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МЕСТО ПАЦИЕНТОВ С ПРОМЕЖУТОЧНОЙ ФРАКЦИЕЙ ВЫБРОСА ЛЕВОГО ЖЕЛУДОЧКА В ОБЩЕЙ ПОПУЛЯЦИИ БОЛЬНЫХ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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Position of Patients with Mid-Range Ejection Fraction in the General Chronic Heart Failure Population

Резюме

В 2016г в рекомендациях Европейского общества кардиологов по диагностике и лечению острой и хронической сердечной недостаточности (ХСН) выделена новая группа пациентов с промежуточной фракцией выброса левого желудочка (пФВ ЛЖ), референтный интервал которой лежит в диапазоне 40-49%. В представленном обзоре освещены вопросы эпидемиологии, этиологии и диагностики ХСНпФВ, профиль биомаркеров и динамические фенотипы пациентов, рассмотрены принципы лечения и факторы, определяющие прогноз заболевания. Особое внимание уделено особенностям формирования разнородной когорты пациентов и целесообразности расширения существующей на сегодняшний день классификации ХСНпФВ путем введения двух переходных фенотипов.

Ключевые слова: *хроническая сердечная недостаточность, левый желудочек, промежуточная фракция выброса, динамические фенотипы, прогноз, принципы лечения*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The European society of cardiology guideline for the diagnosis and treatment of acute and chronic heart failure (CHF) in 2016 identified a new group of patients with mid-range left ventricular ejection fraction (LVEF) with reference interval in the range of 40-49%. This review highlights the issues of epidemiology and etiology of CHF, outlines the echocardiographic portrait, biomarker profile and patients` dynamic phenotypes, considers the guidelines of their managements and the prognosis of the disease determiner's factors. Special attention is paid to the peculiarities of the formation of this heterogeneous cohort of patients and the feasibility of expanding the existing CHF classification by introducing two transitional phenotypes.

Keywords: *chronic heart failure, left ventricle, mid-range ejection fraction, transition phenotypes, prognosis, guidelines of treatment*

Conflict of interests

The authors declare no conflict of interests

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ACE inhibitors / ARBs — angiotensin-converting enzyme / angiotensin type II receptor blockers, AHF — acute heart failure, BB — beta-blockers, BNP — natriuretic peptide type B, CHF — chronic heart failure, CHFmrEF — chronic heart failure with mid-range ejection fraction, CHFpEF — chronic heart failure with preserved ejection fraction, CHFrEF — chronic heart failure with reduced ejection fraction, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, DM — diabetes mellitus, ECHO-CG — echocardiography, EF — ejection fraction, ESC — European Society of Cardiology, FC — functional class, HF — heart failure, HFA — Heart Failure Association, HR — heart rate, hs-CRP — highly sensitive C-reactive protein, hs-TnT — highly sensitive troponin T, IHD — ischemic heart disease, LA — left atrium, LV — left ventricle, MI — myocardial infarction, MRA — mineralocorticoid-receptor antagonists, NP — natriuretic peptide, NT-proBNP — N-terminal pro-brain natriuretic peptide, NYHA — classification of the New York Heart Association, Ro-Th — X-ray of thoracic organs, ST2 — soluble suppression of tumorigenicity-2, STfR — soluble transferrin receptor

Introduction

About 26 million people worldwide suffer from chronic heart failure (CHF) today. Approximately 1–2% of the adult population in developed countries falls in this category of patients. Almost 70% of the population aged over 90 has this pathology. CHF is the most common cause of repeated hospitalizations among individuals over 65 years and ranks third in the structure of cardiovascular mortality after myocardial infarction and sudden cardiac death, respectively [3].

CHF is not only a severe medical problem; it also has a negative social and economic impact. The cost of managing CHF in Europe and the USA ranges from 1 to 2% of the healthcare budget, which is five times higher than the cost of managing oncological diseases. The frequency of hospitalizations for CHF continues to rise steadily. By 2050, CHF prevalence is expected to increase by 60% compared to 2010, mainly due to the elderly population [3, 4]. On the one hand, this is due to the growing risk factors for ischemic heart disease (IHD), and on the other hand, the improved quality of management of cardiovascular diseases and longer life expectancy of the population [5].

Classification of heart failure (HF) is conventionally based on the systolic function of the left ventricle (LV) that is demonstrated on ECHO-CG as ejection fraction (EF). For a long time, all patients with CHF were divided into two categories: CHF with reduced LVEF (CHFrEF) and with preserved LVEF (CHFpEF) [3, 6, 9, 10, 12]. However, there was no consensus on the threshold value of EF that divides these two categories: American, European and Russian guidelines cited different criteria (35–40%). International randomized studies also provided no single definition of reduced LVEF: some studies included patients with EF less than 35%, others — with EF less than 30%, and some — with EF less than 40%, which led to a wide variation in results.

Background

Clinical guidelines of the European Society of Cardiology for the diagnosis and management of acute and chronic heart failure 2012 referred to LVEF within the range of 35–50% as a «gray zone», but this group was still classified as CHFrEF due to insufficient prognostic data [10, 12, 15]. Shortly after, in 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) said in their recommendations that patients with EF from 40% to 50% belong to a mid-range group, but no specific name was given to it [10]. In studies performed by C. S. P. Lamand and S. D. Solomon in 2014, the term «chronic heart failure with mid-range LVEF (CHFmrEF)» was used for the first time instead of «gray zone»; it described patients with LVEF in the range from 40 to 49% [7, 8, 11]. At the same time, the previous recommendations of 2015 for the diagnosis and management of acute heart failure (AHF) and CHF still included two categories

of patients: CHFrEF with EF below 50% and CHFpEF with EF higher than 50%.

Therefore, the idea of a targeted study of CHF in patients long in the shadows arose long ago. However, it was advanced only in 2016 [12] when Adriaan Voors, while addressing the European Congress on Heart Failure and the World Congress on AHF in Florence, argued that this group of patients should be marked as a new phenotype. He called on researchers to work in this area as intensively as possible to better understand pathophysiological and clinical features of this category of patients, outline the goals of treatment, and study the outcomes and prognosis [7, 12]. After this congress, the guidelines of the European Society of Cardiology (ESC) officially included the term "CHF with mid-range (CHFmrEF) or moderately reduced LVEF" in HF classification [6, 13]. It was decided that patients with EF in the range of 40–49% fall in a new category of patients with HF that differs from others. The non-uniformity of available data on CHFmrEF posed new challenges for scientists in studying epidemiology, etiology, clinical and prognostic features of this type of HF. An important reason for the separate group of patients with CHFmrEF was their response to targeted therapy that differs from that in patients with CHFpEF and CHFrEF [7, 8, 11–15, 17, 18, 21].

Epidemiology and Etiology of Heart Failure in Patients with Mid-Range (40–49%) Ejection Fraction

According to multicenter studies and large registers (ESC HF Long-Term Registry, Koch, SwedeHF), the prevalence of CHFmrEF in the general population of patients with HF ranges from 10–24.9% [7, 12, 18–24].

Despite the relatively large number of studies conducted to date, data on gender and age characteristics of patients with CHFmrEF remain controversial [7, 8, 11–15, 17–24]. Some authors argue that the demographic parameters of patients with CHFmrEF are in many respects close to those with CHFrEF, while others demonstrate their greater similarity with CHFpVF. The mean age of patients with CHFmrEF in ESC HF Long-Term registry (n = 42,987) was comparable to CHFrFV (64.2 ± 14.2 years and 64.0 ± 12.6 years, respectively), while patients with CHFpEF were significantly older (68.6 ± 13.7 years, $p < 0.001$). In the CHART-2 study, age characteristics of patients with CHFmrEF were, on the contrary, closer to the patients with CHFpEF (69.0 ± 11.6 years and 71.7 ± 10.9 years, respectively), while individuals with CHFrEF were significantly younger (66.9 ± 12.7 years, $p <0.001$) [20].

Researchers also had contradictory views on gender characteristics of patients with CHFmrEF: according to some papers, male patients were predominant according to others, females were predominant [8, 12, 21, 23, 28, 42, 45].

According to large-scale registries (ESC HF — Long-Term, SwedeHF) and studies (TIME-CHF), the prevalence of IHD among patients with CHFmrEF varies between 42–61% [25–27]. Based on the analysis of the SwedeHF registry, in general, among the causes of CHFmrEF, arterial hypertension (AH) ranks first (64%), followed by atrial fibrillation (AF) (58%), IHD (53%), cardiomyopathy (CMP) (43%), and valvular defects (10%) [17, 21]. The high prevalence of IHD, dilated CMP and valvular defects make patients with CHFmrEF more similar to CHFrEF, while AH brings them closer to those with CHFpEF [15, 17, 20, 21].

High comorbidity is typical for patients with CHFmrEF. Chronic obstructive pulmonary disease (COPD) (12–36%), chronic kidney disease (CKD) (26%), diabetes mellitus (DM) (27%) and anemia (27–35%) are found in such patients with high frequency [11, 12, 17–19, 23, 26, 29, 30].

Diagnosis of CHF with Mid Range Ejection Fraction (40–49%)

According to current European and Russian recommendations, criteria for the diagnosis of CHF depend on LVEF. Diagnosis of CHFmrEF is valid in the presence of clinical symptoms of HF, decreased LVEF to 40–49%, increased level of natriuretic peptides, as well as structural changes in the heart (LV hypertrophy and/or increased size of the left atrium (LA)) and/or diastolic dysfunction (Table 1) [56].

In 2019, ESC proposed a new HFA-PEFF diagnostic algorithm that provided a step-by-step transition from initial clinical assessment to more specialized tests (Fig. 1). It includes finding symptoms of HF, conducting echocardiography (ECHO-CG) at rest and during exercise, determination of natriuretic peptide level (NP), as well as an invasive assessment of hemodynamics and determination of HF etiology [60]. How applicable this algorithm is to patients with CHFmrEF is not yet known. Specific studies will help assess its validity for this category of patients.

Echocardiographic profile of patients with heart failure with mid-range (40–49%) ejection fraction. There is still no clear echocardiographic profile of patients with CHFmrEF. Along with moderate LV systolic dysfunction, they often have diastolic rigidity and an enlarged left atrium. LV volume in these patients is between those in patients with CHFpEF and CHFrEF [12, 21, 31].

Table 1. *Determination of heart failure with preserved, mid-range and reduced left ventricular ejection fraction (adapted from Tereshchenko S. N., Galyavich A. S., Uskach T. M., etc. Chronic heart failure. Clinical Guidelines 2020". Russian Journal of Cardiology. 2020;25(11):4083. doi:10.15829/1560-4071-2020-4083).*

Type of CHF		CHFrEF	CHFmrEF	CHFpEF
Criteria	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	EF LV <40%	EF LV 40-49%	EF LV ≥50%
	3	-	1. NP level up[b]	1. NP level up[b]
			2. At least one of the additional criteria: a. appropriate structural change (LV hypertrophy and / or LA dilation) b. diastolic dysfunction	2. At least one of the additional criteria: a. appropriate structural change (LV hypertrophy and / or LA dilation) b. diastolic dysfunction

Note: [a]-signs may not be observed in the early stages of HF and in patients treated with diuretics, [b]-BNP >35 pg/ml and/or NT-proBNP >125 pg/ml
Abbreviations: BNP-B-natriuretic peptide type B, NP-natriuretic peptide, NT-proBNP-N-terminal fragment of brain natriuretic peptide, EF-ejection fraction, LV-left ventricle, LA-left atrium

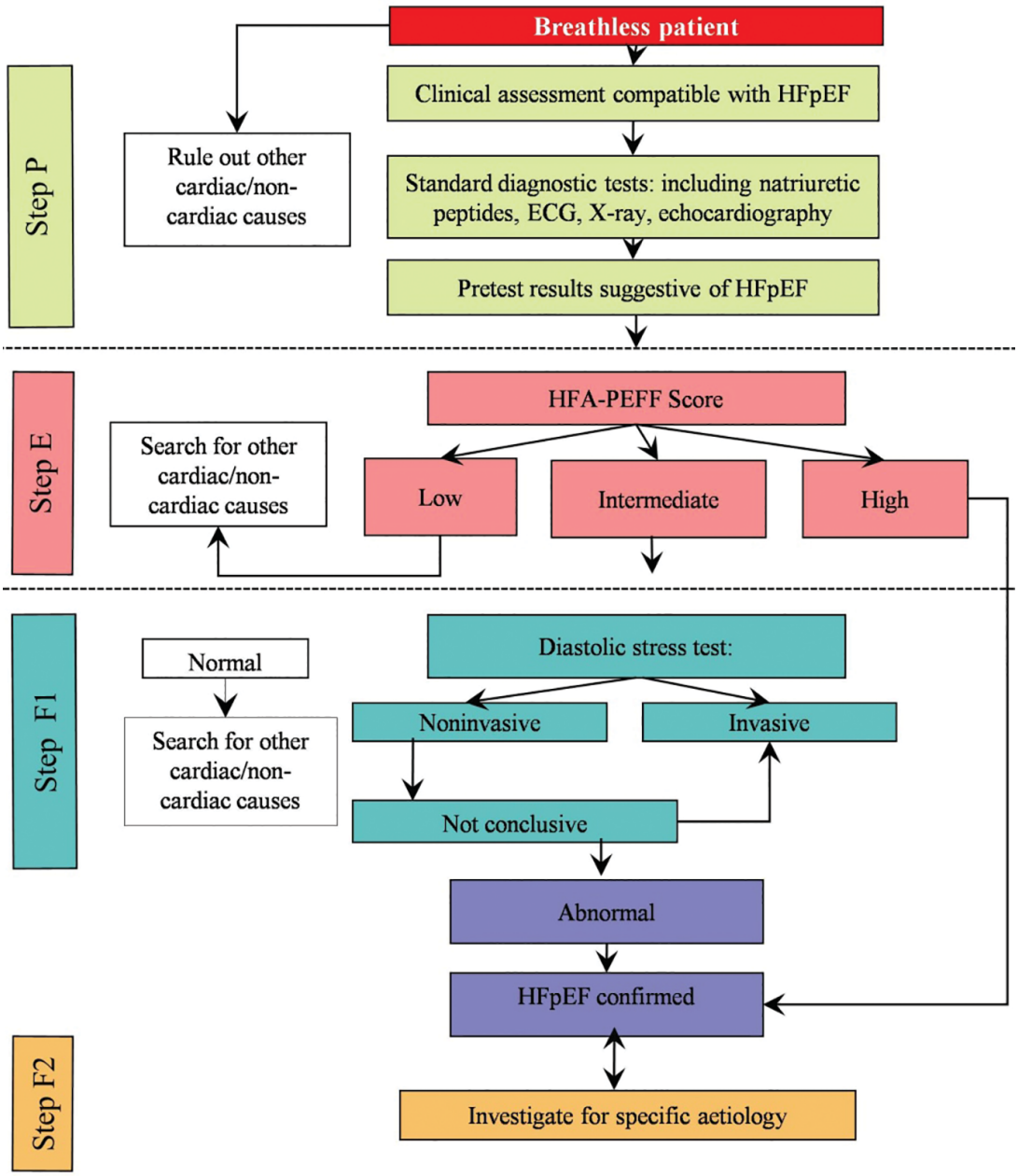

Figure 1. *The diagnostic algorithm of chronic heart failure with preserved left ventricular ejection fraction*
Abbreviations: HFA — Heart Failure Association, step P — Pretest Assessment, step E — Echocardiographic and Natriuretic Peptide Score, if it was not determined at the first stage, step F1-Functional testing in Case of Uncertainly, step F2- Final Aetiology, (adapted from Pieske B, in Tschöpe c, De Boer RA et al. How to Diagnose heart failure with Preserved ejection fraction: The HFA Diagnostic Algorithm-PDF: Consensus recommendation of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019;40(40):3297-3317. doi: 10.1093/eurheartj/ehz64)

Table 2. *Risk of the primary composite end-point: cardiovascular death or HF-related hospitalization, according to the ESC LV EF classification. (adapted from P. Moliner, et al., Bio-profiling and bio-prediction of chronic heart failure with an average ejection fraction, Int J European repair.2018;257:188-192, Doi: 10.1016/j. ijcard. 2018. 01. 119).*

	CHFrEF (n=800)			CHFmrEF (n=134)			CHFpEF (n=135)		
	HR	95% CI	p-Value	HR	95% CI	p-Value	HR	95% CI	p-Value
NT-proBNP	1.74	(1.53-1.98)	<0.001	**2.57**	**(1.81-3.65)**	**<0.001**	1.22	(0.94-1.57)	0.13
hs-TnT	1.67	1.74-1.89)	<0.001	**4.72**	**(2.81-7.94)**	**<0.001**	1.76	(1.34-2.32)	<0.001
ST2	1.39	1.23-1.56)	<0.001	**2.00**	**(1.45-2.76)**	**<0.001**	1.04	(0.80-1.35)	0.79
Galectin-3	1.38	(1.23-1.56)	<0.001	1.69	(1.34-2.15)	<0.001	**1.72**	**(1.31-2.27)**	**<0.001**
hs-CRP	1.33	(1.14-1.54)	<0.001	**1.58**	**(1.09-2.28)**	**0.016**	1.18	(0.88-1.58)	0.28
Cystatine-C	1.37	(1.23-1.53)	<0.001	**1.62**	**(1.29-2.05)**	**<0.001**	1.33	(1.08-1.64)	0.007
Neprilysin	1.13	(1.00-1.27)	<0.05	1.14	(0.85-1.50)	0.35	**1.38**	**(1.12-1.70)**	**0.002**
STfR	1.12	(1.05-1.36)	0.006	**1.54**	**(1.12-2.14)**	**0.009**	1.19	(0.86-1.60)	0.25

Abbreviations: NT-proBNP – N-terminal pro-brain natriuretic peptide, ST2 – soluble suppression of tumorigenicity type 2, hs-TnT – high-sensitivity troponin T, hs-CRP – high-sensitivity C-reactive protein, STfR – растворимый soluble transferrin receptor

CHFmrEF is believed to be an early stage of CHFrEF. Diastolic dysfunction of the left ventricle due to its eccentric remodeling brings these patients closer to patients with CHFrEF. For more accurate diagnosis, stress ECHO-CG or invasive measurement of LV filling pressure is used [54].

Profile of biomarkers in patients with heart failure with mid-range ejection fraction. In general, the biomarker profile of patients with CHFmrEF is more similar to that of CHFrEF, with the exception of pro-brain natriuretic peptide (NT-proBNP) — this parameter in patients with CHFmrEF is similar to patients with CHFpEF [38].

In order to predict the risk of death and re-hospitalization in patients with CHFmrEF, the same biomarkers can be used as in cases of CHFrEF (Table 2): NT-proBNP, galectin-3, soluble suppression of tumorigenicity-2 (ST2), highly sensitive troponin T (hs-TnT), cystatin C, highly sensitive C-reactive protein (hs-CRP) and soluble transferrin receptor (STfR). It is noteworthy that the prognostic value of these biomarkers in cases of CHFmrEF is higher than in cases of CHFrEF. Hs-TnT has the highest predictive value in this category of patients, which is apparently due to their high sensitivity, even to minimal ischemic myocardial damage [33, 38].

Heart Failure with Mid-Range Ejection Fraction (40–49%) as a Transitional Phenotype

Currently, most of the data related to CHFmrEF are based on a single assessment of LVEF. However, it is known that LVEF is not a fixed parameter and can vary under the influence of several factors. Heart rate (HR) during examination, rhythm and conduction disorders, hemodynamic overload of valvular or non-valvular origin, as well as ischemic changes in the myocardium, have a significant effect on LVEF. So, in patients with IHD the true level of LVEF can be distorted due to the presence of several segments of the myocardium with different grades of ischemia. Patients with AF and ventricular tachysystole may experience a false decrease in LVEF; accurate assessment of LVEF is difficult in patients with left bundle branch block and implanted pacemakers [15, 45].

This raises the question of whether patients with CHFmrEF are a separate pathophysiological cohort or whether they are better described as a transition phenotype between CHFpEF and CHFrEF. In most cases, individuals with CHFmrEF are either patients with a history of CHFrEF who have recovered LV systolic function or patients with CHFpEF, who, on the contrary, have this function decreased. Clear evidence of this assumption is the results of a five-year observation performed by Dunlay S. M et al. (2012) among 1,233 in patients with HF with initially reduced EF who had it increased by an average of 7% (p <0.001). A greater increase was observed in women, younger patients, individuals with atrial fibrillation, without ischemic heart disease, diabetes mellitus, shorter duration of HF, higher functional class (FC) according to NYHA (classification of the New York Heart Association) and those who received treatment in accordance with evidence-based medicine. In turn, elderly patients and those with ischaemic heart disease with preserved LV systolic function demonstrated a decrease in EF by 6% (p <0.001) [7, 41, 42].

Another confirmation of a «transition phenotype» is the CHART-2 study that included 3,480 patients with CHF; patients dynamically switched from one category of LVEF to another within three years of follow-up (Fig. 2).

Rate of EF changes was highest in patients with CHFmrEF: by the end of the first year of follow-up, almost half of these patients moved to the group of CHFpEF,

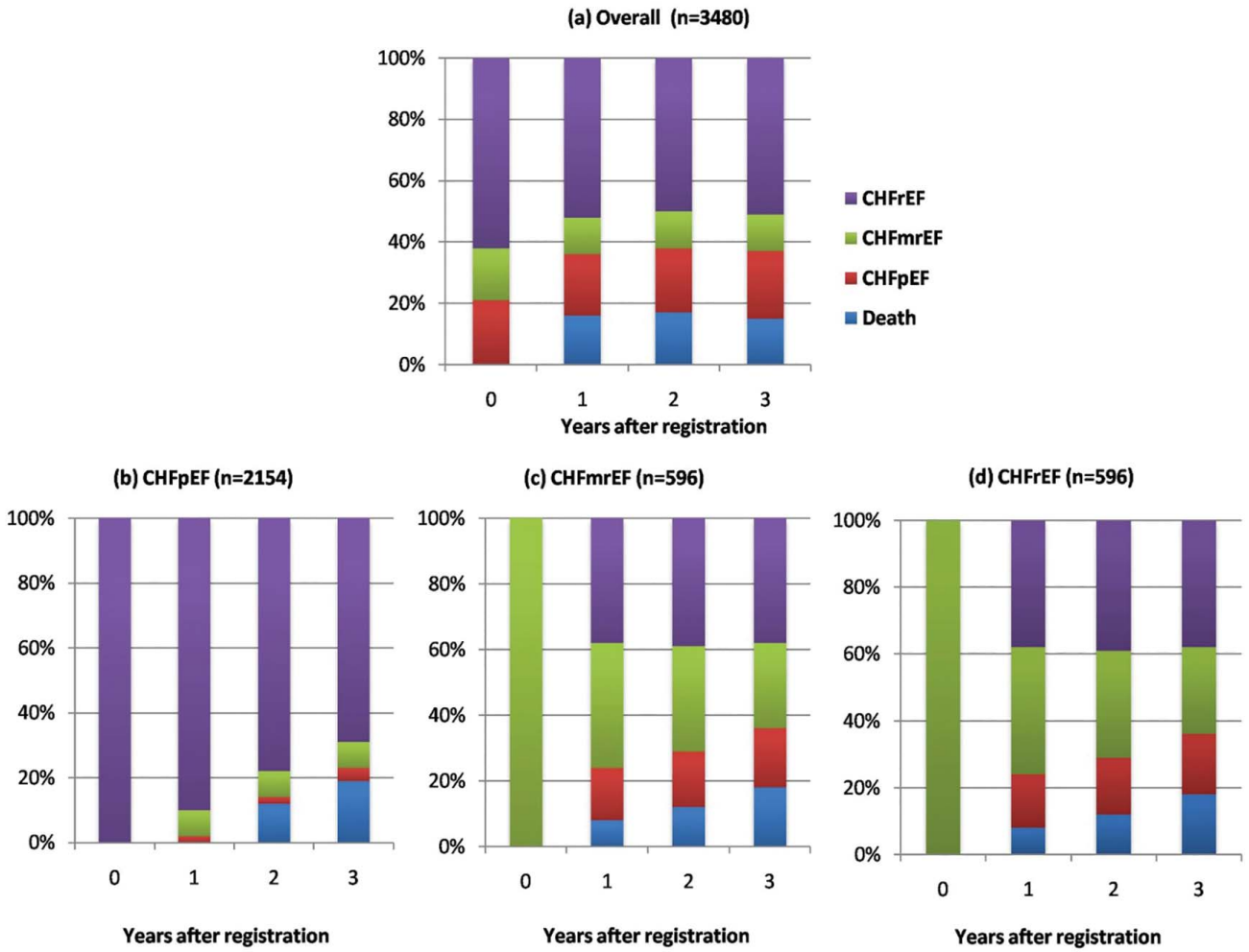

Figure 2. *Transitions of heart failure among heart failure patients by left ventricular ejection fraction.*
Abbreviations: (a) Overall population, (b) chronic heart failure with preserved ejection fraction (CHFpEF), (c) chronic heart failure with mid-range ejection fraction (CHFmrEF), and (d) chronic heart failure with reduced ejection fraction (CHFrEF) patients. (adapted from Tsuji K., Sakata Y., Nochioka K., et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction — a report from the CHART-2 Study. European journal of Heart Failure. 2017; 19(10): 1258-1269. doi: 10.1002/ejhf.807. 1-12.)

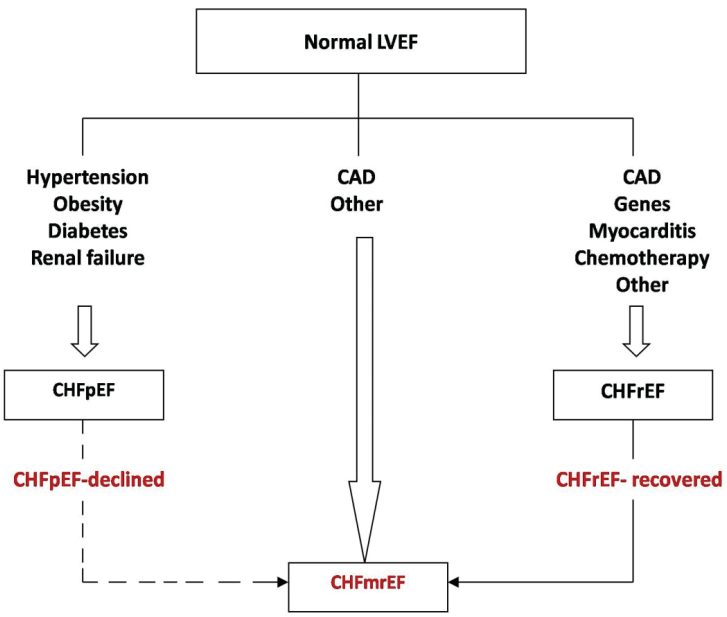

Figure 3. *Dynamic phenotypes of heart failure with mid-range left ventricular ejection fraction (adapted from Bayés-Genís A., Núñez J., Lupón J. Heart Failure with mid-range ejection fraction: a transition phenotype? European journal of Heart Failure. 2017; 19(12): 1635-1637. doi: 10.1002/ejhf.977)*

16% — to the group of CHFrEF, and only one in thirteen — from CHFpEF to CHFmrEF. It is worth noting that 20% of patients with CHFrEF managed to restore EF to mid-range EF. During the three-year follow-up period, one in five patients with CHFrEF and CHFmrEF was able to both restore and reduce LVEF [20].

In particular, IHD is most likely the most common cause of LVEF decrease [15, 25, 43, 44]. According to numerous studies, patients with CHFpEF who develop myocardial infarction (MI) gradually, within 4–5 years, move to the CHFrEF group, passing the stage of mid-range EF [12]. Patients with CHFpEF and no optimal management of IHD demonstrated progressively decreased LVEF. At the same time, patients receiving adequate treatment showed a slower decrease in EF [7, 8, 12, 20, 21, 23, 41, 42].

Therefore, controversial results of studies that demonstrate the similarity of some patients with CHFmrEF with patients with CHFrEF, and others — with CHFpEF, can be explained by the fact that mid-range EF is, in some cases, "recovered" CHFrEF, and in the other cases — "reduced" CHFpEF. Therefore, some researchers argue for expanding the current classification of CHF and introducing two transitional phenotypes of CHFmrEF: CHFrEF-restored and CHFpEF-reduced. In their opinion, patients with seemingly the same EF can have different pathophysiological mechanisms of LV systolic dysfunction, which means different outcomes and treatment approaches (Fig. 3) [7, 15].

Prognosis of Chronic Heart Failure with Mid-Range Ejection Fraction

In patients with cardiovascular diseases, LVEF is one of the most powerful predictors of fatal and non-fatal cardiovascular events. The theory that CHF prognosis closely correlates with the extent of the decrease in LV systolic function was confirmed in a large Cardiovascular Health Study that included 5,532 patients aged 65 and over. According to the results of the five-year follow-up, the highest mortality rate was observed in patients with CHFrEF (154 per 1,000 person-years), slightly lower — in individuals with CHFmrEF (115 deaths per 1,000 person-years) and the lowest — in patients with CHFpEF (87 deaths per 1,000 person-years, $p < 0.001$) [12, 46]. Analysis of the ESC-HF-LT register that included 16,354 patients also showed that, among patients with CHFmrEF, mortality from all causes did not significantly differ from mortality in CHFrEF ($p = 0.07$) or CHFpEF ($p = 0.17$). The rate of non-cardiovascular mortality turned out to be significantly higher in patients with CHFmrEF and CHFpEF (27.8% and 30.7%, respectively) compared with CHFrEF (20.1%, $p = 0.059$) [21].

Independent predictors of an adverse outcome in patients with CHFmrEF included elderly age, CKD, mitral regurgitation, and NYHA class III–IV CHF [21, 53]. Patients with restored EF had better survival and a more favorable biomarker profile compared with patients with CHF with stable EF, regardless of its values [34, 42, 43, 46–48]. As long as CHFmrEF is stable, the prognosis for it is comparable to CHFpEF. If myocardial infarction or CHF decompensation develops and hospitalization is required, the risk of mortality increases and reaches that with CHFrEF.

Treatment Principles of Patients with Heart Failure with Mid-Range Ejection Fraction

In 2019, the expert consensus of the ESC Heart Failure Association was published that included recommendations for the management of CHFmrEF [58]. Authors of this document emphasize that no prospective studies have been carried out that include patients with CHFmrEF; all available information about this category of patients is based on the results of retrospective studies that included mainly patients with CHFpEF, and to a lesser extent — with CHFrEF [49, 58].

The treatment principle for patients with CHFmrEF primarily focuses on the control of cardiovascular diseases that cause HF (AF, AH, IHD, pulmonary hypertension) and comorbidities (diabetes, CKD, anemia, DM, iron deficiency, COPD, pneumonia, obesity) [50]. Since patients with CHFmrEF usually suffer from AH, AF or IHD, the most commonly prescribed drugs are angiotensin-converting enzyme inhibitors / type II angiotensin receptor inhibitors (ACE inhibitors/ARBs) and beta-blockers (BB), less commonly — mineralocorticoid-receptor antagonists (MRA) [15]. These groups of agents have a proven effect on prognosis in patients with CHFrEF. Since CHFmrEF is often a restored CHFrEF [7, 8, 12, 20, 21, 23, 41, 42], it is reasonable to assume the effectiveness of these agents for the treatment of this category of patients. The importance of drug treatment aimed at restoring LVEF and preventing its further decrease is not questioned [20].

According to the results of the analysis of the Swedish Heart Failure registry, the efficacy of ACE inhibitors/ARBs in improving prognosis in patients with CHFmrEF is higher than in patients with CHFpEF [15]. In the CHARM study, the use of candesartan equally improved the prognosis of patients with CHFmrEF and CHFrEF [55]. Data from several systematic reviews and meta-analyses suggest that the use of valsartan/sacubitril can reduce the severity of

clinical manifestations of HF and the risk of hospitalization not only in patients with CHFrEF but also in individuals with CHFmrEF [59].

Information on the effectiveness of BB in patients with CHFmrEF is contradictory [12]. Some sources indicate that BB contribute to the increase in LVEF, while others demonstrate the opposite [20, 42]. Results of the CHART-2 study and the analysis of the Swedish Heart Failure registry demonstrate that BB improve the outcome in patients with CHFmrEF only if these patients have IHD [15, 17, 20]. A number of studies showed that the effectiveness of BB with CHFmrEF in relation to the prognosis depends on the patient's heart rhythm: BB reduce mortality in patients with sinus rhythm, while in cases of AF, they have no significant effect on the prognosis, despite the improvement in EF [52, 58]. According to the expert consensus decision of the ESC Association of Heart Failure 2019, BB can be considered for outpatient treatment in cases of symptomatic CHF with sinus rhythm in order to reduce the risk of general and cardiovascular mortality [58].

Whether MRA is advisable in patients with CHFmrEF remains an open question since all the evidence was obtained based on a retrospective study of a small subgroup of patients. According to the TOPCAT study that included patients with LVEF in the range of 44–85%, the administration of MRA did not bring down mortality from cardiovascular causes [51]. The subsequent subanalysis of this study suggests that MRA can be considered for patients with LVEF more than 45% in order to reduce the risk of cardiovascular mortality and hospitalization rate due to HF decompensation [55, 56, 16, 58].

Iron deficiency developing along with CHF negatively affects the quality of life, disease course and prognosis. Current guidelines highlight the need for iron deficiency screening in patients with NYHA FC II–IV CHF, regardless of LVEF and hemoglobin level [61]. Intravenous administration of iron is recommended for patients with CHFrEF. However, for patients with CHFmrEF, the feasibility of this has not yet been proven. Results of FAIR-HF, CONFIRM-HF, and EFFECT-HF studies are expected; these studies also evaluated the efficacy and safety of intravenous iron administration, including 40–45% of patients with LVEF [56, 58].

Experts of the European Consensus 2019 of ESC Association of Heart Failure noted that since 2016, no new information on using diuretics in patients with CHF was published [58]. In this connection, further randomized clinical trials are required to evaluate the effectiveness of different groups of diuretics. Given the lack of clear data on the positive effect of diuretics on LVEF, these agents are recommended for use only for congestions in patients with CHF [57, 58].

According to the clinical recommendations of RCS-2020, using digoxin in patients with CHFmrEF should be carried out according to the same principles and the same rules as for patients with CHFrEF [56].

Conclusion

Patients with CHF and EF within the range of 40–49% for many years belonged to the so-called «gray zone»; they were excluded from most clinical studies or were put in the same category as patients with CHFrEF. After being grouped in a separate phenotype of CHFmrEF in 2016, this group of patients was analyzed in detail. However, the results of studies conducted to date remain controversial. This highlights that the further study of clinical, morphological and laboratory characteristics of CHFmrEF should be conducted, and factors that cause a decrease or contribute to the restoration of LV systolic function should be determined. Further prospective studies will possibly allow developing an effective treatment strategy for this poorly studied group of patients.

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