Begrambekova Yu. L.[1], Mareev Yu. V.[12], Mareev V. Yu.[1], Orlova Ya. A.[1], Kobalava Zh. D. [3,4], Karapetyan L. V. [3, 4], Galochkin S. A.[3, 4], Kazakhmedov E. R.[3, 4], Lapshin A. A.[3, 4], Garganeeva A. A.[5], Kuzheleva E. A.[5], Efremushkina A. A.[6, 7], Kiseleva E. V.[7], Barbarash O. L.[8], Pecherina T. B.[8], Galyavich A. A.[9], Galeeva Z. M.[9], Baleeva L. V.[9], Koziolova N. A.[10], Veklich A. S.[10], Duplyakov D. V.[11, 12], Maksimova M. N.[12], Yakushin S. S.[13, 14], Smirnova E. A.[14], Sedykh E. V.[13, 14], Shaposhnik I. I.[15], Makarova N. A.[15], Zemlyanukhina A. A.[16], Skibitsky V. V.[17], Fendrikova A. V.[17], Skibitsky A. V.[17], Spiropoulos N. A.[18], Seredenina E. M.[1], Errolanova K. A.[19], Kotovskaya Yu. V.[19], Tkacheva O. N.[19], Fedin M. A.[19, 20]

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Female and Male Phenotypes of Iron Deficiency in CHF. Additional analysis of the «The Prevalence of Iron Deficiency in Patients With Chronic Heart Failure in the Russian Federation (J-CHF-RF)» study

Aim	To evaluate the incidence of iron deficiency (ID) in men and women with chronic heart failure (CHF) and to compare clinical and functional indexes in patient with and without ID depending on the gender.
Material and methods	An additional analysis of the study «Prevalence of Iron Deficiency in Patients With Chronic Heart Failure in the Russian Federation (ID–CHF-RF)» was performed. The study included 498 (198 women, 300 men) patients with CHF, in whom, in addition to iron metabolism, the quality of life and exercise tolerance (ET) were studied. 97% of patients were enrolled during their stay in a hospital. ID was defined in consistency with the European Society of Cardiology (ESC) Guidelines. Also, and additional analysis was performed according to ID criteria validated by the morphological picture of the bone marrow.
Results	ID was detected in 174 (87.9%) women and 239 (79.8%) men (p=0.028) according to the ESC criteria, and in 154 (77.8%) women and 217 (72.3%) men (p=0.208) according to the criteria validated by the morphological picture of the bone marrow. Men with ID were older and had more severe CHF. They more frequently had HF functional class (FC) III and IV (63.4% vs. 43.3% in men without ID); higher concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) and lower ET. HF FC III increased the probability of ID presence 3.4 times (p=0.02) and the probability of HF FC IV 13.7 times (p=0.003). This clinical picture was characteristic of men when either method of determining ID was used. In women, ID was not associated with more severe CHF.
Conclusion	Based on the presented analysis, it is possible to characterize the male and female ID phenotypes. The male ID phenotype is associated with more severe CHF, low ET, and poor quality of life. In females of the study cohort, ID was not associated with either the severity of CHF or with ET.

Keywords Iron deficiency; CHF; exercise tolerance; 6-min walk test; phenotype; sex; ID-CHF-RF

For citations Begrambekova Yu. L., Mareev Yu. V., Mareev V. Yu., Orlova Ya. A., Kobalava Zh. D., Karapetyan L. V. et al. Female and Male Phenotypes of Iron Deficiency in CHF. Additional Analysis of the «The Prevalence of Iron Deficiency in Patients With Chronic Heart Failure in the Russian Federation (J-CHF-RF)» study. Kardiologiia. 2023;63(9):3 – 13. [Russian: Беграмбекова Ю. Л., Мареев Ю. В., Мареев В. Ю., Орлова Я. А., Кобалава Ж. Д., Карапетян Л. В. и др. Женский и мужской фенотипы дефицита железа при ХСН. Дополнительный анализ исследования «Распространенность дефицита железа у пациентов с хронической сердечной недостаточностью в Российской Федерации (ДЖ–ХСН–РФ)». Кардиология. 2023;63(9):3–13].

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Introduction

According to the Framingham study, the overall lifetime risk of chronic heart failure (CHF) is roughly comparable between male and female patients [1]. However, heart failure with reduced ejection fraction (HFrEF) is more characteristic of male patients, while female patients are more likely to develop heart failure with preserved ejection fraction (HFpEF), which is evidenced by the international and Russian studies [2]. The female and male phenotypes of CHF differ quite significantly not only in terms of left ventricular ejection fraction (LVEF). The differences begin with risk factors [3] and comorbidity [4], determine the features of pathogenesis [5, 6], prognosis [7], and exercise tolerance, psycho-emotional state, and quality of life [8–10].

Iron deficiency (ID) and anemia are some of the most prevalent concomitant conditions in HF, both associated with a negative prognosis, reduced exercise tolerance, and quality of life (QoL) [11–13]. ID is significantly more common in patients with CHF than anemia. It is detected in 60% of outpatients and 80% of inpatients with HF [14, 15]. In Russia, ID is found in more than 80% of hospitalized patients [16]. ID has been shown to be more common in female patients [14, 17]. Due to the differences in CHF phenotypes in male and female patients, it can be assumed that clinical manifestations of ID may also be sex dependent.

We conducted an additional analysis of findings of a multicenter study of ID in Russian patients with CHF, which have been published earlier [16].

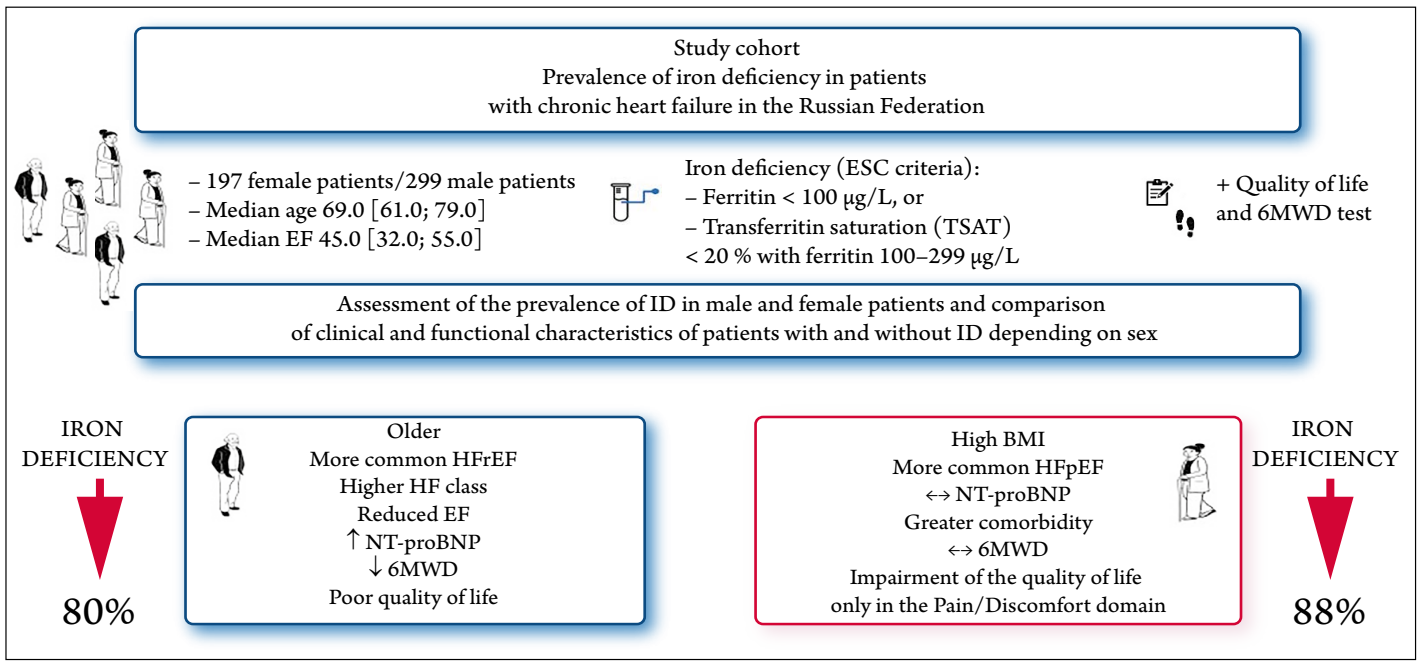
Objective of the analysis

The objective of the presented additional analysis is to assess the prevalence of iron deficiency (ID) in male and female patients with chronic heart failure (CHF) and compare clinical and functional characteristics of patients with and without ID depending on sex.

Material and methods

The design of the multicenter observational study Prevalence of Iron Deficiency in Patients with Chronic Heart Failure in the Russian Federation has been previously described in detail [16].

Central illustration. Female and Male Phenotypes of Iron Deficiency in CHF. Additional analysis of the «The Prevalence of Iron Deficiency in Patients With Chronic Heart Failure in the Russian Federation (J-CHF-RF)» study



ISSN 0022-9040. Kardiologiia. 2023;63(9). DOI: 10.18087/cardio.2023.9.n2413

Indicators of iron metabolism were examined in 498 (198 female and 300 male) patients, their quality of life and exercise tolerance were also assessed. Patients signed the voluntary informed consent before being subjected to any study procedures. 97% of patients were included in the hospital. Iron metabolism parameters and NT-proBNP were evaluated in a central laboratory. Quality of life indicators were assessed using the EQ-5D™ questionnaire (EuroQol Group). This questionnaire was translated into Russian and validated [18]. The survey results were interpreted by scoring each patient's response from 0 to 5 depending on the severity of the impairment of the quality of life by individual subscales, where 0 corresponds to the absence of violations and 5 is inability to cope with a particular type of exercise. The total score for all domains of the questionnaire was analyzed separately. ID was determined according to the ESC guidelines (ferritin<100 ng/ml or transferrin saturation (TSAT) ratio<20% in ferritin 100–299 ng/ml) [19]. The prevalence and characteristics of ID were also evaluated using the criteria validated according to the bone marrow morphology (TSAT≤19.8% or iron (Fe) ≤13 μmol/L [20]). In the first stage of the analysis, we compared a group of male and female patients in general without separating depending on the presence of ID. In the second stage of the study, we compared the clinical characteristics of patients with ID versus patients without ID depending on the sex.

Statistical analysis

Categorical variables were expressed as percentages, and intergroup differences were estimated using the Chi-squared test or the Fisher's exact test. Nonparametrically distributed continuous variables are expressed as the medians (Me) [1st quartile; 3rd quartile], and normally distributed continuous variables are presented as the means and standard deviations (SD). The statistical significance of intergroup differences was assessed using the Mann-Whitney test or using the paired Student's t-test depending on the type of distribution. The intergroup differences were statistically significant with p value less than 0.05. Multiple logistic regression was used to identify variables associated with the presence of ID.

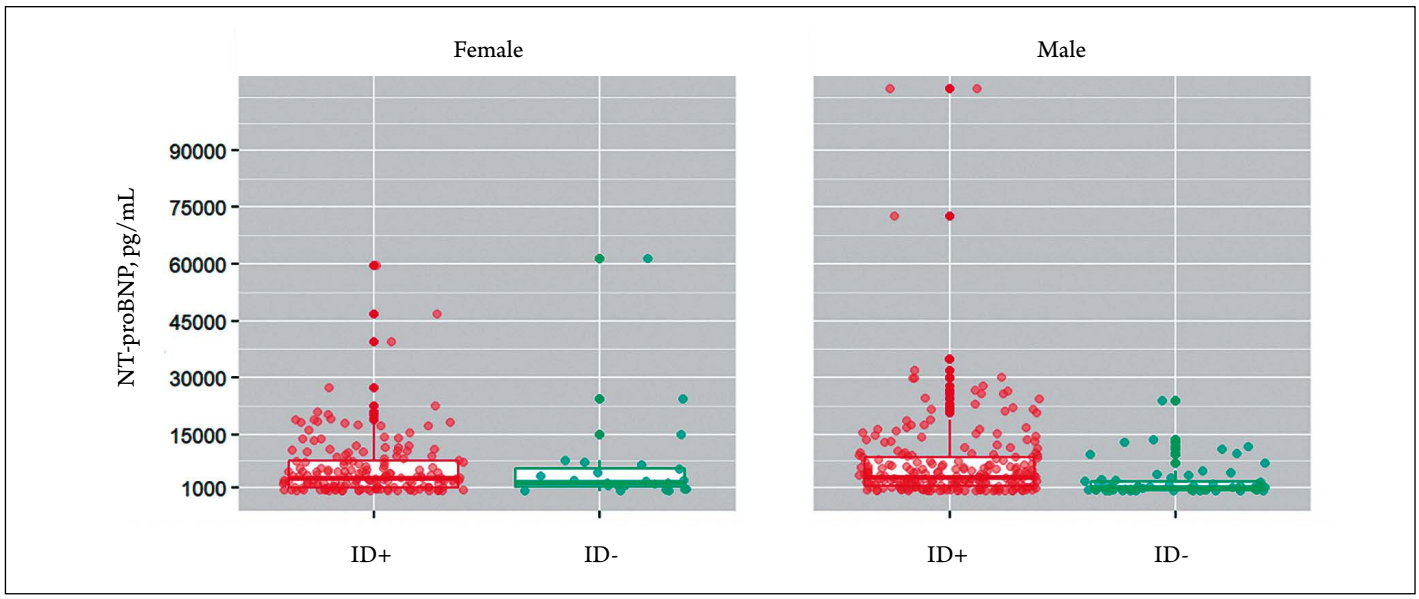
Results

Additional analysis included 497 individuals: 198 (39.8%) female and 299 (60.2%) female patients. In the first stage of the analysis, we compared a group of male and female patients as a whole. The protocol provided for the diagnosis of ID following the ESC criteria. In this article, we will focus on the characteristics of ID depending on the sex according to these criteria and briefly discuss the differences in the clinical and demographic characteristics of ID depending on the sex using the criteria validated by the bone marrow morphology.

Diagnosis of ID according to the ESC criteria

The data analysis found that the prevalence of HFpEF was higher among female patients who also bore an expectedly greater comorbidity burden, while HFrEF was more prevalent in male patients. Clinical characteristics of patients are provided in Table 1. Mean age of female patients was 8 years higher than that of male patients, the median body mass index (BMI)

Figure 1. NT-proBNP in patients with and without ID (ESC criteria)



The figure is a combination of a boxplot and a dotplot. Each point is the patient's NT-proBNP value. Since some patients have the same NT-proBNP values, the jitter function is used in the plot (the points are slightly spaced apart) and some points are more transparent. ID+, the presence of iron deficiency; ID – , the absence of iron deficiency.

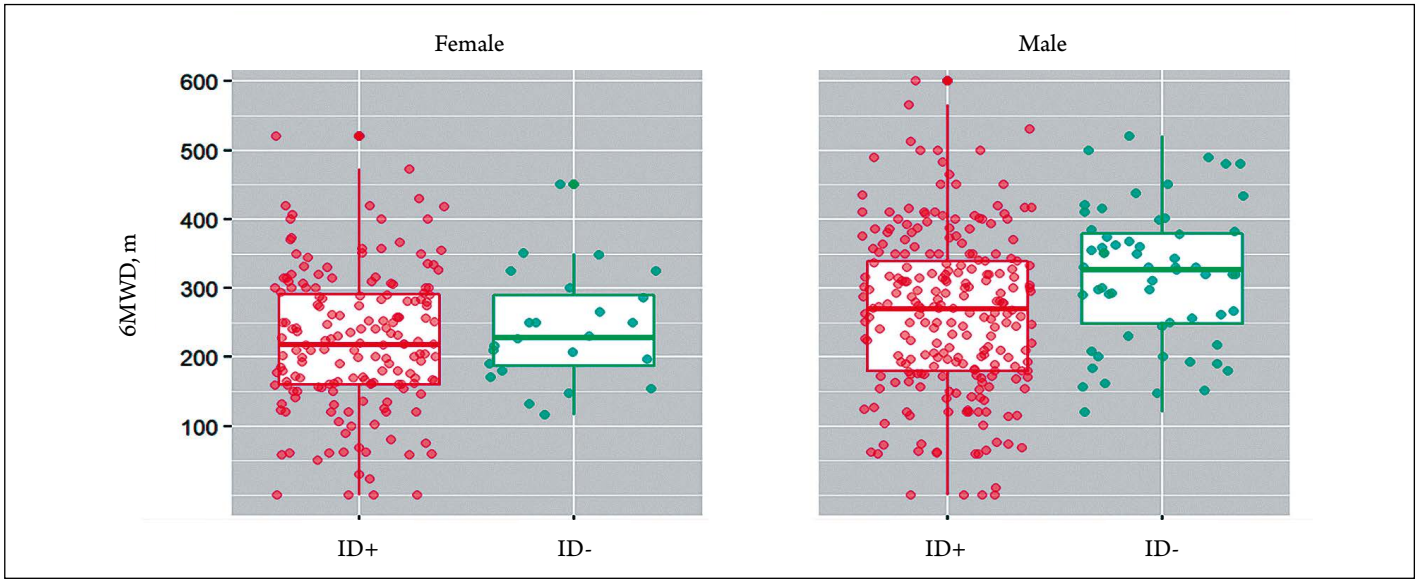
Таблица 1. Clinical and demographic characteristics of patients of different sexes (ESC criteria)

Parameter	Total, n=497	Female, n=198	Male, n=299	p
Age, years, Me [Q1; Q3]	69.0 [61.0;79.0]	74.0 [66.0;82.0]	66.0 [59.0;74.0]	<0.001
BMI, kg/m2, Me [Q1; Q3]	30.4 [26.0;35.1]	31.9 [27.4;37.0]	29.4 [25.6;33.8]	<0.001
Iron deficiency (ESC criteria), n (%):	413 (83.1)	174 (87.9)	239 (79.9)	0.028
Anemia, n (%)	201 (40.4)	77 (38.9)	124 (41.5)	0.631
AF, n (%)	286 (57.5)	119 (60.1)	167 (55.9)	0.398
Alcohol misuse, n (%):				<0.001*
• Present	36 (7.24)	5 (2.53)	31 (10.4)	
• Past	40 (8.05)	6 (3.03)	34 (11.4)	
• Never	421 (84.7)	187 (94.4)	234 (78.3)	
Diabetes mellitus, n (%)	157 (31.6)	86 (43.4)	71 (23.7)	<0.001
Hypothyroidism, n (%)	19 (3.82)	14 (7.07)	5 (1.67)	0.005
Hyperthyroidism, n (%)	3 (0.60)	3 (1.52)	0 (0.00)	0.068
Type of CHF, n (%)				<0.001*
HFpEF	202 (40.6)	107 (54.0)	95 (31.8)	
HFrEF	212 (42.7)	65 (32.8)	147 (49.2)	
HFmrEF	83(16.7)	26 (13.1)	57 (19.1)	
LVEF, %, Me [Q1; Q3]	45.0 [32.0;55.0]	51.0 [37.0;58.0]	41.0 [30.0;53.0]	<0.001
Hemoglobin, g/dL, Me [Q1; Q3]	13.1 [11.6;14.4]	12.5 [11.1;13.6]	13.5 [11.8;14.9]	<0.001
TSAT, %, Me [Q1; Q3]	13.8 [8.14;22.4]	13.1 [8.14;20.8]	14.0 [8.23;23.0]	0.179
Ferritin, ng/dL, Me [Q1; Q3]	67.7 [35.5;129]	52.0 [29.0;110]	79.2 [39.1;137]	0.001
Iron, μmol/L, Me [Q1; Q3]	9.10 [5.55;14.1]	8.95 [5.44;13.0]	9.28 [5.64;15.0]	0.379
Transferrin, g/L, Me [Q1; Q3]	2.71 [2.29;3.17]	2.82 [2.33;3.24]	2.66 [2.29;3.11]	0.089
RBC, ×1012/L, Me [Q1; Q3]	4.47 [4.00;4.91]	4.38 [3.91;4.78]	4.52 [4.03;5.00]	0.003
WBC, ×109/L, Me [Q1; Q3]	7.43 [6.21;9.10]	7.28 [6.05;8.80]	7.60 [6.32;9.10]	0.134
MCH, pg, Me [Q1; Q3]	29.2 [26.9;30.9]	28.7 [26.8;30.1]	29.7 [27.1;31.2]	<0.001
MCV, fl, Me [Q1; Q3]	89.3 [83.9;94.1]	88.2 [83.1;92.0]	90.9 [85.0;94.8]	0.002
RDW CV, %, Me [Q1; Q3]	15.0 [13.8;17.1]	14.9 [14.0;17.0]	15.0 [13.7;17.2]	0.796
RDW SD, fl, Me [Q1; Q3]	50.1 [44.5;56.0]	49.2 [45.1;56.0]	50.4 [43.4;55.4]	0.922
NT-proBNP, pg/mL, Me [Q1; Q3]	3251 [995;7733]	3434 [1118;7823]	3176 [952;7536]	0.602
HF NYHA class, n (%):				<0.001*
I	19 (3.82)	2 (1.01)	17 (5.69)	
II	141 (28.4)	40 (20.2)	101 (33.8)	
III	261 (52.5)	121 (61.1)	140 (46.8)	
IV	76 (15.3)	35 (17.7)	41 (13.7)	
ACE inhibitors, n (%)	292 (58.8)	112 (56.6)	180 (60.2)	0.476
ARBs, n (%)	120 (24.1)	65 (32.8)	55 (18.4)	<0.001
ARNIs, n (%)	50 (10.1)	8 (4.04)	42 (14.0)	0.001
ACE inhibitors or ARBs or ARNIs, n (%)	462 (93.0)	185 (93.4)	277 (92.6)	0.874
Beta-blockers, n (%)	451 (90.7)	182 (91.9)	269 (90.0)	0.564
MCRAs, n (%)	363 (73.0)	138 (69.7)	225 (75.3)	0.207
Ivabradine, n (%)	5 (1.01)	2 (1.01)	3 (1.00)	1.000
Diuretics, any, n (%)	445 (89.5)	184 (92.9)	261 (87.3)	0.063
Loop diuretics, n (%)	426 (85.7)	170 (85.9)	256 (85.6)	1.000
Cardiac glycosides, n (%)	65 (13.1)	29 (14.6)	36 (12.0)	0.479
6MWD, m, mean (SD)	255 (110)	225 (97.8)	274 (114)	<0.001

* For alcohol misuse, type of CHF, and NYHA class variables, p values are given for the comparisons between all categories.
For alcohol misuse, whether there was a difference between three categories (no present and past alcohol misuse, past alcohol misuse, and present alcohol misuse). For NYHA class and type of CHF, whether there was a difference between the three types of CHF and all four NYHA classes.
Data are presented as the absolute numbers of patients and their percentage of the total number of patients in the group, or the medians with 25th and 75th quartiles, or the means and standard deviations. AF, atrial fibrillation; DM, diabetes mellitus; CHF, chronic heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; LVEF, left ventricular ejection fraction; TSAT, transferrin saturation; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA class, functional class of heart failure according to the New York Heart Association classification; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MCRA, mineralocorticoid receptor antagonist; 6MWD, 6 minute walk distance; RDW SD, RDW CV, red blood cell distribution width.

ISSN 0022-9040. Kardiologiia. 2023;63(9). DOI: 10.18087/cardio.2023.9.n2413

Figure 2. 6MWD in patients with and without ID (ESC criteria)



The figure is a combination of a boxplot and a dotplot. Each point is the patient's 6MWD value. Since some patients have the same 6MWD values, the jitter function is used in the plot (the points are slightly spaced apart) and some points are more transparent. ID+, the presence of iron deficiency; ID–, the absence of iron deficiency; 6MWD, 6 minute walk distance.

corresponded in female patients to grade 1 obesity (31.9 [27.4; 37.0]). HFpEF was more common in female patients (54.0% vs. 31.8% in male patients). The median LVEF was 51.0 [37.0; 58.0] in female patients compared to 45.0 [32.0; 55.0] in male patients (p<0.001 in all cases). Male and female patients also differed statistically significantly in CHF class. HF class III and IV was diagnosed in 78.8% of female patients and 60.5% of male patients (p<0.001). Female patients walked a statistically significantly shorter 6-minute walk distance (6MWD) than male patients: 225±97.8 m and 274±114 m, respectively (p<0.001). A higher percentage of male patients were present and past alcohol users (p=0.002). Female patients were more likely to have comorbidity than male patients (43.4% versus 23.7%, p<0.001). Female patients had a statistically significantly higher BMI (p<0.001) and were more likely to have thyroid dysfunction (asymptomatic hypothyroidism) (p<0.001). ID was also more common in female patients than in male patients (87.9% and 79.9%, respectively; p=0.028). Mean transferrin and red blood cell size values were statistically significantly lower in the female group than in the male group. Drug therapy also differed between the groups. Sartans were more often administered in female patients (p<0.001), and

Таблица 2. Quality of life as assessed using the EQ-5D™ questionnaire in male and female patients (ESC criteria)

Parameter	Total, N=497	Female, N=198	Male, N=299	p, overall	N
Mobility, binary indicator, n (%):				0.001	497
– no or minimal impairments	154 (31.0)	44 (22.2)	110 (36.8)		
– moderate to severe impairments	343 (69.0)	154 (77.8)	189 (63.2)		
Self-care, binary indicator, n (%):				<0.001	497
– none to minimal impairments	277 (55.7)	88 (44.4)	189 (63.2)		
– moderate to severe impairments	220 (44.3)	110 (55.6)	110 (36.8)		
Usual activities, binary indicator, n (%):				<0.001	497
– none to minimal impairments	182 (36.6)	53 (26.8)	129 (43.1)		
– moderate to severe impairments	315 (63.4)	145 (73.2)	170 (56.9)		
Pain/discomfort, binary indicator, n (%):				00020	497
– none to minimal impairments	254 (51.1)	88 (44.4)	166 (55.5)		
– moderate to severe impairments	243 (48.9)	110 (55.6)	133 (44.5)		
Anxiety/depression, binary indicator, n (%):				<00001	497
– none to minimal impairments	291 (58.6)	91 (46.0)	200 (66.9)		
– moderate to severe impairments	206 (41.4)	107 (54.0)	99 (33.1)		

* The p-values are given for the comparisons of differences in all levels of impairments in each of the categories.

Таблица 3. Quality of life as assessed using the EQ-5D™ questionnaire in male and female patients depending on the presence of ID (ESC criteria)

Parameters	Female			Male		
Domains	**With ID N=174**	**Without ID N=24**	**p**	**With ID N=239**	**Without ID N=60**	**p**
Mobility, Me [Q1; Q3]	3.00 [3.00;4.00]	3.00 [3.00;4.00]	0.828	3.00 [2.00;4.00]	2.00 [2.00;3.00]	0.004
Self-care, Me [Q1; Q3]	3.00 [2.00;3.00]	2.00 [1.00;3.00]	0.080	2.00 [1.00;3.00]	1.00 [1.00;2.00]	<0.001
Usual activities, Me [Q1; Q3]	3.00 [2.00;4.00]	3.00 [2.00;4.00]	0.774	3.00 [2.00;4.00]	2.00 [1.00;3.00]	<0.001
Pain/discomfort, Me [Q1; Q3]	3.00 [2.00;4.00]	2.00 [2.00;3.00]	0.022	2.00 [1.00;3.00]	2.00 [1.00;3.00]	0.176
Anxiety/depression, Me [Q1; Q3]	3.00 [2.00;3.00]	3.00 [1.75;3.00]	0.915	2.00 [1.00;3.00]	1.00 [1.00;2.00]	0.018
All domains, Me [Q1; Q3]	14.0 [11.0;17.0]	12.5 [11.0;16.2]	0.281	12.0 [9.00;16.0]	9.00 [7.00;12.0]	<0.001

ARNIs were more often prescribed to male patients (p=0.001) (Table 1).

QoL parameters related to functional reserve were also statistically significantly lower in female patients (Table 2).

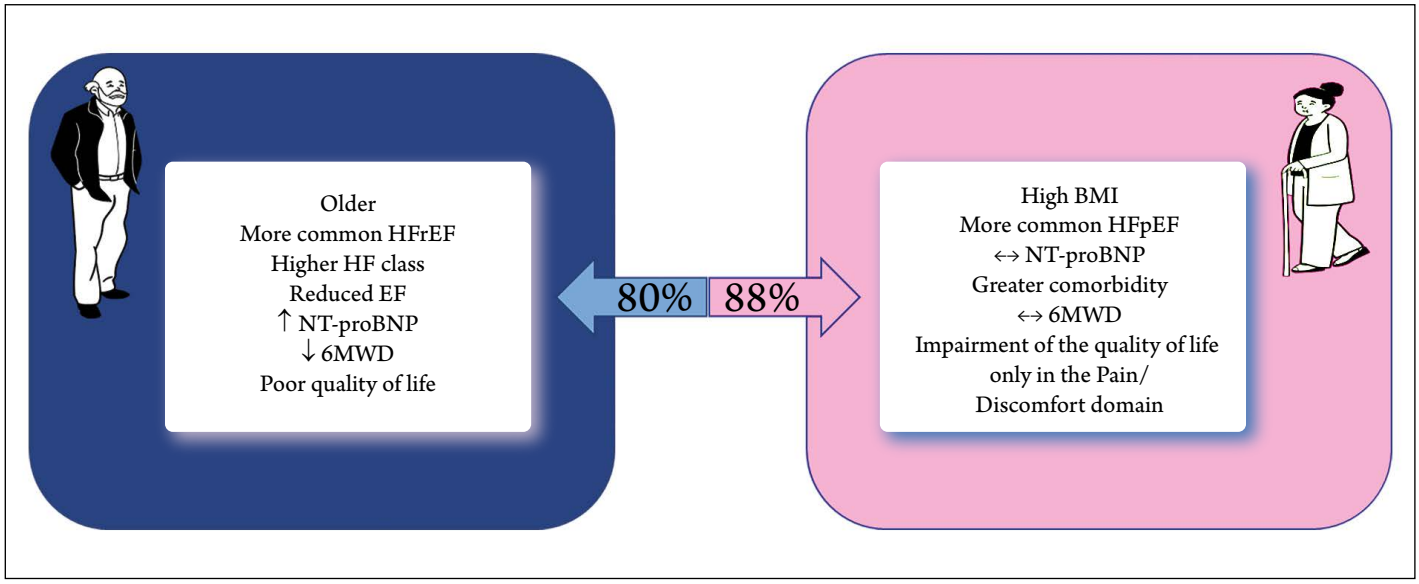
At the second stage, we conducted a comparative analysis of clinical characteristics depending on the presence of ID in male and female patients. Male patients with ID were statistically significantly older than those without ID. They had a more severe course of CHF: they were more likely to have HF class III and IV (63.4% versus 43.3% of male patients without ID); higher levels of NT-proBNP and lower exercise tolerance [Figure 1–2 (see Table 1 in the supplementary materials published in the journal website)].

Female patients with and without ID differed statistically significantly only by red cell distribution width, which was also characteristic of male patients. Female patients with ID were more likely to have AF and anemia. At the same time, the logistic regression analysis showed no association of ID with a more severe course of CHF in female patients. On the other hand, male patients with HF class III and IV were respectively 3.4 (p=0.02) and 13.7 (p=0.003) times more likely to have ID.

Quality of life indicators assessed using the EQ-5D™ questionnaire were statistically significantly different in male patients with and without ID. There were statistically significant differences in the Mobility, Self-Care, Usual Activities, and Anxiety/Depression domains. The presence of ID was associated in female patients only with higher scores in the Pain/Discomfort domain (Table 3).

A detailed description of the analysis results according to the criteria validated by the bone marrow morphology will be presented in the next article (see Table 2 in the supplementary materials published in the journal website). However, we conducted additional calculations to analyze whether the male and female phenotypes of ID would be different with other ID criteria applied. Thus, it can be stated that the female and male phenotypes of ID in CHF differ significantly for any diagnostic criteria used. According to the ESC criteria and the criteria validated by the bone marrow morphology, ID occurred in 79.8% and 72.3% of male patients, respectively. Male patients with ID according to the criteria validated by the bone marrow morphology have a more severe course of CHF, a poorer quality of life and walk a shorter 6MWD than those

Figure 3. Female and male phenotypes of iron deficiency in CHF (ESC criteria)



ISSN 0022-9040. Kardiologiia. 2023;63(9). DOI: 10.18087/cardio.2023.9.n2413

without ID. ID according to the same criteria was less prevalent in female patients (87.9% and 77.8%, respectively). Female patients with ID were more likely to have DM, AF and higher NT-proBNP levels (Figure 4).

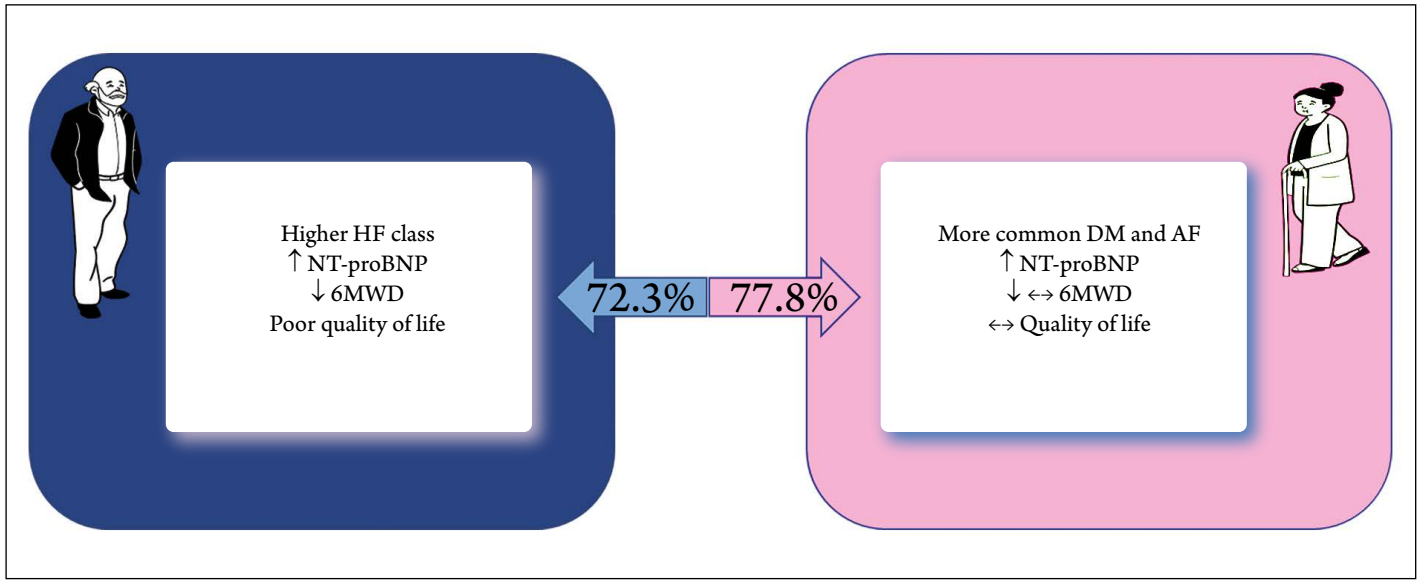
Discussion

In our study cohort, the female patients were older and had a median BMI corresponding to grade 1 obesity. BMI was 31.9 [27.4; 37.0] in female patients versus 29.4 [25.6; 33.8] in male patients. Female patients were more likely to have HFpEF (54%). They had more severe HF classes. HF class III and IV was found in 78.8% of female patients and 60.5% of male patients. Female patients had more concomitant diseases, walked a statistically significantly shorter 6MWD, and thus had lower functioning scores of the quality of life than male patients ($p<0.001$). Male patients had HFrEF and HFmrEF more often (68% of male patients had EF<50%). These findings are consistent with other papers. A study that combined data of 28,820 patients from 4 countries, who were followed up for a mean of 12 years, HFrEF was almost 2 times more likely to develop in male patients [21]. In the Swedish HF registry (42,987 patients), 55% of patients with HFpEF and only 29% of patients with HFrEF were female [22]. It was shown in the Russian study that analyzed a sample of patients hospitalized with signs of concomitant acute decompensated HF (N=848) in Nizhny Novgorod that female patients were statistically significantly more likely to develop decompensated HF in preserved or mid-range LVEF, as for male patients, they developed decompensated HF more often during HFrEF [23]. Thus, the clinical characteristics of the female and male phenotypes of HF in our analysis are generally consistent with similar data from other studies.

In our study, the prevalence of ID according to the ESC criteria among patients with symptomatic CHF was high in male patients and even higher in female patients (79.9% and 87.9%, respectively, $p=0.028$). The prevalence of ID according to the criteria validated by the bone marrow morphology was 72.3% in male patients and 77.8% in female patients. Moreover, we identified significant differences in the clinical characteristics of male and female patients with ID, which allows suggesting the female and male phenotypes of ID in patients with CHF.

Unlike male patients, female patients with and without ID had no statistically significant differences in age and almost no differences in clinical parameters. This phenomenon persisted for ID both according to the ESC criteria and the criteria validated by the bone marrow morphology. The only statistically significant differences were more frequent presence of comorbidity in female patients with ID (AF in ID diagnosed according to the ESC criteria and DM and AF in ID diagnosed according to the criteria validated by the bone marrow morphology) and the administration of loop diuretics. There was almost no difference in the concentration of NT-proBNP in female patients with and without ID according to the ESC criteria (Figure 1). At the same time, there was no statistically significant differences in BMI in the groups with and without ID both in female and male patients. Thus, elevated NT-proBNP cannot be attributed to body weight in female patients without ID. In extremely low exercise tolerance characteristic of female patients in our study cohort (6MWD 225±97.8 m), the presence of ID according to the ESC criteria was not accompanied in female patients by an additional decrease in exercise tolerance and associated parameters of quality of life (Figure 2, Table 2).

Figure 4. Female and male phenotypes of iron deficiency. Criteria validated according to the bone marrow morphology



The analysis results allow formulating the following characteristics of the female and male phenotypes of ID (Figure 3). The male phenotype of ID is associated with a more severe course of CHF, reduced exercise tolerance, and poor quality of life. Unfortunately, our findings do not allow concluding whether the severity of CHF in male patients determined the onset of ID or whether existing ID worsens the course of CHF. Both scenarios include several well-studied mechanisms associated with chronic inflammation, impaired intestinal iron binding, increased iron loss, and malnutrition [24–27]. According to our analysis, the severity of CHF was not associated with ID in the female phenotype. The presence of ID was not associated with an additional decrease in exercise tolerance, and probably developed before CHF.

According to epidemiological studies, ID is almost 3 times more common in female patients of any age than in male patients and is formed before menopause with two peaks during the life: during pregnancy and lactation and perimenopause [28]. According to the EPOCH-O-CHF population study, the peak of the probability density of physical inactivity and excess weight occurs at the age of 55–60 years, that is, in the perimenopausal and menopausal periods, and the likelihood of HFpEF increases about ten years later [29]. Thus, HF (mainly HFpEF) forms in female patients by the age of 65–75 years and it is characterized by a high prevalence of ID [2, 30]. In our study, female patients were characterized by an extremely low exercise tolerance, high predominance of HFpEF, and median BMI corresponding to grade 1 obesity. There was no statistically significant difference in LVEF when ID was determined according to the criteria validated by the bone marrow morphology, but mean BMI was 32.4 and DM was almost twice as likely in female patients with ID. Concentric remodeling characteristic of HFpEF, obesity, and DM was shown to entail more pronounced restrictions in diastolic reserve and high pulmonary artery pressure both at rest and during exercise, a decrease in oxygen utilization in the muscles, which leads to higher lactate threshold during exercise and a rapid onset of a feeling of fatigue [31, 32]. In a study including 19,485 patients followed up for 10 years, overweight in middle age was associated with an increased risk of hospitalization for CHF at the age ≥ 65 years. When adjusting for age, sex, and other risk factors, only indicators of cardiorespiratory fitness, instead of BMI, were statistically significantly associated with the risk of CHF. Thus, according to our findings, it is poor cardiorespiratory fitness that explains the association of BMI with the development of CHF [33]. Thus, regardless of the presence of ID, female patients in our cohort had more pronounced cardiac and non-cardiac limitations of exercise tolerance than male patients. The effect of ID could be neutralized by other important factors that determine exercise tolerance and related parameters of the quality of life. In a previously published analysis of our findings, the characteristics of patients with and without ID were consistent with similar studies, in which the analysis was carried out irrespective of sex [13]. Patients with ID were older and had a more severe course of CHF [16]. Our findings on ID in female patients open up several new questions. It can be assumed that the presence of ID can be an etiological factor in the formation of HFpEF in female patients by additionally affecting the state of skeletal muscles and myocardium, reducing exercise tolerance, and thus aggravating physical inactivity and related poor cardiorespiratory fitness. Our findings emphasize the importance of investigating the contribution of non-cardiac factors in reduced exercise tolerance, especially in female patients. These issues should be studied further and some of them will be considered in the subsequent analysis. In future studies, we will also compare the results of different ID criteria and take a detailed look at the characteristics of male and female patients when determining ID according to the criteria validated by the bone marrow morphology.

Limitations

The group of female patients without ID was small, which could affect the results of our study.

Funding

The study «Prevalence of Iron Deficiency in Patients with Chronic Heart Failure in the Russian Federation (ID–CHF-RF)» was funded by an unlimited grant from the company Vifor Pharma.

The article was received on 26/01/2023

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ISSN 0022-9040. Kardiologiia. 2023;63(9). DOI: 10.18087/cardio.2023.9.n2413

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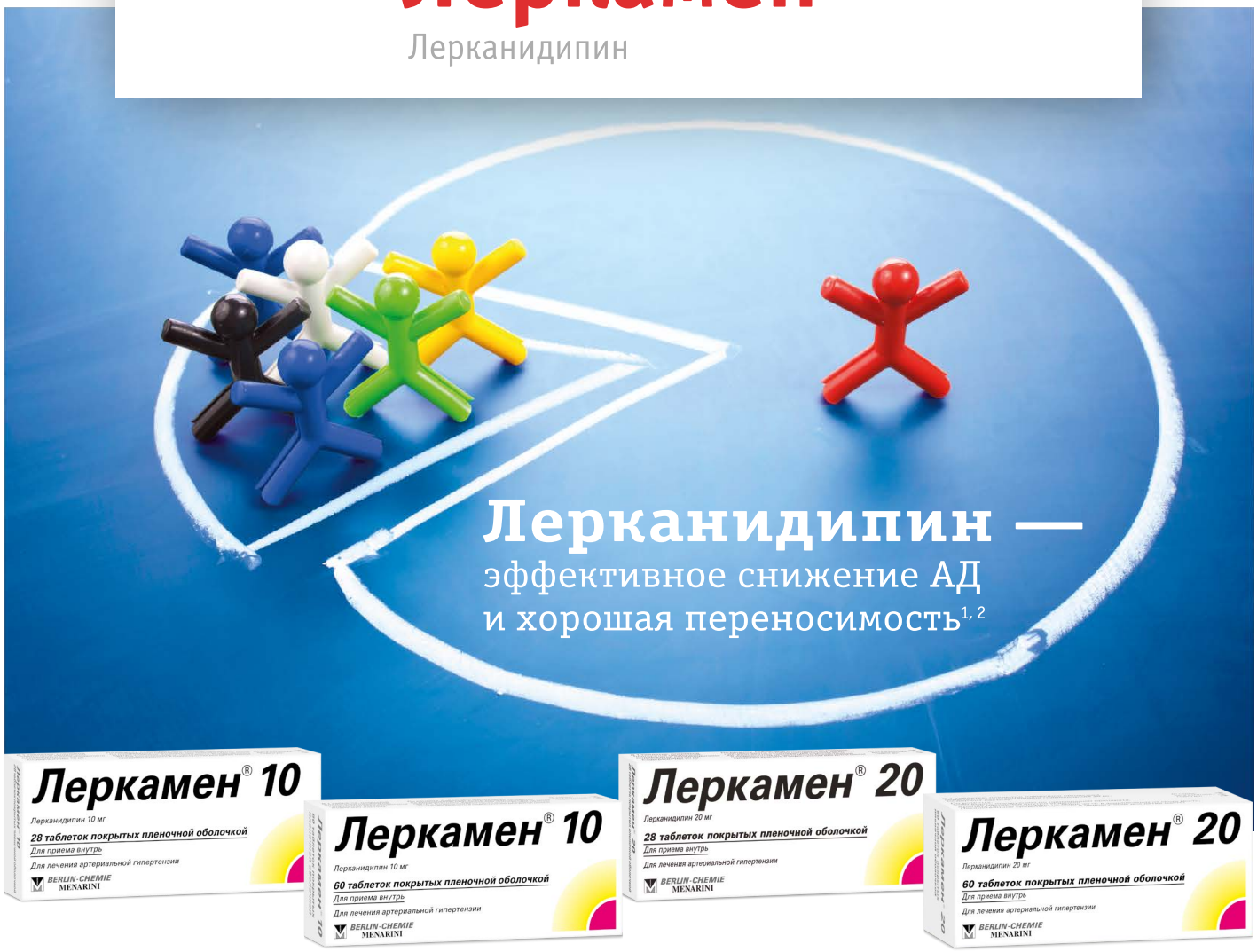

Сокращенная инструкция по медицинскому применению препарата «Леркамен®» (международное непатентованное наименование: лерканидипин, дозы 10 мг и 20 мг)
Лекарственная форма: таблетки, покрытые пленочной оболочкой
Показания к применению. Артериальная гипертензия I-II степени у взрослых пациентов.
Способ применения и дозы. Внутрь по 10 мг (1 таблетка препарата Леркамен® 10 или 1/2 таблетки препарата Леркамен® 20) 1 раз в сутки не менее чем за 15 минут до еды, предпочтительно утром, не разжевывая, запивая достаточным количеством воды. В зависимости от индивидуальной переносимости препарата пациентом, доза может быть увеличена до 20 мг (2 таблетки препарата Леркамен® 10 или 1 таблетка препарата Леркамен® 20). Терапевтическая доза подбирается постепенно, так как максимальное антигипертензивное действие развивается приблизительно через 2 недели после начала приема препарата. Препарат содержит менее 1 ммоля натрия (23 мг) на 1 таблетку, то есть практически не содержит натрия.
Противопоказания. Повышенная чувствительность к лерканидипину, другим производным дигидропиридинового ряда или любому компоненту препарата; застойная сердечная недостаточность без лечения; нестабильная стенокардия; обструкция выносящего тракта левого желудочка; острый инфаркт миокарда и в течение 1 месяца после перенесенного инфаркта миокарда; тяжелая печеночная недостаточность; тяжелая почечная недостаточность (СКФ <30 мл/мин) включая пациентов, находящихся на диализе; непереносимость лактозы, дефицит лактазы, синдром глюкозо-галактозной мальабсорбции; беременность и период грудного вскармливания; применение у женщин детородного возраста, не пользующихся надежными методами контрацепции; возраст до 18 лет (эффективность и безопасность не изучены); одновременное применение с мощными ингибиторами CYP3A4 (кетоконазол, итраконазол, эритромицин, ритонавир, тролеандомицин); с циклоспорином; одновременное применение с грейпфрутом или грейпфрутовым соком.
С осторожностью. Синдром слабости синусового узла (без электрокардиостимулятора); дисфункция левого желудочка сердца; ишемическая болезнь сердца; нарушения функции печени средней степени тяжести; нарушения функции почек легкой и средней степени тяжести; перитонеальный диализ; одновременное применение с индукторами/субстратами изофермента CYP3A4, мидазоламом, метопрололом, дигоксином; хроническая сердечная недостаточность (до начала применения препарата необходимо достичь компенсации хронической сердечной недостаточности); пожилой возраст.
Побочное действие. Наиболее частыми нежелательными реакциями в клинических исследованиях и при обобщении данных постмаркетингового опыта применения являются следующие: периферические отеки, головная боль, приливы, тахикардия и сердцебиение.
Подробная информация содержится в инструкции по медицинскому применению лекарственного препарата Леркамен® 10 ЛСР-007057/09-250822 от 25.08.2022 г. и Леркамен® 20 ЛСР-006976/08-230822 от 23.08.2022 г.

1. *Barrios V., et all. ELYPSE STUDY. Blood Pressure, 2002; 11: 95-100.*

Антигипертензивная эффективность и переносимость лерканидипина в повседневной клинической практике: исследование ELYPSE. В исследовании ELYPSE оценивали эффективность и переносимость лерканидипина у пациентов с артериальной гипертензией (АГ) 1 или 2 степени. Это было открытое, наблюдательное, многоцентровое исследование в реальной клинической практике. Главная цель исследования была оценить антигипертензивную эффективность и переносимость препарата. Вторичная цель состояла в оценке комплаенса пациента. Лерканидипин 10 мг в сутки назначали пациентам (n=9059), которым было показано применение дигидропиридиновых антагонистов кальция. Длительность наблюдения 3 месяца. Средний возраст пациентов 63 года. Результаты: исходное АД 160±10/96±7 мм рт ст, ЧСС 77±9 уд в мин. Через 3 месяца наблюдения АД составило 141±11/83±7 мм рт. ст. и ЧСС 75± 8 уд в мин (p <0.001). Общая частота нежелательных явлений (НЯ) составила 6,5%, среди которых наиболее часто наблюдались головная боль (2,9%), отек ног (1.2%), приливы (1,1%) и сердцебиение (0,6%). Отмена терапии из-за НЯ составила менее 1%. В этом исследовании лерканидипин продемонстрировал хорошую эффективность и переносимость в повседневной клинической практике.

2. *Leonetti G. et al. COHORT Study. Am J Hypertens. 2002 Nov;15(11):932-40.*

Переносимость длительного лечения лерканидипином по сравнению с амлодипином и лацидипином у пожилых пациентов с артериальной гипертензией. В исследовании COHORT изучали профиль переносимости лерканидипина по сравнению с двумя другими антагонистами кальция (амлодипин и лацидипин) у пожилых пациентов с артериальной гипертензией. Это многоцентровое, двойное слепое, в параллельных группах исследование, с участием 828 пожилых пациентов, ≥60 лет, рандомизированных в группы лерканидипина 10 мг/день (n=420), амлодипина 5 мг/день (n=200) или лацидипина 2 мг/день (N=208). При неудовлетворительном контроле АД дозу препарата удваивали, далее к терапии добавляли эналаприл или атенолол (при необходимости - диуретики). Пациентов наблюдали в среднем 12 месяцев. Первичной конечной точкой исследования была оценка частоты развития периферического отека в трех группах лечения. Также безопасность препаратов оценивалась на основании частоты развития других нежелательных явлений, симптомах, изменениях самочувствия пациента, частоте сердечных сокращений, лабораторных тестах и ЭКГ. Результаты: У пациентов, получавших амлодипин, значительно чаще наблюдались отеки ног (19%; p<0.001) и чаще встречались случаи раннего отказа от терапии из-за отека (8,5%); по сравнению с лерканидипином (9% и 2.1%) и лацидипином (4% и 1.4%). Также симптомы, связанные с отеком (отек и тяжесть в нижних конечностях), значительно чаще (P <0,01) возникали при применении амлодипина (50% и 45% соответственно), чем при применении лерканидипина (35% и 33%) и лацидипина (34% и 31%). Большинство случаев отеков ног возникало в течение первых 6 месяцев, при этом разница между видами лечения была очевидна с момента начала лечения. Другие побочные эффекты, связанные с приемом препарата, не различались между видами лечения. Артериальное давление было одинаково эффективно снижено в трех группах. В группе лерканидипина в течение 6 месяцев АД, измеренное стоя, достоверно снизилось с 169 ± 11/ 98 ± 7 до 140 ± 15/84 ± 9 mm Hg (P<0.01). Случаев ортостатической гипотензии во время исследования не зарегистрировано. Два липофильных дигидропиридиновых антагониста кальция, лерканидипин и лацидипин, обладают антигипертензивным действием, сравнимым с таковым амлодипина, но имеют лучший профиль переносимости.

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Динамика распространённости модифицируемых факторов риска сердечно-сосудистых заболеваний в европейской части Российской Федерации. Южно-Российский журнал терапевтической практики. 2021;2(2):16-25]. DOI: 10.21886/2712-8156-2021-2-2-16-25
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