

## Consensus Document

## Heart failure with preserved ejection fraction: updated diagnostic and therapeutic strategies. SEMI consensus document

*Insuficiencia cardíaca con fracción de eyección preservada: actualización en estrategias diagnósticas y terapéuticas. Documento de consenso de la SEMI*

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## ABSTRACT

Heart failure (HF) is associated with high morbidity and mortality. HF with preserved left ventricular ejection fraction (HF-pEF) accounts for up to 50% of all HF cases, being the most common in elderly patients. In addition, these subjects frequently present other comorbidities. For all these reasons, the diagnosis of patients with HF-pEF is complex and requires a careful approach. In addition, there are secondary or HF-pEF forms that must also be discarded. The treatment of HF-pEF has evolved very significantly in recent years due to evidence from clinical trials. Until a few years ago, the management was based on the treatment of congestive symptoms with diuretics and comorbidities, to this was added the indication of treatment with SGLT2 inhibitors, after being shown to reduce hospitalizations due to HF, and more recently new evidence of clinical benefit with other drugs such as finerenone, semaglutide or tirzepatide has been published. All this makes it necessary to update the recommendations regarding the management of patients with HF-pEF.

## RESUMEN

La insuficiencia cardíaca (IC) está asociada con una elevada morbimortalidad. La IC con fracción de eyección del ventrículo izquierdo preservada (IC-FEp) alcanza hasta el 50% de todos los casos de IC, siendo la más frecuente en los pacientes añosos. Además, estos sujetos suelen presentar frecuentemente otras comorbilidades. Por todo ello, el diagnóstico de los pacientes con IC-FEp es complejo y requiere de un abordaje cuidadoso. Además, existen formas "secundarias" o que simulan IC-FEp que también es necesario descartar. El tratamiento de la IC-FEp ha evolucionado de manera muy importante en los últimos años debido a las evidencias provenientes de los ensayos

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Sacubitrilo-Valsartán  
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clínicos. Hasta hace pocos años su manejo se basaba en el tratamiento de los síntomas congestivos con diuréticos y las comorbilidades, a esto se añadió la indicación de tratamiento con los inhibidores SGLT2, tras haberse demostrado que reducen las hospitalizaciones por IC, y más recientemente se han publicado nuevas evidencias de beneficio clínico con otros fármacos como la finerenona, semaglutida o tirzepatida. Todo esto hace que sea necesario actualizar las recomendaciones acerca del manejo del paciente con IC-FEp.

## Introduction

Heart failure with preserved ejection fraction (HF-pEF) is a clinical syndrome characterized by signs and symptoms of heart failure (HF), increased left ventricular filling pressure and/or diastolic dysfunction, with an ejection fraction of  $\geq 50\%$ .<sup>1</sup>

HF is a major public health problem affecting more than 56 million people worldwide.<sup>2</sup> Its prevalence in adults is estimated to be 2.3%, with similar figures in Europe (1.5–3%) and Spain (1.9–2.3%).<sup>3–6</sup> Although the incidence has stabilized in developed countries, aging of the population and increased survival with effective therapies predict a progressive increase in the number of cases.<sup>2</sup> Between 24–47% of all patients with HF have HF-pEF. This variability is attributable to differences in demographics, healthcare and diagnostic criteria.<sup>5,7,8</sup>

It is a chronic, complex and heterogeneous syndrome resulting from multiple pathophysiological mechanisms, including cardiac aging, cardiometabolic disorders, and chronic systemic inflammation.<sup>9–12</sup> Cardiovascular-kidney-metabolic syndrome has been defined as a progressive condition in which pathophysiological interactions between the cardiovascular system, renal dysfunction, and metabolic risk factors such as obesity and diabetes mellitus, can lead to multiple organ dysfunction, excess morbidity and premature mortality. This syndrome, in which the inflammatory substrate plays a key role, is currently considered to be the basis of the pathophysiology of HF-pEF.<sup>9–12</sup>

With regard to this pathophysiology, in recent years drugs have been identified that act upon metabolism, inflammation and fibrosis, affording benefits at cardiovascular and renal level, and specifically in patients with HF-pEF, thereby transforming management of the disorder. The European guidelines of 2023 have incorporated SGLT2 inhibitors as standard treatment, and new evidence with GLP-1 receptor agonists or mineralocorticoid receptor antagonists such as finerenone, make it necessary to update the clinical recommendations.<sup>1,10,11,13–17</sup>

HF-pEF is now a priority clinical challenge due to its high prevalence, diagnostic complexity, and because it predominantly affects elderly individuals with multiple disease conditions, known as pluripathology. Internal medicine, because of its comprehensive vision and experience in the management of complex patients, plays a key role in the approach to this disorder. In this context, the Spanish Society of Internal Medicine (SEMI) has endorsed this consensus document with the aim of offering an evidence-based practical guide adapted to the reality of care that facilitates global and coordinated management to improve the prognosis and quality of life of these patients.

A literature search was made in PubMed (MEDLINE) covering the period between January 2000 and April 2025, using the MeSH terms: heart failure with preserved ejection fraction, diagnosis, treatment, SGLT2 inhibitors, mineralocorticoid receptor antagonists, GLP1 receptor agonists, dual GIP/GLP1 agonists, angiotensin receptor-neprilysin inhibitors and inhibitors of the renin-angiotensin system. Randomized clinical trials, systematic reviews and clinical practice guides were reviewed, without language restriction.

## Impact of HF-pEF

As compared to HF with reduced ejection fraction (HF-rEF), patients with HF-pEF are older, predominantly female, and have a high comorbidity burden, particularly obesity, type 2 diabetes mellitus, high blood pressure, atrial fibrillation, chronic kidney disease and obstructive sleep apnea syndrome - all components of the so-called

cardiovascular-kidney-metabolic syndrome or more recently (as defined by the European Society of Cardiology [ESC], systemic metabolic disorders.<sup>18–20</sup> These comorbidities not only coexist with HF-pEF, but contribute to its development and progression. Among them, arterial hypertension and obesity are the conditions most closely associated with HF-pEF.<sup>21</sup>

Frailty is also common and implies a poorer prognosis in elderly patients with HF-pEF by intensifying the symptoms, comorbidities and mortality. This situation requires comprehensive, multidisciplinary and individualized management aimed at preserving patient function and quality of life.<sup>22</sup>

A number of studies have shown mortality and the risk of hospitalization in HF-pEF to be high and comparable to those in HF-rEF,<sup>5,23–26</sup> though with a higher proportion of non-cardiovascular mortality.<sup>13,23,27–32</sup> In the RICA registry, which included patients hospitalized due to HF in Departments of Internal Medicine in Spain, the mortality rate per year reached 24%.<sup>32</sup> Similarly, the national registry of the Spanish Society of Cardiology, with data from 45 heart failure units, reported a mortality rate of 15.6% and a readmissions rate of 26.7% per 100 person-years in the subgroup with HF-pEF.<sup>23</sup>

The economic impact is also considerable: hospitalization accounts for about 75% of the healthcare expenditure associated with HF-pEF.<sup>33</sup> Consequently, reducing readmissions through effective therapies is a key strategy for improving the clinical outcomes and optimizing resources.

Finally, the consequences of HF-pEF extend beyond the cardiovascular context, affecting other organs and systems: brain, lungs, kidneys, and vascular and musculoskeletal function, underlining its systemic and multisectoral nature (Supplementary Fig. 1).<sup>13</sup>

## Diagnostic approach

### Preliminary considerations

The diagnosis of HF-pEF is more complex than that of other HF phenotypes, particularly in elderly patients with multiple comorbidities who often present normal findings at first examination, with coexisting conditions that can mimic HF-pEF. In addition, the European Society of Cardiology (ESC) criteria,<sup>1</sup> based on younger and more stable populations, may have limited applicability in the typical profile seen in internal medicine, especially during acute episodes.<sup>34,35</sup>

The existence of certain conditions in the clinical history that are well-known risk factors for the development of HF-pEF, such as advanced age, obesity, arterial hypertension, diabetes mellitus, chronic kidney disease and atrial fibrillation increase the likelihood that the clinical condition of the patient is due to the presence of HF-pEF.<sup>36</sup>

### Diagnostic criteria

The diagnosis requires the following<sup>1</sup>:

- Signs and symptoms consistent with clinical HF syndrome (*indispensable requirement*)
- Left ventricular ejection fraction (LVEF)  $\geq 50\%$  (second *indispensable requirement*) accompanied by
- Evidence of structural or functional LV dysfunction (hypertrophy, left atrial dilatation, or diastolic dysfunction) and/or natriuretic peptide (NP) elevation.

The signs and symptoms are those classical of HF. None alone or in combination are sufficiently specific to be able to establish a clear diagnosis of the HF phenotype according to LVEF.<sup>18</sup> The diagnosis of HF will always be more likely in the presence of more specific clinical manifestations (orthopnea, bendopnea, paroxysmal nocturnal dyspnea, jugular vein distension, hepatojugular reflux and/or progressive bilateral edema). However, in elderly people it is not uncommon for the clinical manifestations to be more nonspecific (exertional dyspnea, fatigue, asthenia, loss of appetite, confusional state) and to be entirely or partially secondary to some other non-cardiac condition sharing signs and symptoms with HF (anemia, chronic respiratory disease, renal failure, venous insufficiency, protein malnutrition, immobility, sarcopenia, etc.). All of this requires a careful history and physical examination in an attempt to identify the presence of these clinical confounders, known in the American literature as non-cardiological *mimics*.<sup>18</sup>

## Complementary tests

### Basic initial study

First of all, patients with suspected HF-pEF should undergo the following:

- Electrocardiogram (ECG): A strictly normal tracing reduces the probability of HF-pEF, but does not rule it out. The presence of hypertrophy or enlargement of the left atrium supports the diagnosis.
- Chest X-ray: The absence of congestion or cardiomegaly suggests against the diagnosis, though without excluding it.
- Basic laboratory tests: These tests can rule out other causes that may explain the symptoms or identify etiological or triggering factors (anemia, renal failure, infection, ischemia).<sup>1</sup>

### Echocardiogram

If clinical suspicion persists on the basis of the signs and symptoms, together with the ECG findings, the next step is to perform a protocolized transthoracic echocardiogram (TTE), since the ESC definition implies the identification of morphological or functional abnormalities that are difficult to assess in an acute/subacute scenario in non-expert hands or with *point-of-care ultrasound* (POCUS) devices. If LVEF is  $\geq 50\%$ , the structural or functional abnormalities allowing the clinical manifestations of HF to be attributed to the existence of HF-pEF (regardless of the presence or not of non-cardiological *mimics*) are the following<sup>1,36</sup>:

- Markers of LV hypertrophy (structural): interventricular septum thickness  $\geq 12$  mm or a relative LV wall thickness  $> 0.42$ . LV mass  $\geq 115$  g/m<sup>2</sup> (in males) or  $\geq 95$  g/m<sup>2</sup> (in females) may also be considered indicative.
- Markers of LV filling abnormality in diastole (functional): E/e' ratio  $> 9$ , e'  $< 7$  cm/s or left atrial volume index (LAVI)  $> 34$  mL/m<sup>2</sup> (for patients with atrial fibrillation [AF]) or 29 mL/m<sup>2</sup> (for patients with sinus rhythm).
- Markers of pulmonary hypertension: systolic pulmonary artery pressure  $> 35$  mmHg or tricuspid regurgitation velocity  $> 2.8$  m/s.

The greater the number of abnormalities, the greater the probability that the observed clinical manifestations are secondary to HF-pEF.

On the other hand, TTE can also detect alterations that are not part of this list and which constitute secondary HF-pEF, known in the American literature as cardiological *mimics* (significant valvular disease, right ventricular dysfunction, pericardial disease, hypertrophic cardiomyopathy, hyperdynamic situations, etc.). As with non-cardiological *mimics*, their presence may be simultaneous with the TTE findings defining "primary" HF-pEF. In fact this situation is not uncommon in elderly patients with

multiple potential simultaneous causes of HF (arterial hypertension, cardiac ischemia, valvular disease, pulmonary hypertension, etc.).<sup>1</sup>

### Natriuretic peptides

Finally, plasma NP levels should be found to be elevated in HF-pEF, particularly in an acute decompensated scenario. In fact, elevated NP has the same condition as a diagnostic indicator of LV filling abnormality as the E/e' ratio, e' value, or LAVI.<sup>1</sup> It is very important to emphasize that elevated NP levels are not mandatory to establish the diagnosis: normal NP levels are plausible in relatively young and scarcely symptomatic patients with HF-pEF and obesity.<sup>37</sup> However, this is not the usual scenario in internal medicine, and elevated NP levels are thus usually found.

Although some studies suggest that in the HF-pEF population, the NP values are somewhat lower than those found in patients with HF and a mildly reduced ejection fraction (HF-mrEF) or HF-rEF,<sup>38</sup> the guidelines do not recommend differential cut-off values suggestive of one phenotype or another. Overall, the plasma NP levels that reinforce the clinical suspicion of HF are more demanding in prototypical elderly patients seen in internal medicine.<sup>39</sup> In addition, a wide range of alternative causes are usually present in this population that may (even if only partially) account for the increase in NP levels (Supplementary Table 1).<sup>1</sup> Thus, the contribution of NP levels as an aid to the diagnostic process is not as relevant as the combination of compatible clinical manifestations, together with objective TTE findings.

The NT-proBNP cut-off values suggestive of HF are<sup>1,36,40</sup>:

- Acute HF (widespread use, values independent of LVEF, but increasing according to age):  $> 450$  pg/mL ( $< 50$  years),  $> 900$  pg/mL (50–75 years),  $> 1800$  pg/mL ( $> 75$  years).
- HF-pEF in the stable patient: variable values of non-widespread use, which according to the ESC consensus range from  $> 125$  pg/mL (in patients with sinus rhythm) to  $> 660$  pg/mL (in patients with AF).

### Role of diagnostic indices

Considering the complexity of the mentioned diagnostic process (as opposed to the simplicity of the diagnosis of HF-rEF and HF with mildly reduced LVEF (HF-mrEF), both the American Heart Association (AHA)/American College of Cardiology (ACC) and the ESC have proposed scores that help calibrate the probability (high/intermediate/low) that the clinical manifestations suggesting HF in the presence of LVEF  $\geq 50\%$  are actually secondary to the existence of HF-pEF. The American H<sub>2</sub>FPEF score<sup>41</sup> is easy to apply and was developed from three clinical and two echocardiographic parameters derived from a relatively young patient cohort with objective evidence of LV filling anomalies in diastole, obtained through hemodynamic testing. In contrast, the European HFA-PEFF score<sup>36</sup> was created by expert consensus based on multiple clinical, laboratory and echocardiographic data, and incorporates a stepwise diagnostic algorithm that in doubtful cases requires the consideration of an advanced functional or invasive study (Table 1).<sup>36,41</sup>

Although both indices are of clinical interest, the fact is that their real value has not been clearly established.<sup>42</sup> In the particular case of the usual patient seen in internal medicine, the H<sub>2</sub>FPEF score is probably not sufficiently discriminative, and the HFA-PEFF is too lengthy and difficult to apply through to its final consequences (stress echocardiogram and hemodynamic study) if a diagnostic doubt is really to be clarified in a patient presenting an intermediate probability. However, nothing prevents these scores from being applied if wished to refine the diagnostic evaluation in selected patients.

The key aspects for the diagnosis of HF-pEF are summarized in Fig. 1 and Supplementary Table 2.

**Table 1**  
Risk scores for the diagnosis of HF-pEF.

H <sub>2</sub> FPEF			
	Parameter	Definition	Points
H <sub>2</sub>	Obesity	BMI > 30 kg/m <sup>2</sup>	2
F	AHT	≥ 2 anti-hypertensive drugs	1
F	AF	Paroxysmal or persistent	3
P	Pulmonary hypertension	sPAP > 35 mmHg	1
E	Age	> 60 years	1
F	Elevated filling pressure	E/e' > 9	1
HFA-PEFF			
Major criterion (2 points)		Minor criterion (1 point)	
Functional	Septal e' < 7 cm/s		E/e' 9-14
	Lateral e' < 10 cm/s		
	E/e' ≥ 15		Global longitudinal strain < 16%
Morphological	TRV > 2.8 m/s		
	LAVI > 34 ml/m <sup>2</sup> (> 40 ml/m <sup>2</sup> if AF)	LAVI 29-34 ml/m <sup>2</sup> (35-40 ml/m <sup>2</sup> if AF)	
	LVMI ≥ 149/122 g/m <sup>2</sup> and RWT > 0.42	LVMI > 115/95 g/m <sup>2</sup> RWT > 0.42 LVWT ≥ 12 mm	
Biomarkers			
Sinus rhythm	NT-proBNP > 220 pg/ml; BNP > 80 pg/ml	NT-proBNP 125-220 pg/ml; BNP 35-80 pg/ml	
AF	NT-proBNP > 660 pg/ml; BNP > 240 pg/ml	NT-proBNP 365-660 pg/ml; BNP 105-240 pg/ml	
Probability of HF-pEF			
LOW	INTERMEDIATE		HIGH
H <sub>2</sub> FPEF 0-1, HFA-PEFF 0-1	H <sub>2</sub> FPEF 2-5, HFA-PEFF 2-4 Consider advanced study (Stress TTE or hemodynamic measurements with catheterization)		H <sub>2</sub> FPEF > 6, HFA-PEFF ≥ 5

LA: left atrium; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; AHT: arterial hypertension; BMI: body mass index; HF-pEF: heart failure with preserved LVEF; LAVI: left atrial volume index; LVMI: left ventricular mass index; LVWT: left ventricular wall thickening; sPAP: systolic pulmonary artery pressure; RWT: relative wall thickness; TRV: tricuspid regurgitation velocity; LV: left ventricle. In the usual population with HF in internal medicine (octogenarian and pluripathological individuals with a high prevalence of AF and AHT), the H<sub>2</sub>FPEF score is probably less discriminative than HFA-PEFF. Table generated from Refs. 36,41.

**The extended diagnosis: triggering factors and causes**

Finally, once the diagnosis of HF-pEF has been assumed, the potential causes should be assessed. Excluding those situations already discussed as causes of secondary HF-pEF (valvular, pericardial, cardiopulmonary or hyperdynamic disorders), the most common scenario is HF-pEF developed in the presence of arterial hypertension or ischemic heart disease, and often within the context of cardiovascular-kidney-metabolic syndrome. However, there is a considerable spectrum of alternative diagnoses that are much less common, but which ideally should be ruled out if there are elements suggesting their presence (Supplementary Table 3).<sup>43,44</sup> The most common alternative diagnosis is probably transthyretin amyloid cardiomyopathy (ATTR-CM). Its prevalence in elderly patients diagnosed with HF reaches up to 23% in some series,<sup>45</sup> and it has specific and simple clinical suspicion criteria and diagnostic explorations.<sup>46</sup> Recently, a predictive model of the probability of the presence of ATTR-CM in patients with HF-pEF and a clinical suspicion of cardiac amyloidosis (T-Amylo, <https://www.t-amylo.com/>) has been presented.<sup>47</sup>

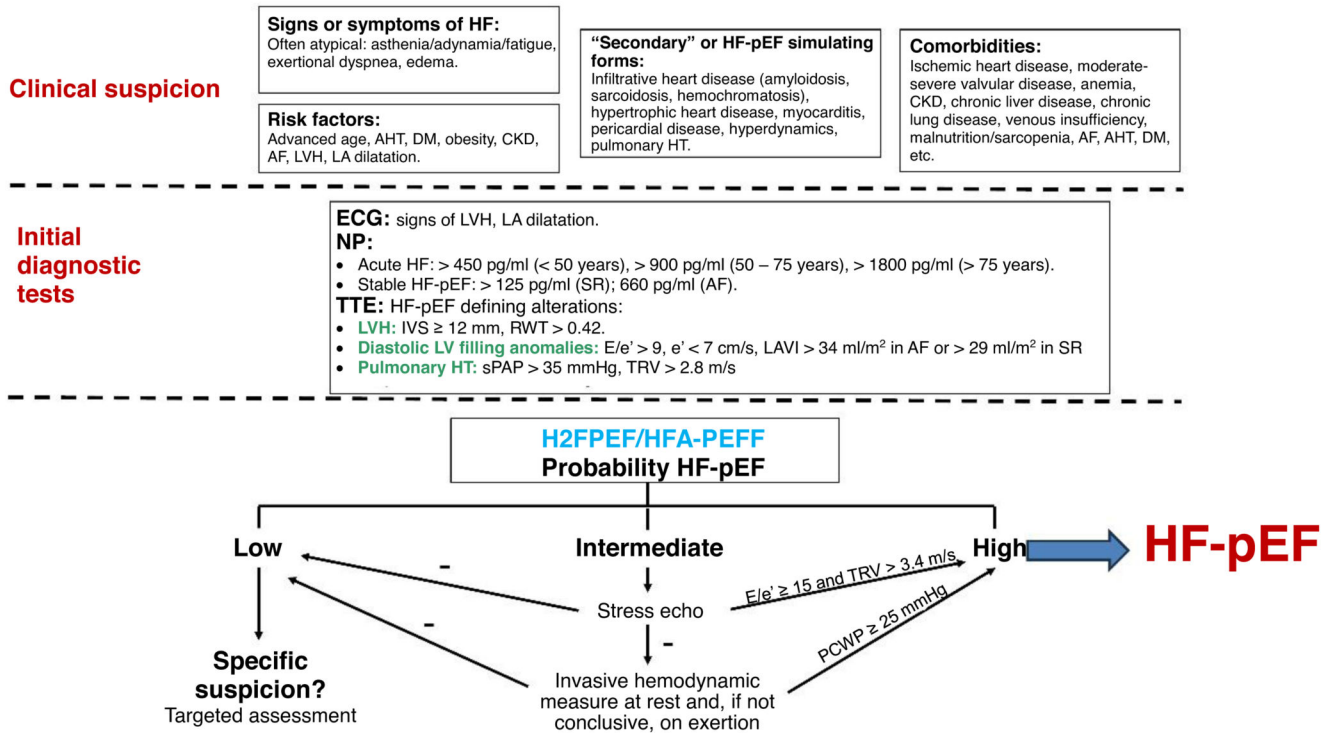
In the typical patient seen in internal medicine, the etiological study rarely extends any further. However, if there is reasonable suspicion and the patient is in a condition to undergo further studies, we should always consider a more thorough evaluation to assess the presence of coronary artery disease (coronary CT scan, ischemia screening tests, coronary angiography), specific cardiomyopathies such as infiltrating or

inflammatory disorders (cardiac MRI), myocarditis (CK, serology) or even functional abnormalities such as chronotropic incompetence.<sup>48,49</sup>

On the other hand, in the case of acute decompensation of HF-pEF, it is essential to evaluate all the circumstances that may have led to it. These are referred to as triggering factors, both cardiological (tachyarrhythmias, coronary ischemia) and non-cardiological (fever, anemia, respiratory failure, pulmonary thromboembolism, drugs, etc.). As commented in the previous paragraphs, it should not be forgotten that many non-cardiological triggering factors may have played a dual role as *mimics* generating clinical manifestations consistent with HF, especially if they were already present previously.<sup>18</sup>

In summary, the diagnostic process of HF-pEF is always associated with a certain margin of uncertainty, given the absence of a diagnostic *gold standard*. In this respect, an overall assessment is needed, due to the difficulty of disassociating primary from secondary HF-pEF and non-cardiological comorbidity in the typical patient seen in internal medicine. In any case, if after this entire process, we are convinced that the clinical condition of the patient is due to HF-pEF, accepting the diagnosis implies the start of a treatment strategy whose potential effectiveness could be assumed as *ex juvantibus* confirmation of the presence of the disease.

Finally, new technologies, particularly artificial intelligence (AI), are showing very promising results in the diagnosis and follow-up of patients with HF-pEF. This will undoubtedly facilitate both early diagnosis and management of this complex patient population, allowing for an



**Figure 1.** Diagnostic algorithm for HF-pEF.

LA: left atrium; DM: diabetes mellitus; ECG: electrocardiogram; TTE: transthoracic echocardiogram; CKD: chronic kidney disease; AF: atrial fibrillation; HR: heart rate; LVEF: left ventricular ejection fraction; AHT: arterial hypertension; LVH: left ventricular hypertrophy; HF-pEF: heart failure with preserved ejection fraction; LAVI: left atrial volume index; sPAP: systolic pulmonary artery pressure; NP: natriuretic peptide; SR: sinus rhythm; RWT: relative wall thickness; IVS: interventricular septum; TRV: tricuspid regurgitation velocity; LV: left ventricle.

Figure generated from Refs. 10,11,13,14,34,37,40,41.

earlier start of those therapies that have been shown to reduce progression of the disease.<sup>50,51</sup>

### Therapeutic approach

#### Drug therapy

The European guidelines of 2021 established as treatment recommendations for patients with HF-pEF the screening and treatment of the causes and comorbidities (cardiovascular and non-cardiovascular), as well as the diuretic treatment of patients with congestion in order to alleviate the symptoms and signs of HF-pEF.<sup>1</sup> In 2023, following clinical trials with the sodium-glucose cotransporter-2 inhibitors (SGLT2i) empagliflozin and dapagliflozin,<sup>52,53</sup> the ESC updated the guidelines, including these drugs as first-line treatment for patients with HF-pEF.<sup>14</sup> Since then, new evidence has been published with other drug classes that have demonstrated clinical benefit in this patient population, mainly sacubitril-valsartan, finerenone, semaglutide, and tirzepatide, which offer the potential to expand the therapeutic options in certain patients.<sup>54-57</sup>

#### Diuretics: treatment of congestion

Diuretics are the treatment of choice for congestion, particularly loop diuretics. In acute decompensation, it is usually necessary to administer diuretics intravenously and at high doses, and they can be combined with hydrochlorothiazide during the acute phase - especially in patients who receive baseline treatment with 80 mg or more of furosemide every 24 h.<sup>58</sup> Resistance to treatment with diuretics is defined as a decreased response to these drugs, which prevents adequate elimination of sodium and water, causing the persistence of congestion despite the administration of high doses. In this case, treatment strategies inclu-

de dose escalation, the combination of different types of diuretics (e.g., loop diuretics and thiazides), or the administration of hypertonic saline in conjunction with furosemide to enhance its action.<sup>59</sup>

During the stability phase, loop diuretics should be used at the lowest possible dose, even considering their discontinuation in situations of euolemia, or switching to hydrochlorothiazide in the case of arterial hypertension.<sup>11</sup>

#### SGLT2 inhibitors

SGLT2i represent the first drug class to be shown to reduce the risk of events in patients with HF-pEF. In this regard, the EMPEROR-Preserve (empagliflozin) and DELIVER (dapagliflozin) studies achieved significant reductions in the primary endpoint (cardiovascular mortality or hospitalization due to HF in the first study, and cardiovascular mortality or worsening of HF in the second study), of 21% and 18%, respectively. These findings were mainly due to a marked decrease in hospitalizations due to HF, with a trend towards a reduction in cardiovascular mortality (Supplementary Table 4).<sup>52,53</sup> Thus, the guidelines consider SGLT2i to be the cornerstone treatment for patients with HF-pEF, with grade IA recommendation.<sup>10,14</sup>

#### MRA

Among the clinical trials conducted with steroidal mineralocorticoid receptor antagonists (MRA), mention should be made of the Aldo-DHF study, which showed that treatment with spironolactone was able to reduce left ventricular mass, diastolic function, and NP levels, but with no significant improvement in either symptoms or quality of life.<sup>60</sup> In turn, the TOPCAT study reported that spironolactone did not significantly reduce the composite endpoint of death from cardiovascular causes, recovery from cardiac arrest, or hospitalization due to HF in patients with

HF-pEF, though statistical significance was reached after excluding the patients from Georgia and Russia from the analysis, and a 17% decrease in the secondary endpoint of admissions due to HF was observed.<sup>61,62</sup>

With regard to non-steroidal MRA such as finerenone (the only such drug currently marketed in Spain), the results have been different. The FINEARTS-HF study, conducted in patients with HF and LVEF  $\geq$  40%, treatment with finerenone versus placebo significantly reduced (by 16%) the composite primary endpoint of total events of worsening HF (first or recurrent hospitalization or unplanned emergency room visit due to HF) and cardiovascular death (HR 0.84; 95%CI 0.74–0.95) (Supplementary Table 4).<sup>55</sup>

#### GLP1 receptor agonists/semaglutide

Another drug class that has shown clinical benefit in the subgroup of patients with HF-pEF and obesity has been the GLP1 receptor agonists, particularly semaglutide 2.4 mg via the subcutaneous (s.c.) route. In the STEP-HF-pEF study, compared with placebo, weekly semaglutide s.c. improved patient quality of life and exercise tolerance, and reduced inflammation and body weight in individuals with obesity-associated HF-pEF.<sup>63</sup> In the STEP-HF-pEF DM study, which included patients with HF-pEF, obesity and type 2 diabetes, semaglutide 2.4 mg s.c. produced, as in patients without DM, improvement of the HF symptoms and physical limitations (improved quality of life), as well as significant reduction of body weight, after one year of treatment.<sup>64</sup> In the pre-specified pooled analysis of both studies, not only were these results confirmed, but the use of semaglutide 2.4 mg s.c. was also associated as a tertiary objective with a significant reduction in time to the first HF event and time to the first HF event or cardiovascular death.<sup>65</sup> In the recent pooled analysis of patients with HF-pEF in the SELECT (individuals with atherosclerotic cardiovascular disease and who are overweight or obese), FLOW (subjects with type 2 diabetes and chronic kidney disease), STEP-HF-pEF and STEP-HF-pEF DM studies, treatment with semaglutide s.c. was associated with significant 31% reductions in the risk of cardiovascular death or HF events (HR 0.69; 95%CI 0.53–0.89) and 41% reductions in the risk of worsening HF events (HR 0.59; 95%CI 0.41–0.82) (Supplementary Table 4).<sup>56</sup>

#### Tirzepatide

The last drug class to show benefits in patients with HF-pEF and obesity are the dual G1P/GLP1 agonists, particularly tirzepatide. Thus, in the SUMMIT study, in patients presenting HF with LVEF  $\geq$  50%, and body mass index (BMI)  $\geq$  30 kg/m<sup>2</sup>, compared to placebo, tirzepatide (up to 15 mg s.c. weekly) reduced the risk of the primary endpoint (first event worsening HF or cardiovascular death) by 38% (HR 0.62; 95%CI 0.41–0.95), as well as the risk of HF worsening events by 46% (HR 0.54; 95%CI 0.34–0.85), in addition to improving health status and quality of life (Supplementary Table 4).<sup>57</sup>

#### ACEI/ARAI

Different clinical trials have analyzed the role of renin-angiotensin system inhibitors in patients with HF-pEF, with discrete results. Thus, neither the CHARM (candesartan) nor the I-PRESERVE (irbesartan) study reported any significant reduction in the primary endpoint, although candesartan was associated with a 16% lowering of the incidence of the secondary objective HF hospitalizations.<sup>66,67</sup> Similarly, in the PEP-CHF study, perindopril 4 mg/day was not able to reduce the primary endpoint of the study, although it was associated with a lower risk of hospitalization due to HF.<sup>68</sup> Therefore, renin-angiotensin system inhibitors would be indicated in patients with HF-pEF, particularly in the treatment of comorbidities such as high blood pressure.<sup>11</sup>

#### ARNI

With regard to the angiotensin receptor neprilysin inhibitors (ARNIs), the PARAGON-HF study, which evaluated the use of sacubitril-valsartan in a cohort of 4822 patients with HF and LVEF  $\geq$  45%, reported a trend towards a decrease in the composite primary endpoint of cardiovascular death or hospitalization due to HF in the sacubitril-valsartan group compared to valsartan (HR 0.87; 95%CI 0.75–1.01;  $p = 0.06$ ). The benefit appears to be greater in women (HR 0.73; 95%CI 0.59–0.90) and in subjects with LVEF  $<$  57% (HR 0.78; 95%CI 0.64–0.95) (Supplementary Table 4).<sup>54</sup> The PARAGLIDE-HF and PARALLAX studies reported significant reductions in NP levels in patients with HF-pEF.<sup>69,70</sup> In a pooled analysis of the PARAGLIDE-HF and PARAGON-HF studies, in which patients admitted due to HF-pEF within 30 days before entering the trial were analyzed, treatment with sacubitril-valsartan was associated with a 22% reduction in admissions due to HF and cardiovascular mortality.<sup>71</sup> Consequently, the use of sacubitril-valsartan should be considered in subjects with HF with LVEF  $<$  60% who remain symptomatic despite cornerstone treatment (SGLT2i, finerenone and tirzepatide/semaglutide in the case of obesity).

#### Beta-blockers

As regards beta-blockers (BB), clinical trials conducted with nebivolol or carvedilol have shown no benefit in terms of mortality or hospitalizations due to HF, although the SENIORS study reported a favorable trend in the subgroup of patients with LVEF  $>$  35%.<sup>72,73</sup> It is important to note that BB may cause chronotropic incompetence in patients with HF-pEF.<sup>74</sup> Therefore, the indication of BB in patients with HF-pEF would be reserved for those subjects with specific conditions such as ischemic heart disease, AF or an inappropriately high heart rate.<sup>10,11,14</sup>

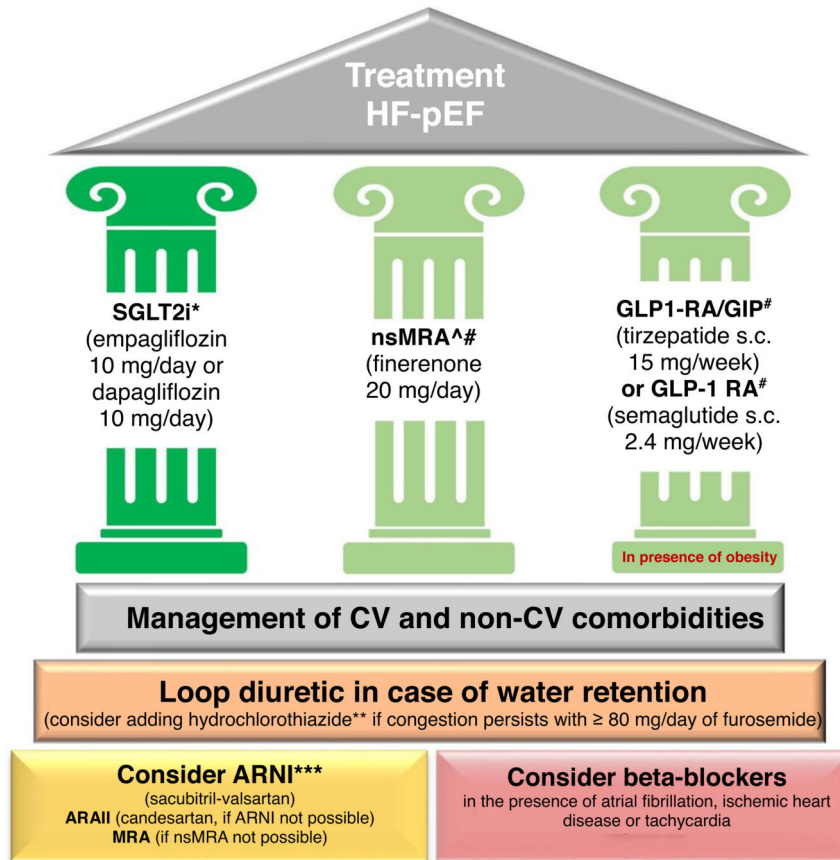
On the other hand, it is expected that in the future we will have evidence of new approaches helping to further complete the pharmacological treatment of patients with HF-pEF. In this regard, the efficacy of the aldosterone synthase inhibitor vicadrostal combined with empagliflozin versus empagliflozin in patients with HF-pEF (NCT06424288) is currently being investigated.

In short, in the light of all this evidence, including the most recent data, the management of patients with HF-pEF has changed substantially, as now there are different drugs that have been shown to be able to modify the course of the disease, and which make it necessary to update the treatment algorithm. To summarize, the background treatment which these patients should receive is expanded, specifically diuretics in the case of water retention, SGLT2i (empagliflozin or dapagliflozin) and finerenone, which would be indicated in all patients. Likewise, in the case of obese individuals, tirzepatide 15 mg or semaglutide 2.4 mg weekly (both via the s.c. route) could be used (Fig. 2). Given the clinical benefits of these drugs, and whenever possible, combined early initiation is important, depending on the patient characteristics.<sup>75,76</sup>

In the acute phase, in addition to diuretics for the treatment of congestive symptoms, we have evidence to support the use of SGLT2i, since empagliflozin has shown benefit in the EMPULSE study and dapagliflozin has shown safety in the DAPA-ACT study. For the rest of drugs, evidence on the treatment of HF-pEF comes mainly from stabilized patients without fluid overload. Thus, recommendations on their use are mainly focused on this patient population, although we advocate the early initiation of disease-modifying drugs once the patient is stabilized.

#### Non-pharmacological treatment

Non-pharmacological measures are a fundamental part of the management of patients with HF-pEF. It is important to ensure adequate calorie and protein intake in this group of patients, avoiding excess salt in the diet and controlling fluid intake. In addition, in cases of malnu-



**Figure 2.** Pharmacological therapeutic approach recommended in patients with chronic HF-pEF.

\* Except type 1 DM, history of diabetic ketoacidosis or eGFR < 20 mL/min/1.73 m<sup>2</sup> for empagliflozin and < 25 mL/min/1.73 m<sup>2</sup> for dapagliflozin, according to the EMPEROR-Preserved (empagliflozin) and DELIVER (dapagliflozin) trials.

\*\* Acute phase evidence in CLOROTIC trial with dose adjusted according to estimated glomerular filtration rate. Monitor renal function and ions early.

\*\*\* If symptoms persist and LVEF ≤ 60%, based on pooled analysis of PARAGON-HF and PARAGLIDE-HF.

† Except if potassium > 5 mmol/l and/or eGFR < 25 mL/min/1.73 m<sup>2</sup>. Dose for diabetic kidney disease, in HF-pEF or HF-mrEF. Consider spironolactone if symptoms persist and finerenone is not possible.

# No approved indication for HF-pEF.

ARAI: angiotensin II receptor antagonist; GLP1-RA: GLP1 receptor agonist; GLP1-RA/GIP: dual agonists of the GLP1 receptor and gastric inhibitory polypeptide; MRA: mineralocorticoid receptor antagonist; nsMRA: non-steroidal mineralocorticoid receptor antagonist; ARNI: angiotensin receptor-neprilysin inhibitor; CV: cardiovascular; DM: diabetes mellitus; DM2: type 2 diabetes mellitus; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; HF-pEF: heart failure with preserved ejection fraction; HF-mrEF: heart failure with mildly reduced ejection fraction; SGLT2i: sodium-glucose cotransporter-2 (SGLT2) inhibitor; s.c.: subcutaneous.

trition or sarcopenia, nutritional supplements play an essential role. Physical exercise (aerobic and strength) should be encouraged, adapted to the patient characteristics (age, frailty, mobility, etc.) and implemented on a gradual basis (Supplemental Table 5).<sup>10,11,13–17,44,77,78</sup> Further details on these recommendations can be found in Appendix 1 of the Supplementary material.

### Treatment of comorbidities

One of the key aspects in the management of patients with HF-pEF is the approach to their comorbidities. These not only increase the overall disease burden, but also promote polypharmacy and thus the risk of drug interactions, adverse effects, and relevant clinical events (such as falls, functional impairment, sarcopenia, readmissions, and mortality). The most common comorbidities in HF-pEF include diabetes mellitus, high blood pressure, obesity, chronic obstructive pulmonary disease, obstructive sleep apnea, chronic kidney disease, ischemic heart disease, iron deficiency, anemia, and AF.<sup>10,11,13–15,17,44,77,79–83</sup> The main recommendations for the management of each of these conditions in patients with HF-pEF are summarized in Table 2.

Despite the demonstrated benefits of disease-modifying therapies, their use remains limited in frail patients, contributing to poorer clinical outcomes. Given the high burden of complications in this group of patients, it is essential to reinforce the implementation of evidence-based therapies that improve their prognosis and quality of life.<sup>84</sup>

### Importance of the care units and continuity of care

Patients with HF-pEF are often older and have multiple associated comorbidities, which means that management should be performed from a holistic approach, considering all aspects in a global manner. The best approach is represented by the multidisciplinary HF units, particularly the Comprehensive Management Units for Patients with Heart Failure (Unidades de Continuidad Asistencial [UMIPIC]) and the Continuity of Care Units (Unidades de Continuidad Asistencial [UCAS]), where all aspects required by complex patients with HF-pEF can be addressed. In fact, several experiences with the success of multidisciplinary units in Spain led by Internal Medicine have been published, with significant reductions in cardiovascular and non-cardiovascular complications, including decreased mortality and HF admissions. Nursing staff

**Table 2**  
Management of comorbidities in patients with HF-pEF.

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Type 2 diabetes mellitus

- Blood glucose control (HbA1c < 7.0%) to reduce the risk of microvascular complications.
- Preferred: SGLT2i (in all), GLP-1 RA (in the presence of high vascular risk or obesity), dual G1P/GLP1 agonists (in the presence of obesity).
- Glitazones are contraindicated. Among the DPP4i, avoid saxagliptin.

Arterial hypertension

- Target systolic blood pressure control 120–130 mmHg, except if evidence of orthostatic hypotension, frailty, advanced age, or limited life expectancy.
- Background use of renin-angiotensin system inhibitors in combination with thiazide/thiazide-type diuretics.

Obesity

- Weight loss improves hemodynamics, performance status, and quality of life.
- U-shaped curve for mortality in HF according to BMI.
- Encourage caloric restriction and increased physical activity.
- Preferred: GLP-1 RA (semaglutide s.c.) and dual G1P/GLP1 agonists (tirzepatide).
- Bariatric surgery for patients with very high BMI despite previous measures.

COPD

- Up to 20% of COPD exacerbations could be triggered by HF decompensation and arrhythmias.
- Spirometry should be performed in a stable state with euvolemia. FEV1 is an independent risk factor for HF.
- Echocardiography is recommended in the event of elevated NT-pro-BNP in patients with COPD.
- Cardioselective  $\beta$ -1 blockers reduce COPD exacerbations and mortality in patients with HF.
- Bronchodilator treatment the same as when there is no HF.

OSA

- Test for OSA if there is high clinical suspicion.
- Recommend weight loss.
- Treat OSA to improve daytime sleepiness, improve sleep quality and quality of life (CPAP).
- Treatment of severe nocturnal hypoxemia (CPAP + nocturnal oxygen).
- Treat OSA in individuals with resistant hypertension and consider in patients with AF treated with rhythm control strategies.

CKD

- Creatinine may be falsely decreased due to loss of muscle mass and hemodilution.
- Empagliflozin can be used with eGFR > 20 mL/min/1.73 m<sup>2</sup> and dapagliflozin with eGFR > 25 mL/min/1.73 m<sup>2</sup>.
- Functional decline in eGFR may occur with initiation of SGLT2i; do not suspend.
- Optimize renin-angiotensin system inhibition in subjects with proteinuria or diabetic nephropathy.
- In the presence of diabetic nephropathy with albuminuria  $\geq$  30  $\mu$ g/g and GFR  $\geq$  25 mL/min/1.73 m<sup>2</sup>, consider finerenone.

Ischemic heart disease

- Perform diagnostic tests based on patient symptoms.
- For persistent symptoms of HF or uncontrolled angina despite medical treatment, consider revascularization.
- Do not use long-acting nitrates routinely.

Iron deficiency/anemia

- Anemia and iron deficiency without anemia worsen functional class and increase the risk of hospitalization.
- Definition of iron deficiency: Ferritin < 100  $\mu$ g/l (absolute) or ferritin 100-300  $\mu$ g/l + TSI < 20% (functional).
- In iron deficiency without anemia, unless other disease is suspected, consider in the context of HF and proceed directly to its treatment (iron carboxymaltose)
- If anemia is present, identify the etiology for targeted therapy.

Table 2 (Continued)

AF

- Rhythm control preferable to heart rate control, if possible, to maintain atrial contraction and favor diastolic function.
- Heart rate control: avoid excessive reduction so as not to reduce stroke volume too much and low exercise reserve. Use beta-blockers or non-dihydropyridine calcium antagonists, associated with digoxin if necessary.
- Indication of chronic oral anticoagulation, unless contraindicated, preferably DOAC (vs VKA).

DOAC: Direct oral anticoagulants; GLP1-RA: GLP-1 receptor agonists; VKA: vitamin K antagonists; CPAP: continuous positive airway pressure; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; eGFR: estimated glomerular filtration rate; HF: heart failure; DPP4i: dipeptidyl peptidase-4 inhibitors; BMI: body mass index; SGLT2i: sodium-glucose cotransporter-2 (SGLT2) inhibitors; OSA: obstructive sleep apnea.

Table generated with data from Refs. 10,11,13–15,17,44,77,79–83.

play an essential part in these units, given their central role in the organization of the unit, educational work, and patient follow-up.<sup>85–87</sup>

Telemonitoring allows remote monitoring of patients with HF, collecting key data such as body weight, blood pressure and heart rate to prevent decompensations and reduce hospitalizations. The devices send this information to the hospital, where the staff can proactively adopt therapeutic measures. Given the clinical usefulness of telemonitoring, its use should also be extended in the HF-pEF population.<sup>88</sup> As part of the strategies aimed at reducing readmissions, it is important to identify those patients who will potentially benefit from adequate palliative care. In this regard, the EPICTER scale has demonstrated its clinical utility.<sup>89</sup>

HF-pEF not only requires a multidisciplinary approach within the hospital; an adequate transition from the time of discharge, ensuring continuity of care with primary care, also play a central role in the effective and efficient care of these patients. The primary care physician is essential to the initial approach, starting with diagnostic suspicion, in addition to outpatient follow-up of chronic patients, stabilizing them, the early detection of decompensation, checking of adequate treatment adherence, or the detection of potential treatment-related complications, among others. Thus, it is necessary to implement locally consensus-based protocols, as well as to ensure adequate training of all the professionals involved in the care of these patients.<sup>90,91</sup>

## Conclusions

HF-pEF is a common condition and is associated with high morbidity and mortality. The diagnosis is often complex because of the older age and comorbidities of these patients. Treatment has evolved due to new evidence of drugs that reduce progression and complications, and their early initiation is therefore required. In effect, early detection and treatment are key to reducing the burden of HF and the cardiovascular-kidney-metabolic axis.

## Authorship

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## Declaration of competing interest

José María Fernández Rodríguez states that he has no conflicts of interest. María Belén Alonso-Ortiz has received honoraria for lectures, presentations, articles, manuscript writing, and participation in educational events from AstraZeneca, Bayer, Bias, Chiesi, FAES Farma, Ferrer, GSK, Nestlé Health Science, and Neuraxpharm Spain; as well as support for meetings and/or travel from Almirall, Fresenius, GSK, and Novo Nordisk. In addition, she has performed scientific advisory functions for Adventia Pharma. Jesús Casado Cerrada declares that he has no conflicts of interest. David Chivite Guillen states that he has no conflicts of interest. Pilar Cubo Romano has participated in talks, lectures or courses in the past 10 years, sponsored by: Esteve, Nestlé, GlaxoSmithKline, Novartis, Gebro Pharma, Fresenius Kabi, Advanz Pharma, Menarini, Boehringer Ingelheim, Zambon, and FAES Farma. Rocío García Alonso states that she has no conflicts of interest. Ana Lorenzo Almorós has received honoraria in the past for scientific activities from Boehringer. José Pablo Miramontes-González has participated in activities sponsored by Boehringer Ingelheim, Lilly and Novartis. Llanos Soler Rangel states that she has no conflicts of interest. José Pérez-Silvestre declares that he has no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.rceng.2026.502471>.

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