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Cardiovascular Therapeutics

Treating Heart Failure with Preserved Ejection Fraction: A Challenge for Clinicians

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Despite a decline in many forms of cardiovascular disease, heart failure (HF) continues to increase. Heart failure with preserved ejection fraction (HFpEF) is common, especially among persons with multiple comorbidities. HFpEF presents many challenges for clinicians due to the incomplete understanding of the underlying mechanisms and lack of consensus on the most effective strategies for treatment. Angiotensin and beta receptor–blocking drugs, which form the cornerstone for the treatment of systolic HF, have failed to show similar benefits in patients with impaired diastolic function. This article provides an overview of drug therapy for HFpEF, including newer agents now under investigation.

Heart failure (HF) affects an estimated 5 million individuals in the United States, a number that is expected to grow to 8 million by 2030.[1] Newer technologies and drugs have dramatically increased survival from coronary disease, but many patients live longer only to develop HF. HF results in over one million hospitalizations each year, with an estimated average 30-day readmission rate of 25%.[1,2] In approximately half of patients, HF is associated with a reduced left ventricular ejection fraction (LVEF) resulting from systolic dysfunction (HFrEF). The remaining 50% of patients have impaired left ventricular function with a normal or preserved ejection fraction (HFpEF) most commonly due to diastolic dysfunction.[3] This article will discuss current issues and challenges surrounding the use of drug therapy for patients with HFpEF.

CLINICAL PRESENTATION

A major limitation when interpreting the literature on HFpEF has been the lack of a consistent definition and the variable terminology used to describe the condition. Until recently, the term diastolic HF was commonly used, however, due to the lack of specificity with this terminology, HFpEF is now the preferred term.[4] Another point of confusion in the literature is the variability in LVEF cutpoints used to define HFpEF, which have included greater than 40%, 45%, 50%, or 55%.[3,4] Based on the 2013 guidelines from the American College of Cardiology/American Heart Association (ACC/AHA), patients with a LVEF greater than or equal to 50% are defined as having HFpEF while those with LVEF less than or equal to 40% are defined as HFrEF.[4] Patients with LVEFs between 41% and 49% are termed borderline or intermediate but are considered to have characteristics and outcomes more similar to HFpEF.

The diagnosis of HFpEF can be challenging. In general, it is based on patient history, HF signs and symptoms, absence of LV systolic dysfunction, and exclusion of other conditions that may mimic HF (eg, valvular or pericardial disease).[4] Dyspnea on exertion is a key clinical finding. Brain natriuretic protein (BNP) or pro-BNP plasma levels are often elevated in HFpEF, although to a lesser degree than what is generally seen with HFrEF. While elevated levels help to confirm the diagnosis and generally predict a worse outcome, the absence of elevation does not rule out the diagnosis of HFpEF.[5,6] A common hemodynamic finding in HFpEF is an exaggerated increase in pulmonary capillary wedge pressure and pulmonary artery pressure during exercise with an attenuated increase in cardiac output.[7] An electrocardiogram may indicate LV hypertrophy or atrial enlargement. Doppler echocardiography is useful for identifying diastolic abnormalities. Other procedures

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that may be helpful in some patients include exercise testing, stress echocardiography, and cardiac catheterization to directly measure LV diastolic pressure.

Both the ACC/AHA stages of HF and the New York Heart Association (NYHA) Functional Classification are useful for assessing and monitoring patients with HFpEF.[8,9] The ACC/AHA staging provides information about development and progression of HF, whereas the NYHA classes are helpful for assessing exercise and functional capacity, severity of symptoms, and response to therapy.

HFpEF is commonly seen in the elderly, the obese, and women.[5] Patients with HFpEF tend to have many comorbidities including hypertension, coronary disease, atrial fibrillation, metabolic syndrome, and diabetes.[8,10] Of these, hypertension is by far the most common comorbidity, with a prevalence of 60% to 89% reported in various trials and registries.[11] A study of patients with HFpEF reported a 5-year mortality rate of 43%, and overall the prognosis appears to be comparable to that seen in patients with HFrEF.[12,13]

PATHOPHYSIOLOGY

The underlying pathophysiology of HFpEF is poorly understood and, given the many common comorbidities, likely multifactorial. The absence of animal or experimental models that accurately represent HFpEF has further hindered research into the underlying causes. Nonetheless, diastolic dysfunction is believed to be a major contributor in the majority of cases. The ability of the ventricle to relax and fill during diastole is affected by multiple factors including plasma volume, structural characteristics of the LV wall (stiffness), active energy-driven processes involved in LV relaxation, atrial contraction, and the integrity of the mitral valve.[5,10] Focal or diffuse scarring secondary to myocardial infarction or chronic inflammation is often seen. Over time, these changes result in increased collagen deposition and fibrosis that may further impair diastolic function. In patients with HFpEF, a common finding is LV hypertrophy and increasing stiffness secondary to hypertension.[5] Increased stiffness reduces ventricular compliance or the ability of the ventricle to relax and fill during diastole. Another common finding is concentric remodeling or an increased LV wall thickness relative to the cavity size. Although the processes that trigger these changes are not entirely understood, it is likely that neurohormones such as angiotensin II, aldosterone, and norepinephrine play a role in this remodeling similar to what occurs in HFrEF or following myocardial infarction.[5,10] It is rational to theorize that drugs that interfere with these processes and neurohormonal systems could be beneficial in HFpEF.

DRUG TREATMENT

Treatment goals for all patients with HF focus on reducing symptoms, improving functional capacity, enhancing quality of life, and delaying progression of the disease. Guidelines for the treatment of patients with HFrEF are well established.[4] Drugs that inhibit neurohormonal activation including angiotensin and aldosterone inhibitors and beta blockers have been proven to interrupt the cycle of systolic dysfunction and improve survival. Somewhat surprisingly, these drugs have not shown similar benefits in patients with HFpEF. These differences further highlight our incomplete understanding of the mechanisms involved in HFpEF

Diuretics

Loop diuretics are the primary treatment for reducing congestive symptoms associated with hypervolemia. However, in HFpEF, maintaining optimal volume status is often difficult. Patients with HFpEF are highly sensitive to volume changes and generally have a narrow window between volume overload causing congestive symptoms and hypovolemia. Overly aggressive diuresis may result in further reductions in cardiac output, hypotension, and decreased renal function.[14] In most cases, this preload dependence requires the use of doses substantially lower than one might use in HFrEF.

Nonetheless, volume overload must be managed as it often leads to repeat hospitalizations. A clinical trial, now underway, will evaluate the impact of the diuretic administration route (bolus or continuous infusion) with or without the addition of low-dose dopamine.[15] The primary endpoint is renal function at 72 hours as measured by change in GFR. Secondary endpoints for readmission, functional capacity, quality of life, and amount of diuresis will also be examined. The estimated completion date is late 2015.

ACE Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors block the production of angiotensin II, which promotes LV hypertrophy and fibrosis that may lead to impaired relaxation. Findings of clinical trials, however, have been disappointing. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial randomized 850 patients with HF and

echocardiographic evidence of diastolic dysfunction.[16] After a mean follow-up of 2.1 years, there was no reduction in the primary endpoint of all-cause mortality and HF-related hospitalizations. During the first year, however, significant reductions in symptoms, improved exercise capacity, and fewer HF hospitalizations were seen. Interpretation of the findings was limited by unexpectedly low enrollment and event rates and high withdrawal rates, which resulted in insufficient power for the primary endpoint.

Overall, studies of angiotensin receptor blockers (ARB) have also been disappointing. In the Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial of 4,128 patients with LVEF greater than 45% and NYHA II-IV HF, irbesartan did not reduce the composite endpoint of all-cause mortality or cardiovascular (CV) hospitalization.[17] In another trial, candesartan was evaluated in 3,023 patients with NYHA II-IV HF and LVEF greater than 40%.[18] The Effects of Candesartan in Patients with Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction (CHARM-Preserved) trial failed to demonstrate a reduced composite primary endpoint of CV death or HF hospitalization. However a secondary endpoint of HF hospitalizations was reduced (230 vs 279; *P* = .017).

Beta Blockers

Theoretically, beta blockers could be beneficial in HFpEF secondary to their negative inotropic and chronotropic effects, which may promote diastolic relaxation. Nebivolol, a beta-one selective agent with vasodilator properties, has been studied. The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial evaluated the effect of nebivolol on all-cause mortality and CV hospitalizations.[19] The trial included 2,128 seniors with HF and a broad range of LVEFs. However, approximately one-third of patients had an LVEF greater than 35%. Overall, the primary endpoint was reduced with nebivolol vs placebo 31.1% versus 35.3% (HR 0.86; 95% CI, 0.74-0.99; *P* = .039). When analyzed by LVEF (≤35% or >35%), similar reductions were seen in the composite endpoint, indicating efficacy across a broad range of patients. It should be noted that the LVEF cutpoint for diastolic dysfunction was considerably lower than other studies of diastolic HF and therefore may have included patients with some degree of systolic dysfunction.

In a more recent but substantially smaller randomized trial, the effects of carvedilol were studied. The Japanese Diastolic Heart Failure Study (J-DHF) enrolled 245 patients with HF and LVEF greater than 40%.[20] After a mean follow-up of 3.2 years, the primary outcome of CV death or HF hospitalization was not reduced with carvedilol compared to placebo. It should be noted that although the target dose for carvedilol was 20 mg daily, the median prescribed dose was 7.5 mg daily. Further analysis revealed that compared to the control group, the composite outcome was lower in those receiving greater than 7.5 mg daily (HR 0.539; 95% CI, 0.303-0.959; *P* = .0356) compared to less than or equal to 7.5 mg daily (HR 1.070; 95% CI, 0.650-1.763; *P* = .7893).

Digoxin

The Digitalis Investigation Group (DIG) trial was a large randomized placebo trial of 6,800 participants designed to evaluate the efficacy of digoxin in HFrEF.[21] However, a parallel trial, the DIG ancillary trial, was also conducted to assess the efficacy of digoxin in 988 patients with HFpEF, defined as LVEF greater than 45%.[22] Digoxin was added to standard therapy with ACE inhibitors and diuretics. The primary outcome was HF hospitalization or HF mortality. After a mean of 37 months, digoxin did not reduce the primary endpoint or the individual components. This finding was consistent with the results seen in the larger trial for HFrEF. Trends toward decreased HF hospitalizations were seen in both the HFrEF and HFpEF trials but did not reach significance in the ancillary trial, most likely due to the smaller sample size.

Aldosterone Antagonists

Recent trials of aldosterone antagonists have yielded some of the most promising results in patients with HFpEF. Benefits are believed to be primarily related to the ability of these drugs to inhibit myocardial hypertrophy, collagen deposition, and fibrosis.

The effect of spironolactone on diastolic function and exercise capacity in patients with HFpEF (Aldo-DHF) trial included 422 patients with LVEF greater than or equal to 50%, NYHA II–III symptoms, and evidence of diastolic dysfunction.[23] Patients were randomized to spironolactone 25 mg daily or placebo. The co-primary endpoints were echocardiographic-based changes in diastolic function and maximal exercise capacity at 12 months. Spironolactone therapy was associated with significant improvement

in diastolic function but had no effect on maximal exercise capacity. Reverse remodeling was also seen as indicated by decreases in LV mass index and natriuretic peptide-proBNP plasma levels. Compared to placebo, there were no significant differences in either HF symptoms or quality of life scores and a slight reduction in 6-minute walk distance with spironolactone. The investigators speculated that the lack of clinical improvement may have resulted from the low event rate, suggesting that the population was likely early stage HF and that longer follow-up may have been needed. However, based on the encouraging echocardiographic evidence, a larger trial appeared justified in order to examine the effects of aldosterone antagonist therapy on clinical outcomes.

The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial included 3,445 patients with symptomatic HF and LVEF greater than 45%.[24] After a mean follow-up of 3.3 years, spironolactone 15 to 45 mg daily failed to reduce the primary composite outcome of cardiovascular death, aborted cardiac arrest, or HF hospitalization compared to placebo (18.6% vs 20.4% respectively) (HR 0.89; 95% CI, 0.77-1.04; $P = .14$). However, hospitalization for HF was reduced with spironolactone compared to placebo (12% vs.14.2%) (HR 0.83; 95% CI, 0.69-0.99; $P = .04$). Additionally, improvement was seen in the primary outcome among those patients who had been enrolled based on elevations in plasma BNP, suggesting that therapy may be most beneficial in those with higher baseline risk. A post hoc analysis revealed substantial geographic variations in event rates for the placebo group; it was suggested that these differences in practice patterns may have biased the study toward the null hypothesis. An analysis of patients enrolled in North or South America only where event rates were higher and more consistent revealed a significant reduction in the primary composite endpoint with spironolactone.[24,25]

Statins

Statins, which are widely used in CV patients, have a number of pleiotropic properties that may be beneficial for diastolic function including reducing hypertrophy and fibrosis.[26,27] Although several earlier observational studies yielded mixed results, a meta-analysis of 11 studies suggested a significant survival benefit.[26,27] A more recent observational study with 5 years of follow-up included 270 patients with HFpEF (LVEF ≥50%). Statin therapy was associated with improved survival after adjustment for potential confounders including baseline differences, comorbidities and other medications (HR 0.65; 95% CI, 0.45-0.95; $P = .029$).[28] CV hospitalization rates were unchanged. These findings require further confirmation in prospective trials.

Under Investigation: Neprilysin Inhibition

Neprilysin is a zinc-dependent metalloprotease that degrades biologically active natriuretic peptides including atrial natriuretic peptide and BNP. These peptides play an important role in natriuresis and diuresis, promote myocardial relaxation, and reduce hypertrophy.[29] LCZ696 combines a neprilysin inhibitor, sacubitril, with the angiotensin receptor blocker, valsartan. Recently, this combination drug was shown to be superior to enalapril for preventing death and HF hospitalization in a clinical trial of 8,442 patients with HFrEF.[30] Additional studies are examining the drug's benefit in HFpEF. In a phase 2 clinical trial, 292 patients were randomized to LCZ696 or valsartan. NT-proBNP levels and blood pressure were significantly reduced after 12 weeks therapy with LCZ696 compared to valsartan alone.[29] To determine whether these findings translate into improved clinical outcomes, the PARAGON-HF trial is currently recruiting patients.[31] The purpose is to compare the effects of LCZ696 with valsartan alone on CV death and HF hospitalizations in patients with HFpEF (NYHA II-IV HF with LVEF ≥45%). The study began in mid 2014 and is anticipated to continue through May 2019.

CONCLUSION

HFpEF is relatively common and continues to present major challenges in terms of both diagnosis and treatment. Many of the drugs that have been proven to improve survival in patients with impaired systolic function have unfortunately failed to show similar benefits in patients with diastolic dysfunction. As a result, current treatment is primarily aimed at reducing morbidity and aggressively controlling risk factors. Further research is needed to determine the underlying mechanisms associated with mortality due to HFpEF and better target therapeutic strategies.

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