The Diabetic Heart Failure With Preserved Ejection Fraction Phenotype

Is it Real and Is It Worth Targeting Therapeutically?

Article, see p 724

Brian R. Lindman, MD, MSc

For investigators, physicians, and patients, the inability to identify therapies to improve clinical outcomes, particularly mortality, in patients with heart failure with preserved ejection fraction (HFpEF) has been particularly vexing and stands in stark contrast to the progress made in the treatment of patients with heart failure with reduced ejection fraction (HFrEF). This has prompted a return to the proverbial drawing board, forcing a reconsideration of long-held assumptions and paradigms. Despite different underlying etiologies, patients with HFrEF are generally responsive to several classes of medications that target the neurohormonal axis. Conversely, the lack of benefit of these therapies in patients with HFpEF has prompted a reevaluation of whether HFpEF is 1 disease or many. Is there a unifying pathophysiology of HFpEF or is it better characterized as an amalgamation of distinct, albeit overlapping, phenotypes?

Increasingly embraced is the notion that HFpEF is an umbrella term for distinct phenotypes, characterized by different clinical presentations and predisposing factors.[1,2] Unbiased data-driven analytic strategies have identified distinct phenotypes or clusters of patients with HFpEF, including phenotypes that are clinically recognizable.[3,4] Accordingly, there is movement away from a one-size-fits-all therapeutic strategy to more selective therapeutic strategies targeting these different phenotypes.[1,2] Along with a focus on multiple phenotypes of HFpEF, there has been a re-examination of HFpEF as simply a disease of diastolic function to a reconceptualizing of it as more of a systemic disease, characterized by inflammation and microvasculature dysfunction with adverse sequelae in multiple organs, including, but not limited to, the heart.[5,6] In line with this, attention has been directed at whether the presence of diabetes mellitus identifies an important phenotype of HFpEF that may have implications for therapeutic strategies.

Earlier studies have aimed to characterize the diabetic HFpEF phenotype and evaluate the association between diabetes mellitus and clinical outcomes. CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) enrolled patients with EF >40% and showed that diabetes mellitus was associated with an adjusted 2-fold increase in cardiovascular death or hospitalization for heart failure and an 80% increase in the hazard of all-cause mortality.[7] The DIG (Digitalis Investigation Group) study enrolled patients with EF >45% and showed that patients with diabetes mellitus had an adjusted hazard of 1.68 for heart failure death or hospitalization.[8] RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) was a smaller study of patients with HFpEF (EF ≥50%) but had more rigorous phenotyping with biomarkers, echocardiography, cardiac magnetic resonance imaging, and exercise testing. Patients with diabetes mellitus were characterized by multimorbidity, left ventricular hypertrophy, impaired chronotropic reserve, and activation of inflammatory, pro-oxidative, vasoconstrictor, and profibrotic pathways.[9] Both maximal (peak

Correspondence to: Brian R. Lindman, MD, MSc, Cardiovascular Division, Washington University School of Medicine, Campus Box 8086, 660 S Euclid Ave, St Louis, MO 63110. E-mail brlindman@wustl.edu

Key Words: Editorials ■ diabetes mellitus ■ ejection fraction ■ heart failure ■ therapy

oxygen uptake) and submaximal (6-minute walk distance) exercise capacity were impaired in patients with diabetes mellitus, and hospitalization rates for cardiac or renal causes were increased.

In this issue of *Circulation*, Kristensen et al[10] confirm and extend these earlier findings by characterizing patients with diabetes mellitus in the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial and evaluating their outcomes (Table). The strengths of this analysis include the large number of patients, subgroup analyses based on insulin use, biomarker data, information on quality of life, distinction between cardiovascular and noncardiovascular clinical end points, and detailed echocardiographic measurements on a large subgroup. The I-PRESERVE trial enrolled >4000 patients with HFpEF (EF ≥45%) and tested whether irbesartan improved the composite outcome of all-cause death or cardiovascular hospitalization.[12] There was no difference in the primary outcome between the irbesartan and placebo groups, and this was not altered by diabetes mellitus status. Patients with diabetes mellitus represented 27% of trial patients, 30% of whom were treated with insulin. Patients with diabetes mellitus were characterized by a greater prevalence of obesity, coronary disease, anemia, and obstructive lung disease, but similar age, sex distribution, renal function, and prevalence of atrial fibrillation. Despite a similar New York Heart Association class, quality of life was worse in patients with diabetes mellitus, and there was evidence of increased volume in terms of rales, congestion on chest radiography, distended neck veins, and a higher natriuretic peptide level, despite being on higher doses of loop diuretics. On echocardiography, patients with diabetes mellitus had a larger left ventricular chamber and increased left ventricular wall thickness and mass. Although systolic function and several measures of diastolic function were similar, there was evidence of increased filling pressures in the patients with diabetes mellitus in terms of E/e' and left atrial area. Patients with diabetes mellitus had worse clinical outcomes even after adjustment for clinical covariates, ejection fraction, and natriuretic peptide level. The hazard for worse clinical outcomes was higher among those patients treated with insulin compared with those not on insulin. However, in the subgroup of patients with detailed echocardiographic data, the adverse association between diabetes mellitus and clinical outcomes was attenuated after adjustment for left ventricular end-systolic volume, left ventricular mass, E/e', and left atrial area. Of note, this attenuation was only with respect to cardiovascular-specific end points.

Putting this study in the context of others, what have we learned about the diabetic HFpEF phenotype? These patients are characterized by multimorbidity, increased inflammation, greater intravascular volume, increased hypertrophic remodeling, impaired chronotropic reserve, and presumed abnormalities in the periphery. Collectively, these and other factors predispose patient with diabetes mellitus to worse quality of life, worse exercise capacity, increased hospitalizations, and increased mortality. Not unexpectedly, patients with diabetes mellitus are a higher risk subgroup of patients with HFpEF. However, further mechanistic studies with control patients and other identified subgroups of patients without diabetes mellitus with HFpEF are needed to clarify whether HFpEF patients with diabetes mellitus represent a more severe form of HFpEF along a disease spectrum or whether there is a differentiated underlying pathophysiology.

THERAPEUTICALLY TARGETING THE HFPEF DIABETIC PHENOTYPE

Regardless of whether diabetes mellitus simply marks a more severe form of HFpEF or a somewhat distinct pathophysiology, what potential therapeutic targets in these patients are likely to yield the most benefit? The diastolic properties of the heart and associated higher filling pressures are a common place to start, and there is evidence supporting this approach. Preclinical studies have pointed to increased cardiomyocyte resting tension, advanced glycation end products, and abnormal titin phosphorylation as potential underlying mechanisms to be targeted to alter the myocardial milieu to promote better diastolic function.[13] Given the increased intravascular volume among patients with diabetes mellitus with HFpEF, regardless of their effect on the diastolic properties of the heart, strategies to reduce the volume load may have salutary effects. Addressing chronotropic incompetence, more common among patients with diabetes mellitus, may improve exercise capacity and quality of life. Looking beyond the heart, targeting peripheral mechanisms, including peripheral oxygen delivery and extraction and skeletal muscle function, may also be important avenues for improving exercise capacity and quality of life. The jury is still out on the role of cardiac and vascular reserve function in impaired exercise function in patients with diabetes mellitus.

What tools should be applied to these targets, particularly in the pharmacological realm? To date, in the treatment of HFpEF, attention has centered on drugs intended to target the heart. However, with recent data on empagliflozin, an inhibitor of sodium-glucose cotransporter 2, our categories of drug classes and intended use have blurred.[14] Diabetes drugs, of which sodium-glucose cotransporter 2 inhibitors are a class, are generally used to reduce glucose levels. In the case of sodium-glucose cotransporter 2 inhibitors, glucose reabsorption in the kidney is blocked, producing a glucosuria. Until recently, the question has generally been, "Do glucose-lowering drugs cause cardiovascular harm?" With the EMPA-REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) results showing a benefit in terms of cardiovascular mortality and heart failure hospi-

Table. Comparison of HFpEF Patients With and Without Diabetes Mellitus From Clinical Trials or Large Registries

Authors	Cohort	Subjects	Characteristics of Patients With Diabetes Mellitus	Clinical Outcomes
Aguilar et al[8]	DIG ancillary trial	n=987 Preexistent heart failure EF >45% Diabetes mellitus in 29%	Clinical: younger, female, higher BMI, HTN, ischemic heart disease, increased peripheral edema and congestion on radiography Medications: higher usage of diuretics, nitrates	Adjusted HR for: Total mortality: 1.48 (95% CI 1.10–1.99) Cardiovascular mortality: 1.54 (95% CI 1.08–2.18) Heart failure death or hospitalization for worsening heart failure: 1.68 (95% CI 1.26–2.25)
MacDonald et al[7]	CHARM trial	n=3023 Preexistent heart failure EF >40% Diabetes mellitus in 28%	Comparisons are qualitative due to lack of statistical comparisons in the paper Clinical: higher BMI, HTN, ischemic heart disease, worse renal function, higher NYHA class, more signs and symptoms of volume overload Medications: higher usage of diuretics, ACE-inhibitors, nitrates, digoxin, calcium channel blockers, lipid-lowering drugs; insulin (34%)	Rates per 1000 patients years of follow-up: Total mortality: Diabetic (77.4) vs Nondiabetic (46.0), $P<0.001$ Cardiovascular mortality: Diabetic (58.6) vs Nondiabetic (31.1), $P<0.001$ 1st hospital admission for heart failure: Diabetic (116.6) vs Nondiabetic (45.9), $P<0.001$
From et al[11]	Olmsted County–population-based study	n=1760 No preexisting heart failure All patients had diabetes mellitus and a tissue Doppler assessment of diastolic function	Diastolic dysfunction was defined as an E/e' ratio >15. Characteristics of patients with diabetes mellitus with diastolic dysfunction included: Clinical: older, female, lower BMI, HTN, ischemic heart disease Echocardiography: nominally lower EF, larger LA volume, increased left ventricular hypertrophy, similar LV chamber dimensions and deceleration time	Adjusted HR of diastolic dysfunction for incident heart failure: 1.61 (95% CI 1.17–2.20) Total mortality: The cumulative probability of death was higher for patients with diabetes mellitus with versus without diastolic dysfunction at 1 y (6.9% vs 3.1%) and 5 y (30.8% vs 12.1%), $P<0.001$.
Lindman et al[9]	RELAX trial	n=216 Preexistent heart failure EF ≥50% Diabetes in 43%	Clinical: younger, male, higher BMI, HTN, ischemic heart disease, worse renal function, noncardiac multimorbidity Medications: higher usage of diuretics, calcium channel blockers, statins; insulin (42%) Echocardiography/MRI: increased left ventricular hypertrophy, E/e' (trend); similar systolic function; similar resting vascular properties Biomarkers: higher circulating levels of endothelin-1, galectin-3, uric acid, C-reactive protein, carboxy-terminal telopeptide of collagen type 1 Exercise: chronotropic incompetence, shorter 6-min walk distance, lower peak VO_2	Hospitalization for heart failure 1 y before trial: Diabetic (47%) vs Nondiabetic (28%), $P=0.004$ Hospitalization for cardiac or renal cause during 6-mo trial period: Diabetic (23.7%) vs nondiabetic (4.9%), $P<0.001$
Kristensen et al[10]	I-PRESERVE trial	n=4128 Preexistent heart failure EF ≥45% Diabetes mellitus in 27%	Clinical: younger, non-White, higher BMI, ischemic heart disease, anemia, more signs and symptoms of volume overload, worse quality of life Medications: higher usage of loop diuretics, ACE-inhibitors, nitrates, lipid-lowering drugs; insulin (30%) Echocardiography: increased left ventricular hypertrophy, E/e', left atrial area; similar systolic function Biomarkers: higher circulating levels of natriuretic peptide, neutrophils	Diabetes mellitus is associated with an increased adjusted hazard of all-cause, cardiovascular, and noncardiovascular mortality and hospitalization. Patients with diabetes mellitus treated with insulin generally have worse outcomes than those not treated with insulin. In the subgroup of patients with detailed echocardiographic measurements, adjustment for echocardiographic variables attenuated the adverse association between diabetes mellitus and cardiovascular-specific end points.

ACE indicates angiotensin-converting enzyme; BMI, body mass index; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CI, confidence interval; DIG, Digitalis Investigation Group; EF, ejection fraction; HR, heart rate; HTN, hypertension; HFpEF, Heart Failure With Preserved Ejection Fraction; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction; LA, left atria; LV, left ventricle; NYHA, New York Heart Association; and RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction.

talization, there is now interest in and optimism regarding whether these drugs may actually help patients with preexisting heart failure. Although the mechanisms by which sodium-glucose cotransporter 2 inhibitors manifest these favorable cardiovascular effects remain to be elucidated, there is evidence pointing to a diuretic effect, which may address a problem particularly relevant to patients with diabetes mellitus. It also improves renal function and may reduce visceral adiposity and improve vascular stiffness, offering other mechanisms by which this class of "diabetes medications" may benefit HFpEF patients, particularly, but perhaps not limited to, those with diabetes mellitus.

A new paradigm of HFpEF points to comorbidities and metabolic abnormalities fueling systemic inflammation and oxidative stress, which, in turn, drive coronary and systemic microvascular dysfunction and other untoward sequelae.[5] Accordingly, it may be time to focus more attention on drugs that target metabolism, inflammation, and nitric oxide bioavailability.[15] "Turning the water off" in terms of improving the metabolic milieu and reducing systemic inflammation may be more effective than "mopping up the floor" in terms of trying to reverse the cardiac and vascular remodeling and dysfunction that characterize HFpEF. In short, the line between cardiovascular and metabolic/diabetes mellitus drugs may begin to fade in the treatment of HFpEF.

When contemplating new therapies for patients with HFpEF and diabetes mellitus, it is also important to consider how to appropriately match the therapeutic tool to the intended pathophysiological target and evaluate it by measuring a fitting outcome.[16] Although improved clinical outcomes in terms of reduced hospitalizations and improved survival are highly desirable, improving functional capacity and quality of life are also important goals. Factors that contribute to these various outcomes may diverge to some extent, so trials need to be clear about what is being targeted and whether the hypothesized or known mechanism of action of the drug or device is likely to have the intended effect on the outcome chosen.

Failure to identify therapies for the large number of patients with HFpEF has fostered new thinking about disease mechanisms and potential therapies. In many areas of medicine, there is an increasing recognition of the need for precision medicine—namely, matching the right therapy to the right patient to maximize the opportunity for therapeutic benefit. Our understanding of how diabetes mellitus alters the pathophysiology and clinical outcomes in patients with HFpEF is one piece of that puzzle, but there is much work yet to be done in order to identify, test, and adopt therapies that will improve the lives of these patients.

DISCLOSURES

Dr Lindman serves on the scientific advisory board for Roche Diagnostics and has received research grants from Edwards Lifesciences and Roche Diagnostics.

AFFILIATION

From Washington University School of Medicine, St Louis, MO.

FOOTNOTES

Circulation is available at http://circ.ahajournals.org.

REFERENCES

1. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. *Circulation*. 2016;134:73–90. doi: 10.1161/CIRCULATIONAHA.116.021884.
2. Senni M, Paulus WJ, Gavazzi A, Fraser AG, Díez J, Solomon SD, Smiseth OA, Guazzi M, Lam CS, Maggioni AP, Tschöpe C, Metra M, Hummel SL, Edelmann F, Ambrosio G, Stewart Coats AJ, Filippatos GS, Gheorghiade M, Anker SD, Levy D, Pfeffer MA, Stough WG, Pieske BM. New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. *Eur Heart J*. 2014;35:2797–2815. doi: 10.1093/eurheartj/ehu204.
3. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, Bonow RO, Huang CC, Deo RC. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation*. 2015;131:269–279. doi: 10.1161/CIRCULATIONAHA.114.010637.
4. Kao DP, Lewsey JD, Anand IS, Massie BM, Zile MR, Carson PE, McKelvie RS, Komajda M, McMurray JJ, Lindenfeld J. Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response. *Eur J Heart Fail*. 2015;17:925–935. doi: 10.1002/ejhf.327.
5. Paulus WJ, Tschöpe 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;62:263–271. doi: 10.1016/j.jacc.2013.02.092.
6. Lam CS, Brutsaert DL. Endothelial dysfunction: a pathophysiologic factor in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2012;60:1787–1789. doi: 10.1016/j.jacc.2012.08.004.
7. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ; CHARM investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J*. 2008;29:1377–1385. doi: 10.1093/eurheartj/ehn153.
8. Aguilar D, Deswal A, Ramasubbu K, Mann DL, Bozkurt B. Comparison of patients with heart failure and preserved left ventricular ejection fraction among those with versus without diabetes mellitus. *Am J Cardiol*. 2010;105:373–377. doi: 10.1016/j.amjcard.2009.09.041.
9. Lindman BR, Dávila-Román VG, Mann DL, McNulty S, Semigran MJ, Lewis GD, de las Fuentes L, Joseph SM, Vader J, Hernandez AF, Redfield MM. Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. *J Am Coll Cardiol*. 2014;64:541–549. doi: 10.1016/j.jacc.2014.05.030.
10. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D, Win S, Køber L, McKelvie RS, Zile MR, Anand IS, Komajda M, Gottdiener JS, Carson PE, McMurray JJV. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve trial (Irbesartan in Heart Fail-

ure With Preserved Ejection Fraction). *Circulation*. 2017;135:724–735. doi: 10.1161/CIRCULATIONAHA.116.024593.
11. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol*. 2010;55:300–305. doi: 10.1016/j.jacc.2009.12.003.
12. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A; I-PRESERVE investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456–2467. doi: 10.1056/NEJMoa0805450.
13. van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, Ijsselmuiden AJ, Schalkwijk CG, Bronzwaer JG, Diamant M, Borbély A, van der Velden J, Stienen GJ, Laarman GJ, Niessen HW, Paulus WJ. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation*. 2008;117:43–51. doi: 10.1161/CIRCULATIONAHA.107.728550.
14. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720.
15. Sharma K, Kass DA. Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies. *Circ Res*. 2014;115:79–96. doi: 10.1161/CIRCRESAHA.115.302922.
16. Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, Shah SJ, Ahmed A, Bonow RO, Cleland JG, Cody RJ, Chioncel O, Collins SP, Dunnmon P, Filippatos G, Lefkowitz MP, Marti CN, McMurray JJ, Misselwitz F, Nodari S, O'Connor C, Pfeffer MA, Pieske B, Pitt B, Rosano G, Sabbah HN, Senni M, Solomon SD, Stockbridge N, Teerlink JR, Georgiopoulou VV, Gheorghiade M. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. *JACC Heart Fail*. 2014;2:97–112. doi: 10.1016/j.jchf.2013.10.006.

The Diabetic Heart Failure With Preserved Ejection Fraction Phenotype: Is it Real and Is It Worth Targeting Therapeutically?

Brian R. Lindman

Circulation. 2017;135:736-740; originally published online January 4, 2017;
doi: 10.1161/CIRCULATIONAHA.116.025957
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539