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Heart failure with preserved and mildly reduced ejection fraction — from diagnosis to treatment

Niewydolność serca z zachowaną i łagodnie obniżoną frakcją wyrzutową — od diagnozy do leczenia

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Abstract

While diagnostic algorithms and management of heart failure with reduced ejection fraction (HFrEF) are well established, this is not the case for the two remaining HF phenotypes (HF with mildly reduced, HFmrEF, and preserved ejection fraction, HFpEF). The recent 2021 European Society of Cardiology and the 2022 American College of Cardiology/ /American Heart Association/Heart Failure Society of America guidelines share similarities but also demonstrate some differences in their approach to HFmrEF and HFpEF, both with respect to diagnosis and treatment. The aim of this review is to provide some insight into the current knowledge of HFmrEF and HFpEF with a primary focus on epidemiology, diagnosis and pharmacological treatment, including a comparison of the European and American guidelines.

Keywords: heart failure with preserved ejection fraction, heart failure with mildly reduced ejection fraction, diagnosis, drug therapy

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Introduction

Since the introduction of a third phenotype of heart failure (HF) — HF with mid-range (subsequently renamed "mildly reduced") left ventricular ejection fraction (LVEF) in 2016 [1, 2] there has been a growing interest in this so-called "middle child" of HF [3] with over 600 publications in MEDLINE on this specific topic alone. Even more attention has been given to the "youngest child" of HF [3] — HF with preserved LVEF (HFpEF) with over 10,000 publications in MEDLINE. Importantly, patients with HF with mildly reduced LVEF (HFmrEF) were often a part of HFpEF trials, and in the previous American HF guidelines, patients with HF and LVEF between 41 and 49% were part of the HFpEF group as "borderline HFpEF" [4–7]. Both, the 2021 European Society of Cardiology (ESC) guidelines and the 2022 AHA/ACC/ /HFSA Guideline, divide HF into three phenotypes: HF with reduced LVEF (HFrEF; LVEF ≤ 40%), HFmrEF (LVEF 41–49%) and HFpEF (LVEF ≥ 50%). Despite positive outcomes of the EMPEROR-Preserved [4] and DELIVER trials [5], HFmrEF and HFpEF remain a challenge in terms of treatment as well as diagnosis. This review focuses on HFmrEF and HFpEF in the context of their epidemiology, risk factors, diagnosis, pharmacological and non-pharmacological treatment, and

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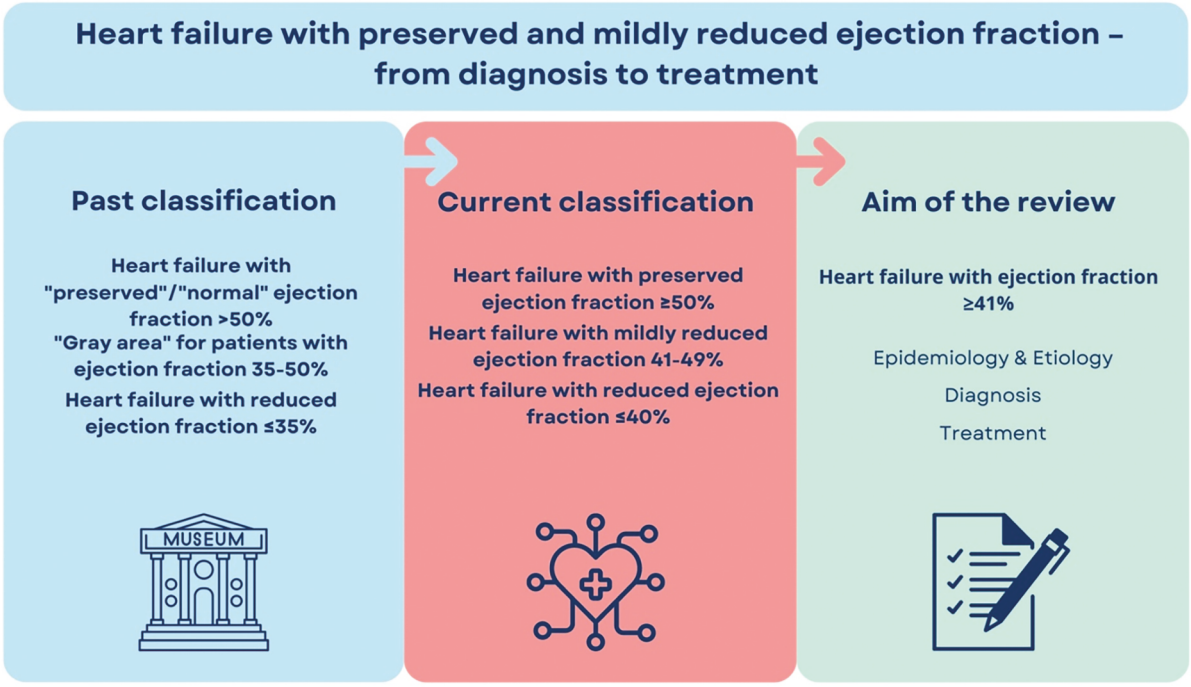

Figure 1. Graphical abstract

compares the approach to HFmrEF and HFpEF in the most recent European and American guidelines.

Epidemiology & Aetiology

HFpEF makes up a large proportion of HF patients — depending on the studied population (chronic vs. acute HF) even over half of HF patients. Still, the proportion of HFpEF patients may remain underestimated, given that they are most often outpatients, frequently treated by primary care physicians, and, if hospitalized, often admitted to internal or geriatric wards (contrary to HFrEF patients who are usually admitted to cardiology wards). In contrast, HFmrEF, with its narrow span of LVEF (41–49%), is the smallest of the three groups, usually constituting from 10 to 25% of HF patients [8–10] (Figure 2).

HFpEF patients are usually older compared to patients with HFrEF and HFmrEF. In comparison with HFmrEF and HFrEF, there is a greater representation of women in the HFpEF patient population [11]. Obesity has been proposed as a main cause of subclinical systemic inflammation and myocardial remodelling in HFpEF and, along with hypertension, is considered the main modifiable risk factor for HFpEF. Although the prevalence of diabetes is similar among the three HF phenotypes, obesity-related cardiometabolic traits (including insulin resistance) are stronger risk factors for developing future HFpEF than HFrEF, with a higher risk for HFpEF in women than men [12]. HFpEF

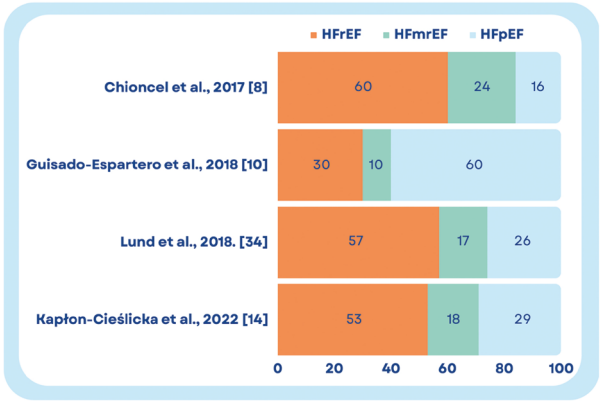

Figure 2. Proportions of heart failure subgroups

has a higher incidence of atrial fibrillation (AF) than HFrEF, probably because HFpEF and AF share common risk factors (older age, hypertension, obesity, inflammation) [13]. With regard to many characteristics listed above (e.g. age, gender, hypertension), HFmrEF often appears "in-between" HFpEF and HFrEF. Still, an important common feature of HFmrEF and HFrEF is the prevalence of epicardial coronary artery disease — significantly higher than in HFpEF [14]. In contrast, the PROMIS-HFpEF study reported a high occurrence of coronary microvascular dysfunction in HFpEF [15]. Table 1 compares the main characteristics between HFpEF, HFmrEF and HFrEF.

Table 1. Main characteristics of heart failure patients in relation to ejection fraction category.

	Chioncel et al., 2017 [8] (Ambulatory patients)			Guisado-Espartero et al., 2018 [10] (Hospitalized patients)			Lund et al., 2018 [34] (Ambulatory patients)			Kapłon-Cieślicka et al., 2022 [14] (Hospitalized patients)		
	HFpEF	HFmrEF	HFrEF	HFpEF	HFmrEF	HFrEF	HFpEF	HFmrEF	HFrEF	HfpEF	HFmrEF	HFrEF
Number of patients	1462 (16%)	2212 (24%)	5460 (60%)	1664 (60%)	281 (10%)	808 (30%)	1953 (26%)	1322 (17%)	4323 (57%)	1729 (29%)	1082 (18%)	3140 (53%)
Age, years	69	64	64	81	80	79	67	65	65	74	71	66
Female, %	48	32	22	63	42	38	46	30	26	56	40	25
BMI, kg/m^2	28,4	28,6	27,8	29	28	27	29	28	27	-	-	-
SBP, mmHg, mean	131	127	122	139	140	130	140	130	126	140	130	120
NYHA III–IV, %	20	18	31	35	37	43	39	42	66	76	78	86
DM, %	29	31	32	47	54	49	28	29	27	34	38	35
AF, %	32	22	18	61	56	15	31	26	26	58	56	44
COPD, %	14	12	15	25	21	29	-	-	-	20	19	18
CKD, %	20	17	20	39	45	45	-	-	-	24	23	26
HT, %	85	70	60	89	83	81	28	13	49	74	68	58
IHD, %	24	42	49	16	38	49	50	67	65	31	52	54
Valve disease, %	20	10	4	21	19	11	-	-	-	20	14	6.2

AF — atrial fibrillation; BMI — body mass index; CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease; DM — diabetes mellitus; HFmrEF — heart failure with mildly reduced ejection fraction; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction; HT — hypertension; IHD — ischaemic heart disease; NYHA — New York Heart Association Functional Classification; SBP — systolic blood pressure.

On the other hand, HFmrEF may constitute a transitioning stage between HFpEF and HFrEF, with an overlap of patients worsening from preserved LVEF and those improving from HFrEF (with some of them fulfilling the criteria of HF with improved LVEF, HFimpEF) [16]. Interestingly, there are some discrepancies between the 2022 American guidelines, the 2021 European guidelines and the earlier 2021 Universal Definition and Classification of HF with regard to the diagnostic criteria of HFimpEF [2, 17, 18]. All of those definitions include previous LVEF ≤ 40% (HFrEF) but differ with respect to the required follow-up LVEF measurement (> 40% in the American, ≥ 50% in the European, and > 40% with a rise of at least 10% in the Universal definition). In the 2022 American guidelines, HFimpEF is considered a subgroup of HFrEF [17].

Analogously to HFrEF, which can have different aetiologies, further subtypes can be identified within HFpEF, depending on its direct cause (e.g. hypertrophic cardiomyopathy, infiltrative cardiomyopathies (such as amyloidosis, sarcoidosis, or haemochromatosis), storage diseases (such as Fabry disease, glycogen storage diseases, or Gaucher disease), autoimmune diseases, but also on a specific cluster of characteristics and risk factors (e.g. obese phenotype, elderly patients with high prevalence of kidney disease, etc.) [19].

Definitions and diagnosis

Diagnosis of HFmrEF

According to the ESC guidelines [2], the following criteria are required to diagnose HFmrEF:

— the presence of symptoms and/or signs of HF and
— LVEF between 41 and 49%.

Evidence of structural heart disease is not necessary for the diagnosis, however, makes it much more likely. In comparison to the European guidelines, the American guidelines [17] do require evidence of increased left ventricular (LV) filling pressures (such as elevated levels of natriuretic peptides or E/e' ratio of ≥ 15 on echocardiography) to establish HFmrEF diagnosis.

Diagnosis of HFpEF

There is still no consensus on HFpEF diagnostic criteria. No single parameter — whether echocardiographic or biochemical — can clearly confirm or exclude the diagnosis of HFpEF. Moreover, a multitude of definitions of HFpEF results from the complex and not fully understood pathophysiology of this disease [2, 20, 21]. As a result, some patients are overdiagnosed, although in other cases, HFpEF is overlooked.

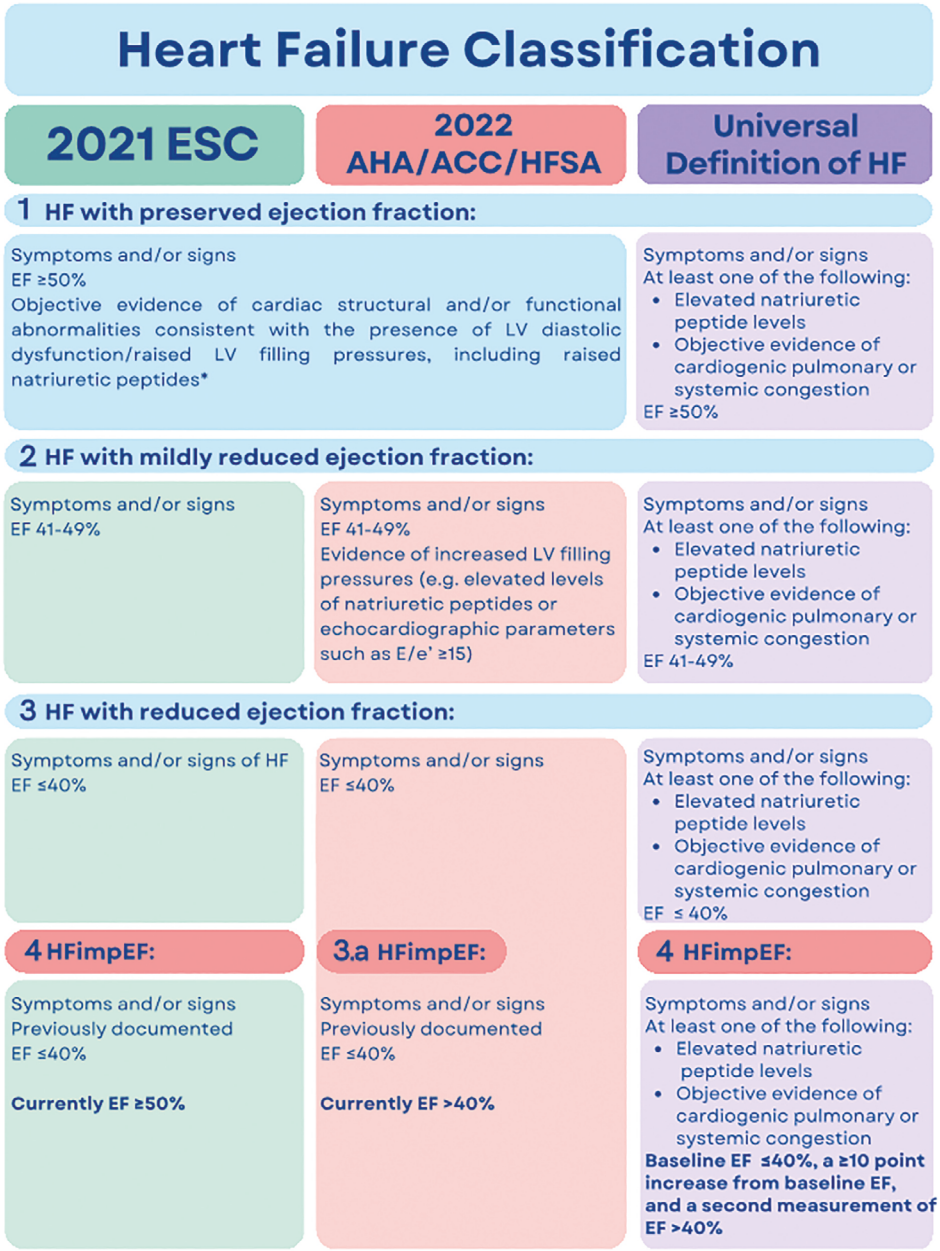

Figure 3. Heart failure classification. *similar criteria with slightly different thresholds in the evidence of increased LV filling pressures. 2021 ESC — 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure; 2022 AHA/ACC/HFSA — 2022 AHA/ /ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines; EF — ejection fraction; HF — heart failure; HFimpEF — heart failure with improved ejection fraction; LV — left ventricular.

The 2021 ESC guidelines [2] recommend a simplified approach to the definition of HFpEF. The criteria required for the diagnosis are:

— symptoms and signs of HF,
— LVEF ≥ 50%,
— objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides and echocardiographic indices of concentric LV hypertrophy, enlarged left atrium, elevated LV filling pressures (E/e' of > 9) and/or increased estimated pulmonary artery pressure. The likelihood of HFpEF diagnosis is enhanced with the number of positive parameters.

In contrast to the 2016 ESC guidelines [1], elevated levels of natriuretic peptides are no longer a separate criterion necessary for the diagnosis. The definition of HFpEF in the 2022 AHA/ACC/HFSA guideline [17] is very similar to

HFA-PEFF Diagnostic score (adapted from 20)

Measurement	Criterion	Points
Functional echocardiographic parameters	Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP>35mm/Hg) or Age < 75 years: septal e' < 7 cm/s or lateral e' < 10 cm/s or Age ≥ 75 years: septal e' < 5 cm/s or lateral e' < 7 cm/s	2
	Average E/e' ratio 9–14 or GLS < 16%	1
Morphological echocardiographic parameters	LAVI>34/40 mL/m^2 (SR/AF) or LVMI≥149/122 g/m^2 (m/w) and RWT>0,42	2
	LAVI 29-34/34-40 mL/m^2(SR/AF) or LVMI ≥115/95 g/m^2(m/w) or RWT>0,42 or LV wall thickness≥ 12mm	1
Natriuretic peptide levels in sinus rhythm	BNP > 80 pg/mL NT-proBNP > 220 pg/mL	2
	BNP 35 – 80 pg/mL NT-proBNP 125 – 220 pg/mL	1
Natriuretic peptide levels in atrial fibrillation	BNP > 240 pg/mL NT-proBNP > 660 pg/ml	2
	BNP 105-240 pg/mL NT-proBNP 375-660 pg/mL	1

H_2FPEF score (adapted from 21)

Clinical variable	Value	Points
Heavy	BMI > 30kg/m2	2
Hypertensive	At least 2 antihypertensive drugs	1
Atrial Fibrillation	Paroxysmal or persistent	3
Pulmonary hypertension	PASP >35mm	1
Elder	Age > 60 yrs	1
Filling pressure	Doppler echocardiography E/e'>9	1

Figure 4. The Heart Failure Association (HFA)-PEFF and the H_2FPEF score. AF — atrial fibrillation; BMI — body mass index; BNP — brain natriuretic peptide; GLS — global longitudinal strain; LAVI — left atrial volume index; LV — left ventricular; LVMI — left ventricular mass index; (m/w) — men/women; NT-proBNP — N-terminal pro-brain natriuretic peptide; PASP — pulmonary artery systolic pressure; RWT — relative wall thickness; SR — sinus rhythm; TR — tricuspid regurgitation

that in the 2021 ESC guidelines, however, with somewhat different thresholds for some of those criteria.

Figure 3 compares HF classifications between the 2021 ESC, 2022 AHA/ACC/HFSA guidelines and the Universal Definition and Classification of HF.

Before the publication of the current European and American guidelines, two scores have been proposed to estimate the probability of HFpEF in symptomatic patients with preserved LVEF. The European HF Association (HFA)-PEFF score [20] is based on the experts' opinions and focuses on major and minor criteria in three categories: echocardiographic measurement of function, morphology and natriuretic peptide concentrations. The American H_2FPEF score [21] is cohort-derived and includes 4 clinical variables (body mass index, antihypertensive treatment, presence of AF and age) and 2 echocardiographic parameters (E/e ratio, pulmonary artery systolic pressure). Both scores are presented in Figure 4. A diagnostic score for HFpEF in the HFA-PEFF score is ≥ 5 points, and in the H_2FPEF score ≥ 6 points; an HFA-PEFF score of 2–4 points and H_2FPEF of 2–5 points requires additional testing; HFA-PEFF score ≤ 1 and H_2FPEF score ≤ 1 makes HFpEF diagnosis very unlikely. Unsurprisingly, the two scores identify partially different patients as having HFpEF. While the American H_2FPEF score relies mostly on comorbidities, it was referred to be a good tool for the initial assessment of the risk of HFpEF by physicians of various specialities, while the European HFA-PEFF score for the final diagnosis or exclusion of the disease by cardiologists, including HF specialists. The validity of H_2FPEF and HFA-PEFF scores in clinical practice has been studied multiple times [22–26]. Most of the current data suggests that these scores are very reliable tools in HFpEF diagnosis. They're characterized by high diagnostic accuracy and association with abnormal diastolic function, lower cardiac output and exercise intolerance. Unfortunately, these scores are not very popular in daily clinical use [27].

However, the diagnosis of HFpEF remains challenging. The diagnosis of chronic HFpEF is particularly problematic because the symptoms are induced by exercise, and routine echocardiography is performed at rest. Invasive haemodynamic testing, and in particular invasive stress testing, is considered the reference method for diagnosing HFpEF. Nevertheless, its use is limited by the large number

Figure 5. Recommendations for the treatment of heart failure with preserved ejection fraction (HFpEF) and mildly reduced ejection fraction (HFmrEF). 2021 ESC* — 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure with the 2023 Focused Update; 2022 AHA/ACC/HFSA — 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines; ACE-I — angiotensin-converting enzyme inhibitors; ARB — angiotensin (II) receptor blockers; ARNi — angiotensin receptor-neprilysin inhibitors; HF — heart failure; HFmrEF — heart failure with mildly reduced ejection fraction; HFpEF — heart failure with preserved ejection fraction; MRA — mineralocorticoid receptor antagonist; SGTL2i — sodium-glucose cotransporter-2 inhibitors

of patients suspected of having HFpEF and the uncertain benefit-risk ratio of invasive testing. Therefore, the diagnostic criteria for HFpEF should be based mainly on commonly available non-invasive tests, with the possibility of referral to echocardiographic diastolic stress testing, and then to invasive haemodynamic testing in case of doubts about the diagnosis [28, 29].

Moreover, depending on the suspected underlying aetiology of HFpEF, specific diagnostic measures should be indicated. These might include cardiac magnetic resonance, 99mTc-DPD scintigraphy, positron emission tomography, cardiac or non-cardiac biopsies, and/or specific laboratory tests, including genetic testing [2].

Pharmacological treatment

Figure 5 summarizes recommendations for the treatment of HFpEF and HFmrEF.

Diuretics

Diuretics reduce congestion and decrease the severity of HF symptoms. The efficacy of diuretics is comparable throughout the spectrum of LVEF. They are recommended to ease symptoms of congestion in HFmrEF and HFpEF (class I of recommendation) by European and American guidelines. Importantly, the American guidelines recommend diuretics not only to improve symptoms but also to prevent HF worsening [2, 17].

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists (MRA) belong to the four pillars of HFrEF treatment. However, their efficacy is less well-established in HFpEF and HFmrEF. In the ESC guidelines, MRA have a IIb class of recommendation in HFmrEF and are not listed as a treatment for HFpEF, and in the American guidelines, they have a IIb recommendation in both HFmrEF and HFpEF, but with an annotation that in HFpEF they are more effective in those with lower LVEF (closer to 50%) [2, 17].

The ALDO-DHF trial aimed to assess the impact of spironolactone treatment on HFpEF patients. A total of 422 patients were included in the study. After 12 months of drug or placebo treatment, diastolic function improved (E/e' values significantly decreased) in the spironolactone group, however, peak VO2 did not change in comparison to the placebo group. Furthermore, spironolactone had a positive effect on cardiac function and remodelling: increased LVEF, decreased LV end-diastolic diameter and LV mass index, decreased NT-proBNP levels and reduced systolic blood pressure. Spironolactone did not influence patients' symptoms or quality of life (QoL) [30].

The TOPCAT trial investigated the effects of spironolactone in 3445 patients with HF, preserved LVEF (≥ 45%) and elevated NT-proBNP or a history of HF hospitalization. Spironolactone treatment lowered the risk of HF hospitalization (hazard ratio [HR], 0.83) in comparison to placebo. However, it did not influence other components of the primary endpoint (cardiovascular mortality and aborted cardiac arrest) [31]. Importantly, almost half of the patients were recruited in Russia and Georgia. Those patients differed significantly from TOPCAT patients enrolled in both Americas who bore more clinical resemblance with typical HFpEF patients and had significantly worse prognoses. TOPCAT patients recruited in Russia or Georgia were younger, less often had AF, less often received diuretic treatment and more frequently experienced myocardial infarction

with two-thirds reporting angina. Their HF hospitalization rate was comparable to the one observed in hypertension trials, but not in HF ones. Thus, when data from TOPCAT patients from the Americas was analysed separately, spironolactone significantly reduced cardiovascular mortality (HR, 0.74) and HF hospitalization (HR, 0.82) [32].

Sodium-glucose co-transporter-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT2) inhibitors (empagliflozin and dapagliflozin) constitute another pillar of HFrEF therapy. Since 2021, SGLT2 inhibitors have been the first treatment to improve outcomes in HFpEF. As the 2021 ESC guidelines were published alongside the results of the EMPEROR-Preserved and DELIVER trial, they did not include SGLT2 inhibitors in recommendations for the treatment of HFmrEF and HFpEF [2, 17]. However, in the 2023 Focused Update of the 2021 ESC Guidelines [33] both dapagliflozin and empagliflozin are recommended in patients with HF to reduce the risk of HF hospitalization or CV death regardless of LVEF.

The EMPEROR-Preserved trial involved 5988 participants and assessed empagliflozin impact in patients with HF and LVEF > 40% (i.e. HFpEF and HFmrEF). Empagliflozin in comparison to placebo significantly reduced cardiovascular mortality or HF hospitalization (HR, 0.79) [4]. The reduction of the primary endpoint relied mostly on the reduction of HF hospitalizations (HR, 0.71), cardiovascular mortality was not reduced.

The DELIVER was an international, multicentre, double-blind, randomized trial which studied dapagliflozin efficacy in 6263 patients with HFmrEF or HFpEF. The included patients were ≥ 40 years old, with NYHA class II–IV, elevated concentrations of NT-proBNP and evidence of structural heart disease. Dapagliflozin reduced the risk of cardiovascular death or worsening HF (HR, 0.82), similarly to EMPEROR-Preserved cardiovascular mortality itself was not significantly reduced [5]. Vaduganathan et al. [34] investigated the time to the onset of clinical benefit in the group treated with dapagliflozin. Within 2 weeks of randomization, a significant reduction in the primary endpoint was observed and persisted until the final trial follow-up. The benefit of dapagliflozin was consistent across: the range of frailty [35], the spectrum of age [36], the AF status [37], and the baseline NT-proBNP levels [38].

Prior to the DELIVER trial, the PRESERVED-HF assessed whether dapagliflozin would improve symptoms and exercise capacity in 291 patients with HFpEF, both with and without type 2 diabetes. A change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 weeks was the primary outcome of this trial. Dapagliflozin improved KCCQ at 12 weeks ($p = 0.001$). Furthermore, in the dapagliflozin group, there was an improvement in the 6-minute walk test (6MWT) distance and greater weight loss [39]. Trials with empagliflozin and dapagliflozin are the landmark studies in HFpEF and HFmrEF.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

The European [2] and the American guidelines [17] recommend the use of angiotensin-converting enzyme inhibitors (ACE-I) in HFmrEF (class IIb of recommendation), but not in HFpEF. Conversely, angiotensin receptor blockers (ARB) have a IIb recommendation in both HFmrEF (European and American guidelines) and HFpEF (American guidelines). Thus, despite the low level of recommendation, ARB might be considered preferable to ACE-I in HFpEF. This is opposite to what is known for HFrEF, where ACE-Is (or angiotensin receptor-neprilysin inhibitors, ARNIs) are preferred over ARBs, which should only be used in case of contraindications to ACE-I/ARNI or their intolerance. This is because, in contrast to ARBs, ACE-I has proven favourable effects on prognosis in HFrEF. This does not apply to patients with HFimpEF who should continue pharmacotherapy which resulted in an improvement of LVEF. Nevertheless, many HFpEF patients are treated with ACE-I or ARB e.g. for hypertension.

There are few studies assessing the effect of ACE-I in HFpEF and HFmrEF. The PEP-CHF study [40] compared perindopril with placebo in patients with a diagnosis of HF and LVEF > 40%. Although, in the first year of observation patients assigned to perindopril experienced an improvement in symptoms (assessed with NYHA class) and exercise capacity (assessed with 6MWT), there was no difference in the risk of death or HF hospitalization between perindopril and placebo by the end of the entire follow-up. In contrast, a trial from Hong Kong assessed the effect of diuretics alone or combined with irbesartan or ramipril on QoL measured by Minnesota Living with Heart Failure Questionnaire (MLHFQ) and exercise capacity measured by 6MWT in HF patients with LVEF > 45%. Diuretic therapy alone improved significantly QoL. Neither combination showed significant improvement over sole diuretic therapy. The result of 6MWT did not change in either group [41]. The CHARM study showed some benefit of treatment with candesartan in HFmrEF, but not in HFpEF. Therapy with candesartan demonstrated a significant reduction in the primary endpoint (first HF hospitalization or cardiovascular death) as well as HF rehospitalizations in patients with LVEF of up to 50% (60% for HF rehospitalizations) [42].

Angiotensin receptor-neprilysin inhibitors (sacubitril/valsartan)

ARNI have a low IIb class of recommendation in HFmrEF (American and European guidelines) and HFpEF (American guidelines) [2, 17]. Similarly to ARB and MRA, ARNI are also considered more beneficial in HFpEF patients in

a lower spectrum of LVEF [17]. The PARAGON-HF trial [6] compared sacubitril-valsartan to valsartan in patients with HF and an LVEF ≥ 45% missed its primary endpoint (total HF hospitalizations and cardiovascular deaths). However, a reduction in the primary endpoint was observed in two subgroups: patients with LVEF below 57% (HR, 0.78) and in women (HR, 0.73). Results of a combined analysis of the PARADGIM-HF and PARAGON-HF trials suggest that, in comparison to valsartan or enalapril, sacubitril-valsartan may reduce HF hospitalizations in HF patients with an LVEF < 62.5%. This effect persisted with higher LVEF values in women [43].

Beta-blockers

The use of beta-blockers in managing HFrEF is well-established [2]. Some studies show their beneficial effects also in HFmrEF [44, 45]. While beta-blockers have been proven to lower the incidence of sudden and HF-related deaths, they have no effect on decreasing the frequency of cardiovascular hospitalizations [46]. The ESC and the AHA/ACC/ /HFSA guidelines consistently state that using beta-blockers could lessen the likelihood of HF hospitalization as well as cardiovascular death in HFmrEF, however, with a low class of recommendation (IIb). Again, the low class of recommendation does not apply to those with HFimpEF. As for HFpEF, beta-blocker treatment shows no significant benefit and is not recommended by the current guidelines [2, 17]. In a recent meta-analysis of 5 clinical trials no beneficial effect of beta-blockers on NYHA class, exercise capacity or BNP levels was observed in HFpEF [47]. In contrast, beta-blockers may hinder the heart's capacity to increase its rate appropriately during physical activity and therefore aggravate exercise intolerance in HFpEF (especially in those with underlying chronotropic incompetence). Nonetheless, beta-blockers are frequently prescribed in HFpEF [10, 48]. Beta-blockers should be considered as a part of HFpEF therapy for comorbidities such as angina or AF [2, 17].

Vericiguat

Impairment and deficiency of soluble guanylate cyclase (sGC) in cyclic guanosine monophosphate (cGMP) may play a role in cardiomyocyte hypertrophy, stiffness and interstitial fibrosis in HFpEF [49]. Vericiguat, as a sGC stimulator, generates cGMP and restores the sGC sensitivity to nitric oxide (NO) [50]. During the 2017 phase 2 SOCRATES--PRESERVED study, HFpEF patients were administered vericiguat in dosages 1,25/2,5/5/10 mg for 12 weeks. Although the trial showed no reduction in NT-proBNP levels or left atrial volume relative to placebo, patients receiving two higher dosages of vericiguat experienced an improvement in QoL based on the KCCQ physical limitation score compared to the placebo group [51]. The 2020 VITALITY-HFpEF trial showed no significant differences in the KCCQ physical limitation score changes at 24 weeks from baseline between vericiguat and placebo. The 6-MWT distance was also comparable. [50] Both studies included patients with LVEF ≥ 45% which encompassed both HFpEF and HFmrEF patients.

Treatment of specific aetiologies of HFpEF and HFmrEF

Transthyretin amyloid cardiomyopathy

Both European [2] and American [17] guidelines currently consider tafamidis as the only treatment option (class I of recommendation) to improve cardiovascular outcomes in patients with transthyretin (TTR) amyloid cardiomyopathy (ATTR-CM). In the ATTR-ACT trial, 441 patients with hereditary (pathogenic mutations in the TTR gene) (ATTRm) or wild type (ATTRwt) transthyretin cardiac amyloidosis and NYHA class I to III were assigned to tafamidis or placebo group. After 30 months of trial, participants from the treatment group had lower all-cause mortality (HR, 0.70) and a lower rate of cardiovascular-related hospitalizations (relative risk ratio, 0.68). Importantly, benefits related to mortality were seen across all subgroups (including TTR status (ATTRwt vs. ATTRm), NYHA class (I or II vs. III), and tafamidis dose (80 mg vs. 20 mg). Likewise, the frequency of cardiovascular-related hospitalizations was less favoured tafamidis over placebo in patients, however, except for those with NYHA class III. Moreover, tafamidis significantly lowered the rate of decline in 6MWT and KCCQ [52].

Hypertrophic cardiomyopathy

Guideline-recommended therapy in patients with symptomatic, hypertrophic cardiomyopathy (HCM) and left ventricular outflow tract obstruction (LVOTO) ≥ 50 mmHg includes beta-blockers, non-dihydropyridine calcium channel blockers, disopyramide or invasive treatment: alcohol septal ablation or surgical septal myomectomy. The 2023 ESC guidelines for the management of cardiomyopathies recommend mavacamten — first, reversible, cardiac myosin inhibitor in addition to beta-blockers (or verapamil/ /dilitiazem) or as monotherapy (in case of intolerance or contraindications to other drugs) to improve symptoms in HCM patients with LVOTO (second-line treatment) [53, 54]. EXPLORER-HCM was a large, randomized trial that evaluated mavacamten effectiveness in a group of 251 obstructive HCM (oHCM) patients. The primary endpoint was either a ≥ 3.0 mL/kg/min improvement in pVO2 and stable NYHA class or a ≥ 1.5 mL/kg/min increase in pVO2 and ≥ 1 NYHA class reduction. After 30 weeks of trial, 37% of participants from the treatment group and 17% from the control group met the primary endpoint (p = 0.0005). Mavacamten was also associated with a positive impact on all secondary endpoints, including KCCQ and HCM

Symptom Questionnaire Shortness-of-Breath subscore [55]. The authors of the VALOR-HCM trial assessed whether mavacamten can improve symptoms in patients with oHCM to no longer meet guideline criteria for septal reduction therapy (SRT). After 16 weeks, only 17.9% in the mavacamten group and 76.8% of patients in the placebo group still met the criteria to undergo SRT (treatment difference 58.9%; $p \leq 0.001$) [56]. Moreover, Bishev et al. conducted a systematic review in which data from 4 oHCM trials were analysed. Mavacamten had a positive impact on NYHA class, LVOT gradient reduction and increase of pVO2. Moreover, therapy with myosin inhibitor was well tolerated, none of the participants withdrew permanently from either trial [57]. Recently a study with aficamten — second cardiac myosin inhibitor has been completed. After 10 weeks of study on a group of 41 patients, aficamten significantly reduced LVOT gradients and NT-proBNP levels [58].

In 2020 data from MAVERICK-HCM was published, and in this trial, mavacamten was well tolerated in most patients with nonobstructive HCM (non-oHCM). Treatment was also associated with significant cardiac troponin I and NT-proBNP reduction after 16 weeks of trial [59]. However, further analysis is needed to assess the safety and efficacy of cardiac myosin inhibitors especially in patients with non-oHCM. The trials with mavacamten (ODYSSEY-HCM) [60] and aficamten (ACACIA-HCM) [61] in HCM patients without LVOTO are currently underway.

Treatment of comorbidities

In comparison to HFrEF, HFpEF is characterized by a higher prevalence of comorbidities, including non-cardiac comorbidities [62], which have an impact on the course of the disease. In fact, compared to HFrEF, patients with HFpEF have a significantly higher risk of non-cardiovascular death and hospitalizations [14]. Moreover, within HFpEF, those with a higher comorbidity burden (including obesity and diabetes) tend to have a worse quality of life, more signs of congestion and a worse prognosis [63]. Thus, in HFpEF, identification and treatment of risk factors and comorbidities (both cardiac and non-cardiac) is recommended by the current guidelines (class I of recommendation) [2, 17].

Non-pharmacological treatment

Exercise training and dietary interventions constitute a mainstay of the management of obesity, which is one of the most important risk factors for HFpEF development. One study assessed the effect of caloric restriction and aerobic exercise training on peak oxygen consumption and QoL measured by MLHFQ in older and obese HFpEF patients. Both interventions resulted in an increased peak VO_2, however, none of them affected QoL measured by MLHFQ. Still, caloric restriction, significantly improved different QoL scores: the KCCQ and ShortForm 36 Health Survey physical component score (a general QoL score) [64]. In another study, inspiratory muscle training (IMT), functional electrical stimulation (FES) and both combined significantly increased peak VO_2 and improved QoL measured by MLHFQ in HFpEF. The peak VO_2 results persisted in IMT, FES, and IMT+FES groups and in MLHFQ the results persisted in the IMT group over the 12 weeks of follow-up after 12 weeks of interventions [65]. Both studies indicate that physical activity and caloric restriction have a positive impact on patients with HFpEF. However, the obesity paradox applies also to HFpEF and in an analysis based on the I-PRESERVE trial, patients with a body mass index (BMI) of 26.5 to 30.9 kg/m^2 had the lowest rate of cardiovascular hospitalization or death and patients with BMI < 23.5 kg/m^2 (HR, 1.27) and ≥ 35 kg/m^2 (HR, 1.27) were at higher risk of cardiovascular hospitalization or death [66]. Thus, the effect of weight reduction in obese HFpEF patients is listed among evidence gaps and future research directions in the current guidelines [17].

Future consideration

Comorbidities significantly impact the progression of HFpEF through various pathophysiological mechanisms. It seems that a personalized approach to the treatment of HFpEF patients will be crucial in the future.

Authors of the STEP-HFpEF study assumed that most HFpEF patients have an overweight or obese phenotype, which determines the occurrence and progression of HFpEF. However, until now this has not been reflected in the treatment of patients with HFpEF, there are no therapies specifically targeting obesity in HFpEF as it has not been previously studied. STEP-HFpEF study aimed to evaluate the effectiveness and safety of glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide, a drug with proven effectiveness in significant weight loss in patients with obese phenotype and HFpEF. This study included 529 patients with confirmed HFpEF and BMI ≥ 30 kg/m^2. Benefits from semaglutide were observed in all analysed endpoints. Significant weight loss and improvement in KCCQ were noticed in the semaglutide arm of patients (these were the primary endpoints). Furthermore, semaglutide had a significant impact on secondary endpoints: 6MWT improvement, C-reactive protein reduction and improvement in the composite endpoint proving the advantage of semaglutide treatment in HFpEF. This is the first study to demonstrate that GLP-1 receptor agonist provides effective weight control while improving outcomes in patients with HFpEF [67]. The results of the STEP-HFpEF trial begin a new era of treatment research for patients with HFpEF.

Conclusions

Although LVEF is fundamental to the classification of HF, identification of HF phenotypes based merely on LVEF is not sufficient and has its caveats, as it does not reflect varied pathophysiological backgrounds and coexisting conditions. Patients often transit from one LVEF category to another, and the most common method of LVEF assessment (echocardiography) is associated with a relatively high intra- and inter-observer variability [68, 69]. Still, for now, HF classification based on the LVEF category seems the most pragmatic and reasonable approach, especially given the evidence accumulated for pharmacotherapy and device therapy in HFrEF. Despite ongoing research, HFpEF and HFmrEF seem more elusive and pose a greater challenge in terms of both diagnosis and treatment, which explains the discrepancies in recommendations between the American and European guidelines.

Additional information

Conflict of interest

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Streszczenie

Algorytmy diagnostyczne i postępowanie w przypadku niewydolności serca z obniżoną frakcją wyrzutową (HFrEF) są dobrze znane, sytuacja wygląda zupełnie inaczej w odniesieniu do dwóch pozostałych typów niewydolności serca (niewydolność serca z łagodnie obniżoną frakcją wyrzutową, HFmrEF oraz niewydolność serca z zachowaną frakcją wyrzutową, HFpEF). Najnowsze wytyczne europejskiego (European Society of Cardiology) oraz amerykańskich towarzystw (American College of Cardiology/American Heart Association/Heart Failure Society of America) mimo podobieństw, prezentują nieco odmienne strategie diagnostyki i leczenia HFmrEF oraz HFpEF. Celem tego artykułu jest przedstawienie aktualnej wiedzy na temat HFmrEF i HFpEF, ze szczególnym uwzględnieniem epidemiologii, diagnostyki i leczenia farmakologicznego, w tym porównanie wytycznych europejskich i amerykańskich.

Słowa kluczowe: niewydolność serca z zachowaną frakcją wyrzutową, niewydolność serca z łagodnie obniżoną frakcją wyrzutową, diagnostyka, farmakoterapia

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