failure before, reaching the age of 60 in men; over 75 years old – in women. There were no gender differences in the CC- and CT-genotypes in old age. The TT-genotype of the rs10927875 polymorphism of the ZBTB17 gene in men we found with equal frequency in all age groups, while in women, mainly at the age of 60–75 years.

Currently, heart failure is recognized as a typical polygenic disease. It is characterized by variability of the phenotype, including as a result of gene expression disorders or their mutations responsible for certain links in the pathogenesis of the syndrome. In this work, we studied the polymorphism of the ZBTB17 gene, involved in apoptosis and myocardial remodeling in patients with CHF of ischemic origin. The available literature presents the results of GWAS – studies on the role of the rs10927875 polymorphism of the ZBTB17 gene in heart failure due to dilated cardiomyopathy; at the same time, there are no studies in CHF against the background of ischemic heart disease. The analysis of the rs10927875 polymorphism ZBTB17 gene showed the variability of clinical characteristics in terms of sex and age: women of CC- and TT-genotypes had a higher level of total cholesterol in comparison with men, women of CT genotype of CHF with an increased frequency of FC III-IV CHF. Men with CT genotype had MI less frequently than women ($p = 0.008$).

One of the significant gender-related differences in CHF, identified in this study, is the development in women the phenotype of heart failure with preserved ejection fraction. The number of patients with HFpEF is significant, accounting for more than 50% of the total (Dunlay *et al.*, 2017). It is known that the risk of heart failure with low EF developing is much lower in women than in men. Our study showed that LV functions were 2 times more in men with HF with low EF than in women, in the absence of differences in the FC CHF.

With an increase in life expectancy, comorbid diseases, joining CHF, increases exponentially, mainly in middle-aged (93%) and elderly people (98%) (Fortin *et al.*, 2005). This study of concomitant CHF conditions showed that 40% of men had CHF combined with COPD, 47.3% of women with CKD, and 32.2% with diabetes. The established differences in the prevalence and significance of comorbidities in men and women with CHF are consistent with the results of other authors (Knöll *et al.*, 2011). Analysis of comorbid conditions in persons of different sex of the same genotype demonstrated a frequent combination of CHF and COPD in men of CT and TT genotypes (37.5%). CKD is associated with 57.6% of women of the ST genotype of CHF, and 36.2% of women with diabetes mellitus. No statistically significant comorbid conditions were found in patients of the TT genotype.

Conclusion

Thus, the study showed age, gender differences in the clinical characteristics of chronic heart failure. For each genotype (CC, CT, TT), the number of phenotypic characteristics for men and women has been determined: age period of CHF formation; the value of myocardial infarction suffered in the past; the value of the ejection fraction of the left ventricle, the level of total blood cholesterol; concomitant pathology that changes the clinical portrait. Determination of the polymorphism of the ZBTB17 gene, taking into account the patient's gender, creates the prerequisites for calculating the genetic variants of the formation of heart failure and determining the personalized genetic risk.

We have nothing to declare. No financial support.

Supplementary

Suppl. Table 1

Clinical features in CHF patients TT-genotype

Parameter	Men *n* = 24	Women *n* =23	*P*/*p*
Age, M± SD	64,7 ± 14,3	67,7 ± 8,18	$P = 0{,}574$
< 60 years old, %	39,1%	8,7%	$\chi^2 = 8{,}6$ $p = 0{,}014$
60–75 years old, %	26,1%	65,2%	
> 75 years old, %	34,8%	26,1%	
COPD, %	37,5%	4,3%	$\chi^2 = 7{,}5$, $P = 0{,}01$
CKD, %	41,7%	69,6%	$p = 0{,}1$
Diabetes mellitus, %	43,5%	26,1%	$P = 0{,}216$
Myocardial infarction, %	41,7%	56,5%	$p = 0{,}308$
Atrial fibrillation, %	12,5%	17,4%	$p = 0{,}638$
Glucose level, mmol/l	6,67 ± 2,85	6,95 ± 2,29	$p = 0{,}809$
GFR, ml/min/1,73м^2	60,6 ± 16,4	61,6 ± 22,6	$p = 0{,}617$
Cardiovascular anamnesis, %	50%	43,5%	$p = 0{,}654$
Smoking, %	33,3%	0%	$P = 0{,}002$
Systolic BP, mm Hg	144 ± 18,1	153 ± 17,2	$p = 0{,}165$
Diastolic BP, mm Hg	80,3 ± 14,7	90,4 ± 8,11	$p = 0{,}009$
Pulse rate, beats per min	76,7 ± 14,8	85,3 ± 10,3	$p = 0{,}016$
6 minute walking test, m.	175 ± 113	229 ± 124	$p = 0{,}129$
Body mass index, kg/m^2	30,2 ± 8,14	30,6 ± 7,15	$p = 0{,}644$
I-II functional class CHF, %	29,2%	34,7%	$p = 0{,}737$
III-IV functional class CHF, %	70,8%	65,5%	
Total cholesterol, mmol/l	4,87 ± 1,06	5,65 ± 1,26	$p = 0{,}048$
triglicerids, mmol/l	1,71 ± 0,953	1,81 ± 0,741	$P = 0{,}648$
high density lipoproteins, mmol/l	1,12 ± 0,302	1,15 ± 0,369	$p = 0{,}804$
Ejection fraction, %	50,9 ± 8,01	55,0 ± 7,15	$p = 0{,}170$
Clinical assessment scale, grade	6,92 ± 2,68	7,0 ± 2,95	$p = 0{,}965$
Quality of life, grade	40,6 ± 10,9	34,9 ± 20,0	$p = 0{,}258$
HF preserved Ejection fraction (EF ≥ 50%), %	66,7%	56,5%	$p = 0{,}131$
HF mid-range ejection fraction (EF 40–49%), %	22,2%	43,5%	
HF low ejection fraction (EF < 40%), %	11,1%	5,9%	

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