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Authors

Butler, Javed
Fonarow, Gregg C
Zile, Michael R
et al.

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Developing Therapies for Heart Failure with Preserved Ejection Fraction: Current State and Future Directions

Javed Butler, MD, MPH[1], **Gregg C. Fonarow, MD**[2], **Michael R. Zile, MD**[3], **Carolyn S. Lam, MD**[4], **Lothar Roessig, MD**[5], **Erik B. Schelbert, MD, MS**[6], **Sanjiv J. Shah, MD**[7], **Ali Ahmed, MD**[8], **Robert O. Bonow, MD**[7], **John GF Cleland, MD**[9], **Robert J. Cody, MD, MBA**[10], **Ovidiu Chioncel, MD, PhD**[11], **Sean P. Collins, MD**[12], **Preston Dunnmon, MD**[13], **Gerasimos Filippatos, MD**[14], **Martin P. Lefkowitz, MD**[15], **Catherine N. Marti, MD**[1], **John J. McMurray, MD**[16], **Frank Misselwitz, MD**[5], **Savina Nodari, MD**[17], **Christopher O'Connor, MD**[18], **Marc A. Pfeffer, MD**[19], **Burkert Pieske, MD**[20], **Bertram Pitt, MD**[21], **Guiseppe Rosano, MD**[22], **Hani N. Sabbah, PhD**[23], **Michele Senni, MD**[24], **Scott D. Solomon, MD**[19], **Norman Stockbridge, MD, PhD**[13], **John R. Teerlink, MD**[25], **Vasiliki V. Georgiopoulou, MD**[1], and **Mihai Gheorghiade, MD**[7]

[1]Emory Cardiovascular Clinical Research Institute, Emory University, Atlanta, GA

[2]University of California, Los Angeles

[3]Division of Cardiology, Medical University of South Carolina, Charleston and RHJ Department of Veterans Affairs Medical Center, Charleston, SC

[4]National University Health System, Singapore

[5]Global Clinical Development, Bayer HealthCare AG, Wuppertal, Germany

[6]University of Pittsburgh Medical Center Heart and Vascular Institute, Pittsburgh, PA

[7]Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, IL

[8]University of Alabama at Birmingham, Birmingham, AL

[9]Castle Hill Hospital, Hull York Medical School, Kingston-Upon-Hull, UK

[10]Cardiovascular & Metabolism, Janssen Pharmaceuticals, Raritan, NJ

[11]Institute of Emergency for Cardiovascular Diseases, Cardiology 1, Bucuresti, Romania

[12]Vanderbilt University, Nashville, TN

[13]Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

Address correspondence to: Javed Butler, MD MPH, Emory Clinical Cardiovascular Research Institute, 1462 Clifton Road NE, Suite AT 504, Atlanta, GA 30322. Telephone No: 404-778-5136 Fax No: 404-778-5285 javed.butler@emory.edu.

[14]Attikon University Hospital, Athens, Greece

[15]Novartis Pharmaceuticals Inc, East Hanover, NJ

[16]University of Glasgow, Glasgow, UK

[17]Division of Cardiology, University of Brescia, Brescia, Italy

[18]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC

[19]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA

[20]Department of Cardiology, Medical University Graz, Graz, Austria

[21]Division of Cardiology, University of Michigan School of Medicine, Ann Arbor, MI

[22]Centre for Clinical and Basic Science, San Raffaele-Roma, Rome, Italy

[23]Department of Medicine, Henry Ford Hospital, Detroit, MI

[24]Cardiovascular Department, Ospedale Papa Giovanni XXIII, Bergamo, Italy

[25]University of California San Francisco, and San Francisco Veterans Affairs Medical Center, San Francisco, CA

Abstract

The burden of heart failure with preserved ejection fraction (HFpEF) is considerable and is projected to worsen. To date, there are no approved therapies available for reducing mortality or hospitalizations for these patients. The pathophysiology of HFpEF is complex and includes alterations in cardiac structure and function, systemic and pulmonary vascular abnormalities, end-organ involvement, and comorbidities. There remain major gaps in our understanding of HFpEF pathophysiology. To facilitate a discussion of how to proceed effectively in future with development of therapies for HFpEF, a meeting was facilitated by the FDA and included representatives from academia, industry and regulatory agencies. This document summarizes the proceedings from this meeting.

Keywords

Heart failure; preserved ejection fraction; epidemiology; prognosis; treatment

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Epidemiologic studies suggest that the prevalence and hospitalizations related to heart failure (HF) with preserved ejection fraction (HFpEF) is rising (1), and the growing elderly population guarantees further worsening of these trends. To date, there are no approved therapies to reduce hospitalization or mortality for HFpEF. There remains a lack of consensus on the basic pathophysiology and definition, classification, therapeutic targets, and goals for therapy for this syndrome. To facilitate consensus for the next steps in developing therapies for HFpEF, the Food and Drug Administration hosted a meeting on February 6, 2013 that was attended by representatives from academia, industry, and the regulatory agencies from the United States and Europe. This meeting was not industry-sponsored. This document represents the proceedings from this meeting.

IMPORTANCE

Considering its prevalence and outcomes, future projections, and lack of effective therapies, HFpEF represents the single largest unmet need in cardiovascular medicine.

Epidemiology

Table 1 summarizes the epidemiology of HFpEF and the difference in prevalence and outcomes based on the definitions used and the population studied (1–7). Hospitalizations for HFpEF have increased over time while those for HFrEF have declined. These patients have longer length of stay and are more likely to require skilled nursing care (1). Mortality in outpatient cohorts appears to be lower for HFpEF than HFrEF (8), but data are inconsistent for in-hospital mortality (5,6). Observational studies show a higher mortality for HFpEF than clinical trials (9). The combined mortality and readmission rates 60–90 days post-discharge are comparable for HFrEF (36.1%) and HFpEF (35.3%) (7). In the Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) and the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) trials, 70% of mortality in HFpEF was cardiovascular (8,10), whereas in HFrEF, cardiovascular causes accounted for 83% of deaths (8). Exercise capacity and quality of life are similarly reduced in HFpEF and HFrEF (11,12).

Summary of Clinical Trials in HFpEF

No specific treatment for HFpEF is established and management is limited to diuretics and treatment of comorbidities. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers were not effective in reducing mortality (13–19) [Table 2 (13–30)]. Digoxin had no effect on mortality in either HFrEF or HFpEF, but had similar benefits on the composite of hospitalizations or death due to worsening HF regardless of EF (25). β-blockers have not shown benefits in HFpEF (14,22,23,29,30). Therapy with spironolactone (27) showed improvement in diastolic function and hypertrophy but not in clinical outcomes, which may be related to inclusion of relatively stable patients. Sildenafil (28) showed no improvement in exercise capacity, quality of life, or clinical status in HFpEF. The Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blockers on Management of HFpEF (PARAMOUNT) trial (31) showed favorable effects of angiotensin receptor neprilysin inhibitor on natriuretic peptides and left atrial (LA) volumes, and a phase III trial with this agent is ongoing. Exercise training in HFpEF has been shown to improve symptoms and quality of life (32–37).

CLINICAL VARIANTS

Although there are common comorbidity profiles among patients with HFpEF, specific underlying etiologies are only seen in a small proportion of patients. The vast majority of patients do not have any known *specific* genetic, pericardial, myocardial, or valvular etiology. The most urgent need is to develop therapies targeting this majority of HFpEF patients; however, future trials will benefit from enhanced phenotypic characterization and categorization that may allow improved targeting of experimental therapies.

There are several specific etiologies of HFpEF, e.g. hypertrophic cardiomyopathy, but the vast majority does not have a specific underlying primary cardiac cause. Better understanding of the pathophysiologic pathways may allow identification of better therapeutic targets. Studies suggest that HFpEF is a heterogeneous entity and careful phenotyping is needed to target the right population for understanding the pathophysiology and response to treatments (38–40). Most patients have one or more comorbidities that may worsen HFpEF. Nevertheless, many of these patients do not have any yet identified specific primary cardiac pathology. Understanding the basic disease process and targeting novel therapies to this vast majority of typical HFpEF patients is urgently needed.

PATHOPHYSIOLOGY

The pathophysiology of HFpEF is incompletely understood. There are no animal models ideally suitable for drug testing. Changes leading to hospitalization and the differences between hospitalized versus outpatients are incompletely understood. Future research should focus on understanding the basic and clinical mechanisms of HFpEF.

The pathophysiology of HFpEF is complex, incompletely understood, and related to cardiac structural and functional alterations, and systemic and pulmonary vascular abnormalities, which coupled with extra-cardiac causes of volume overload, e.g. kidney disease, can lead to the signs and symptoms of HF.

Left Ventricle

Left ventricular (LV) abnormalities in HFpEF are varied and compounded by abnormal ventricular-arterial coupling, poor vasodilator reserve, chronotropic incompetence, coronary disease, microvascular dysfunction and right ventricular dysfunction with or without co-existing pulmonary vascular disease.

Structural changes—LV size is normal or near normal in most patients with HFpEF. Most patients have increased LV mass or relative wall thickness, and may have concentric remodeling or hypertrophy. In one study, mean LV mass index was 102±29 g/m^2; 27% had concentric LV remodeling, 26% had concentric LV hypertrophy, and 16% had eccentric LV hypertrophy in HFpEF (41). Changes in myocyte structure (42) with increased diameter in HFpEF than HFrEF has been reported.

Diastolic function—Diastolic dysfunction in HFpEF can result from increased LV stiffness from hypertrophy and interstitial fibrosis, as well as from abnormal LV relaxation due to abnormal calcium cycling. Titin functions as a bidirectional spring responsible for early diastolic recoil and late diastolic distensibility, regulates diastolic function. Alterations in titin phosphorylation cause diastolic dysfunction, suggesting that titin may be a therapeutic target (43,44). Abnormal myocardial energetics in HFpEF can impact relaxation and filling. Ischemia and microvascular dysfunction is associated with changes in intracellular calcium and are related to HFpEF. Diastolic dysfunction results in ineffective LA emptying and LV filling, and reduced ability to augment cardiac output with exercise, increases in pulmonary pressure, which then results in symptoms and fluid retention. HFpEF patients have increased LV stiffness (41) with increased passive elastance.

Echocardiography can describe impaired relaxation using longitudinal mitral annular early diastolic tissue velocity (e′), and increased LV filling pressures via the ratio of early mitral inflow (E) to e′, i.e., E/e′ ratio. Measurement of chamber compliance requires analysis of end-diastolic pressure volume relationship, which is shifted upward- and leftward in HFpEF. Assessment of diastolic function and filling pressures during exercise has emerged as a useful tool (45). Left bundle branch block deteriorates diastolic dysfunction with increased E/e′, LA diameter and reduced deceleration and isovolumic relaxation time (46).

Systolic function—While LVEF is preserved and some patients may even have normal appearing LV size and geometry, systolic function may be abnormal in HFpEF, including an increase in end-systolic elastance (47). However, when normalized for remodeling, the end-systolic elastance/volume to mass ratio is normal. The increases in end-systolic elastance and effective arterial elastance may contribute to decreased exercise capacity due to limited ability to increase both above baseline. In HFpEF, longitudinal strain is typically reduced whereas radial strain is preserved, resulting in preservation of LVEF despite longitudinal systolic dysfunction (48). Systolic reserve during exercise is also impaired in HFpEF (38).

Interstitial matrix—Diffuse myocardial fibrosis maybe a mediator or a modifier of HFpEF. Myocytes embedded in fibrotic tissue are prone to energy starvation as fibrosis effects capillary blood supply by interposing collagen and by perivascular collagen limiting vasomotor reserve. Diffuse fibrosis is linked with diastolic dysfunction, vasomotor dysfunction, arrhythmias, and mortality (49). Experimental models have produced HF by creating diffuse fibrosis from cardiac fibroblast activation (50) suggesting a primary role for fibroblast activity.

Left Atrium

HFpEF patients may have ineffective LA emptying, increased size, and abnormal function. In the CHARM-Preserved study, LA volume index was >32 ml/m^2 in 71% of the patients (51), and in the I-PRESERVE echocardiographic substudy, 66% of patients had LA enlargement (52). The LA size is a predictor of outcomes (52). Recruitment of LA contractility during stress is impaired in HFpEF and may contribute to the transition from asymptomatic state to overt HFpEF (53).

Endothelial Function and Arterial Stiffness

Endothelial function and nitric oxide influences arterial stiffness in HFpEF and arterial stiffness increases with hypertension. Arterial distending pressure leads to recruitment of inelastic collagen fibers (54). Age and cardio-metabolic abnormalities are related to arterial stiffness, which in turn is associated with HFpEF. Increases in LV end-systolic and arterial elastance occur with aging, particularly in women, and may result in ventricular-vascular stiffening leading to HFpEF (55). Pulse wave velocity is higher (56) and venous capacitance lower in HFpEF than in HFrEF, explaining why these patients are more sensitive to vasodilators and diuretics (47). Worsening vascular failure is proposed as a precipitant for hospitalization in HFpEF, but few data are available. HFpEF patients have limited vasodilatory response to exercise. Endothelial dysfunction in HFpEF is associated with

adverse outcomes (57) and it also affects microvasculature that in turn may modulate diastolic function via paracrine effects (58).

Pulmonary Hypertension

Increased LV stiffness augments end-diastolic pressure (59) leading to increased pulmonary venous pressure and a passive increase in pulmonary artery pressure. Chronically elevated pressures induce a reactive component (60) and the trans-pulmonary gradient increases out of proportion to the wedge pressure, leading to a higher mean pressures than expected. Pulmonary vasculopathy similar to HFrEF can be postulated in HFpEF, but has not yet been shown.

Right Ventricle

The right ventricle better tolerates volume than pressure (61), leading to high prevalence of dysfunction when pulmonary hypertension develops. Right ventricular dysfunction worsens prognosis and is related to the transmission of elevated LV filling pressures to the pulmonary bed. The chronic elevated pulmonary pressure leads to right ventricular hypertrophy and later, to contractile dysfunction, tricuspid regurgitation, and diminished cardiac output. Subendocardial right ventricular dysfunction in HFpEF has been shown (62).

Animal Models

A few animal models of HFpEF that have been described but they mimic some but not all of the characteristics described in humans with HFpEF, significantly limiting their usefulness for testing novel therapies. Development of better animal models, especially large animal models that mimic human disease more closely, may be useful in drug testing in future. However, until that time, the lack of animal models should not prevent human testing of promising therapies.

COMORBIDITIES

HFpEF patients usually have multiple comorbid conditions, treatment of which may improve outcomes.

Comorbidities are highly prevalent in these patients and are related to ventricular-vascular dysfunction and prognosis (63). Hypertension affects risk of developing HFpEF and treatment substantially lower this risk. Obesity, anemia, diabetes and renal dysfunction are associated with unique ventricular-vascular characteristics contributing to HFpEF; however, changes seen in HFpEF cannot be accounted for by these comorbidities alone (64). Subclinical lung disease is related to HFpEF (65). The exact role of sleep apnea in HFpEF needs further study. Atrial fibrillation is prognostically important in HFpEF (66). Comorbidity burden increases hospitalization risk in HFpEF, with more non-HF admissions compared to HFrEF (63). In these patients, 30% of mortality is non-cardiovascular, underscoring the importance of comorbidities.

Whether HFpEF simply represents a collection of comorbidities has been questioned. Campbell et al. (9) compared mortality in HFpEF patients with similar age, gender and comorbidity distribution to patients enrolled in other cardiovascular trials. Striking

differences were found in mortality between non-HFpEF (11–47/1000 patient-years) and HFpEF (53–76/1000 patient-years) patients, suggesting that HFpEF risk goes beyond that explained by age and comorbidities. A recent paper suggest that both the cardiac and vascular abnormalities seen in HFpEF may be related to an underlying milieu of systemic inflammation that is related to the combination of various comorbidities seen commonly in HFpEF patients (67).

THERAPEUTIC TARGETS AND ENDPOINTS

PHASE II TRIALS

There are many structural and functional targets that may be amenable to novel interventions. Further research is needed to assess the magnitude and the time frame of change in these targets, and how they relate to clinical outcomes (Table 3, Figure 1).

Left Ventricle and Left Atrium—Multiple LV and LA parameters predict outcomes (Table 4) (51,52,68–71). Diastolic dysfunction, increased LV mass, mass/volume ratio, LA area, diastolic wall stress and e′ that is relatively preload-independent predict outcomes. One may target the fundamental cellular and molecular signaling pathways that result in increased LV distensibility and improve relaxation, recoil, and filling, and diastolic function. The best way of measuring LV diastolic function to assess therapy remains to be clarified, but may include assessing relaxation, untwist, suction, stiffness, distensibility, compliance, elastance, and ventriculo-arterial coupling. Other potential parameters include volume, mass, wall thickness, LVEF, E/e′ ratio, e′ velocity, and longitudinal strain. Diffuse fibrosis is prognostically important (72,73). Dynamic measures of LV function may be normal at rest but become abnormal during exercise. The role of exercise in improving surrogate markers of LV function in clinical trials needs studying. Changes in LA size may integrate extent and duration of increased diastolic pressure and changes related to diastolic dysfunction, mitral regurgitation, and atrial fibrillation. Magnetic resonance imaging, tissue Doppler techniques including transmitral flow (A velocity) and longitudinal velocity of the mitral annulus attributable to LA systolic function (tissue Doppler a′ velocity), and speckle-tracking echocardiography can provide insight through analysis of regional and global LV and LA function. A comprehensive list of variable for patients with HFpEF is presented in Figure 2.

Hemodynamics—HF is characterized by altered hemodynamics. Detailed analysis of contractility, relaxation, and volumes require methods such as conductance catheters, which show impaired adaptation including blunted increase in stroke volume with heart rate in HFpEF (74). Exercise during hemodynamic assessment may unmask HFpEF (45). Data in acute HFpEF are limited. Increases in intracardiac pressures occur days before the onset of clinical signs and symptoms. Information from an implanted pulmonary artery pressure sensor was associated with a 30% reduction in HF hospitalization at 6-months and 38% per year; 23% of participants had HFpEF in this study (75). Continuous hemodynamic monitoring-based management strategy (76) showed a non-significant 21% reduction in the HF hospitalizations; 25% of participants had HEpEF.

Vascular and Endothelial Function—Higher pulse pressure is seen in HFpEF (77). Increased pulse wave velocity and augmentation index are associated with systolic and

diastolic dysfunction. Impaired flow mediated dilation and changes in peripheral artery tonometry are associated with worse outcomes in HF (78).

Biomarkers—Collagen expression is increased in HFpEF and increases in collagen related biomarkers are associated with hypertrophy and diastolic dysfunction. The association between galectin-3 and the risk of mortality and readmission is stronger in HFpEF than HFrEF (79). In animal models, galectin-3 was causally implicated in the HFpEF pathophysiology, suggesting galectin-3 as a possible target. Inhibition of galectin-3 is associated with attenuation of diastolic dysfunction and LV fibrosis (80). Several other collagen related biomarkers correlate with higher risk (81). Other biomarkers reflecting different mechanisms and may be useful in HFpEF include growth differentiation factor 15, ST2, and cardiac troponins.

Natriuretic peptides (NPs) are lower in HFpEF and many patients have B-type NP levels of <100 pg/ml (82). Irbesartan is associated with improved outcomes in patients with NP levels below but not above median (83). The role of NP as markers of potential responders is being investigated. In the PARAMOUNT trial, N terminal pro B-type NP was reduced more with LCZ696 than valsartan (31). NP may be normal or near normal in symptomatic HFpEF patients but indicate poor outcome once elevated. Selection of patients on the basis of elevated NP may identify a cohort with higher risk and lowering NPs may be a target. This needs to be studied, however, since patients with elevated NP levels may have advanced HFpEF with fibrosis and/or atrial fibrillation, which will make the myocardium less responsive to intervention.

Exercise Capacity—Exercise training studies show that the improved arterial-venous oxygen difference after exercise may be responsible for the improved exercise capacity. The exact underlining mechanisms for this are uncertain and improved peripheral vascular microvascular function and/or increased oxygen utilization has been proposed. Skeletal muscles can be relatively rapidly rejuvenated and represent a possible target for interventions. Symptom limited exercise tests offer important information about the maximum exercise capacity whereas submaximal tests provide information about the ability to independently complete daily activities. In the Exercise training in Diastolic Heart Failure pilot trial, 3 months of exercise training improved exercise capacity in HFpEF (33).

Comorbidities—Important targets for HFpEF treatment include comorbidities. Benefits of treating hypertension and coronary disease are known. Treatment with continuous positive airway pressure may reverse diastolic dysfunction in sleep apnea (84). Maintaining sinus rhythm, and if not possible then rate control is important. Catheter ablation of atrial fibrillation improves diastolic function (85). Renal denervation has shown promise in animal models, but specific human HFpEF data are lacking. Treatment of cardiometabolic diseases also represents potential targets.

PHASE III TRIALS

Mortality and hospitalization rates remain important targets; however, most patients with HFpEF are elderly and many will die of conditions other than HF. Improving symptoms and

maintaining independence and exercise capacity are important for this population. A novel endpoint focusing on the “patient journey” should be developed and tested.

The goals for HFpEF treatment remain only partially understood. These patients are generally older and the competing risk for death is substantial. Targeting HFpEF related abnormalities may improve physiology and patient status but not mortality. Due to increased HF readmission scrutiny, care is increasingly being shifted to other venues. Also, the determinants of quality of life in general depend on issues larger than any specific disease process and data in this regard are problematic, e.g. patients using tobacco report better quality of life (86), defibrillators may worsen quality of life but improve survival, and inotropes improve symptoms but worsen mortality. Though all these remains important endpoints, considering their limitations, there is a need to develop new endpoints. The common HFpEF manifestation includes worsening congestion, requirement to frequently alter therapy, declining functionality, and end-organ dysfunction. One may develop an endpoint that is both related to HF and responsive to changes over time, acting not as a surrogate for *hard outcomes* but as an additional *primary* outcome. The pertinent domains of such an endpoint may include cardiac structure and function, congestion and medication status, and functionality. Designing, scoring, and validating such an endpoint needs further research.

CLINICAL TRIAL PROTOCOL DEVELOPMENT AND CONDUCT

Careful attention should be focused on clinical trial protocol development, patient selection, and the trial execution.

Hospitalized Heart Failure

Whether patients with dyspnea who have preserved EF truly have HFpEF in the outpatient setting is often debated. The criteria used to select patients in previous trials have varied (Table 5) and most included a clinical diagnosis and an LVEF above a certain threshold, which in turn also varied and was arbitrary. In contrast, hospitalized patients with obvious fluid overload may provide a more definitive HFpEF population, who are also at a significantly higher risk. There is a tremendous need to identify HFpEF treatment in general, but especially in patients who are hospitalized.

Need for Sustained Therapies

For the most part, only transient intravenous therapies have been studied in hospitalized patients. Most of these did not improve outcomes, with the exception of seralaxin. In the Relaxin in Acute Heart Failure trial (87), about 45 % of patients had LVEF ≥40%, hence representing one potential avenue to treat hospitalized HFpEF patients. However, considering the continued worsening post-discharge outcomes, oral long-term therapies are needed to improve outcomes. Length of hospital stay, degree of decongestion at discharge, changes in standard treatment, and post-discharge monitoring, all bring additional heterogeneities that need consideration in trial conduct.

Study Population

It is important to identify the drivers of adverse events in HFpEF. Determining how the risks can be identified with routine parameter vs. specific tests, e.g. exercise pulmonary pressure measurement, needs study. It is unclear whether patients with specific cause leading to admission, e.g. hypertensive emergency or tachyarrhythmia, should be included in trials. Other markers such as wedge pressure remain ill characterized; e.g., how high does it need to be at rest or exercise to identify a responder population and how does its role differ in hospitalized versus ambulatory patients. Biomarkers may be helpful, but most have often been mostly validated in HFrEF and their role may differ in HFpEF, necessitating better characterization in this population.

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Abbreviations

EF	ejection fraction
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HHF	hospitalized heart failure
LV	left ventricular
LA	left atrial
NP	natriuretic peptide

References

1. Steinberg BA, Zhao X, Heidenreich PA, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation. 2012; 126:65–75. [PubMed: 22615345]
2. Philbin EF, Rocco TA Jr, Lindenmuth NW, Ulrich K, Jenkins PL. Systolic versus diastolic heart failure in community practice: clinical features, outcomes, and the use of angiotensin-converting enzyme inhibitors. Am J Med. 2000; 109:605–13. [PubMed: 11099679]
3. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol. 1999; 33:1948–55. [PubMed: 10362198]
4. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol. 2006; 47:76–84. [PubMed: 16386668]
5. 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. 2006; 355:251–9. [PubMed: 16855265]
6. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med. 2006; 355:260–9. [PubMed: 16855266]

7. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007; 50:768–77. [PubMed: 17707182]
8. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation. 2005; 112:3738–44. [PubMed: 16330684]
9. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? J Am Coll Cardiol. 2012; 60:2349–56. [PubMed: 23141494]
10. Zile MR, Gaasch WH, Anand IS, et al. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. Circulation. 2010; 121:1393–405. [PubMed: 20231531]
11. Farr MJ, Lang CC, Lamanca JJ, et al. Cardiopulmonary exercise variables in diastolic versus systolic heart failure. Am J Cardiol. 2008; 102:203–6. [PubMed: 18602522]
12. Lewis EF, Lamas GA, O'Meara E, et al. Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. Eur J Heart Fail. 2007; 9:83–91. [PubMed: 17188020]
13. Aronow WS, Kronzon I. Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction. Am J Cardiol. 1993; 71:602–4. [PubMed: 8438750]
14. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. Am J Cardiol. 1997; 80:207–9. [PubMed: 9230162]
15. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003; 362:777–81. [PubMed: 13678871]
16. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006; 27:2338–45. [PubMed: 16963472]
17. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008; 359:2456–67. [PubMed: 19001508]
18. Yip GW, Wang M, Wang T, et al. The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. Heart. 2008; 94:573–80. [PubMed: 18208835]
19. Kitzman DW, Hundley WG, Brubaker PH, et al. A randomized double-blind trial of enalapril in older patients with heart failure and preserved ejection fraction: effects on exercise tolerance and arterial distensibility. Circ Heart Fail. 2010; 3:477–85. [PubMed: 20516425]
20. Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. Am J Cardiol. 1990; 66:981–6. [PubMed: 2220622]
21. Hung MJ, Cherng WJ, Kuo LT, Wang CH. Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure. Int J Clin Pract. 2002; 56:57–62. [PubMed: 11831838]
22. Nodari S, Metra M, Dei Cas L. Beta-blocker treatment of patients with diastolic heart failure and arterial hypertension. A prospective, randomized, comparison of the long-term effects of atenolol vs. nebivolol. Eur J Heart Fail. 2003; 5:621–7. [PubMed: 14607201]
23. Bergstrom A, Andersson B, Edner M, Nylander E, Persson H, Dahlstrom U. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). Eur J Heart Fail. 2004; 6:453–61. [PubMed: 15182771]
24. Mottram PM, Haluska B, Leano R, Cowley D, Stowasser M, Marwick TH. Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. Circulation. 2004; 110:558–65. [PubMed: 15277317]

25. Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation. 2006; 114:397–403. [PubMed: 16864724]
26. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF). J Card Fail. 2011; 17:634–42. [PubMed: 21807324]
27. 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. 2013; 309:781–91. [PubMed: 23443441]
28. 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. 2013:1–10.
29. 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. 2012; 14:219–25. [PubMed: 22147202]
30. Yamamoto K, Origasa H, Hori M. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail. 2013; 15:110–8. [PubMed: 22983988]
31. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012; 380:1387–95. [PubMed: 22932717]
32. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail. 2010; 3:659–67. [PubMed: 20852060]
33. Edelmann F, Gelbrich G, Dungen HD, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol. 2011; 58:1780–91. [PubMed: 21996391]
34. Smart NA, Haluska B, Jeffriess L, Leung D. Exercise training in heart failure with preserved systolic function: a randomized controlled trial of the effects on cardiac function and functional capacity. Congest Heart Fail. 2012; 18:295–301. [PubMed: 22536983]
35. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. J Am Coll Cardiol. 2012; 60:120–8. [PubMed: 22766338]
36. Fujimoto N, Prasad A, Hastings JL, et al. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. Am Heart J. 2012; 164:869–77. [PubMed: 23194487]
37. Kitzman DW, Brubaker PH, Herrington DM, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. J Am Coll Cardiol. 2013; 62:584–92. [PubMed: 23665370]
38. Borlaug BA, Olson TP, Lam CS, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2010; 56:845–54. [PubMed: 20813282]
39. 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. 2010; 56:855–63. [PubMed: 20813283]
40. Paulus WJ. Culprit Mechanism(s) for Exercise Intolerance in Heart Failure With Normal Ejection Fraction. J Am Coll Cardiol. 2010; 56:864–6. [PubMed: 20813284]
41. 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. 2007; 115:1982–90. [PubMed: 17404159]

42. van Heerebeek L, Borbely A, Niessen HW, et al. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation. 2006; 113:1966–73. [PubMed: 16618817]
43. Kotter S, Gout L, Von Frieling-Salewsky M, et al. Differential changes in titin domain phosphorylation increase myofilament stiffness in failing human hearts. Cardiovasc Res. 2013; 99:648–56. [PubMed: 23764881]
44. Chung CS, Hutchinson KR, Methawasin M, et al. Shortening of the elastic tandem immunoglobulin segment of titin leads to diastolic dysfunction. Circulation. 2013; 128:19–28. [PubMed: 23709671]
45. 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. 2010; 3:588–95. [PubMed: 20543134]
46. Bruch C, Stypmann J, Grude M, Gradaus R, Breithardt G, Wichter T. Left bundle branch block in chronic heart failure-impact on diastolic function, filling pressures, and B-type natriuretic peptide levels. J Am Soc Echocardiogr. 2006; 19:95–101. [PubMed: 16423676]
47. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. Heart Fail Clin. 2008; 4:23–36. [PubMed: 18313622]
48. Shah SJ. Evolving approaches to the management of heart failure with preserved ejection fraction in patients with coronary artery disease. Curr Treat Options Cardiovasc Med. 2010; 12:58–75. [PubMed: 20842482]
49. Tamarappoo BK, John BT, Reinier K, et al. Vulnerable Myocardial Interstitium in Patients With Isolated Left Ventricular Hypertrophy and Sudden Cardiac Death: A Postmortem Histological Evaluation. J Am Heart Assoc. 2012; 1
50. Thum T, Gross C, Fiedler J, et al. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature. 2008; 456:980–4. [PubMed: 19043405]
51. Persson H, Lonn E, Edner M, et al. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence:results from the CHARM Echocardiographic Substudy-CHARMES. J Am Coll Cardiol. 2007; 49:687–94. [PubMed: 17291934]
52. Zile MR, Gottdiener JS, Hetzel SJ, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. Circulation. 2011; 124:2491–501. [PubMed: 22064591]
53. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. J Am Coll Cardiol. 2007; 49:198–207. [PubMed: 17222731]
54. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens. 2002; 15:426–44. [PubMed: 12022246]
55. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation. 2005; 112:2254–62. [PubMed: 16203909]
56. Balmain S, Padmanabhan N, Ferrell WR, Morton JJ, McMurray JJ. Differences in arterial compliance, microvascular function and venous capacitance between patients with heart failure and either preserved or reduced left ventricular systolic function. Eur J Heart Fail. 2007; 9:865–71. [PubMed: 17644472]
57. Akiyama E, Sugiyama S, Matsuzawa Y, et al. Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol. 2012; 60:1778–86. [PubMed: 23040568]
58. Lam CS, Brutsaert DL. Endothelial dysfunction: a pathophysiologic factor in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2012; 60:1787–9. [PubMed: 23040569]
59. Borlaug BA, Kass DA. Mechanisms of diastolic dysfunction in heart failure. Trends Cardiovasc Med. 2006; 16:273–9. [PubMed: 17055383]
60. Guazzi M, Arena R. Pulmonary hypertension with left-sided heart disease. Nat Rev Cardiol. 2010; 7:648–59. [PubMed: 20924360]

61. Abel FL, Waldhausen JA. Effects of alterations in pulmonary vascular resistance on right ventricular function. J Thorac Cardiovasc Surg. 1967; 54:886–94. [PubMed: 6059019]
62. Morris DA, Gailani M, Vaz Perez A, et al. Right ventricular myocardial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. J Am Soc Echocardiogr. 2011; 24:886–97. [PubMed: 21601421]
63. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol. 2012; 59:998–1005. [PubMed: 22402071]
64. Mohammed SF, Borlaug BA, Roger VL, et al. Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community-based study. Circ Heart Fail. 2012; 5:710–9. [PubMed: 23076838]
65. Lam CS, Lyass A, Kraigher-Krainer E, et al. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. Circulation. 2011; 124:24–30. [PubMed: 21670229]
66. McManus DD, Hsu G, Sung SH, et al. Atrial fibrillation and outcomes in heart failure with preserved versus reduced left ventricular ejection fraction. J Am Heart Assoc. 2013; 2:e005694. [PubMed: 23525446]
67. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013; 62:263–71. [PubMed: 23684677]
68. Grewal J, McKelvie RS, Persson H, et al. Usefulness of N-terminal pro-brain natriuretic Peptide and brain natriuretic peptide to predict cardiovascular outcomes in patients with heart failure and preserved left ventricular ejection fraction. Am J Cardiol. 2008; 102:733–7. [PubMed: 18773998]
69. Rossi A, Cicoira M, Florea VG, et al. Chronic heart failure with preserved left ventricular ejection fraction: diagnostic and prognostic value of left atrial size. Int J Cardiol. 2006; 110:386–92. [PubMed: 16325283]
70. Ohtani T, Mohammed SF, Yamamoto K, et al. Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodelling and poor outcomes in heart failure with preserved ejection fraction. Eur Heart J. 2012; 33:1742–9. [PubMed: 22645191]
71. Wang M, Yip GW, Wang AY, et al. Tissue Doppler imaging provides incremental prognostic value in patients with systemic hypertension and left ventricular hypertrophy. J Hypertens. 2005; 23:183–91. [PubMed: 15643141]
72. Wong TC, Piehler K, Meier CG, et al. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. Circulation. 2012; 126:1206–16. [PubMed: 22851543]
73. Wong TC, Piehler KM, Kang IA, et al. Myocardial extracellular volume fraction quantified by cardiovascular magnetic resonance is increased in diabetes and associated with mortality and incident heart failure admission. Eur Heart J. 2013
74. 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. 2009; 30:3027–36. [PubMed: 19720638]
75. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011; 377:658–66. [PubMed: 21315441]
76. Bourge RC, Abraham WT, Adamson PB, et al. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. J Am Coll Cardiol. 2008; 51:1073–9. [PubMed: 18342224]
77. Sweitzer NK, Lopatin M, Yancy CW, Mills RM, Stevenson LW. Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (> or =55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (<40%) fractions. Am J Cardiol. 2008; 101:1151–6. [PubMed: 18394450]
78. Katz SD, Hryniewicz K, Hriljac I, et al. Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. Circulation. 2005; 111:310–4. [PubMed: 15655134]

79. de Boer RA, Lok DJ, Jaarsma T, et al. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. Ann Med. 2011; 43:60–8. [PubMed: 21189092]
80. Yu L, Ruifrok WP, Meissner M, et al. Genetic and pharmacological inhibition of galectin-3 prevents cardiac remodeling by interfering with myocardial fibrogenesis. Circ Heart Fail. 2013; 6:107–17. [PubMed: 23230309]
81. Krum H, Elsik M, Schneider HG, et al. Relation of peripheral collagen markers to death and hospitalization in patients with heart failure and preserved ejection fraction: results of the I-PRESERVE collagen substudy. Circ Heart Fail. 2011; 4:561–8. [PubMed: 21750125]
82. 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. 2012; 110:870–6. [PubMed: 22681864]
83. Anand IS, Rector TS, Cleland JG, et al. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. Circ Heart Fail. 2011; 4:569–77. [PubMed: 21715583]
84. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Mediano O, Martinez I, Villamor J. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. Circulation. 2005; 112:375–83. [PubMed: 16009798]
85. Cha YM, Wokhlu A, Asirvatham SJ, et al. Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: a comparison to systolic dysfunction and normal ventricular function. Circ Arrhythm Electrophysiol. 2011; 4:724–32. [PubMed: 21747059]
86. Allen LA, Gheorghiade M, Reid KJ, et al. Identifying patients hospitalized with heart failure at risk for unfavorable future quality of life. Circ Cardiovasc Qual Outcomes. 2011; 4:389–98. [PubMed: 21693723]
87. Teerlink JR, Cotter G, Davison BA, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet. 2013; 381:29–39. [PubMed: 23141816]
88. Little WC, Zile MR, Kitzman DW, Hundley WG, O'Brien TX, Degroof RC. The effect of alagebrium chloride (ALT-711), a novel glucose cross-link breaker, in the treatment of elderly patients with diastolic heart failure. J Card Fail. 2005; 11:191–5. [PubMed: 15812746]
89. Zile MR, Bourge RC, Bennett TD, et al. Application of implantable hemodynamic monitoring in the management of patients with diastolic heart failure: a subgroup analysis of the COMPASS-HF trial. J Card Fail. 2008; 14:816–23. [PubMed: 19041044]
90. Orozco-Gutierrez JJ, Castillo-Martinez L, Orea-Tejeda A, et al. Effect of L-arginine or L-citrulline oral supplementation on blood pressure and right ventricular function in heart failure patients with preserved ejection fraction. Cardiol J. 2010; 17:612–8. [PubMed: 21154265]
91. 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. 2011; 124:164–74. [PubMed: 21709061]
92. Desai AS, Lewis EF, Li R, et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. Am Heart J. 2011; 162:966–72. e10. [PubMed: 22137068]

SUMMARY

HFpEF prevalence is increasing and these patients face impaired health status and an unabated high risk for adverse outcomes. The economic burden of HFpEF is substantial. To date, there is no approved therapy for these patients. To identify new therapies, a deeper understanding of the sub-populations that fit under the HFpEF umbrella, and more specific molecular targets for engagement, are needed. The following are the summary recommendations from the meeting:

1. There is an urgent need to focus on drug and device development for HFpEF and clinical, translational and basic research should receive high priority for support from academia, industry, non-governmental organizations, and federal agencies.
2. The diagnostic certainty and the high post-discharge event rate identify hospitalized HFpEF patients as a particularly important HFpEF population.
3. Currently, there are no animal models that sufficiently recapitulate enough of the HFpEF syndrome to require drug and device testing before application to human studies. Research to develop relevant animal models is needed.
4. The lack of animal models should not, however, prevent human testing of promising therapies. To promote fundamental understanding, animal models of HFpEF should be developed alongside attempts to understand better the clinical phenotypes of HFpEF.
5. There is a need to characterize HFpEF further to understand better clinical manifestations, contribution of comorbidities, and mechanisms. This may aid development of objective classification of HFpEF. Developing longitudinal registries focused on collecting clinical, imaging, laboratory, treatment patterns, and outcomes data may facilitate this.
6. There are many potential cardiovascular structural and functional targets for phase II trials. However, their responsiveness to change and correlation with phase III outcomes are not known. All phase II HFpEF studies should consider incorporating a set of cardiovascular structural and functional parameters, biomarkers, and functional capacity indicators, to improve our understanding of the basic mechanisms of the disease. Currently, there is no consensus in this regard, necessitating the need for a dialogue between academia, industry, and regulators.
7. Though many mechanisms for the development and progression of HFpEF are cited, e.g. endothelial dysfunction, data for them are sparse, underscoring the need for further human mechanistic studies.
8. Further data are needed to understand the differences between hospitalized and stable outpatients with HFpEF, and the triggers for decompensation, to develop new therapies.

9. Novel phase III outcome measures that supplement mortality and hospitalization risk, and incorporate features reflective of the “patient journey” with HFpEF longitudinally should be developed.

10. Careful patient selection and a focus on safety in drug development are important considerations in HFpEF.

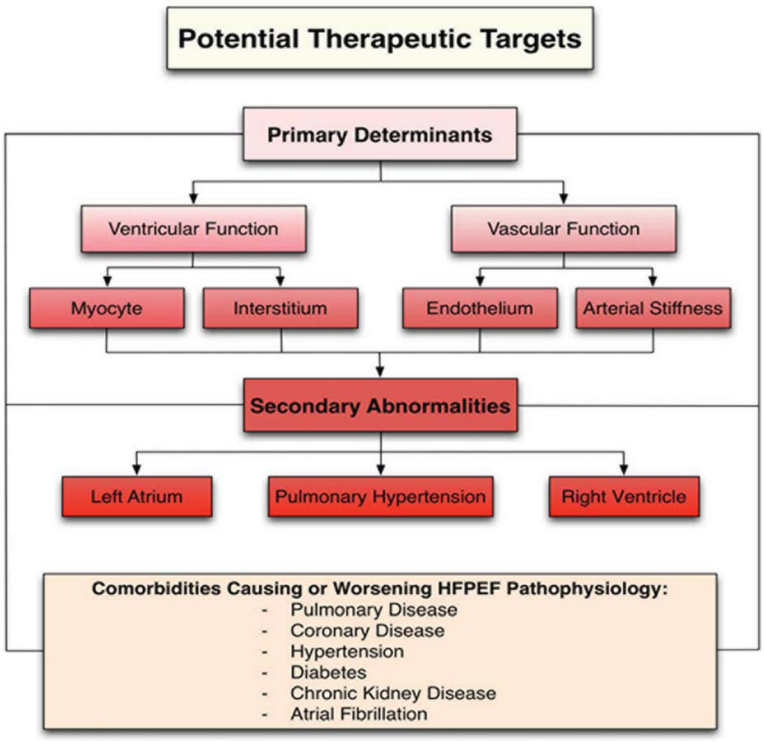

Figure 1.
Potential Therapeutic Targets in Heart Failure with Preserved Ejection Fraction

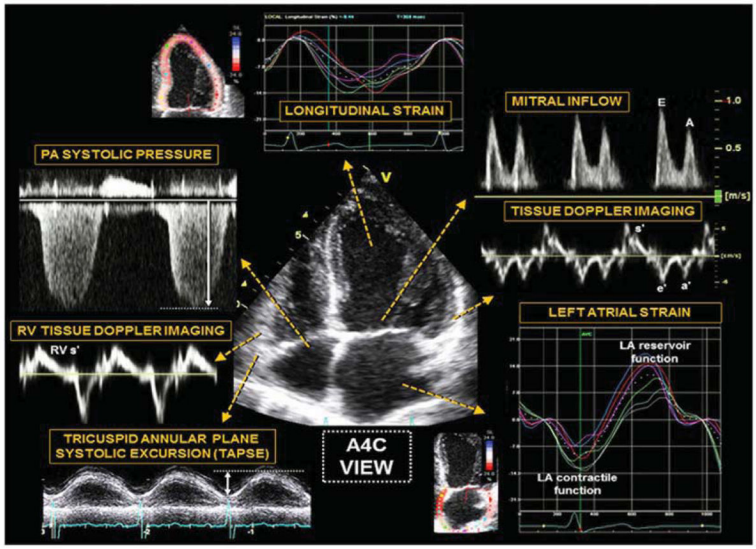

Figure 2.

Comprehensive Echocardiographic Phenotypic Analysis of Heart Failure with Preserved Ejection Fraction

Comprehensive echocardiography, including two dimensional, Doppler, tissue Doppler, and speckle tracking, allows for detailed phenotypic analysis of cardiac structure, function, and mechanics in patients with heart failure with preserved ejection fraction. The figure shows examples of information that can be obtained from the apical 4-chamber view. Clockwise from the top: speckle-tracking echocardiography for assessment of LV regional and global longitudinal strain (early diastolic strain rate can also be obtained in this view). Mitral inflow and tissue Doppler imaging of the septal and lateral mitral annulus provide information on LV diastolic function grade and estimated LV filling pressure (E/e′ ratio), along with assessment of longitudinal systolic (s′) and atrial (a′) function. Speckle-tracking analysis of LA function provides peak LA contractile function (peak negative longitudinal LA strain) and LA reservoir function (peak positive longitudinal LA strain). Tricuspid annular plane systolic function (TAPSE) and basal RV free wall peak longitudinal tissue Doppler velocity (RV s′) provide information on longitudinal RV function, as does speckle tracking echocardiography of the RV (not shown). Finally, analysis of the tricuspid regurgitant jet Doppler profile, when added to the estimated RA pressure, provides an estimate of the PA systolic pressure. Additional data available from the apical 4-chamber view include assessment of LV volumes and ejection fraction, LA volume, and RV size and global systolic function (e.g., RV fractional area change).

LV = left ventricular; LA = left atrial; PA = pulmonary artery; RV = right ventricular; RA = right atrial; A4C = apical 4-chamber

Courtesy – Sanjiv J Shah, MD

Table 1

Epidemiology of Heart Failure with Preserved Ejection Fraction

Type of Studies	Population	Prevalence and Ejection Fraction	Mortality	Readmission
Cohort Studies				
Vasan, 1999 (3) **(FHS)**	73 outpatients	51%, EF≥50%	**Annual during median 6.2 yr:** 8.7%	
Owan, 2006 (5) **(Olmsted County)**	4596 HHF patients	47%, EF≥50%	**1 yr:** 29% **5-yr:** 65%	
Bhatia, 2006 (6) **(Ontario)**	2802 HHF patients	31%, EF≥50% 13%, 40%≤EF<50%	**30 d:** 5.3 **1 yr:** 22.2%	**30 d:** 4.5, EF≥50% **1 yr:** 13.5%, EF≥50%
Steinberg, 2012 (1) **(GWGL-HF)**	110,621 HHF patients	36%, EF≥50% 14%, 40%≤EF<50%	**In-hospital:** 2.5%, EF≥50% 2.3%, 40%≤EF<50%	
Registries				
Philbin, 2000 (2) **(MISCHF)**	1,291 HHF patients	24%, EF≥50% 18%, 40%≤EF<50%	**In-hospital:** 3.0%, EF>50% 5.0%, 40%≤EF<50%; **6 mo:** 14.0%, EF>50% 15.0%, 40%≤EF<50%	
Fonarow, 2007 (7) **(OPTIMIZE-HF)**	41,267 HHF patients	51.2%, EF≥40% 34.6%, 40%≤EF<50% 47.6%, EF>50%	**In-hospital:** 2.9%, EF≥40% 3.0%, 40%≤EF<50%, 2.9%, EF>50% **60–90 d:** 9.5%, EF≥40% 9.2%, 40%≤EF<50%, 9.3%, EF>50%	**60–90 d:** 29.2%, EF≥40% 29.0%, 40%≤EF<50% 30.9%, EF>50%
Yancy, 2006 (4) **ADHERE**	52,187 HHF patients	50.4%, EF≥40%	**In-hospital:** 2.8%, EF≥40%	

ADHERE: Acute Decompensated Heart Failure National Registry; FHS: Framingham Heart Study; GWGL-HF: Get With the Guidelines – Heart Failure; HHF: hospitalized heart failure, MISCHF: Management to Improve Survival in Congestive Heart Failure; OPTIMIZE-HF: Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure

Table 2

Clinical Trials in Patients with Heart Failure and Preserved Ejection Fraction

Trial/Intervention	Duration (months)	N	Systolic Function	Diastolic Function as Inclusion Criterion	Positive outcomes	Mortality/Readmission
Medication Trials						
Setaro, 1990 (20) **Verapamil**	1.25	40	LVEF >45%	Peak filling rate <2.5 edv/sec	Improved clinical status Increased exercise time and diastolic filling rate	
Aronow, 1993 (13) **Enalapril**	3	21	LVEF >50%	Not determined	Improved clinical status Increased exercise time Decreased LV mass/increased E/A ratio	
Aronow, 1997 (14) **Propanolol + ACEI**	12	158	LVEF ≥40%	Not determined	Reduced Mortality −30% & combined mortality + nonfatal MI Increased LVEF - Reduced LV mass	**1 y:** 65.8%
Hung, 2002 (21) **Verapamil**	3	30	LVEF >50%	Not determined	Improved clinical status Increased exercise time Increased mitral A wave duration/pulmonary venous atrial systolic reversal duration & isovolumic relaxation	
Nodari, 2003 (22) **Nebivolol vs. Atenolol**	6	26	LVEF ≥ 50%, LVEDD <60 mm or <32 mm/m^2	E/A <1.0 & PCWP rest >12 mm Hg or exercise >20 mm Hg	Nebivolol: Improved exercise capacity (VO_2peak; VO_2AT; VE/VCO_2). Decreased LVED posterior wall thickness. Decreased mPAP & PCWP at rest and exercise. Both: Reduced LV mass. Increased E/A. Decreased LVED septal wall thickness	
Yusuf, 2003 (15) **Candesartan**	36.6 (median)	3,023	LVEF >40%	Not determined	Reduction in CV death+HF-hospitalization Fewer recurrent HF-hospitalizations	**Median 36.6 mo:** 11.3%/17.1% (for HF)
Bergström, 2004 (23) **Carvedilol**	6	97	LVEF >45%, LVWMI ≤1.2	E/A <ARRV or IVRT>ARRV; E/A normal plus PVS/DV <ARRV or PVARD-MAD >20 ms or PVARV >ARRV	Increased E/A	
Mottram, 2004 (24) **Spironolactoce**	6	30	LVEF >50%	E/A <1 DT >250m/sec	Increased SR and peak systolic strain Decreased LA area and PVARV	
Ahmed, 2006 (25) **Digoxin**	37 (mean)	988	LVEF >45%	Not determined	No long-term effect on mortality or HF-hospitalization	**Mean 37 mo:** 23.4%/20% (for HF)
Cleland, 2006 (16) **Perindopril**	25.2	850	LVEF >40%, LVWMI: 1.4–1,6	LAD >25 mm/m^2 or >40 mm; LVWT ≥12 mm, IVRT >105 ms, E/A <0.5 DT >280 ms,	Reduced mortality + HF-hospitalization trend at 1 yr Reduced HF-hospitalization at 1 yr Improved NYHA at 1 yr and 6MWT at 1 yr	**1y:** 13.1% combined mortality + HF admission 10.2% HF admission

Trial/Intervention	Duration (months)	N	Systolic Function	Diastolic Function as Inclusion Criterion	Positive outcomes	Mortality/Readmission
Massie, 2008 (17) **Irbesartan**	49.5	4,128	LVEF ≥45%	LVH and LAD >46 mm in men & 42 mm in women	None	**Mean 49.5 mo:** 36.5% combined mortality + CV admission
Yip, 2008 (18) **Ramipril vs. Irbesartan**	12	151	LVEF >45%	Not determined	Short term increased Em and Sm Decreased NT-proBNP levels at 1 yr	**1 y:** 2.7%/11.3% (for HF)
Kitzman, 2010 (19) **Enalapril**	12	71	LVEF ≥50%	Not determined	None	
Deswal, 2011 (26) **Eplerenone**	6	44	LVEF ≥50%	Not determined	Reduced collagen turnover circulating biomarkers Decreased E/e′	**6 mo:** 0%/6.8% (for HF)
Conraads, 2012 (29) **Nebivolol**	6	116	LVEF >45% LVEDD <3.2 cc/m^2 or LVEDVI <102 mL/m^2	E/e′ >15 or E/e′: 8–15 if: E/A <0.5 DT >280 ms	None	
Solomon, 2012 (31) **Neprilysin**	3	301	LVEF ≥45%	Not determined	NT-proBNP reduced	**3 mo:** 1%/3.3% (for HF)
Yamamoto, 2013 (30) **Carvedilol**	38	245	LVEF >40%	Not determined	None	**38 mo:** 25.7% mortality + HF admission
Edelmann, 2013 (27) **Aldosterone**	13	422	LVEF ≥50%	Grade ≥1	E/e′ declined at 6 mo and maintained at 12 mo LVEDD and LVM index decreased	
Redfield, 2013 (28) **Sildenafil**	6	216	LVEF ≥50%	Not determined	None	
Other Type of Trials						
Kitzman, 2010 (32) **aerobic exercise**	4	53	LVEF ≥50%	Not determined	Improved exercise capacity (VO_2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). Increased HRpeak, HRR, O_2pulse. Improved physical score of MLHFQ	
Edelmann, 2011 (33) **aerobic & anaerobic exercise**	3	64	LVEF ≥50%	Grade ≥1	Improved exercise capacity (VO_2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). Improved E/e′. Decreased LAVI. Improved SF-36 and MLHFQ scores. Reduced procollagen type 1 blood levels	
Smart, 2012 (34) **aerobic exercise**	4	30	LVEF >45%	Delayed relaxation or pseudonormal filling pattern	Increased exercise capacity (VO_2peak, workload). Increased CO. Improved strain rate, SV, and CO, in patients with >10% increase in VO_2peak	
Haykowsky, 2012 (35) **aerobic exercise**	4	40	LVEF ≥50%	Not determined	Improved exercise capacity (VO_2peak).	

Trial/Intervention	Duration (months)	N	Systolic Function	Diastolic Function as Inclusion Criterion	Positive outcomes	Mortality/Readmission
					Increased HRpeak, HRR. Increased estimated peak and reserve A-VO2 Diff. Increased HRpeak, HRR. Increased estimated peak and reserve A-VO2 Diff. Increased estimated peak and reserve circulatory power	
Fujimoto, 2012 (36) **aerobic exercise**	12	20	LVEF >50%	Not determined	Improved E/A	
Kitzman, 2013 (37)	4	63	LVEF ≥50%	Not determined	Improved exercise capacity (VO2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). Increased HRpeak, Improved SF-36 score	

6MWT: six minute walk test; ARRV: age-related reference value; A-VO2 Diff: arterial-venous oxygen difference; CO: cardiac output; DT: deceleration time; edv: end diastolic volumes; Em: peak early diastolic velocity; HRpeak: peak heart rate; HRR: heart rate reserve; IQR: interquartile range; IVRT: isovolumic relaxation time; LAD: left atrial diameter; LAVI: left ventricular atrial volume; LV: left ventricular; LVED: left ventricular end-diastolic; LVEDD: left ventricular end-diastolic diameter; LVEDVI: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; LVM: left ventricular mass; LVWMI: left ventricular wall motion index; LVWT: left ventricular wall thickness; MAD: mitral atrial duration; MI: myocardial infarction; mo: months; MLHFQ: Minnesota Living with Heart Failure Questionnaire; mPAP: mean pulmonary artery pressure; NT-proBNP: N terminal pro brain natriuretic peptide; NYHA: New York Heart Association; PCWP: pulmonary capillary wedge pressure; PVARD: pulmonary vein atrial reversal duration; PVARV: pulmonary vein systolic diastolic velocity; PVS/DV: pulmonary vein systolic/diastolic velocity; SF-36: 36-Item Short Form Health Survey; Sm: peak systolic velocity; SR: strain rate; VAT: ventilatory anaerobic threshold; VO_2peak: peak oxygen consumption; VO_2AT: oxygen consumption at anaerobic threshold; VE/VCO_2: ventilatory equivalent for carbon dioxide; yrs: years

Table 3

Potential Phase II Clinical Trial Targets

Parameters	
Left Ventricle	
Systolic Function	
Ejection fraction	Systolic time intervals
Regional myocardial velocities, strain, systolic strain rate	Isovolumic contraction time
dP/dt	Noninvasive single-beat end-systolic elastance
End-systolic pressure/volume ratio	End-systolic stress – velocity of circumferential fiber shortening relation
Stroke work	Preload recruitable stroke work
Diastolic Function	
E wave velocity	E/A ratio
E wave deceleration time	Pulmonary venous flow
Color M-mode velocity of propagation	E′
E/e′ ratio	Noninvasive single-beat end-systolic elastance
End-diastolic pressure/end-diastolic volume	End-diastolic pressure/stroke volume
Early diastolic strain rate	
Structure	
Left ventricular end-systolic volume index	Left ventricular end-diastolic volume index
Left ventricular mass index	Extracellular volume fraction
Relative wall thickness	LV mass/volume ratio
Left Atrium	
Left atrial volume/index (LAVI)	Left atrial strain
A velocity	a′ velocity
Left atrial function/index (LAFI)	
Hemodynamics	
Right Heart Catheterization	
Pulmonary capillary wedge pressure	Pulmonary artery pressure
Pulmonary vascular resistance	Trans-pulmonary gradient (mPAP-PCWP)
Pulmonary vascular gradient (PADP-PCWP)	

Parameters	
Echocardiogram-derived	
Pulmonary capillary wedge pressure approximation by E/e′	Mean pulmonary artery pressure by end-diastolic pulmonary regurgitation gradient
Systolic pulmonary artery pressure by tricuspid regurgitation gradient	Pulmonary vascular resistance approximation by TR velocity/TVIRVOT ratio or RVSP-E/e′/RVOT VTI
Vascular and Endothelial Function	
Central pulse pressure	Pulse wave velocity
Flow mediate dilatation	Reactive hyperemia index
Augmentation Index	
Exercise Capacity	
Walking tests	
6 minute walk test	Shuttle walking test
Cardiopulmonary Exercise Test	
VO_2max	VO_2 at anaerobic threshold
VE/VCO_2	Exercise oscillatory breathing (EOB)
Biomarkers	
Cardiac Load and Wall Stress	
Natriuretic Peptides	
Cardiac Fibrosis and Collagen Turnover	
Procollagen type I N-terminal pro-peptides	Procollagen type III N-terminal pro-peptides
Matrix metalloproteinases	Tissue inhibitors of matrix metalloproteinases
β-galactoside-binding protein Galectin-3	
Inflammation	
Growth differentiation factor 15	High sensitivity C reactive protein
Interleukins	
Myocardial Injury	
High sensitivity Troponin T	

TR: tricuspid regargitation; TVIRVOT: right ventricular outflow tract time-velocity integral; VE/VCO_2: ventilatory equivalent ratio for carbon dioxide; VO_2: oxygen consumption; VO_2max: maximum oxygen consumption

Table 4

Echocardiographic Changes, Biomarkers, and Prognosis of Heart Failure with Preserved Ejection Fraction

Marker (Method)	Study	Population	Outcome	Predictive properties
E/A (severity of DD) (Echocardiography	Persson, 2007 (51)	293 HF patients with LVEF>40% participating in CHARMES	Composite CV mortality or HF admission	Moderate or severe DD HR 3.27 (1.41–7.56) [1]
e´ (Echocardiography)	Wang, 2005 (71)	174 hypertensive individuals with LVH	Cardiac mortality	HR 0.49 (0.32–0.76) [2]
LV Mass[3] (Echocardiography)	Zile, 2012 (52)	745 HF patients with LVEF≥45% participating in I-PRESERVE	All-cause mortality or hospitalization for worsening HF, MI, stroke, unstable angina, or ventricular or atrial dysrhythmia	HR 1.019 (1.009–1.029) [4]
LV Mass/Volume (Echocardiography				HR 1.296 (1.074–1.564) [4]
Enlarged LA[5] (Echocardiography				HR 1.470 (1.029, 2.101) [4]
LAD[6] (Echocardiography)	Rossi, 2006 (69)	183 HF patients with LVEF>45%	All-cause mortality	HR 2.45 (1.12 – 5.41) [7]
Diastolic wall stress[8] (Echocardiography)	Ohtani, 2012 (70)	327 HF patients with LVEF≥50%	Composite CV mortality or HF admission	HR 1.03 (1.01–1.06) [9]
Natriuretic peptides (blood sample analysis)	Grewal, 2008 (68)	181 HF patients with LVEF>40% participating in CHARMES	Composite CV mortality or HF admission or MI or stroke	NT-proBNP>300 pg/ml HR 5.8 (1.3–26.4) Nt-proBNP>600 pg/ml HR 8.0 (2.6–24.8) BNP>100 pg/ml HR 3.1 (1.2–8.2)

[1] After adjustment for age, gender, LVEF, diabetes mellitus, atrial fibrillation, previous HF admission, and treatment arm

[2] After adjustment for age, and inter-ventricular septal thickness in diastole, left ventricular ejection fraction, peak velocity during systole, peak velocity during late diastole, peak E-wave velocity to peak velocity during early diastole ratio (E/Em) and pseudonormal diastolic filling pattern or restrictive diastolic filling pattern

[3] Indexed to height$^{2.7}$

[4] After adjustment for log NT-proBNP, age, diabetes mellitus, hospitalization for worsening HF within 6 months preceding randomization, COPD or asthma, neutrophils, and LVEF

[5] Mildly enlarged LA if LA area was 20 to 30 cm^2 and moderately-to-severely enlarged LA if LA area was >31 cm^2

[6] Left atrial diameter >5 cm used to define left atrial enlargement

[7] After adjustment for clinical and echocardiographic parameters

[8] Diastolic wall stress was defined, as the ratio of the posterior wall thickness at end-systole minus the posterior wall thickness at end-diastole to the posterior wall thickness at end-systole

[9] After adjustment for age, gender, echocardiographic variables, and log BNP

BNP: B-type natriuretic peptide; CI: confidence interval; CV: cardiovascular; DD: diastolic dysfunction; HF: heart failure; LVEF: left ventricular ejection fraction; MI; myocardial infarction; HR: hazard ratio; NT-proBNP: N terminal pro brain natriuretic peptide

Table 5

Inclusion Criteria in Randomized Clinical Trials in Patients with Heart Failure with Preserved Ejection Fraction

Trial	Inclusion criteria
Setaro, 1990 (20)	Not determined etiology LVEF >45%[1] LV peak filling rate >2.5 edv/s
Aronow, 1997 (14)	Prior MI (>6 months) LVEF ≥40%
Nodari, 2003 (22)	Mild hypertension VO_2peak ≤25 ml/kg/min LVEF ≥ 50% LVEDD <60 mm or <32 mm/m^2 E/A <1.0 PCWP rest >12 mm Hg or exercise >20 mm Hg
Bergström, 2004 (23)	LVEF >45% LVWMI ≤1.2[2] At least one of the following: E/A <ARRV IVRT>ARRV E/A normal plus PVS/DV <ARRV or PVARD-MAD >20 ms or PVARV >ARRV
Little, 2005 (88)	LVEF >50%
Cleland, 2006 (16)	At least 2 of the following criteria LVEF >40% LVWMI: 1.4–1,6 LAD >25 mm/m^2 or >40 mm LVWT ≥12 mm At least 1 of the following criteria E/A <0.5 Isovolumic relaxation time >105 ms
Zile, 2008 (89)	LVEF ≥50%
Kitzman, 2010 (19)	No other conditions (cardiac/pulmonary/other) that could mimic HF LVEF ≥50%
Orozco-Gutierrez, 2010 (90)	LVEF ≥ 45% Fractional shortening ≥ 28% LAD > 45 mm LV septal & posterior thickness > 12 mm Slow, inverted, pseudo-normal or restrictive pattern of transmitral Doppler flow
Guazzi, 2011 (91)	In sinus rhythm LVEF ≥50% SPAP ≥40 mmHg

Trial	Inclusion criteria
Conraads, 2012 (29)	LVEF >45% LVEDD <3.2 cc/m^2 or LVEDVI <102 ml/m^2 E/e′ >15 or E/e′: 8–15 if: E/A <0.5 in patients >50 yrs DT >280 ms in patients >50 yrs Ard-Ad >30 ms LAVI >40 ml/m^2 LVMI >149 g/m^2 & >122 g/m in women
Smart, 2012 (34)	LVEF >45% Delayed relaxation or pseudonormal filling
Edelmann, 2013 (27)	LVEF ≥50% Diastolic dysfunction grade ≥1 or atrial fibrillation VO_2peak ≤25 ml/kg/min
Maurer, 2013	LVEF >40%
Aronow, 1993 (13)	Prior MI (>6 months) LVEF >50%
Hung, 2002 (21)	LVEF >50%
Yusuf, 2003 (15)	LVEF >40%
Mottram, 2004 (24)	Hypertension requiring antihypertensive medication and exertional dyspnea No MI or angina LVEF >50% E/A <1 DT >250m/sec
Ahmed, 2006 (25)	In sinus rhythm LVEF >45%
Massie, 2008 (17)	LVEF ≥45% LVH LAD >46 mm in men & >42 mm in women
Yip, 2008 (18)	LVEF >45%
Kitzman, 2010 (32)	No other conditions (cardiac/pulmonary/other) that could mimic HF LVEF ≥50%
Deswal, 2011 (26)	LVEF ≥50% BNP ≥100 pg/mL
Desai, 2011 (92)	LVEF ≥ 45% BNP ≥100 pg/ml or NT-proBNP ≥360 pg/ml
Solomon, 2012 (31)	LVEF ≥ 45% NT-proBNP >400 pg/ml
Yamamoto, 2013 (30)	LVEF >40%
Redfield, 2013 (28)	LVEF ≥50% LA enlargement

Trial	Inclusion criteria
	VO_2peak ≤60%[3] NT- proBNP ≥400 pg/ml or NT- proBNP <400 pg/ml PCWP 20 mmHg at rest and >25 mmHg at exercise

[1]Determined by radionuclide ventriculograms

[2]Determined as akinesia of one segment or less or hypokinesia of 2 segments or less, using a 16 segment model with at least 10 segments visible

[3]Based on the age- and sex–specific normal value while respiratory exchange ration is ≥1.0

Ard-Ad: reverse pulmonary vein atrial systole flow–mitral valve atrial wave flow; ARRV: age-related reference value; BNP: B-type natriuretic peptide; DT: deceleration time; edv: end diastolic volumes ; IVRT: isovolumic relaxation time; LAD: left atrial diameter; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; LVWMI: left ventricular wall motion index; LVWT: left ventricular wall thickness; MAD: mitral atrial duration; MI: myocardial infarction; NT-proBNP: N terminal pro brain natriuretic peptide; PCWP: pulmonary capillary wedge pressure; PVARD: pulmonary vein atrial reversal duration; PVARV: pulmonary vein systolic diastolic velocity; PVS/DV: pulmonary vein systolic/diastolic velocity; s: second; SPAP: pulmonary artery systolic pressure; VO_2peak: peak oxygen consumption; yrs: years