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ANMCO position paper: diagnosis and treatment of heart failure with preserved systolic function

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Heart failure is the leading cardiovascular cause of hospitalization with an increasing prevalence, especially in older patients. About 50% of patients with heart failure have preserved ventricular function, a form of heart failure that, until a few years ago, was orphaned by pharmacological treatments effective in reducing hospitalization and mortality. New trials, which have tested the use of gliflozins in patients with heart failure with preserved ejection fraction (HFpEF), have for the first time demonstrated their effectiveness in changing the natural history of this insidious and frequent form of heart failure. Therefore, diagnosing those patients early is crucial to provide the best treatment. Moreover, the diagnosis is influenced by the patient's comorbidities, and some HFpEF patients have symptoms common to other rare diseases that, if unrecognized, develop an unfavourable prognosis. This position paper aims to provide the clinician with a useful tool for diagnosing and treating patients with HFpEF, guiding the clinician towards the most appropriate diagnostic and therapeutic pathway.

Introduction

Heart failure (HF) is the leading cardiovascular cause of hospitalization with an increasing prevalence especially in older patients. About 50% of patients with HF have preserved ventricular function, a form of HF that until a few years ago lacked effective drug treatments that could reduce hospitalization and mortality. Therapy then was based solely on the consumption of diuretics, used to reduce congestion, and control of comorbidities. The new trials, which tested the use of glyflozines in patients with preserved HF, have for the first time demonstrated efficacy in changing the natural history of this insidious and frequent form of HF. Thus, early diagnosis is very important, but is often concealed by the patients' comorbidities, which therefore complicate the diagnostic pathway; in addition, some patients have symptoms common to other rare diseases that, if unrecognized, decay insidiously. Therefore, the purpose of this position paper is to provide the clinician with a useful tool for the diagnosis and treatment of patients with HF preserved function, guiding them towards the most appropriate diagnostic and therapeutic course possible. This Position Paper aims to provide the clinician with a useful tool for diagnosing and treating patients with HFpEF, guiding the clinician towards the most appropriate and therapeutic pathway.

Definition of heart failure with preserved systolic function

In line with the 2016 European Society of Cardiology (ESC) definition, HF is a clinical syndrome characterized by typical symptoms (e.g. dyspnoea, declivous oedema, and asthenia/fatigue) that may be accompanied by signs of pulmonary and/or peripheral congestion (e.g. elevated jugular venous pressure, crackles at the lung bases, and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in reduced cardiac output and/or elevated intracardiac pressure at rest or during exertion.[1] Heart failure with preserved ejection fraction (HFpEF), commonly known by the Anglo-Saxon acronym HFpEF refers to a nosologic entity characterized by:

(1) HF clinical syndrome.
(2) 'Preserved' left ventricular EF ≥50%.
(3) Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of left ventricular diastolic dysfunction/ increased left ventricular filling pressure, including increased natriuretic peptides.[2]

However, this clinical definition does not always overlap with the data on which we rely on to define the epidemiology and outcomes of HFpEF. For example, by taking hospital discharge records into account and thus relying on ICD-9 codes, the specificity of the diagnosis may be underestimated and consequently the prevalence estimates reduced and the association with mortality increased.[3] A second issue with the codes of the hospital discharge forms stems from the lack, at least in Italy, of EF data, which is generally not entered at discharge, hence the need to obtain complete data from observational cohort studies or interventional studies. These on the other hand have the fault of 'selecting' the study populations regardless and consequently do not extensively represent the prevalence of the condition. A third problem affecting EF, primarily echocardiographic EF, the still most widely used diagnostic method for estimating left ventricular function, lies in the interobserver and intraobserver variability found in clinical settings.

A 'surrogate' method for EF, because of its greater simplicity and access availability, is to use natriuretic peptides in the diagnosis of HFpEF. Relying solely on biomarkers, however, the diagnosis may be underestimated (natriuretic peptides do not detect about one-third of all affected patients), particularly in some subgroups such as patients with obesity or of African ethnicity.[3,4] Practically, HFpEF remains underestimated in many subgroups, for example, in patients with obesity precisely because of the particular reduction in circulating levels of natriuretic peptides.

Finally, a number of specific diseases [amyloidosis, haemochromatosis, sarcoidosis, Fabry disease, hypertrophic cardiomyopathy (HCM), cardiotoxicity or radiation disease, pericarditis, etc.] cause HF clinical

syndrome along with normal EF, but each has their own particular pathophysiology, natural history, and treatment. These aetiologies should not be considered as true phenotypes of HFpEF because of their distinguishing characteristics and specific treatments.[3]

Epidemiology

About 6 million people in the USA suffer from HF, which is the second leading cause of hospitalization in the adult population[5]; of these, HFpEF accounts for about 50% of all HF diagnoses.[1]

By 2030, the prevalence of all HF cases (with any EF) in the USA is expected to reach about 8 million cases, about 3.0% of people ≥18 years of age.[5] Globally, it is estimated that more than 64 million people are affected by HF.[6] Two cohort studies, the Cardiovascular Lifetime Risk Pooling Project and the Multi-Ethnic Study of Atherosclerosis, have estimated that the lifetime risk of developing HF (lifetime risk) starting at 45 years of age, depending on sex and race, can be quantified between 20 and 46%.[7,8] Of all HF patients, at least 50% had a phenotype of preserved EF HF.[9,10] The prevalence of HFpEF among patients hospitalized for HF compared with reduced EF HF (HFrEF) shows a steadily increasing temporal trend (from about 38% in 1987 to about 54% in 2001),[8,11] which is likely to be explained by both increased diagnostic capacity and the higher prevalence of risk factors such as age, hypertension, and obesity[12] as well as with a higher survival of patients surviving the acute phase of coronary syndromes as a result of interventional and pharmacological therapies in the acute phase (greater myocardial tissue conservation but higher incidence of patients surviving and developing additional comorbidities in addition to ischaemic heart disease). The incidence of HFpEF is reported in 1–4 cases per 1000 persons depending on the characteristics of the cohorts studied and the period of observation.[13] In a large prospective multistudy, 13 risk factors for incident HFpEF were identified. Among these, the main predictors of risk were advanced age [hazard ratio (HR), 2.0 for each 10-year increment], high blood pressure (HR 1.7), obesity [HR 1.3 for each 4-unit increase in body mass index (BMI)], diabetes (HR 1.8), and coronary artery disease (HR 1.6).[14] Collectively, these data suggest that HFpEF will become the dominant HF phenotype in the near future, affecting about 1 in 10 adults during their lifetime.

In Italy, data from the National Outcomes Program show that HF is the highest impacting condition, based on the number of cases (130 000 hospitalizations in 2022), among potentially 'avoidable' hospitalizations. It is a high-prevalence and high-incidence condition that is the leading cause of hospitalization in patients ≥65 years of age. In Italy, about 600 000 people suffer from HF and its prevalence is estimated to double with each decade of age (after the age of 65 it reaches about 10%) (Ministry of Health data) with still substantial differences in hospitalization rates by geographic area (*Figure 1*). The ARNO Study derived data on HF prevalence, clinical characteristics, prescribed therapies, and rehospitalization rate from a population of five Italian local health units. Of the 2 456 739 subjects included in the database, 54 059 (2.2%) had been hospitalized for HF (41 413 discharged alive). The mean age was 78 ± 11 years, and 51.4% were women. The most frequent comorbidities were diabetes (30.7%), chronic obstructive pulmonary disease (30.5%), and depression (21%). Unfortunately, data on EF were not available, so it was not possible to estimate the prevalence of HFpEF.[15]

The prevalence of asymptomatic cardiac dysfunction and preclinical decompensation was observed in the PREDICTOR (Evaluation of the PREvalence of asynTOmatic cardiac DIsfunction and caRdiac decompensation)[16] study. The population included a sample of 2001 subjects, residents of the Lazio Region, between 65 and 84 years of age who had undergone a physical examination, complete biochemical evaluation, N-terminal fragment of B-type natriuretic

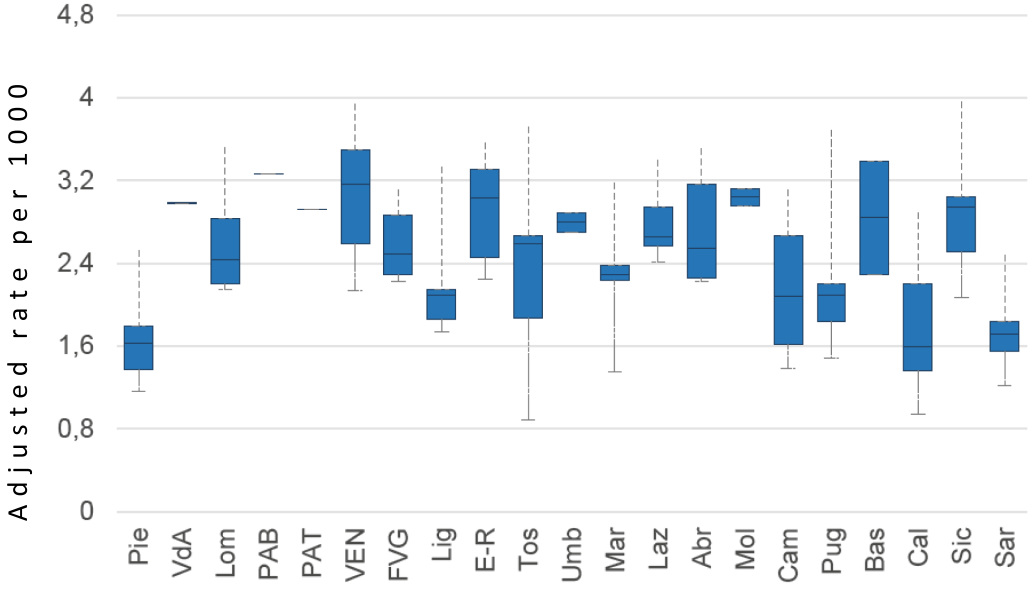

Figure 1 Heart failure: hospitalization rates according to the geographical area (Italy, 2022). Data from AGENAS National Outcomes Program, 2023 edition (https://pne.agenas.it/assets/documentation/report/agenas_pne_report_2023.pdf).

propeptide (NT-proBNP) assay, ECG, and colour Doppler echocardiography. Systolic left ventricular dysfunction (LVD) was defined by a LVEF <50%. Diastolic LVD was determined by a multiparametric algorithm derived from Doppler echocardiography. The overall prevalence of HF was 6.7% [95% confidence interval (CI) 5.6–7.9], mainly due to HFpEF (4.9%; 95% CI 4.0–5.9), and did not differ by sex. The prevalence of HFpEF increased with age to 9% in men and 7.4% in women >75 years of age. The prevalence of diastolic dysfunction was 42.8% in the asymptomatic population ($n = 589$) and 41.5% in the symptomatic population ($n = 145$).

Asymptomatic diastolic DVS was comparable gender-wise (men: 35.8%; 95% CI 32.7–38.9; women: 35.0%; 95% CI 31.9–38.2). NT-proBNP levels and DVS severity increased with age. A total of 1623 subjects (81.1% of the entire study population) had preclinical HF (stage A: 22.2% and stage B: 59.1%). On the sideline, it was observed that a large number of subjects with stage B HF showed nontarget levels of risk factors.

Several observational studies[10] have reported a prevalence of female gender patients with HFpEF (55–65% of the total). Although the incidence of HFpEF is similar between the genders, the prevalence of HFpEF is higher in women than in men.[17] In a study that examined HFpEF hospitalizations, women outnumbered men by a ratio of 2:1. When considering estimates of lifetime risk of HF, the risk of developing HFpEF is almost twice that of HFrEF among women (10.7% vs. 5.8%), while among men, the risk of developing HFpEF is similar to that of developing HFrEF.[18] In a large multicohort study, the incidence of HFpEF adjusted on the basis of age and other risk factors was numerically but not significantly higher in women than in men.[14] On the contrary, the incidence of HFrEF was substantially lower among women than men, even after adjustment for age and other risk factors.

Studies on race/ethnicity differences in HFpEF are evolving. Data from the Atherosclerosis Risk in Communities (ARIC) study of HF-related hospitalizations conducted in four US communities between 2005 and 2014 show that the mean event rates for first hospitalization for HFpEF were higher among black women (7.4 per 1000 person-years; 95% CI 6.7–8.1) than black men (6.2 per 1000 person-years; 95% CI 5.5–7.0), white women (5.9 per 1000 person-years; 95% CI 5.5–6.2), and white men (4.9 per person-years; 95% CI 4.5–5.3). During the observational period, the annual percentage change for first hospitalization for HFpEF increased for all four race and gender groups and was particularly pronounced among black women.[19]

Heart failure with preserved ejection fraction in different stages of the disease

Stage A

Although most of the traditional risk factors for HF are shared for both HFpEF and HFrEF, such as advanced age, hypertension, and ischaemic heart disease, others such as obesity, metabolic syndrome, and physical inactivity seem to specifically predispose more to HFpEF than HFrEF. In a community-based study that included four cohorts, higher BMI and insulin resistance were associated with the future development of HFpEF, particularly in women.[20] Sedentary lifestyle and physical inactivity were associated with a higher risk of HFpEF than HFrEF in a dose-dependent manner.[21]

Stage B: functional and structural alterations of the right ventricle and preclinical heart failure

The progression from risk factor exposure (stage A) to cardiac remodelling and preclinical HFpEF (stage B) and eventual clinically manifest HFpEF (stages C and D) is still not quite clear. Patients with stage B HF are referred to as asymptomatic but with evidence of structural heart disease (e.g. left ventricular hypertrophy, dilatation, or altered chamber geometry), abnormalities of cardiac function (e.g. diastolic dysfunction and/or elevated filling pressures), and/or elevated levels of B-type natriuretic peptide (BNP) or cardiac troponin. The common pathophysiologic key between preclinical dysfunction and HFpEF is diastolic dysfunction, which must be recognized but may be absent at rest and only reveal itself during exertion. The recognition of asymptomatic LVD as a cornerstone of the diagnosis of preclinical HF (often with preserved EF) has been studied in different contexts. This study subsequently evaluated the accuracy and cost-effectiveness of different screening strategies to identify asymptomatic systolic and/or diastolic LVD and preclinical HF (stage B).[22] Five strategies were evaluated including ECG, NT-proBNP, transthoracic colour Doppler echocardiography, and their combinations. Subjects >75 years of age with at least two additional risk factors were defined as high risk for HF ($n = 435$), while the remaining 1017 were defined as low risk. The cost-effectiveness (cost per case) screening comparison of the five strategies for predicting asymptomatic systolic (EF < 50%) or diastolic LVD and preclinical HF (stage B) showed that NT-proBNP was the most accurate and cost-effective screening strategy for identifying moderate to severe systolic and diastolic LVD, with no difference between the high- and low-risk groups. The addition of ECG to the NT-proBNP assessment did not improve the recognition of preclinical HF, and the transthoracic echocardiography was effective only as a subsequent confirmatory test. A recent study has shown that even among patients in whom HFpEF has been ruled out, an increasing burden of risk factors for HFpEF and functional abnormalities based on echocardiography are strongly correlated with haemodynamic changes typical (but less severe) of those observed in patients with clinically manifest HF, i.e. stage C.[23] The study was based on the score proposed by the Mayo Clinic researchers that gives the probability of HFpEF in the patient with dyspnoea of unknown origin (H_2FPEF).[22] The score includes six clinical-echocardiographic variables [hypertension, age, BMI, atrial fibrillation (AF), pulmonary systolic blood pressure, and E/e′ ratio]. Although it may represent a first tool to be applied in clinical practice in order to raise the diagnostic suspicion of HFpEF, however, it should be emphasized that the importance given by the score to BMI, in addition to the low age cut-off used to make the diagnosis, are elements that make it difficult to apply it extensively in an Italian context, without integrating it with other diagnostic elements.[24] In consideration of the role of potential HFpEF preventive therapies, clearly defining preclinical HFpEF will be critical in the near future. In an observational study on cardiologists' awareness of preclinical HF, VASTISSIMO [Evaluation of the

Appropriateness of the Preclinical Phase (Stage A and Stage B) of Heart Failure Management in Outpatient Clinics in Italy], of the 3322 patients included in the study, the data needed to identify stage B HF were collected in 2106 (63.4%). In many cases, the risk was underestimated: 16.2% of those with previous acute myocardial infarction, 23.1% with left ventricular hypertrophy on ECG/echocardiography, 30% with systolic–diastolic dysfunction, and 14.3% with valvular disease. Management of stage B HF appeared adequate in just over one-third of cases.[25]

Stage C: under-recognition of heart failure with preserved ejection fraction

Recently developed scoring systems now provide a tool to select larger patient populations and estimate the potential extent of undiagnosed HFpEF in the community. Among individuals with unexplained dyspnoea but no diagnosis of HFpEF in ARIC, the H_2FPEF score showed a high risk (≥5) in 35% of cases, indicating that a substantial proportion of elderly people with HFpEF in the community are probably undiagnosed. Underdiagnosis might be even more evident among black patients, who are known to have lower natriuretic peptide levels than white individuals, and who constituted a higher percentage of patients with undiagnosed dyspnoea in the ARIC analysis.

Outcomes of heart failure with preserved ejection fraction

Patients with HFpEF have a similar survival rate compared to patients with HFrEF. In community-based cohorts, the incidence rate of all-cause mortality among individuals with newly diagnosed HFpEF compared with HFrEF was 394 vs. 459 events per 10 000 person-years.[26] Among the individuals included in the GWTG-HF (Get With The Guidelines-Heart Failure) Registry with Medicare data up until 2014, the 5-year mortality rate was 75.3% among those with HFpEF and 75.7% among those with HFrEF.[27] However, the causes of death differed by HF phenotype, with a lower proportion of cardiovascular deaths compared to non-cardiovascular deaths in the HFpEF group as opposed to the HFrEF group.[28] Similar to the manner of death, the proportion of re-hospitalizations due to cardiovascular causes appears to be lower in patients with HFpEF than in patients with HFrEF and HF with mildly reduced EF, emphasizing the importance of the management of non-cardiac comorbidities in HFpEF.[29]

Pathophysiology and phenotypes of heart failure with preserved function

The pathophysiology of HFpEF is extremely complex and heterogeneous, and involves several vascular and nonvascular mechanisms[30,31] (*Figure 2*). Importantly, the so-called ‘typical garden variety’ of HFpEF excludes by definition those conditions where diastolic dysfunction is not at the heart of the syndrome, such as valvulopathies and high output HF, which have always been exclusion criteria in trials conducted in patients with HFpEF.[32]

The traditional pathophysiological model and the role of metabolic inflammation

Over time, two main pathophysiological models have been described. The first model, referred to as the traditional model, recognizes the origin of HFpEF in arterial hypertension and vascular dysfunction leading to concentric hypertrophy of the left ventricle, its fibrosis, diastolic dysfunction, and finally, by a cascading mechanism, alterations in the left atrium, right ventricle, and right atrium. This hypothesis was supported by the evidence, at structural level, of increased hypertrophy and elongation of cardiomyocytes compared with that found in the hearts of patients with HFrEF.[33] However, subsequent population studies have shown that up to 30% of patients have normal ventricular geometry or only concentric remodelling, in the absence of hypertrophy.[34] The second pathophysiological model, referred to as pro-inflammatory/metabolic, is the emerging one and recognizes systemic inflammation, derived from the various comorbidities involved, as the *primum movens* of this disease. As a consequence of endothelial inflammation, oxidative stress increases and there is a cascade reduction in nitric oxide levels and thus in the cyclic GMP.[33,35] This eventually leads to hypertrophy, stiffness, and diastolic and vascular dysfunction. At the same time, altered myocyte ‘signalling’ is created, which draws macrophages into the myocardial interstitium. This results in the conversion of fibroblasts to myofibroblasts and subsequent collagen deposition. Finally, vascular inflammation leads to rarefaction of coronary microcirculation in all the layers of the myocardium.[36]

Preserved function heart failure phenotypes, left ventricle, and its remodelling

At the structural level, cardiomyocytes in patients with HFpEF are in most cases thicker and less elongated than those observed in patients with HFrEF. Within the cohort of patients included in the Olmsted County Registry, 42% had left ventricular hypertrophy. Fifty-three per cent had a concentric distribution while eccentric hypertrophy was observed in 16% of cases. Geometry was normal in 31% of the patients.[37] An analysis of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial shows that only 14% of the patients had a normal left ventricle,[38] whereas in the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) trial, this percentage reached 46%.[39] Despite the variability in the data just presented, left ventricular hypertrophy is an important predictor of HF hospitalizations and mortality, regardless of the clinical parameters or of the presence of diastolic dysfunction.

Systolic dysfunction

The nomenclature given to the patient with HFpEF suggests the presence of preserved systolic function. However, some studies suggest, on the contrary, a significant alteration in the myocardial contractile function in comparison to healthy controls when measured by tissue Doppler, longitudinal strain, or circumferential strain. It would thus appear that, with aging, first the longitudinal systolic function and, later,

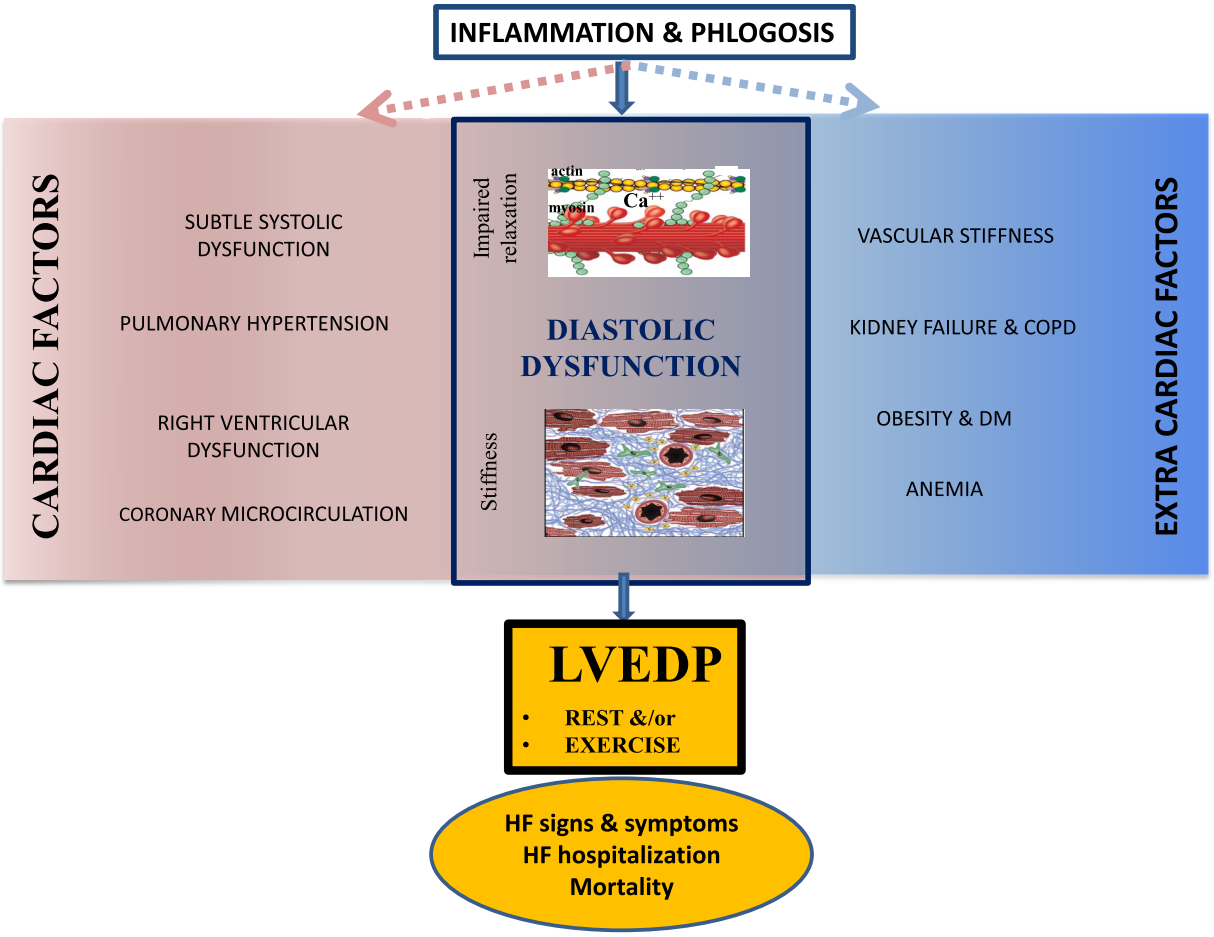

Figure 2 Pathophysiology of heart failure (HF) with preserved ejection fraction: cardiac factors. AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; LVEDP, left ventricular end-diastolic pressure; RV, right ventricular. Modified from Gori *et al*.

the circumferential function alter in order to maintain adequate EF. Subtle deficits of the systolic performance at rest become apparent during physiological stress. These subtle alterations turn out to have a predictive value, as shown in the TOPCAT[40] trial.

Diastolic dysfunction

In the 'stiff' hearts of patients with HFpEF, the pressure decay time during the isovolumetric release phase increases. In particular, the ability to implement the release mechanism in response to an increase in heart rate with consequent elevation of pressures in the left heart chambers seems to be lost. A second compensation mechanism involved is the reduction of the physiological suction effect by the left ventricle in response to the increased venous return that occurs, for example, during exercise, in order to reduce pressures in the left atrium. Passive ventricular stiffness also plays a role in determining the increase in filling pressures. It is quantified on the basis of the slope of the pressure-volume curve and increases with aging, even when arterial pressure is well controlled and there is no concentric remodelling.[41] Most studies show that this parameter increases in patients with HFpEF[42] and the reason seems to lie in the alteration of the sarcomeric macromolecule titin.[43] Although filling pressures are increased, at rest or under stress, left ventricular preload is generally not compromised. In fact, these patients usually have normal heart chamber sizes.[44] Diastolic dysfunction is observed at rest in two-thirds of patients with HFpEF,[40] although many individuals develop elevated filling pressures only during physical exertion, especially in the early stages of disease.[45] A prolonged increase in left-chamber filling pressures leads to secondary pulmonary hypertension and atrial remodelling that predispose to right ventricular dysfunction and AF, respectively. Importantly, asymptomatic diastolic dysfunction in the presence of normal EF is associated with increased risk of HF and death, even in a preclinical setting.[46]

Role of the right ventricle and pulmonary circulation

Right HF is a common finding in patients with HFpEF. In a recent meta-analysis that considered studies enrolling patients with HFpEF, the prevalence of right ventricular dysfunction was 18, 21, and 28% depending on the echocardiographic parameter used for the diagnosis (fractional area change, S' wave at tissue Doppler free wall, and tricuspid annular plane systolic excursion, respectively).[47] A study conducted using cardiac MRI also showed right ventricular dysfunction in 19% of patients

with HFpEF.[48] The prevalence of pulmonary hypertension (defined as pulmonary systolic blood pressure >35 mmHg) was 68%. Data from the TOPCAT trial, however, show a prevalence of 36%. Because of the diastolic LVD and loss of atrial compliance typical of the hearts of these patients, an increase in pressure in the left atrium affects preferentially and in a pulsatile manner the pulmonary venous system and then passively the right sections. However, right HF in patients with HFpEF is not only the result of this passive event. Indeed, some studies have shown that right ventricular function is impaired regardless of the degree of pulmonary hypertension and that the right ventricle appears to show increased sensitivity to afterload precisely because, like the left, it exhibits increased diastolic stiffness.[49] An additional proportion of right HF appears to arise from ventricular interdependence. The latter correlation is mediated by helical fibres, shared by both ventricles, and the interventricular septum. These structures are responsible, under normal conditions, for ~30% of the right ventricular systolic performances.[50] Other conditions that may affect right ventricular function are ischaemic heart disease, obesity, renal failure, and chronic obstructive pulmonary disease, through both afterload-dependent and independent modes.[51] Pulmonary hypertension, whatever the cause, is associated with more disabling symptoms, reduced physical capacity, elevated natriuretic peptide levels, and increased rates of hospitalization and death.[52]

Coronary microcirculation

Ischaemia and myocardial damage are common in patients with HFpEF, and they correlate with abnormalities in ventricular function. Ischaemia may occur as a result of an imbalance between oxygen demand and availability due to elevated filling pressures, macrovascular disease of epicardial vessels, or coronary microvascular dysfunction. An autopsy study showed that microvascular density is reduced in patients with HFpEF and that microcirculation rarefaction is correlated to the amount of myocardial fibrosis. Along with these anatomical causes, there is also an alteration in coronary flow reserve, which is a marker of a more advanced degree of disease.[53]

Haemodynamic alterations, stiffness, and vascular dysfunction

Along with the aforementioned cardiac and pulmonary vascular abnormalities, systemic vascular function is also impaired in patients with HFpEF. The inability of the left ventricle to reduce its telesystolic volume and increase systolic output also depends in part on the dysfunction and rigidity of the vascular system as a whole. Impaired vasodilation leads to dynamic limitations of the ventricular–arterial coupling during exercise.[54] In addition, increased arterial stiffness can lead to dramatic fluctuations in blood pressure for any pre- or afterload change. These vascular abnormalities explain the common and marked blood pressure lability in patients with HFpEF. These mechanisms appear to be mediated by a certain degree of endothelial dysfunction, a parameter related to a worse prognosis and considered central to the pathophysiology of this disease.[55]

The central role of comorbidities

Our epidemiological data show that the prevalence of comorbidities increases with age and the decrease of socioeconomic status.[56] When looking at the results of an Italian registry, a temporal trend, from the 1980s-1990s to the present day, it is apparent that there has been an increase in the burden of comorbidities that proceed in parallel with the increase in average age.[57] Compared to patients with HFrEF, patients with HFpEF seem to have more comorbidities. Data from cohort studies, however, show an equal prevalence of comorbidities, with the exception of obesity and hypertension (*Table 1*).[58-65] The presence of coexisting diseases affects patients' symptomatology, since it decreases tolerance to physical exertion. Furthermore, it also has effects on the prognosis as it increases the risk of hospitalization from all causes and the mortality rate.[66] Each comorbidity taken individually worsens the outcome of patients with HFpEF, but the contribution of comorbidities with respect to prognosis does not appear to be different from that observed in patients with HFrEF.

Cardiac comorbidities

Arterial hypertension

The prevalence of hypertension in patients with HFpEF is 55–93%, depending on the context being considered (hospital populations vs. randomized trials, vs. cohort studies).[67] It is higher than that calculated in patients with HFrEF. It is considered one of the risk factors for the development of HF. In HFpEF, high blood pressure levels are responsible for a richer parade of symptoms and, often, are a trigger for flare-ups.

Atrial fibrillation

The prevalence of AF in patients with HFpEF is 21–61%,[68] depending on the context being considered. This is a mutual comorbidity in that it is not only a cause of decompensation but can also be a consequence of structural and haemodynamic alterations such as increased filling pressures, dysregulation of intracellular calcium levels, and autonomic and neuroendocrine dysfunction. Over their lifetime, patients with HFpEF have a 67% chance of developing AF. Finally, the presence of AF is associated with unfavourable outcomes.[69]

Ischaemic heart disease

The prevalence of ischaemic heart disease in patients with HFpEF is 21–59%.[70] It results lower than that calculated in patients with HFrEF. Data on a possible underestimation of the presence of ischaemic heart disease in patients with HFpEF emerged from a study that enrolled 376 patients with previous hospitalization for HFpEF without a known diagnosis of ischaemic heart disease by systematically subjecting them to coronarography. The presence of significant coronary artery disease (stenosis >50% in at least one medium-calibre epicardial vessel, previous infarction, or previous revascularization) was observed in two-thirds of the patients (68%). In addition, patients with HFpEF and ischaemic heart disease treated with medical therapy or incomplete revascularization showed a greater tendency for EF deterioration and a significantly inferior survival span.

Table 1 Prevalence of non-cardiac comorbidities in the populations of registries and cohort studies

	Registry populations						
	ADHERE[58] (2001-04)		OPTIMIZE-HF[59] (2003-04)		ESC Heart Failure Pilot Survey[60] (2011-12)		ASIAN-HF[61] (2012-16)
	HFpEF [*n* = 26 322 (50%)]	HFrEF [*n* = 25 865 (50%)]	HFpEF [*n* = 21 149 (51%)]	HFrEF [*n* = 20 118 (49%)]	HFpEF [*n* = 1249 (38%)]	HFrEF [*n* = 1580 (52%)]	HFpEF (*n* = 1204)
Type of patients	Acute heart failure		Acute heart failure		Inpatients and outpatients		Outpatients
Age (years)	74 ± 13	70 ± 14	75 ± 13	70 ± 14	66 ± 14		68 ± 12
Female gender	62%	40%	62%	38%	30%		50%
Comorbidities							
Chronic obstructive pulmonary disease	31%	27%	15%	21%	14%	16%	9%
IRC	26%	26%	—	—	39%	41%	50%
Anaemia	—	—	—	—	30%	28%	57%
Diabetes mellitus	45%	40%	26%	24%	28%	30%	45%

	Cohort study populations						
	Olmsted County[62] (2003-05)		Danish Registry[63] (1983-2012)	SwedeHF Registry[64] (2000-12)		Registro di Trieste[65] (2009-13)	
	HFpEF [*n* = 308 (55%)]	HFrEF [*n* = 248 (45%)]	HF (*n* = 317 161)	HFpEF [*n* = 6488 (21%)]	HFrEF [*n* = 24 856 (79%)]	HFpEF [*n* = 1373 (59%)]	HFrEF [*n* = 941 (41%)]
Type of patients	Inpatients		Outpatients	Outpatients		Outpatients	
Age (years)	77 ± 12	73 ± 14	78 (69-84)	77 ± 10	71 ± 12	79 ± 9	76 ± 10
Female gender	57%	42%	48%	53%	30%	51%	30%
Comorbidities							
Chronic obstructive pulmonary disease	38%	30%	13%	35%	27%	24%	22%
IRC	11%	9%	3%	55%	45%	40%	42%
Anaemia	53%	49%	—	44%	34%	26%	24%
Diabetes mellitus	36%	38%	10%	30%	27%	34%	35%

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; CRI, chronic renal failure; HF, heart failure.

Non-cardiac comorbidities

Diabetes mellitus

The prevalence of diabetes mellitus (DM) in patients with HFpEF has increased over the past three decades and is between 26 and 49%. It turns out to be slightly lower than that calculated in patients with HFrEF. It represents a major risk factor for the onset of diastolic dysfunction and the development of HFpEF since it directly affects the myocardium through mechanisms independent of the other risk factors, such as lipotoxicity, lipoapoptosis, free fatty acid oxidation, oxidative stress, altered nitric oxide bioavailability, mitochondrial dysfunction, and myocardial fibrosis.[71] This comorbidity is able to influence total and cardiovascular mortality and the number of HF hospitalizations.[72]

Obesity and sedentary lifestyle

The prevalence of obesity in patients with HFpEF is between 33 and 56%. It is higher than that calculated in patients with HFrEF. Together with reduced physical activity, obesity is a powerful predictor of HFpEF, more so than HFrEF.[21] The mechanisms hypothesized to be involved are inflammation of adipose tissue, endocrine effects of adiposity, and chronic increase in volume overload. The echocardiographic evaluation of obese diabetic and non-diabetic adolescent patients compared with healthy peers showed higher telediastolic volume, left ventricular mass index, E/e′ ratio, left atrium volume, and reduced left ventricular longitudinal strain in subjects with higher BMI.[73] One recent *post hoc* analysis of the I-PRESERVE trial showed that BMI values were found to be correlated with outcome in a U-shaped relationship: indeed, the highest rates of adverse events occurred in patients with extremely low or high BMI compared to normal.[74] These results would thus seem to rule out the presence of the paradox observed in patients with HFrEF.

Chronic obstructive pulmonary disease

The prevalence of chronic obstructive pulmonary disease in patients with HFpEF is between 14 and 34%. Even if not in all studies, it is slightly higher than that calculated in patients with HFrEF. Although HF and chronic obstructive pulmonary disease share a number of risk factors, several studies have shown a strong and independent relationship between the degree of severity of pulmonary obstruction and the incidence of HF.[75] In patients with chronic obstructive pulmonary disease, the function of both ventricles is depressed, especially when pulmonary hypertension sets in. When present, moreover, chronic obstructive pulmonary disease worsens the outcome of the patient with HF, whatever the EF.[76] Finally, in a large retrospective study, HF was found to be an independent predictor for the incidence of at least two chronic obstructive pulmonary disease exacerbations per year.[77,78]

Anaemia

The prevalence of anaemia in patients with HFpEF is between 21 and 68%. It is slightly higher than that calculated in patients with HFrEF. It represents a risk factor for HF, to which it is associated with a U-shaped curve, although direct association between these two diseases is infrequent in the absence of other risk factors, such as hypertension, ischaemic heart disease, and renal failure. Haemodynamic changes accompanying severe anaemia include increased preload, reduced peripheral resistance, and increased cardiac output. These adaptive responses of the body may eventually lead to increased ventricular mass. The most frequent cause of anaemia is iron deficiency, which is sometimes also present in non-anaemic patients with HF (17–32% depending on the study).[79] Finally, mortality in anaemic patients with HF is higher, whatever the EF.[80]

Chronic kidney disease

The prevalence of chronic kidney disease (CKD) in patients with HFpEF is between 5 and 70%. It appears to be equally prevalent in patients with HFrEF. In the PARAMOUNT (Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction) study, kidney failure was associated with altered ventricular geometry, reduced fractional shortening, and higher NT-proBNP levels.[80] Mechanisms appear to include pressure and volume overload, increased arterial stiffness, anaemia, abnormal calcium and phosphorus metabolism, uraemic toxicity, increased inflammatory markers, endothelial dysfunction, and oxidative stress. Regarding its effects on prognosis, moderate or severe CKD and/or worsening renal function, over time, independently predicts mortality for all subgroups of HF patients.[81] In addition, CKD is considered an important risk factor for the development of HF.[82]

Specific causes of heart failure with preserved ejection fraction

Primary or secondary cardiomyopathies may occur with HFpEF, prevalently when they manifest a hypertrophic phenotype. Identifying them is of paramount importance, because in many cases, a specific ‘disease modifying’ treatment is possible, and by acting on the specific cause of HFpEF, it results in an additional benefit to standard therapy, with an impact on the incidence of HFpEF flare-ups and short- and long-term survival.

Cardiac amyloidosis

Cardiac amyloidosis is an inflammatory disease characterized by an extracellular deposit of misfolded proteins in the myocardium.[83] A pathognomonic histological feature of this condition, unrelated to the amyloidogenic protein, is the apple-green birefringence to Congo Red staining, observed under polarized light. Although it has always been considered a rare disease, it has become apparent in recent years that cardiac amyloidosis is underdiagnosed especially as a cause of HFpEF. Indeed, it has been shown that about 13% of patients >60 years of age and >12 mm left ventricular parietal thickness with a diagnosis of HFpEF have ‘wild-type’ transthyretin amyloidosis (ATTRwt).[84]

Among the various types of cardiac amyloidosis, the most common are monoclonal immunoglobulin light chain (AL) amyloidosis and ATTR, which can be hereditary (ATTRv) or acquired (ATTRwt).[83] The AL form, often much more aggressive, can rapidly evolve to HFrEF because of the additional effect caused by the direct toxic damage exerted by the light chains. For comparison, the ATTR form progresses more slowly and can easily lead to increased parietal stiffness and diastolic dysfunction, promoting the development of HFpEF. Cardiac amyloidosis as a cause of HFpEF should be suspected in patients with increased left ventricular parietal thickness, especially in the presence of cardiac or extracardiac ‘red flags’ and in specific clinical settings, particularly in patients >65 years of age. Furthermore, although there is a wide clinical overlap between ATTRwt and other forms of HFpEF, it has been observed that individuals with ATTRwt have both higher mean NT-proBNP and troponin I values besides a higher incidence of pericardial effusion and in need of pacemaker implantation.[84] Early diagnosis is crucial, as there are specific therapies for both the ATTR and AL forms that can slow or halt the progression of the disease. However, once significant myocardial damage is established, it is rarely reversible, stressing the importance of timely and accurate diagnosis. Currently, there is a well-defined diagnostic algorithm to identify cardiac amyloidosis effectively, as recently described by the ANMCO position paper ‘Amyloidosis for the Clinical Cardiologist’, to which we refer.[85] In short, after ruling out the presence of a monoclonal component through blood and urine tests, myocardial scintigraphy with diphosphonates is generally sufficient to diagnose ATTR. On the other hand, histologic examination by cardiac or extracardiac biopsy is necessary for the diagnosis of AL amyloidosis. For both forms, there are specific therapies that act at etiologic level. In addition, recent studies show that glyflozines and mineralocorticoid receptor antagonists (MRAs) can improve the survival of these patients, regardless of EF.[86,87]

Fabry disease

Anderson–Fabry disease is a rare X-linked metabolic disorder caused by a pathogenic variant in the GLA gene that causes a deficiency in the enzyme α-galactosidase A (α-Gal A).[88] This deficiency leads to the accumulation of

globotriaosylceramide (Gb3) in lysosomes, causing cellular dysfunction and activation of hypertrophy pathways similar to other hypertrophic cardiomyopathies. The disease has a multisystem impact, affecting the heart, kidneys, and brain, with males usually more affected than females, who may show different degrees of disease depending on the percentage of healthy and pathological X chromosome inactivation. There are two clinical phenotypes: the classical form, characterized by almost complete absence of enzyme activity and early onset of symptoms, and a nonclassical, late-onset form with residual enzyme activity and predominantly cardiac involvement.[89] It has been shown that 41% of patients with Fabry disease have HF at the time of the diagnosis and, in 91% of cases, it is HFpEF, emphasizing the significant role of this pathology in the context of HFpEF.[90] Anderson-Fabry disease should be suspected in patients with left ventricular hypertrophy and other indicative cardiac and extracardiac clinical signs (*Table 2*). Diagnosis is confirmed by assessing α-Gal A enzyme activity and measuring lyso-Gb3 in male patients, with subsequent and necessary demonstration of genetic mutation; for females, only genetic testing is usually indicative of the disease, as normal values of enzyme activity and biomarkers are possible (*Figure 3*). The therapy of Anderson-Fabry disease is mainly based on enzyme replacement, which is indicated for all symptomatic patients at the first signs of organ involvement.[91] This therapy aims to restore α-Gal A levels and reduce Gb3 accumulation in tissues. However, in advanced cases with irreversible organic damage, the efficacy of enzyme replacement therapy is limited, stressing the importance of early treatment initiation.

Table 2 Cardiac and extracardiac 'red flag' characteristic of Fabry disease

Extracardiac 'red flags'	Cardiac 'red flags'
• Absence of patrilineal transmission • Renal pathology (dialysis, transplantation) in family members • Family history of left ventricular hypertrophy • Family/personal history of stroke in youth • Angiokeratomas • Kidney Failure • Proteinuria/albuminuria • Verticillate cornea • Hypoacusis, tinnitus, vertigo • Neuropathic pain • Hypo-anhidrosis • Heat/cold and exercise intolerance • Gastrointestinal symptoms (vomiting, pain, diarrhoea)	• Electrocardiogram: short PR interval, conduction disturbances, atrioventricular blocks, left ventricular hypertrophy, chronotropic incompetence • Echocardiogram: left ventricular hypertrophy, papillary muscle hypertrophy, valve leaflet and septa thickening, binary sign, reduction of the global longitudinal strain • Cardiac MRI: left ventricular hypertrophy, late basal infero-posterior gadolinium enhancement, reduced native T_1 time, focal T_2 enhancement • Laboratory tests: slight increase in troponin

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is the most common genetic cardiomyopathy and is the leading cause of HFpEF among primary myocardial diseases, with a prevalence of 1 in 500 in the general population.[92] The clinical phenotype is complex and mainly characterized by asymmetric left ventricular hypertrophy, not attributable to altered loading conditions, mitral valve abnormalities, microvascular remodelling, and myocardial 'disarray'. At molecular level, mutations in sarcomere protein genes cause a hypercontractile phenotype that results in calcium overload in cardiomyocytes, electrophysiological remodelling, mitochondrial dysfunction, energy depletion, myocardial ischaemia, and replacement fibrosis.[93] These factors contribute to impaired release and increased myocardial stiffness, rapidly leading to increased filling pressures, diastolic dysfunction, and the complex picture of HFpEF, often aggravated by a dynamic ventricular outflow tract obstruction and systolic anterior motion mitral insufficiency. In advanced stages, left ventricular systolic dysfunction associated with extensive myocardial fibrosis and reduced EF may occur instead. Data from the EURObservational Research Program registry indicate that 67% of patients with HCM develop symptoms of HF, predominantly in the form of HFpEF.[94] To date, none of the classical treatments for HF, including renin-angiotensin-aldosterone system (RAAS) inhibitors and spironolactone, have been shown to improve the progression or outcomes of HCM. However, beta-blockers and, in cases of intolerance or contraindications, calcium channel blockers or, eventually, disopyramide[89] can be used effectively to reduce outflow obstruction. Furthermore, remarkable results in terms of reduced obstruction severity and improved quality of life have been obtained with the use of selective myosin inhibitors, such as mavacamten. In particular, in the recent EXPLORER-HCM [Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy], mavacamten significantly reduced the efflux obstruction and improved exercise capacity when compared to placebo. Twenty-seven per cent of treated patients saw a gradient reduction to <30 mmHg and an improvement to New York Heart Association (NYHA) class I. The drug was well tolerated, with only a small percentage of patients developing transient systolic dysfunction, which was resolved by temporary suspension of treatment.[95] A second study, VALOR-HCM (A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Who Are Eligible for Septal Reduction Therapy), has shown that mavacamten significantly reduces the percentage of patients with obstructive MIC who require septal reduction therapy.[96] In case of failure of the medical therapy, it is possible to intervene with invasive options such as cardiosurgical septostomy or septal alcohol ablation.[89]

Sarcoidosis

Cardiac sarcoidosis is a rare form of infiltrative cardiomyopathy caused by myocardium granulomatous inflammation, with a prevalence of 35.2 cases per 100 000 inhabitants.[97] The most common manifestations

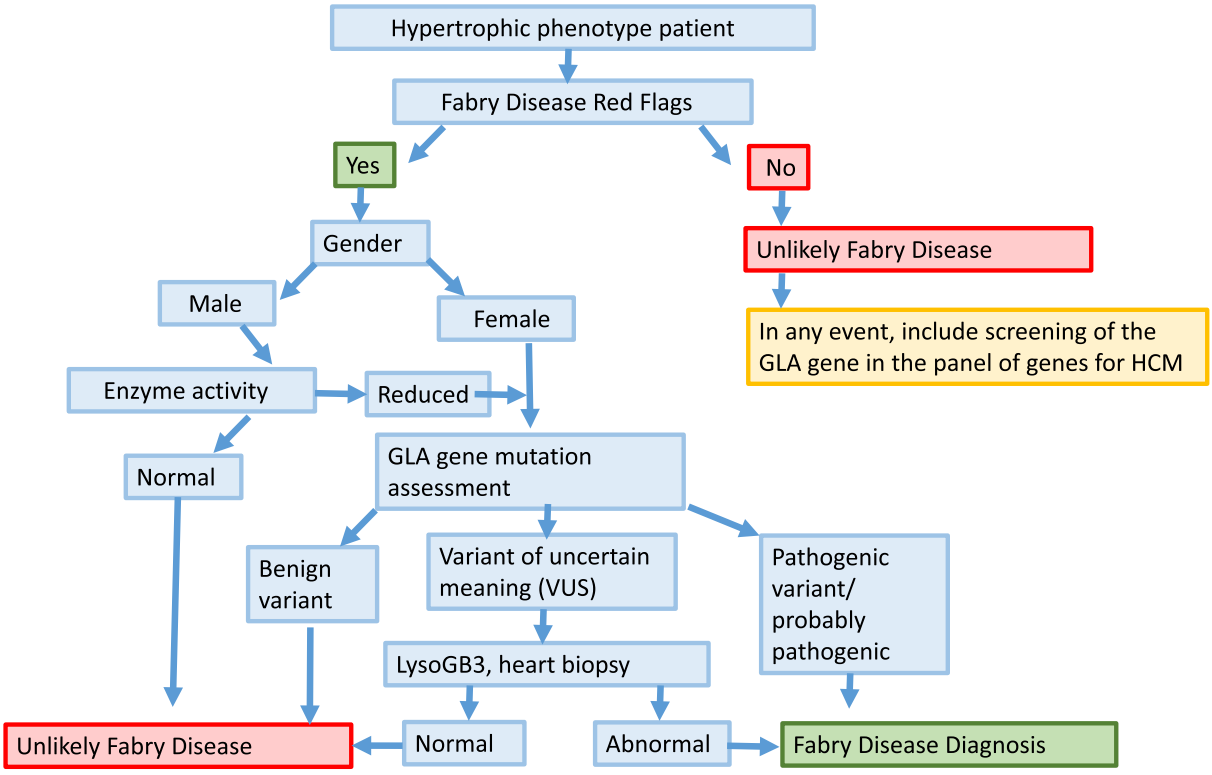

Figure 3 Diagnostic flowchart of Fabry disease. HCM, hypertrophic cardiomyopathy.

include atrioventricular blocks, arrhythmias, and HFpEF.[98] Diagnosis is complex due to the variable and non-specific clinical presentations. An integrated approach combining multimodal imaging and multidisciplinary collaboration is needed to accurately assess cardiac sarcoidosis.

Although cardiac involvement in systemic sarcoidosis may affect about 20% of the patients undergoing imaging, the disease clinically manifests in only 5% of the cases. Up to 90% of cases[99] are affected by the lungs, which are the most frequently involved organ. Diagnosis of cardiac sarcoidosis must integrate clinical, pathological, and imaging criteria, as imaging alone is not sufficient to confirm the disease. Laboratory data, such as hypercalcaemia due to the increase in 1,25-dihydroxyvitamin D, can provide useful clues. Cardiac MRI imaging and fluorodeoxyglucose positron emission tomography are essential for accurate diagnosis of cardiac sarcoidosis. Histologic confirmation requires the finding of noncaseous granulomas (without other identifiable cause) in the myocardial tissue, which is obtained by endomyocardial biopsy. However, the cardiac biopsy has limited sensitivity because of the focal nature of myocardial infiltration.[99] Currently, corticosteroids and immunosuppressive agents are considered the first-line treatment for cardiac sarcoidosis.[100]

Haemochromatosis

Haemochromatosis is the most frequent autosomal recessive disorder in the general population and represents one of the possible potentially preventable causes of HFpEF.[101] In its early stages, the disease is often characterized by diastolic dysfunction and arrhythmias, while in advanced stages, it may progress to dilated cardiomyopathy. It may be accompanied by signs of damage of other organs due to iron accumulation; especially common is hepatopathy and hypogonadism. The diagnosis of iron overload is based on high levels of transferrin saturation (>55%) and serum ferritin (>300 ng/mL). Cardiac MRI with T2* relaxation time measurement, which allows quantification of myocardial iron overload, is critical for diagnosis and monitoring response to therapy.[102] In the diagnostic pathway, it is first of all necessary to rule out secondary causes of iron overload and then to perform genetic testing to identify mutations in the HFE (high iron) gene and in other proteins such as haemojuvelin, transferrin receptor, and ferroportin. The main treatment includes therapeutic phlebotomy and iron chelation. In patients with severe untreated cardiac disease, the average survival is <1 year. However, if the condition is treated early and aggressively, survival can approach that of patients with HFpEF unrelated to haemochromatosis.[101]

Myocarditis

Myocarditis is an inflammation of the heart muscle that can be caused by several factors, including viral infections, exposure to drugs or toxic substances, and alterations in the immune response, either in isolation or within a systemic autoimmune disease.[103] The disease may be asymptomatic or have pseudo-infarctual,

arrhythmic, or HF onset. Although acute myocarditis rarely presents itself as HFpEF, it is possible that in the chronic phase or following post-acute fibrotic outcomes, myocarditis may contribute to a HFpEF scenario. Diagnosis is mainly based on clinical evaluations, ECG, laboratory tests for myocardial damage enzyme dosage, and imaging, with a focus on cardiac magnetic resonance imaging. Endomyocardial biopsy, considered the 'gold standard' for confirming the diagnosis and initiating targeted treatment, is usually reserved for the most severe cases requiring specific intervention.[104]

Constrictive pericarditis

Constrictive pericarditis is a condition characterized by impaired diastolic filling of the ventricles due to a stiffening of the pericardium. This condition can arise as a result of various pericardial disease processes. The risk of progression of constrictive pericarditis depends mostly on the aetiology: it is low (<1%) in viral and idiopathic pericarditis, intermediate (2–5%) in immune-mediated pericarditis and neoplastic pericardial disease, and high (20–30%) in bacterial pericarditis, particularly purulent pericarditis.[105] Although tuberculosis is a rare cause of constrictive pericarditis in developed countries, it is still a major cause in developing countries. Clinically, constrictive pericarditis manifests with symptoms typical of HFpEF. The diagnosis of constrictive pericarditis is based on a combination of signs and symptoms of right HF and impaired diastolic filling caused by pericardial constriction, and is confirmed through various imaging methods, including echocardiography, computed tomography, cardiac MRI, and cardiac catheterization.[105] The main differential diagnosis is with restrictive cardiomyopathy. In chronic and permanent cases, the main treatment is surgical.

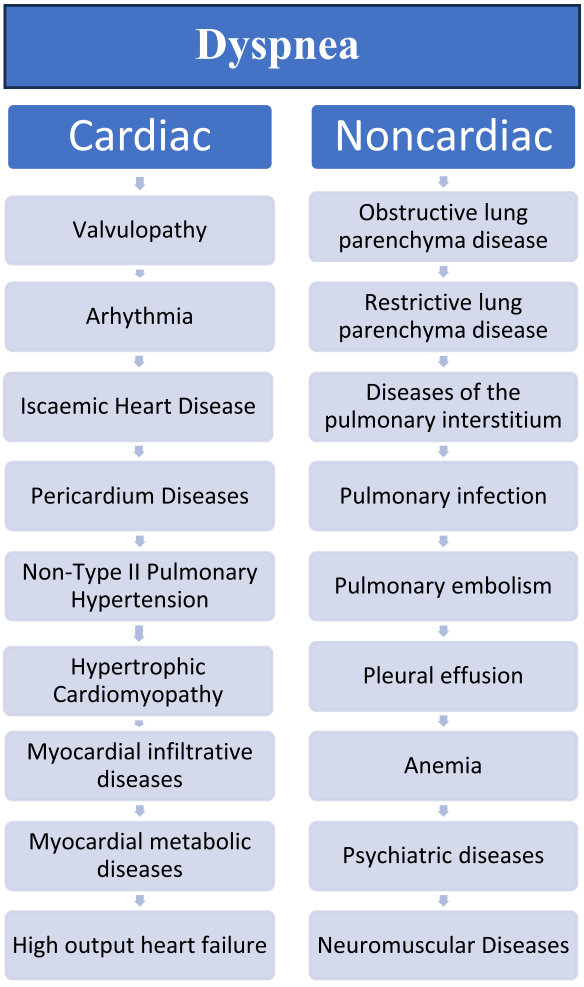

Figure 4 Differential diagnosis of dyspnoea.

Diagnosis

Heart failure with preserved ejection fraction in the new universal classification is defined as that clinical condition characterized by signs and symptoms of HF, caused by morphologic or structural changes in the presence of ≥50% LVEF, which results in increased natriuretic hormones and/or objective evidence of pulmonary and/or systemic congestion.[2] The crucial aspects of this definition are research of signs and symptoms and identification of increased pressure in the left atrium. For example, an obese hypertensive patient on calcium antagonist drugs may report to their physician with dyspnoea and declivous oedema, signs and symptoms that may not be referable to increased left ventricular preload. Differential diagnosis, especially in outpatients, may therefore be difficult and require complex diagnostic tests.[106] In order to facilitate the clinician in the diagnostic pathway, a very thorough diagnostic approach aimed at excluding secondary causes or rare diseases, which may mimic HF with preserved systolic function, should be followed. The presence of comorbidities or associated diseases, such as pneumopathy, anaemia, and obesity, may, in fact, mimic the clinical symptoms and the features of HF, thus making it difficult to define the diagnosis. Of course, the simultaneous presence of these conditions and HFpEF cannot be ruled out, making the diagnosis even more difficult. In the diagnostic pathway, the identification of specific symptoms and signs is of the utmost importance. The first approach to the patient should be very meticulous aimed initially at investigating the symptom of dyspnoea and then identifying any central and peripheral signs of congestion. Differential diagnosis of dyspnoea classified as cardiac or non-cardiac is crucial (*Figure 4*). For example, the presence of a new-onset murmur in a patient with limited functional capacity should direct the clinician towards a valvulopathy; in a dyslipidaemic diabetic patient with exertional dyspnoea, ischaemic heart disease should always be ruled out. Worsening dyspnoea in a known chronic obstructive pulmonary disease patient should be reassessed by spirometry; similarly, anaemia could be the cause of dyspnoea in a patient on anticoagulant therapy. While the differential diagnosis of dyspnoea can be complex and require second- or third-level examinations, the presence of declivous oedema also requires careful clinical evaluation. The oedema may be of cardiac or non-cardiac origin, due, for instance, to decreased oncotic pressure or iatrogenic (*Figure 5*). Calcium antagonists are a frequent cause of declivous oedema in hypertensive patients; similarly, the presence of diffuse oedema is common in cirrhotic patients or in malnutrition with

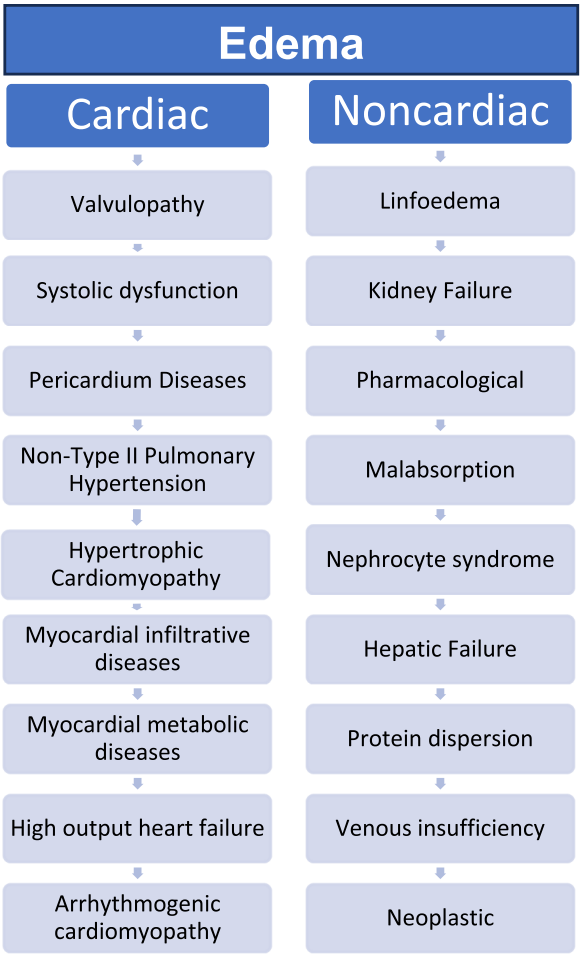

Figure 5 Differential diagnosis of oedema.

protein dispersion. If, after careful clinical analysis and any instrumental tests indicated to exclude secondary causes of symptoms, clinical suspicion of HF with preserved systolic function persists, it is always recommended to perform both natriuretic hormone (BNP or NT-proBNP) assay and an echocardiogram. However, it should be remembered that an NT-proBNP value <125 pg/mL is present in 37% of patients with HFpEF, and the echocardiogram may be normal at rest in 30% of patients.[1]

Hospitalized patients

In an acute setting of a patient showing up at the ER for dyspnoea or signs of congestion, natriuretic hormone assay is always recommended, and as suggested by the ESC, NT-proBNP is preferred over BNP. The threshold value of NT-proBNP to rule out the presence of HF is <300 pg/mL, while to confirm the diagnosis, the reference values change according to the age of the patient. The so-called grey areas are thus between 300 pg/mL and the respective values considered in the different age groups.[107] The diagnostic approach in this uncertain clinical setting should be aimed at identifying clinical signs of congestion and using echocardiography to detect structural changes typical of decompensation with preserved function, such as left atrial dilatation and left ventricular hypertrophy, as well as echocardiographic signs of high left and right ventricular filling pressures. In this clinical setting, the diagnosis is also facilitated by an eventual clinical response to the diuretic therapy, which not only reduces the signs of congestion but also tends to decrease natriuretic hormone values.

Outpatients

Role of natriuretic hormones

While the natriuretic hormone assay is very useful in the diagnosis of acute HF in outpatients, their diagnostic power is lower. The main limiting variables are comorbidities such as age, AF, and kidney failure, which increase the values, while obesity decreases them, making it more difficult to identify a true diagnostic threshold. The ESC proposes a BNP level <35 pg/mL and NT-proBNP <125 pg/mL as diagnostic cut-offs to rule out the presence of HF. Again, however, the values should be stratified according to the patient's age. A recent consensus statement from the ESC Heart Failure Association (HFA) recommends stratified NT-proBNP values according to age groups; furthermore, based on expert opinion, it suggests different values depending on the presence of comorbidities such as kidney failure, obesity, and AF.[108]

In the presence of an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, the NT-proBNP value should increase by 35%, in the presence of eGFR 30-45 mL/min/1.73 m^2 by 25%, and in the presence of eGFR 45-60 mL/min/1.73 m^2 by 15%. If BMI is between 30 and 35 kg/m^2, NT-proBNP should be reduced by 25%, for BMI between 35 and 40 kg/m^2 by 30%, and for BMI > 40 kg/m^2 by 40%. In the presence of AF and a heart rate <90 b.p.m., the NT-proBNP value should increase by 50% and by 100% in the case of a heart rate >90 b.p.m.

The role of scores

It seems evident that the diagnosis in the outpatient is complex due to the high comorbidities of patients that may simulate different diagnoses and affect the validity of natriuretic hormones. Such an inconsistent clinical context has led to the search for a diagnostic approach based on the use of multiple variables to be used in combination with each other. Two diagnostic scores have consequently been proposed: the first from Europe and the second from the USA (*Table 3*).[22,109] The HFA-PEFF, devised by the ESC HFA in 2019, is based on major and minor criteria by considering functional, morphological, and laboratory parameters in the presence or absence of AF. The difference between major and minor criteria is given by their reference values considering 2 points for each major criterion and 1 point for each minor criterion. Confirmatory diagnosis is reached for values ≥5 points, uncertain for values between 2 and 5, and is excluded for values <1 point. In the presence of uncertain values, a stress echocardiography or stress catheterization is recommended. The score involves four different steps: in the first, the clinician must estimate the likelihood of the disease; in the second, the calculation of major or minor criteria takes place, evaluating echocardiographic and laboratory parameters; and in the third and fourth, third-level tests are performed to confirm an uncertain diagnosis or exclude pathologies that might mimic HFpEF,

Table 3 Score for the diagnosis of heart failure with preserved ejection fraction

HFA-PEFF score				H_2FPEF score	
Functional criteria	**Morphological criteria**	**Biomarker**	**Score**	**Variable**	**Score**
Major criteria			2	BMI >30 kg/m^2[21]	2
e' septal <7 cm/s	LAVI >34 mL/m^2	NT-proBNP >220 pg/mL or		≥2 antihypertensive drugs	1
e' lateral <10 cm/s	LVMI ≥149/122 g/m^2	BNP >80 pg/mL se in sinus rhythm			
E/e' medium ≥15	RWT >0.42	NT-proBNP >660 pg/mL or		FA (of any type)	3
TR speed >2.8 cm/s		BNP >240 pg/mL se FA		Pulmonary blood pressure ≥35 mmHg	1
Minor criteria			1		
E/e' medium 9-14	LAVI 29-34 mL/m^2	NT-proBNP 125-220 pg/mL or BNP		Age >60 anni	1
GLS <16%	LVMI >115/95 g/m^2	35-80 pg/mL if in sinus rhythm		E/e' >9	1
	RWT >0.42	NT-proBNP 365-660 pg/mL or BNP			
	Parietal thickness ≥12 mm	105-240 pg/mL se FA			
Confirmed diagnosis v			≥5	Confirmed diagnosis	≥6
Inconclusive diagnosis			2-4	Inconclusive diagnosis	2-5
Excluded diagnosis			0-1	Excluded diagnosis	0-1

BMI, body mass index; BNP, B-type natriuretic peptide; AF, atrial fibrillation; GLS, global longitudinal strain; LAVI, indexed left atrial volume; LVMI, indexed left ventricular mass index; NT-proBNP, N-terminal fragment of B-type natriuretic propeptide; RWT, relative parietal thickness; TR, tricuspid regurgitation.

such as cardiac amyloidosis. For comparison, the score proposed by the Mayo Clinic H2FPEF group, recommended by the American College of Cardiology, validated and obtained through exercise catheterization, uses simple clinical and echocardiographic parameters. The diagnosis of certainty is reached for values ≥6 points, of uncertainty for values between 2 and 4, and is ruled out for values ≤1; in case of uncertainty, exercise catheterization is recommended. Both scores have advantages and drawbacks such as the difficulty to perform a stress test limits the HFA-PEFF score, while the H_2FPEF appears to perform less well in non-obese patients who are also less frequent in the European population. However, a recent international multicentre study comparing the two scores, in which capillary pressure during stress (>25 mmHg) was used as the 'gold standard', found important differences. The H_2FPEF score showed an area under the curve (0.845; 95% CI 0.810-0.875; $P < 0.001$) when compared to the HFA-PEFF score (0.710; 95% CI 0.659-0.756; $P < 0.001$), and also the frequency of false negatives was higher with the HFA-PEFF score (55% vs. 25% of the H_2FPEF score). Furthermore, if patients with a high-intermediate HFA-PEFF score were considered and compared to the group of patients with low H_2FPEF, the true prevalence of HFpEF was 30%, while in the opposite case it was 78%.[106]

Role of stress catheterization

For a certain diagnosis, in the presence of uncertain score values and in the presence of a capillary wedge pressure (CFP) < 15 mmHg, a stress catheterization should be performed, this being the 'gold standard' test for diagnosis, but despite the fact that the test is then recommended, it is still available in few centres.[106] Most studies performed the examination in the supine position, which has the advantage of a greater ease in executing the test and provides a better analysis of the curves. However, the examination represents an effort that is not entirely physiological, because it does not reflect the patient's daily activity. After a baseline haemodynamic assessment, it is recommended to place the legs on the pedals at an angle of about 50° and repeat the measurements after 3 min (leg raise) considering the test positive for CFP values ≥19 mmHg. The effort starts at 20 W for about 3-5 min, increasing from 10 to 20 W every 2 min until the patient is exhausted. At each step, it is recommended to measure the cardiac output (CO) through the direct Fick method when possible or by thermodilution and haemodynamic readings, and evaluate the CFP at the end of exhalation. Pathological values are considered to be a CFP ≥25 mmHg or a ΔPCP/ΔCO slope >2 mmHg/L/min (*Figure 6*).

Trial inclusion criteria

The trials that used glyflozines, finerenone, and semaglutide for the treatment of HFpEF, EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction),[110] respectively, DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure),[111] FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure),[112] and STEP-HFpEF (Effect of Semaglutide 2. 4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction),[113] used different diagnostic criteria from the guidelines (*Table 4*).

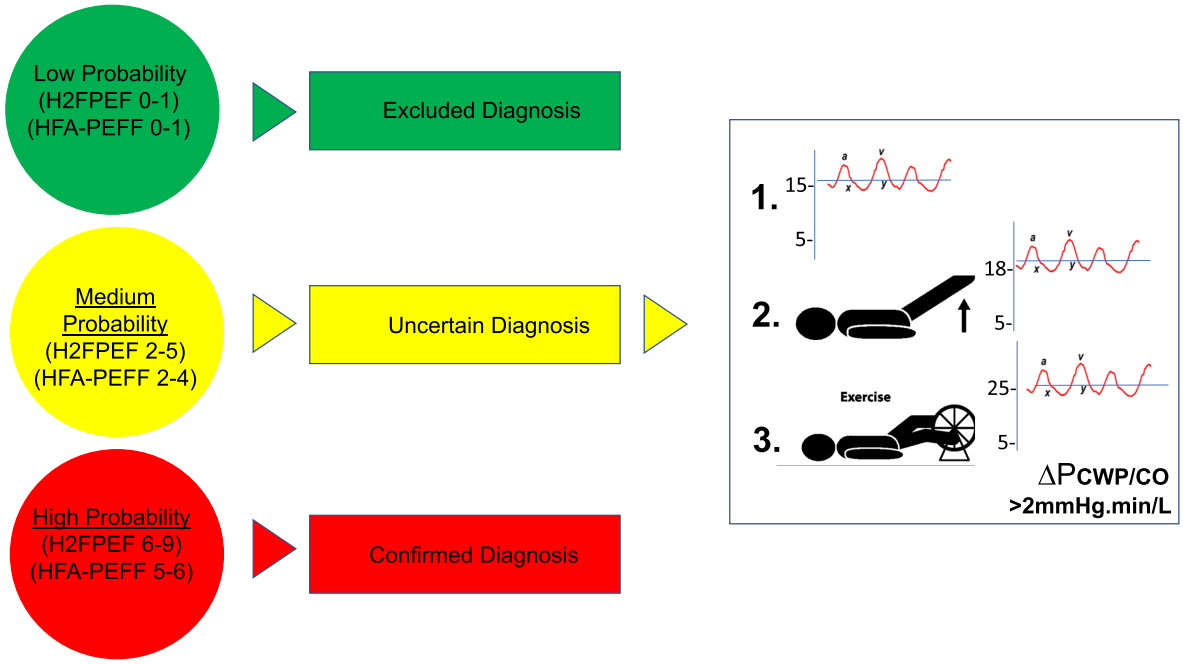

Figure 6 Diagnostic flowchart. CO, cardiac output; PCWP, capillary wedge pressure.

Table 4 Diagnostic criteria used in trials

Trial	Characteristics of the population	Echocardiographic parameters

EMPEROR-Preserved[110] e FINEARTS-HF[112]	• Patient with signs and symptoms of HF diagnosed for at least 3 months in NYHA classes II-IV with EF >40%.
	• NT-proBNP value >300 pg/mL if with sinus rhythm or >900 pg/mL if AF
	• Presence of one or more of the following changes:
	  • Structural changes in the echocardiogram (left atrial dilatation or left ventricular hypertrophy)
	  • Hospitalization for HF in the previous 12 months
		• Wave is septal and lateral mean <9 cm/s, E/e' mean ≥13)[a]
		• Dilated left atrium (size ≥4.0 cm or in length ≥5.0 cm or area ≥20.0 cm^2 or volume ≥55 mL/m^2 or indexed ≥34 mL/m^2)
		• Left ventricular hypertrophy (septal thickness ≥1.1 cm or mass ≥115 g/m^2 in males or ≥95 g/m^2 in females)

DELIVER[111]	• Patient with signs and symptoms of HF diagnosed for at least 6 weeks in NYHA classes II-IV with EF >40% with the presence of structural changes: left atrial dilatation or left ventricular hypertrophy • NT-proBNP value >300 pg/mL if in sinus rhythm or >600 pg/mL if in AF	• Dilated left atrium (size ≥3.8 cm or in length ≥5.0 cm or area ≥20 cm^2 or volume ≥55 mL or index ≥29 mL/m^2) • Left ventricular hypertrophy (septal or posterior wall thickness ≥1.1 cm or mass ≥115 g/m^2 in males or ≥95 g/m^2 in females)
STEP-HFpEF[113]	• Patient with signs and symptoms of HF in NYHA classes II-IV with BMI <35 kg/m^2: NT-proBNP value ≥220 pg/mL if with sinus rhythm or ≥660 pg/mL if AF; if BMI ≥35 k/m^2: NT-proBNP ≥125 pg/mL if with sinus rhythm or ≥375 pg/mL if AF in the presence of at least one of the echocardiographic criteria of high left filling pressure on echocardiogram	• Wave e' septal <7 cm/s or e' lateral <10 cm/s or E/e' mean ≥15) • Systolic pulmonary artery pressure >35 mmHg • Dilated left atrium (size ≥3.8 cm or in length ≥5.0 cm or area ≥20.0 cm^2 or volume ≥55 mL or index ≥29 mL/m^2) • Left ventricular hypertrophy (septal or posterior wall thickness ≥1.2 cm)

BMI, body mass index; AF, atrial fibrillation; EF, ejection fraction; NT-proBNP, N-terminal fragment of B-type natriuretic propeptide; NYHA, New York Heart Association; HF, heart failure.
[a]Only for EMPEROR-Preserved.

Recommendations for the diagnostic criteria

The positive results of the trials suggest adopting the inclusion criteria used in these studies for the diagnosis of HFpEF, in order to select patients who might benefit from the currently available and proven effective therapies. In conclusion, it seems reasonable to base the diagnostic approach on clinical, NT-proBNP levels and echocardiographic evidence of structural alterations. In doubtful cases, it may be useful to use stress catheterization for further evaluation.[110,111]

Treatment of comorbidities

The high prevalence of comorbidities in patients with HFpEF is also well known and evident in selected populations of randomized clinical trials. Numerous studies have shown an association between comorbidities and cardiovascular events, emphasizing the negative impact of this condition on the prognosis in patients with HFpEF. Specifically, in the elderly population, multicomorbidity represents the clinical condition most frequently associated with the worst prognosis and progression of HF.[65,114] While aware of the negative impact on the prognosis, to this date, there is a lack of dedicated studies in the context of patients with HFpEF with multicomorbidities, and the choice of treatment is based on the specific profile in the context of a high clinical complexity. In these patients, it is indeed of paramount importance to treat the single comorbidity while keeping in mind the multiple diseases with which they often coexist. This goal is further complicated by a potential reduction in treatment adherence due to the complexity of the treatment regimens required to treat the different associated pathologies. As part of precision medicine, and in the hope of being able to identify more effective therapeutic targets, the search for distinct phenotypes within HFpEF should also include the existence of comorbidities. In this regard, data from the Trieste Observational Registry are of interest, showing that adherence to unvalidated HF drugs in randomized trials in HF patients are found to be associated with a better real-world outcome even in HFpEF patients with an impact that overlaps that obtained in HFrEF patients. This result not only emphasizes the importance of adherence to prescribed treatment but also the possible benefit of individually applied therapy.[114]

Arterial hypertension

Of all the comorbidities, hypertension is certainly among the most prevalent with at least three-quarters of patients living with a history of hypertension[115] and that is frequently associated with other comorbidities such as DM, obesity, AF, and CRI. Dedicated studies show that the treatment of hypertension leads to a dramatic decrease in the HFpEF incidence with a reduction of about 40%.[116,117] Similarly, in patients with an overt HF picture, uncontrolled hypertension contributes to a more rapid progression of the disease. Although there are no dedicated studies on specific blood pressure targets in patients with HFpEF, a PAS value <130 mmHg is associated with a favourable prognosis,[118] while the OPTIMIZE-HF Registry has shown that a PAS value <120 mmHg in elderly patients is associated with an adverse prognosis.[118] Despite the prevalence and prognostic role of hypertension, international guidelines do not provide recommendations to support specific therapeutic approaches, and therefore, the preferred choice is goal-oriented. Regarding pharmacological treatment, from the onset, the use of combination therapy with two pharmacological classes appears reasonable.[119,120] Such an approach, in addition to achieving better efficacy *per se*, could implement the tolerability profile with the use of lower dosages by reducing dose-dependent adverse effects and improving therapeutic adherence in patients with frequent need for a multidrug therapy. Given the benefits of MRAs obtained in HFpEF patients, this class of drugs should be considered in the pharmacological armamentarium of the hypertensive HFpEF patient. In addition, often associated comorbidities, such as diabetes and proteinuria, or cardiovascular comorbidities, such as AF or ischaemic heart disease, should be considered in the choice of treatment. For example, angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARBs) and sodium-glucose cotransporter type 2 (SGLT2i) inhibitors might be considered the first choice in patients with diabetes with proteinuria, while a beta-blocker drug might be reasonable, particularly nebivolol, if the patient has ischaemic heart disease or AF (*Figure 7*).

Atrial fibrillation

Atrial fibrillation coexists with HFpEF in ~50–70% of patients and may precede established HF or emerge after a diagnosis of HF complicating its course.[121] This combination has been associated with a worse prognosis with increased mortality risk and hospitalizations for HF.[122] Given the impact on HFpEF incidence, factors favouring AF should be appropriately treated (sleep apnoea, thyroid disorders, obesity, valvular disease, and hypertension). Among the comorbidities associated with AF, stroke prevention remains of paramount importance. Considering that the occurrence of HFpEF is prevalent after 65 years of age (CHA_2DS_2-VASc score ≥2), attention should also be paid to silent AF. With this in mind, US guidelines encourage screening for AF in patients >65 years of age. This screening strategy may be even more desirable in patients with HFpEF, given the higher incidence of AF and the high-risk profile in this clinical setting.

When established, the association between HF and AF intercepts high-risk clinical profiles, such as the combination with pulmonary hypertension, right ventricular dysfunction, and tricuspid insufficiency. Differently from a clear clinical benefit from a rhythm control strategy demonstrated in some subgroups of HFrEF patients, in patients with HFpEF, there is still no strong evidence for such a therapeutic strategy even though recent publications on small case studies show positive relapses of AF ablation even in HFpEF in terms of reduced PCP, increased peak oxygen consumption, reduced BNP, and improved quality of life (Minnesota Living with Heart Failure questionnaire).[123] It is also reasonable to think that HFpEF patients might benefit from the treatment of underlying triggers (e.g. valvulopathy, uncontrolled hypertension, and obesity), with a subsequent rhythm control approach where

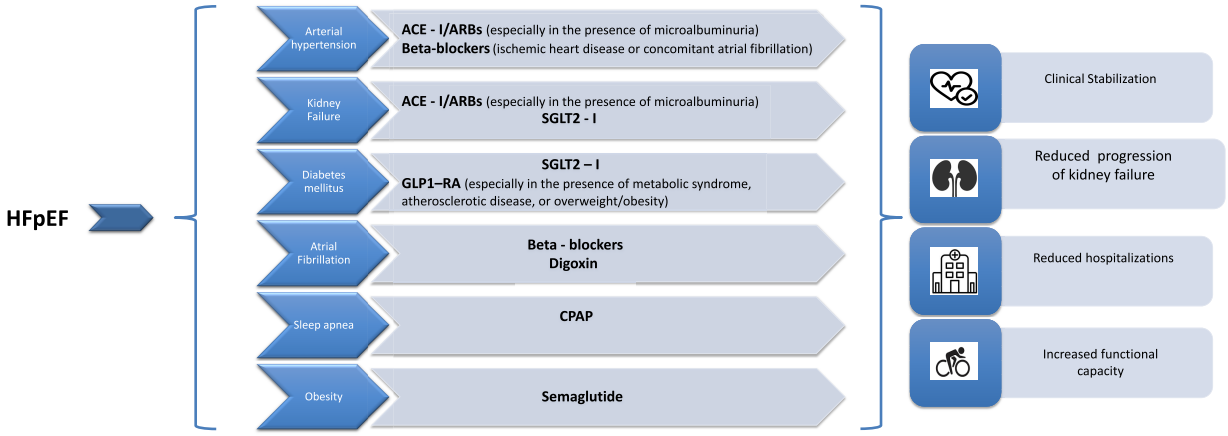

Figure 7 Treatment effects of comorbidities. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; CPAP, continuous positive airway pressure; GLP1-RA, glucagon-like peptide-1 receptor agonist; HFpEF, heart failure with preserved ejection fraction; SGLT2i, sodium-glucose cotransporter type 2 inhibitor.

possible. A rhythm control strategy appears viable, and favourable, especially in the early stages of AF onset. In this regard, a subanalysis of the Early Treatment for Atrial Fibrillation for Stroke Prevention (EAST) trial shows that early treatment of AF in patients with HF reduces cardiovascular events regardless of EF (56% patients with HF with EF >50%).[124]

When the choice is for a rate control strategy, beta-blockers, digitalis, and calcium antagonists should be considered frontline drugs. If satisfactory heart rate control is not achieved with this approach, their combination is a recommended strategy.

Kidney failure

In selected populations, about half of the patients have kidney failure,[125,126] reaching and exceeding 60% in real-world populations. Unlike patients with HFrEF, where the neurohormonal stimulus drives the development and worsening of kidney dysfunction, in the HFpEF patient scenario, this close relationship does not emerge and the mechanisms are, to date, unclear.[127] In particular, kidney failure emerges as an adverse prognosis factor, and specifically, a direct linear relationship emerges between cardiovascular risk and worsening eGFR.[128]

With this in mind, we should maximize our efforts to reduce its incidence in patients with clinical profiles at high risk of developing kidney failure. In this context, it might be preferable to use ACE-I/ARB, SGLT2i, and, prospectively, finerenone, which have demonstrated nephroprotective effects. In particular, the use of SGLT2i is associated with a slower decline in renal function than placebo.[129] It should be remembered, however, that some HF drugs should be used with caution when there is an acute worsening of kidney function. In particular, RAAS-related worsening of kidney function has been associated with a worse prognosis,[128] whereas randomized clinical trials show that the use of SGLT2i in such a scenario is favourable from a metabolic and nephroprotective perspective, and therefore without the need for discontinuation even in the presence of worsening kidney failure.

Sleep apnoeas

The presence of sleep-related breathing disorders, often associated with obesity, is an independent predictor of mortality, hospitalization, and cardiovascular events in HF patients.[130] In particular, obstructive sleep apnoea (OSA) is a respiratory sleep disorder most frequently associated with HFpEF.[131] Obstructive sleep apnoea *per se* is associated with an increased incidence of type 2 DM, systemic hypertension, pulmonary hypertension, coronary artery disease, AF, and stroke. Despite the high prevalence of OSA in patients with HFpEF and its negative impact on prognosis, its treatment has not been shown to be effective in improving outcome in patients with HF, and so far no randomized clinical trial has selectively explored the long-term effect of continuous positive airway pressure (CPAP) therapy on the prognosis of patients with HFpEF and OSA. Therefore, a treatment of OSA to improve outcome does not appear to be justified at present. However, its treatment could be important in patients with resistant hypertension profiles where treatment of OSA results in improved pressor control.[132] Also important is the impact on the incidence of AF, where recognition and treatment of OSA result in a reduction in the incidence of recurrent AF.

Diabetes mellitus type 2

Diabetes mellitus, found in about one-third of patients with HFpEF, defines a phenotypic cluster in which systemic arterial hypertension, kidney failure, and vascular disease are frequently associated.[133] In this respect, DM, in addition to being an independent therapeutic target, elevates the patient's overall risk profile, worsens the risk of adverse outcome, and imposes an intensive effort to prevent macrovascular/atherosclerotic damage as well as microvascular damage. Regarding atherosclerotic prevention, for example, it should be acknowledged that a large proportion of patients with DM (regardless of concomitant established ischaemic disease) qualify as being at 'high' or 'very high' risk and therefore require reduction of LDL cholesterol values <70 or <55 mg/dL, respectively.[134]

Observational clinical studies have now shown how DM is a risk factor for the development of HF.[135,136] However, the risk of developing HF is also present in settings of glucose changes without a clear diagnosis of DM; Held *et al.*[137] have shown how a 1 mmol/L increase in fasting blood glucose is associated with a 1.23-fold increase in the risk of HF hospitalization. In addition, small subgroup analyses have correlated the presence of insulin resistance with the incidence of HF and the development of systolic–diastolic dysfunction.[138,139]

Glycaemic targets for patients with HFpEF do not differ from those recommended for the general population of diabetic patients, balancing the burden of comorbidities and the risk of hypoglycaemic episodes. The latter, although found to be associated in some studies with an increased risk of HF hospitalization, would not be interpreted as causal factors, however, but as markers of frailty and comorbidity. The clinical benefit of SGLT2i treatment is well established in patients with type 2 DM and established atherosclerotic disease or high cardiovascular risk profile. In the EMPA-REG OUTCOME study, empagliflozin determined a significant reduction in the primary composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke[140]; in the same study, empagliflozin was shown to be effective in reducing mortality from cardiovascular causes, all-cause mortality, and HF hospitalizations. In the DECLARE-TIMI 58 study (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58), dapagliflozin showed a reduction in the composite mortality endpoint from cardiovascular causes and hospitalizations due to HF.[141] A reduction in the composite mortality endpoint due to cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke associated with a reduction in HF hospitalizations was also demonstrated for canagliflozin in the CANVAS (Canagliflozin Cardiovascular Assessment Study)[142] study and, only limited to HF hospitalizations, in the VERTIS-CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial) study with ertugliflozin.[143] SGLT1/2i sotagliflozin was shown to be effective in reducing the endpoint of cardiovascular mortality, HF hospitalizations, and urgent visits for HF flare-ups in the SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) study.[144] In addition, all these drugs exert a favourable effect on reducing the progression of kidney damage and preventing terminal kidney failure.

Glucagon-like peptide-1 receptor (GLP1-RA) agonists have been found to be effective in reducing the risk of myocardial infarction, stroke, and cardiac mortality.[145] Recently, the STEP-HFpEF DM (Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction and Diabetes Mellitus) study showed that treatment with semaglutide administered weekly subcutaneously, in a population of HF patients with EF $\geq$45%, obesity (BMI > 30 kg/m^2) resulted in a reduction in the primary endpoints of the study (improvement in quality of life as measured by the Kansas City Cardiomyopathy Questionnaire clinical summary score; reduction in body weight) as well as offering important insights regarding the outcome on exploratory endpoints.[146] In the study, semaglutide treatment determined a statistically significant reduction in the composite endpoint of hospitalization or urgent visits for HF in addition to a greater reduction in NT-proBNP values than placebo. In addition, it was shown that treatment with this drug resulted in a reduction in C-reactive protein values (95% CI 0.55–0.8) and an improvement in gait test compared with the placebo group. These results seem to suggest mechanisms of action of semaglutide beyond weight loss, including a direct effect on decongestion, mitochondrial, vascular, and skeletal muscle function, a reduction in epicardial adipose tissue, and an improvement in insulin resistance and inflammation.

Metformin, widely used in this subgroup of patients, has been shown to be safe in the incidence of HF; however, its use in patients with eGFR <30 mL/min/1.73 m^2 or liver failure is not recommended due to the risk of lactic acidosis.[147] Treatment with the dipeptidyl peptidase-4 (DPP-4) inhibitors alogliptin, sitagliptin, and linagliptin showed a neutral effect on HF hospitalizations[148,149] while treatment with saxagliptin resulted in a 27% increase in HF hospitalizations.[150] Results from the meta-analysis consider the effect on mortality or cardiovascular events to be neutral with regard to treatment with DPP-4.[151] Caution, especially in the early stages of treatment, should be given to those patients with type 1 or type 2 DM who require treatment with insulin; the latter, having sodium retention action, which could determine an increased fluid overload. Sulfanilureas and thiazolidinediones are contraindicated in patients with HF as they cause an increase in hospitalizations.[152,153]

Obesity

Obesity represents a global and ever-expanding health problem. It should be considered in all respects as a chronic, progressive disease with a high reoccurrence rate. Epidemiological studies have identified an independent correlation between obesity and HF.[21,154] To define the degree of obesity, calculation with BMI is traditionally used; however, from the same BMI value, a different cardiovascular risk may be derived, as the presence of visceral, rather than subcutaneous, obesity appears to be more implicated in causing insulin resistance, inflammation, and mitochondrial dysfunction.[155] The presence of obesity, even without an established history of HF, is associated with significant preclinical changes such as hypertrophy of the left ventricle,[156] sometimes also of the right ventricle,[73] dilatation of the ventricular cavity, parietal stiffness, and atrial remodelling and dysfunction.[157] The presence of epicardial fat causes increased production of pro-inflammatory cytokines (interleukin-1β, interleukin-6, and tumour necrosis factor-α) resulting in the remodelling and dysfunction of cardiac and skeletal muscle and mitochondrial dysfunction.[158] Obesity also causes inefficiency in cardiac energy production by increasing energy production through the use of free fatty acids at the expense of glucose usage.[159] Obesity also causes dysregulation of neurohormonal systems such as the RAAS and sympathetic nervous system either through direct production of adiponectin (leptin) or

through mechanical compression on the kidneys. Leptin, in turn, is able to result in direct activation of the RAAS and sympathetic nervous system.[160] Obesity complicates the diagnosis of HF; ventricular filling pressures expressed by the E/e′ ratio often underestimate the degree of congestion in obese patients,[161] and natriuretic peptide levels are often within limits or slightly altered and this, in part, is explained by various mechanisms: increased kidney clearance of BNP in the obese due to a tendency for kidney hyperfiltration in these patients, increased expression of BNP clearance receptors on adipocytes (NPR-C), increased interdependence between the heart and pericardium (through increased epicardial fat), and increased circulating values of testosterone that are associated with decreased natriuretic peptide levels.[162] Until recently, treatment was based on lifestyle changes, adoption of an appropriate diet plan associated with physical activity with the use of bariatric surgery only reserved to major cases. Drug therapies used to facilitate weight loss (e.g. sibutramine) have not led to a reduction in cardiovascular endpoints.[163] More recently, the use of GLP1-RA drugs has provided the first important indications in the treatment of obese patients. The SELECT study (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) showed that treatment with semaglutide, administered subcutaneously weekly, in a population of non-diabetic obese patients at high cardiovascular risk reduced the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, and stroke and the composite endpoint of hospitalization for HF, visits for HF, or death from cardiovascular causes, thereby opening interesting prospects for treatment with this drug.[164] More recently, the use of tirzepatide, which combines the properties of GLP1-RA associated with glucose-dependent insulinotropic polypeptide function, has been tested in this specific setting. In the SURMOUNT-1 Study [A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight], the use of tirzepatide, administered subcutaneously weekly, was shown to be effective in reducing body weight with an incremental response as the dose administered increased[165] with persistence of the result at a prolonged follow-up of an additional year.[166]

In conclusion, although the search for specific phenotypic profiles appears to be the path of action, there is currently no consensus on how to phenotype according to the profile of associated comorbidities. However, after strict exclusion of specific aetiologies (e.g. amyloidosis, hypertrophic/restrictive cardiomyopathies, and severe valvulopathies) that would require a targeted therapeutic approach, the phenotyping of the patient with HFpEF should consider multiple comorbidities, supporting individualized treatment aimed at treating the comorbidity, while taking into account the beneficial effects on other associated co-pathologies. Prospectively, treatment should be tailored from the perspective of comorbidities and the weight of individual comorbidities as determinants of the confirmed pattern of HF and as factors favouring its progression. One way forward could be a therapeutic approach of 'pharmacological compromise' that takes into account these different aspects. In this respect, it will be all the more applicable as a treatment is simple, practicable with the available therapies, and verifiable in clinical practice (*Figure 8*).

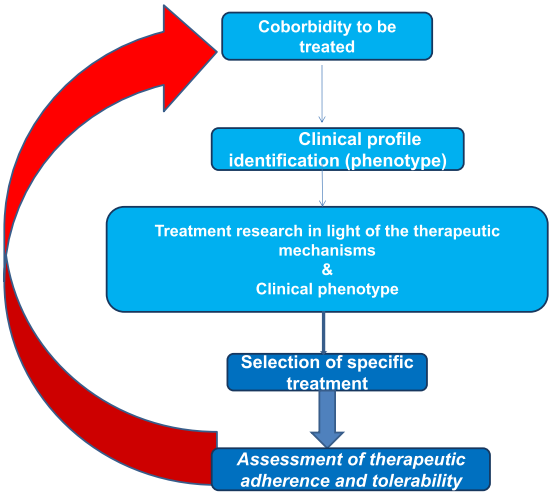

Figure 8 Overall approach to comorbidities.

Drug therapy

When the latest 2021 guidelines on the management of HF[167] were written and published, the authors pointed out that none of the trials published in those years on HFpEF had reached the primary endpoint. In particular, no benefit was reported regarding hospitalization and mortality with perindopril [PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure)],[168] candesartan [CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity)-Preserved],[169] irbesartan (I-PRESERVE),[170] spironolactone (TOPCAT),[38] digital [Digitalis Investigation Group (DIG)-Preserved],[171] and sacubitril/valsartan [PARAGON-HF (Prospective comparison of ARNI with ARB Global Outcomes in Conserved Ejection Fraction Heart Failure)].[126] The same statement was then confirmed the following year in 2022 by the US guidelines.[172] Apart from the diuretics that are reported in class 1, all other drugs are placed in class 2b. However, there is a difference between the European and American guidelines. In fact, in 2021, the EMPEROR-Preserved[110] study was published and the benefit of empagliflozin is considered in the American guidelines on a level of evidence not 1, but 2a.

This is because the reduction in the primary endpoint is primarily driven by the reduction in HF hospitalizations while there is no effect on total mortality, and also because for EF patients >60% there appears to be no benefit.

In 2023, the ESC guidelines also introduce an update[173] to take into account the published data with SGLT2i that had been extended in the meantime with the publication of the DELIVER study with dapagliflozin.[111] In *Table 5*, which addresses the therapy of patients with HFpEF, the diuretics, empagliflozin and dapagliflozin, and the treatment of cardiovascular and non-cardiovascular comorbidities are presented in class I. Based on these premises, the drugs that represent the most modern

Table 5 Major trials performed in patients with mildly reduced or preserved ejection fraction heart failure

Trial	Drug	No. of patients	Enrolment criteria	Follow-up	Primary endpoint	Summary of results
ACE-I						
PEP-CHF[168]	Perindopril 4 mg/day vs. placebo	850	• Age >70 years of age • EF >40% • Atrial dilatation (25 mm/m^2 or >40 mm • Thickness of the septum or back wall >12 mm • E/A < 0.5 or deceleration time >280 ms at mitral inflow or isovolumetric release time >105 ms • AF • SBP <100 mmHg • K^+ < 5.4 mEq/L • Creatinine <200 mmol/L	2.1 years	Composite endpoint: hospitalizations for HF or cardiovascular mortality	Primary endpoint not met (HR 0.919; 95% CI 0.7001.208; $P = 0.545$) Significant reduction in HF hospitalizations at 1 year (HR 0.628; 95% CI 0.408-0.966; $P = 0.033$)
ARNi						
CHARM-Preserved[169]	Candesartan 32 mg/day vs. placebo	3023	• EF ≥40% • NYHA II-IV	36.6 months	Composite endpoint: hospitalizations for HF or cardiovascular mortality	Primary endpoint not met (HR 0.89; 95% CI 0.77-1.03; $P = 0.118$; after correction for covariates HR 0.86; 95% CI 0.74-1.0, $P = 0.051$)
I-PRESERVE[170]	Irbesartan 300 mg/day vs. placebo	4128	• Age ≥ 60 years of age • NYHA II-IV • FE ≥45% • SBP >160 mmHg • SBP <100 mmHg • Creatinine >2.5 mg/dL	49.5 months	Death from all causes or hospitalization for cardiovascular cause, HF, myocardial infarction, angina, arrhythmia, stroke	
PARAGON-HF[126]	Sacubitril/valsartan (97/103 mg bid) vs. valsartan (160 mg bid)	4822	• EF >45% • NYHA II-IV • Atrial dilatation or ventricular hypertrophy[a] • Elevated natriuretic peptides[a] • SBP >100 mmHg • GFR >30 mL/min/1.73 m^2	35 months	Composite endpoint: hospitalizations for HF or cardiovascular mortality	• Non-significant reduction in the primary endpoint (RR 0.87; 95% CI 0.75-1.01; $P = 0.06$) • Significant benefit in the female gender and in the lower EF subgroup
PARAGLIDE-HF[174]	Sacubitril/valsartan (97/103 mg bid) vs. valsartan (160 mg bid)	466	• Hospitalization or urgent visit due to worsening HF • NYHA II-IV • EF >40% • NT-proBNP >500 pg/mL • K^+ < 5.2 mEq/L • SBP >100 mmHg • eGFR >20 mL/min/1.73 m^2	4-8 weeks	Reduction NT-proBNP	Significant reduction in the primary endpoint sacubitril/valsartan (0.85; 95% CI 0.73-0.999; $P = 0.049$)

Continued

Table 5 Continued

Trial	Drug	No. of patients	Enrolment criteria	Follow-up	Primary endpoint	Summary of results
MRA						
TOPCAT[38]	Spironolactone (50 mg/day) vs. placebo	3445	• EF ≥45% • NYHA II–IV • SBP <140 mmHg or ≤160 mmHg (if 3 or more drug classes) • K^+ < 5.0 mEq/L • Hospitalization <12 months • BNP ≥100 pg/mL • NT-proBNP ≥360 pg/mL	3.3 years	Composite endpoint: hospitalizations for HF or mortality	• Primary endpoint not met (HR 0.89; 95% CI 0.77–1.04; $P = 0.14$) • Significant reduction in hospitalizations
SGLT2i						
EMPEROR-Preserved[110]	Empagliflozin (10 mg/day) vs. placebo	5988	• NYHA II–IV • EF >40% • Structural heart disease[b] • NT-proBNP >300 pg/mL (structural sinus rhythm) or 900 pg/mL (AF) • SBP >100 and <180 mmHg • eGFR ≥20 mL/min/1.73 m^2	26.2 months	Composite endpoint: hospitalizations for HF or cardiovascular mortality	Significant reduction in the primary endpoint (HR 0.79; 95% CI 0.69–0.90; $P < 0.001$)
DELIVER[111]	Dapagliflozin (10 mg/day) vs. placebo	6263	• NYHA II–IV • EF >40% • NT-proBNP >300 pg/mL (structural sinus rhythm) or 600 pg/mL (FA) • Atrial dilatation or left ventricular hypertrophy[c] • SBP >100 and <180 mmHg • eGFR ≥25 mL/min/1.73 m^2	2,3 years	Composite endpoint: hospitalizations for HF or cardiovascular mortality	Significant reduction in the primary endpoint (HR 0.79; 95% CI 0.69–0.91; $P < 0.001$)

ACE, angiotensin-converting enzyme; ARNi, angiotensin receptor inhibitor and neprilysin; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; AF, atrial fibrillation; EF ejection fraction; HR, hazard ratio; CI, confidence interval; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal fragment of B-type natriuretic propeptide; NYHA, New York Heart Association; SBP, systolic blood pressure; RR, rate ratio; HF, heart failure; SGLT2i, sodium-glucose cotransporter type 2 inhibitor.

[a]Atrial diameter >3.8 cm or length >5.0 cm or area >20 cm^2 or volume >55 mL or >29 mL/m^2; NT-proBNP >200 pg/mL (sinus rhythm) or >600 pg/mL (atrial fibrillation) if hospitalization for heart failure in the last 9 months; NT-proBNP >300 pg/mL (sinus rhythm) or >900 pg/mL (atrial fibrillation) in the absence of hospitalization.

[b]Atrial dilatation or left ventricular hypertrophy.

[c]Left atrial dilatation defined as maximum diameter ≥3.8 cm or length ≥5.0 cm, area ≥20 cm^2, or volume ≥55 mL or ≥29 mL/m; left ventricular hypertrophy (interventricular septum ≥1.1 cm).

therapy of function-preserved HF today are re-examined in the following paragraphs, mainly considering an EF >50% as an identifying cut-off.

Diuretics

As mentioned earlier, diuretics, along with SGLT2i, are the only drug class recommended with level I in patients with HFpEF.[167] The recommendation is not based on randomized trials, but on the ability of that class to control congestion and improve HF-related symptoms. This particularly concerns loop diuretics, whose dose should be the lowest dose capable of keeping the patient stable. This is even more relevant in some aetiologies of HFpEF, in which filling and output are critically dependent on volaemia. Torasemide has been proposed as an alternative to furosemide because of its favourable bioavailability[175]; however, no significant benefit of this class of drugs has been demonstrated.[176]

In the ESC 2021[167] Guidelines, the only publication that is reported regarding diuretic therapy in HF is a 2002 meta-analysis[177] that reviewed studies published in the years 1966–99. The primary objective of the meta-analysis was to evaluate the effect of diuretic therapy on mortality and morbidity in HF patients. Eighteen trials, which were randomized towards placebo or other drugs, such as ACE-I, ibopamine, and digoxin, were selected. In the available trials towards placebo (221 patients), the reduction in mortality by diuretic therapy was significant [odds ratio (OR) 0.25; 95% CI 0.07–0.84; $P = 0.03$]. Similarly, the reduction in HF hospitalizations was significant ($n = 448$; OR 0.31; 95% CI 0.15–0.62; $P = 0.001$). In six studies comparing diuretic therapy with other drugs, diuretics significantly improved functional capacity (OR 0.37; 95% CI 0.10–0.64; $P = 0.007$).[177]

Sodium-glucose cotransporter type 2 inhibitors

SGLT2i represent the first drug class that has been shown to improve prognosis in both patients with HFrEF and patients with HFpEF and HFmrEF. Evidence supporting the use of SGLT2i in patients with HFpEF is based on two randomized trials, EMPEROR-Preserved[110] and DELIVER,[111] that compared empagliflozin and dapagliflozin vs. placebo, respectively.

The first of the two studies to be published was EMPEROR-Preserved, which enrolled a population of 5988 patients diagnosed with chronic HF with EF >40%, still symptomatic (NYHA classes II–IV), with or without type 2 DM. Inclusion criteria included elevated NT-proBNP concentrations, evidence of structural heart damage, or previous hospitalization for HF in the past 12 months. At a median follow-up of 26 months, empagliflozin was shown to significantly reduce the primary endpoint consisting of cardiovascular death or hospitalizations for HF (6.9 vs. 8.7 events per 100 patient-years; HR 0.79; $P = 0.0001$), with a 'number needed to treat' of 31. The favourable outcome was achieved predominantly by the reduction in HF hospitalizations. Similar to what was observed in patients with reduced EF, the protective effect resulted in nephroprotection characterized by a slower decline in eGFR (−1.25 vs. −2.62 mL/min/1.73 m^2/year; $P < 0.0001$) in patients treated with empagliflozin vs. placebo.

Similar results were achieved by the DELIVER study.[111] The enrolled population again suffered from HF, in NYHA classes II–IV, with EF >40%. The 6263 patients enrolled were randomized to be treated with dapagliflozin or placebo. At a median follow-up of 2.3 years, dapagliflozin was effective in significantly reducing the composite endpoint of HF-related cardiovascular death/hospitalization (HR 0.79; 95% CI 0.69–0.91; $P < 0.001$).

For the first time, with empagliflozin and dapagliflozin, efficacy in improving the prognosis of HF patients was demonstrated to be independent of EF. This evidence was confirmed by the meta-analysis of studies conducted in patients with reduced and preserved EF.[178,179]

Based on this evidence, the recent updated ESC Guidelines recommend the use of SGLT2i in patients with HFpEF with class I and level of evidence A.[167] It should, however, be recalled how in the case of both EMPEROR-Preserved and DELIVER patients with HFpEF with HCM and amyloidosis were excluded. These conditions currently influence the indication and the reimbursability for HFpEF patients with these diseases.

Neurohormonal modulation

Evidence from randomized trials

Neurohormonal modulation, which is the cornerstone of the treatment for patients with HFrEF, has not shown similar efficacy in reducing HF progression in patients with HFpEF.[167]

Angiotensin-converting enzyme inhibitors

In the PEP-CHF,[168] the efficacy of perindopril vs. placebo was tested in a group of HF patients <70 years of age with evidence of diastolic dysfunction and EF >40%. No significant reduction in the composite endpoint of death or hospitalization for HF was observed (HR 0.919; 95% CI 0.700–1.208; $P = 0.545$). The 1-year event analysis demonstrated only a slight but significant reduction in HF hospitalizations (HR 0.628; 95% CI 0.408–0.966; $P = 0.033$).

Angiotensin receptor antagonists

The efficacy of ARBs was tested by the CHARM-Preserved study that compared candesartan titrated up to the dose of 32 mg/day vs. placebo.[169] The study enrolled 3023 patients with EF >40% in NYHA classes II–IV. At a median follow-up of 36 months, candesartan was not effective in significantly reducing the combined endpoint of HF cardiovascular death or hospitalization (HR 0.89; 95% CI 0.77–1.03; $P = 0.118$; after correction for covariates HR 0.86; 95% CI 0.74–1.0, $P = 0.051$).

Similar results were obtained from the I-PRESERVE Trial, which tested the efficacy of irbesartan vs. placebo in a population of patients aged 60 or more with EF >45%, in NYHA classes II–IV.[170] The study showed no significant reduction in the primary composite endpoint (death from all causes or hospitalization for cardiovascular causes: HF, myocardial infarction, angina, arrhythmia, and stroke).

Mineralocorticoid receptor antagonists

The efficacy of MRAs in treating patients with HFpEF was tested by the TOPCAT study.[38] Patients aged >50 years of

age with EF >45% and history of hospitalization in the previous 12 months and a BNP level ≥100 pg/mL or NT-proBNP level ≥360 pg/mL were enrolled. Spironolactone was not effective in reducing the composite outcome of HF hospitalization (HR 0.89; 95% CI 0.77–1.04; $P = 0.14$), although a significant reduction in HF hospitalizations was observed (HR 0.83; 95% CI 0.69–0.99; $P = 0.04$).

In a *post hoc* analysis, however, it was found that there were significant regional differences in the results of the TOPCAT study. Patients enrolled in American nations had higher event rates but also higher spironolactone efficacy than patients enrolled in Russia and Georgia.[31] This finding likely indicates an enrolment bias in eastern countries, where low-risk patients with clinical features that made MRA therapy less effective were enrolled.

Angiotensin and neprilysin receptor inhibitors

Angiotensin and neprilysin receptor inhibitors (ARNi) are a drug class where the only drug formulation currently available is sacubitril/valsartan. This drug formulation is capable of inhibiting angiotensin II type 1 receptors and neprilysin, an endothelial endopeptidase involved in the degradation of natriuretic peptides.[180] In the PARADIGM-HF study, this dual action, able to modulate two neurohormonal systems[180] more effectively in HF, allowed a significant improvement in the prognosis of patients with HFrEF.[181] In patients with HFpEF, the efficacy of sacubitril/valsartan was tested in the PARAGON-HF study.[126] The study enrolled patients with chronic HF, EF ≥45%, evidence of structural heart disease (atrial dilatation or left ventricular hypertrophy), symptomatic (NYHA classes II–IV) despite diuretic therapy, and with elevated natriuretic peptide levels. These patients were randomized to treatment with sacubitril/valsartan titrated to 97/103 mg bid or with valsartan titrated to 160 mg bid. The study results showed a reduction in the composite endpoint (HF hospitalizations or cardiovascular mortality) on the borderline of statistical significance (rate ratio 0.87; 95% CI 0.75–1.01; $P = 0.06$).[126] More recently, the PARAGLIDE-HF study (Prospective comparison of ARNI with ARB Given Following Stabilization in Decompensated HFpEF) compared sacubitril/valsartan vs. titrated valsartan at the same dosages as PARAGON-HF in 466 patients with recent worsening of HF responsible for hospitalization or urgent visits and EF >40%.[174] The design of the PARAGLIDE-HF study was also confirmed by the subanalysis of the PARAGON-HF study, which showed a greater benefit in the subgroup of patients with recent hospitalization for HF.[182] The primary endpoint of the study was the reduction to 4 and 8 weeks of the NT-proBNP values. The study results showed that the mean reduction in NT-proBNP values over time was greater with sacubitril/valsartan (0.85; 95% CI 0.73–0.999; $P = 0.049$).[174] Finally, a meta-analysis of PARAGON-HF and PARAGLIDE-HF provided further evidence of the ability of sacubitril/valsartan to reduce events in HFpEF patients.[183]

Beta-blockers

Available evidence regarding the use of beta-blockers in patients with HFpEF has not shown any benefit related to their use. Specifically, a meta-analysis of data from 14 262 patients enrolled in 11 randomized trials showed a correlation between the efficacy of beta-blockers according to EF and baseline heart rate.[184] The endpoints analysed were all-cause mortality and cardiovascular mortality at a median follow-up of 1.3 years. In this analysis, only 575 patients had EF between 40 and 49% and 244 had EF ≥50%. Beta-blockers were effective in reducing all-cause and cardiovascular mortality compared to the placebo in all patients who had sinus rhythm, with the exception of patients with HFpEF. Similar results were observed in the AF group.

Phenotypes that benefit from neurohormonal modulation

Based on the evidence from randomized trials, the current ESC Guideline recommendations do not recommend the use of beta-blockers, ARBs, ARNi, and MRA in patients with HFpEF.[167] Differently, the American Heart Association/American College of Cardiology Guidelines recommend ARNi, MRA, and ARB with recommendation level IIb, based on a number of subanalyses of studies that identified certain subgroups of patients with HFpEF who could benefit most from them.[172]

Female gender and ejection fraction

Subanalyses of the studies that evaluated neurohormonal modulation in patients with HFpEF generally indicated a progressive increase in benefit with the reduction of EF. These analyses have also shown that for ARNi[185] and MRA,[186] but not for ARB, this benefit is already significant starting from values of EF >50%, thus including a portion of patients with HFpEF.

For ARNi, this analysis was also confirmed by combining the data from the PARADIGM-HF and the PARAGON-HF studies,[187] which showed that the prognostic benefit of sacubitril/valsartan is significant with an EF <60% in terms of significant reduction in the combined endpoint of death and HF hospitalization.

Importantly, in female patients, the benefit begins to be apparent with higher EF values. This evidence is common to the CHARM,[188] TOPCAT,[189] and PARAGON-HF[190] studies. Therefore, in female HFpEF patients, the use of MRA and ARNi or, if the latter are not tolerated, ARB is indicated regardless of EF, whereas in the male gender, they should be reserved for patients with an EF <55–60%.[191]

Uncontrolled arterial hypertension

Another subgroup of patients who could benefit from pharmacological classes capable of modulating neurohormonal activation is the group of patients with drug-resistant hypertension, which represents a clinical phenotype that characterizes ~15–17% of HFpEF patients.[192,193] This group of patients in the PARAGON-HF study was characterized by a higher incidence of events. Subanalyses from the same PARAGON-HF study and the TOPCAT study suggest that the presence of poorly controlled hypertension may benefit from the use of MRA and sacubitril/valsartan.[194] In the clinical context of hypertension, the possible utility of the RAAS inhibition in the clinical phenotype characterized by hypertrophy and concentric remodelling of the left ventricle[195] should also be emphasized.

Heart rate

In order to control anginal symptoms and ventricular AF response rate,[167] heart rate control by beta-blockers may be a therapeutic strategy in the clinical phenotypes of patients with a history of myocardial infarction.[196] On the other hand, beta-blockers should be avoided in the presence of chronotropic incompetence because of the possibility of accentuating the limitation of patients' functional capacity[191]

Finerenone

Finerenone is a nonsteroidal MRA with a high potency and an enhanced selectivity for the mineralocorticoid receptor. The drug was first used in the CRI and type 2 DM patient population in the FIDELIO-DKD[197] and FIGARO-DKD[198] clinical trials. In both trials, the drug showed a significant reduction in both combined cardiovascular outcome and HF hospitalizations. Based on these trials, finerenone was tested in the double-blind randomized trial FINEARTS-HF[112] demonstrating the reduction of the combined primary outcome consisting of death from cardiovascular causes [14.9 vs. 17.7/100 patient-years (rate ratio 0.84, 95% CI 0.74–0.95; $P = 0.007$)] and the total number of hospitalizations (rate ratio 0.82, 95% CI 0.71–0.94; $P = 0.006$), while nothing significant was observed with regard to mortality from cardiovascular causes (HR 0.93, 95% CI 0.78–1.11). The drug is not yet on the market in Italy, but study results show that the molecule is an additional effective therapeutic weapon in patients with function-preserved HF.[112]

In conclusion, after years of negative studies in patients with preserved function HF, the SGLT2i treatment has shown clear efficacy. This has led to having in addition to diuretics another class of class I drugs in the guidelines for the treatment and therapy of preserved function HF. Given the pathophysiologically nonhomogeneous nature of these patients, another important concept is the need to carefully consider cardiovascular and non-cardiovascular comorbidities as a key element in the therapy of function-preserved HF. Indeed, in the treatment of some comorbidities such as hypertension, myocardial ischaemia, or AF, drugs that counteract neurohormonal activation may return to play a relevant role even if not demonstrated as class therapy. Likewise, active treatment of all major non-cardiovascular comorbidities such as anaemia, obesity, and kidney failure can significantly change the course of the disease.

Non-pharmacologic therapy

Non-pharmacological therapy in function-preserved HF includes lifestyle interventions (and particularly those aimed at treating a very important predisposing factor such as obesity), use of devices, and support through palliative care.

Caloric restriction and exercise

Among the major risk factors for function-preserved HF, obesity certainly plays an important role, acting through multiple mechanisms such as inflammation, hypertension, insulin resistance, and dyslipidaemia. In addition, alterations in cardiac function (diastolic and systolic dysfunction) increased arterial stiffness and musculoskeletal alterations are found in obese subjects; for example, there is an increase in plasma volume, concentric remodelling of the left ventricle, dilation and dysfunction of the right ventricle, an increase in pericardial fat thickness with consequent pericardial constriction, and ventricular interdependence.[191,199,200] Therefore, body weight reduction is an important feature of the treatment.[190]

Even before the publication of data on the use of GLP1-RAs aimed at reducing body weight in this context, a randomized trial had already shown that weight loss achieved through 5 months of calorie restriction resulted in improved functional class and reduced symptoms in obese patients with HFpEF, as well as improved oxygen consumption. Exercise (and in particular, aerobic physical activity three times a week) also demonstrated an improvement in functional capacity in the same trial. The benefit achieved through these two strategies was similar in magnitude, and additive, but the improvement in the quality of life was greater due to the caloric restriction than to the exercise. In contrast, the addition of resistance exercise to aerobic activity and caloric restriction showed a benefit related to the lower extremity muscle strength in elderly patients with HFpEF.[201]

In view of the above, overweight or obese HFpEF subjects could also benefit from a cardiovascular rehabilitation pathway including nutritional guidance and a structured physical activity programme, and where necessary, targeted drug treatment (see appropriate section) and bariatric surgery should also be considered.[200]

A recent network meta-analysis of 13 randomized trials (totalling 869 patients) compared 6 different lifestyle intervention strategies, extending its focus to caloric restriction and physical activity in subjects with HFpEF regardless of their baseline nutritional status. The meta-analysis determined that an improvement in functional capacity could be achieved with different exercise modalities or combinations of exercise and low-calorie diet, but not with low-calorie diet alone, while only high-intensity interval training and low-intensity exercise were able to improve quality of life; overall, the most effective strategy was found to be high-intensity interval training at a follow-up of 4 weeks to 3 years.[202]

New implantable devices

The role of new implantable devices, either aimed directly at treatment or useful in monitoring filling pressures in order to optimize diuretic therapy to counteract water overload, is emerging in the treatment of HFpEF.

Haemodynamic monitoring devices were the first to be developed in this context: this category includes in particular the sensor placed in the pulmonary artery called CardioMEMS. Data on CardioMEMS are derived in particular from the CHAMPION and GUIDE-HF studies: in the former in particular, in which patients with HF in NYHA functional class III were enrolled, the subgroup with LVEF $\geq$40% also benefited in terms of reduction in hospitalizations from therapy guided by monitoring using the implantable sensor.[203,204]

However, this was not a blinded study, a limitation that the GUIDE-HF study did not have, and on whose final neutral result, however, the COVID-19 pandemic[205] probably played an important role.

In view of these data, the placement of a haemodynamic monitoring sensor could be considered in patients in NYHA functional class III despite optimal medical therapy and who have had at least one hospitalization for HF, or in outpatients who have a weak volaemic status, or with cardio-renal syndrome, or even with comorbidities (obesity, pulmonary pathology) for which it would be difficult to recognize dyspnoea on a cardiogenic basis. Obviously, these patients must then be monitored remotely on a regular basis by the referral centre.[191]

On the other hand, devices with a putative direct therapeutic action include those capable of creating a left–right shunt at the level of the interatrial septum: Corvia Interatrial Shunt Device (Corvia IASD, Corvia Medical), Ventura Interatrial Shunt (Ventura IAS, V-Wave Medical), Atrial Flow Regulator (AFR, Occlutech), and others under development. The main devices are circular in shape with a central hole, self-expanding, made from nitinol. Evidence to support this approach is still limited, as the randomized REDUCE LAP-HF II trial did not in fact show any significant benefit assessed on clinical endpoints of the Corvia IASD device in a population with EF ≥40%; however, the role of latent pulmonary vascular pathology, which may be the element that could identify patients who would not benefit from the creation of an interatrial shunt,[206,207] has not been definitively clarified. In addition, data from the RELIEVE-HF (Reducing Lung Congestion Symptoms in Advanced Heart Failure) randomized trial[208] reported a possible disadvantage from using the Ventura IAS device compared to the placebo procedure in patients with EF ≥40%.

At the same time, however, and pending the outcome of other large randomized trials [RESPONDER-HF (NCT05425459) and FROST-HF (NCT03751748)] that are still ongoing, a recent meta-analysis of 6 small studies (a total of 324 patients, mainly treated with Corvia IASD) suggested how these devices are able to reduce left atrial pressure at rest and exertion, with a potential reduction in symptoms and increase in exercise tolerance, at the expense of an increase in right atrial pressure, the effects of which, however, will need to be further investigated, as well as the long-term outcomes, since the included studies involved ≤12 months of follow-up.[209]

Among other interventional approaches evaluated in the context of HFpEF, permanent atrial pacing was not found to be effective in improving exercise capacity or quality of life in patients with chronotropic failure in the RAPID-HF (Rate Adaptive Atrial Pacing in Diastolic Heart Failure) trial.[210] Finally, other interventional options including modulation of cardiac contractility, baroreceptor activation, renal denervation, and vagus nerve stimulation[211] are still in the early stages of evaluation.

Palliative care

While considering that mortality in patients with HFpEF is high and similar to that in patients with HFrEF, it should be highlighted that in the higher EF range, non-cardiovascular causes of death increase in percentage. This evidence is related to both co-pathologies in individuals with HFpEF and extracardiac involvement in certain conditions, such as amyloidosis and sarcoidosis, which are causes of secondary HFpEF.[212] Furthermore, in a study of patients hospitalized for exacerbated HF, some conditions such as anxiety, depression, and physical limitation were found to be more frequent in patients with HFpEF than in those with HFrEF, which also caused an important impact on the family.[213]

On the basis of these data, and also considering that palliative care is effective throughout the course of the disease and not only in the terminal phase, it is easily understandable how activating a ‘team-based’ or nurse-led palliative care system can translate into a major benefit on the patient’s quality of life and symptoms and on both patient and caregiver satisfaction.[214-216] It is therefore desirable that, as the cardiology community becomes more aware of the characteristics, prognosis, and predictors of HFpEF adverse events, the ability to stratify the risk of HFpEF improves and, with the multidisciplinary involvement of other specialists (based on the subject’s co-pathology), a palliative care approach aimed at improving the quality of life of the patients, as well as a better management of the end-of-life phase, is initiated if necessary in a timely manner.[212]

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