

## VIEWPOINT

# Angiotensin Neprilysin Inhibition for Patients With Heart Failure

## What If Sacubitril/Valsartan Were a Treatment for Cancer?

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Editor's Note  
page 973

**Imagine you are caring** for a patient with a lethal disease. She has responded well and has few symptoms, but the disease is still present and will worsen in the future. Suddenly, a new drug becomes available that can extend life by 1 to 2 years more than you can achieve with the current therapy. What do you do?

Oncologists would adopt the new drug as the standard of care in a heartbeat, but US physicians who treat patients with heart failure often do little. Heart failure is a fatal disorder, and current drugs achieve only a brief clinical remission. Two years ago, sacubitril/valsartan was shown to be superior to a conventional inhibitor of the renin-angiotensin system in reducing the risk of cardiovascular death,<sup>1</sup> and it received expedited US Food and Drug Administration approval for treatment of chronic heart failure. Owing to cost, third-party payors discouraged the use of the drug by requiring high patient copays and administrative preapprovals. Oncologists are accustomed to overcoming these distractions, but other physicians are not. Consequently, uptake of sacubitril/valsartan by US practitioners has been slow.

### What Does Sacubitril/Valsartan Do for Patients With Heart Failure?

Sacubitril/valsartan inhibits both angiotensin and neprilysin, promoting greater normalization of neurohormonal abnormalities than inhibiting the renin-angiotensin system alone. In the Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, patients receiving sacubitril/valsartan had a 20% lower risk of cardiovascular death and lived 1 to 2 years longer than those receiving enalapril,<sup>1</sup> largely owing to a decrease in the risk of sudden death in clinically stable patients with only mild symptoms. The reduction in sudden cardiac death was greater than could be achieved by an antifibrillatory device.<sup>2</sup> Patients receiving sacubitril/valsartan also remained in clinical remission longer than those treated with enalapril, with less instances of worsening heart failure requiring hospitalization, intensification of therapy, implantation of a device, or cardiac transplantation.<sup>3</sup>

The strength of evidence of the PARADIGM-HF trial was persuasive to a degree that had few precedents in cardiovascular trials. The level of statistical significance ( $P = .00008$ ) established replicability equal to 4 independently conducted trials, each showing a reduction in cardiovascular mortality (all  $P < .05$ ). If the

PARADIGM-HF trial were split at its chronological midpoint and analyzed as 2 sequentially executed, self-contained trials, robust levels of statistical significance would have been achieved in both halves of the study.<sup>4</sup>

### Did PARADIGM-HF Compare the Right Doses of Drugs in the Right Patients?

In the PARADIGM-HF trial, 8399 patients with chronic heart failure and a reduced ejection fraction were randomized to receive double-blind treatment with enalapril (10 mg twice daily) or sacubitril/valsartan (97/103 mg twice daily) for up to 5 years. The renin-angiotensin system was inhibited to a similar degree in the 2 treatment arms<sup>5</sup>; thus, any difference was related to the inhibition of neprilysin by sacubitril/valsartan.

The dose of enalapril in the trial was mandated by regulatory agencies and was the same as in other trials that used an angiotensin-converting enzyme (ACE) inhibitor comparator. Ten milligrams of enalapril twice daily is the only renin-angiotensin inhibitor regimen that has been shown to reduce long-term mortality, especially in patients with mild to moderate symptoms.<sup>4</sup> Although 20 mg of enalapril twice daily is approved for use, it is poorly tolerated, and there is little long-term controlled experience with the dosage. Regardless, the average dose of enalapril in the PARADIGM-HF trial exceeded that achieved in any prior large-scale heart failure trial.<sup>1</sup> Because angiotensin receptor blockers (ARBs) have not been shown to reduce the risk of death in patients with heart failure, they were not used as the comparator.

When the analysis of the PARADIGM-HF trial was restricted to patients enrolled in the United States, the reduction in cardiovascular death or hospitalization for patients with heart failure remained significant (hazard ratio, 0.66; 95% CI, 0.47-0.92). Of the US cohort, 26% of participants were African American, and 60% of the patients had an implantable cardioverter defibrillator. The benefits of sacubitril/valsartan in these subgroups were superimposable on those seen in the entire trial.<sup>1,2</sup>

### Which Patients Should Be Switched to Sacubitril/Valsartan?

Although physicians often prescribe a new drug to patients who are responding poorly to their current regimen, this strategy is inappropriate for sacubitril/valsartan; most patients in the PARADIGM-HF trial had only mild symptoms and responded well to treatment. The purpose of switching patients to sacubitril/valsartan is not to improve symptoms (although this oc-

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curs) but instead to maintain clinical remission in patients who are destined to develop worsening heart failure or die suddenly.

Which patients receiving a conventional renin-angiotensin inhibitor should be switched to sacubitril/valsartan? Some have proposed that sacubitril/valsartan be restricted to patients receiving target doses of an ACE inhibitor. However, sacubitril/valsartan has survival benefits not provided by increments in dosing of an ACE inhibitor,<sup>6</sup> and physicians should switch patients receiving subtarget doses of a renin-angiotensin inhibitor to sacubitril/valsartan rather than increase the existing inhibitor to target doses. In the PARADIGM-HF trial, sacubitril/valsartan was superior to enalapril even in patients treated with subtarget doses of the 2 drugs.<sup>6</sup>

Of note, approximately 5500 patients were receiving low to moderate doses of various ACE inhibitors or ARBs when they were screened for the PARADIGM-HF study. They were enrolled with the intent that half would be switched and uptitrated to target doses of enalapril and half would be switched and uptitrated to target doses of sacubitril/valsartan. Before randomization, these patients were exposed to both study drugs for a few weeks to ensure their tolerability. Switching therapy to and uptitrating patients with sacubitril/valsartan yielded a greater reduction in the risk of cardiovascular death or heart failure hospitalization ( $P = .001$ ) and a greater reduction in cardiovascular death alone ( $P = .002$ ) than switching to and uptitrating with enalapril.<sup>4</sup> The dose of a renin-angiotensin system inhibitor taken before the study did not influence the degree to which sacubitril/valsartan was superior to enalapril.

### Which Is Safer—Sacubitril/Valsartan or an ACE Inhibitor?

In the PARADIGM-HF trial, patients switched to sacubitril/valsartan were less likely than those switched to enalapril to experience renal insufficiency and hyperkalemia requiring discontinuation of the study medication.<sup>1</sup> Consequently, patients tolerated higher doses of a renin-angiotensin system inhibitor when it was combined with a neprilysin inhibitor than when it was used alone, providing another reason why patients taking low doses of a conventional renin-angiotensin inhibitor should be switched to an angiotensin receptor neprilysin inhibitor before efforts are made to achieve target doses of an ACE inhibitor or ARB.<sup>6</sup>

The most important concern with sacubitril/valsartan is hypotension. Because the initial hypotensive response to renin-angiotensin inhibition is unpredictable, there is little reason to complicate matters by adding a neprilysin inhibitor during commencement of treatment. When switching to sacubitril/valsartan,

it is prudent to select a dose of the angiotensin receptor neprilysin inhibitor that mimics the patient's previous level of renin-angiotensin blockade. If target doses cannot be achieved, patients should be maintained on a lower dose of sacubitril/valsartan rather than being returned to treatment with an ACE inhibitor or ARB.

Because survival benefits led to early termination of the study, 10- and 20-year controlled safety data could not ethically be obtained in the PARADIGM-HF trial nor will it be possible to acquire such data in the future. For the same reason, long-term controlled safety data are not available for any of the life-saving drugs that we currently prescribe for heart failure. Although some might wonder if sacubitril/valsartan might produce an untoward effect in patients after several decades of use, it serves little purpose to speculate about a future that would not exist in the absence of having been treated with the drug. Theoretical concerns about toxicity occurring after 10 to 20 years are irrelevant if these durations exceed the lifespans of patients who should be treated with the drug.

This view is important in interpreting claims that neprilysin inhibition may slow the clearance of brain amyloid and impair cognitive function if sustained for 10 to 20 years. The isoforms of amyloid modulated by neprilysin inhibition are not believed to have a role in Alzheimer disease.<sup>4</sup> Furthermore, angiotensin II contributes to neurocognitive decline<sup>7</sup>; angiotensin suppression exerts benefits on amyloid metabolism that exceed any detriment that may result from neprilysin inhibition. Simultaneous inhibition of neprilysin and angiotensin has not led to the accumulation of pathogenetic forms of amyloid in humans, and long-term inhibition of neprilysin inhibitors has not increased reports of dementia or memory impairment in large-scale trials.<sup>4</sup> Interestingly, ACE inhibitors are preferred over ARBs in patients with heart failure because of the greater certainty of their survival benefits, even though ARBs may have more favorable neurocognitive effects.<sup>7</sup>

### Conclusions

The fact that sacubitril/valsartan prolongs life more than the highest doses of an ACE inhibitor achieved in a clinical trial should encourage its broad use in patients who can tolerate initial doses of a renin-angiotensin inhibitor. Patients with heart failure and a reduced ejection fraction have a clinical course similar to serious forms of cancer; the risk of progression and death are high even in patients in clinical remission. Accordingly, patients with heart failure should be treated with as much energy as those with cancer. They deserve nothing less.

#### ARTICLE INFORMATION

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#### REFERENCES

- McMurray JJ, Packer M, Desai AS, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.
- 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(30):1990-1997.
- Packer M, McMurray JJ, Desai AS, et al; PARADIGM-HF Investigators and Coordinators. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015;131(1):54-61.
- Packer M. Kicking the tyres of a heart failure trial [published online August 10, 2016]. *Eur J Heart Fail*. doi:10.1002/ejhf.623
- Pfeffer MA, McMurray JJ, Velazquez EJ, et al; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349(20):1893-1906.
- Packer M. Love of angiotensin-converting enzyme inhibitors in the time of cholera [published online April 12, 2016]. *JACC Heart Fail*. doi:10.1016/j.jchf.2016.02.012
- Fournier A, Oprisiu-Fournier R, Serot JM, et al. Prevention of dementia by antihypertensive drugs. *Expert Rev Neurother*. 2009;9(9):1413-1431.