Journal Pre-proof

A Portuguese expert panel position paper on the management of heart failure with preserved ejection fraction - Part I: Pathophysiology, diagnosis and treatment

José Silva-Cardoso Emília Moreira Rachel Tavares de Melo Pedro Moraes-Sarmento Nuno Cardim Mário Oliveira Cristina Gavina Brenda Moura Inês Araújo Paulo Santos Marisa Peres Cândida Fonseca João Pedro Ferreira Irene Marques Aurora Andrade Rui Baptista Dulce Brito Rui Cernadas Jonathan dos Santos Adelino Leite-Moreira Lino Gonçalves Jorge Ferreira Carlos Aguiar Manuela Fonseca Ricardo Fontes-Carvalho Fátima Franco Carolina Lourenço Elisabete Martins Hélder Pereira Mário Santos Joana Pimenta

PII: S0870-2551(25)00064-2

DOI: https://doi.org/doi:10.1016/j.repc.2024.11.011

Reference: REPC 2412

To appear in: *Revista Portuguesa de Cardiologia*

Received Date: 12 November 2024

Accepted Date: 19 November 2024

Please cite this article as: Silva-Cardoso J, Moreira E, de Melo RT, Moraes-Sarmento P, Cardim N, Oliveira M, Gavina C, Moura B, Araújo I, Santos P, Peres M, Fonseca C, Ferreira JP, Marques I, Andrade A, Baptista R, Brito D, Cernadas R, Santos Jd, Leite-Moreira A, Gonçalves L, Ferreira J, Aguiar C, Fonseca M, Fontes-Carvalho R, Franco F, Lourenço C, Martins E, Pereira H, Santos M, Pimenta J, A Portuguese expert panel position paper on the management of heart failure with preserved ejection fraction - Part I: Pathophysiology, diagnosis and treatment, *Revista Portuguesa de Cardiologia* (2025), doi: https://doi.org/10.1016/j.repc.2024.11.011

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2025 Published by Elsevier España, S.L.U. on behalf of Sociedade Portuguesa de Cardiologia.

Journal Pre-proof

A Portuguese expert panel position paper on the management of heart failure with preserved ejection fraction - Part I: Pathophysiology, diagnosis and treatment

José Silva-Cardosoa, Emília Moreirab, Rachel Tavares de Meloc, Pedro Moraes-Sarmentod, Nuno Cardime, Mário Oliveiraf, Cristina Gavinag, Brenda Mourah, Inês Araújoi, Paulo Santosj, Marisa Peresk, Cândida Fonsecal, João Pedro Ferreiram, Irene Marquesn, Aurora Andradeo, Rui Baptistap, Dulce Britoq, Rui Cernadasr, Jonathan dos Santoss, Adelino Leite-Moreirat, Lino Gonçalvesu, Jorge Ferreirav, Carlos Aguiarw, Manuela Fonsecax, Ricardo Fontes-Carvalhoy, Fátima Francoz, Carolina Lourençoaa, Elisabete Martinsab, Hélder Pereiraac, Mário Santosad, Joana Pimentaae

a Medicine Department, Faculdade de Medicina da Universidade do Porto, Porto, Portugal; Cardiology Department, Unidade Local de Saúde São João, Porto, Portugal; RISE-Health, Porto Portugal

b Faculdade de Medicina da Universidade do Porto, Porto, Portugal; RISE-Health, Porto, Portugal; Hospital Lusíadas Porto, Porto, Portugal.

c Medical Department, Boehringer Ingelheim, Lisboa, Portugal.

d Heart Failure Day Hospital, Hospital da Luz Lisboa, Lisboa, Portugal; Católica Medical School, Universidade Católica Portuguesa, Lisboa, Portugal.

e Cardiology Department, Hospital CUF Descobertas, Lisboa, Portugal, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Nova Medical School, Lisboa, Portugal.

f Autonomous Arrhythmology, Pacing and Electrophysiology Unit, Hospital de Santa Marta, Unidade Local de Saúde São José, Lisboa, Portugal; CCUL - Faculdade de Medicina de Lisboa, Lisboa, Portugal.

g UnIC@RISE, Faculdade de Medicina, Universidade do Porto, Porto, Portugal; Department of Cardiology, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal.

h Hospital das Forças Armadas- Polo do Porto, Porto, Portugal; Faculdade de Medicina da Universidade do Porto, Porto, Portugal.

i Heart Failure Clinic, Medicine Department, Hospital São Francisco Xavier, Unidade Local de Saúde de Lisboa Ocidental, Lisboa, Portugal; NOVA Medical School, Universidade Nova de Lisboa, Lisboa, Portugal.

j Community Medicine Department, Information and Health Decision Sciences (MEDCIDS), Porto, Portugal; Center for Health Technology and Services Research (CINTESIS@RISE), Porto, Portugal; Faculty of Medicine, University of Porto, Porto, Portugal.

k Cardiology Department, Hospital de Santarém, Santarém, Portugal.

l Heart Failure Clinic, Hospital de São Francisco Xavier, Medicine Department, Unidade Local de Saúde Lisboa Ocidental, Lisboa Portugal; Nova Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal.

m Centre d'Investigations Cliniques Plurithématique 1433, INSERM, Université de Lorraine, CIC 1439, Institut Lorrain du Coeur et des Vaisseaux, CHU 54500, Vandoeuvre-lès-Nancy & F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), INSERM U1116, Centre Hospitalier Régional Universitaire de Nancy, Nancy, France; UnIC@RISE, Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculdade de Medicina, Universidade do Porto, Porto, Portugal; Heart Failure Clinic, Internal Medicine Department, Unidade Local de Saúde de Gaia, Espinho, Portugal.

n Department of Internal Medicine, Centro Hospitalar Universitário de Santo António, Unidade Local de Saúde de Santo António, Porto, Portugal; Unidade Multidisciplinar de Investigação Biomédica (UMIB), Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, Porto, Portugal; ITR - Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal; CAC ICBAS-CHP - Centro Académico Clínico Instituto de Ciências Biomédicas Abel Salazar, Unidade Local de Saúde Santo António, Porto, Portugal.

o Heart Failure Clinic, Cardiology Department, Hospital Padre Américo, Unidade Local de Saúde Tâmega e Sousa, Penafiel, Portugal.

p Department of Cardiology, Unidade Local de Saúde de Entre o Douro e Vouga, Santa Maria da Feira, Portugal; Faculdade de Medicina, Universidade de Coimbra, Coimbra, Portugal; Universidade de Coimbra, Center for Innovative Biomedicine and Biotechnology (CIBB), Coimbra, Portugal; Clinical Academic Center of Coimbra (CACC), Coimbra, Portugal.

q Cardiology Department, Unidade Local de Saúde Santa Maria, Lisboa, Portugal; CCUL@RISE, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal.

r Serviços Clínicos Continental-Mabor, Lousado, Portugal.

s RISE-Health, Porto, Portugal; Instituto CUF Porto, Porto, Portugal.

t Department of Surgery and Physiology, UnIC@RISE, Faculdade de Medicina, Universidade do Porto, Porto, Portugal; Department of Cardiothoracic Surgery, Unidade Local de Saúde de São João, Porto, Portugal.

Journal Pre-proof

u Cardiology Department, Hospitais da Universidade de Coimbra, Unidade Local de Saúde de Coimbra, Coimbra, Portugal; iCBR, Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal.

v Cardiology Department, Hospital de Santa Cruz, Unidade Local de Saúde de Lisboa Ocidental, Carnaxide, Portugal.

w Advanced Heart Failure Unit, Hospital Santa Cruz, Unidade Local de Saúde de Lisboa Ocidental, Carnaxide, Portugal; Cardiac Transplantation Unit, Hospital Santa Cruz, Unidade Local de Saúde de Lisboa Ocidental, Carnaxide, Portugal.

x Unidade Local de Saúde São João, Porto, Portugal; CINTESIS-RISE-HEALTH, Faculdade de Medicina Universidade do Porto, Porto, Portugal.

y Cardiology Department, Unidade Local de Saúde de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal; UnIC@RISE, Department of Surgery and Physiology, Faculdade de Medicina da Universidade do Porto, Porto, Portugal.

z Advanced Heart Failure Unit, Unidade Local de Saúde de Coimbra, Coimbra, Portugal.

aa Advanced Heart Failure Treatment Unit, Unidade Local de Saúde de Coimbra, Coimbra, Portugal.

ab Medicine Department, Faculdade de Medicina do Porto, Porto, Portugal; Cintesis@RISE, Faculdade de Medicina do Porto, Porto, Portugal; Cardiology Department, Unidade Local de Saúde São João, Porto, Portugal.

ac Cardiology Department, Hospital Garcia de Orta, Almada, Portugal; Faculdade de Medicina de Lisboa, Lisboa, Portugal

ad Cardiology Department, Pulmonary Vascular Disease Unit, Centro Hospitalar Universitário de Santo António, Porto, Portugal; CAC ICBAS-CHP – Centro Académico Clínico Instituto de Ciências Biomédicas Abel Salazar, Centro Hospitalar Universitário de Santo António, Porto, Portugal; Department of Immuno-Physiology and Pharmacology, UMIB - Unit for Multidisciplinary Research in Biomedicine, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal; ITR - Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal.

ae Internal Medicine Department, Unidade Local de Saúde de Gaia e Espinho, Portugal; Medicine Department, UnIC@RISE, Cardiovascular Research and Development Center, Faculdade de Medicina do Porto, Porto, Portugal.

*Corresponding author

E-mail address: silvacardoso30@gmail.com (J. Silva Cardoso)

Abstract

Heart failure (HF) with preserved ejection fraction (HFpEF) affects more than 50% of HF patients worldwide, and more than 70% of HF patients aged over 65. This is a complex syndrome with a clinically heterogeneous presentation and a multifactorial pathophysiology, both of which make its diagnosis and treatment challenging.

A Portuguese HF expert panel convened to address HFpEF pathophysiology and therapy, as well as appropriate management within the Portuguese context. This initiative resulted in two position papers that examine the most recently published literature in the field.

The present Part I includes a review of the HFpEF literature covering pathophysiology, clinical presentation, diagnosis and treatment, including pharmacological and non-pharmacological strategies.

Part II, the second paper, addresses the development of a holistic and integrated HFPEF clinical care system within the Portuguese context that is capable of reducing morbidity and mortality and improving patients' functional capacity and quality of life.

KEYWORDS

Heart failure; Heart failure with preserved ejection fraction; HFpEF; Pathophysiology; Diagnosis; Treatment

Journal Pre-proof

Artigo de posicionamento de peritos portugueses sobre a gestão da ICFEp – Parte I: Fisiopatologia, Diagnóstico e Tratamento

Resumo

A insuficiência cardíaca com fração de ejeção preservada (ICFEp) afeta mais de 50% dos doentes com IC em todo o mundo e mais de 70% dos doentes com IC com mais de 65 anos. É uma síndrome complexa, com uma apresentação clinicamente heterógena, e com uma fisiopatologia multifactorial, o que torna o seu diagnóstico e tratamento desafiantes.

Um painel de peritos portugueses em IC reuniu-se para abordar fisiopatologia e terapêutica da ICFEp, bem como a sua gestão adequada no contexto português. Este trabalho resultou em dois artigos de posicionamento, considerando a literatura da área publicada mais recentemente.

A presente Parte I inclui uma revisão da literatura sobre ICFEp abrangendo a fisiopatologia, apresentação clínica, diagnóstico e tratamento, incluindo estratégias farmacológicas e não farmacológicas.

A Parte II, num segundo artigo, integra o desenvolvimento de um sistema de cuidados clínicos de ICFEp holístico e integrado no contexto português, capaz de reduzir a morbi-mortalidade e melhorar a capacidade funcional e a qualidade de vida dos doentes.

Palavras-chave: Insuficiência cardíaca; Insuficiência cardíaca com fração de ejeção preservada; ICEp; Fisiopatologia; Diagnóstico; Tratamento

Introduction

According to the European Society of Cardiology (ESC), the diagnosis of heart failure (HF) with preserved ejection fraction (HFpEF) is made when patients with established HF have left ventricular ejection fraction (LVEF) ≥50%.[1] In the presence of supranormal LVEF (>65-70%), diseases like hypertrophic cardiomyopathy or cardiac amyloidosis should be investigated, since supranormal LVEF may be due to reduced end-diastolic volume.[2] The American College of Cardiology defines HFpEF as a clinical diagnosis of HF and LVEF ≥50% not due to infiltrative or hypertrophic cardiomyopathy, valvular or pericardial disease, or a high output state.[3]

HFpEF affects more than 50% of HF patients worldwide,[4,5] and its prevalence increases sharply with age, affecting 70% of HF patients aged over 65 years.[6]

The recent PORTuguese Heart failure prevalence Observational Study (PORTHOS), a population-based cross-sectional study, screened over 6000 participants aged ≥50 years.[7] HF prevalence was 16.5%, higher in older people (odds ratio [OR] 10.6 in ≥70 vs. 50-59 years) and in women (OR 2.3 vs. men).[8] Most HF patients presented with HFpEF (15.2% vs. 1.3% of HF with reduced/mildly reduced ejection fraction

Journal Pre-proof

[HFrEF/HFmrEF]). Three quarters of HFpEF patients were women and the same proportion were aged ≥70 years.[8]

The prevalence of HFpEF is expected to increase further in the near future due to aging of the population and the growing burden of comorbidities, particularly obesity, metabolic syndrome, diabetes, hypertension, atrial fibrillation (AF), and coronary artery disease.[5,9]

In addition to its increasing prevalence, HFpEF is a complex syndrome, clinically heterogeneous and with a multifactorial pathophysiology, which makes its diagnosis and treatment challenging. Considering the importance of HFpEF and the most recently published literature in the field, a panel of Portuguese heart failure experts convened to address HFpEF management within the Portuguese context. This position paper consists of two articles (Part I and Part II). The present Part I includes a review of the HFpEF literature covering pathophysiology, clinical presentation, and clinical management. Part II addresses the current status of HFpEF care in Portugal, identifies unmet needs, proposes a pragmatic approach to HFpEF management, and presents a diagnosis and referral roadmap, along with a strategy for treatment implementation.

Pathophysiology of heart failure with preserved ejection fraction

HFpEF is particularly common in older, overweight women with multiple comorbidities and elevated inflammatory plasma biomarkers.[10–12] Unlike HFrEF, in which neurohormonal activation plays a central role, chronic low-grade systemic inflammation is key in HFpEF.[13,14] Inflammation may be induced or aggravated by comorbidities such as obesity, metabolic syndrome and chronic kidney disease (CKD), together with the natural process of aging.[15] Chronic systemic inflammatory disorders such as rheumatoid arthritis also increase the occurrence of HFpEF.[16,17]

Obesity, age-related metabolic changes and systemic inflammatory disorders at the inception of heart failure with preserved ejection fraction

During the 1970s and 1980s HFpEF was most frequently associated with hypertension, but obesity is currently the most common associated comorbidity.[18–20] Obesity is an independent risk factor for HFpEF, more markedly in females than in males, while older women with central obesity are at the highest risk.[19,20]

Central obesity is defined as increased visceral (intra-abdominal) adipose tissue (VAT).[21] Intra-abdominal fat is highly metabolically active, and produces a chronic inflammatory state, as well as hemodynamic imbalance, both of which damage the heart and blood vessels.[22]

Intra-abdominal adipocytes produce leptin, neprilysin and aldosterone, and promote beta-2 adrenegic

Journal Pre-proof

receptor and renal sympathetic nerve activation.[23] Neprylisin degrades natriuretic peptides, while aldosterone promotes sodium retention, resulting in plasma volume expansion and hence congestion.[23] Additionally, neprilysin and aldosterone, as well as adipokines (leptin and others), induce a low-grade chronic inflammatory state, promoting myocardial and vascular fibrosis.[24,25] Sodium retention is further amplified by the direct action of beta-2 adrenergic activation, which stimulates mineralocorticoid receptors, leading to cardiac and vascular fibrosis, sodium retention, and consequent plasma volume expansion.[23]

In sum, adiposity-driven plasma volume expansion is coupled with reduced ventricular and vascular distensibility due to fibrosis, induced by the overstimulation of cardiac and vascular mineralocorticoid receptors. This leads to a marked increase in end-diastolic pressure (hemodynamic congestion), resulting in dyspnea and peripheral edema (clinical congestion).[26]

Epicardial tissue expansion and inflammation

The above-mentioned persistent systemic inflammatory state results, in turn, in expansion and inflammation of epicardial adipose tissue. The latter creates a substrate for AF and induces coronary microvascular endothelial inflammation, contributing to myocardial dysfunction and remodeling.[13,27,28] Cardiac fibroblasts are activated, leading to interstitial myocardial fibrosis.[29]

This chain of events leads to myocardial diastolic dysfunction and left ventricular (LV) concentric remodeling, both resulting, again, in a marked increase in end-diastolic pressure.[15]

Atrial fibrillation and left ventricular diastolic dysfunction

As the sequence of events described above involves the left atrium, it can lead to AF and, by involving the left ventricle, promotes diastolic dysfunction, both of which are associated with HFpEF.[13]

The emergence of AF is very common and important in HFpEF patients, since in a small ventricle with diminished distensibility, the contribution of atrial kick is extremely important to maintain LV filling and cardiac output. Thus, the presence of AF reduces LV filling, leading to diminished output. Additionally, a stiff ventricle is more dependent on diastolic time for adequate filling. Rapid AF dramatically reduces LV diastolic time and thus may lead to flash pulmonary edema.[30]

Accordingly, the H_2FPEF score attributes the greatest weight to the presence of AF among all variables considered when predicting the likelihood that HFpEF is present in an individual patient.[31]

Furthermore, ventricular fibrosis also occurs in HFpEF and may lead to an increased risk of ventricular arrhythmias and sudden cardiac death.[32,33]

Journal Pre-proof

Hypertension and heart failure with preserved ejection fraction

Between 55% and 90% of HFpEF patients have arterial hypertension, which is the most prevalent comorbidity in HFpEF.[34,35]

Important mechanisms linking hypertension and HFpEF include LV hypertrophy, myocardial fibrosis, and subsequent diastolic dysfunction.

Myocardial fibrosis and reduced capillary density, in the presence of LV hypertrophy, result in myocardial ischemia, thus worsening LV diastolic function.[34–36]

Additionally, aortic stiffness consequent to hypertension is responsible for increased arterial wave reflection velocity, inducing late systolic load, thus contributing to LV diastolic dysfunction.

Vascular fibrosis and stiffening

Vascular fibrosis and stiffening also play an important role in HFpEF, since they reduce arterial compliance, increasing LV diastolic dysfunction and producing left and right ventricular-arterial uncoupling.[37,38]

Diabetes and heart failure with preserved ejection fraction

The association between diabetes and HFpEF may be mediated by hyperinsulinemia, which can suppress autophagy and promote mitochondrial dysfunction. Increased sympathetic activation and cardiac hypertrophy are important consequences of hyperinsulinemia.[28] It can also activate Na-H exchangers in renal tubules and cardiomyocytes, and cause expansion of epicardial fat, which is associated with microcirculatory dysfunction and myocardial fibrosis.[13]

Additionally, the myocardium can become insulin-resistant with obesity, and gender and obesity interact in predicting myocardial glucose uptake and insulin sensitivity.[39]

Chronic kidney disease and the cardiovascular-kidney-metabolic syndrome

Chronic kidney disease is present in about half of patients with HFpEF. Pathophysiological mechanisms implicated in HFpEF are linked to the association of CKD with hypertension and metabolic abnormalities, which activate a systemic inflammatory reaction, endothelial dysfunction, and myocardial fibrosis, including increased central venous and intra-abdominal pressures, renin-angiotensin system activation, oxidative stress, and chronic inflammation.[34,35]

Considering the overlap between the cardiorenal and cardiometabolic syndromes, it has been suggested that a wider concept of a cardiovascular-kidney-metabolic (CKM) syndrome should be adopted.[40] The molecular mechanisms of CKM syndrome include a variety of interconnected factors; however, what links

Journal Pre-proof

risk factors for CKM to cardiovascular disease and CKD remains unclear.[40]

Other pathophysiological mechanisms in heart failure with preserved ejection fraction

Impaired cellular calcium regulation, loss of muscle mass and decline in muscle strength, among many other factors, may play a role in the pathogenesis of HFpEF.[41,42]

Chronotropic incompetence, defined as a significantly lower peak heart rate during exercise compared to that of normal individuals of the same age group, has also been consistently associated with exercise intolerance in HFpEF, by limiting these patients' ability to increase cardiac output.[43]

The particular case of women

It is still unclear why HFpEF is more prevalent in women. Women, particularly when older and obese, tend to have greater epicardial and intramyocardial fat volume and higher levels of adipocyte-associated proinflammatory mediators than men.[19] Additionally, women with increased visceral adipose tissue (VAT) present 33% greater exercise pulmonary capillary wedge pressure than those without, whereas this was not observed in men.[18] Moreover, women tend to show greater arterial stiffness, and a smaller, thicker and stiffer left ventricle than men.[44]

Clinical presentation and diagnosis of heart failure with preserved ejection fraction

Diagnosing HFpEF requires the investigation of specific etiologies that may present with or without HF signs and symptoms and preserved LVEF, but require specific diagnostic assessment and therapeutic management.[3] These include conditions such as amyloid, hypertrophic or other restrictive/infiltrative cardiomyopathies, and valvular or pericardial diseases.[3]

Additionally, in patients with dyspnea and other signs and symptoms associated with HF, diagnosing HFpEF is not straightforward, since the presence of preserved LVEF requires differential diagnosis with non-cardiac causes of dyspnea. In some cases, advanced imaging or invasive cardiopulmonary exercise testing may be required in patients who only develop physical manifestations of congestion during exercise.[6,45]

Two tools have been developed to help in the diagnosis of HFpEF: the H_2FPEF score and the HFA-PEFF algorithm.[31,45]

The H_2FPEF score was created using an invasively diagnosed HFpEF cohort, and was subsequently tested in a validation cohort. It is based on six clinical variables, most of which are readily assessed in clinical practice, and an online calculator is available.[31]

The HFA-PEFF algorithm was created by an expert consensus panel and is more complex than the

Journal Pre-proof

H_2FPEF score. An initial probability of HFpEF is established, based on clinical assessment complemented by a diagnostic work-up including natriuretic peptides, electrocardiography, chest X-ray, and advanced echocardiography.[45] If this probability is low, HFpEF is excluded, while if it is high, HFpEF is confirmed.[45] When the probability of HFpEF is intermediate, a diastolic stress test should be performed.[45] This uses exercise right heart catheterization to directly measure HFpEF-defining parameters, and is therefore the diagnostic gold standard. However, this is an invasive technique, requires operator expertise and has high associated costs, making it unsuitable as an universal diagnostic tool.[6] The HFA-PEFF algorithm incorporates diastolic stress testing only on a case-by-case basis.

Treatment of heart failure with preserved ejection fraction

Addressing etiology and comorbidities

Both the 2021 ESC and the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) heart failure guidelines recommend the identification and treatment of HFpEF etiology and comorbidities with a class I indication[1,34,46,47] and consider them core elements of HFpEF management.[1,34,46,47] They also recommend increased physical activity and reduction of body weight in overweight and obese patients.[1,46]

Physical activity

Exercise intolerance is a major feature of HFpEF, affecting quality of life. Impaired exercise capacity in HFpEF is due to various pathophysiological mechanisms involving the heart, lungs, vessels, and skeletal muscles. Regular exercise has demonstrated a pleiotropic array of positive effects that can ameliorate these cardiac and extracardiac abnormalities.[48] Current guidelines strongly advocate exercise training for HF patients, assigning it a class I recommendation (level of evidence A).[48] Several trials have consistently shown improvements in exercise capacity in HFpEF patients through various exercise modalities, including facility-based and home-based interventions.[48,49]

Reduction of body weight

Weight loss via caloric restriction or aerobic exercise reduced LV mass and inflammatory markers and improved exercise capacity and quality of life in a seminal clinical trial in older obese patients with HFpEF, with the combination of the two interventions being additive.[50] Weight loss can be achieved through a combination of lifestyle interventions including diet and exercise training, pharmacotherapy, and bariatric surgery.

In the recently published STEP-HFpEF trial, the glucagon-like peptide-1 (GLP-1) agonist semaglutide

Journal Pre-proof

led to reductions in symptoms and physical limitations and greater exercise capacity and weight loss, compared with placebo in non-diabetic obese HFpEF patients, across obesity categories.[51,52] The magnitude of benefit was directly related to the extent of weight reduction, supporting the drug as a key treatment strategy in the obese HFpEF phenotype. The recent STEP-HFpEF DM trial showed similar results with semaglutide in patients with obesity-related HFpEF and type 2 diabetes.[53] Recently released data from the SUMMIT trial with tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 agonist, showed a 38% relative risk reduction in the co-primary endpoint of time to first cardiovascular death, HF urgent visit/hospitalization, or oral diuretic intensification with tirzepatide vs. placebo over a median follow-up of 104 weeks in 731 patients with obesity (body mass index ≥30 kg/m^2) and New York Heart Association (NYHA) class II–IV HFpEF (LVEF ≥50%), with N-terminal pro-brain natriuretic peptide (NT-proBNP) >200 pg/ml (>600 pg/ml with AF) and estimated glomerular filtration rate (GFR) between 15 and 70 ml/min/1.73 m^2, and without glycated hemoglobin ≥9.5%, uncontrolled diabetes, or a major cardiovascular event in the last 90 days of screening.[54] Additionally, mean body weight reduction from baseline to week 52 was observed with tirzepatide, with an approximate 15.7% body weight reduction vs. 2.2% in the placebo arm.[54,55]

Although bariatric surgery is associated with significant and sustained weight reduction, there are no data on HFpEF patients or randomized trials assessing its effect on cardiovascular outcomes; however, observational data support its association with a reduced incidence of HF.[56]

Diuretics: congestion control

Congestion is central in HFpEF, and thus loop diuretics are a crucial part of therapy.[1,46] Elevated LV filling pressures, as measured by LV end-diastolic pressure (LVEDP), are needed to ensure appropriate diastolic filling, which is essential to maintain cardiac output. However, increased LVEDP, if above a certain level, leads to pulmonary congestion. On the one hand, diuretics are key to reducing congestion and dyspnea in HFpEF by lowering LVEDP. On the other hand, in the context of a stiff ventricle, this may compromise LV filling, impairing cardiac output and causing hypotension.[57,58] This is why in HFpEF the window between volume overload and hypovolemia is very narrow; thus, diuretics must be managed with caution. Additionally, considering the preload dependence of HFpEF, congestion correction requires smaller doses of diuretics than in HFrEF.[58] Despite the paucity of evidence from randomized controlled trials, diuretics have a class I indication for HFpEF treatment in both the European and American guidelines.[1,46]

Journal Pre-proof

Sodium-glucose co-transporter-2 inhibitors: the first prognosis-modifying drugs for heart failure with preserved ejection fraction

Sodium-glucose co-transporter-2 inhibitors (SGLT2is) were initially shown to reduce HF hospitalizations in patients with type 2 diabetes, and subsequently demonstrated a reduction in HF hospitalizations and cardiovascular and all-cause mortality in HFrEF patients.[59,60]

In patients with HFpEF, the EMPEROR-Preserved[61] and DELIVER[62] studies showed that SGLT2is, regardless of the presence of diabetes, reduced the combined risk of cardiovascular death/HF hospitalization (EMPEROR-Preserved) and the risk of cardiovascular death/worsening HF (DELIVER). The combined results of these two studies met the criteria for a class I indication, level of evidence A, from the ESC[1] and a II-A recommendation from the AHA/ACC/HFSA guidelines.[46] Currently, SGLT2is are the only class of drugs with this level of indication in HFpEF. All patients with HFpEF should be under an SGLT2i (empagliflozin or dapagliflozin), unless not tolerated or contraindicated.

Several hypothetical mechanisms of action for SGLT2is in HFpEF have been advanced to explain their cardioprotective role. These include a modest direct decrease in blood pressure and an increase in diuresis/natriuresis. The latter results in a more selective reduction in extravascular rather than intravascular congestion. Additional possibilities include decreased epicardial fat mass, inflammation prevention, reduction of neurohormonal activation, increase in autophagy and lysosomal degradation, decreased oxidative stress, and the prevention of ischemia/reperfusion injury, among others.[63–66] Although the blood pressure-lowering effects of SGLT2is were initially thought to be secondary to diuresis and natriuresis, they have been shown to persist even after a decline in GFR. This suggests that additional mechanisms of action (possibly involving reduced arterial stiffness, changes in sympathetic nervous system activity or improved endothelial function) may play a role as well.[64] One of the most recent hypotheses to explain the effects of SGLT2is on cardiac function involves the possible modification of cardiomyocyte metabolic pathways induced by these agents (specifically, the use of ketogenic metabolism rather than fatty acid and glucose metabolism), resulting in improved cardiac efficiency.[64,67] It has been proposed that SGLT2 acts as a nutrient surplus sensor, and so its inhibition enhances nutrient deprivation signaling and activates an autophagic flux that reduces cellular stress and promotes cellular survival.[68] Another hypothesis involves SGLT2i-induced improvement in myocardial ionic homeostasis.[64,67]

Renin-angiotensin-aldosterone system inhibitors

Renin-angiotensin-aldosterone system inhibitors (RAASis) include angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), angiotensin receptor/neprilysin inhibitors

Journal Pre-proof

(ARNIs) and mineralocorticoid receptor antagonists (MRAs). None of the large trials involving RAASis in HFpEF met the composite endpoint of reducing cardiovascular mortality/HF hospitalizations. These include PEP-CHF (with perindopril), CHARM-Preserved[69] (with candesartan), PARAGON-HF[70] (with sacubitril/valsartan) and TOPCAT[71] (with spironolactone). Nevertheless, although cardiovascular mortality was not reduced in the active arm in any of the above studies, candesartan and spironolactone reduced HF hospitalizations and sacubitril/valsartan showed a trend with no statistical significance.

The TOPCAT study deserves some additional comments. A pre-specified subgroup analysis suggested that the primary outcome was significantly reduced by spironolactone in patients with elevated natriuretic peptide levels at baseline. A subsequent subanalysis restricted to patients enrolled in North and South America showed a significant reduction in the primary composite endpoint (time to cardiovascular death, aborted cardiac arrest, or hospitalization for management of heart failure) in the intervention arm compared to placebo, whereas this was not observed in the European cohort.[72,73] It is noteworthy that among the Russian cohort, a higher percentage of participants showed undetectable levels of canrenone (an active metabolite of spironolactone) compared to American and Canadian subjects.[74]

Considering the importance of vascular and cardiac fibrosis in HFpEF, it is plausible that antagonizing the mineralocorticoid receptor may have a positive impact on prognosis.[75]

ARNIs, ARBs and MRAs received a class II-B indication in the AHA/ACC/HFSA guidelines for HFpEF patients, with the disclaimer of higher benefit demonstrated in patients with LVEF closer to 50%.[1,46]

Additionally, following the FIDELIO-DKD and FIGARO-DKD trials, finerenone, a non-steroidal MRA with high binding affinity, has a class I level A recommendation for the prevention of HF hospitalizations in patients with albuminuric CKD and type 2 diabetes.[76] Pre-specified subgroup analyses of these two studies suggested a potential beneficial effect of finerenone in HF patients without symptomatic HFrEF.[77,78] This effect was recently confirmed in the FINEARTS-HF study, which included 6016 NYHA class II–IV HFmrEF/HFpEF (LVEF ≥40%; LVEF ≥60% capped at 20%) patients with structural cardiac abnormalities, NT-proBNP ≥300 pg/ml (≥900 pg/ml if AF), K+ ≤5.0 mmol/l, estimated GFR ≥25 ml/min/1.73 m^2, and on diuretic treatment for ≥30 days. This study met the primary endpoint with a statistically significant and clinically meaningful reduction in the composite of cardiovascular death and total HF events vs. placebo.[79,80]

Beta-blockers

There is no prospective evidence of a positive impact of beta-blockers on HFpEF. Some studies suggest

Journal Pre-proof

a deleterious effect, with a higher risk of hospitalizations.[81]

Treatment of heart failure with preserved ejection fraction: future avenues

Ferric carboxymaltose

Iron supplementation with IV administration of ferric carboxymaltose (FCM) has a clear beneficial effect on HFrEF patients.[82,83] However, there are scarce data on the potential of iron supplementation in patients with HFpEF. Small-sample randomized clinical trials and retrospective studies have shown that supplementation with FCM significantly improves cardiac performance of HFpEF patients.[84,85] Results from the ongoing PREFER-HF and FAIR-HFpEF trials may add evidence on this subject.[86,87]

Glucagon-like peptide-1 receptor agonists

Although they reduce epicardial fat and inflammation, GLP-1 receptor agonists pose challenges with sodium retention in HFpEF.[88] As stated above, in the STEP-HFpEF trial, the GLP-1 agonist semaglutide demonstrated significant benefits in non-diabetic obese HFpEF patients, including reduced symptoms, enhanced exercise capacity, and greater weight loss compared to placebo across obesity categories.[51,52] Notably, the degree of benefit correlated directly with weight reduction, emphasizing its pivotal role as a treatment strategy in the obesity phenotype of HFpEF.

Metformin

Metformin reduces epicardial tissue expansion and inflammation, as well as myocardial fibrosis.[88] In observational studies, it appeared to reduce the incidence of AF and HFpEF.[88]

Thiazolidinediones and dipeptidyl peptidase-4 inhibitors

Thiazolidinediones and dipeptidyl peptidase-4 inhibitors reduce epicardial adipose tissue dysfunction and could potentially reduce the risk of AF and HFpEF.[88] However, although thiazolidinediones have favorable effects on experimental HFpEF and AF, their antinatriuretic properties make them inappropriate for use in HFpEF patients.[88]

Targeting visceral adipose tissue

VAT is a highly active endocrine organ that secretes cytokines and other mediators. As pointed out above, increased VAT seen in central obesity leads to epicardial fat expansion and inflammation, a major step in the genesis of HFpEF. Thus, targeting VAT may be a future approach to HFpEF through dietary, drug and/or surgical weight loss strategies.[89]

Journal Pre-proof

Anti-inflammatory agents

Epicardial adipose tissue expansion and associated inflammatory activity may be reduced by statins and anticytokine agents.[88] These agents could, in theory, thereby reduce the incidence of AF and HFpEF.[88]

Ongoing clinical trials

The ongoing EMPA-PRED and ENRICH-PEF clinical trials are expected to provide further evidence on HFpEF management. The EMPA-PRED study aims to assess the safety and efficacy of empagliflozin in patients with end-stage renal disease and HFpEF.[90] The effects of enavogliflozin on exercise performance, diastolic dysfunction, and quality of life in HFpEF patients will be investigated in the ENRICH-PEF trial.[91] Additionally, trials with aldosterone synthase inhibitors, such as baxdrostat, for treatment-resistant hypertension are ongoing.[92]

Non-pharmacological alternatives under study

Atrial pacing, atrial shunting and AF ablation are three non-pharmacological alternatives that are being studied in HFpEF, although the evidence is not consistent. In the RAPID-HF trial, atrial pacing increased early and peak exercise heart rate, but no improvement in exercise performance or quality of life was observed.[93] The CABA-HFPEF trial will assess whether catheter-based AF ablation can improve cardiovascular outcomes compared to conventional treatment in these patients.[94] Lastly, the first large trial of an atrial shunt device, designed to lower left atrial pressure, presented neutral overall results. Ongoing trials are expected to add evidence in this field.[95]

Conclusion

Worldwide population aging, changes in lifestyle and the resulting diabesity epidemic are leading to a steep increase in the prevalence of HFpEF, which is becoming the dominant HF phenotype. The epidemiology, pathophysiology, diagnostic work-up and treatment of HFpEF differ from HFrEF.

The clinical management of HFpEF requires the involvement of multidisciplinary teams, covering hospital and outpatient settings. It is essential to address its multiple dimensions, from diagnosis to follow-up and therapy, in order to reduce morbidity and mortality and improve patients' functional capacity and quality of life.

A better understanding of this condition can help develop an effective, holistic and integrated clinical management of HFpEF. This will be the subject of Part II of this expert panel position paper, which will address the burden of HFpEF and organization of care, while proposing a pragmatic approach to its management.

Journal Pre-proof

Acknowledgments

We would like to thank Ana Santos, medical writer from Prime Focus, for her excellence in scientific accuracy, consolidation of co-authors' contributions and data management for an extensive expert panel, during a two-year project execution period.

Conflicts of interest

JSC, EM, MO, MP, DB, RC, ALM, LG, MF, FF, HP, MS have no conflicts of interest to declare.

RTM is an employee of Boehringer Ingelheim.

PMS has received speaker/consultant fees from AstraZeneca, Bayer, Bial, Boehringer Ingelheim, Novartis, and Novo Nordisk.

NC has received speaker fees and participated in congresses supported by Bristol Myers Squibb, Cytokinetics, Pfizer, Boehringer, Ferrer, and Bial.

CG has received speaker and/or advisory board fees from AstraZeneca, Bial, Boehringer-Ingelheim, Lilly, Novartis, Novo Nordisk, and Servier.

BM has received speaker or advisory fees from AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Servier, Vifor Pharma, and Viartris.

IA has received speaker fees from AstraZeneca, Bial, Novartis, Servier, and advisory fees from AstraZeneca, Novartis, and Boehringer Ingelheim/Lilly.

PS has received speaker or consulting fees, or investigational grants from AstraZeneca, Boehringer Ingelheim, Ferrer, GSK, Lilly, Medinfar, MSD, and Tecnimede.

CF has received speaker and consultant fees from Astra Zeneca, Bayer, Boehringer Ingelheim, Novartis, Pfizer, Roche, Sanofi, and CSL Vifor.

JPF has performed consultancy for Boehringer-Ingelheim, Novartis, Bayer, Salamandra, Bial, AstraZeneca, and Abbott.

IM has received speaker and consultant fees from Astra Zeneca, Bayer, Bial, CSL Vifor, Daiichi-Sankyo, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Servier.

AA has received speaker or advisory board fees from AstraZeneca, Boehringer Ingelheim, Bial.

RB has received consultancy and/or speaking fees from AstraZeneca, Bayer, Bial, Boehringer-Ingelheim, Lilly, MSD, Novartis, Servier and Vifor Pharma.

JS has received speaker/consultant fees from AstraZeneca, Boehringer Ingelheim, Lilly, Novartis, Roche, Merck, Viatris, and Pfizer.

Journal Pre-proof

JF has received speaker and consultant fees from Amgen, AstraZeneca, Boehringer-Ingelheim, Merck Sharp & Dohme, and Novartis.

CL has received speaker/consultant fees from Boehringer, Bial, and Novartis.

CA has received speaker and consultant fees from Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Lilly, Novartis, and Servier.

RFC has received speaker and consultant fees from AstraZeneca, Bayer, Bial, Boehringer Ingelheim, Novartis, and Servier.

EM has received speaker and consultant fees from AstraZeneca, Bial, Amicus Therapeutics, Sanofi, Amgen, and Pfizer.

JP has received speaker/consultant fees from AstraZeneca, Bayer, Bial, Boehringer Ingelheim/lilly, Daiichi-Sankyo, GSK, Novartis, Pfizer, Servier, and Vifor Pharma.

Funding

The authors meet criteria for authorship, as recommended by the ICMJE.

The authors did not receive payment related to the development of the manuscripts.

Ana Santos of Prime Focus provided medical writing, editorial support, and formatting assistance, which was contracted and funded by Boehringer Ingelheim and Lilly Portugal.

Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

References

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–726.
2. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–726. https://doi.org/10.1093/eurheartj/ehab368
3. Kittleson MM, Ruberg FL, Ambardekar A V., et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis. J Am Coll Cardiol. 2023;81:1076–126. https://doi.org/10.1016/j.jacc.2022.11.022
4. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14:591–602.
5. Savarese G, Becher PM, Lund LH, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;118:3272–87. https://doi.org/10.1093/CVR/CVAC013
6. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2020;17:559–73.

Journal Pre-proof

7. Baptista R, Silva Cardoso J, Canhão H, et al. Portuguese Heart Failure Prevalence Observational Study (PORTHOS) rationale and design – A population-based study. Rev Port Cardiol. 2023;42:985–95. https://doi.org/10.1016/j.repc.2023.10.004
8. Portuguese Heart Failure Prevalence Observational Study (PORTHOS). Available at: https://esc365.escardio.org/presentation/277288 [accessed 3 june 2024].
9. Sidney S, Go AS, Jaffe MG, et al. Association between Aging of the US Population and Heart Disease Mortality from 2011 to 2017. JAMA Cardiol. 2019;4:1280–6. https://doi.org/10.1001/jamacardio.2019.4187
10. Upadhya B, Pisani B, Kitzman DW. Evolution of a Geriatric Syndrome: Pathophysiology and Treatment of Heart Failure with Preserved Ejection Fraction. J Am Geriatr Soc. 2017;65:2431–40. https://doi.org/10.1111/jgs.15141
11. Khera A, Vega GL, Das SR, et al. Sex differences in the relationship between C-reactive protein and body fat. J Clin Endocrinol Metab. 2009;94:3251–8. https://doi.org/10.1210/jc.2008-2406
12. Packer M. Epicardial Adipose Tissue May Mediate Deleterious Effects of Obesity and Inflammation on the Myocardium. J Am Coll Cardiol. 2018;71:2360–72. https://doi.org/10.1016/j.jacc.2018.03.509
13. Packer M. Differential Pathophysiological Mechanisms in Heart Failure With a Reduced or Preserved Ejection Fraction in Diabetes. JACC Heart Fail. 2021;9:535–49. https://doi.org/10.1016/J.JCHF.2021.05.019
14. Lourenço AP, Leite-Moreira AF, Balligand JL, et al. An integrative translational approach to study heart failure with preserved ejection fraction: a position paper from the Working Group on Myocardial Function of the European Society of Cardiology. Eur J Heart Fail. 2018;20:216–27. https://doi.org/10.1002/EJHF.1059
15. Paulus WJ, Tschöpe C. A Novel Paradigm for Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2013;62:263–71.
16. Huang S, Cai T, Weber BN, et al. Association Between Inflammation, Incident Heart Failure, and Heart Failure Subtypes in Patients With Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2023;75:1036–45. https://doi.org/10.1002/acr.24804
17. Mesquita T, Lin YN, Ibrahim A. Chronic low-grade inflammation in heart failure with preserved ejection fraction. Aging Cell. 2021;20(9):e13453. https://doi.org/10.1111/ACEL.13453
18. Oktay AA, Rich JD, Shah SJ. The Emerging Epidemic of Heart Failure with Preserved Ejection Fraction. Curr Heart Fail Rep. 2013;10:401–10. https://doi.org/10.1007/s11897-013-0155-7
19. Packer M, Lam CSP, Lund LH, et al. Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease. Eur J Heart Fail. 2020;22:1551–67. https://doi.org/10.1002/EJHF.1902
20. Borlaug BA, Jensen MD, Kitzman DW, et al. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. Cardiovasc Res. 2023;118:3434–50. https://doi.org/10.1093/cvr/cvac120
21. Sorimachi H, Obokata M, Takahashi N, et al. Pathophysiologic importance of visceral adipose tissue in women with heart failure and preserved ejection fraction. Eur Heart J. 2021;42:1595–605.

Journal Pre-proof

https://doi.org/10.1093/EURHEARTJ/EHAA823

22. Reddy YNV, Anantha-Narayanan M, Obokata M, et al. Hemodynamic Effects of Weight Loss in Obesity: A Systematic Review and Meta-Analysis. JACC Heart Fail. 2019;7:678–87. https://doi.org/10.1016/J.JCHF.2019.04.019
23. Packer M. Leptin-Aldosterone-Neprilysin Axis: Identification of Its Distinctive Role in the Pathogenesis of the Three Phenotypes of Heart Failure in People With Obesity. Circulation. 2018;137:1614–31. https://doi.org/10.1161/CIRCULATIONAHA.117.032474
24. Cooper LB, Cotugno A, Defilippi C. Efficacy of Neprilysin Inhibition in Women With HFpEF: Beyond Phenotypes and Natriuretic Peptides. Circulation. 2021;143:618–20. https://doi.org/10.1161/CIRCULATIONAHA.120.046634
25. Buffolo F, Tetti M, Mulatero P, et al. Aldosterone as a Mediator of Cardiovascular Damage. Hypertension. 2022;79:1899–911. https://doi.org/10.1161/HYPERTENSIONAHA.122.17964
26. Packer M. Derangements in adrenergic-adipokine signalling establish a neurohormonal basis for obesity-related heart failure with a preserved ejection fraction. Eur J Heart Fail. 2018;20:873–8. https://doi.org/10.1002/EJHF.1167
27. Shimabukuro M, Hirata Y, Tabata M, et al. Epicardial adipose tissue volume and adipocytokine imbalance are strongly linked to human coronary atherosclerosis. Arterioscler Thromb Vasc Biol. 2013;33:1077–84. https://doi.org/10.1161/ATVBAHA.112.300829
28. Krishnan A, Sharma H, Yuan D, et al. The Role of Epicardial Adipose Tissue in the Development of Atrial Fibrillation, Coronary Artery Disease and Chronic Heart Failure in the Context of Obesity and Type 2 Diabetes Mellitus: A Narrative Review. J Cardiovasc Dev Dis. 2022;9:217. https://doi.org/10.3390/jcdd9070217
29. Peet C, Ivetic A, Bromage DI, et al. Cardiac monocytes and macrophages after myocardial infarction. Cardiovasc Res. 2020;116:1101–12. https://doi.org/10.1093/CVR/CVZ336
30. Gladden JD, Linke WA, Redfield MM. Heart failure with preserved ejection fraction. Pflügers Arch - Eur J Physiol. 2014;466:1037–53. https://doi.org/10.1007/s00424-014-1480-8
31. Reddy YNV, Carter RE, Obokata M, et al. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation. 2018;138:861–70. https://doi.org/10.1161/CIRCULATIONAHA.118.034646
32. Kanagala P, Cheng ASH, Singh A, et al. Relationship Between Focal and Diffuse Fibrosis Assessed by CMR and Clinical Outcomes in Heart Failure With Preserved Ejection Fraction. JACC Cardiovasc Imaging. 2019;12:2291–301. https://doi.org/10.1016/j.jcmg.2018.11.031
33. Cho JH, Zhang R, Aynaszyan S, et al. Ventricular Arrhythmias Underlie Sudden Death in Rats With Heart Failure and Preserved Ejection Fraction. Circ Arrhythm Electrophysiol. 2018;11:e006452. https://doi.org/10.1161/CIRCEP.118.006452
34. Anker SD, Usman MS, Anker MS, et al. Patient phenotype profiling in heart failure with preserved ejection fraction to guide therapeutic decision making. Eur J Heart Fail. 2023;25:936–55. https://doi.org/10.1002/ejhf.2894
35. Kasiakogias A, Rosei EA, Camafort M, et al. Hypertension and heart failure with preserved ejection fraction: position paper by the European Society of Hypertension. J Hypertens. 2021;39:1522–45.

Journal Pre-proof

https://doi.org/10.1097/HJH.0000000000002910

36. Tam MC, Lee R, Cascino TM, et al. Current Perspectives on Systemic Hypertension in Heart Failure with Preserved Ejection Fraction. Curr Hypertens Rep. 2017;19:12. https://doi.org/10.1007/s11906-017-0709-2
37. Packer M. Atrial Fibrillation and Heart Failure With Preserved Ejection Fraction in Patients With Nonalcoholic Fatty Liver Disease. Am J Med. 2020;133:170–7. https://doi.org/10.1016/j.amjmed.2019.09.002
38. Borlaug BA, Kane GC, Melenovsky V, et al. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. Eur Heart J. 2016;37:3294–302. https://doi.org/10.1093/eurheartj/ehw241
39. Peterson LR, Soto PF, Herrero P, et al. Impact of Gender on the Myocardial Metabolic Response to Obesity. JACC Cardiovasc Imaging. 2008;1:424–33. https://doi.org/10.1016/j.jcmg.2008.05.004
40. Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. Circulation. 2023;148:1606–35. https://doi.org/10.1161/CIR.0000000000001184
41. Warbrick I, Rabkin SW. Effect of the peptides Relaxin, Neuregulin, Ghrelin and Glucagon-like peptide-1, on cardiomyocyte factors involved in the molecular mechanisms leading to diastolic dysfunction and/or heart failure with preserved ejection fraction. Peptides. 2019;111:33–41. https://doi.org/10.1016/J.PEPTIDES.2018.05.009
42. Upadhya B, Kitzman DW. Heart failure with preserved ejection fraction: New approaches to diagnosis and management. Clin Cardiol. 2020;43:145–55.
43. Ton VK, Lewis GD. Does chronotropic incompetence in HFpEF cause or result from exercise intolerance? Circ Heart Fail. 2020;13(3):e006872. https://doi.org/10.1161/CIRCHEARTFAILURE.120.006872
44. St. Pierre SR, Peirlinck M, Kuhl E. Sex Matters: A Comprehensive Comparison of Female and Male Hearts. Front Physiol. 2022;13:831179. https://doi.org/10.3389/fphys.2022.831179
45. Pieske B, Tschöpe C, De Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: The HFA-PEFF diagnostic algorithm: A consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019;40:3297–317.
46. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79:1757–80. https://doi.org/10.1016/j.jacc.2021.12.011
47. Kittleson MM, Panjrath GS, Amancherla K, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2023;81:1835–78. https://doi.org/10.1016/j.jacc.2023.03.393
48. Sachdev V, Sharma K, Keteyian SJ, et al. Supervised Exercise Training for Chronic Heart Failure With Preserved Ejection Fraction: A Scientific Statement From the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2023;81:1524–42. https://doi.org/10.1016/j.jacc.2023.02.012

Journal Pre-proof

49. Mueller S, Winzer EB, Duvinage A, et al. Effect of High-Intensity Interval Training, Moderate Continuous Training, or Guideline-Based Physical Activity Advice on Peak Oxygen Consumption in Patients With Heart Failure With Preserved Ejection Fraction. JAMA. 2021;325:542-551. https://doi.org/10.1001/jama.2020.26812
50. Kitzman DW, Brubaker P, Morgan T, et al. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction. JAMA. 2016;315:36-46. https://doi.org/10.1001/jama.2015.17346
51. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 2023;389(12):1069-1084. https://doi.org/10.1056/NEJMOA2306963
52. Borlaug BA, Kitzman DW, Davies MJ, et al. Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial. Nat Med. 2023;29(9):2358-2365. https://doi.org/10.1038/S41591-023-02526-X
53. Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. N Engl J Med. 2024;390:1394–407. https://doi.org/10.1056/NEJMoa2313917
54. A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction (HFpEF) and Obesity: The SUMMIT Trial. Available at: https://clinicaltrials.gov/study/NCT04847557 [accessed 10 April 2024].
55. Lilly's tirzepatide successful in phase 3 study showing benefit in adults with heart failure with preserved ejection fraction and obesity. Available at: https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-successful-phase-3-study-showing-benefit [accessed 14 August 2024].
56. van Veldhuisen SL, Gorter TM, van Woerden G, et al. Bariatric surgery and cardiovascular disease: a systematic review and meta-analysis. Eur Heart J. 2022;43:1955–69. https://doi.org/10.1093/eurheartj/ehac071
57. Pagel PS, Tawil JN, Boettcher BT, et al. Heart Failure With Preserved Ejection Fraction: A Comprehensive Review and Update of Diagnosis, Pathophysiology, Treatment, and Perioperative Implications. J Cardiothorac Vasc Anesth. 2021;35:1839–59. https://doi.org/10.1053/J.JVCA.2020.07.016
58. Howard PA. Treating Heart Failure with Preserved Ejection Fraction: A Challenge for Clinicians. Hosp Pharm. 2015;50:454–9. https://doi.org/10.1310/HPJ5006-454
59. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME® trial. Eur Heart J. 2016;37:1526–34. https://doi.org/10.1093/eurheartj/ehv728
60. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020;396:819–29. https://doi.org/10.1016/S0140-6736(20)31824-9
61. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385:1451–61. https://doi.org/10.1056/nejmoa2107038
62. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced

Journal Pre-proof

or Preserved Ejection Fraction. N Engl J Med. 2022;387:1089–98. https://doi.org/10.1056/nejmoa2206286

63. Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC Basic to Transl Sci. 2020;5:632–44. https://doi.org/10.1016/j.jacbts.2020.02.004
64. Joshi SS, Singh T, Newby DE, et al. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart. 2021;107:1032–8. https://doi.org/10.1136/heartjnl-2020-318060
65. Butler J, Hamo CE, Filippatos G, et al. The potential role and rationale for treatment of heart failure with sodium–glucose co-transporter 2 inhibitors. Eur J Heart Fail. 2017;19:1390–400. https://doi.org/10.1002/ejhf.933
66. Brito D, Bettencourt P, Carvalho D, et al. Sodium-Glucose Co-transporter 2 Inhibitors in the Failing Heart: a Growing Potential. Cardiovasc Drugs Ther. 2020;34:419–36. https://doi.org/10.1007/s10557-020-06973-3
67. Anker SD, Khan MS, Shahid I, et al. Sodium–glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction: reasons for optimism. Eur J Heart Fail. 2021;23:1250–5.
68. Packer M. Critical Reanalysis of the Mechanisms Underlying the Cardiorenal Benefits of SGLT2 Inhibitors and Reaffirmation of the Nutrient Deprivation Signaling/Autophagy Hypothesis. Circulation. 2022;146:1383–405. https://doi.org/10.1161/CIRCULATIONAHA.122.061732
69. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-Preserved trial. Lancet. 2003;362:777–81. https://doi.org/10.1016/S0140-6736(03)14285-7
70. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019;381:1609–20. https://doi.org/10.1056/nejmoa1908655
71. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2014;370:1383–92. https://doi.org/10.1056/NEJMoa1313731
72. Miller RJH, Howlett JG. Evolving role for mineralocorticoid receptor antagonists in heart failure with preserved ejection fraction. Curr Opin Cardiol. 2015;30:168–72. https://doi.org/10.1097/HCO.0000000000000147
73. Pfeffer MA, Claggett B, Assmann SF, et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. Circulation. 2015;131:34–42. https://doi.org/10.1161/CIRCULATIONAHA.114.013255
74. de Denus S, O'Meara E, Desai AS, et al. Spironolactone Metabolites in TOPCAT — New Insights into Regional Variation. N Engl J Med. 2017;376:1690–2. https://doi.org/10.1056/NEJMc1612601
75. Chilton RJ, Silva-Cardoso J. Mineralocorticoid receptor antagonists in cardiovascular translational biology. Cardiovasc Endocrinol Metab. 2023;12;12(3):e0289. https://doi.org/10.1097/XCE.0000000000000289
76. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023;44:3627–39. https://doi.org/10.1093/eurheartj/ehad195

Journal Pre-proof

77. Filippatos G, Anker SD, Agarwal R, et al. Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial. Circulation. 2022;145:437–47. https://doi.org/10.1161/CIRCULATIONAHA.121.057983
78. Filippatos G, Pitt B, Agarwal R, et al. Finerenone in patients with chronic kidney disease and type 2 diabetes with and without heart failure: a prespecified subgroup analysis of the FIDELIO-DKD trial. Eur J Heart Fail. 2022;24:996–1005. https://doi.org/10.1002/ejhf.2469
79. Study to Evaluate the Efficacy (Effect on Disease) and Safety of Finerenone on Morbidity (Events Indicating Disease Worsening) & Mortality (Death Rate) in Participants With Heart Failure and Left Ventricular Ejection Fraction (Proportion of Blood Expelled Per Heart Stroke) Greater or Equal to 40% (FINEARTS-HF). Available at: https://clinicaltrials.gov/study/NCT04435626 [accessed 10 April 2024].
80. Finerenone meets primary endpoint in Phase III FINEARTS-HF cardiovascular outcomes study in patients with heart failure with mildly reduced or preserved ejection fraction. Available at: https://www.bayer.com/media/en-us/finerenone-meets-primary-endpoint-in-phase-iii-finearts-hf-cardiovascular-outcomes-study-in-patients-with-heart-failure-with-mildly-reduced-or-preserved-ejection-fraction/. [accessed 14 August 2024];
81. Arnold S V., Silverman DN, Gosch K, et al. Beta-Blocker Use and Heart Failure Outcomes in Mildly Reduced and Preserved Ejection Fraction. JACC Hear Fail. 2023;11:893–900. https://doi.org/10.1016/j.jchf.2023.03.017
82. Anker SD, Comin Colet J, Filippatos G, et al. Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency. N Engl J Med. 2009;361:2436–48. https://doi.org/10.1056/NEJMoa0908355
83. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J. 2015;36:657–68. https://doi.org/10.1093/eurheartj/ehu385
84. Mollace A, Macrì R, Mollace R, et al. Effect of Ferric Carboxymaltose Supplementation in Patients with Heart Failure with Preserved Ejection Fraction: Role of Attenuated Oxidative Stress and Improved Endothelial Function. Nutrients. 2022;14:5057. https://doi.org/10.3390/nu14235057
85. López-Vilella R, Lozano-Edo S, Arenas Martín P, et al. Impact of intravenous ferric carboxymaltose on heart failure with preserved and reduced ejection fraction. ESC Hear Fail. 2022;9:133–45. https://doi.org/10.1002/ehf2.13753
86. Effects of Iron Therapy in Heart Failure With Preserved Ejection Fraction and Iron Deficiency (PREFER-HF) (PREFER-HF). Available at: https://clinicaltrials.gov/study/NCT03833336 [accessed 10 April 2024].
87. Effect of IV Iron in Patients With Heart Failure With Preserved Ejection Fraction (FAIR-HFpEF). Available at: https://www.clinicaltrials.gov/study/NCT03074591 [accessed 10 April 2024].
88. Packer M. Drugs That Ameliorate Epicardial Adipose Tissue Inflammation May Have Discordant Effects in Heart Failure With a Preserved Ejection Fraction as Compared With a Reduced Ejection Fraction. J Card Fail. 2019;25:986–1003. https://doi.org/10.1016/J.CARDFAIL.2019.09.002
89. Lingvay I, Brown-Frandsen K, Colhoun HM, et al. Semaglutide for cardiovascular event reduction in people with overweight or obesity: SELECT study baseline characteristics. Obesity. 2023;31:111–22.

Journal Pre-proof

https://doi.org/10.1002/oby.23621

90. EMPAgliflozin in Heart Failure With PReserved Ejection Fraction and End Stage Renal Disease (EMPA-PRED). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT06249945 [accessed 10 April 2024].
91. The Efficacy of Enavogliflozin in Heart Failure With Preserved Ejection Fraction (ENRICH-PEF). Available at: https://clinicaltrials.gov/study/NCT06350487 [accessed 10 April 2024].
92. Freeman MW, Halvorsen YD, Marshall W, et al. Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension. N Engl J Med. 2023;388:395–405. https://doi.org/10.1056/NEJMoa2213169
93. Reddy YN V., Koepp KE, Carter R, et al. Rate-Adaptive Atrial Pacing for Heart Failure With Preserved Ejection Fraction. JAMA. 2023;329:801-809. https://doi.org/10.1001/jama.2023.0675
94. CAtheter-Based Ablation of Atrial Fibrillation Compared to Conventional Treatment in Patients With Heart Failure With Preserved Ejection Fraction (CABA-HFPEF). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05508256 [accessed 10 April 2024].
95. Jagadeesan V, Gray WA, Shah SJ. Atrial Shunt Therapy for Heart Failure: An Update. J Soc Cardiovasc Angiogr Interv. 2023;2(6Part B):101203. https://doi.org/10.1016/j.jscai.2023.101203

Journal Pre-proof