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CME

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 G. F. 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] Giuseppe 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] Mihai Gheorghiade, MD[7]

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CME Objective for This Article: After reading this article, the reader should be able to discuss the following: 1) the prevalence of HFpEF (heart failure with preserved ejection fraction) is increasing, these patients face a high risk for adverse outcomes, and the associated economic consequences are rising; 2) there are no approved therapies for these patients; and 3) to identify new therapies, a deeper understanding of the sub-populations that fit under the HFpEF umbrella, more specific molecular targets for engagement, and improvements in clinical trial design, are needed.

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From the [1]Department of Medicine, Emory Cardiovascular Clinical Research Institute, Emory University, Atlanta, Georgia; [2]Department of Medicine, University of California, Los Angeles, California; [3]Division of Cardiology, Medical University of South Carolina, and RHJ Department of Veterans Affairs Medical Center, Charleston, South Carolina; [4]Cardiovascular Research Institute, National University Health System, Singapore; [5]Global Clinical Development, Bayer HealthCare AG, Wuppertal, Germany; [6]Department of Medicine, University of Pittsburgh Medical Center Heart and Vascular Institute, Pittsburgh, Pennsylvania; [7]Department of Medicine, Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, Illinois; [8]Division of Gerontology, University of Alabama at Birmingham, Birmingham, Alabama; [9]Department of Cardiology, Castle Hill Hospital, Hull York Medical School, Kingston-Upon-Hull, England; [10]Cardiovascular & Metabolism Division, Janssen Pharmaceuticals, Raritan, New Jersey; [11]Institute of Emergency for Cardiovascular Diseases, Cardiology, Bucharest, Romania; [12]Department of Emergency Medicine, Vanderbilt University, Nashville, Tennessee; [13]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland; [14]Department of Cardiology, Athens University Hospital, Attikon, Athens, Greece; [15]Novartis Pharmaceuticals Inc., East Hanover, New Jersey; [16]British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland; [17]Division of Cardiology, University of Brescia, Brescia, Italy; [18]Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; [19]Department of Medicine, Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts; [20]Department of Cardiology, Medical University Graz, Graz, Austria; [21]Division of Cardiology, Department of Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan; [22]Centre for Clinical and Basic Science, San Raffaele-Roma, Rome, Italy; [23]Department of Medicine, Henry Ford Hospital, Detroit, Michigan; [24]Cardiovascular Department, Ospedale Papa Giovanni XXIII, Bergamo, Italy; and the [25]University of California San Francisco and San Francisco Veterans Affairs Medical Center, San Francisco, California. The opinions and information in this article are those of the authors, and do not represent the views and/or policies of the U.S. Food and Drug Administration. Dr. Fonarow has served as a consultant for Novartis, Medtronic, and Gambro; and has received research support from Gambro, the National Institutes of Health, and the Agency for Healthcare Research and Quality. Dr. Zile has received research support from NHLBI, VA, Alere, Bayer, CVRx, Medtronic, Novartis, Sanofi-Aventis; and has served as a consultant for Abbott, Alere, Bayer, BG Med, BMS, Cardiome, Celledon, CorAssist, CVRx, GE Health, HDL, Idenex, Intersection Medical, Medtronic, MicroVide, Novartis, ONO Pharma, Sanofi-Aventis, and Up-To-Date. Dr. Lam has served as a consultant for Bayer and Novartis; and has received research grant support from Boston Scientific, Medtronic, and Vifor Pharma. Dr. Roessig is an employee of Bayer Pharma. Dr. Schelbert received a Prohance contrast as a gift from Bracco for research purposes. Dr. Cleland has received research funding from Amgen; and honoraria from Novartis. Dr. Cody is an employee of Janssen R&D. Dr. Collins has served as a consultant for Novartis, Radiometer, Medtronic, The Medicines Company, Trevena, and Thermo-Fisher Scientific. Dr. Filippatos has served on the steering committee in trials sponsored by Bayer and Corthera. Dr. Lefkowitz is an employee of Novartis. Dr. McMurray was a committee member and co-principal investigator for the PARAGON-HF trial with LCZ696 in HF-PEF, which was sponsored by Novartis. Dr. Misselwitz is an employee of and owns stock for Bayer. Dr. Pfeffer has served as a consultant for Aastrom, Amgen, Bristol-Myers-Squibb, Cerenis, Concert, Genzyme, Hamilton Health Sciences, Keryx, Medtronic, Merck, Novartis, Roche, Servier, Teva, the University of Oxford, and Xoma. Dr. Pieske has received honoraria from Bayer, Servier, Medtronic, Menarini, Daiichi-Sankyo, and Boehringer Ingelheim. Dr. Pitt has served as a consultant for Pfizer, Bayer, Relypsa, Stealth Peptides, and Mesoblast. Dr. Solomon has received research support from and has served as a consultant for Novartis and Bayer. Dr. Teerlink has received research support and consulting fees from Novartis. Dr. Gheorghiade has served as a consultant for Novartis, Bayer, Takeda, and Janssen. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Developing Therapies for Heart Failure With Preserved Ejection Fraction

Current State and Future Directions

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 Food and Drug Administration and included representatives from academia, industry, and regulatory agencies. This document summarizes the proceedings from this meeting. (J Am Coll Cardiol HF 2014;2:97–112) © 2014 by the American College of Cardiology Foundation

Epidemiologic studies suggest that the prevalence and hospitalizations related to heart failure 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, whereas those for heart failure with reduced ejection fraction (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 at 60 to 90 days post-discharge are comparable for HFrEF (36.1%) and HFpEF (35.3%) (7). In the I-PRESERVE (Irbesartan in Heart Failure With Preserved Systolic Function) and the CHARM (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity) 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) (see also 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 PARAMOUNT (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blockers on Management of HFpEF) 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

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Abbreviations and Acronyms

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

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 1 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 coexisting 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 1 study, mean LV mass index was 102 ± 29 g/m^2; 27% of patients 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 have 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 are 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

Table 1 Epidemiology of HF With Preserved EF

First Author (Ref. #) (Trial)	Population	Prevalence and EF	Mortality	Readmission
Cohort studies				
Vasan et al. (3) (FHS)	73 outpatients	51%, EF ≥50%	Annual during median 6.2 yrs: 8.7%	
Owan et al. (5) (Olmsted County)	4,596 HHF patients	47%, EF ≥50%	1 yr: 29% 5 yrs: 65%	
Bhatia et al. (6) (Ontario)	2,802 HHF patients	31%, EF ≥50% 13%, 40% ≤ EF <50%	30 days: 5.3 1 yr: 22.2%	30 days: 4.5, EF ≥50% 1 yr: 13.5%, EF ≥50%
Steinberg et al. (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 et al. (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 months: 14.0%, EF >50% 15.0%, 40% ≤ EF <50%	
Fonarow et al. (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 days: 9.5%, EF ≥40% 9.2%, 40% ≤ EF <50% 9.3%, EF >50%	60–90 days: 29.2%, EF ≥40% 29.0%, 40% ≤ EF <50% 30.9%, EF >50%
Yancy et al. (4) ADHERE	52,187 HHF patients	50.4%, EF ≥40%	In-hospital: 2.8%, EF ≥40%	

ADHERE = Acute Decompensated Heart Failure National Registry; EF = ejection fraction; FHS = Framingham Heart Study; GWGL-HF = Get With the Guidelines – Heart Failure; HF = 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.

pressure, and resulting 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 the 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. Although 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 affects 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 (Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity), 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 transpulmonary 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 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, the 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 the risk of developing HFpEF and treatment substantially lowers 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

Table 2 Clinical Trials in Patients With Heart Failure and Preserved Ejection Fraction

First Author (Ref. #) Drug	Duration (months)	n	Systolic Function	Diastolic Function as Inclusion Criterion	Positive Outcomes	Mortality/ Readmission
Medication Trials						
Setaro et al. (20) Verapamil	1.25	40	LVEF >45%	Peak filling rate <2.5 edv/s	Improved clinical status Increased exercise time and diastolic filling rate	
Aronow and Kronzon (13) Enalapril	3	21	LVEF >50%	Not determined	Improved clinical status Increased exercise time Decreased LV mass/increased E/A ratio	
Aronow et al. (14) Propanolol + ACEI	12	158	LVEF ≥40%	Not determined	Reduced mortality: 30% and combined mortality + nonfatal MI Increased LVEF: reduced LV mass	1 yr: 65.8%
Hung et al. (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 and isovolumic relaxation	
Nodari et al. (22) Nebivolol versus atenolol	6	26	LVEF ≥50%, LVEDD <60 mm or <32 mm/m^2	E/A <1.0 and 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 and PCWP at rest and exercise. Both: reduced LV mass. Increased E/A. Decreased LVED septal wall thickness	
Yusuf et al. (15) Candesartan	36.6 (median)	3,023	LVEF >40%	Not determined	Reduction in CV death+HF-hospitalization Fewer recurrent HF-hospitalizations	Median 36.6 months: 11.3%/17.1% (for HF)
Bergström et al. (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 et al. (24) Spironolactone	6	30	LVEF >50%	E/A <1 DT >250 m/s	Increased SR and peak systolic strain Decreased LA area and PVARV	
Ahmed et al. (25) Digoxin	37 (mean)	988	LVEF >45%	Not determined	No long-term effect on mortality or HF-hospitalization	Mean 37 months: 23.4%/20% (for HF)
Cleland et al. (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 functional class at 1 yr and 6MWT at 1 yr	1yr: 13.1% combined mortality + HF admission 10.2% HF admission
Massie et al. (17) Irbesartan	49.5	4,128	LVEF ≥45%	LVH and LAD >46 mm in men and 42 mm in women	None	Mean 49.5 months: 36.5% combined mortality + CV admission
Yip et al. (18) Ramipril versus irbesartan	12	151	LVEF >45%	Not determined	Short term increased Em and Sm Decreased NT-proBNP levels at 1 yr	1 yr: 2.7%/ 11.3% (for HF)

Continued on the next page

Table 2 Continued

First Author (Ref. #) Drug	Duration (months)	n	Systolic Function	Diastolic Function as Inclusion Criterion	Positive Outcomes	Mortality/ Readmission
Kitzman et al. (19) Enalapril	12	71	LVEF ≥50%	Not determined	None	
Deswal et al. (26) Eplerenone	6	44	LVEF ≥50%	Not determined	Reduced collagen turnover circulating biomarkers Decreased E/e'	6 months: 0%/ 6.8% (for HF)
Conraads et al. (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 et al. (31) Neprilysin	3	301	LVEF ≥45%	Not determined	NT-proBNP reduced	3 months: 1%/ 3.3% (for HF)
Yamamoto et al. (30) Carvedilol	38	245	LVEF >40%	Not determined	None	38 months: 25.7% mortality + HF admission
Edelmann et al. (27) Aldosterone	13	422	LVEF ≥50%	Grade ≥1	E/e' declined at 6 months and maintained at 12 months LVEDD and LVM index decreased	
Redfield et al. (28) Sildenafil	6	216	LVEF ≥50%	Not determined	None	
Other Types of Trials						
Kitzman et al. (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_2 pulse. Improved physical score of MLHFQ	
Edelmann et al. (33) Aerobic and 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 et al. (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 et al. (35) Aerobic exercise	4	40	LVEF ≥50%	Not determined	Improved exercise capacity (VO_2peak). Increased HRpeak, HRR. Increased estimated peak and reserve A-VO_2 Diff and peak and reserve circulatory power	
Fujimoto et al. (36) Aerobic exercise	12	20	LVEF >50%	Not determined	Improved E/A	
Kitzman et al. (37)	4	63	LVEF ≥50%	Not determined	Improved exercise capacity (VO_2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). increased HRpeak, Improved SF-36 score	

6MWT = 6-min walk test; ACEI = angiotensin-converting enzyme inhibitor; 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; MLHFQ = Minnesota Living with Heart Failure Questionnaire; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal pro–B-type 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; VE/VCO_2 = ventilatory equivalent for carbon dioxide; VO_2peak = peak oxygen consumption; VO_2AT = oxygen consumption at anaerobic threshold.

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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	Pre-load 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	Transpulmonary gradient (mPAP-PCWP)
Pulmonary vascular gradient (PADP-PCWP)	
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 mediated dilation	Reactive hyperemia index
Augmentation index	
Exercise capacity	
Walking tests	
6-min 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	

LV = left ventricular; mPAP = mean pulmonary artery pressure; PADP = pulmonary artery diastolic pressure; PCWP = pulmonary capillary wedge pressure; RVOT = right ventricular outflow tract; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation; 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.

admissions compared with HFrEF (63). In these patients, 30% of mortality is noncardiovascular, 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, sex, and comorbidity distribution to patients enrolled in other cardiovascular trials. Striking differences were found in mortality between non-HFpEF patients (11 to 47 per 1,000 patient-years) and HFpEF mortality rate (53 to 76 per 1,000 patient-years) patients, suggesting that HFpEF risk goes beyond that explained by age and comorbidities. A recent paper suggested 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, Fig. 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 pre-load 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 ventriculoarterial coupling. Other potential parameters include volume, mass, wall thickness, LVEF, E/e' ratio, e' velocity, and longitudinal strain. Diffuse fibrosis is

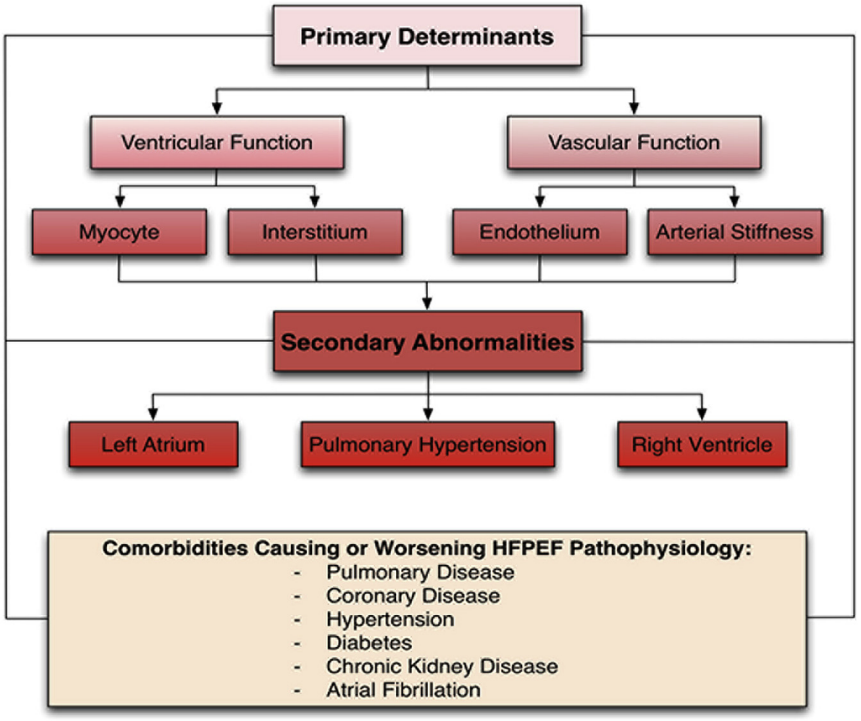

Figure 1 **Potential Therapeutic Targets in HFpEF**

HFpEF = heart failure with preserved ejection fraction.

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 nonsignificant 21% reduction in HF hospitalizations; 25% of participants had HFpEF.

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 that reflect 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

Table 4 Echocardiographic Changes, Biomarkers, and Prognosis of Heart Failure With Preserved Ejection Fraction

Marker (Method)	First Author (Ref. #)	Population	Outcome	Predictive Properties HR (95% CI)
E/A (severity of DD) (echocardiography)	Persson et al. (51)	293 HF patients with LVEF >40% participating in CHARMES	Composite CV mortality or HF admission	Moderate or severe DD 3.27 (1.41–7.56)*
e' (echocardiography)	Wang et al. (71)	174 hypertensive individuals with LVH	Cardiac mortality	0.49 (0.32–0.76)†
LV mass‡ (echocardiography)	Zile et al. (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	1.019 (1.009–1.029)§
LV mass/volume (echocardiography)				1.296 (1.074–1.564) §
Enlarged LA‖ (echocardiography)				1.470 (1.029–2.101) §
LAD¶ (echocardiography)	Rossi et al. (69)	183 HF patients with LVEF >45%	All-cause mortality	2.45 (1.12–5.41)#
Diastolic wall stress** (echocardiography)	Ohtani et al. (70)	327 HF patients with LVEF ≥50%	Composite CV mortality or HF admission	1.03 (1.01–1.06)††
Natriuretic peptides (blood sample analysis)	Grewal et al. (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 5.8 (1.3–26.4) NT-proBNP >600 pg/ml 8.0 (2.6–24.8) BNP >100 pg/ml 3.1 (1.2–8.2)

*After adjustment for age, sex, left ventricular ejection fraction (LVEF), diabetes mellitus, atrial fibrillation, previous heart failure (HF) admission, and treatment arm. †After adjustment for age, and interventricular septal thickness in diastole, LVEF, 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. ‡Indexed to height$^{2.7}$. §After adjustment for log N-terminal pro–B-type natriuretic peptide (NT-proBNP), age, diabetes mellitus, hospitalization for worsening HF within 6 months preceding randomization, chronic obstructive pulmonary disease or asthma, neutrophils, and LVEF. ‖Mildly enlarged left atrium (LA) if LA area was 20 to 30 cm^2 and moderately to severely enlarged LA if LA area was >31 cm^2. ¶LA diameter >5 cm used to define LA enlargement. #After adjustment for clinical and echocardiographic parameters. **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. ††After adjustment for age, sex, echocardiographic variables, and log B-type natriuretic peptide (BNP).

CHARMES = CHARM Echocardiographic Substudy; CI = confidence interval; CV = cardiovascular; DD = diastolic dysfunction; HR = hazard ratio; I-PRESERVE = Irbesartan in Heart Failure With Preserved Systolic Function; LVH = left ventricular hypertrophy; MI; myocardial infarction.

with NP levels below but not above the median (83). The role of NP as a marker 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, because 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 Ex-DHF (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. The 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 of these remain important endpoints, considering their limitations, there is a need to develop new endpoints. The common HFpEF

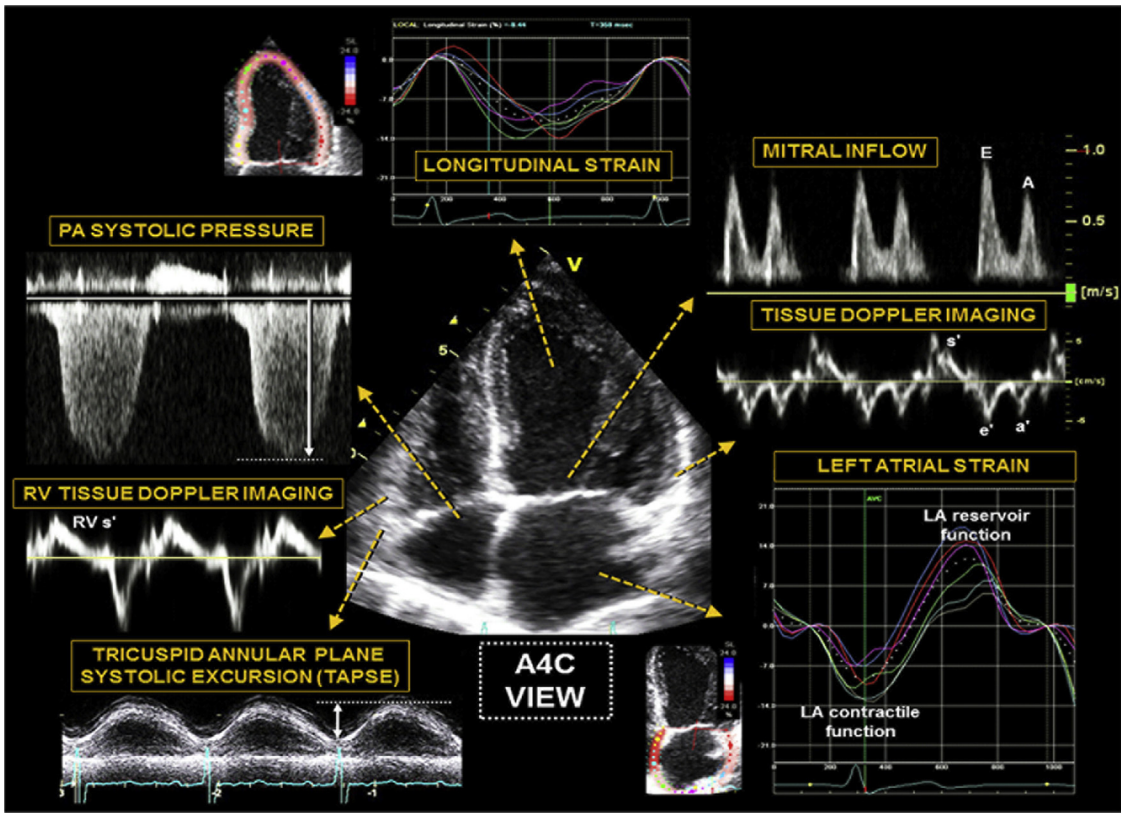

Figure 2 **Comprehensive Echocardiographic Phenotypic Analysis of Heart Failure With Preserved Ejection Fraction**

Comprehensive echocardiography, including 2-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 (A4C) view. Clockwise from the top: speckle-tracking echocardiography for assessment of left ventricular (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 left atrial (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 right ventricular (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 right atrial (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). PA = pulmonary artery. Figure courtesy of Sanjiv J. Shah, MD.

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 HF. 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 serelaxin. In the RELAX-AHF (Relaxin in Acute Heart Failure) trial (87), about 45% of patients had LVEF $\geq$40%, hence representing 1 potential avenue to treat hospitalized HFpEF patients. However, considering the continued worsening post-discharge outcomes, oral long-term therapies are needed to improve

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Table 5 Inclusion Criteria in Randomized Clinical Trials for Patients With Heart Failure With Preserved Ejection Fraction

First Author (Ref. #)	Inclusion Criteria	First Author (Ref. #)	Inclusion Criteria
Setaro et al. (20)	Not determined etiology LVEF >45%* LV peak filling rate >2.5 edv/s	Aronow and Kronzon (13)	Prior MI (>6 months) LVEF >50%
Aronow et al. (14)	Prior MI (>6 months) LVEF ≥40%	Hung et al. (21)	LVEF >50%
Nodari et al. (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	Yusuf et al. (15)	LVEF >40%
Bergström et al. (23)	LVEF >45% LVWMI ≤1.2† At least 1 of the following: • E/A < ARRV • IVRT > ARRV • E/A normal plus PVS/DV < ARRV or PVARD-MAD >20 ms or PVARV > ARRV	Mottram et al. (24)	Hypertension requiring antihypertensive medication and exertional dyspnea No MI or angina LVEF >50% E/A <1 DT >250 m/s
Little et al. (88)	LVEF >50%	Ahmed et al. (25)	In sinus rhythm LVEF >45%
Cleland et al. (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	Massie et al. (17)	LVEF ≥45% LVH LAD >46 mm in men and >42 mm in women
Zile et al. (89)	LVEF ≥50%	Yip et al. (18)	LVEF >45%
Kitzman et al. (19)	No other conditions (cardiac/pulmonary/other) that could mimic HF LVEF ≥50%	Kitzman et al. (32)	No other conditions (cardiac/pulmonary/other) that could mimic HF LVEF ≥50%
Orozco-Gutierrez et al. (90)	LVEF ≥45% Fractional shortening ≥28% LAD >45 mm LV septal and posterior thickness >12 mm Slow, inverted, pseudonormal, or restrictive pattern of transmitral Doppler flow	Deswal et al. (26)	LVEF ≥50% BNP ≥100 pg/ml
Guazzi et al. (91)	In sinus rhythm LVEF ≥50% SPAP ≥40 mm Hg	Desai et al. (92)	LVEF ≥45% BNP ≥100 pg/ml or NT-proBNP ≥360 pg/ml
Conraads et al. (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 and >122 g/m in women	Solomon et al. (31)	LVEF ≥45% NT-proBNP >400 pg/ml
Smart, 2012 (34)	LVEF >45% Delayed relaxation or pseudonormal filling	Yamamoto et al. (30)	LVEF >40%
Edelmann et al. (27)	LVEF ≥50% Diastolic dysfunction grade ≥1 or atrial fibrillation VO_2peak ≤25 ml/kg/min	Redfield et al. (28)	LVEF ≥50% LA enlargement VO_2peak ≤60%‡ NT-proBNP ≥400 pg/ml or NT-proBNP <400 pg/ml PCWP 20 mm Hg at rest and >25 mm Hg at exercise
Maurer et al., 2013 (93)	LVEF >40%		

*Determined by radionuclide ventriculograms. †Determined as akinesia of ≤ 1 segment or hypokinesia of ≤ 2 segments , using a 16-segment model with at least 10 segments visible. ‡Based on the age- and sex-specific normal value while respiratory exchange ration is ≥1.0. Bulleted items indicate where 1 or more diagnostic findings can be sued to fulfill a criterion.

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; HF = heart failure; 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–B-type 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; SPAP = pulmonary artery systolic pressure; VO_2peak = peak oxygen consumption.

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 versus specific tests (e.g., exercise pulmonary pressure measurement), needs study. It is unclear whether patients with a 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 vs. 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.

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 subpopulations 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 a high priority for support from academia, industry, nongovernmental 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 approximate the HFpEF syndrome to allow 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.

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Reprint requests and correspondence: Dr. Javed Butler, Emory Clinical Cardiovascular Research Institute, 1462 Clifton Road Northeast, Suite AT 504, Atlanta, Georgia 30322. E-mail: javed.butler@emory.edu.

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Key Words: epidemiology ■ heart failure ■ preserved ejection fraction ■ prognosis ■ treatment.

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