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PRACA POGLĄDOWA
REVIEW

Heart failure with preserved left ventricular ejection fraction – clinical perspectives

Niewydolność serca z zachowaną frakcją wyrzutową lewej komory – perspektywy kliniczne

Małgorzata Niemiec[1,2], Bartosz Gruchlik[1,2], Nicola Dyrek[1,2], Jan Niemiec[1,2], Bartosz Basiaga[1,2], Krzysztof Bednarz[1,2], Dorota Piłat[1,2], Kinga Czepczor[1,2], Maciej Podolski[1,2], Katarzyna Mizia-Stec[1,2]

[1]1st Department of Cardiology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[2]Member of the European Reference Network on Heart diseases – ERN GUARD-HEART

ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is an increasingly recognized subtype of heart failure, particularly affecting older adults and women. It accounts for approximately 51–63% of heart failure cases, and its prevalence continues to rise, largely due to aging populations and an increasing burden of comorbidities such as hypertension, diabetes, obesity, and chronic kidney disease. The European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines emphasize a combination of clinical symptoms, preserved left ventricular ejection fraction (LVEF ≥ 50%), elevated natriuretic peptides, and echocardiographic markers of diastolic dysfunction for diagnosis. Additionally, diagnostic algorithms such as the HFA-PEFF score and H_2FPEF score aid in differentiating HFpEF from other cardiovascular and non-cardiovascular diseases. Until recently, HFpEF treatment focused mainly on symptom relief and comorbidity management. However, newer pharmacological therapies have demonstrated benefits in reducing hospitalizations and improving cardiovascular outcomes. Prognosis in HFpEF remains poor, with a 5-year mortality rate of approximately 75%. Thus patients with HFpEF require comprehensive management that includes lifestyle modifications, optimized pharmacotherapy, and rigorous control of comorbid conditions. Currently presented review summarizes practical aspects of HFpEF diagnosis, pathophysiology, treatment and prognosis focusing on multidisciplinary approaches and early intervention strategies may improve outcomes for patients affected by this challenging condition.

KEYWORDS

heart failure, heart failure with preserved ejection fraction, diastolic dysfunction

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Address for correspondence: Małgorzata Niemiec, Klinika Kardiologii I Katedry Kardiologii, Śląski Uniwersytet Medyczny w Katowicach, ul. Ziołowa 47, 40-635 Katowice, tel. +48 32 359 88 90, e-mail: malgorzata.t.niemiec@gmail.com

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STRESZCZENIE

Niewydolność serca z zachowaną frakcją wyrzutową (*heart failure with preserved ejection fraction* – HFpEF) jest coraz częściej rozpoznawanym podtypem niewydolności serca, dotykającym głównie osoby starsze i kobiety. Odpowiada za około 51–63% przypadków niewydolności serca, a jej częstość występowania nadal rośnie, głównie ze względu na starzenie się populacji oraz wzrastające obciążenie chorobami współistniejącymi, takimi jak nadciśnienie tętnicze, cukrzyca, otyłość i przewlekła choroba nerek. Wytyczne Europejskiego Towarzystwa Kardiologicznego (European Society of Cardiology – ESC) oraz Amerykańskiego Towarzystwa Kardiologicznego (American Heart Association – AHA) wskazują konieczność spełnienia kryteriów diagnostycznych obejmujących objawy kliniczne, zachowaną frakcję wyrzutową lewej komory (*left ventricular ejection fraction* – LVEF ≥ 50%), podwyższony poziom peptydów natriuretycznych oraz echokardiograficzne markery dysfunkcji rozkurczowej. Ponadto algorytmy diagnostyczne, takie jak skale HFA-PEFF i H_2FPEF, wspomagają różnicowanie HFpEF z innymi chorobami sercowo-naczyniowymi i pozasercowymi. Do niedawna leczenie HFpEF koncentrowało się głównie na łagodzeniu objawów oraz kontrolowaniu chorób współistniejących. Jednak nowsze terapie farmakologiczne wykazały korzyści w zakresie redukcji liczby hospitalizacji oraz poprawy wyników sercowo-naczyniowych. Rokowanie w HFpEF pozostaje niekorzystne; 5-letnia śmiertelność wynosi około 75%. Dlatego pacjenci z HFpEF wymagają kompleksowego postępowania obejmującego modyfikację stylu życia, optymalizację leczenia farmakologicznego oraz ścisłą kontrolę chorób współistniejących. Niniejszy przegląd podsumowuje praktyczne aspekty diagnostyki, patofizjologii, leczenia i rokowania HFpEF, koncentrując się na podejściu interdyscyplinarnym i strategiach wczesnej interwencji, które mogą poprawić wyniki leczenia pacjentów dotkniętych tym wymagającym schorzeniem.

SŁOWA KLUCZOWE

niewydolność serca, niewydolność serca z zachowaną frakcją wyrzutową, dysfunkcja rozkurczowa

Introduction

The estimated incidence of heart failure in the population of developed countries is 10,000 to 20,000 cases per million people [1]. It is believed that 51–63% of these cases are heart failure with preserved ejection fraction (HFpEF), and this percentage is constantly increasing relative to heart failure with reduced ejection fraction (HFrEF) [2,3,4,5,6,7]. This increase is particularly visible in the older age group [8]. In people over 60 years of age, HFpEF affects up to 5% of the population [9].

Women are more often affected [1]. The age of people who develop HFpEF is on average 6 years older than in people with HFrEF [10]. The incidence of hospitalization due to HFpEF is increasing and is one of the main causes of hospitalization in patients with acute heart failure [11]. In the African-American population, HFpEF accounts for 70% of all heart failure cases [12].

It is assumed that comorbidities are more common in HFpEF than HFrEF, and this is particularly true for conditions such as hypertension and obesity [13,14]. Arterial hypertension is also the most common cardiovascular disease that occurs in the majority of patients with HFpEF [8]. Although coronary artery disease is more often associated with HFrEF, it is worth emphasizing that it also co-occurs in 30–60% of HFpEF cases [15]. When a patient with HFpEF has coronary artery disease, the risk of a progressive decline in left ventricular ejection fraction (LVEF) increases, as does the risk of mortality [16].

The numerous comorbidities associated with HFpEF that may influence its development include: diabetes (incidence 20–40% of cases), chronic renal failure (20–30% of cases), obesity (50% of cases) and atrial fibrillation [15]. Mortality among patients with HFpEF is comparable to that observed in people with HFrEF, but some studies have shown that it may be slightly lower in HFpEF [5,7,17].

For effective treatment of HFpEF, a thorough understanding of its pathophysiology and etiology is necessary. In recent years, significant progress has been made in understanding the hemodynamic and cellular processes that contribute to the development of HFpEF. The development of HFpEF begins with diastolic dysfunction, manifested by incomplete relaxation of the myocardium and increased passive stiffness of the heart walls, which leads to left atrial enlargement. Arterial hypertension, as the most common comorbid disease, is one of the key factors contributing to this process. The increase in arterial wall stiffness increases the filling pressure of the left ventricle. Combined with the relatively normal function of the mitral valve, this leads to increased pressure in the left atrium. In the later stages of the disease, pulmonary hypertension develops, which leads to damage to the right side of the heart. Moreover, changes in the lungs result in a reduction of the gas exchange surface, remodeling of pulmonary vessels and impairment of lung function. Additionally, overhydration, often associated with comorbidities such as kidney disease, can lead to right ventricular overload, increasing filling pressure and contributing to disease progression. These processes have a significant impact on hemodynamic changes in the heart. At the cellular level, the theory of systemic inflammation is a promising direction of research. Increased production of inflammatory factors resulting from many comorbidities leads to damage to inflammatory vessels, which in turn affects the

bioavailability of nitric oxide, cyclic guanosine monophosphate (cGMP) concentration and titin phosphorylation in the myocardium. Changes in cellular metabolism, including anaerobic glycolysis and switching to less favorable metabolic pathways, also affect cardiac cell function. These processes rarely occur in isolation. They often coexist, enhancing each other, which affects the entire heart muscle [18]. As a result, the etiology and pathophysiology of HFpEF is a complex set of processes that interact to lead to cardiac dysfunction. Understanding these mechanisms is crucial for further progress in the treatment and improvement of the quality of life of patients with HFpEF [1]. The scheme of development of right ventricular failure in HFpEF is presented in Figure 1.

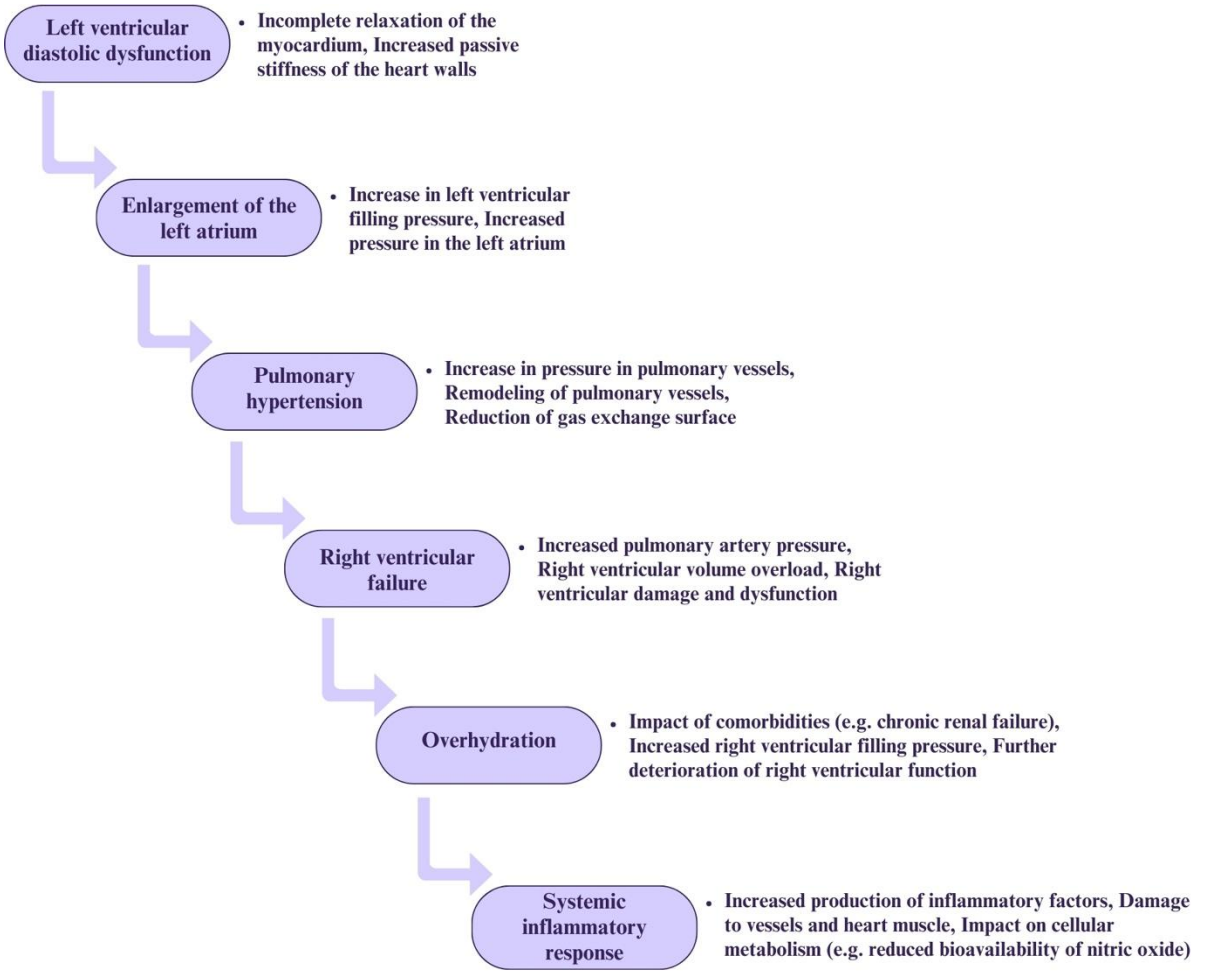

Fig. 1. Diagram of development of right ventricular failure in heart failure with preserved ejection fraction.

Clinical characteristics of patients with HFpEF

The diagnosis of HFpEF is based on the identification of symptoms and signs in patient with LVEF ≥ 50%. Patients with HFpEF often report dyspnea on exertion, which interferes with daily functioning. There is also fatigue and reduced exercise tolerance. Characteristic symptoms include orthopnoea, i.e. shortness of breath when lying down, and paroxysmal nocturnal dyspnea, manifested by sudden episodes of shortness of breath during sleep. Patients may also experience heart rhythm disturbances.

During physical examination in patients with HFpEF, symptoms mainly include: peripheral edema, especially of the lower limbs, pulmonary rales, dilated jugular veins and hepatojugular reflux. A third heart sound, which suggests increased left ventricular end-diastolic pressure, may also be present in HFpEF. Cardiac apex enlargement, i.e. a change in the position or enlargement of the heart apex palpable, is also possible. Moreover, increased jugular venous pressure is typical in patients with HFpEF [19,20].

One of the invasive tests assessing the level of B-type natriuretic peptide (BNP), used to exclude heart failure

in patients with shortness of breath and preserved ejection fraction (> 50%), revealed the following symptoms: dyspnea on exertion in 91% of patients, orthopnea in 48%, paroxysmal nocturnal dyspnea in 29%, increased pressure in the jugular veins (average 10.4 ± 2.8 cm H_2O) in 72% and lower limb edema in 66%. The patients included in the study also had echocardiographic abnormalities consistent with HFpEF [9,21,22,23].

The quality of life in patients with HFpEF is as low or even worse than in patients with HFrEF. The level of physical activity in these patients is similarly limited to that in people with moderate to severe chronic obstructive pulmonary disease (COPD) [24].

Table I. Structural and functional parameters of heart in diagnosis of heart failure with preserved ejection fraction

Parameter	Threshold
LV mass index	≥ 95 g/m² (female) / ≥ 115 g/m² (male)
Relative wall thickness	> 0.42
LA volume index	> 34 mL/m² (SR)
E/e' ratio at rest	> 9
NT-proBNP	> 125 (SR) or > 365 (AF) pg/mL
BNP	> 35 (SR) or > 105 (AF) pg/mL
PA systolic pressure	> 35 mmHg
TR velocity at rest	> 2.8 m/s

LV – left ventricle; LA – left atrium; NT-proBNP – N-terminal pro-B-type natriuretic peptide; BNP – B-type natriuretic peptide; PA systolic pressure – pulmonary artery systolic pressure; TR velocity – tricuspid regurgitation velocity; SR – sinus rhythm; AF – atrial fibrillation.

Diagnosis of HFpEF

The diagnosis of HFpEF is complex due to its nonspecific symptoms and multifactorial etiology. Various algorithms and guidelines have been developed to facilitate the identification of this form of heart failure.

The first step in diagnosing HFpEF in patients presenting with symptoms should involve ruling out other non-cardiac causes of dyspnea and/or edema [25]. Non-cardiac causes include lung diseases, kidney diseases, liver diseases, neuromuscular disorders, anemia, depression, and others.

The next diagnostic step, based on the European Society of Cardiology (ESC) guidelines, requires fulfilling the following diagnostic criteria for HFpEF (all these criteria must be met to confirm the diagnosis of HFpEF) [26,27]:

- presence of subjective and/or objective symptoms of heart failure
- preserved left ventricular systolic function with LVEF ≥ 50%
- elevated levels of natriuretic peptides: BNP ≥ 35 pg/ml and/or N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 125 pg/ml
- evidence of structural heart disease (e.g. left atrial enlargement or left ventricular hypertrophy) or diastolic dysfunction.

Structural and functional parameters of the heart in the diagnosis of HFpEF are presented in Table I.

Elevated NT-proBNP levels are a key diagnostic criterion, but their interpretation in HFpEF requires caution due to variability. Factors influencing NT-proBNP levels include:

- reduced natriuretic peptide release (e.g. associated with obesity or diabetes)
- increased NT-proBNP levels in atrial fibrillation, pulmonary hypertension, or primary right ventricular dysfunction
- the effects of certain medications, such as angiotensin receptor-neprilysin inhibitors (ARNIs) [21,28,29,30,31,32,33,34, 35,36].

Echocardiography remains a cornerstone in diagnosing HFpEF. Key echocardiographic findings include an increased left atrial volume index (LAVI > 34 ml/m²), left ventricular hypertrophy (LV wall thickness > 11 mm), diastolic dysfunction (e.g. E/e' ratio > 9), and mitral valve abnormalities such as severe atrial functional mitral regurgitation [28,29,30,31,32].

The further step in clinical evaluation is to assess the cardiac diseases imitating HFpEF – among others: cardiomyopathies, sarcoidosis, cardiac amyloidosis, other storage and infiltrative diseases, pericardial diseases, and more.

The diagnostic process can be further supported by tools such as the Heart Failure Association–Preserved Ejection Fraction (HFA-PEFF) algorithm and the H_2FPEF (Heavy, Hypertensive, atrial Fibrillation,

Pulmonary hypertension, Elder, Filling pressure) score, which assess the probability of HFpEF [33].

The HFA-PEFF algorithm includes four steps:

1. Pretest assessment (P):
   - evaluation of heart failure symptoms (subjective and/or objective)
   - identification of comorbidities and risk factors
   - standard laboratory tests, including natriuretic peptides
   - resting electrocardiogram and exercise tests (e.g. 6-minute walk test)
   - preliminary echocardiography.
2. Echocardiography and natriuretic peptides (E):
   - advanced echocardiographic assessment (e.g. left atrial volume index, diastolic function)
   - measurement of natriuretic peptides (BNP ≥ 35 pg/ml or NT-proBNP ≥ 125 pg/ml).
3. Functional and hemodynamic assessment (F):
   - functional echocardiography (e.g. E/e' ratio, tricuspid regurgitation velocity)
   - hemodynamic evaluation using invasive techniques (e.g. pulmonary capillary wedge pressure, left ventricular end-diastolic pressure)
   - additional tests such as cardiac magnetic resonance imaging, positron emission tomography, or myocardial biopsy in challenging cases.
4. Etiological assessment (F2):
   - comprehensive analysis to determine the etiology of HFpEF
   - use of genetic testing, biomarkers, and advanced imaging techniques.

The H_2FPEF score is another valuable simple tool to assess the likelihood of HFpEF in patients with HF symptoms. This scoring system includes the following parameters:

H: Heavy (obesity, BMI > 30 kg/m²) – 2 points
H: Hypertension (≥ 2 antihypertensive medications) – 1 point
A: Atrial fibrillation (paroxysmal or persistent) – 3 points
P: Pulmonary hypertension (PASP > 35 mmHg) – 1 point
E: Elderly (age > 60 years) – 1 point
F: Filling pressure (E/e' > 9) – 1 point.

Patients with an H_2FPEF score ≥ 6 have a high likelihood of HFpEF. For intermediate scores (2––5 points), invasive hemodynamic testing may be necessary, including:

- right heart catheterization (RHC) to evaluate pulmonary artery pressure
- assessment of pulmonary artery wedge pressure (PAWP): PAWP > 18 mmHg confirms HFpEF, while PAWP < 11 mmHg excludes it [36,37,38,39,40].

The diagnosis of HFpEF involves a comprehensive evaluation of clinical, laboratory, imaging, and functional findings. Diagnostic algorithms such as HFA-PEFF and scoring systems like H_2FPEF assist in distinguishing HFpEF from other conditions and identifying underlying etiologies. In complex cases, advanced echocardiographic and invasive assessments may be required to confirm the diagnosis and guide treatment [9,33,38,39,40,41,42,43,44].

A summary of the steps in diagnosing HFpEF is presented in Table II.

Table II. Summary of steps in diagnosing heart failure with preserved ejection fraction

Step	Assessment	Elements
1	Non-cardiac causes	COPD, obesity, anemia, chronic kidney disease, pulmonary embolism, cirrhosis
2	Heart failure definition	symptoms + cardiac dysfunction + response to treatment
3	Heart failure mimics	pericardial diseases, muscular, neurological disordes
4	H_2FPEF score	H: Heavy (obesity, BMI > 30 kg/m²), H: Hypertension (≥ 2 antihypertensive medications), A: Atrial fibrillation, P: Pulmonary hypertension (PASP > 35 mmHg), E: Elderly (age > 60 years), F: Filling pressure (E/e' > 9)
5	HFA-PEFF score	structure, diastolic, biomarkers

COPD – chronic obstructive pulmonary disease; BMI – body mass index; PASP – pulmonary artery systolic pressure.

Treatment of HFpEF

Until recently, there was no effective therapy specifically designed for HFpEF. Current guidelines emphasize the importance of managing comorbid conditions as the primary treatment strategy. The management of HFpEF is generally divided into pharmacological and non-pharmacological approaches [45].

Pharmacological treatment

Pharmacological treatment of HFpEF focuses primarily on symptom reduction, hemodynamic stabilization, and the reduction of cardiovascular risk factors. The main classes of drugs used in the treatment of HFpEF according to the latest American guidelines that have shown benefits include:

Sodium-glucose cotransporter-2 inhibitors (Class I recommendation)

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as empagliflozin and dapagliflozin, have received Class I recommendations for reducing heart failure hospitalizations and cardiovascular mortality. These drugs are particularly effective in patients with diabetes or chronic kidney disease. Initially developed for glycemic control in type 2 diabetes mellitus (T2DM), SGLT2 inhibitors have shown significant cardiovascular benefits in patients with and without T2DM, particularly in heart failure. They reduce hospitalization and cardiovascular death across all ejection fraction subgroups, making them a key treatment option for HFpEF patients without contraindications. Early initiation of heart failure guideline-directed therapy (GDMT) improves long--term adherence. Studies like SOLOIST-WHF demonstrated that sotagliflozin (not FDA-approved) significantly reduced cardiovascular deaths and heart failure-related hospitalizations in recently hospitalized T2DM patients across all ejection fraction ranges. Similarly, the EMPULSE trial found empagliflozin safe and effective in acutely decompensated heart failure patients, improving decongestion and clinical outcomes, with benefits seen across different ejection fraction groups.

Diuretics for symptom relief (Class I recommendation)

Diuretics play a key role in the symptomatic treatment of HFpEF, particularly in reducing fluid retention and alleviating congestion. Loop diuretics, such as furosemide, bumetanide, and torasemide, are the most commonly used and the most potent diuretics. They act by inhibiting sodium and chloride reabsorption in the loop of Henle, leading to intense diuresis. Torasemide has better bioavailability and a longer duration of action compared to furosemide, which may result in better symptom control and fewer hospitalizations. In some cases, thiazide diuretics (bendroflumethiazide, chlorthalidone, hydrochlorothiazide, indapamide, or metolazone) are used in patients with diuretic resistance. Thiazide diuretics act on the distal tubule, increasing sodium excretion and enhancing the effect of loop diuretics. Additionally, mineralocorticoid receptor antagonists (MRAs), such as spironolactone or eplerenone, may be used, especially in patients with elevated natriuretic peptides, significant fluid retention, or coexisting hypertension. MRAs not only help regulate fluid volume but also reduce fibrosis and inflammation, which play a crucial role in the pathophysiology of HFpEF.

Other pharmacological options (Class IIb recommendations)

- MRAs: drugs such as spironolactone or eplerenone may benefit selected patients, particularly those with elevated natriuretic peptides or evidence of significant fluid overload
- ARNIs: in patients with HFpEF, especially those with LVEF below 55–60%, ARNI agents like sacubitril/valsartan may be beneficial; their use is associated with improved hemodynamics and a reduced risk of heart failure hospitalizations
- angiotensin receptor blockers (ARBs): for patients unable to tolerate ARNIs due to intolerance or high cost, ARBs such as valsartan or losartan can be used as an alternative; these are particularly useful for optimizing blood pressure and alleviating symptoms of fluid overload
- angiotensin-converting enzyme inhibitors **(**ACEIs): in the treatment of HFpEF, the use of ACEIs, including perindopril, ramipril, and enalapril, can be considered; however, they are mainly used in the presence of coexisting hypertension.

On the flowchart (Figure 2), a simplified scheme for pharmacological treatment of HFpEF is presented.

The European Society of Cardiology (ESC) provides evidence-based recommendations to optimize treatment, focusing on symptom relief, hemodynamic stabilization, and reducing the risk of hospitalization and cardiovascular mortality. Table III provides a summary of the key pharmacological interventions recommended by the ESC for the management of HFpEF, along with their respective classes of recommendation and levels of evidence.

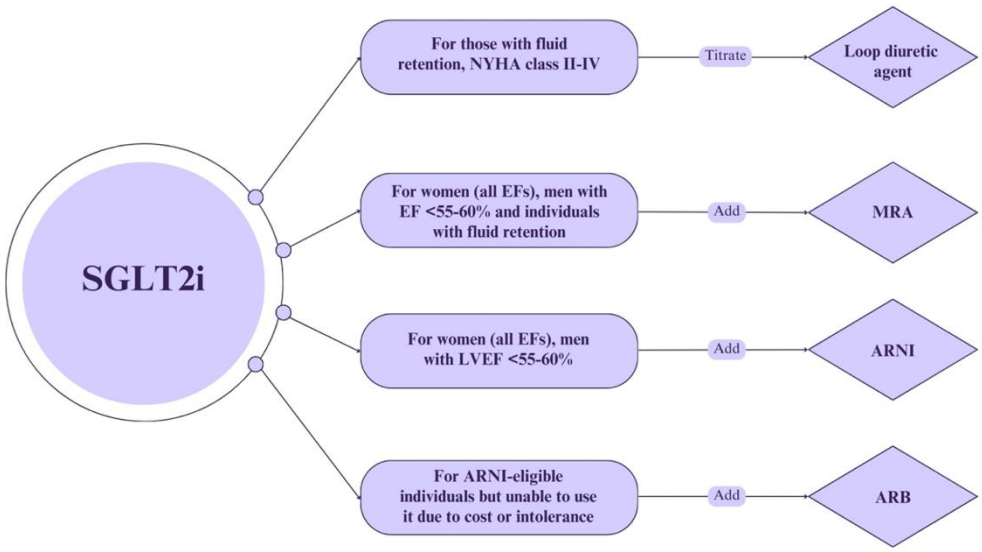

Fig. 2. Heart failure with preserved ejection fraction treatment according to the American College of Cardiology guidelines (based on [33]). SGLT2i – sodium--glucose cotransporter-2 inhibitors; NYHA – New York Heart Association (classification); EF – ejection fraction; MRA – mineralocorticoid receptor antagonist; LVEF – left ventricular ejection fraction; ARNI – angiotensin receptor-neprilysin inhibitor; ARB – angiotensin receptor blocker.

Table III. European Society of Cardiology heart failure with preserved ejection fraction treatment recommendations

Drug class	Recommendation class	Primary benefits
Sodium-glucose cotransporter-2 inhibitors	Class I	Reduces HF hospitalizations and CV mortality, beneficial in patients with and without diabetes.
Diuretics	Class I	Relieves congestion and fluid overload symptoms.
Mineralocorticoid receptor antagonists	Class IIb	May reduce HF hospitalizations in selected patients with elevated natriuretic peptides.
Angiotensin receptor-neprilysin inhibitors	Class IIb	May improve outcomes in HFpEF patients with LVEF below 55–60%.
Angiotensin receptor blockers	Class IIb	Alternative for patients who cannot tolerate ARNI.
Angiotensin-converting enzyme inhibitors	Class IIb	Used in patients with HFpEF and hypertension, though benefits in HFpEF remain uncertain.

HF – heart failure; CV – cardiovascular; HFpEF – heart failure with preserved ejection fraction; LVEF – left ventricular ejection fraction; ARNI – angiotensin receptor-neprilysin inhibitor.

In addition to optimizing blood pressure control, treating comorbidities is essential in HFpEF, as they significantly influence disease progression and patient outcomes. The main comorbidities and their targeted treatments include:

Hypertension

The treatment of hypertension in HFpEF aims to maintain blood pressure within recommended targets, similar to HFrEF. The goal is < 140/90 mmHg, with a preferred systolic range of 120–130 mmHg in patients with left ventricular hypertrophy (LVH). ACEIs, ARBs, calcium channel blockers (CCBs), diuretics, and MRAs are commonly used antihypertensive agents.

Comparative studies, such as ALLHAT, have demonstrated that ACEIs, including perindopril, offer superior long-term cardiovascular protection compared to other antihypertensive classes, reducing the risk of myocardial infarction, stroke, and heart failure hospitalizations, particularly in high-risk populations with diabetes and obesity [46,47,48,49,50,51,52]. Perindopril has also been shown to reduce vascular resistance and myocardial stiffness, improving hemodynamics and alleviating symptoms such as dyspnea, fatigue, and edema.

The ACCOMPLISH trial highlighted the benefits of combining perindopril with amlodipine, showing greater cardiovascular protection than diuretic-based regimens. Similarly, studies like ASCOT and Brisighella Heart Study confirmed that this combination is more effective than beta-blockers or thiazide diuretics in stabilizing blood pressure and improving lipid profiles.

Patients with obesity or difficult-to-control hypertension may particularly benefit from perindopril plus indapamide, as demonstrated in the FORSAGE study, where over 70% of patients achieved target blood pressure (BP) within three months. Additionally,

single-pill combinations (SPC) improve adherence and long-term cardiovascular outcomes, as observed in recent trials [46,47,48,49,50,51,52].
ACEIs, including perindopril, are generally well tolerated, with fewer metabolic side effects than beta--blockers or thiazide diuretics. Although some patients experience cough or hyperkalemia, these are usually mild, making ACEIs a preferred choice for long-term hypertension management in HFpEF.

Diabetes

Diabetes is one of the most common comorbidities in patients with HFpEF, significantly contributing to disease progression and poor cardiovascular outcomes. The EMPEROR-Preserved trial evaluated the efficacy of empagliflozin, an SGLT2 inhibitor, in treating HFpEF in patients with and without diabetes. The results demonstrated a significant reduction in heart failure hospitalizations and improved cardiovascular outcomes, establishing empagliflozin as a key therapy in HFpEF management [1,53,54].

Obesity

Obesity is a major risk factor for the development and progression of HFpEF, contributing to increased left ventricular stiffness, systemic inflammation, and elevated filling pressures. For patients with obesity, preferred treatments include glucagon-like peptide 1 (GLP-1) receptor agonists and lifestyle modifications [55].

Atrial fibrillation

Key strategies include rhythm or rate control and anticoagulation to reduce the risk of stroke and improve hemodynamics. The COMMANDER HF study evaluates the effectiveness of anticoagulants in reducing thrombosis risk. Additionally, some studies suggest that statins may reduce the incidence of atrial fibrillation in HFpEF, consistent with the inflammatory response theory [1,55,56,57,58,59].

Pulmonary hypertension

Pulmonary hypertension is a frequent complication in HFpEF, mainly due to increased left atrial pressure and pulmonary vascular remodeling. Treatment focuses on optimizing volume status, improving left ventricular diastolic function, and managing left heart disease.

Chronic kidney disease

Chronic kidney disease is commonly seen in HFpEF and is associated with worse clinical outcomes. Post-hoc analysis of the TOPCAT trial suggests spironolactone may reduce cardiac deaths and hospitalizations, especially in patients with LVEF > 45% [1,55].

Obstructive sleep apnea

Obstructive sleep apnea is a highly prevalent but often underdiagnosed condition in HFpEF patients. Recurrent nocturnal hypoxia and sympathetic activation contribute to hypertension, increased left ventricular filling pressures, and systemic inflammation, all of which exacerbate HFpEF progression. Patients with sleep-disordered breathing may benefit from continuous positive airway pressure (CPAP) therapy.

Anemia

Anemia and iron deficiency are common in HFpEF and are associated with increased morbidity and reduced exercise tolerance. Impaired oxygen delivery to tissues worsens fatigue and dyspnea, significantly impacting quality of life. Patients with anemia or iron deficiency may require intravenous iron supplementation.

Non-pharmacological treatment

Non-pharmacological management plays a crucial role in improving outcomes in HFpEF patients. Lifestyle modifications and targeted interventions can alleviate symptoms, reduce disease progression, and enhance overall cardiovascular health. These approaches are particularly important in patients with multiple comorbidities, where pharmacotherapy alone may not be sufficient.

Lifestyle modifications

Regular physical activity (e.g. aerobic exercise) improves exercise capacity and quality of life. Dietary recommendations, including a low-sodium diet and caloric restriction, also play a crucial role [60].

Management of comorbidities

This includes targeted therapy for obstructive sleep apnea, anemia, thyroid disorders, and electrolyte imbalances.

Patient education

Regular follow-up visits are essential for tailoring treatment plans and monitoring disease progression.
Managing HFpEF requires a comprehensive approach addressing the underlying disease mechanisms, symptoms, and comorbidities. Evidence-based pharmacological therapies, such as SGLT2 inhibitors, and lifestyle modifications play a central role in improving patient outcomes. Ongoing research continues to refine therapeutic strategies, offering hope

for more effective management of this complex condition [33].

Prognosis

The prognosis for HFpEF is usually variable and depends on many factors, such as the stage of the disease, the presence of comorbidities, the effectiveness of treatment, and the patient's lifestyle. Overall, HFpEF is a complex condition, and the prognosis may vary from patient to patient.

The stage of heart failure is one of the main prognostic factors. Patients with HFpEF are often classified according to the New York Heart Association (NYHA) functional category, with stage I indicating mild symptoms and stage IV representing severe heart failure [61]. The presence of other diseases, such as hypertension, diabetes, chronic kidney disease, or cardiovascular disease, may influence the prognosis. Control of these comorbidities is crucial [62]. The response to treatment, including pharmacotherapy, control of risk factors, and possible interventional procedures, affects the prognosis. Regular assessment and adaptation of the treatment plan are essential. The PARAGON-HF study confirms that patients with HFpEF treated with sacubitril/valsartan had a lower risk of cardiovascular events, which may improve prognosis [63]. The PARAMOUNT study, which examined the treatment of patients with HFpEF with irbesartan, showed that this therapy reduces the risk of hospitalization due to heart failure [64]. The TOPCAT study assessed the effectiveness of spironolactone in patients with HFpEF. The results suggest that spironolactone may reduce the risk of hospitalization due to heart failure, which impacts prognosis [65].

The prognosis of HFpEF is generally poor, with a 5-year mortality rate of 75.3%, according to the Get With The Guidelines (GWTG) registry. Additionally, HFpEF patients have a 30-day all-cause readmission rate of 21%, which underscores the disease's high burden and risk of recurrent hospitalizations. Compared to HFrEF, HFpEF incidence and prevalence are steadily rising, with an increasing proportion of HF cases being attributed to HFpEF rather than HFrEF. Over time, both incidence and prevalence continue to increase, driven largely by an aging population and the growing prevalence of comorbid conditions such as obesity and diabetes.

Sex differences also play a role in HFpEF prognosis. While HFpEF is more prevalent in women, clinical outcomes tend to be worse in men, who exhibit higher cardiovascular mortality. However, survival remains poor in both sexes. Compared to HFrEF, HFpEF patients have similarly poor survival rates, though cardiovascular mortality appears slightly lower in HFpEF than in HFrEF.

Patient age is another element influencing prognosis, as older patients often face additional treatment challenges and slower recovery. Potential complications, such as pulmonary embolism, cardiac arrhythmias, or thrombosis, may further impact patient outcomes. Each patient may vary in their individual response to therapy. Therefore, it is essential to monitor and adjust treatment based on the patient's response [66].

Since HFpEF remains an area of intense research, the prognosis may improve as scientific knowledge advances and new therapies emerge. Ensuring that patients with HFpEF receive specialized care tailored to their individual needs is crucial. Regular check-ups and close control of risk factors remain key to optimizing the care of HFpEF patients.

Assessment of prognosis in HFpEF includes a wide range of factors that are taken into account. Various questionnaires can help in collecting data and evaluating different aspects that affect a patient's prognosis. Some useful tools include the Kansas City Cardiomyopathy Questionnaire (KCCQ) for quality of life assessment, the NYHA classification for functional status, and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score, which integrates multiple risk factors to estimate mortality in heart failure patients.

Conclusions

HFpEF is becoming the predominant form of heart failure, particularly among older individuals and women, highlighting the need for intensified research into its pathogenesis, diagnosis, and treatment. This condition has a multifactorial etiology, involving diastolic dysfunction, myocardial fibrosis, hypertension, obesity, and chronic inflammation. The coexistence of multiple comorbidities, such as diabetes, chronic kidney disease, and atrial fibrillation, further complicates its course and prognosis.

Until recently, HFpEF treatment primarily focused on symptom management and the treatment of comorbid conditions. However, new drug classes are now playing an increasingly significant role. SGLT2 inhibitors, such as empagliflozin and dapagliflozin, have demonstrated benefits in reducing heart failure hospitalizations and cardiovascular mortality, even in patients without diabetes. Diuretics remain essential for symptom control in congestion, while MRAs, including spironolactone and the newer agent finerenone, show promise in reducing fibrosis and inflammation. ARNIs, particularly sacubitril/valsartan, have been shown to lower hospitalization rates. Beta--blockers, ACEIs, and ARBs are used in selected patients, especially those with coexisting hypertension or ischemic heart disease. Additionally, emerging therapies targeting systemic inflammation and

myocardial remodeling, such as novel anti-fibrotic agents, are being explored. These advances are reshaping the landscape of HFpEF management and offering new hope for improved patient outcomes.

Blood pressure control remains a key component of therapy. Comparative studies have provided evidence that ACEIs, including perindopril, offer superior long--term cardiovascular protection compared to other classes of antihypertensive drugs. ACEI-based therapies have been more effective in reducing the risk of cardiovascular events, such as myocardial infarction and stroke, particularly in high-risk populations, including patients with diabetes, hypertension, and other comorbidities.

Non-pharmacological approaches to HFpEF management include lifestyle modifications, regular physical activity, and a low-sodium diet, all of which can significantly improve patients' quality of life. The prognosis in HFpEF varies and depends on multiple factors, including disease severity, the presence of comorbidities, treatment efficacy, and adherence to lifestyle recommendations. Survival rates in HFpEF are comparable to those observed in HFrEF, although some studies suggest slightly better outcomes in HFpEF. Recent clinical trials, such as PARAGON-HF, EMPEROR-Preserved, and TOPCAT, have demonstrated benefits from new pharmacological treatments, including ARNI, SGLT2 inhibitors, and spironolactone, offering hope for improved patient outcomes.

The introduction of diagnostic tools such as the HFA-PEFF algorithm and the H_2FPEF score allows for a more precise identification of HFpEF patients and the implementation of optimal treatment strategies. Since HFpEF remains an area of intensive research, the future of its therapy appears promising, and further advancements in understanding the disease mechanisms may contribute to better quality of life and prolonged survival for affected patients.

Authors' contribution

Study design – M. Niemiec, J. Niemiec, N. Dyrek, K. Bednarz, B. Basiaga, B. Gruchlik
Data collection – M. Niemiec, J. Niemiec, D. Piłat, K. Bednarz, N. Dyrek, B. Basiaga
Manuscript preparation – M. Niemiec, N. Dyrek, B. Gruchlik, M. Podolski, B. Basiaga
Literature research – M. Niemiec, B. Gruchlik, N. Dyrek, K. Czepczor, K. Bednarz, K. Mizia-Stec
Final approval of the version to be published – K. Mizia-Stec

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