JACC: Heart Failure
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 1, No. 2, 2013
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2013.01.001

EDITORIAL COMMENT

Evaluative Framework for Phase II Studies in Patients With Heart Failure and Preserved Ejection Fraction*

Mihai Gheorghiade, MD,†
Muthiah Vaduganathan, MD, MPH,‡
Sanjiv J. Shah, MD§
Chicago, Illinois; and Boston, Massachusetts

Heart failure with preserved ejection fraction (HFpEF) is now recognized as a major public health problem, accounting for approximately 50% of all patients with HF (1), and morbidity and mortality rates in HFpEF approximate those of HF with reduced EF (HFrEF) (2). Aside from supervised exercise training programs (3), evidence-based treatments are unfortunately lacking in HFpEF. Challenges in the design and conduct of Phase II clinical trials may explain why finding evidence-based therapies for HFpEF remains an elusive challenge. The lack of a robust definition of HFpEF for enrollment into trials, not matching HFpEF subtypes to the mechanism of a given experimental therapy, and suboptimal evaluation metrics and endpoints, all plague Phase II clinical trials in HFpEF. Thus, to effectively improve management in HFpEF, we need optimal Phase II trials that truly inform subsequent Phase III studies.

See page 115

HFpEF is a heterogeneous clinical syndrome, with several underlying etiologies and pathophysiologies, including diastolic dysfunction. Abnormal cardiomyocyte sodium and calcium handling has been proposed as a potential mechanism that contributes to diastolic dysfunction (4). Mechanistically, the late inward sodium current (which is enhanced in diseased myocytes), results in diastolic calcium overload via increased sodium-calcium exchange within myocytes. Ranolazine, a potent inhibitor of the late inward sodium channel, was originally approved for use for the indication of refractory stable angina in Europe and the United States. Theoretically, inhibition of this sodium channel in HFpEF with ranolazine may reduce intracellular calcium levels and augment diastolic relaxation (5).

In this issue of *JACC: Heart Failure*, Maier et al. (6) describe the results of RALI-DHF (RAnoLazIne for the Treatment of Diastolic Heart Failure), a novel Phase IIa proof-of-concept study of the acute effects of ranolazine on hemodynamics and diastolic function in outpatients with chronic HFpEF. In this small pilot study, the investigators randomized 20 patients to either ranolazine or placebo. Therapy involved 24 hours of intravenous infusion of the study drug followed by 2 weeks of oral therapy. Short-term intravenous ranolazine therapy was associated with modest reductions in invasively measured left ventricular (LV) filling pressures and pulmonary artery pressures, without concomitant changes in relaxation kinetics or pulmonary or systemic vascular resistance. Unfortunately, cardiac output also decreased with ranolazine, presumably due to reduced LV filling pressure. After completion of the 2-week oral regimen, no significant changes in exercise capacity and noninvasive indexes of diastolic function, measured by cardiopulmonary exercise testing and echocardiography, respectively, were demonstrated (6).

RALI-DHF provides an excellent early opportunity to evaluate the potential challenges faced by Phase II trials. The study appropriately employed strict inclusion criteria in defining HFpEF, consistent with a consensus report from the European Society of Cardiology (7). The investigators used an agent with known effects on diastolic function and appropriately measured its short-term effects on various LV relaxation parameters. In terms of evaluation and endpoint analysis, Maier et al. (6) utilized invasive hemodynamic testing, echocardiography, and cardiopulmonary exercise testing to monitor drug efficacy in their patient sample. However, RALI-DHF was limited by its small sample size, which resulted in an underpowered study. In addition, the study could have benefited from exercise testing instead of pacing to increase heart rate during the invasive hemodynamic procedure, thereby allowing for a more realistic and physiological assessment of the effects of ranolazine during increases in heart rates. Finally, echocardiographic evaluation after only 2 weeks of oral therapy was too early and

*Editorials published in *JACC Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC Heart Failure* or the American College of Cardiology.

From the †Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, Illinois; ‡Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; and the §Division of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois. Dr. Gheorghiade has received research support or consultation fees from Abbott Laboratories, Astellas, AstraZeneca, Bayer Schering Pharma AG, Cardiorentis Ltd, CorThera, Cytokinetics, CytoPherx, Inc., DebioPharm S.A., Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Intersection Medical, Inc., Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Ono Parmaceuticals USA, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein Design Laboratories, sanofi-aventis, Sigma Tau, Solvay Pharmaceuticals, Sticares InterACT, Takeda Pharmaceuticals North America, Inc., and Trevena Therapeutics; and has received significant (>$10,000) support from Bayer Schering Pharma AG, DebioPharm S.A., Medtronic, Novartis Pharma AG, Otsuka Pharmaceuticals, Sigma Tau, Solvay Pharmaceuticals, Sticares InterACT, and Takeda Pharmaceuticals North America, Inc. Dr. Shah has received grants from the National Institutes of Health, American Heart Association, and Gilead Sciences; and has served on an advisory board for Bristol-Myers Squibb. Dr. Vaduganathan has reported that he has no relationships relevant to the contents of this paper to disclose.

JACC: Heart Failure Vol. 1, No. 2, 2013
April 2013:123–6

Table 1 Comprehensive Recommendations for the Conduct of Phase II Trials in Heart Failure With Preserved Ejection Fraction*

Parameter	Problems	Recommendations
Patient enrollment	Many trials have been small, single-center experiences	Appropriately powered, multicenter investigations Must balance sample size with financial considerations Optimal Phase II trial sample size likely 100–200 range
Inclusion/exclusion criteria	Poorly defined inclusion criteria ("one size fits all" approach) Heterogeneous patient population with varying underlying etiologies, pathophysiologies	Use of specific consensus guideline-based criteria to enroll patients who meet criteria for HFpEF Signs and symptoms of HF present at time of enrollment LVEF >50%, LV end-diastolic volume index <97 ml/m^2, and evidence of increased LV filling pressures Presence of a high-risk marker (previous HF hospitalization within last 6 months or elevated natriuretic peptides) Exclusion of subgroups within HFpEF where off-target mechanisms drive symptoms and outcomes
Subtypes	Current HFpEF studies make no or little effort to enroll specific etiologic/pathophysiological subtypes	Target specific etiologic and pathophysiological subtypes based on mechanism(s) of experimental therapeutic agent being tested Recognize diverse HFpEF pathophysiologies (diastolic dysfunction, pulmonary hypertension/right heart failure, abnormal ventricular-arterial coupling, chronotropic incompetence, extracardiac fluid overload), and tailor trial enrollment and outcomes accordingly Recognize clinical HFpEF subtypes† ("garden-variety," CAD-associated, atrial arrhythmia-predominant, right heart failure, HCM-like, restrictive cardiomyopathy, high-output, valvular), and tailor trial enrollment and outcomes accordingly
Enrollment	Difficult, slow enrollment	Create HFpEF specialty clinical programs that specifically diagnose/treat HFpEF and enroll patients in clinical trials Use EMR to enhance and automate patient identification and enrollment
Comorbidities	Aside from exclusion criteria, little assessment of comorbidities	Comprehensive assessment of comorbidities, competing risks Obesity and physical inactivity: assessment of visceral adiposity, metabolic profile; fitness tracker (e.g., pedometer, accelerometer) CAD: defined algorithm for diagnosis of CAD, including stress testing and coronary angiography when necessary Hypertension: ambulatory blood pressure monitoring, arterial tonometry Parenchymal lung disease: pulmonary function testing Sleep apnea: overnight polysomnography; sleep tracker Chronic kidney disease: urinary and serum biomarkers of renal function at baseline and throughout the study Atrial arrhythmias: continuous ambulatory ECG monitoring Diabetes mellitus: fasting glucose, HOMA-IR, hemoglobin A_{1c}, assessment of diabetes complications Medication noncompliance: assessment of compliance of all drugs (not just experimental study drug) using devices that scan and track medications
Targets	Limited understanding of markers/targets	Further collection of registry and trial data in patients with HFpEF Instead of large-scale registries with few data points, smaller registries with high-density phenotypic data are needed
Duration of therapy	Short-term duration	Longer-term follow-up and drug administration, thorough dose-finding and exposure analysis
Evaluation metrics	Predominantly invasive evaluation without physiological dynamic testing Echocardiographic evaluation of left heart structure and basic function only No tissue characterization	Predominantly noninvasive, dynamic exercise challenge and/or maneuver-based evaluation Echocardiography: serial measurements of cardiac structure and function; comprehensive analysis of diastolic function (includes Doppler and tissue Doppler); speckle tracking for assessment of strain; noninvasive pulmonary artery pressure and pulmonary vascular resistance; comprehensive assessment of RV structure and function Cardiac MR: gold standard for volume and mass, wall motion, scar; tissue characterization (e.g., T1 mapping for assessment of diffuse fibrosis, T2 mapping for edema); assessment of microvascular dysfunction, NMR spectroscopy for metabolic profiling of the myocardium Arterial tonometry: assessment of arterial wave reflections, pulse-wave velocity, augmentation index, ventricular-arterial coupling Exercise testing: diastolic stress echocardiography, cardiopulmonary exercise testing, exercise echocardiography; assessment of chronotropic and vasodilatory response to exercise Biomarker: natriuretic peptides, troponin, renal function, galectin-3; match biomarkers with target of drug; measure study drug concentration, pharmacokinetics; collect blood and urine for banking to allow for future studies ECG/telemetry: continuous ambulatory ECG monitoring for assessment of arrhythmias; standard 12-lead ECG for assessment of QT and T-peak-to-T-end intervals; measure heart rate variability Physical activity: measure ambulatory activity level using pedometer or similar fitness tracker as an outcome measure Invasive hemodynamics: use of provocative maneuvers; physiological maneuvers (such as supine cardiac catheterization table bicycle ergometer testing) are preferred, but leg raise or fluid challenge (or provocative drug testing such as vasodilator challenge) can also be performed, depending on mechanism of the experimental therapeutic being tested

Continued on the next page

Table 1 Continued

Parameter	Problems	Recommendations
Endpoints	Mismatch between surrogate short-term endpoints and long-term end outcomes	Match intermediate endpoint to mechanism of action to increase translation of improved short-term outcomes to long-term benefit Collect data on cardiac and noncardiac hospitalizations, causes of death; collect data on frequency of hospitalizations Consider implantable hemodynamic monitoring

*The comprehensive list of tests provided for comorbidity assessment and evaluation metrics should not all be performed in every study; instead, these tests should be tailored to each particular study based on the trial budget and the specific mechanism of action for the study drug. †HFpEF subtypes are based on clinical classification; in the clinical trial setting, specific criteria should be used to diagnose each clinical subtype if being used for trial inclusion/exclusion. The "garden-variety" subtype of HFpEF refers to the typical elderly hypertensive HFpEF patient with obesity, metabolic syndrome and/or diabetes, and chronic kidney disease.

CAD = coronary artery disease; ECG = electrocardiography; EMR = electronic medical record; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HOMA-IR = homeostatic model assessment–insulin resistance; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = magnetic resonance; NMR = nuclear magnetic resonance; RV = right ventricular.

likely prevented the investigators from identifying potential longer-term effects of ranolazine in HFpEF.

Invasive hemodynamic testing, a key feature of RALI-DHF, requires further scrutiny. The role of invasive hemodynamic assessment in Phase II HFpEF studies is presently uncertain. Two decades of experience from drug development programs in HFrEF have suggested a lack of correlation between short-term hemodynamic or symptomatic parameters and long-term clinical endpoints. There appears to be a distinct disconnect between successful Phase II programs and subsequent negative Phase III clinical trials in this area. Agents such as inotropes that acutely improve systolic function (but increase cardiac workload) in HFrEF may have neutral or even deleterious effects on long-term safety endpoints. By contrast, established therapies in HFrEF such as beta-blockers that may acutely contribute to decompensation of the failing myocardium have consistently demonstrated longer-term clinical outcome benefit. Additional major drawbacks to invasive investigations are high trial costs and the limited number of enrolled subjects. The investigators of RALI-DHF recognize that small, single-center studies may be underpowered to provide definitive answers, and in a heterogeneous syndrome such as HFpEF, may not be generalizable enough to lay the groundwork for definitive Phase III studies.

Invasive hemodynamic monitoring therefore likely has a limited and specific role in the setting of HFpEF trials. Hemodynamic data may be most useful for: 1) developing a mechanistic understanding of a novel drug's action, thereby bridging pre-clinical and clinical studies during the exploratory T1 translational phase (8); 2) clarifying optimal dosages in dose-ranging investigations; and 3) identifying specific subgroups that are most likely to benefit in later Phase III trials. In Phase II HFpEF studies, invasive hemodynamic testing is most likely to be helpful if it is comprehensive (i.e., includes pressure–volume analysis and contemporaneous echocardiography) and includes dynamic exercise testing.

Although RALI-DHF represents a small, underpowered, short-term invasive hemodynamic Phase II trial, the recently published PARAMOUNT (Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction) study (9), which evaluated a novel angiotensin-receptor neprilysin inhibitor (LCZ696), represents the other end of the Phase II spectrum, and exemplifies many features of a well-conducted early-phase study in HFpEF. PARAMOUNT collected safety and efficacy data on over 300 patients from 65 centers and 13 different countries. Drug monitoring was achieved using biomarkers and echocardiography during a treatment period spanning 36 weeks (9). PARAMOUNT might serve as the paradigm for the evaluation of upcoming drugs or devices in this area, although its relatively large size and scope for a Phase II trial might prove to be too costly to be the norm. For the majority of agents with established mechanisms of actions, appropriately powered, multicenter Phase II HFpEF studies with sample sizes in the 100 to 200 range, with detailed echocardiography and/or cardiac magnetic resonance imaging, might be the most optimal trial design.

Thus far, the management of patients with HFpEF has revolved around active detection and aggressive treatment of comorbidities (10). Based on available clinical trial data, therapies known to be effective in HFrEF appear to have a limited role in patients with HFpEF. Thus, novel treatment targets and agents are required in HFpEF in the near future to ameliorate the high morbidity and mortality burden. The exploratory RALI-DHF study represents 1 of several ongoing early Phase II studies in HFpEF, an area that is largely uncharted, lacking an effective roadmap. An established paradigm for the routine testing and evaluation of new therapies for patients with HFpEF is therefore sorely needed. Recent advances in cardiac imaging and biomarkers related to HF have expanded the available arsenal clinicians and trialists can use to diagnose, characterize, and monitor treatment response in HFpEF (11). As data begin to accrue in patients with HFpEF, a concrete evaluative framework is required to help guide initial drug development programs. Further understanding of this unique patient population through large registries and trials (12), along with specific recommendations for patient selection and intermediate endpoints (Table 1), provides an initial starting point for this process.

Reprint requests and correspondence: Dr. Mihai Gheorghiade, Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, 645 North Michigan Avenue, Suite 1006, Chicago, Illinois 60611. E-mail: m-gheorghiade@northwestern.edu.

JACC: Heart Failure Vol. 1, No. 2, 2013
April 2013:123–6

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.
2. 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.
3. Kitzman DW, Brubaker PH, Morgan TM, et al. 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.
4. Valdivia CR, Chu WW, Pu J, et al. Increased late sodium current in myocytes from a canine heart failure model and from failing human heart. J Mol Cell Cardiol 2005;38:475–83.
5. Sossalla S, Wagner S, Rasenack EC, et al. Ranolazine improves diastolic dysfunction in isolated myocardium from failing human hearts. J Mol Cell Cardiol 2008;45:32–43.
6. Maier LS, Layug B, Karwatowska-Prokopczuk E, et al. RAnoLazIne for the treatment of diastolic heart failure in patients with preserved ejection fraction: the RALI-DHF proof-of-concept study. J Am Coll Cardiol HF 2013;1:115–22.
7. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–50.
8. Gheorghiade M, Pang PS, O'Connor CM, et al. Clinical development of pharmacologic agents for acute heart failure syndromes: a proposal for a mechanistic translational phase. Am Heart J 2011;161:224–32.
9. 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.
10. Shah SJ, Gheorghiade M. Heart failure with preserved ejection fraction: treat now by treating comorbidities. JAMA 2008;300:431–3.
11. Shah SJ, Fonarow GC, Gheorghiade M, Lang RM. Phase II trials in heart failure: the role of cardiovascular imaging. Am Heart J 2011;162:3–15.
12. Shah SJ, Heitner JF, Sweitzer NK, et al. Baseline characteristics of patients in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. Circ Heart Fail 2012 Dec 20 [E-pub ahead of print].

Key Words: diastolic dysfunction ■ heart failure with preserved ejection fraction ■ late sodium current inhibition.