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Pharmacologic Approaches and Evidence in Diagnosing and Treating Heart Failure with Preserved Ejection Fraction: An Updated Review for Pharmacists

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome characterized by heart failure symptoms despite a normal left ventricular ejection fraction (≥50%). HFpEF accounts for nearly half of all heart failure hospitalizations and is associated with significant morbidity and mortality. The pathophysiology of HFpEF is multifactorial, involving impairments in cardiac, pulmonary, vascular, and peripheral function, often driven by comorbidities such as aging, obesity, hypertension, and metabolic disorders. Diagnosis of HFpEF requires the presence of compatible symptoms and signs, elevated natriuretic peptide levels, and objective evidence of cardiac structural and functional alterations. The H2FPEF score and the HFA-PEFF diagnostic algorithm have been proposed to aid in the diagnosis of HFpEF. Despite numerous clinical trials, no pharmacological therapies have consistently demonstrated a reduction in mortality or hospitalizations in HFpEF patients. Current management focuses on symptom relief with diuretics and treatment of comorbidities. Promising therapies under investigation include SGLT2 inhibitors, anti-inflammatory agents, anti-fibrotic drugs, and novel devices targeting interatrial shunting and left atrial pacing. Non-pharmacological interventions, such as exercise training and dietary modifications, have shown improvements in exercise capacity and quality of life in HFpEF patients. Further research is needed to elucidate the complex pathophysiology of HFpEF and develop targeted therapies that improve clinical outcomes in this challenging patient population.

KEYWORDS: HFpEF, pharmacologic therapy, heart failure.

1. Introduction

Heart failure (HF) with preserved ejection fraction (EF; HFpEF) represents a clinical condition marked by HF symptoms despite a "preserved" (i.e., 50%) left ventricular (LV) ejection fraction (LVEF) and is associated with cardiac dysfunction as a primary factor contributing to symptoms (for example, abnormal LV filling and elevated filling pressures). At present, HFpEF impacts around 4.9% of individuals aged ≥60 in the general population and constitutes nearly half of all HF hospitalizations retrospective and observational studies focusing primarily on hospitalized patients, classified according to LVEF alone, indicated that hospitalization and mortality rates among HFpEF patients were comparable to those in patients diagnosed with HF with reduced EF (HFrEF)(Owan et al., 2006; Van Riet et al., 2016). In prospective and randomized studies where HFpEF diagnosis was based on stricter criteria, excluding other causes of HF (such as valvular heart diseases, restrictive or infiltrative cardiomyopathies, and pericardial diseases), cardiovascular (CV) mortality observed in HFpEF was lower than in HFrEF patients (Del Buono et al., 2018).

To date, numerous randomized controlled trials have not identified pharmacological therapies that positively impact clinical outcomes in HFpEF, potentially due to the unfavourable "one-size-fits-all" approach applied to its management (Borlaug, 2020). There is an increasing interest for clinicians and clinical scientists in

understanding the pathophysiological mechanisms underlying HFpEF and its phenotypic diversity, with the hope of developing novel therapeutic strategies. The purpose of the present review is to preview of HFpEF pathophysiology and diagnostic pathways, focusing on recent advances in treatment strategies and their possible applications in clinical practice (Shah et al., 2020).

HFpEF Pathophysiology

HFrEF is defined by distinct cardiac abnormalities, with a central feature of impaired LV systolic function, while HFpEF has conventionally been diagnosed as a clinical HF syndrome occurring with a normal EF (Braunwald, 2013). Diastolic dysfunction has emerged as central to the drome, with substantial evidence indicating failure of the Frank-Starling mechanism, defined as the inability to translate an increase in LV filling pressure into an increase in cardiac output or doing so only with abnormally elevated filling pressures (Borlaug, 2014). Key determinants of diastolic dysfunction include impaired Lon (impaired lusitropy) and/or increased LV stiffness (decreased compliance), both of which frequently co-exist, leading to increased LV end-diastole and hindered ventricular filling, as indicated by changes in the LV pressure-volume loop. In recent years, however, there has been a shift in perspective from HFpEF as HF" to a complex multiorgan syndrome caused by a combination of multiple significant abnormalities, which often co-occur. These include LV systolic dysfunction (reduced LV long-axis systolic function), right ventricular systolic dysfunction, pulmonary hypertension, chronotropic incompetence (CI)/autonomic dysfunction, atrial dysfunction (reduced left atrial [LA] reservoir and contractile function), systemic vascular dysfunction, pericardial restraint, abnormal cardiorenal interaction, and peripheral abnormalities (skeletal muscle dysfunction) (Del Buono, Arena, et al., 2019; Houstis et al., 2018). Many of these abnormalities are not noticeable at rest but manifest only under physiological reserve capacity. These impairments in cardiac, pulmonary, vascular, and peripheral reserve can be attributed to common risk factors like ageing, obesity, hypertension, and systemic metabolic disorders (Abudiab et al., 2013). A unifying hypothesis suggests that a pro-inflammatory environment driven by systemic multimorbidity may promote widespread micro vascular inflammation, leading to microvascular rarefaction and cardiac and extracardiac fibrosis that jointly contribute to the development and progression of HFpEF (Pfeffer et al., 2019). Notably, patients presenting with HF, LVEF ≥50%, and symptoms resulting from an identifiable cause of diastolic dysfunction and exercise intolerance as HFpEF but rather as "HFpEF mimics" or "secondary" HFpEF (e.g., due to valvular, myocardial, or pericardial diseases) (Borlaug, 2020). Classifying these secondary HFpEF phenotypes is crucial for selecting the most appropriate treatment, which can significantly improve symptoms. Additionally, the prognostic outlook considerably depending on the underlying pathology, which may be treatable (e.g., valvular heart disease, pericardial disease) or untreatable (e.g., restrictive cardiomyopathy following radiotherapy).

HFpEF Definition and Diagnostic Algorithm

According to the most recent guidelines from the European Society of Cardiology (ESC), the diagnosis of HFpEF requires the presence of compatible symptoms and signs, a “preserved” EF (defined as LVEF ≥50%), elevated levels of natriuretic

peptides (brain natriuretic peptide [BNP] >35 pg/mL and/or N-terminal-pro hormone BNP [NT-proBNP] >125 pg/mL), and objective evidence of cardiac functional and structural alterations consistent with HF . In cases where there is diagnostic uncertainty, stress testing or invasive measures of elevated LV filling pressures may be necessary (Obokata, Kane, et al., 2017; Ponikowski et al., 2016).

Over recent years, additional diagnostic criteria have been suggested, emphasizing an integrated approach (Reddy et al., 2018). In 2018, Reddy et al. introduced a novel scoring system, the H2FPEF score, designed to differentiate HFpEF from non-cardiac causes of dyspnea. The H2FPEF score (ranging from 0 to 9) is derived from universally accessible criteria and includes six clinical and echocardiographic parameters: obesity (body mass index [BMI] >30 kg/m²), 2 points; atrial fibrillation (AF), 3 points; age >60 years, 1 point; treatment with two or more antihypertensive drugs, 1 point; E/e' ratio >9, 3 points; and pulmonary artery systolic pressure >35 mmHg, 1 point . The H2FPEF score's primary advantage is that it accurately estimates the probability of HFpEF as the cause of symptoms, guiding further diagnostic evaluation (Reddy et al., 2018). A low score (0–1) correlates with a pretest probability of <20%, making HFpEF diagnosis unlikely and pointing to non-cardiac causes of symptoms. In contrast, a high score (6–9) correlates with a >90% probability of HFpEF, strongly suggesting its diagnosis. Patients with intermediate scores (2–5) require further assessment for a conclusive diagnosis (Reddy et al., 2018).

Some H2FPEF criteria, such as older age and obesity, are non-specific to HFpEF and are often observed in populations without the disease (Del Buono, Carbone, et al., 2019). Consequently, the score should only be applied clinically as initially studied: to patients presenting with unexplained dyspnea.

Recently, the Heart Failure Association (HFA) of the ESC released a consensus document with updated information on HFpEF pathophysiology and diagnostics, which introduced the HFA-PEFF diagnostic algorithm (Pieske et al., 2019). This algorithm uses a stepwise approach in four stages. Step 1 (P=Pre-test assessment) takes place in an outpatient setting and involves evaluating HF symptoms and signs, clinical characteristics associated with the HFpEF phenotype, laboratory testing (including NT-proBNP values), and electrocardiography. When overt non-cardiac causes of dyspnea are absent, HFpEF is suspected if LVEF is normal (>50%), there is no significant valvular disease or ischemia, and at least one typical risk factor is present. Elevated natriuretic peptide levels support diagnosis, but normal levels do not exclude HFpEF, as NT-proBNP increases are generally less pronounced in HFpEF than in HFrEF due to factors like high obesity prevalence (which associates with greater clearance and reduced synthesis of natriuretic peptides) and elevated LV filling pressures that appear only during exercise testing (especially in early syndrome stages) (Obokata, Reddy, et al., 2017).

Upon completing the initial assessment, Step 2 (E: Echocardiography and Natriuretic Peptide Score) follows. This stage requires input from a cardiovascular or HF specialist, as it includes comprehensive echocardiography. To enhance specificity, higher natriuretic peptide thresholds are recommended as a primary criterion, with

stratification based on sinus rhythm or AF. As previously noted, normal natriuretic peptide levels do not definitively rule out HFpEF in cases of clinical suspicion, which necessitates further evaluation (e.g., hemodynamic exercise testing) (Obokata, Kane, et al., 2017).

Using echocardiographic functional, morphological, and biomarker domains, major (2 points) and minor (1 point) criteria were established to create a comprehensive scoring system, with each domain contributing up to 2 points. A score ≥5 indicates a definitive HFpEF diagnosis, whereas ≤1 suggests an unlikely diagnosis. An intermediate score (2–4 points) indicates diagnostic uncertainty, warranting Step 3 (F1: Functional testing) with echocardiographic or invasive hemodynamic exercise stress tests. The latter is currently considered the "gold standard" for HFpEF diagnosis due to its high accuracy and its capability for early detection. A recent study involving 267 individuals with normal filling pressures at rest found that 45% exhibited elevated filling pressures only during invasive hemodynamic exercise testing (Reddy et al., 2018). Finally, Step 4 (F2: Final etiology) is recommended to identify any specific "secondary" cause of HFpEF or alternative explanations for symptoms (Pieske et al., 2019). The HFA consensus document underscores the importance of distinguishing between “primary” and “secondary/masquerade” HFpEF forms.

Pharmacological and Non-Pharmacological Treatments of HFpEF

Currently, no treatment has been shown to reduce clinical events such as cardiovascular or all-cause mortality in HFpEF. Therefore, guidelines only recommend diuretics for fluid management and symptom relief (e.g., edema (Adamson et al., 2014)) and the management of comorbidities (e.g., hypertension, obesity, chronic obstructive pulmonary disease) (Ponikowski et al., 2016). Treatments such as beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor-neprilysin inhibitors (ARNIs) have not met their primary endpoints in cardiovascular outcomes trials, although some have shown potential benefits in secondary outcomes. The lack of effective therapeutic options on clinical outcomes is likely due to the complexity of HFpEF pathophysiology; various factors can contribute to HFpEF development and progression, and new pathophysiological pathways are being investigated as potential therapeutic targets. Additionally, innovative interventional devices and techniques have shown promising results.

Pharmacological Treatments

Beta-blockers

While BBs have consistently demonstrated reductions in death and hospitalizations among HFrEF patients (EF <35%), this benefit has not been observed in HFpEF patients. In the SENIORS trial (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure), which evaluated nebivolol, a beta-1-selective antagonist with vasodilatory properties, in elderly HF patients, approximately one-third of whom had an EF >35% (Flather et al., 2005), nebivolol improved the composite outcome of death or cardiovascular

hospitalization. This benefit appeared to be similar among HF patients with both impaired and preserved EF; however, all-cause mortality was not reduced. The ELANDD study (The Effect of Long-term Administration of Nebivolol on clinical symptoms, exercise capacity, and left ventricular function in patients with Diastolic Dysfunction), which examined nebivolol's effects in an HFpEF population (LVEF >45%), found that nebivolol treatment did not improve the 6-minute walk distance (6MWD), peak oxygen consumption (VO2), New York Heart Association (NYHA) classification, or Minnesota Living with HF questionnaire scores when compared with placebo (Conraads et al., 2012; Flather et al., 2005). The JDHF study (Japanese Diastolic Heart Failure Study), which included HFpEF patients (LVEF >40%), found no reduction in the primary composite outcome (cardiovascular or all-cause death and unplanned hospitalization for cardiovascular causes) with carvedilol compared to placebo (Yamamoto et al., 2013). Finally, a patient-level meta-analysis of 11 randomized controlled trials of BBs in HF patients revealed no evidence of benefit in the subgroup of patients in sinus rhythm with LVEF ≥50% (Cleland et al., 2018).

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)

ACEIs and ARBs are critical pharmacotherapies in counteracting maladaptive overactivation of the renin-angiotensin-aldosterone system (RAAS) in heart failure with reduced ejection fraction (HFrEF). However, three randomized controlled trials focused on heart failure with preserved ejection fraction (HFpEF) did not achieve positive outcomes in HFpEF cohorts. These trials include the Candesartan in Patients with Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction (CHARM preserved (Yusuf et al., 2003)) perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) (Cleland, 2006), and Irbesartan in heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) (Massie et al., 2008).

The CHARM- Preserved randomized 3023 patients with New York Heart Association (NYHA) class II–IV heart failure, a history of cardiac hospitalization, and an LVEF >40% (according to site reports) to receive either candesartan or a placebo. After a median follow-up of 36.6 months, the primary composite endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF) occurred in 22% of patients in the candesartan group compared to 24% in the placebo group (hazard ratio [HR], 0.89; 95% confidence interval [CI]: 0.77–1.03; P = 0.12), with a statistically significant reduction in HF hospitalizations in the candesartan group (adjusted HR 0.84; 95% CI: 0.70–1.00; P = 0.047).

The PEP-CHF trial included 850 HF patients aged ≥70 years, each with an LVEF >40% and evidence of diastolic dysfunction on echocardiography and randomized them to perindopril or placebo. With an average follow-up of 26.2 months, perindopril did not reduce the primary composite endpoint of all-cause mortality and HF hospitalization (HR, 0.92; CI: 0.70–1.21; P = 0.55), nor the secondary endpoint of HF hospitalization alone (HR, 0.86; CI: 0.61–1.20; P = 0.38). Patients receiving perindopril showed improvements in NYHA functional class and in 6-minute walking distance (6MWD). However, the trial was underpowered due to lower-than-expected enrolment, event rates, and a high rate of treatment discontinuation in the

perindopril group.

In the I-PRESERVE trial, 4128 individuals aged ≥60 years with NYHA class II–IV HF and an LVEF ≥45% were randomized to receive either irbesartan or placebo. No improvement was observed in the primary endpoint of all-cause mortality or CV hospitalization, nor in any prespecified secondary endpoints (Massie et al., 2008).

In conclusion, although RAAS inhibition theoretically appears justified in HFpEF, clinical outcomes have largely been neutral, with only a slight positive signal from candesartan for reducing HF hospitalizations (Yusuf et al., 2003).

Mineralocorticoid receptors (MRAs)

MRAs including spironolactone and eplerenone, have demonstrated efficacy in reducing overall mortality and hospitalizations for HFrEF (Pitt et al., 1999; Zannad et al., 2011). In the ALDO-DHF study, MRAs improved measures of diastolic function but did not impact maximal exercise capacity, symptoms, or quality of life (QoL) in patients with HFpEF (Edelmann et al., 2013). The TOPCAT trial (Treatment of Preserved Cardiac Function with an Aldosterone Antagonist) randomized 3445 HF patients with LVEF ≥45% to receive either spironolactone or placebo (Pitt et al., 2014). At a mean follow-up of 3.3 years, there was no significant difference outcome of CV death, aborted cardiac arrest, or HF hospitalizations (HR, 0.89; CI: 0.77–1.04; P = 0.14), though a reduction in the secondary endpoint of HF hospitalizations favoured spironolactone (HR, 0.83; CI: 0.69–0.99; P = 0.04). A significant interaction was noted based on geographic location, with patients in the Americas experiencing reduced primary outcome events (HR, 0.82; CI: 0.69–0.98; P = 0.03), unlike those in Russia or Georgia, where event rates were low. Ongoing studies, such as the SPIRRIT trial (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction, aim to clarify spironolactone's therapeutic efficacy (Pitt et al., 2014).

The STRUCTURE study (Spironolactone in myocardial dysfunction with reduced capacity) found that six months of spironolactone treatment improved exercise capacity in HFpEF patients with NYHA class II–III symptoms and an elevated exertional E/e' ratio (>13). This improvement in exercise capacity, measured by cardiopulmonary exercise testing parameters, seemed to correlate with better E/e' ratios during exertion. By enrolling patients with elevated exertional E/e' ratios, while excluding those with atrial arrhythmias and ischemic heart disease, the study may have selected a subgroup more responsive to MRAs (Kosmala et al., 2016).

Angiotensin receptor-neprilysin inhibitors (ARNI)

ARNI specifically sacubitril/valsartan, RAAS inhibition and enhancement of endogenous vasoactive peptides. The PARAGON-HF trial (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) (McMurray et al., 2014; Solomon et al., 2019), conducted after sacubitril/valsartan's success in HFrEF in the PARADIGM-HF study and its NT-proBNP-lowering effects in HFpEF patients in the PARAMOUNT trial, assigned 4822 HFpEF patients with LVEF ≥45% to either sacubitril/valsartan or valsartan alone (Solomon et al., 2019). of total HF hospitalizations and CV death saw a 13% relative reduction, missing statistical significance a narrow margin (rate ratio [RR] 0.87; 95% CI: 0.75–1.01; P =

0.06). Secondary analyses indicated a modest reduction in HF hospitalization rates with sacubitril/valsartan (RR 0.85; CI: 0.72–1.00).

Notably, subgroup analyses revealed a significant primary endpoint reduction in patients with an EF below the 57% median (RR 0.78; CI: 0.64–0.95) and among women (RR 0.73; CI: 0.59–0.90) (Del Buono et al., 2020; O'Connor & deFilippi, 2019). A recent post-hoc analysis of PARAGON-HF demonstrated an efficacy gradient, with greater relative risk reduction in primary events for p 30 days of prior hospitalization, underscoring the potential advantage of early intervention with sacubitril/valsartan in high-risk periods (Vaduganathan et al., 2020; Ventura et al., 2020). The PARAGLIDE-HF study (Safety and Tolerability of In-hospital Initiation of LCZ696 Compared to Valsartan in HFpEF Patients with Acute Decompensated Heart t Failure [ADHF] Who Have Been Stabilized During Hospitalization will assess sacubitril-valsartan's effects on natriuretic peptides within 4–8 weeks for HFpEF patients hospitalized for acute decompensated HF.

Digoxin

Digoxin is among the oldest and least expensive drugs for HF management, retains a role in managing HFrEF and atrial fibrillation by reducing ventricular rate. The Ancillary Digitalis Investigation Group (DIG) trial examined digoxin's impact on ambulatory patients in sinus rhythm with HF and LVEF >45% compared to placebo but found no significant effect on HF mortality or HF hospitalization as a primary endpoint (Ahmed et al., 2006).

Ivabradine

a selective sinus node inhibitor, has shown beneficial effects in HFrEF patients with LVEF ≤35% and sinus heart rates ≥70 beats per minute who were on beta-blockers in the EDIFY trial (prEserveD left ventricular ejection fraction chronic heart Failure with ivabradine Study), ivabradine failed to improve diastolic function, exercise capacity, NP levels in HFpEF patients after eight months of treatment (Komajda et al., 2017).

Nitrates

In HFpEF, the presence of comorbidities contributes to a low-grade systemic inflammatory state that results in endothelial dysfunction and a consequent reduction in nitric oxide (NO) synthesis. This deficiency in NO impairs stimulation of soluble guanylate cyclase (sGC), which then reduces cyclic guanosine monophosphate (cGMP) and protein kinase G (PKG) signalling (Greene et al., 2013). Studies have shown that the cGMP pathway is essential for cardiovascular functionality, and its activity is notably decreased in HF, including HFpEF [48]. In initial clinical trials aimed at restoring intracellular cGMP signalling, the NEAT-HFpEF study (Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction) investigated isosorbide mononitrate, and the INDIE-HFpEF trial (Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure with Preserved Ejection Fraction) evaluated inhaled inorganic nitrite. Unfortunately, both trials failed to demonstrate improved exercise tolerance; in NEAT-HFpEF, a decrease in overall

physical activity measured by an accelerometer was observed (Redfield et al., 2015). Ongoing trials are testing oral inorganic nitrate/nitrite formulations in HFpEF the lack of significant benefits may be attributed to the limitations inherent in NO substitution via nitrates, such as tolerance, pseudo-tolerance, paradoxical endothelial dysfunction, or issues with nitrite inhalation delivery devices (Borlaug, Anstrom, et al., 2018).

Phosphodiesterase-5 Inhibitors

The phosphodiesterase-5a (PDE-5a) isoform, known to break down cGMP, which is integral to NO and natriuretic peptide signalling, has been targeted by PDE-5 inhibitors such as sildenafil (Bishu et al., 2011). In a single-center trial involving 44 HFpEF patients (LVEF ≥50%) with pulmonary hypertension (systolic pulmonary artery pressure > 40 mmHg), sildenafil improved hemodynamic parameters and quality of life (QoL) after 6 and 12 months. However, these results were not replicated in the larger, multi-center RELAX trial, which found no benefits of sildenafil for HFpEF patients regardless of pulmonary hypertension status (Komajda et al., 2017; Redfield et al., 2013). It was hypothesized that sildenafil might still benefit HFpEF patients with comorbid pulmonary hypertension, but subsequent smaller trials failed to observe any hemodynamic or clinical improvements in this subgroup (Hoendermis et al., 2015). The limited efficacy might be due to impaired endothelial NO synthase function, which results in insufficient endogenous cGMP production rather than excessive PDE-5-mediated cGMP breakdown. This insight has led to interest in direct sGC stimulators, which can enhance cGMP production independently of NO.

Soluble Guanylate Cyclase (sGC) Activators

Vericiguat, an sGC stimulator, was tested in the phase II SOCRATES-PRESERVED trial, where it did not reduce NT-proBNP levels or left atrial (LA) volume, which were the prespecified endpoints over a 12-week period. Despite this, post-hoc analyses suggested significant improvements in the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, highlighting improvements in patient-relevant health measures. The recently concluded VITALITY-HFpEF trial (Evaluate the Efficacy and Safety of the Oral sGC Stimulator Vericiguat to Improve Physical Functioning in Daily Living Activities of Patients with Heart Failure and Preserved Ejection Fraction, NCT03547583) was designed to explore whether vericiguat can enhance physical function in HFpEF patients, though the findings have not yet been published (Pieske et al., 2017).

Iloprost

Iloprost, a prostacyclin analogue, causes vasodilation in systemic and pulmonary circulation, limits vascular smooth muscle proliferation, and can reduce pulmonary vascular resistance with long-term use (Lang & Gaine, 2015). The ILO-HOPE trial (Inhaled Iloprost and Exercise Hemodynamics and Ventricular Performance in Heart Failure with Preserved Ejection Fraction, is an ongoing double-blind, randomized, placebo-controlled study wherein HFpEF participants undergo invasive hemodynamic testing before and after treatment with either inhaled iloprost or a placebo during exercise. A preliminary study in ILO-HOPE participants revealed

that inhaled iloprost before exercise enhanced left ventricular (LV) systolic performance, assessed by global longitudinal systolic strain (GLS), and decreased LV diastolic filling load, as evidenced by improvements in E/Strain Rate during isovolumic relaxation and pulmonary pressures estimated from tricuspid regurgitation gradient (Huang et al., 2020).

Adenosine A1-Agonists

Neladenoson bialanate, a partial agonist of the adenosine A1 receptor, has shown potential in preclinical research to improve mitochondrial function, enhance sarco/endoplasmic reticulum Ca2+ ATPase activity, and optimize energy utilization, all without the typical adverse effects of complete A1 receptor agonists or antagonists (Greene et al., 2016). Such partial agonists have demonstrated benefits for mitochondrial function in skeletal muscle and myocardium, key contributors to exercise intolerance in HFpEF (Voors et al., 2018). However, phase 2b studies including the PANTHEON trial (A Trial to Study Neladenoson Bialanate Over 20 Weeks in Patients with Chronic Heart Failure with Reduced Ejection Fraction) and PANACHE trial (Partial Adenosine A1 receptor agonist in patients with Chronic Heart failure and preserved Ejection fraction) did not yield significant clinical benefits, with no improvements in exercise capacity in HFpEF patients (Voors et al., 2019, 2019).

SGLT2-Inhibitors

Large-scale clinical trials in patients with type 2 diabetes mellitus have shown that sodium-glucose cotransporter 2 (SGLT2) inhibitors, including dapagliflozin, empagliflozin, and canagliflozin, effectively reduce hospitalization rates for heart failure and, in some cases, lower all-cause mortality and cardiovascular death, particularly with empagliflozin, while similar trends are noted with canagliflozin (Neal et al., 2017; Wiviott et al., 2019; Zinman et al., 2015). Post-hoc analyses of these trials indicate a pronounced benefit in decreasing heart failure events in patients with HFrEF (Figtree et al., 2019; Kato et al., 2019). Notably, these beneficial outcomes appear early in treatment, suggesting that SGLT2 inhibitors may operate through mechanisms beyond those commonly associated with glucose-lowering therapies (Carbone, Dixon, et al., 2018; Verma & McMurray, 2018). SGLT2 inhibitors facilitate osmotic diuresis and natriuresis, leading to favorable hemodynamic effects on cardiac and renal function without activating the RAAS (Carbone, Canada, et al., 2018). Moreover, they interact with the sodium-hydrogen exchanger in the kidneys, potentially helping to counteract the diuretic resistance commonly observed in heart failure. In myocardial tissue, this exchanger is implicated in hypertrophy, fibrosis, remodeling, and systolic dysfunction processes. Additionally, SGLT2 inhibitors may yield metabolic benefits related to myocardial energetics and endothelial function (Kang et al., 2020).

The DAPA-HF trial (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) directly assessed the safety and efficacy of dapagliflozin in patients with HFrEF, finding that dapagliflozin lowered the risk of worsening heart failure or cardiovascular death, even in patients without type 2 diabetes mellitus. This trial also

demonstrated improvements in HF patients' quality of life (QoL) as measured by the KCCQ (McMurray et al., 2019). Two ongoing trials, DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure, and EMPEROR-PRESERVED (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction, are examining whether dapagliflozin and empagliflozin, respectively, can reduce cardiovascular death or heart failure events in HFpEF patients, regardless of diabetes status. However, preliminary results from EMPERIAL-reduced (Exercise Ability and Heart Failure Symptoms in Patients with Chronic Heart Failure with Reduced Ejection Fraction, and EMPERIAL-preserved (Exercise Ability and Heart Failure Symptoms in Patients with Chronic Heart Failure with Preserved Ejection Fraction trials have shown no improvements in exercise capacity, as measured by the 6MWD, in either HFrEF or HFpEF populations after 12 weeks of empagliflozin treatment. Another trial, PRESERVED-HF (Dapagliflozin in Preserved Ejection Fraction Heart Failure, is currently investigating the effects of dapagliflozin on QoL and 6MWD.

Anti-Inflammatory Drugs

Interleukin-1 (IL-1) is a cytokine with a critical role in promoting fever and systemic inflammation (Van Tassell, Toldo, et al., 2013). Early studies have shown that IL-1 exerts cardiodepressant effects on systolic function, decreases cardiac index, and impairs diastolic function by modulating sarcoplasmic reticulum proteins such as phospholamban and calcium-ATPase (Van Tassell et al., 2012; Van Tassell, Seropian, et al., 2013). In the D-HART2 trial (Diastolic Heart Failure Anakinra Response Trial 2), patients with HFpEF treated with anakinra, a recombinant IL-1 receptor antagonist, for 12 weeks showed a reduction in systemic inflammation, as evidenced by lower C-reactive protein (CRP) levels. However, anakinra did not improve aerobic exercise capacity or ventilatory efficiency in these patients (Van Tassell et al., 2018). This finding contrasts with the favorable results of the earlier D-HART pilot study, which may be partly explained by D-HART2's limited sample size and the influence of non-cardiac factors, such as obesity, which can severely restrict exercise capacity and diminish anakinra's potential beneficial effects. Notably, while there was no improvement in aerobic capacity or ventilatory efficiency, anakinra was associated with positive trends in NT-proBNP reduction, increased exercise time, and improved QoL. Further large-scale studies are required to determine whether IL-1 inhibition through anakinra or other agents targeting the IL-1 pathway will prove beneficial for patients with HFpEF.

Anti-Fibrotic Drugs

The pathological similarities between idiopathic pulmonary fibrosis (IPF), where repeated lung injury leads to an overproduction of fibrotic mediators and excessive extracellular matrix deposition, and HFpEF, where comorbidities induce a systemic pro-inflammatory state followed by microvascular endothelial dysfunction and collagen deposition, have led researchers to hypothesize that anti-fibrotic therapies used in IPF may benefit cardiac outcomes in HFpEF (Graziani et al., 2018). In IPF, two large phase III trials, ASCEND (Efficacy and Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis) and INPULSIS (Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients), demonstrated that the

anti-fibrotic agents pirfenidone and nintedanib, respectively, slowed disease progression with manageable side effects (King et al., 2014; Richeldi et al., 2014). Pirfenidone inhibits collagen synthesis stimulated by TGF-β [82], while nintedanib antagonizes receptors for vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) (Varone et al., 2018). Currently, pirfenidone is being tested in the PIROUETTE phase 2 trial involving HFpEF patients (PIRfenidOne in patients with heart Failure and preserved Left Ventricular Ejection fraction).

Iron Supplementation

Iron deficiency is prevalent among HFrEF and HFpEF patients, affecting nearly 50% regardless of anemia status, and it is associated with poorer exercise capacity and functional outcomes, though there are mixed results regarding its impact on hospitalization rates and mortality (Beale et al., 2019; Klip et al., 2013). Due to limited oral absorption and common gastrointestinal side effects, intravenous iron supplementation is currently under investigation in the FAIR-HFpEF trial (Effect of IV Iron in Patients with Heart Failure with Preserved Ejection Fraction, to evaluate its potential to improve exercise capacity, as assessed by the 6MWD test.

Non-pharmacological interventions

Non-pharmacological interventions remain the most effective approach for improving exercise capacity and quality of life (QoL) in HFpEF patients, though the long-term clinical outcomes of these strategies are not yet well-defined.

Lifestyle Interventions

Physical inactivity, low fitness, and obesity are closely linked with HF risk over time and with structural cardiac abnormalities, such as left ventricular (LV) stiffness, which are often seen in HFpEF (Pandey, Garg, et al., 2015; Pandey et al., 2018). Interestingly, the HF risk associated with physical inactivity remains significant across all BMI categories, highlighting the cumulative impact of both obesity and lack of physical activity (Kenchaiah et al., 2009). In HFpEF patients, physical activity has been observed to correlate with improvements in QoL and the six-minute walk distance (6MWD); however, only high-intensity physical activity has shown a significant association with peak oxygen consumption (VO2), as noted in a secondary analysis of the ALDO-DHF trial (Bobenko et al., 2018).

The prevalence of overweight and obesity in HFpEF is high, with over 80% of patients meeting these criteria in most studies, which contributes substantially to exercise limitations. Higher BMI is a stronger predictor for HFpEF than for heart failure with reduced ejection fraction (HFrEF) (Carbone et al., 2016; Kokkinos et al., 2019). Despite its risk factor status, obesity appears to confer a better short- and medium-term prognosis in established HF cases, a phenomenon termed the "obesity paradox," potentially due to BMI's limitations in characterizing obesity severity (Carbone et al., 2017; Carbone, Canada, et al., 2019; Carbone, Elagizi, et al., 2019).

The strong association between physical inactivity, low fitness, obesity, and HFpEF risk underscores the value of lifestyle interventions focused on enhancing exercise

capacity, with the potential to improve clinical outcomes (Billingsley et al., 2019). Supervised exercise programs have shown QoL and exercise capacity benefits in HFpEF patients, though these gains have not correlated with changes in LV systolic or diastolic function, suggesting benefits may arise from extracardiac mechanisms such as improved muscle oxygen utilization or extraction (Pandey, Parashar, et al., 2015). Furthermore, intentional weight loss has demonstrated significant positive effects on hemodynamics and QoL in HFpEF (Reddy et al., 2019; Rodriguez Flores et al., 2017).

Additionally, evidence suggests that dietary improvements, particularly an increase in unsaturated fatty acids, may enhance exercise capacity in HFpEF patients, independent of calorie intake (Carbone, Billingsley, et al., 2019). Combined exercise and diet interventions were examined in a randomized controlled trial by Kitzman et al., revealing an additive benefit on exercise capacity, with a 17.5% improvement in peak VO2 compared to <10% with either exercise or diet alone.

The Training HF trial recently demonstrated that inspiratory muscle training and functional electrical stimulation significantly enhanced exercise capacity (peak VO2) and QoL in HFpEF, without notable changes in echocardiographic diastolic indices, suggesting extracardiac effects (Palau et al., 2019). Further insights into the mechanisms driving the beneficial impacts of physical activity and weight loss could aid in developing more targeted exercise, dietary, and pharmacologic therapies. In summary, active lifestyle changes through exercise and healthy eating should be a core component of HFpEF management, given their broader health benefits and positive impact on exercise capacity.

Interventional and Device Therapies

With limited pharmacological options effectively addressing the altered biological pathways in HFpEF, several mechanical and device-based approaches have been explored to counteract the associated structural maladaptation.

Inter-atrial Shunts

Interatrial shunts are devices designed to lower left atrial (LA) pressure by creating an artificial inter-atrial passage. Devices like the V-Wave® (Rodés-Cabau et al., 2018) and the IASD® (Interatrial Shunt Device (Hasenfuß et al., 2016)) have shown promising safety profiles in initial studies. The REDUCE LAP-HF I trial, a sham-controlled study, randomized 44 patients with an ejection fraction (EF) ≥40% to receive the IASD® or control; the IASD® group showed significant reductions in pulmonary capillary wedge pressure during exercise after one month (Feldman et al., 2018). Enhancements in pulmonary blood flow and oxygen content from septostomy have been associated with improved pulmonary artery function, particularly compliance, in HFpEF patients (Obokata et al., 2019). The REDUCE LAP-HF II trial will further investigate the IASD® device's effects on a primary composite endpoint comprising cardiovascular (CV) mortality, ischemic stroke, HF hospital admissions, and baseline changes in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score at 12 months.

LV Expanders

The LV CORolla® device aims to enhance LV diastolic function, LV filling, and reduce LA pressure via an internal self-expanding mechanism. A clinical trial is underway to assess the safety and feasibility of the CORolla® in HFpEF patients with NYHA class III/IV symptoms, over a 12-month follow-up.

Left Atrial Pacing

HFpEF patients demonstrate increased intra-atrial dyssynchrony and decreased LA systolic and diastolic function, suggesting the "atrial hypothesis" of HFpEF (Sanchis et al., 2015). A pilot study by Laurent et al. inserted a coronary sinus led to actively pace the LA in six HFpEF patients with NYHA III/IV status and atrial dyssynchrony. After three months, pacing improved 6MWD and echocardiographic parameters, with a reversible response upon pacing deactivation. These effects await confirmation in the randomized LEAD study (Laurent et al., 2013).

Rate-Adaptive Pacing

Chronotropic incompetence (CI) is a major limiter of exercise capacity in HFpEF, making it a target for interventions (Borlaug et al., 2006). Trials such as RAPID-HF and PREFECTUS are examining rate-adaptive atrial pacing and cardiac resynchronization therapy (CRT), respectively, to assess their impact on diastolic and systolic echocardiographic indices and exercise capacity in HFpEF patients.

Cardiac Contraction Modulation (CCM)

CCM therapy uses a device like a pacemaker that delivers non-excitatory electrical pulses to the right ventricular septum. A 24-week study is currently investigating CCM therapy’s effect on QoL (KCCQ score) in patients with HFpEF and an EF ≥50%.

Pericardiectomy

Elevated LV filling pressures in HFpEF may be influenced by pericardial restraint, rather than solely by LV diastolic function (Borlaug et al., 2011). Animal models of HFpEF have shown that partial or complete pericardiectomy can reduce these pressures during volume loading (Borlaug et al., 2017). Borlaug et al. demonstrated in a pilot study that surgical pericardiotomy reduced LV filling pressures in humans with HFpEF risk factors and no pericardial disease (Borlaug, Schaff, et al., 2018). A clinical trial is currently assessing pericardiectomy’s safety and long-term efficacy in HFpEF. Further studies are needed to confirm this intervention’s safety and sustained benefit.

2. Conclusion

while various pharmacological and non-pharmacological treatments have been investigated for HFpEF, outcomes remain limited and primarily focused on symptom management rather than mortality reduction. With the complexity of HFpEF’s

pathophysiology involving multiple organ systems and comorbidities, effective therapeutic options are challenging to develop. Promising approaches include SGLT2 inhibitors, anti-inflammatory, and anti-fibrotic therapies, as well as innovative devices like interatrial shunts and LV expanders, which target mechanical dysfunction. Lifestyle modifications, particularly exercise and dietary changes, demonstrate benefits in exercise tolerance and QoL and should be integral to management. Ongoing research into tailored therapies and precision medicine approaches may eventually yield treatments that improve long-term clinical outcomes in HFpEF.

References

Abudiab, M. M., Redfield, M. M., Melenovsky, V., Olson, T. P., Kass, D. A., Johnson, B. D., & Borlaug, B. A. (2013). Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. European Journal of Heart Failure, 15(7), 776–785. https://doi.org/10.1093/eurjhf/hft026

Adamson, P. B., Abraham, W. T., Bourge, R. C., Costanzo, M. R., Hasan, A., Yadav, C., Henderson, J., Cowart, P., & Stevenson, L. W. (2014). Wireless Pulmonary Artery Pressure Monitoring Guides Management to Reduce Decompensation in Heart Failure With Preserved Ejection Fraction. Circulation: Heart Failure, 7(6), 935–944. https://doi.org/10.1161/CIRCHEARTFAILURE.113.001229

Ahmed, A., Rich, M. W., Fleg, J. L., Zile, M. R., Young, J. B., Kitzman, D. W., Love, T. E., Aronow, W. S., Adams, K. F., & Gheorghiade, M. (2006). Effects of Digoxin on Morbidity and Mortality in Diastolic Heart Failure: The Ancillary Digitalis Investigation Group Trial. Circulation, 114(5), 397–403. https://doi.org/10.1161/CIRCULATIONAHA.106.628347

Beale, A. L., Warren, J. L., Roberts, N., Meyer, P., Townsend, N. P., & Kaye, D. (2019). Iron deficiency in heart failure with preserved ejection fraction: A systematic review and meta-analysis. Open Heart, 6(1), e001012. https://doi.org/10.1136/openhrt-2019-001012

Billingsley, H. E., Rodriguez-Miguelez, P., Del Buono, M. G., Abbate, A., Lavie, C. J., & Carbone, S. (2019). Lifestyle Interventions with a Focus on Nutritional Strategies to Increase Cardiorespiratory Fitness in Chronic Obstructive Pulmonary Disease, Heart Failure, Obesity, Sarcopenia, and Frailty. Nutrients, 11(12), 2849. https://doi.org/10.3390/nu11122849

Bishu, K., Hamdani, N., Mohammed, S. F., Kruger, M., Ohtani, T., Ogut, O., Brozovich, F. V., Burnett, J. C., Linke, W. A., & Redfield, M. M. (2011). Sildenafil and B-Type Natriuretic Peptide Acutely Phosphorylate Titin and Improve Diastolic Distensibility In Vivo. Circulation, 124(25), 2882–2891. https://doi.org/10.1161/CIRCULATIONAHA.111.048520

Bobenko, A., Bartels, I., Münch, M., Trippel, T., Lindhorst, R., Nolte, K., Herrmann-Lingen, C., Halle, M., Duvinage, A., Düngen, H., Gelbrich, G., Tschöpe, C., Hasenfuss, G., Wachter, R., Pieske, B., & Edelmann, F. (2018). Amount or intensity? Potential targets of exercise interventions in patients with heart failure with preserved ejection fraction. ESC Heart Failure, 5(1), 53–62. https://doi.org/10.1002/ehf2.12227

Borlaug, B. A. (2014). The pathophysiology of heart failure with preserved ejection fraction. Nature Reviews Cardiology, 11(9), 507–515. https://doi.org/10.1038/nrcardio.2014.83

Borlaug, B. A. (2020). Evaluation and management of heart failure with preserved ejection fraction. Nature Reviews Cardiology, 17(9), 559–573. https://doi.org/10.1038/s41569-020-0363-2

Borlaug, B. A., Anstrom, K. J., Lewis, G. D., Shah, S. J., Levine, J. A., Koepp, G. A., Givertz, M. M., Felker, G. M., LeWinter, M. M., Mann, D. L., Margulies, K. B., Smith, A. L., Tang, W. H. W., Whellan, D. J., Chen, H. H., Davila-Roman, V. G., McNulty, S.,

Desvigne-Nickens, P., Hernandez, A. F., … for the National Heart, Lung, and Blood Institute Heart Failure Clinical Research Network. (2018). Effect of Inorganic Nitrite vs Placebo on Exercise Capacity Among Patients With Heart Failure With Preserved Ejection Fraction: The INDIE-HFpEF Randomized Clinical Trial. JAMA, 320(17), 1764. https://doi.org/10.1001/jama.2018.14852

Borlaug, B. A., Carter, R. E., Melenovsky, V., DeSimone, C. V., Gaba, P., Killu, A., Naksuk, N., Lerman, L., & Asirvatham, S. J. (2017). Percutaneous Pericardial Resection: A Novel Potential Treatment for Heart Failure With Preserved Ejection Fraction. Circulation: Heart Failure, 10(4). https://doi.org/10.1161/CIRCHEARTFAILURE.116.003612

Borlaug, B. A., Jaber, W. A., Ommen, S. R., Lam, C. S. P., Redfield, M. M., & Nishimura, R. A. (2011). Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. Heart, 97(12), 964–969. https://doi.org/10.1136/hrt.2010.212787

Borlaug, B. A., Melenovsky, V., Russell, S. D., Kessler, K., Pacak, K., Becker, L. C., & Kass, D. A. (2006). Impaired Chronotropic and Vasodilator Reserves Limit Exercise Capacity in Patients With Heart Failure and a Preserved Ejection Fraction. Circulation, 114(20), 2138–2147. https://doi.org/10.1161/CIRCULATIONAHA.106.632745

Borlaug, B. A., Schaff, H. V., Pochettino, A., Pedrotty, D. M., Asirvatham, S. J., Abel, M. D., Carter, R. E., & Mauermann, W. J. (2018). Pericardiotomy Enhances Left Ventricular Diastolic Reserve With Volume Loading in Humans: Implications for the Surgical Management of Heart Failure With Preserved Ejection Fraction. Circulation, 138(20), 2295–2297. https://doi.org/10.1161/CIRCULATIONAHA.118.036006

Braunwald, E. (2013). Heart Failure. JACC: Heart Failure, 1(1), 1–20. https://doi.org/10.1016/j.jchf.2012.10.002

Carbone, S., Billingsley, H. E., Canada, J. M., Kadariya, D., Medina De Chazal, H., Rotelli, B., Potere, N., Paudel, B., Markley, R., Dixon, D. L., Trankle, C. R., Van Tassell, B. W., Celi, F. S., & Abbate, A. (2019). Unsaturated Fatty Acids to Improve Cardiorespiratory Fitness in Patients With Obesity and HFpEF. JACC: Basic to Translational Science, 4(4), 563–565. https://doi.org/10.1016/j.jacbts.2019.04.001

Carbone, S., Canada, J. M., Billingsley, H. E., Kadariya, D., Dixon, D. L., Trankle, C. R., Buckley, L. F., Markley, R., Vo, C., Medina De Chazal, H., Christopher, S., Buzzetti, R., Van Tassell, B. W., & Abbate, A. (2018). Effects of empagliflozin on cardiorespiratory fitness and significant interaction of loop diuretics. Diabetes, Obesity and Metabolism, 20(8), 2014–2018. https://doi.org/10.1111/dom.13309

Carbone, S., Canada, J. M., Billingsley, H. E., Siddiqui, M. S., Elagizi, A., & Lavie, C. J. (2019). Obesity paradox in cardiovascular disease: Where do we stand? Vascular Health and Risk Management, Volume 15, 89–100. https://doi.org/10.2147/VHRM.S168946

Carbone, S., Canada, J. M., Buckley, L. F., Trankle, C. R., Dixon, D. L., Buzzetti, R., Arena, R., Van Tassell, B. W., & Abbate, A. (2016). Obesity Contributes to Exercise Intolerance in Heart Failure With Preserved Ejection Fraction. Journal of the American College of Cardiology, 68(22), 2487–2488. https://doi.org/10.1016/j.jacc.2016.08.072

Carbone, S., Dixon, D. L., Buckley, L. F., & Abbate, A. (2018). Glucose-Lowering Therapies for Cardiovascular Risk Reduction in Type 2 Diabetes Mellitus: State-of-the-Art Review. Mayo Clinic Proceedings, 93(11), 1629–1647. https://doi.org/10.1016/j.mayocp.2018.07.018

Carbone, S., Elagizi, A., & Lavie, C. J. (2019). The Obesity Paradox in Cardiovascular Diseases. Journal of Clinical Exercise Physiology, 8(1), 30–40. https://doi.org/10.31189/2165-6193-8.1.30

Carbone, S., Lavie, C. J., & Arena, R. (2017). Obesity and Heart Failure: Focus on the Obesity Paradox. Mayo Clinic Proceedings, 92(2), 266–279. https://doi.org/10.1016/j.mayocp.2016.11.001

Cleland, J. G. F. (2006). The perindopril in elderly people with chronic heart failure (PEP-CHF) study. European Heart Journal, 27(19), 2338–2345. https://doi.org/10.1093/eurheartj/ehl250

Cleland, J. G. F., Bunting, K. V., Flather, M. D., Altman, D. G., Holmes, J., Coats, A. J. S., Manzano, L., McMurray, J. J. V., Ruschitzka, F., Van Veldhuisen, D. J., Von Lueder, T. G., Böhm, M., Andersson, B., Kjekshus, J., Packer, M., Rigby, A. S., Rosano, G., Wedel, H., Hjalmarson, Å., … Beta-blockers in Heart Failure Collaborative Group. (2018). Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: An individual patient-level analysis of double-blind randomized trials. European Heart Journal, 39(1), 26–35. https://doi.org/10.1093/eurheartj/ehx564

Conraads, V. M., Metra, M., Kamp, O., De Keulenaer, G. W., Pieske, B., Zamorano, J., Vardas, P. E., Böhm, M., & Dei Cas, L. (2012). Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: Results of the ELANDD study. European Journal of Heart Failure, 14(2), 219–225. https://doi.org/10.1093/eurjhf/hfr161

Del Buono, M. G., Arena, R., Borlaug, B. A., Carbone, S., Canada, J. M., Kirkman, D. L., Garten, R., Rodriguez-Miguelez, P., Guazzi, M., Lavie, C. J., & Abbate, A. (2019). Exercise Intolerance in Patients With Heart Failure. Journal of the American College of Cardiology, 73(17), 2209–2225. https://doi.org/10.1016/j.jacc.2019.01.072

Del Buono, M. G., Bonaventura, A., Vecchié, A., Wohlford, G. F., Dixon, D. L., Van Tassel, B. W., & Abbate, A. (2020). Sacubitril–Valsartan for the Treatment of Heart Failure: Time for a Paragon? Journal of Cardiovascular Pharmacology, 75(2), 105–107. https://doi.org/10.1097/FJC.0000000000000782

Del Buono, M. G., Buckley, L., & Abbate, A. (2018). Primary and Secondary Diastolic Dysfunction in Heart Failure With Preserved Ejection Fraction. The American Journal of Cardiology, 122(9), 1578–1587. https://doi.org/10.1016/j.amjcard.2018.07.012

Del Buono, M. G., Carbone, S., & Abbate, A. (2019). Letter by Del Buono et al Regarding Article, "A Simple, Evidence-Based Approach To Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction." Circulation, 139(7), 990–991. https://doi.org/10.1161/CIRCULATIONAHA.118.038072

Edelmann, F., Wachter, R., Schmidt, A. G., Kraigher-Krainer, E., Colantonio, C., Kamke, W., Duvinage, A., Stahrenberg, R., Durstewitz, K., Löffler, M., Düngen, H.-D., Tschöpe, C., Herrmann-Lingen, C., Halle, M., Hasenfuss, G., Gelbrich, G., Pieske, B., & Aldo-DHF Investigators, F. T. (2013). Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction: The Aldo-DHF Randomized Controlled Trial. JAMA, 309(8), 781. https://doi.org/10.1001/jama.2013.905

Feldman, T., Mauri, L., Kahwash, R., Litwin, S., Ricciardi, M. J., Van Der Harst, P., Penicka, M., Fail, P. S., Kaye, D. M., Petrie, M. C., Basuray, A., Hummel, S. L., Forde-McLean, R., Nielsen, C. D., Lilly, S., Massaro, J. M., Burkhoff, D., & Shah, S. J. (2018). Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients With Heart Failure]): A Phase 2, Randomized, Sham-Controlled Trial. Circulation, 137(4), 364–375. https://doi.org/10.1161/CIRCULATIONAHA.117.032094

Figtree, G. A., Rådholm, K., Barrett, T. D., Perkovic, V., Mahaffey, K. W., De Zeeuw, D., Fulcher, G., Matthews, D. R., Shaw, W., & Neal, B. (2019). Effects of Canagliflozin on Heart Failure Outcomes Associated With Preserved and Reduced Ejection Fraction in Type 2 Diabetes Mellitus: Results From the CANVAS Program. Circulation, 139(22), 2591–2593. https://doi.org/10.1161/CIRCULATIONAHA.119.040057

Flather, M. D., Shibata, M. C., Coats, A. J. S., Van Veldhuisen, D. J., Parkhomenko, A., Borbola, J., Cohen-Solal, A., Dumitrascu, D., Ferrari, R., Lechat, P., Soler-Soler, J., Tavazzi, L., Spinarova, L., Toman, J., Böhm, M., Anker, S. D., Thompson, S. G., & Poole-Wilson, P. A. (2005). Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure

(SENIORS). European Heart Journal, 26(3), 215–225. https://doi.org/10.1093/eurheartj/ehi115

Graziani, F., Varone, F., Crea, F., & Richeldi, L. (2018). Treating heart failure with preserved ejection fraction: Learning from pulmonary fibrosis. European Journal of Heart Failure, 20(10), 1385–1391. https://doi.org/10.1002/ejhf.1286

Greene, S. J., Gheorghiade, M., Borlaug, B. A., Pieske, B., Vaduganathan, M., Burnett, J. C., Roessig, L., Stasch, J., Solomon, S. D., Paulus, W. J., & Butler, J. (2013). The cGMP Signaling Pathway as a Therapeutic Target in Heart Failure With Preserved Ejection Fraction. Journal of the American Heart Association, 2(6), e000536. https://doi.org/10.1161/JAHA.113.000536

Greene, S. J., Sabbah, H. N., Butler, J., Voors, A. A., Albrecht-Küpper, B. E., Düngen, H.-D., Dinh, W., & Gheorghiade, M. (2016). Partial adenosine A1 receptor agonism: A potential new therapeutic strategy for heart failure. Heart Failure Reviews, 21(1), 95–102. https://doi.org/10.1007/s10741-015-9522-7

Hasenfuß, G., Hayward, C., Burkhoff, D., Silvestry, F. E., McKenzie, S., Gustafsson, F., Malek, F., Van Der Heyden, J., Lang, I., Petrie, M. C., Cleland, J. G. F., Leon, M., & Kaye, D. M. (2016). A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): A multicentre, open-label, single-arm, phase 1 trial. The Lancet, 387(10025), 1298–1304. https://doi.org/10.1016/S0140-6736(16)00704-2

Hoendermis, E. S., Liu, L. C. Y., Hummel, Y. M., Van Der Meer, P., De Boer, R. A., Berger, R. M. F., Van Veldhuisen, D. J., & Voors, A. A. (2015). Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: A randomized controlled trial. European Heart Journal, 36(38), 2565–2573. https://doi.org/10.1093/eurheartj/ehv336

Houstis, N. E., Eisman, A. S., Pappagianopoulos, P. P., Wooster, L., Bailey, C. S., Wagner, P. D., & Lewis, G. D. (2018). Exercise Intolerance in Heart Failure With Preserved Ejection Fraction: Diagnosing and Ranking Its Causes Using Personalized O2 Pathway Analysis. Circulation, 137(2), 148–161. https://doi.org/10.1161/CIRCULATIONAHA.117.029058

Huang, C.-Y., Lee, J.-K., Chen, Z.-W., Cheng, J.-F., Chen, S.-Y., Lin, L.-Y., & Wu, C.-K. (2020). Inhaled Prostacyclin on Exercise Echocardiographic Cardiac Function in Preserved Ejection Fraction Heart Failure. Medicine & Science in Sports & Exercise, 52(2), 269–277. https://doi.org/10.1249/MSS.0000000000002145

Kang, S., Verma, S., Hassanabad, A. F., Teng, G., Belke, D. D., Dundas, J. A., Guzzardi, D. G., Svystonyuk, D. A., Pattar, S. S., Park, D. S. J., Turnbull, J. D., Duff, H. J., Tibbles, L. A., Cunnington, R. H., Dyck, J. R. B., & Fedak, P. W. M. (2020). Direct Effects of Empagliflozin on Extracellular Matrix Remodelling in Human Cardiac Myofibroblasts: Novel Translational Clues to Explain EMPA-REG OUTCOME Results. Canadian Journal of Cardiology, 36(4), 543–553. https://doi.org/10.1016/j.cjca.2019.08.033

Kato, E. T., Silverman, M. G., Mosenzon, O., Zelniker, T. A., Cahn, A., Furtado, R. H. M., Kuder, J., Murphy, S. A., Bhatt, D. L., Leiter, L. A., McGuire, D. K., Wilding, J. P. H., Bonaca, M. P., Ruff, C. T., Desai, A. S., Goto, S., Johansson, P. A., Gause-Nilsson, I., Johanson, P., … Wiviott, S. D. (2019). Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. Circulation, 139(22), 2528–2536. https://doi.org/10.1161/CIRCULATIONAHA.119.040130

Kenchaiah, S., Sesso, H. D., & Gaziano, J. M. (2009). Body Mass Index and Vigorous Physical Activity and the Risk of Heart Failure Among Men. Circulation, 119(1), 44–52. https://doi.org/10.1161/CIRCULATIONAHA.108.807289

King, T. E., Bradford, W. Z., Castro-Bernardini, S., Fagan, E. A., Glaspole, I., Glassberg, M. K., Gorina, E., Hopkins, P. M., Kardatzke, D., Lancaster, L., Lederer, D. J., Nathan, S. D., Pereira, C. A., Sahn, S. A., Sussman, R., Swigris, J. J., & Noble, P. W. (2014). A Phase 3

Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. New England Journal of Medicine, 370(22), 2083–2092. https://doi.org/10.1056/NEJMoa1402582

Klip, Ij. T., Comin-Colet, J., Voors, A. A., Ponikowski, P., Enjuanes, C., Banasiak, W., Lok, D. J., Rosentryt, P., Torrens, A., Polonski, L., Van Veldhuisen, D. J., Van Der Meer, P., & Jankowska, E. A. (2013). Iron deficiency in chronic heart failure: An international pooled analysis. American Heart Journal, 165(4), 575-582.e3. https://doi.org/10.1016/j.ahj.2013.01.017

Kokkinos, P., Faselis, C., Franklin, B., Lavie, C. J., Sidossis, L., Moore, H., Karasik, P., & Myers, J. (2019). Cardiorespiratory fitness, body mass index and heart failure incidence. European Journal of Heart Failure, 21(4), 436–444. https://doi.org/10.1002/ejhf.1433

Komajda, M., Isnard, R., Cohen-Solal, A., Metra, M., Pieske, B., Ponikowski, P., Voors, A. A., Dominjon, F., Henon-Goburdhun, C., Pannaux, M., Böhm, M., & on behalf of the prEserveD left ventricular ejectIon fraction chronic heart Failure with ivabradine studY (EDIFY) Investigators. (2017). Effect of ivabradine in patients with heart failure with preserved ejection fraction: The EDIFY randomized placebo-controlled trial. European Journal of Heart Failure, 19(11), 1495–1503. https://doi.org/10.1002/ejhf.876

Kosmala, W., Rojek, A., Przewlocka-Kosmala, M., Wright, L., Mysiak, A., & Marwick, T. H. (2016). Effect of Aldosterone Antagonism on Exercise Tolerance in Heart Failure With Preserved Ejection Fraction. Journal of the American College of Cardiology, 68(17), 1823–1834. https://doi.org/10.1016/j.jacc.2016.07.763

Lang, I. M., & Gaine, S. P. (2015). Recent advances in targeting the prostacyclin pathway in pulmonary arterial hypertension. European Respiratory Review, 24(138), 630–641. https://doi.org/10.1183/16000617.0067-2015

Laurent, G., Eicher, J. C., Mathe, A., Bertaux, G., Barthez, O., Debin, R., Billard, C., Philip, J. L., & Wolf, J. E. (2013). Permanent left atrial pacing therapy may improve symptoms in heart failure patients with preserved ejection fraction and atrial dyssynchrony: A pilot study prior to a national clinical research programme. European Journal of Heart Failure, 15(1), 85–93. https://doi.org/10.1093/eurjhf/hfs150

Massie, B. M., Carson, P. E., McMurray, J. J., Komajda, M., McKelvie, R., Zile, M. R., Anderson, S., Donovan, M., Iverson, E., Staiger, C., & Ptaszynska, A. (2008). Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction. New England Journal of Medicine, 359(23), 2456–2467. https://doi.org/10.1056/NEJMoa0805450

McMurray, J. J. V., Packer, M., Desai, A. S., Gong, J., Lefkowitz, M. P., Rizkala, A. R., Rouleau, J. L., Shi, V. C., Solomon, S. D., Swedberg, K., & Zile, M. R. (2014). Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. New England Journal of Medicine, 371(11), 993–1004. https://doi.org/10.1056/NEJMoa1409077

McMurray, J. J. V., Solomon, S. D., Inzucchi, S. E., Køber, L., Kosiborod, M. N., Martinez, F. A., Ponikowski, P., Sabatine, M. S., Anand, I. S., Bělohlávek, J., Böhm, M., Chiang, C.-E., Chopra, V. K., De Boer, R. A., Desai, A. S., Diez, M., Drozdz, J., Dukát, A., Ge, J., … Langkilde, A.-M. (2019). Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine, 381(21), 1995–2008. https://doi.org/10.1056/NEJMoa1911303

Neal, B., Perkovic, V., Mahaffey, K. W., De Zeeuw, D., Fulcher, G., Erondu, N., Shaw, W., Law, G., Desai, M., & Matthews, D. R. (2017). Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine, 377(7), 644–657. https://doi.org/10.1056/NEJMoa1611925

Obokata, M., Kane, G. C., Reddy, Y. N. V., Olson, T. P., Melenovsky, V., & Borlaug, B. A. (2017). Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation, 135(9), 825–838. https://doi.org/10.1161/CIRCULATIONAHA.116.024822

Obokata, M., Reddy, Y. N. V., Pislaru, S. V., Melenovsky, V., & Borlaug, B. A. (2017). Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. Circulation, 136(1), 6–19.

https://doi.org/10.1161/CIRCULATIONAHA.116.026807

Obokata, M., Reddy, Y. N. V., Shah, S. J., Kaye, D. M., Gustafsson, F., Hasenfuβ, G., Hoendermis, E., Litwin, S. E., Komtebedde, J., Lam, C., Burkhoff, D., & Borlaug, B. A. (2019). Effects of Interatrial Shunt on Pulmonary Vascular Function in Heart Failure With Preserved Ejection Fraction. Journal of the American College of Cardiology, 74(21), 2539–2550. https://doi.org/10.1016/j.jacc.2019.08.1062

O'Connor, C. M., & deFilippi, C. (2019). PARAGON-HF — Why We Do Randomized, Controlled Clinical Trials. New England Journal of Medicine, 381(17), 1675–1676. https://doi.org/10.1056/NEJMe1912402

Owan, T. E., Hodge, D. O., Herges, R. M., Jacobsen, S. J., Roger, V. L., & Redfield, M. M. (2006). Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. New England Journal of Medicine, 355(3), 251–259. https://doi.org/10.1056/NEJMoa052256

Palau, P., Domínguez, E., López, L., Ramón, J. M., Heredia, R., González, J., Santas, E., Bodí, V., Miñana, G., Valero, E., Mollar, A., Bertomeu González, V., Chorro, F. J., Sanchis, J., Lupón, J., Bayés-Genís, A., & Núñez, J. (2019). Entrenamiento de la musculatura inspiratoria y la electroestimulación muscular funcional en el tratamiento de la insuficiencia cardiaca con función sistólica conservada: Estudio TRAINING-HF. Revista Española de Cardiología, 72(4), 288–297. https://doi.org/10.1016/j.recesp.2018.01.024

Pandey, A., Garg, S., Khunger, M., Darden, D., Ayers, C., Kumbhani, D. J., Mayo, H. G., De Lemos, J. A., & Berry, J. D. (2015). Dose–Response Relationship Between Physical Activity and Risk of Heart Failure: A Meta-Analysis. Circulation, 132(19), 1786–1794. https://doi.org/10.1161/CIRCULATIONAHA.115.015853

Pandey, A., Parashar, A., Kumbhani, D. J., Agarwal, S., Garg, J., Kitzman, D., Levine, B. D., Drazner, M., & Berry, J. D. (2015). Exercise Training in Patients With Heart Failure and Preserved Ejection Fraction: Meta-Analysis of Randomized Control Trials. Circulation: Heart Failure, 8(1), 33–40. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001615

Pandey, A., Patel, K. V., Vaduganathan, M., Sarma, S., Haykowsky, M. J., Berry, J. D., & Lavie, C. J. (2018). Physical Activity, Fitness, and Obesity in Heart Failure With Preserved Ejection Fraction. JACC: Heart Failure, 6(12), 975–982. https://doi.org/10.1016/j.jchf.2018.09.006

Pfeffer, M. A., Shah, A. M., & Borlaug, B. A. (2019). Heart Failure With Preserved Ejection Fraction In Perspective. Circulation Research, 124(11), 1598–1617. https://doi.org/10.1161/CIRCRESAHA.119.313572

Pieske, B., Maggioni, A. P., Lam, C. S. P., Pieske-Kraigher, E., Filippatos, G., Butler, J., Ponikowski, P., Shah, S. J., Solomon, S. D., Scalise, A.-V., Mueller, K., Roessig, L., & Gheorghiade, M. (2017). Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: Results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) study. European Heart Journal, 38(15), 1119–1127. https://doi.org/10.1093/eurheartj/ehw593

Pieske, B., Tschöpe, C., De Boer, R. A., Fraser, A. G., Anker, S. D., Donal, E., Edelmann, F., Fu, M., Guazzi, M., Lam, C. S. P., Lancellotti, P., Melenovsky, V., Morris, D. A., Nagel, E., Pieske-Kraigher, E., Ponikowski, P., Solomon, S. D., Vasan, R. S., Rutten, F. H., … Filippatos, G. (2019). 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). European Heart Journal, 40(40), 3297–3317. https://doi.org/10.1093/eurheartj/ehz641

Pitt, B., Pfeffer, M. A., Assmann, S. F., Boineau, R., Anand, I. S., Claggett, B., Clausell, N., Desai, A. S., Diaz, R., Fleg, J. L., Gordeev, I., Harty, B., Heitner, J. F., Kenwood, C. T., Lewis, E. F., O'Meara, E., Probstfield, J. L., Shaburishvili, T., Shah, S. J., … McKinlay,

S. M. (2014). Spironolactone for Heart Failure with Preserved Ejection Fraction. New England Journal of Medicine, 370(15), 1383–1392. https://doi.org/10.1056/NEJMoa1313731

Pitt, B., Zannad, F., Remme, W. J., Cody, R., Castaigne, A., Perez, A., Palensky, J., & Wittes, J. (1999). The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. New England Journal of Medicine, 341(10), 709–717. https://doi.org/10.1056/NEJM199909023411001

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., Falk, V., González-Juanatey, J. R., Harjola, V.-P., Jankowska, E. A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J. T., Pieske, B., Riley, J. P., Rosano, G. M. C., Ruilope, L. M., Ruschitzka, F., … Van Der Meer, P. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal, 37(27), 2129–2200. https://doi.org/10.1093/eurheartj/ehw128

Reddy, Y. N. V., Anantha-Narayanan, M., Obokata, M., Koepp, K. E., Erwin, P., Carter, R. E., & Borlaug, B. A. (2019). Hemodynamic Effects of Weight Loss in Obesity. JACC: Heart Failure, 7(8), 678–687. https://doi.org/10.1016/j.jchf.2019.04.019

Reddy, Y. N. V., Carter, R. E., Obokata, M., Redfield, M. M., & Borlaug, B. A. (2018). A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation, 138(9), 861–870. https://doi.org/10.1161/CIRCULATIONAHA.118.034646

Redfield, M. M., Anstrom, K. J., Levine, J. A., Koepp, G. A., Borlaug, B. A., Chen, H. H., LeWinter, M. M., Joseph, S. M., Shah, S. J., Semigran, M. J., Felker, G. M., Cole, R. T., Reeves, G. R., Tedford, R. J., Tang, W. H. W., McNulty, S. E., Velazquez, E. J., Shah, M. R., & Braunwald, E. (2015). Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. New England Journal of Medicine, 373(24), 2314–2324. https://doi.org/10.1056/NEJMoa1510774

Redfield, M. M., Chen, H. H., Borlaug, B. A., Semigran, M. J., Lee, K. L., Lewis, G., LeWinter, M. M., Rouleau, J. L., Bull, D. A., Mann, D. L., Deswal, A., Stevenson, L. W., Givertz, M. M., Ofili, E. O., O'Connor, C. M., Felker, G. M., Goldsmith, S. R., Bart, B. A., McNulty, S. E., … Relax Trial, F. T. (2013). Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. JAMA, 309(12), 1268. https://doi.org/10.1001/jama.2013.2024

Richeldi, L., Du Bois, R. M., Raghu, G., Azuma, A., Brown, K. K., Costabel, U., Cottin, V., Flaherty, K. R., Hansell, D. M., Inoue, Y., Kim, D. S., Kolb, M., Nicholson, A. G., Noble, P. W., Selman, M., Taniguchi, H., Brun, M., Le Maulf, F., Girard, M., … Collard, H. R. (2014). Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. New England Journal of Medicine, 370(22), 2071–2082. https://doi.org/10.1056/NEJMoa1402584

Rodés-Cabau, J., Bernier, M., Amat-Santos, I. J., Ben Gal, T., Nombela-Franco, L., García Del Blanco, B., Kerner, A., Bergeron, S., Del Trigo, M., Pibarot, P., Shkurovich, S., Eigler, N., & Abraham, W. T. (2018). Interatrial Shunting for Heart Failure. JACC: Cardiovascular Interventions, 11(22), 2300–2310. https://doi.org/10.1016/j.jcin.2018.07.001

Rodriguez Flores, M., Aguilar Salinas, C., Piché, M.-E., Auclair, A., & Poirier, P. (2017). Effect of bariatric surgery on heart failure. Expert Review of Cardiovascular Therapy, 15(8), 567–579. https://doi.org/10.1080/14779072.2017.1352471

Sanchis, L., Vannini, L., Gabrielli, L., Duchateau, N., Falces, C., Andrea, R., Bijnens, B., & Sitges, M. (2015). Interatrial Dyssynchrony May Contribute to Heart Failure Symptoms in Patients with Preserved Ejection Fraction. Echocardiography, 32(11), 1655–1661.

https://doi.org/10.1111/echo.12927

Shah, S. J., Borlaug, B. A., Kitzman, D. W., McCulloch, A. D., Blaxall, B. C., Agarwal, R., Chirinos, J. A., Collins, S., Deo, R. C., Gladwin, M. T., Granzier, H., Hummel, S. L., Kass, D. A., Redfield, M. M., Sam, F., Wang, T. J., Desvigne-Nickens, P., & Adhikari, B. B. (2020). Research Priorities for Heart Failure With Preserved Ejection Fraction: National Heart, Lung, and Blood Institute Working Group Summary. Circulation, 141(12), 1001–1026. https://doi.org/10.1161/CIRCULATIONAHA.119.041886

Solomon, S. D., McMurray, J. J. V., Anand, I. S., Ge, J., Lam, C. S. P., Maggioni, A. P., Martinez, F., Packer, M., Pfeffer, M. A., Pieske, B., Redfield, M. M., Rouleau, J. L., Van Veldhuisen, D. J., Zannad, F., Zile, M. R., Desai, A. S., Claggett, B., Jhund, P. S., Boytsov, S. A., … Lefkowitz, M. P. (2019). Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. New England Journal of Medicine, 381(17), 1609–1620. https://doi.org/10.1056/NEJMoa1908655

Vaduganathan, M., Claggett, B. L., Desai, A. S., Anker, S. D., Perrone, S. V., Janssens, S., Milicic, D., Arango, J. L., Packer, M., Shi, V. C., Lefkowitz, M. P., McMurray, J. J. V., & Solomon, S. D. (2020). Prior Heart Failure Hospitalization, Clinical Outcomes, and Response to Sacubitril/Valsartan Compared With Valsartan in HFpEF. Journal of the American College of Cardiology, 75(3), 245–254. https://doi.org/10.1016/j.jacc.2019.11.003

Van Riet, E. E. S., Hoes, A. W., Wagenaar, K. P., Limburg, A., Landman, M. A. J., & Rutten, F. H. (2016). Epidemiology of heart failure: The prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. European Journal of Heart Failure, 18(3), 242–252. https://doi.org/10.1002/ejhf.483

Van Tassell, B. W., Arena, R. A., Toldo, S., Mezzaroma, E., Azam, T., Seropian, I. M., Shah, K., Canada, J., Voelkel, N. F., Dinarello, C. A., & Abbate, A. (2012). Enhanced Interleukin-1 Activity Contributes to Exercise Intolerance in Patients with Systolic Heart Failure. PLoS ONE, 7(3), e33438. https://doi.org/10.1371/journal.pone.0033438

Van Tassell, B. W., Seropian, I. M., Toldo, S., Mezzaroma, E., & Abbate, A. (2013). Interleukin-1β induces a reversible cardiomyopathy in the mouse. Inflammation Research, 62(7), 637–640. https://doi.org/10.1007/s00011-013-0625-0

Van Tassell, B. W., Toldo, S., Mezzaroma, E., & Abbate, A. (2013). Targeting Interleukin-1 in Heart Disease. Circulation, 128(17), 1910–1923. https://doi.org/10.1161/CIRCULATIONAHA.113.003199

Van Tassell, B. W., Trankle, C. R., Canada, J. M., Carbone, S., Buckley, L., Kadariya, D., Del Buono, M. G., Billingsley, H., Wohlford, G., Viscusi, M., Oddi-Erdle, C., Abouzaki, N. A., Dixon, D., Biondi-Zoccai, G., Arena, R., & Abbate, A. (2018). IL-1 Blockade in Patients With Heart Failure With Preserved Ejection Fraction: Results From DHART2. Circulation: Heart Failure, 11(8), e005036. https://doi.org/10.1161/CIRCHEARTFAILURE.118.005036

Varone, F., Sgalla, G., Iovene, B., Bruni, T., & Richeldi, L. (2018). Nintedanib for the treatment of idiopathic pulmonary fibrosis. Expert Opinion on Pharmacotherapy, 19(2), 167–175. https://doi.org/10.1080/14656566.2018.1425681

Ventura, H. O., Lavie, C. J., & Mehra, M. R. (2020). Heart Failure With Preserved Ejection Fraction. Journal of the American College of Cardiology, 75(3), 255–257. https://doi.org/10.1016/j.jacc.2019.11.027

Verma, S., & McMurray, J. J. V. (2018). SGLT2 inhibitors and mechanisms of cardiovascular benefit: A state-of-the-art review. Diabetologia, 61(10), 2108–2117. https://doi.org/10.1007/s00125-018-4670-7

Voors, A. A., Bax, J. J., Hernandez, A. F., Wirtz, A. B., Pap, A. F., Ferreira, A. C., Senni, M., Van Der Laan, M., Butler, J., & for the PANTHEON Investigators. (2019). Safety and efficacy of the partial adenosine A1 receptor agonist neladenoson bialanate in patients

with chronic heart failure with reduced ejection fraction: A phase IIb, randomized, double-blind, placebo-controlled trial. European Journal of Heart Failure, 21(11), 1426–1433. https://doi.org/10.1002/ejhf.1591

Voors, A. A., Shah, S. J., Bax, J. J., Butler, J., Gheorghiade, M., Hernandez, A. F., Kitzman, D. W., McMurray, J. J. V., Wirtz, A. B., Lanius, V., Van Der Laan, M., & Solomon, S. D. (2018). Rationale and design of the phase 2b clinical trials to study the effects of the partial adenosine A1-receptor agonist neladenoson bialanate in patients with chronic heart failure with reduced (PANTHEON) and preserved (PANACHE) ejection fraction. European Journal of Heart Failure, 20(11), 1601–1610. https://doi.org/10.1002/ejhf.1295

Wiviott, S. D., Raz, I., Bonaca, M. P., Mosenzon, O., Kato, E. T., Cahn, A., Silverman, M. G., Zelniker, T. A., Kuder, J. F., Murphy, S. A., Bhatt, D. L., Leiter, L. A., McGuire, D. K., Wilding, J. P. H., Ruff, C. T., Gause-Nilsson, I. A. M., Fredriksson, M., Johansson, P. A., Langkilde, A.-M., & Sabatine, M. S. (2019). Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine, 380(4), 347–357. https://doi.org/10.1056/NEJMoa1812389

Yamamoto, K., Origasa, H., Hori, M., & on behalf of the J-DHF Investigators. (2013). Effects of carvedilol on heart failure with preserved ejection fraction: The Japanese Diastolic Heart Failure Study (J-DHF). European Journal of Heart Failure, 15(1), 110–118. https://doi.org/10.1093/eurjhf/hfs141

Yusuf, S., Pfeffer, M. A., Swedberg, K., Granger, C. B., Held, P., McMurray, J. J., Michelson, E. L., Olofsson, B., & Östergren, J. (2003). Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-Preserved Trial. The Lancet, 362(9386), 777–781. https://doi.org/10.1016/S0140-6736(03)14285-7

Zannad, F., McMurray, J. J. V., Krum, H., Van Veldhuisen, D. J., Swedberg, K., Shi, H., Vincent, J., Pocock, S. J., & Pitt, B. (2011). Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. New England Journal of Medicine, 364(1), 11–21. https://doi.org/10.1056/NEJMoa1009492

Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., Mattheus, M., Devins, T., Johansen, O. E., Woerle, H. J., Broedl, U. C., & Inzucchi, S. E. (2015). Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. New England Journal of Medicine, 373(22), 2117–2128. https://doi.org/10.1056/NEJMoa1504720