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Review Article

Current updates on heart failure with preserved ejection fraction

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) remains a diagnostic and treatment challenge with its different phenotypic presentation despite its growing prevalence with associated increase in morbidity and mortality. Traditional approaches of heart failure (HF) management based on the neurohormonal hypothesis targeting the renin-angiotensin-aldosterone (RAAS) inhibition have been highly successful in the treatment of heart failure with reduced ejection fraction (HFrEF) but failed to produce outcome benefits in HFpEF. Recent experimental data and the robust outcome benefits from Sodium-Glucose Co-Transporter 2 inhibitor (SGLT2i) trials shed further light into the cellular hypothesis of HF, probably more so for HFpEF. Contrary to the generalized approach, recent focus of research has shifted to phenotype specific mechanisms, targeting of which are expected to result in better outcomes in the management of HFpEF. Apart from lifestyle modification and the currently available limited therapy with SGLT2i, more cellular level interventions and perhaps gene-specific therapy may hold promise in the future direction of HFpEF treatment.

Key Words: heart failure with preserved ejection fraction; diastolic heart failure; pathophysiology; treatment; sodium-glucose co-transporter 2 inhibitor

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) remains a challenging area given its rise in morbidity and mortality,[1,2] heterogeneity in presentation, incomplete understanding of underlying pathophysiology, diagnostic dilemmas, and limited treatment options to improve survival and quality of life in these patients.[3] Though the overall incidence of HF appears to have stabilized, the incidence and prevalence of HFpEF are rising compared to heart failure with reduced ejection fraction (HFrEF)[1,2] as the population ages along with worsening epidemics of obesity, diabetes, and metabolic syndrome.[3] As seen from the GWTG (Get With The Guidelines) registry, the five-year mortality rate for HFpEF is similar compared to HFrEF, approaching 75.3%.

HFpEF is generally defined as a clinical syndrome of either current or prior history of dyspnea, exercise intolerance, and/or fatigue with preserved left ventricular ejection fraction (LVEF) >50%, and evidence of elevated left ventricular (LV) filling pressures.[4-8] Contrary to prior belief, HFpEF is not synonymous to diastolic heart failure, and the echocardiographic findings of diastolic dysfunction are not sufficient to establish the diagnosis of HFpEF. It is rather considered a systemic syndrome with different phenotypic presentations stemming from varying pathophysiology.[9] Over the last several decades, multiple randomized control trials (RCTs) on HFrEF resulted in significant reduction in mortality and morbidity. Unfortunately, there are not many evidence-based effective therapies available to date to show significant outcome benefits in patients with HFpEF. Because of frequent association with other common comorbities, such as obesity, hypertension, diabetes, coronary artery disease (CAD), atrial fibrillation (AF), chronic kidney disease (CKD), sleep apnea, etc., and an incomplete understanding of underlying pathophysiology, HFpEF presents a diagnostic dilemma that further complicates trial designs and treatment advances in this area.

Though HFpEF was initially considered a disease of diastolic dysfunction due to hypertensive heart disease, over the last two decades, it has evolved as a multimorbid disease condition involving obesity, diabetes, metabolic disorder, CAD, AF, CKD and sleep apnea, etc.[10,11] HFpEF manifests as different phenotypes defined by these multiple comorbidities which trigger functional and structural changes that ultimately lead to the syndrome of HFpEF. However, the underlying cellular and pathophysiological mechanisms are still unclear.

Pathophysiology of HFpEF

HFpEF is a complex pathophysiologic process that involves not only cardiomyocytes but also their surrounding and peripheral cellular structures.[12] Endothelial cell dysfunction (ECD),[13] cardiac hypertrophy,[14] myocardial stiffness,[15] and subsequent myocardial fibrosis[16] are instrumental in HFpEF pathophysiology. Myocardial fibrosis is thought to be the subsequent common pathway regardless of the causative factors. Myocardial fibrotic burden is strongly associated with diastolic dysfunction,[17] arrhythmias,[18] mortality, and hospitalization in patients with HFpEF.[19] Frequently associated with HFpEF, hypertension itself leads to ventricular hypertrophy, myocardial stiffness, and subsequent cardiac fibrosis.[20] Other comorbidities, such as obesity, metabolic syndrome, chronic obstructive lung disease (COPD), CKD, and iron deficiency anemia all are known to trigger systemic inflammatory responses by activation of interleukin 6 (IL-6), tumor necrosis factor -alpha (TNF-alpha), pentraxin 3, and solute suppression of tumorigenicity 2 (sST2).[21,22] This systemic inflammatory state stimulates endothelial production of reactive oxygen species (ROS) resulting in endothelial nitric oxide synthase (eNOS) uncoupling and decreased production of nitric oxide (NO), which in turn lowers cyclic guanosine monophosphate (cGMP) and protein kinase G (PKG). PKG is known to mediate titin phosphorylation facilitating early diastolic recoil and late diastolic distensibility. Abnormalities in the NO-cGMP-PKG axis cause hypophosphorylation of titin leading to myocardial stiffness, impaired lusitropy and decreased diastolic reserve, ventricular hypertrophy, and ultimately myocardial fibrosis.[23,24] Mitochondrial abnormalities as well as impairment in oxygen delivery and utilization also appear to be important pathophysiological factors associated with decreased exercise tolerance in HFpEF.[25]

HFpEF patients are unable to adequately increase myocardial blood flow[26] and have reduced phosphocreatine: adenosine triphosphate (ATP) ratio[27] during exercise. ATP is essential for the detachment of myosin head from actin during diastole, and decreased production of ATP is expected to cause incomplete diastolic relaxation. Such recurring myocardial injury, overtime, can lead to myocardial fibrosis and elevated cardiac filling pressures not only with exercise but also at rest.[24] Over the last several years, multiple studies have demonstrated the close link between coronary microvascular dysfunction (CMD) and HFpEF. The PROMISE-HFpEF (Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction) study has shown that about 75% of patients with HFpEF have CMD along with systemic ECD and increased natriuretic peptide (NP) levels.[28] In another study by Rush et al.,[29] CMD was present in 81% of hospitalized HFpEF patients without any significant CAD. HFpEF patients with impaired coronary flow reserve (CFR) have been shown to have worse clinical outcomes compared to HFpEF patients with normal CFR.[13] CMD has been shown to cause capillary rarefaction[30] and myocardial fibrosis.[31] Subendocardial ischemia and abnormal lusitropy both appear to be causally linked and may potentiate CMD in HFpEF.[24]

In recent years, visceral adiposity, in particular, epicardial adipose tissue (EAT) has drawn increased attention in the pathophysiology of HFpEF.[32,33] EAT has a significant association with functional and structural abnormality of the myocardium normally seen in HFpEF, such as ventricular hypertrophy, diastolic dysfunction, and atrial enlargement.[34-36] Patients with HFpEF who are obese have worse exercise capacity, elevated biventricular filling pressures and lower pulmonary vasodilatory reserve compared with those with nonobese HFpEF and controls.[37] This phenotypic group of HFpEF tends to have more right ventricular (RV) dysfunction, increased pericardial restraint and ventricular interaction due to increased epicardial fat,[37,38] and elevated C-reactive protein levels, suggestive of enhanced systemic inflammation in these patients.[39]

The infiltrative-lipotoxic hypothesis postulates that EAT can potentially penetrate underlying myocardium and cause disruption of underlying myocardial ultrastructure leading to functional impairment[40] and also may secrete proinflammatory adipokines to the underlying tissue either directly or via paracrine pathway causing local and systemic inflammation.[40,41] The pericardial restraint hypothesis suggests that EAT can exert direct mechanical restraint when it accumulates within the pericardium, creating a constrictive pericarditis-type phenomenon.[42] In two studies, EAT was associated with increased cardiac filling pressures and ventricular interdependence caused by pericardial restraint.[42,43]

Based on clinical and experimental data over the last decade, Paulus and Zile proposed an inflammatory hypothesis of HFpEF which consists of the following: metabolic and hemodynamic load-induced proinflammatory signaling stimulating migration of immunocompetent cells into the myocardium, endothelial expression of adhesion molecules in early stages of HFpEF, cross-link between components of extracellular matrix and myocyte titin resulting in abnormal titin breakdown, and accumulation of degraded proteins in the myocardium, all promoting myocardial stiffness and fibrosis that eventually lead to diastolic dysfunction.[44]

Abnormality in cardiac relaxation and increased chamber stiffness contribute to elevated LV filling pressures,[6,45,46] and persistent or intermittent LV filling pressures in HFpEF contribute to chamber remodeling and myocardial dysfunction. In particular, left atrial (LA) remodeling and atrial myopathy may lead to AF, indicative of more advanced HFpEF.[47-49] Moreover, persistent elevation in LA pressure triggers pulmonary hypertension which is seen in almost 80% of HFpEF patients.[50-52]

Since HFpEF appears to have complex pathogenesis and different phenotypic presentations, it is better conceptualized as a converging phenomenon of multiple mechanisms in different organ systems leading to a common hemodynamic disorder of elevated LV filling pressures either at rest or with exercise. The question remains whether the different phenotypic groups represent specific disorders or rather different stages of disease progression of HFpEF.[53,54]

Stages in HFpEF

For better understanding of risk factors and pathophysiologic progression, a recent JACC (Journal of American College of Cardiology) scientific statement by Borlaug et al. compared HFpEF stages to those of HFrEF.[55]

In stage A, most traditional risk factors like age, hypertension, and CAD are similar for both HFpEF and HFrEF,[56] but obesity, sedentary life style and metabolic disorder tend to correlate more to HFpEF than HFrEF.[10,57,58]

While stage B in HFrEF is easily defined as asymptomatic LV systolic dysfunction which triggers initiation of HF management, stage B in HFpEF is still ill-defined. The recent consensus definition of stage B in HFpEF has evolved to include individuals who have no symptoms but have structural heart disease, such as myocardial hypertrophy and chamber enlargement, and elevated filling pressures and abnormal diastolic function, or elevated NP or cardiac enzyme levels.[59] It may be necessary to do exercise tolerance tests in this stage to determine whether patients are truly asymptomatic when they are found to have LV hypertrophy and/or diastolic dysfunction. Even if they have exercise intolerance, it becomes challenging to decide whether this is related to cardiac or non-cardiac reasons. Relying on NP levels is also problematic since about one-third of symptomatic HFpEF patients will have low NP levels,[60] particularly patients who are obese, who represent a significant portion of HFpEF.

Stage C in HFpEF is defined as when patients become symptomatic. However, a significant portion of patients in this stage remains underdiagnosed (about 35%), with unexplained dyspnea as seen in the ARIC (Atherosclerotic Risk in Communities Study) registry.

Stage D patients are overtly symptomatic and have poorer prognosis. More advanced HF therapy or palliative care needs to be considered at this stage.

Step by step approach for diagnosis of HFpEF

HFpEF diagnosis requires signs and symptoms of HF (such as dyspnea, exercise intolerance, and objective evidence of cardiogenic pulmonary edema or systemic congestion) along with preserved LVEF of >50%, and most importantly, elevated LV filling pressures, which are the hallmarks of this disease entity.[4,5,7,8,61]

In earlier stages of HFpEF, LV filling pressures may be normal at rest but are markedly elevated during exercise.[62,63] Elevated LV filling pressures are directly correlated with increased risk of hospitalization and death in HFpEF patients.[64,65] The universal definition of HF falls short in HFpEF since one-third of patients with HFpEF will have low NP or N-terminal pro b-type natriuretic peptide (NT-proBNP) levels as commonly seen in individuals who are obese (below the threshold typically used for HF diagnosis) even with elevated LV filling pressures either with rest or with exercise.[60,66] Normal NP levels cannot exclude HFpEF. Moreover, in about one-third of patients with HFpEF, LV filling pressures could be normal at rest but rise only with exercise.[52] That is why exercise-induced hemodynamic assessment during right heart catheterization became the gold standard to establish or exclude the diagnosis of HFpEF.[59,67-69] Elevated pulmonary capillary wedge pressure (PCWP) at end of expiration >15 mmHg at rest or >25 mmHg with exercise[68] establishes the diagnosis of HFpEF. The relative increase of PCWP to increase in cardiac output >2 mmHg/L/min with exercise is also indicative of HFpEF.[65]

Exercise stress echocardiography may be a noninvasive alternative to invasive hemodynamic exercise testing, but poor-quality image acquisition during exercise and false negative results may limit their use, since a number of patients with HFpEF do not have an increase in E/e' ratio or other HFpEF parameters during exercise.[37,70-72]

HFpEF Scoring systems

Given the difficulty and lack of widely available invasive exercise testing, two well-validated clinical scoring systems have been developed, the "Heavy, Hypertensive, Atrial Fibrillation, Pulmonary Hypertension, Elder, and Filling Pressure" (H_2FPEF) and the "Heart Failure Association Pretest Assessment, Echocardiography and Natriuretic Peptide, Functional Testing, Final Etiology" (HFA-PEFF) algorithms to help determine the likelihood of HFpEF in a patient with dyspnea.[68,73-76]

H_2FPEF scoring[73] (Figure 1) includes: Heavy with body mass index (BMI) >30 kg/m2, Hypertension (2 or more antihypertensive medications), atrial fibrillation, Pulmonary hypertension with estimated pulmonary artery pressure >35 mmHg by echo, Elder (age > 60 years), Filling pressures (E/e' ratio >9 by echo Doppler.[73] A score of >6 is highly diagnostic of HFpEF.

Figure 1. H_2FPEF Score

	Criteria	Points	Score	Probability
H_2	Heavy (BMI >30 kg/m2) Hypertension (≥ 2 antihypertensive medicines	2 1	0-1	Low
F	Atrial Fibrillation (any history)	3	2-5	Intermediate
P	Pulmonary hypertension (PASP >35 mmHg by echo	1		
E	Elder (>60 years)	1	6-9	High
F	Filling pressure (E/e' >9 by echo)	1		

BMI = Body Mass Index; PASP = Pulmonary artery systolic pressure.

→ Hemodynamic Stress Test
Exercise echo or
Invasive hemodynamic measurements

The HFA-PEFF scoring system[68] includes 4 steps (Figure 2).

Figure 2. HFA-PEFF Score

Echo and Biomarkers	Major Criteria (2 Points Max per category)	Minor Criteria (1 Point Max Per Category)	Score	Probability
Echo Functional	Septal e' <7 cm/s Lateral e' <10 cm/s Average E/e' ≥15 TR velocity >2.8 m/s	Average E/e' 9-14 GLS <16%	0-1	Low
Echo Structural	LAVI >35 mL/m2 LVMI >149/122 g/m2 (M/F) RWT >0.42	LAVI 29-34 ml/m2 LVMI >115/95 g/m2 (M/F)	2-4	Intermediate
Natriuretic Peptides (Sinus Rhythm)	NT-proBNP >220 pg/mL BNP >80 pg/mL	NT-proBNP 125-220 pg/mL BNP 35-80 pg/mL		
Natriuretic Peptides (Atrial Fibrillation)	NT-proBNP >660 pg/mL BNP >240 pg/mL	NT-proBNP 365-660 pg/mL BNP 105-240 pg/mL	5-6	High

HFA-PEFF = Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology; TR = Tricuspid regurgitation; GLS = Global longitudinal strain; LAVI = Left atrial volume index; LVMI = Left ventricular mass index; RWT = Relative wall thickness; M = Male; F = Female.

→ Hemodynamic Stress Test
Exercise echo or Invasive hemodynamic measurements

Step 1 is the pretest assessment of clinical signs and symptoms of HF, comorbidities, risk factors and standard echo diagnostic parameters.

Step 2 includes NP levels and comprehensive echo findings as shown in Figure 2.

It is important to note that NP levels are included in HFA-PEFF scoring system and they should be interpreted cautiously since NP levels are generally lower in HFpEF patients compared with those of HFrEF, particularly in HFpEF patients who are obese.[66,77,78] The European Society of Cardiology recommended a lower threshold of NP levels (50% lower cutoff values compared to standard used for diagnosis of HF), though it is still not well validated.[79]

Proceeding to step 3, if HFpEF is still uncertain, patients should undergo diastolic stress testing with exercise stress echo, and if needed, right heart catheterization with exercise hemodynamic assessment for more definitive diagnosis.

Since diastolic exercise stress echo or invasive exercise hemodynamic testing are often not readily available or feasible, if clinically suspected, it is prudent to initiate currently available guideline-directed medical therapy for HFpEF, such as diuretic and SGLT2i therapy and watch for any symptomatic improvement.

Step 4 involves further testing to exclude other cardiac HFpEF mimics, like hypertrophic cardiomyopathy, noncompaction, infiltrative or restrictive cardiac diseases, valvular abnormality, pericardial diseases, or right heart failure due to non-HFpEF etiology, which could be a potential cardiac cause for dyspnea or edema.

Do not miss the diagnosis of HFpEF mimics

It is also important to rule out certain HFpEF mimics for which there may be disease-specific therapy available with proven outcome benefits. As proposed in the ACC Expert Consensus Decision Pathway on the management of heart failure with preserved ejection fraction,[80] a step-wise approach to the assessment of dyspnea and/or edema should be followed to rule out non-cardiac or cardiac mimics of HFpEF. A non-cardiac mimic is defined when a non-cardiovascular entity (such as chronic venous insufficiency, kidney failure, or liver failure) is identified as the primary cause of congestion. If a primary non-cardiac mimic is not identified as the cause for congestion in a patient with preserved EF, then investigations should focus on ruling out cardiac mimics of HFpEF (such as infiltrative/restrictive cardiomyopathy, hypertrophic cardiomyopathy, noncompaction, valvular or pericardial diseases), since treatment options for these diseases are completely different, and certain disease-specific therapy have shown proven benefits for these entities. When non-cardiac and cardiac mimics of HFpEF are excluded as potential causes of exertional dyspnea and/or congestion, HFpEF diagnosis can be established by exclusion, and treatment strategies should be implemented. This does not imply that every individual has to go through extensive testing to rule out unusual cardiomyopathies. Rather often, history, physical examination, and echocardiographic findings may be sufficient to point to a diagnosis or raise suspicion for other myocardial or pericardial diseases which need further investigation (such as cardiac magnetic resonance imaging, invasive hemodynamics, or even endomyocardial biopsy.[80]

The presence of typical comorbidities like obesity, diabetes, hypertension, metabolic syndrome, AF, CAD, CKD and older age definitely will increase the pretest probability of HFpEF in the setting of exertional dyspnea, cardiogenic pulmonary edema, or systemic congestion.[81-83]

Low <1 or high score >6 by either HFpEF algorithms can be used to exclude or establish the diagnosis of HFpEF, respectively. Patients with intermediate probability scores (between 1 to 5 by H_2FPEF or 4 to 6 by HFA-PPEF) should undergo further exercise hemodynamic study, preferably by invasive hemodynamic assessment during right heart catheterization, or if not feasible, by non-invasive exercise stress echo.

Treatment of HFpEF

Given the wide-spectrum of phenotypic presentations of HFpEF, treatment is focused on three specific goals:

The first goal is to risk-stratify and treat comorbidities which are commonly associated with HFpEF, such as hypertension, obesity, diabetes, CAD, AF, CKD, and obstructive sleep apnea, etc.

The second goal is to improve aerobic capacity and quality of life by nonpharmacologic means, such as a gradual exercise program to improve exercise tolerance, diet, and weight loss. The possibility of using remote monitoring of pulmonary artery pressure to assess volume status should be explored. The CHAMPION trial clearly demonstrated 50% reduction in HF hospitalization in HFpEF patients when pulmonary artery pressures were remotely monitored by CardioMEMS Sensors.[84]

The third goal of treatment is to improve symptoms and survival of HFpEF patients. Over the last several decades, despite significant success achieved to improve survival and quality of life in the treatment of HFrEF patients by multiple RCTs targeting neurohormonal RAAS systems, until recently, no trials have shown demonstrable benefits in patients with HFpEF that included beta-blockers,[85,86] angiotensin converting enzyme inhibitors (ACEI),[87] nitrates,[88] ivabradine,[89] and sildenafil,[90] etc.

HFpEF and Exercise

Decreased exercise tolerance is the cardinal feature of HFpEF and is associated with poor quality of life.[91,92] Lower VO2 peak with exercise is observed in HFpEF patients, and peak cardiac output is 30-40% lower compared to healthy subjects.[25,93-95] Current evidence suggests that chronotropic incompetence could be a major factor in the reduced cardiac output with subsequent decrease in VO2 peak response to exercise in HFpEF patients.[93-97] Obokata et al.[98] demonstrated that a steep increase in LV filling pressures with exercise as reflected by sharp increase in PCWP was directly related to the degree of dyspnea and lower VO_2 peak in HFpEF patients.

Exercise training has been proven to be effective to improve quality of life, exercise tolerance, and VO_2 peak in patients with HFpEF,[91,99] and improvement of VO_2 peak could be due to peripheral factors resulting in increased extraction of O_2 from exercising muscles.

A recent meta-analysis by Dieberg et al.[100] reported safety of supervised exercise training in HFpEF patients. Exercise training is a proven nonpharmacologic intervention in HFpEF and should be recommended to all HFpEF patients unless specific contraindication exists.

Pharmacologic Treatment of HFpEF

Diuretics

Loop diuretics are still the mainstay of treatment for volume overload in HFpEF patients since elevated LV filling pressures are a major reason for dyspnea and congestion, and they should be used with caution to relieve congestion and improve symptoms.[101] Since SGLT2i have adjunct diuretic and natriuretic effects, addition of these drugs are beneficial in mild volume overload situations, and may help reduce the dose of a loop diuretic needed to optimize volume status in HFpEF patients.

Beta-blockers and heart rate (HR) dilemma in HFpEF

It is well known that elevated HR in HFrEF with or without HF symptoms is associated with worse outcomes.[102-104] However, the outcome data regarding elevated HR in HFpEF are inconsistent, as some showed favorable,[105-107] while others showed unfavorable results.[108,109]

In a limited study, Watcher et al have shown that acute increases in HR in HFpEF patients by atrial pacing to 120 bpm reduced LV end-diastolic pressure from 17 to 8 mmHg along with drops in end-diastolic, end-systolic, and stroke volumes.[110] Though no acute hemodynamic data of lowering HR in HFpEF patients are available, this is expected to prolong diastolic filling and increase LV filling pressures, which in conjunction with low HR-induced decrease in cardiac output may be detrimental to HFpEF patients who may already have elevated filling pressures. However, pacing-induced increased HR hemodynamics are not exactly the same as exercise induced hemodynamics that involve much more complex physiology, increased adrenergic tone, changes in contractility-relaxation coupling and skeletal muscle pumps, and increased venous return, etc. In contrast to normal subjects, exercise markedly increases filling pressures,[63] often with blunted HR response in HFpEF patients[96] suggesting the presence of chronotropic incompetence in these patients,[101] which can further worsen with beta-blockers. Chronotropic incompetence in HFpEF patients is thought to be related to impaired mitochondrial function resulting in energy depletion in myocardial cells.[111]

The ELANDD (Effects of Long-term Administration of Nebivolol on the Clinical symptoms, Exercise Capacity, and Left Ventricular Function of Patients With Diastolic Dysfunction)[112] and the CIBIS-ELD (Cardiac Insufficiency Bisoprolol Study in Elderly)[113] studies both reported worsening of HFpEF symptoms with beta-blockers. The RCT J-DHF (Japanese Diastolic Heart Failure)[114] trial studying carvedilol in patients with LVEF >50% has been neutral without any beneficial or adverse effects of HFpEF symptoms. Trials with ivabradine also did not provide sustained benefit in HFpEF patients.[115,116] Recently, a large meta-analysis of eleven RCTs has shown no outcome benefits in patients with HFpEF when they are in sinus rhythm.[117] With current clinical evidence, it is reasonable to avoid beta-blockers in HFpEF patients, unless in specific conditions like angina control in ischemic heart disease, post-MI up to 3 years, or rate control in AF.[118]

SGLT2i

Recent clinical trials with SGLT2i have shown significant reduction of cardiovascular (CV) death and hospitalization in all HF patients irrespective of EF.[119] Moreover, the EMPEROR-Preserved (Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction) and DELIVER (Dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction heart failure) trials have shown 18% and 21% relative risk reduction, respectively, in HF hospitalization and CV deaths in patients with HF with EF >40%.[120,121] Dapagliflozin also improved quality of life and exercise tolerance in patients with HFpEF.[122] A meta-analysis of SGLT2i trials also reported sustained reduction in CV death in patients with HF with medium range EF and HFpEF.[119] The SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Participants with Type 2 Diabetes Post Worsening Heart Failure) trial[123] and the more recently conducted EMPULSE (Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized) trial[124] both have shown early initiation of SGLT2i while in-hospital or immediately after discharge resulted in significant reduction in CV deaths and hospitalization for HF irrespective of LVEF.[125] The absolute risk reduction in primary outcome in SGLT2i trials was only 3%, mostly driven by HF hospitalization and not by CV death.[120,121] However, SGLT2i medications are one of the limited therapies available today to treat HFpEF patients and should be initiated early as possible even in hospital setting with acute decompensated HF.[80]

The underlying mechanisms of how SGLT2i benefit HFpEF are likely multifactorial and complex both at cardiac and extracardiac cellular levels, further strengthening the concept of cellular hypothesis of HF.[126] SGLT2i have been shown to increase NO bioavailability and improve ECD.[127,128] In isolated human and murine myocardial tissue, SGLT2i were shown to restore impaired phosphorylation of titin by improving NO-sGC-cGMP-PKG signaling that resulted in decreased diastolic tension and myocardial stiffness.[129-131] In multiple studies, SGLT2i were reported to stabilize ionic imbalances,[132-134] improve metabolism and energetics,[135,136] increase autophagic reflux,[135-139] reduce oxidative stress,[32,140,141] and decrease inflammation.[142,143] All of these beneficial effects of SGLT2i have been shown to not only improve cardiac remodeling, myocardial stiffness, and diastolic function, but also reduce renal deterioration.[123,144-148]

Glucagon-Like Peptide-1 (GLP-1) agonists

In HFpEF patients with obesity with BMI >30 kg/m2, RCTs with GLP-1 agonists semaglutide and tirzepatide have been shown to reduce body weight, the rate of HF hospitalization,[149,150] and improve quality of life,[150,151] but not mortality when compared to control group.[4,149,150,152] Patients with higher BMI >35 kg/m2 benefitted the most.[150] As evidenced by recent trials, in HFpEF patients who are obese, a GLP-1 agonist is now recommended in addition to lifestyle modification for weight loss to improve quality of life, exercise intolerance, and reduce HF hospitalization.

Mineralocorticoid Receptor Antagonist (MRA)

Though the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist)

trial[153] with spironolactone did not show a significant reduction in the primary composite outcome of CV death, aborted cardiac arrest, or hospitalization for HF, likely due to large geographical variability in enrollment of patients, sub-analysis of data from North American patients clearly demonstrated significant reduction in the primary composite endpoint and HF hospitalizations.[154] MRAs have been shown to improve diastolic dysfunction in patients with HFpEF.[153,155] In the FINEARTS trial which included patients with HF with mildly reduced EF and LVEF ≥50%, finerenone reduced the rate of HF hospitalization but not mortality.[156] From a pathophysiological point of view, MRAs are beneficial to HFpEF patients to antagonize the aldosterone effect on fluid retention and blood pressure control and are recommended in most HFpEF patients with careful monitoring of kidney function and potassium levels.

Angiotensin Receptor-Neprilysin Inhibitors (ARNI) and Angiotensin Receptor Blockers (ARB)

ARNI was evaluated in the PARAGON-HF (Prospective Comparison of ARNI With Global Outcomes in HF With Preserved Ejection Fraction) trial,[157] enrolling patients with LVEF >45%, where sacubitril/valsartan combination was compared against valsartan. The primary composite end-point of HF hospitalizations and CV death tended to be lower in the ARNI group but did not meet statistical significance (P = 0.06; HR: 0.87; 95% CI: 0.75-1.01).[157] However, subgroup analysis of this study revealed that individuals with borderline low LVEF (45% to 57%) indeed had statistically significant outcome benefit, and women benefitted the most compared to men.[158] ARNI could be beneficial in HFpEF patients with hypertension, but caution should be applied to those with borderline blood pressure for potential adverse effects, such as hypotension.[157]

ARB is not recommended as a monotherapy for HFpEF patients[159,160] since the CHARM-Preserved trial with candesartan[159] and I-PRESERVE trial with irbesartan[160] did not show outcome benefits in HFpEF patients either for mortality or HF hospitalization. If ARNI is contraindicated or not affordable, ARB could be used in hypertensive HFpEF patients with concomitant diabetes or CKD.

The PEP-CHF (Perindopril in Elderly People With Chronic Heart Failure) trial did not show outcome benefit in patients with HF with LVEF >40%, and currently, ACEI is not considered as a primary treatment option for HFpEF.[87]

Phenotype specific treatment of HFpEF

Different phenotype-variations of HFpEF complicate the design of clinical trials, and indiscriminate enrollment of patients with different phenotypes of HFpEF will likely diminish the likelihood of successful results, unless therapeutic interventions are targeted to specific pathobiological processes related to certain phenotypes of HFpEF. HFpEF appears to be a systemic multiorgan syndrome ultimately elevating LV filling pressures.

Depending on the predominant comorbidities, the following HFpEF phenotypes have been proposed: HFpEF with hypertension, HFpEF with diabetes, HFpEF with obesity, HFpEF with cardiometabolic type, HFpEF with CAD, HFpEF with CKD, HFpEF with left atrial myopathy leading to AF, HFpEF with COPD, HFpEF with OSA, HFpEF with pulmonary hypertension, HFpEF with iron-deficiency anemia, HFpEF in the elderly, HFpEF with chronotropic incompetence, HFpEF with genetic subtype of LV hypercontractilty or hypocontractility despite preserved EF, and HFpEF with molecular subtype with plasminogen activator-1 inhibitor. However, there can be combination of multiple comorbidities in a single patient with HFpEF.

Few therapeutic considerations depending on the specific HFpEF phenotypes

HFpEF with hypertension

Left ventricular hypertrophy and myocardial fibrosis leading to diastolic dysfunction appear to be causally linked to HFpEF with hypertension. The HYVET (Hypertension in the Very Elderly Trial) study with a thiazide-like diuretic indapamide showed a 64% reduction in HF in elderly patients with hypertension.[161] A large-scale systematic review and meta-analysis of 123 trials of antihypertensives regimen also demonstrated a 28% reduction in HF, suggesting a pathophysiological role of hypertension in development of HFpEF.[162] Early initiation of MRA and/or ARNI should be preferred as first line antihypertensive therapy in these HFpEF-hypertension phenotype patients as evidenced by potential benefit seen in TOPCAT[163] and PARAGON-HF[164] trials. Caution should be taken not to lower BP < 120 mmHg in elderly patients with HFpEF as this was associated with worse outcomes seen in the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry,[165] and potassium level should be closely monitored with initiation of an MRA. SGLT2i with its mild antihypertensive effect should also be initiated since it has shown proven benefit in all HFpEF patients.

HFpEF with diabetes

Recently, prevalence of type 2 diabetes is rising in newly diagnosed HFpEF patients,[166] and this increases the risk of mortality and HF hospitalization in these patients independently of other risk factors.[153,157,167,168] Though it is not fully understood how diabetes is causally related to HFpEF, some mechanisms have been proposed. Hyperglycemia causes increased production of glycated end-metabolites which have been reported to promote

interstitial fibrosis and stiffness of the myocardium.[169,170] Because of insulin resistance, there is increased utilization of free fatty acids by the myocardium, increased O2 consumption, and production of free radicals. Furthermore, utilization of free fatty acids results in less production of high energy phosphates that ultimately affect cardiac relaxation.[171] Free fatty acid-induced lipotoxicity causes increased production of inflammatory cytokines, leading to myocardial fibrosis and apoptosis.[172] Inflammation and oxidative stress induced by hyperglycemia are also known to cause CMD and ECD.[173]

SGLT2i trials demonstrated a consistent reduction in HF hospitalization in HFpEF patients regardless of previous history of HF or presence of CAD,[174-177] in patients with diabetic nephropathy[147] and in patients with CKD with or without type 2 diabetes.[123,144] In a recent meta-analysis of six trials in patients with type 2 diabetes given SGLT2i, there was a 22% reduction in CV mortality or HF hospitalization. SGLT2i should be a primary choice in treatment of patient with HFpEF with type 2 diabetes. SGLT2i and ACEI/ARB are preferred for HFpEF patients with diabetes and proteinuria.

HFpEF with CKD

In a recent meta-analysis of eight trials (total of 28,961 patients) with HFrEF and HFpEF, RAAS inhibitors were associated with increased risk of worsening renal failure.[178] However, the SGLT2i, empagliflozin, showed a favorable effect on reducing the rate of GFR decline in the EMPEROR-Preserved trial in patients with HFpEF and CKD.[120] Sacubitril/valsartan also showed a reduction in eGFR decline in patients with HFpEF and CKD patients in PARAGON-HF.[179] Recently, the FINEARTS-HF trial[156] (Study to Evaluate The Efficacy and Safety of Finerenone on Morbidity & Mortality in Participants With Heart Failure and Left Ventricular Ejection Fraction Greater or Equal to 40%) with finerenone showed significant reduction of worsening HF and CV death when compared with placebo. Finerenone was associated with slight increased risk of hyperkalemia and reduced risk of hypokalemia.[156]

HFpEF with obesity

Lifestyle intervention with diet and exercise are recommended for all HFpEF patients. In recent trials with the GLP-1 agonist semaglutide and the combined GLP-1/glucose-dependent insulinotropic polypeptide agonist tirzepatide have shown reductions in HF hospitalization in addition with weight loss in HFpEF patients with or without diabetes.[180,181] It is recommended to start these agents in patients with HFpEF and obesity.

HFpEF with left atrial myopathy leading to AF

Pathophysiological hallmarks of HFpEF are elevated ventricular pressures with subsequent rise in atrial pressures that trigger myocardial remodeling and atrial fibrosis, and that along with inflammatory responses, ultimately lead to atrial myopathy creating a milieu for AF. The prevalence of AF in HFpEF is about 50%, and in fact, many HF hospitalizations of HFpEF patients are due to rapid AF.[182] Beta-blocker use in this specific subgroup of HFpEF patients might be beneficial for rate control. Though early rhythm control either by catheter ablation (CASTLE-AF trial)[183] or with antiarrhythmic drugs or ablation (EAST-AFNET 4 trial)[184] has shown outcome benefits of CV deaths, hospitalization, or worsening HF in any LVEF group, the data specific to HFpEF are still lacking. The ongoing German CABA-HFpEF trial is expected to address the specific question of rhythm control strategy towards the outcome benefits in HFpEF patients.[185]

HFpEF with sleep apnea

The SERVE-HF (Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients With Heart Failure) trial showed increases in all-cause and CV death in patients with HFrEF, but the ADVENT-HF (Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure) trial did not demonstrate differences in all-cause mortality, but rather improved both central and obstructive sleep apnea events.[186] In one small trial with 36 patients with HFpEF, adaptive servo ventilation did improve diastolic dysfunction evaluated by echo parameters and reduced CV events in 6 months. No large-scale trial data are available evaluating the effects of positive pressure mask therapy in patients with HFpEF and sleep apnea. However, with conventional experience, patients should continue CPAP or BiPAP for sleep apnea.

HFpEF with CAD

CAD is a common occurrence in HFpEF patients. In a study of 376 patients hospitalized for HFpEF who underwent coronary angiography, 68% of them were found to have CAD.[187] HFpEF patients with obstructive CAD have been shown to have reduced coronary perfusion pressure, more hemodynamic abnormality with exercise, and elevated troponin levels, and myocardial ischemia is thought to be a potential contributor to cardiac myocyte dysfunction and fibrosis.[98] The overall prevalence of CMD is about 71%[188] and 72%[13] respectively, in two separate studies and also was well documented in the PROMIS-HFpEF (Prevalence of microvascular dysfunction in HFpEF) trial, where 75% of patients had coronary flow reserve <2.5, which was associated with both coronary and systemic ECD and elevated NT-proBNP levels.[28] About two-thirds of patients with HFpEF have documented CAD either by angiographic or autopsy studies, which is a potentially reversible cause of HFpEF.[31,189,190] Evaluation for CAD is imperative when angina or anginal equivalent symptoms are present as well as in the setting of known CAD with new HFpEF symptoms even if angina is not present.[190]

HFpEF with pulmonary hypertension

Pulmonary hypertension is highly prevalent in HFpEF patients, from 31% in PARAGON-HF[191] trial to 83% in the Olmstead County study.[51] In most cases, patients are found to have isolated post-capillary pulmonary hypertension, which does not respond to pulmonary vasodilators compared to those with pre-capillary pulmonary hypertension.[192] However, about 55% of patients might have both pre- and post-capillary pulmonary hypertension[193] that should not be missed, and in a small number of RCT studies, phosphodiesterase inhibitors-5 have been shown to improve hemodynamics, RV function, and exercise capacity in those patients.[194,195]

Gender and race disparity

Recent epidemiologic data suggests that HFpEF is more prevalent in women than in men.[196] There is also significant racial disparity for first HFpEF hospitalization event rates, being the highest in Black women,[197] who are also more likely to be underdiagnosed given the presence of lower NP levels in Black individuals compared to other race/ethnic groups.[198] Women with HFpEF were found to have relatively higher systolic and diastolic stiffness than men at any given age[199], greater reduction of LV longitudinal strain with aging,[200] and enhanced cardiac aging compared to men,[20] along with more impairment in calcium handling[201] and myocardial substrate metabolism compared to men.[202] In a study with volume load with saline in HFpEF patients, the slope of mean PCWP was steeper in women compared to men suggesting more impairment of LV diastolic function in women.[203] Hypertension is more common in women in HFpEF and is associated with increased risk of HF than in men.[204] Women are more prone to have ECD and CMD,[205] which play an important role in the development of HFpEF.[31] As another frequent comorbid condition in HFpEF, AF has been shown to increase the risk HF in women[206] along with hospitalization[207] compared to men. Women with diabetes also have increased risk of HF compared to men (5-fold and 2.4-fold respectively).[208] Obesity and metabolic syndrome are relatively more prevalent in women which have higher association with HFpEF.[209,210] Some unique risk factors for HFpEF in women are multiparity and preeclampsia, which are associated with future predisposition to diastolic dysfunction[211] and increased risk of HF.[212] Analyzing the role of sex in different sub-phenotypic presentation of HFpEF could help us better understand the sex-specific mechanisms of HFpEF to develop specific preventive and treatment options in these patients.

Conclusions

HFpEF is a complex syndrome pathophysiologically modulated by multiple comorbidities, and it appears to have variety of disarray in cellular level functions which are still poorly understood. Currently, SGLT2i and diuretics, including MRA, are considered as primary tools in HFpEF treatment, and efficacy of HFpEF management will vary depending on the specific therapies that target different phenotypic mechanisms of HFpEF. Importantly, patients with unexplained dyspnea should be referred early to HF centers for prompt diagnosis and initiation of treatment. Over the last decades, traditional approaches of HF treatment based on neurohormonal hypothesis targeting the RAAS inhibition have been highly successful in the treatment of HFrEF but failed to produce outcome benefits in HFpEF. Only recently, experimental data and robust outcome benefits from SGLT2 trials shed further light into deeper cellular hypothesis of HF, probably more so for HFpEF. The cellular hypothesis of HF suggests a combination of multiple mechanisms at cellular level that impair NO-sGC-CGMP-PKG signaling, cellular autophagy, and ionic balance, as well as increase oxidative stress and inflammation, etc., eventually leading to myocardial stiffness, fibrosis, remodeling, and diastolic dysfunction. Future therapies targeting those factors at the cellular and/or genetic levels might have greater promise in the treatment of HFpEF. Designing a HFpEF trial is critical, since indiscriminate enrollment of patients with different phenotypes may not show clinically significant outcomes, unless therapeutic interventions are targeted to specific pathophysiological mechanisms related to certain phenotypes of HFpEF.

References:

1. Gerber Y, Weston SA, Redfield MM, et al. A Contemporary Appraisal of the Heart Failure Epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Internal Medicine. 2015;175(6):996-1004. doi:10.1001/jamainternmed.2015.0924

2. Tsao CW, Lyass A, Enserro D, et al. Temporal Trends in the Incidence of and Mortality Associated With Heart Failure With Preserved and Reduced Ejection Fraction. JACC Heart Fail. Aug 2018;6(8):678-685. doi:10.1016/j.jchf.2018.03.006

3. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. Oct 2017;14(10):591-602. doi:10.1038/nrcardio.2017.65

4. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J. Oct 2007;28(20):2539-50. doi:10.1093/eurheartj/ehm037

5. Sharma K, Kass DA. Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies. Circ Res. Jun 20 2014;115(1):79-96. doi:10.1161/CIRCRESAHA.115.302922

6. Borlaug BA, Jaber WA, Ommen SR, Lam CS, Redfield MM, Nishimura RA. Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. Heart. Jun 2011;97(12):964-9. doi:10.1136/hrt.2010.212787

7. Andersen MJ, Borlaug BA. Heart failure with preserved ejection fraction: current understandings and challenges. Curr Cardiol Rep. Jul 2014;16(7):501. doi:10.1007/s11886-014-0501-8

8. Reddy YN, Borlaug BA. Heart Failure With Preserved Ejection Fraction. Curr Probl Cardiol. Apr 2016;41(4):145-88. doi:10.1016/j.cpcardiol.2015.12.002

9. Roh J, Hill JA, Singh A, Valero-Munoz M, Sam F. Heart Failure With Preserved Ejection Fraction: Heterogeneous Syndrome, Diverse Preclinical Models. Circ Res. Jun 10 2022;130(12):1906-1925. doi:10.1161/CIRCRESAHA.122.320257

10. Borlaug BA, Jensen MD, Kitzman DW, Lam CSP, Obokata M, Rider OJ. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. Cardiovascular Research. 2022;118(18):3434-3450. doi:10.1093/cvr/cvac120

11. Ng ACT, Delgado V, Borlaug BA, Bax JJ. Diabesity: the combined burden of obesity and diabetes on heart disease and the role of imaging. Nat Rev Cardiol. Apr 2021;18(4):291-304. doi:10.1038/s41569-020-00465-5

12. Cohen JB, Schrauben SJ, Zhao L, et al. Clinical Phenogroups in Heart Failure With Preserved Ejection Fraction: Detailed Phenotypes, Prognosis, and Response to Spironolactone. JACC Heart Fail. Mar 2020;8(3):172-184. doi:10.1016/j.jchf.2019.09.009

13. Yang JH, Obokata M, Reddy YNV, Redfield MM, Lerman A, Borlaug BA. Endothelium-dependent and independent coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. Eur J Heart Fail. Mar 2020;22(3):432-441. doi:10.1002/ejhf.1671

14. Takimoto E, Champion HC, Li M, et al. Chronic inhibition of cyclic GMP phosphodiesterase 5A prevents and reverses cardiac hypertrophy. Nat Med. Feb 2005;11(2):214-22. doi:10.1038/nm1175

15. Bishu K, Hamdani N, Mohammed SF, et al. Sildenafil and B-type natriuretic peptide acutely phosphorylate titin and improve diastolic distensibility in vivo. Circulation. Dec 20 2011;124(25):2882-91. doi:10.1161/CIRCULATIONAHA.111.048520

16. Calderone A, Thaik CM, Takahashi N, Chang DL, Colucci WS. Nitric oxide, atrial natriuretic peptide, and cyclic GMP inhibit the growth-promoting effects of norepinephrine in cardiac myocytes and fibroblasts. J Clin Invest. Feb 15 1998;101(4):812-8. doi:10.1172/JCI119883

17. Zile MR, Baicu CF, Ikonomidis JS, et al. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. Circulation. Apr 7 2015;131(14):1247-59. doi:10.1161/CIRCULATIONAHA.114.013215

18. 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. Aug 2018;11(8):e006452. doi:10.1161/CIRCEP.118.006452

19. 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. Nov 2019;12(11 Pt 2):2291-2301. doi:10.1016/j.jcmg.2018.11.031

20. Gori M, Lam CS, Gupta DK, et al. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. Eur J Heart Fail. May 2014;16(5):535-42. doi:10.1002/ejhf.67

21. Cherneva Z, Valev D, Youroukova V, Cherneva R. Left ventricular diastolic dysfunction in non-severe chronic obstructive pulmonary disease - a step forward in cardiovascular comorbidome. PLoS One. 2021;16(3):e0247940. doi:10.1371/journal.pone.0247940

22. Huttin O, Fraser AG, Lund LH, et al. Risk stratification with echocardiographic biomarkers in heart failure with preserved ejection fraction: the media echo score. ESC Heart Fail. Jun 2021;8(3):1827-1839. doi:10.1002ehf2.13251

23. Simmonds SJ, Cuijpers I, Heymans S, Jones EAV. Cellular and Molecular Differences between HFpEF and HFrEF: A Step Ahead in an Improved Pathological Understanding. Cells. Jan 18 2020;9(1)doi:10.3390/cells9010242

24. Sinha A, Rahman H, Perera D. Coronary microvascular dysfunction and heart failure with preserved ejection fraction: what are the mechanistic links? Curr Opin Cardiol. Nov 1 2023;38(6):521-526. doi:10.1097/HCO.0000000000001082

25. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol. Apr 1991;17(5):1065-72. doi:10.1016/0735-1097(91)90832-t

26. AbouEzzeddine OF, Kemp BJ, Borlaug BA, et al. Myocardial Energetics in Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. Oct 2019;12(10):e006240.doi:10.1161/CIRCHEARTFAILURE.119.006240

27. Phan TT, Abozguia K, Nallur Shivu G, et al. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. J Am Coll Cardiol. Jul 28 2009;54(5):402-9. doi:10.1016/j.jacc.2009.05.012

28. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. European Heart Journal. 2018;39(37):3439-3450. doi:10.1093/eurheartj/ehy531

29. Rush CJ, Berry C, Oldroyd KG, et al. Prevalence of Coronary Artery Disease and Coronary Microvascular Dysfunction in Patients With Heart Failure With Preserved Ejection Fraction. JAMA Cardiology. 2021;6(10):1130-1143. doi:10.1001/jamacardio.2021.1825

30. Kubis N, Richer C, Domergue V, Giudicelli JF, Levy BI. Role of microvascular rarefaction in the increased arterial pressure in mice lacking for the endothelial nitric oxide synthase gene (eNOS3pt-/-). J Hypertens. Aug 2002;20(8):1581-7. doi:10.1097/00004872-200208000-00021

31. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation. Feb 10 2015;131(6):550-9. doi:10.1161/CIRCULATIONAHA.114.009625

32. Packer M, Lam CSP, Lund LH, Maurer MS, Borlaug BA. 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. Sep 2020;22(9):1551-1567. doi:10.1002/ejhf.1902

33. Rao VN, Fudim M, Mentz RJ, Michos ED, Felker GM. Regional adiposity and heart failure with preserved ejection fraction. Eur J Heart Fail. Sep 2020;22(9):1540-1550. doi:10.1002/ejhf.1956

34. van Woerden G, Gorter TM, Westenbrink BD, Willems TP, van Veldhuisen DJ, Rienstra M. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. Eur J Heart Fail. Nov 2018;20(11):1559-1566. doi:10.1002/ejhf.1283

35. Wong CX, Abed HS, Molaee P, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. J Am Coll Cardiol. Apr 262011;57(17):1745-51. doi:10.1016/j.jacc.2010.11.045

36. van Woerden G, van Veldhuisen DJ, Gorter TM, et al. Importance of epicardial adipose tissue localization using cardiac magnetic resonance imaging in patients with heart failure with mid-range and preserved ejection fraction. Clin Cardiol. Jul 2021;44(7):987-993. doi:10.1002/clc.23644

37. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation. Feb 28 2017;135(9):825-838. doi:10.1161/CIRCULATIONAHA.116.024822

38. Borlaug BA, Reddy YNV. The Role of the Pericardium in Heart Failure: Implications for Pathophysiology and Treatment. JACC Heart Fail. Jul 2019;7(7):574-585. doi:10.1016/j.jchf.2019.03.021

39. Reddy YNV, Lewis GD, Shah SJ, et al. Characterization of the Obese Phenotype of Heart Failure With Preserved Ejection Fraction: A RELAX Trial Ancillary Study. Mayo Clin Proc. Jul 2019;94(7):1199-1209. doi:10.1016/j.mayocp.2018.11.037

40. Nalliah CJ, Bell JR, Raaijmakers AJA, et al. Epicardial Adipose Tissue Accumulation Confers Atrial Conduction Abnormality. J Am Coll Cardiol. Sep 8 2020;76(10):1197-1211. doi:10.1016/j.jacc.2020.07.017

41. Shimokawa H, Ito A, Fukumoto Y, et al. Chronic treatment with interleukin-1 beta induces coronary intimal lesions and vasospastic responses in pigs in vivo. The role of platelet-derived growth factor. J Clin Invest. Feb 1 1996;97(3):769-76. doi:10.1172/JCI118476

42. Gorter TM, van Woerden G, Rienstra M, et al. Epicardial Adipose Tissue and Invasive Hemodynamics in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. Aug 2020;8(8):667-676. doi:10.1016/j.jchf.2020.06.003

43. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and Functional Impact of Epicardial Adipose Tissue in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. Aug 2020;8(8):657-666. doi:10.1016/j.jchf.2020.04.016

44. van Woerden G, van Veldhuisen DJ, Westenbrink BD, de Boer RA, Rienstra M, Gorter TM. Connecting epicardial adipose tissue and heart failure with preserved ejection fraction: mechanisms, management and modern perspectives. Eur J Heart Fail. Dec 2022;24(12):2238-2250. doi:10.1002/ejhf.2741

45. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med. May 6 2004;350(19):1953-9. doi:10.1056/NEJMoa032566

46. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation. Apr 17 2007;115(15):1982-90. doi:10.1161/CIRCULATIONAHA.106.659763

47. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail. Mar 2015;8(2):295-303. doi:10.1161/CIRCHEARTFAILURE.114.001667

48. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial Dysfunction in Patients With Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation. J Am Coll Cardiol. Sep 1 2020;76(9):1051-1064. doi:10.1016/j.jacc.2020.07.009

49. Freed BH, Daruwalla V, Cheng JY, et al. Prognostic Utility and Clinical Significance of Cardiac Mechanics in Heart Failure With Preserved Ejection Fraction: Importance of Left Atrial Strain. Circ Cardiovasc Imaging. Mar 2016;9(3) doi:10.1161/CIRCIMAGING.115.003754

50. Verbrugge FH, Guazzi M, Testani JM, Borlaug BA. Altered Hemodynamics and End-Organ Damage in Heart Failure: Impact on the Lung and Kidney. Circulation. Sep 8 2020;142(10):998-1012. doi:10.1161/CIRCULATIONAHA.119.045409

51. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol. Mar 31 2009;53(13):1119-26. doi:10.1016/j.jacc.2008.11.051

52. Omote K, Verbrugge FH, Sorimachi H, et al. Central haemodynamic abnormalities and outcome in patients with unexplained dyspnoea. Eur J Heart Fail. Feb 2023;25(2):185-196. doi:10.1002/ejhf.2747

53. Ho JE, Redfield MM, Lewis GD, Paulus WJ, Lam CSP. Deliberating the Diagnostic Dilemma of Heart Failure With Preserved Ejection Fraction. Circulation. Nov 3 2020;142(18):1770-1780. doi:10.1161/CIRCULATIONAHA.119.041818

54. Senni M, Caravita S, Paulus WJ. Do Existing Definitions Identify Subgroup Phenotypes or Reflect the Natural History of Heart Failure With Preserved Ejection Fraction? Circulation. Jul 30 2019;140(5):366-369. doi:10.1161/CIRCULATIONAHA.119.041657

55.Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. J Am Coll Cardiol. May 9 2023;81(18):1810-1834. doi:10.1016/j.jacc.2023.01.049

56. Ho JE, Enserro D, Brouwers FP, et al. Predicting Heart Failure With Preserved and Reduced Ejection Fraction: The International Collaboration on Heart Failure Subtypes. Circ Heart Fail. Jun 2016;9(6)doi:10.1161/CIRCHEARTFAILURE.115.003116

57. Savji N, Meijers WC, Bartz TM, et al. The Association of Obesity and Cardiometabolic Traits With Incident HFpEF and HFrEF. JACC Heart Fail. Aug 2018;6(8):701-709. doi:10.1016/j.jchf.2018.05.018

58. Pandey A, LaMonte M, Klein L, et al. Relationship Between Physical Activity, Body Mass Index, and Risk of Heart Failure. J Am Coll Cardiol. Mar 7 2017;69(9):1129-1142. doi:10.1016/j.jacc.2016.11.081

59. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail. Mar 2021;23(3):352-380. doi:10.1002/ejhf.2115

60. Verbrugge FH, Omote K, Reddy YNV, Sorimachi H, Obokata M, Borlaug BA. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. Eur Heart J. May 21 2022;43(20):1941-1951. doi:10.1093/eurheartj/ehab911

61. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J. Mar 2011;32(6):670-9. doi:10.1093/eurheartj/ehq426

62. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. Eur Heart J. Nov 14 2016;37(43):3293-3302. doi:10.1093/eurheartj/ehw241

63. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail. Sep 2010;3(5):588-95. doi:10.1161/CIRCHEARTFAILURE.109.930701

64. Dorfs S, Zeh W, Hochholzer W, et al. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. Eur Heart J. Nov 21 2014;35(44):3103-12. doi:10.1093/eurheartj/ehu315

65. Eisman AS, Shah RV, Dhakal BP, et al. Pulmonary Capillary Wedge Pressure Patterns During Exercise Predict Exercise Capacity and Incident Heart Failure. Circ Heart Fail. May 2018;11(5):e004750. doi:10.1161/CIRCHEARTFAILURE.117.004750

66. Anjan VY, Loftus TM, Burke MA, et al. Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic peptide levels in heart failure with preserved ejection fraction. Am J Cardiol. Sep 15 2012;110(6):870-6. doi:10.1016/j.amjcard.2012.05.014

67. Pfeffer MA, Shah AM, Borlaug BA. Heart Failure With Preserved Ejection Fraction In Perspective. Circ Res. May 24 2019;124(11):1598-1617. doi:10.1161/CIRCRESAHA.119.313572

68. Pieske B, Tschope 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. Oct 21 2019;40(40):3297-3317. doi:10.1093/eurheartj/ehz641

69. Omote K, Hsu S, Borlaug BA. Hemodynamic Assessment in Heart Failure with Preserved Ejection Fraction. Cardiol Clin. Nov 2022;40(4):459-472. doi:10.1016/j.ccl.2022.06.010

70. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. J Am Coll Cardiol. Sep 7 2010;56(11):855-63. doi:10.1016/j.jacc.2010.04.040

71. Bhella PS, Pacini EL, Prasad A, et al. Echocardiographic indices do not reliably track changes in left-sided filling pressure in healthy subjects or patients with heart failure with preserved ejection fraction. Circ Cardiovasc Imaging. Sep 2011;4(5):482-9. doi:10.1161/CIRCIMAGING.110.960575

72. Santos M, Rivero J, McCullough SD, et al. E/e' Ratio in Patients With Unexplained Dyspnea: Lack of Accuracy in Estimating Left Ventricular Filling Pressure. Circ Heart Fail. Jul 2015;8(4):749-56. doi:10.1161/CIRCHEARTFAILURE.115.002161

73. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation. Aug 28 2018;138(9):861-870. doi:10.1161/CIRCULATIONAHA.118.034646

74. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. Jul 20 2006;355(3):251-9. doi:10.1056/NEJMoa052256

75. Redfield MM. Heart Failure with Preserved Ejection Fraction. N Engl J Med. Nov 10 2016;375(19):1868-1877. doi:10.1056/NEJMcp1511175

76. Pieske B, Tschope 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 J Heart Fail. Mar 2020;22(3):391-412. doi:10.1002/ejhf.1741

77. Khalid U, Wruck LM, Quibrera PM, et al. BNP and obesity in acute decompensated heart failure with preserved vs. reduced ejection fraction: The Atherosclerosis Risk in Communities Surveillance Study. Int J Cardiol. Apr 15 2017;233:61-66. doi:10.1016/j.ijcard.2017.01.130

78. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. Circulation. Jul 4 2017;136(1):6-19. doi:10.1161/CIRCULATIONAHA.116.026807

79. Mueller C, McDonald K, de Boer RA, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail. Jun 2019;21(6):715-731. doi:10.1002/ejhf.1494

80. Kittleson MM, Panjrath GS, Amancherla K, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. May 9 2023;81(18):1835-1878. doi:10.1016/j.jacc.2023.03.393

81. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail. Mar 2016;18(3):242-52. doi:10.1002/ejhf.483

82. Iyngkaran P, Majoni W, Cass A, et al. Northern Territory perspectives on heart failure with comorbidities - understanding trial validity and exploring collaborative opportunities to broaden the evidence base. Heart Lung Circ.Jun 2015;24(6):536-43. doi:10.1016/j.hlc.2014.12.007

83. Mentz RJ, Kelly JP, von Lueder TG, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol. Dec 2 2014;64(21):2281-93. doi:10.1016/j.jacc.2014.08.036

84. Adamson PB, Abraham WT, Bourge RC,et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail. Nov 2014;7(6):935-44. doi:10.1161/CIRCHEARTFAILURE.113.001229

85. Fonarow GC, Abraham WT, Albert NM, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. Arch Intern Med. Apr 28 2008;168(8):847-54. doi:10.1001/archinte.168.8.847

86. Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. J Am Coll Cardiol. Jan 13 2009;53(2):184-92. doi:10.1016/j.jacc.2008.09.031

87. Cleland JG, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. Oct 2006;27(19):2338-45. doi:10.1093/eurheartj/ehl250

88. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. N Engl J Med. Dec 10 2015;373(24):2314-24. doi:10.1056/NEJMoa1510774

89. Komajda M, Isnard R, Cohen-Solal A, et al. Effect of ivabradine in patients with heart failure with preserved ejection fraction: the EDIFY randomized placebo-controlled trial. Eur J Heart Fail. Nov 2017;19(11):1495-1503. doi:10.1002/ejhf.876

90. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. Mar 27 2013;309(12):1268-77. doi:10.1001/jama.2013.2024

91. Fukuta H, Goto T, Wakami K, Kamiya T, Ohte N. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. Heart Fail Rev. Jul 2019;24(4):535-547. doi:10.1007/s10741-019-09774-5

92. Haykowsky MJ, Brubaker PH, Morgan TM, Kritchevsky S, Eggebeen J, Kitzman DW. Impaired aerobic capacity and physical functional performance in older heart failure patients with preserved ejection fraction: role of lean body mass. J Gerontol A Biol Sci Med Sci. Aug 2013;68(8):968-75. doi:10.1093/gerona/glt011

93. Dhakal BP, Malhotra R, Murphy RM, et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. Circ Heart Fail. Mar 2015;8(2):286-94.doi:10.1161/CIRCHEARTFAILURE.114.001825

95. Abudiab MM, Redfield MM, Melenovsky V, et al. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. Eur J Heart Fail. Jul 2013;15(7):776-85. doi:10.1093/eurjhf/hft026

96. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation. Nov 14 2006;114(20):2138-47.doi:10.1161/CIRCULATIONAHA.106.632745

97. Borlaug BA, Olson TP, Lam CS, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. Sep 7 2010;56(11):845-54. doi:10.1016/j.jacc.2010.03.077

98. Obokata M, Reddy YNV, Melenovsky V, et al. Myocardial Injury and Cardiac Reserve in Patients With Heart Failure and Preserved Ejection Fraction. J Am Coll Cardiol. Jul 3 2018;72(1):29-40. doi:10.1016/j.jacc.2018.04.039

99. Fukuta H, Goto T, Wakami K, Ohte N. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. Eur J Prev Cardiol. Jan 2016;23(1):78-85. doi:10.1177/2047487314564729

100. Dieberg G, Ismail H, Giallauria F, Smart NA. Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. J Appl Physiol (1985). Sep 15 2015;119(6):726-33. doi:10.1152/japplphysiol.00904.2014

101. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. May 3 2022;145(18):e895-e1032.doi:10.1161/CIR.0000000000001063

102. Bohm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet. Sep 11 2010;376(9744):886-94. doi:10.1016/S0140-6736(10)61259-7

103. Fox K, Ford I, Steg PG, et al. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet. Sep 6 2008;372(9641):817-21. doi:10.1016/S0140-6736(08)61171-X

104. DeVore AD, Schulte PJ, Mentz RJ, et al. Relation of Elevated Heart Rate in Patients With Heart Failure With Reduced Ejection Fraction to One-Year Outcomes and Costs. Am J Cardiol. Mar 15 2016;117(6):946-51. doi:10.1016/j.amjcard.2015.12.031

105. Bohm M, Perez AC, Jhund PS, et al. Relationship between heart rate and mortality and morbidity in the irbesartan patients with heart failure and preserved systolic function trial (I-Preserve). Eur J Heart Fail. Jul 2014;16(7):778-87. doi:10.1002/ejhf.85

106. Takada T, Sakata Y, Miyata S, et al. Impact of elevated heart rate on clinical outcomes in patients with heart failure with reduced and preserved ejection fraction: a report from the CHART-2 Study. Eur J Heart Fail. Mar 2014;16(3):309-16. doi:10.1002/ejhf.22

107. O'Neal WT, Sandesara PB, Samman-Tahhan A, Kelli HM, Hammadah M, Soliman EZ. Heart rate and the risk of adverse outcomes in patients with heart failure with preserved ejection fraction. Eur J Prev Cardiol. Jul 2017;24(11):1212-1219. doi:10.1177/2047487317708676

108. Castagno D, Skali H, Takeuchi M, et al. Association of heart rate and outcomes in a broad spectrum of patients with chronic heart failure: results from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) program. J Am Coll Cardiol. May 15 2012;59(20):1785-95. doi:10.1016/j.jacc.2011.12.044

109. Maeder MT, Kaye DM. Differential impact of heart rate and blood pressure on outcome in patients with heart failure with reduced versus preserved left ventricular ejection fraction. Int J Cardiol. Mar 8 2012;155(2):249-56. doi:10.1016/j.ijcard.2010.10.007

110. Wachter R, Schmidt-Schweda S, Westermann D, et al. Blunted frequency-dependent upregulation of cardiac output is related to impaired relaxation in diastolic heart failure. Eur Heart J. Dec 2009;30(24):3027-36. doi:10.1093/eurheartj/ehp341

111. Kumar AA, Kelly DP, Chirinos JA. Mitochondrial Dysfunction in Heart Failure With Preserved Ejection Fraction. Circulation. Mar 12 2019;139(11):1435-1450. doi:10.1161/CIRCULATIONAHA.118.036259

112. Conraads VM, Metra M, Kamp O, et al. 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. Eur J Heart Fail. Feb 2012;14(2):219-25. doi:10.1093/eurjhf/hfr161

113. Edelmann F, Musial-Bright L, Gelbrich G, et al. Tolerability and Feasibility of Beta-Blocker Titration in HFpEF Versus HFrEF: Insights From the CIBIS-ELD Trial. JACC Heart Fail. Feb 2016;4(2):140-149. doi:10.1016/j.jchf.2015.10.008

114. Yamamoto K, Origasa H, Hori M, Investigators JD. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail. Jan 2013;15(1):110-8. doi:10.1093/eurjhf/hfs141

115. Kosmala W, Holland DJ, Rojek A, Wright L, Przewlocka-Kosmala M, Marwick TH. Effect of If-channel inhibition on hemodynamic status and exercise tolerance in heart failure with preserved ejection fraction: a randomized trial. J Am Coll Cardiol. Oct 8 2013;62(15):1330-8. doi:10.1016/j.jacc.2013.06.043

116. Pal N, Sivaswamy N, Mahmod M, et al. Effect of Selective Heart Rate Slowing in Heart Failure With Preserved Ejection Fraction. Circulation. Nov 3 2015;132(18):1719-25.doi:10.1161/CIRCULATIONAHA.115.017119

117. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J. Jan 1 2018;39(1):26-35. doi:10.1093/eurheartj/ehx564

118. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. Circulation. 2012;126(25):e354-e471. doi:doi:10.1161/CIR.0b013e318277d6a0

119. Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. Sep 3 2022;400(10354):757-767. doi:10.1016/S0140-6736(22)01429-5

120. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. Oct 14 2021;385(16):1451-1461. doi:10.1056/NEJMoa2107038

121. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. Sep 22 2022;387(12):1089-1098. doi:10.1056/NEJMoa2206286

122. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. Nov 2021;27(11):1954-1960. doi:10.1038/s41591-021-01536-x

123. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. Jan 14 2021;384(2):117-128. doi:10.1056/NEJMoa2030183

124. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. Mar 2022;28(3):568-574. doi:10.1038/s41591-021-01659-1

125. Packer M, Butler J, Zannad F, et al. Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial. Circulation. Oct 19 2021;144(16):1284-1294.doi:10.1161/CIRCULATIONAHA.121.056824

126. Packer M. Molecular, Cellular, and Clinical Evidence That Sodium-Glucose Cotransporter 2 Inhibitors Act as Neurohormonal Antagonists When Used for the Treatment of Chronic Heart Failure. J Am Heart Assoc. Aug 18 2020;9(16):e016270. doi:10.1161/JAHA.120.016270

127. Durante W, Behnammanesh G, Peyton KJ. Effects of Sodium-Glucose Co-Transporter 2 Inhibitors on Vascular Cell Function and Arterial Remodeling. Int J Mol Sci. Aug 16 2021;22(16)doi:10.3390/ijms22168786

128. Hess DA, Terenzi DC, Trac JZ, et al. SGLT2 Inhibition with Empagliflozin Increases Circulating Provascular Progenitor Cells in People with Type 2 Diabetes Mellitus. Cell Metab. Oct 1 2019;30(4):609-613. doi:10.1016/j.cmet.2019.08.015

129. Salah HM, Verma S, Santos-Gallego CG, et al. Sodium-Glucose Cotransporter 2 Inhibitors and Cardiac Remodeling. J Cardiovasc Transl Res. Oct 2022;15(5):944-956. doi:10.1007/s12265-022-10220-5

130. Pabel S, Wagner S, Bollenberg H, et al. Empagliflozin directly improves diastolic function in human heart failure. Eur J Heart Fail. Dec 2018;20(12):1690-1700. doi:10.1002/ejhf.1328

131. Pabel S, Hamdani N, Luedde M, Sossalla S. SGLT2 Inhibitors and Their Mode of Action in Heart Failure-Has the Mystery Been Unravelled? Curr Heart Fail Rep. Oct 2021;18(5):315-328. doi:10.1007/s11897-021-00529-8

132. Kaplan A, Abidi E, El-Yazbi A, Eid A, Booz GW, Zouein FA. Direct cardiovascular impact of SGLT2 inhibitors: mechanisms and effects. Heart Fail Rev. May 2018;23(3):419-437. doi:10.1007/s10741-017-9665-9

133. Baartscheer A, Schumacher CA, Wust RC, et al. Empagliflozin decreases myocardial cytoplasmic Na(+) through inhibition of the cardiac Na(+)/H(+) exchanger in rats and rabbits. Diabetologia. Mar 2017;60(3):568-573. doi:10.1007/s00125-016-4134-x

134. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. Oct 2018;61(10):2108-2117. doi:10.1007/s00125-018-4670-7

135. Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC Basic Transl Sci. Jun 2020;5(6):632-644. doi:10.1016/j.jacbts.2020.02.004

136. Saucedo-Orozco H, Voorrips SN, Yurista SR, de Boer RA, Westenbrink BD. SGLT2 Inhibitors and Ketone Metabolism in Heart Failure. J Lipid Atheroscler. Jan 2022;11(1):1-19. doi:10.12997/jla.2022.11.1.1

137. De Meyer GR, De Keulenaer GW, Martinet W. Role of autophagy in heart failure associated with aging. Heart Fail Rev. Sep 2010;15(5):423-30. doi:10.1007/s10741-010-9166-6

138. Du J, Liu Y, Fu J. Autophagy and Heart Failure. Adv Exp Med Biol. 2020;1207:223-227. doi:10.1007/978-981-15-4272-5_16

139. Warbrick I, Rabkin SW. Hypoxia-inducible factor 1-alpha (HIF-1alpha) as a factor mediating the relationship between obesity and heart failure with preserved ejection fraction. Obes Rev. May 2019;20(5):701-712. doi:10.1111/obr.12828

140. Gao YM, Feng ST, Wen Y, Tang TT, Wang B, Liu BC. Cardiorenal protection of SGLT2 inhibitors-Perspectives from metabolic reprogramming. EBioMedicine. Sep 2022;83:104215.doi:10.1016/j.ebiom.2022.104215

141. Esterline RL, Vaag A, Oscarsson J, Vora J. MECHANISMS IN ENDOCRINOLOGY: SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism? Eur J Endocrinol. Apr 2018;178(4):R113-R125. doi:10.1530/EJE-17-0832

142. Chen S, Coronel R, Hollmann MW, Weber NC, Zuurbier CJ. Direct cardiac effects of SGLT2 inhibitors. Cardiovasc Diabetol. Mar 18 2022;21(1):45. doi:10.1186/s12933-022-01480-1

143. Theofilis P, Sagris M, Oikonomou E, et al. Anti-inflammatory potential of SGLT2 inhibitors: a systematic review and meta-analysis of preclinical studies in rodents. European Heart Journal. 2022;43(Supplement_2)doi:10.1093/eurheartj/ehac544.2683

144. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. Oct 8 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816

145. Miyata KN, Zhang SL, Chan JSD. The Rationale and Evidence for SGLT2 Inhibitors as a Treatment for Nondiabetic Glomerular Disease. Glomerular Dis. Apr 2021;1(1):21-33. doi:10.1159/000513659

146. Cherney DZ, Odutayo A, Aronson R, Ezekowitz J, Parker JD. Sodium Glucose Cotransporter-2 Inhibition and Cardiorenal Protection: JACC Review Topic of the Week. J Am Coll Cardiol. Nov 19 2019;74(20):2511-2524. doi:10.1016/j.jacc.2019.09.022

147. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. New England Journal of Medicine. 2019;380(24):2295-2306. doi:doi:10.1056/NEJMoa1811744

148. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. J Am Coll Cardiol. Feb 4 2020;75(4):422-434. doi:10.1016/j.jacc.2019.11.031

149. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. Nov 16 2024;doi:10.1056/NEJMoa2410027

150. Kosiborod MN, Deanfield J, Pratley R, et al. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. Lancet. Sep 7 2024;404(10456):949-961. doi:10.1016/S0140-6736(24)01643-X

151. Kosiborod MN, Abildstrom SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. Sep 21 2023;389(12):1069-1084. doi:10.1056/NEJMoa2306963

152. Butler J, Shah SJ, Petrie MC, et al. Semaglutide versus placebo in people with obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF DM randomised trials. Lancet. Apr 27 2024;403(10437):1635-1648. doi:10.1016/S0140-6736(24)00469-0

153. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. Apr 10 2014;370(15):1383-92. doi:10.1056/NEJMoa1313731

154. 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. Jan 6 2015;131(1):34-42. doi:10.1161/CIRCULATIONAHA.114.013255

155. Edelmann F, Wachter R, Schmidt AG, et al. 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. Feb 27 2013;309(8):781-91. doi:10.1001/jama.2013.905

156. Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. New England Journal of Medicine. 2024;391(16):1475-1485. doi:doi:10.1056/NEJMoa2407107

157. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. New England Journal of Medicine. 2019;381(17):1609-1620.doi:doi:10.1056/NEJMoa1908655

158. McMurray JJV, Jackson AM, Lam CSP, et al. Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared With Men With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF. Circulation. Feb 4 2020;141(5):338-351. doi:10.1161/CIRCULATIONAHA.119.044491

159. 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. Sep 6 2003;362(9386):777-81. doi:10.1016/S0140-6736(03)14285-7

160. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. Dec 4 2008;359(23):2456-67. doi:10.1056/NEJMoa0805450

161. Chen P, Chaugai S, Zhao F, Wang DW. Cardioprotective Effect of Thiazide-Like Diuretics: A Meta-Analysis. Am J Hypertens. Dec 2015;28(12):1453-63. doi:10.1093/ajh/hpv050

162. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. Mar 5 2016;387(10022):957-967. doi:10.1016/S0140-6736(15)01225-8

163. Huang R, Lin Y, Liu M, et al. Time in Target Range for Systolic Blood Pressure and Cardiovascular Outcomes in Patients With Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc. Apr 5 2022;11(7):e022765. doi:10.1161/JAHA.121.022765

164. Selvaraj S, Claggett BL, Bohm M, et al. Systolic Blood Pressure in Heart Failure With Preserved Ejection Fraction Treated With Sacubitril/Valsartan. J Am Coll Cardiol. Apr 14 2020;75(14):1644-1656. doi:10.1016/j.jacc.2020.02.009

165. Faselis C, Lam PH, Zile MR, et al. Systolic Blood Pressure and Outcomes in Older Patients with HFpEF and Hypertension. Am J Med. Apr 2021;134(4):e252-e263. doi:10.1016/j.amjmed.2020.08.030

166. Echouffo-Tcheugui JB, Xu H, DeVore AD, et al. Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: Findings from Get With The Guidelines-Heart Failure registry. Am Heart J. Dec 2016;182:9-20. doi:10.1016/j.ahj.2016.07.025

167. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme.

168. Kristensen SL, Mogensen UM, Jhund PS, et al. Clinical and Echocardiographic Characteristics and Cardiovascular Outcomes According to Diabetes Status in Patients With Heart Failure and Preserved Ejection Fraction: A Report From the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). Circulation. Feb 21 2017;135(8):724-735. doi:10.1161/CIRCULATIONAHA.116.024593

169. Goh SY, Cooper ME. Clinical review: The role of advanced glycation end products in progression and complications of diabetes. J Clin Endocrinol Metab. Apr 2008;93(4):1143-52. doi:10.1210/jc.2007-1817

170. Hegab Z, Gibbons S, Neyses L, Mamas MA. Role of advanced glycation end products in cardiovascular disease. World J Cardiol. Apr 26 2012;4(4):90-102. doi:10.4330/wjc.v4.i4.90

171. Herrero P, Peterson LR, McGill JB, et al. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. J Am Coll Cardiol. Feb 7 2006;47(3):598-604. doi:10.1016/j.jacc.2005.09.030

172. Kruger M, Babicz K, von Frieling-Salewsky M, Linke WA. Insulin signaling regulates cardiac titin properties in heart development and diabetic cardiomyopathy. J Mol Cell Cardiol. May 2010;48(5):910-6. doi:10.1016/j.yjmcc.2010.02.012

173. Tabit CE, Chung WB, Hamburg NM, Vita JA. Endothelial dysfunction in diabetes mellitus: molecular mechanisms and clinical implications. Rev Endocr Metab Disord. Mar 2010;11(1):61-74. doi:10.1007/s11154-010-9134-4

174. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. Nov 26 2015;373(22):2117-28. doi:10.1056/NEJMoa1504720

175. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017;377(7):644-657. doi:doi:10.1056/NEJMoa1611925

176. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. Jan 24 2019;380(4):347-357. doi:10.1056/NEJMoa1812389

177. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med. Oct 8 2020;383(15):1425-1435. doi:10.1056/NEJMoa2004967

178. Beldhuis IE, Streng KW, Ter Maaten JM, et al. Renin-Angiotensin System Inhibition, Worsening Renal Function, and Outcome in Heart Failure Patients With Reduced and Preserved Ejection Fraction: A Meta-Analysis of Published Study Data. Circ Heart Fail. Feb 2017;10(2)doi:10.1161/CIRCHEARTFAILURE.116.003588

179. Peikert A, Vaduganathan M, Mc Causland F, et al. Effects of sacubitril/valsartan versus valsartan on renal function in patients with and without diabetes and heart failure with preserved ejection fraction: insights from PARAGON-HF. Eur J Heart Fail. May 2022;24(5):794-803. doi:10.1002/ejhf.2450

180. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. Mar 18 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183

181. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. Jul 21 2022;387(3):205-216. doi:10.1056/NEJMoa2206038

182. Anker SD, Usman MS, Anker MS, et al. Patient phenotype profiling in heart failure with preserved ejection fraction to guide therapeutic decision making. A scientific statement of the Heart Failure Association, the European Heart Rhythm Association of the European Society of Cardiology, and the European Society of Hypertension. Eur J Heart Fail. Jul 2023;25(7):936-955. doi:10.1002/ejhf.2894

183. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. N Engl J Med. Feb 1 2018;378(5):417-427. doi:10.1056/NEJMoa1707855

184. Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. N Engl J Med. Oct 1 2020;383(14):1305-1316. doi:10.1056/NEJMoa2019422

185. Parwani AS, Kaab S, Friede T, et al. Catheter-based ablation to improve outcomes in patients with atrial fibrillation and heart failure with preserved ejection fraction: Rationale and design of the CABA-HFPEF-DZHK27 trial. Eur J Heart Fail. Oct 2024;26(10):2203-2212. doi:10.1002/ejhf.3373

186. Lyons OD, Floras JS, Logan AG, et al. Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: the ADVENT-HF trial. Eur J Heart Fail. Apr 2017;19(4):579-587. doi:10.1002/ejhf.790

187. Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. J Am Coll Cardiol. Jul 1 2014;63(25 Pt A):2817-27. doi:10.1016/j.jacc.2014.03.034

188. Dryer K, Gajjar M, Narang N, et al. Coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. Am J Physiol Heart Circ Physiol. May 1 2018;314(5):H1033-H1042. doi:10.1152/ajpheart.00680.2017

189. Kramer K, Kirkman P, Kitzman D, Little WC. Flash pulmonary edema: association with hypertension and reoccurrence despite coronary revascularization. Am Heart J. Sep 2000;140(3):451-5. doi:10.1067/mhj.2000.108828

190. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. Oct 15 2013;62(16):e147-239. doi:10.1016/j.jacc.2013.05.019

191. Shah AM, Cikes M, Prasad N, et al. Echocardiographic Features of Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction. J Am Coll Cardiol. Dec 10 2019;74(23):2858-2873. doi:10.1016/j.jacc.2019.09.063

192. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. Jan 1 2016;37(1):67-119. doi:10.1093/eurheartj/ehv317

193. Feng S, Janwanishstaporn S, Teerlink JR, et al. Association of left ventricular ejection fraction with worsening renal function in patients with acute heart failure: insights from the RELAX-AHF-2 study. Eur J Heart Fail. Jan 2021;23(1):58-67. doi:10.1002/ejhf.2012

194. Belyavskiy E, Ovchinnikov A, Potekhina A, Ageev F, Edelmann F. Phosphodiesterase 5 inhibitor sildenafil in patients with heart failure with preserved ejection fraction and combined pre- and postcapillary pulmonary hypertension: a randomized open-label pilot study. BMC Cardiovasc Disord. Sep 10 2020;20(1):408. doi:10.1186/s12872-020-01671-2

195. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. Jul 12 2011;124(2):164-74. doi:10.1161/CIRCULATIONAHA.110.983866

196. Ho JE, Gona P, Pencina MJ, et al. Discriminating clinical features of heart failure with preserved vs. reduced ejection fraction in the community. Eur Heart J. Jul 2012;33(14):1734-41. doi:10.1093/eurheartj/ehs070

197. Chang PP, Wruck LM, Shahar E, et al. Trends in Hospitalizations and Survival of Acute Decompensated Heart Failure in Four US Communities (2005-2014): ARIC Study Community Surveillance. Circulation. Jul 3 2018;138(1):12-24. doi:10.1161/CIRCULATIONAHA.117.027551

198. Shah SJ. BNP: Biomarker Not Perfect in heart failure with preserved ejection fraction. Eur Heart J. May 21 2022;43(20):1952-1954. doi:10.1093/eurheartj/ehac121

199. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation. Oct 11 2005;112(15):2254-62.doi:10.1161/CIRCULATIONAHA.105.541078

200. Foll D, Jung B, Schilli E, et al. Magnetic resonance tissue phase mapping of myocardial motion: new insight in age and gender. Circ Cardiovasc Imaging. Jan 2010;3(1):54-64.doi:10.1161/CIRCIMAGING.108.813857

201. Parks RJ, Ray G, Bienvenu LA, Rose RA, Howlett SE. Sex differences in SR Ca(2+) release in murine ventricular myocytes are regulated by the cAMP/PKA pathway. J Mol Cell Cardiol. Oct 2014;75:162-73. doi:10.1016/j.yjmcc.2014.07.006

202. Peterson LR, Soto PF, Herrero P, et al. Impact of gender on the myocardial metabolic response to obesity. JACC Cardiovasc Imaging. Jul 2008;1(4):424-33. doi:10.1016/j.jcmg.2008.05.004

203. Fujimoto N, Borlaug BA, Lewis GD, et al. Hemodynamic responses to rapid saline loading: the impact of age, sex, and heart failure. Circulation. Jan 1 2013;127(1):55-62. doi:10.1161/CIRCULATIONAHA.112.111302

204. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA. May 22-29 1996;275(20):1557-62.

205. Merz AA, Cheng S. Sex differences in cardiovascular ageing. Heart. Jun 1 2016;102(11):825-31. doi:10.1136/heartjnl-2015-308769

206. Meyer S, Brouwers FP, Voors AA, et al. Sex differences in new-onset heart failure. Clin Res Cardiol. Apr 2015;104(4):342-50. doi:10.1007/s00392-014-0788-x

207. O'Neal WT, Sandesara P, Hammadah M, et al. Gender Differences in the Risk of Adverse Outcomes in Patients With Atrial Fibrillation and Heart Failure With Preserved Ejection Fraction. Am J Cardiol. Jun 1 2017;119(11):1785-1790. doi:10.1016/j.amjcard.2017.02.045

208. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. Jul 1974;34(1):29-34. doi:10.1016/0002-9149(74)90089-7

209. Kim HL, Kim MA, Oh S, et al. Sex Difference in the Association Between Metabolic Syndrome and Left Ventricular Diastolic Dysfunction. Metab Syndr Relat Disord. Dec 2016;14(10):507-512. doi:10.1089/met2016.0078

210. Eaton CB, Pettinger M, Rossouw J, et al. Risk Factors for Incident Hospitalized Heart Failure With Preserved Versus Reduced Ejection Fraction in a Multiracial Cohort of Postmenopausal Women. Circ Heart Fail. Oct 2016;9(10)doi:10.1161/CIRCHEARTFAILURE.115.002883

211. Keskin M, Avsar S, Hayiroglu MI, et al. Relation of the Number of Parity to Left Ventricular Diastolic Function in Pregnancy. Am J Cardiol. Jul 1 2017;120(1):154-159.doi:10.1016/j.amjcard.2017.03.244

212. Wu P, Haththotuwa R, Kwok CS, et al. Preeclam - psia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes. Feb 2017;10(2)doi:10.1161/CIRCOUTCOMES.116.003497