VIEWPOINT

Treatment of Heart Failure With Preserved Ejection Fraction
Reflections on Its Treatment With an Aldosterone Antagonist

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Heart failure (HF) with preserved ejection fraction (HFpEF) is a syndrome that occurs in about one-half of all patients with HF and is being recognized with increasing frequency. Although its specific causes have not been elucidated in the majority of patients, HFpEF occurs most commonly in elderly individuals who have 1 or more comorbidities that include hypertension, obesity, diabetes, metabolic syndrome, atrial fibrillation, anemia, and chronic kidney disease. While by its usual definition the left ventricular ejection fraction is 45% or more (and in some instances ≥50%), HFpEF may also be characterized by diastolic dysfunction that impairs ventricular filling resulting from slowed ventricular relaxation and an increase in passive ventricular stiffness. In some patients with HFpEF, this elevation in filling pressure is manifest only during exercise, whereas in others it is more sustained, and results in pulmonary hypertension.[1]

A variety of abnormalities in cardiac structure and/or function occur in HFpEF, including increases in the diameter of cardiomyocytes, and ventricular hypertrophy, as well as expansion of the fibrous tissue that makes up the extracellular cardiac matrix. The latter, which also occurs in patients with HF and reduced ejection fraction (HFrEF), appears to result from augmentation of the synthesis and cross-linking of collagen, accompanied by a reduction of its degradation.

Abnormalities of diastolic function, increased left ventricular mass to volume ratio, and enlargement of the left atrium are key features of HFpEF that can be recognized by echocardiography.[2] However, there is a wide spectrum of echocardiographic features of HFpEF that may be normal in some patients. Patients exhibiting more prominent structural and functional abnormalities are at higher risk for cardiovascular events.[2]

In 1993, Brilla et al[3] reported that the infusion of aldosterone to uninephrectomized rats resulted in an increase of the cardiac extracellular matrix. These effects of aldosterone were blocked by low doses of the mineralocorticoid receptor antagonist (MRA) spironolactone. These seminal observations have been confirmed repeatedly. There is now considerable evidence that links aldosterone to HF. Thus, patients with diastolic dysfunction and preserved ejection fraction exhibit a statistically significant correlation between the level of circulating aldosterone and left ventricular mass. The central role of interstitial fibrosis in the heart (and perhaps the kidney as well) in HF makes these observations particularly important.

Three major placebo-controlled trials, led by Pitt et al[4,5] and Zannad et al,[6] have provided evidence that administration of MRAs improved clinical outcomes, including survival, in patients with HFrEF as well as with left ventricular dysfunction following myocardial infarction. In the RALES trial, extensive cardiac remodeling and poor clinical outcomes were associated with excessive turnover of the extracellular matrix.[7] The extent of clinical benefit from the MRAs appeared to be most prominent in the patients with HFrEF in whom this turnover was reduced. These observations, taken together, underscore the important relationships between aldosterone, the extracellular matrix, ventricular dysfunction, and the severity of clinical HF.

The effects of MRAs on patients with diastolic dysfunction, both with and without HFrEF, have been studied in a variety of patients, including patients with essential hypertension, obesity, and metabolic syndrome, and in elderly individuals. A meta-analysis of 11 randomized trials showed that administration of an MRA was associated with an improvement in diastolic function assessed by echocardiography, as well as with a reduction in the concentration of circulating biomarkers that reflect the collagen turnover associated with myocardial fibrosis.[8]

Based on this rationale and the public health burden resulting from HFpEF, the National Heart, Lung, and Blood Institute initiated the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Patients were selected on the basis of having symptomatic HF and a left ventricular ejection fraction of 45% or more. In addition, patients had to have been hospitalized within 12 months before randomization for HF or to have an elevated brain natriuretic peptide within the 60 days preceding randomization. The major exclusions were uncontrolled hypertension and elevated serum potassium level (≥5.0 mEq/L [to convert to millimoles per liter, multiply by 1]), creatinine level (≥2.5 mg/dL [to convert to micromoles per liter, multiply by 88.4]), or estimated glomerular filtration rate (<30 mL/min per 1.73 m^2).[9] Randomization was to either placebo or spironolactone at a starting dose of 15 mg with a maximum titration to 45 mg in addition to other HF medications.

TOPCAT was conducted in 6 countries involving 2 regions in which 3445 patients were collectively randomized: 1767 in North and South America (United States, Canada, Brazil, and Argentina) and 1678 in Russia and the Republic of Georgia. Overall, the composite primary outcome (cardiovascular death, aborted cardiac arrest, or hospitalization for HF) was numerically but not signifi-

cantly reduced in the spironolactone group (hazard ratio [HR], 0.89; 95% CI, 0.77-1.04; $P = .14$).[9] Approximately two-thirds of the end point events were for HF hospitalization, a secondary end point in TOPCAT, which was significantly lower in the patients randomized to spironolactone (HR, 0.83; 95% CI, 0.69-0.99; $P = .04$). An extreme difference in the primary event rates was observed; among the patients randomized from North and South America, this end point occurred in 11.5 of 100 patients per year, while in patients from Russia and Georgia, it was only 2.4 of 100 patients per year.[9] The observed incidence in North and South America was what had been expected in patients with HFpEF, while the rate of those enrolled in Russia and Georgia was more consistent with that observed in trials of patients with hypertension or type 2 diabetes rather than with HFpEF.

On further examination, it became apparent that the characteristics of the patients enrolled in the 2 regions were distinctly different.[10] Indeed, of 38 key prespecified variables characterizing the enrolled population, statistically significant differences were observed in 34. Although this may explain the marked disparities in the placebo event rates, this post hoc regional analysis also revealed distinct differences in the pharmacologic actions associated with the administration of spironolactone. In North and South America, randomization to spironolactone was, as expected, associated with more frequent hyperkalemia, elevations in creatinine, reductions in blood pressure, and less hypokalemia. None of these anticipated effects of spironolactone were observed in the patients randomized from Russia and Georgia. Both the benign prognosis and lack of the expected pharmacologic actions of spironolactone confound the validity of the data from these 2 countries and raise the question whether these patients actually had HFpEF and even whether one-half of them received spironolactone.

A comparison of the 886 patients randomized to spironolactone with the 881 patients assigned to placebo in North and South America is informative and, we believe, clinically important. The composite primary outcome (HR, 0.82; 95% CI, 0.69-0.98), cardiovascular death (HR, 0.74; 95% CI, 0.57-0.97), and hospitalizations for HF (HR, 0.82; 95% CI, 0.67-0.99) were each reduced significantly. As expected, more patients assigned to spironolactone developed hyperkalemia and an increase in serum creatinine.

From a strictly statistical point of view, the results of TOPCAT must be regarded as neutral. However, HFpEF is often a disabling and life-shortening condition. Other than the administration of diuretics for fluid accumulation and the management of hypertension (if present), there is little to offer these patients. Based on the findings in TOPCAT in North and South America and in the absence of other more definitive data, it now appears reasonable to treat patients with HFpEF resembling those enrolled in North and South America with spironolactone to improve outcomes. This drug is generic, inexpensive, and generally well tolerated, although periodic monitoring of electrolytes and creatinine must be conducted to detect the occasional development of hyperkalemia and renal dysfunction.

An additional lesson can be learned from TOPCAT. It has long been the practice in hospitals to analyze unexpected adverse clinical outcomes and discuss the findings in morbidity and mortality conferences. Indeed, evidence of such efforts designed to improve the quality of patient care must be documented by hospitals to obtain reaccreditation. To enhance the quality of future clinical trials, it seems equally advisable to analyze the conduct of trials such as TOPCAT with unanticipated results that can have profound implications for patient care.

ARTICLE INFORMATION

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REFERENCES

1. Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010;3(5):588-595.

2. Shah AM, Claggett B, Sweitzer NK, et al. Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. *Circ Heart Fail*. 2014;7(5):740-751.

3. Brilla CG, Matsubara LS, Weber KT. Anti-aldosterone treatment and the prevention of myocardial fibrosis in primary and secondary hyperaldosteronism. *J Mol Cell Cardiol*. 1993;25(5):563-575.

4. Pitt B, Zannad F, Remme WJ, et al; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341(10):709-717.

5. Pitt B, Remme W, Zannad F, et al; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348(14):1309-1321.

6. Zannad F, McMurray JJV, Krum H, et al; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1):11-21.

7. Zannad F, Alla F, Dousset B, Perez A, Pitt B; Rales Investigators. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). *Circulation*. 2000;102(22):2700-2706.

8. Pandey A, Garg S, Matulevicius SA, et al. Effect of mineralocorticoid receptor antagonists on cardiac structure and function in patients with diastolic dysfunction and heart failure with preserved ejection fraction: a meta-analysis and systematic review. *J Am Heart Assoc*. 2015;4(10):e002137.

9. Pitt B, Pfeffer MA, Assmann SF, et al; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370(15):1383-1392.

10. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. *Circulation*. 2015;131(1):34-42.