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# Sacubitril-valsartan and the evolution of heart failure care

**T**HREE DECADES AGO, the only drugs we had for treating chronic heart failure were digitalis and loop diuretics. The mortality rate was very high, and heart transplantation was a newly developing treatment that could help only a very few patients.

*See related article, page 693*

The early 80s heralded new hope for patients with heart failure, with the introduction of angiotensin-converting enzyme (ACE) inhibitors<sup>1-5</sup> and, later, beta-blockers. Beta-blockers were considered contraindicated in heart failure until new trials provided evidence of dramatic benefit such as better quality of life and longer survival.<sup>6-8</sup> ACE inhibitors, along with beta-blockers, quickly became the standard of care for all patients with systolic heart failure.

The implantable cardioverter-defibrillator (ICD) required numerous clinical trials in ischemic and nonischemic cardiomyopathy to define its role.<sup>9,10</sup> Cardiac resynchronization therapy did not arrive until 15 years ago and is now indicated in a specific niche of patients with left bundle branch block.<sup>11,12</sup> Mineralocorticoid antagonists required three pivotal clinical trials before their important role in the treatment of systolic heart failure was defined.<sup>13-16</sup>

And in the current decade, the roles of ACE inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, mineralocorticoid antagonists, ICDs, and cardiac resynchronization therapy have been further defined, as reflected in the latest guidelines for the treat-

ment of systolic heart failure.<sup>17</sup>

Guideline-directed medical therapy for systolic heart failure with the agents and devices mentioned above improves quality of life and extends survival. It was therefore hard to imagine that any new additive therapy could offer significant incremental improvement. However, more than 5 years ago, in an ambitious effort, the largest global clinical trial ever performed in chronic heart failure was launched with a novel agent.<sup>18</sup>

## ■ THE PARADIGM-HF TRIAL

In this issue of the *Journal*, Sabe et al<sup>19</sup> describe the results of the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial of the novel combination drug sacubitril-valsartan, designated LCZ696 during its development and now available as Entresto.<sup>20</sup>

The mean age of the 8,442 patients in PARADIGM-HF was 64, and 78% were men. Despite guideline-directed medical therapy (93% of the patients were receiving a beta-blocker, and 60% were receiving a mineralocorticoid receptor antagonist), patients had persistent symptoms and signs of heart failure, diminished health-related quality of life, reduced ejection fraction (mean 29%), and elevated N-terminal pro-B-type natriuretic peptide levels (median 1,608 pg/mL, interquartile range 886–3,221).

The investigators reported a remarkable 20% reduction in the primary outcome of death from cardiovascular causes or hospitalization for heart failure in the patients who received sacubitril-valsartan compared with enalapril.<sup>20</sup>

**It was hard to believe that any new additional therapy would make a significant difference**

\*Dr. Starling has disclosed membership on advisory committee or review panels for Novartis.

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Sacubitril-valsartan was reviewed under a US Food and Drug Administration (FDA) program that provides expedited review of drugs that are intended to treat a serious disease or condition and that may provide a significant improvement over available therapy. It was also granted a fast-track designation, which supports FDA efforts to facilitate the development and expedite the review of drugs to treat serious and life-threatening conditions and fill an unmet medical need. The FDA approved sacubitril-valsartan on July 7, 2015, for use in place of an ACE inhibitor or ARB in patients with New York Heart Association class II, III, or IV heart failure with reduced ejection fraction.<sup>21</sup>

### ■ WHAT WE STILL NEED TO KNOW

The results of PARADIGM-HF are generalizable, and sacubitril-valsartan was well tolerated in patients whose blood pressure was acceptable and who were able to tolerate ACE inhibitors in target doses. More than 90% of patients were receiving a beta-blocker. The dosing of enalapril (target 10 mg twice a day) is the guideline-directed target dose, and ACE inhibition is considered the gold standard for heart failure with reduced ejection fraction. Sacubitril-valsartan vs enalapril was a very appropriate comparison.

Far fewer PARADIGM-HF patients outside the United States had an ICD than those

in the United States, which is a common finding in global clinical trials. However, Desai et al reported that sacubitril-valsartan reduced rates of cardiovascular mortality both from worsening heart failure and from sudden cardiac death, independent of whether the patient had an ICD.<sup>22</sup>

Sacubitril-valsartan is taken twice a day, but most heart failure patients already take medications at several times during the day, so this should not pose a problem.

More information is needed on the use of this new drug in patients with New York Heart Association class IV symptoms, as only 60 patients with class IV symptoms were included in the PARADIGM-HF trial. Also, the efficacy of the drug in patients unable to tolerate a full dose will need to be analyzed.

PARADIGM-HF was conducted in stable, nonhospitalized patients with chronic heart failure; the use of the drug in new-onset heart failure and its initiation in hospitalized patients will require further study. In addition, the PARAGON-HF trial<sup>23</sup> will examine the efficacy of sacubitril-valsartan in patients with heart failure and an ejection fraction of 45% or higher.

Sacubitril-valsartan ushers in a new era in heart failure treatment for patients with reduced ejection fraction and will certainly prompt quick revision of heart failure guidelines.

■ **Sacubitril-valsartan ushers in a new era in treating heart failure with reduced ejection fraction**

### ■ REFERENCES

1. **Captopril Multicenter Research Group.** A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *J Am Coll Cardiol* 1983; 2:755–763.
2. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987; 316:1429–1435.
3. **The SOLVD Investigators.** Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991; 325:293–302.
4. **Cohn JN, Johnson G, Ziesche S, et al.** A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; 325:303–310.
5. **Pfeffer MA, Braunwald E, Moyé LA, et al.** Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992; 327:669–677.
6. **Packer M, Coats AJ, Fowler MB, et al.** Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; 344:1651–1658.
7. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; 353:2001–2007.
8. **Brophy JM, Joseph L, Rouleau JL.** Beta-blockers in congestive heart failure. A Bayesian meta-analysis. *Ann Intern Med* 2001; 134:550–560.
9. **Buxton AE, Lee KL, Fisher JD, et al.** A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; 341:1882–1890.
10. **Moss AJ, Zareba W, Hall WJ, et al.** Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; 346:877–883.
11. **Abraham WT, Fisher WG, Smith AL, et al; MIRACLE Study Group.** Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; 346:1845–1853.
12. **McAlister FA, Ezekowitz J, Hooton N, et al.** Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. *JAMA* 2007; 297:2502–2514.
13. **Pitt B, Zannad F, Remme WJ, et al.** The effect of spironolactone on morbidity and mortality in patients with

- severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; 341:709–717.
14. **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; 348:1309–1321.
  15. **Pitt B, White H, Nicolau J, et al; EPHEBUS Investigators.** Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005; 46:425–431.
  16. **Zannad F, McMurray JJ, Krum H, et al; EMPHASIS-HF Study Group.** Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364:11–21.
  17. **Yancy CW, Jessup M, Bozkurt B, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines.** 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; 62:e147–e239.
  18. **McMurray JJ, Packer M, Desai AS, et al; PARADIGM-HF Committees and Investigators.** Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail* 2013; 15:1062–1073.
  19. **Sabe IA, Jacob MS, Taylor DO.** A new class of drugs for systolic heart failure: The PARADIGM-HF study. *Cleve Clin J Med* 2015; 82:693–701.
  20. **McMurray JJ, Packer M, Desai AS, Gong J, et al; PARADIGM-HF Investigators and Committees.** Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371:993–1004.
  21. **US Food and Drug Administration.** FDA approves new drug to treat heart failure. [www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm453845.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm453845.htm). Accessed September 2, 2015.
  22. **Desai AS, McMurray JJ, Packer M, et al.** Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J* 2015; 36:1990–1997.
  23. **ClinicalTrials.gov.** Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF). <https://clinicaltrials.gov/ct2/show/NCT01920711>. Accessed September 2, 2015.
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