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EDITORIAL COMMENT

Angiotensin Receptor-Neprilysin Inhibition in Heart Failure With Reduced Ejection Fraction

A Paradigm for All?*

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The PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor [ARNI] with Angiotensin-Converting-Enzyme Inhibitor [ACEi] to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial (1) is the first ever to demonstrate improved clinical outcomes with any agent, compared with an ACEi, in patients with HF and reduced left ventricular ejection fraction (LVEF). The strength of statistical evidence for reduced cardiovascular (CV) mortality and morbidity by the ARNI, sacubitril/valsartan, over enalapril, with standard additional background therapy, removes any concern that the findings represent play of chance. A focused guideline update published by the American College of Cardiology, American Heart Association, and Heart Failure Society of America (2) states that "In patients with chronic symptomatic HF (with reduced LVEF) NYHA class II or III who tolerate an ACE inhibitor or ARB [angiotensin receptor blocker], replacement by an ARNI is recommended to further reduce morbidity and mortality." However, many providers and payers are resistant to the proposed breadth of indication for this combination therapy and have sought to define a narrower population for which it might yield a particularly favorable benefit-to-risk relationship and cost-effective profile. Among these efforts has been the suggestion to withhold ARNI therapy in favor of an ACEi or ARB, until there are signs of patient worsening, such as hospitalization for HF. The analysis by Solomon et al. (3) published in this issue of *JACC: Heart Failure* provides a compelling argument against the latter approach, demonstrating that the benefit of sacubitril/valsartan over enalapril therapy was independent of the presence or timing of prior HF hospitalization.

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Table 1 lists questions left unanswered by PARADIGM-HF. Answers to these questions might influence a clinician's judgment regarding the value of and indication for switching to sacubitril/valsartan therapy. However, it is questionable whether these unknowns should impact our decision to act on the data that we now have. Benefit relative to either a higher ACEi dose or to valsartan, 160 mg twice daily, alone, would require another large trial, which may never be performed. Absent evidence that these approaches would replicate the findings with sacubitril/valsartan, there is no proven alternative to the latter combination for achieving a 20% reduction in the hazard of CV morbidity and mortality, relative to a data-driven, commonly used dose of enalapril. Clearer knowledge of the rate of limiting hypotension in clinical practice, where there is no exclusionary "run-in" period, will come through post-marketing surveillance or, more precisely, through patient registries. Knowledge of the precise value of sacubitril/valsartan in patients without prior exposure to an ACEi or ARB would also come only through another trial. However, it seems unlikely that such patients would respond differently. Realistically, this question is moot. If a clinician wants to be rigorous about reproducing PARADIGM-HF's population, he or she can

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TABLE 1 Questions Left Unanswered by PARADIGM-HF

How would sacubitril/valsartan compare with higher doses of an ACEi?
How does sacubitril/valsartan compare with valsartan, 160 mg twice daily?
In practice, what will be the rate of limiting hypotension?
Would the response be different in patients without prior ACEi/ARB exposure?
Are there any long-term adverse effects of sacubitril/valsartan?
Is there benefit in patients without prior or recent decompensation? In other words, why not wait for signs and symptoms of worsening HF?

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HF = heart failure; PARADIGM-HF = Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor [ARNI] with Angiotensin-Converting-Enzyme Inhibitor [ACEi] to Determine Impact on Global Mortality and Morbidity in Heart Failure.

start an ACEi or ARB regimen and then switch to sacubitril/valsartan.

The long-term effects of ARNI therapy are unknown. Concern has been raised based on preclinical findings that neprilysin inhibition may impair the breakdown of amyloid in the brain (4). This theoretical long-term concern seems outweighed by the demonstrated reduction in mortality in a population with a baseline (enalapril group) 3-year CV mortality close to 20%. Cost-effective analyses based on PARADIGM-HF have demonstrated favorability only after long-term (e.g., life long) treatment, assuming maintenance of the risk-benefit relationship (5,6). Further analyses will be needed to substantiate sustained safety for sacubitril/valsartan.

Solomon et al. (3) address the question of whether sacubitril/valsartan therapy is similarly superior to enalapril independent of the prior degree of clinical instability. In the current report, the authors observed that more recent hospitalization was associated with increased risk. However, no inconsistencies were found in the hazard ratios for the primary study endpoint of CV death or HF hospitalization or for CV death alone and for all-cause mortality across groups defined by the presence or absence and the timing of prior HF hospitalization. In other words, there was no significant treatment-by-subgroup interaction. Importantly, for each of these endpoints, the hazard ratio point estimate was numerically strongest for patients with no history of HF hospitalization.

One limitation of the present report is that it is a post hoc subgroup analysis, which cannot provide certainty that no between-group differences exists in the response to sacubitril/valsartan. However, there is no suggestion from the data that any such difference is present, and the pattern of findings, with the most impressive hazard ratio residing within the no-hospitalization subgroup, strongly supports the authors' conclusions. There are other differences among these subgroups that could have influenced the results. For example, patients without prior hospitalization were required to have elevated natriuretic peptide levels; however, findings among patients within the lowest tertile of N-terminal pro-B-type natriuretic peptide levels were consistent with the overall findings.

It is worthwhile to examine the absolute risk reduction, in addition to the hazard ratio. Because the event rates are lowest in the lowest risk group, one would expect a lower absolute risk reduction than in the highest risk group for any given hazard ratio. In that case, a clinician could decide that switching treatment may be less worthwhile, given the increased risk of hypotension. However, Solomon et al. (3) show that, in the lowest risk group, the hazard ratio is also numerically lowest (sacubitril/valsartan vs. enalapril), offsetting the lower event rate. Rates for the primary endpoint in the lowest risk group were 10.7 and 7.6 per 100 patient-years in the enalapril arm and the sacubitril/valsartan arm, respectively, translating to an absolute risk reduction of 3.1 per 100 patient-years (S.D. Solomon, personal communication, July 2016). The corresponding values for the highest risk group were 16.8 and 13.6 per 100 patient-years, for an absolute risk reduction of 3.2 per 100 patient years. In other words, there is minimal attrition of the absolute risk reduction within the lowest risk group.

As the authors point out, 20% of patients in the no-HF hospitalization group had a primary endpoint event, most of which were CV deaths, predominantly adjudicated as sudden cardiac deaths. These observations further support the authors' conclusions of benefit for sacubitril/valsartan over enalapril, even in the absence of prior HF hospitalization. These findings, combined with the prior finding of consistent benefit for sacubitril/valsartan therapy across the spectrum of baseline comprehensive risk (7), should put to rest advocacy for switching to sacubitril/valsartan only after observing worsening symptoms.

The circumstances we are facing with sacubitril/valsartan are not unique. The first major paradigm shift in treating patients with HF, since the advent of diuretics, came from the SOLVD (Studies of Left Ventricular Dysfunction) trial (8). This earlier shift contained 2 components: first, that we could actually save lives through drug treatment across a broad spectrum of patients with reduced LVEF; and second, that to achieve that goal, we should adopt a strategy of initiating treatment and up-titrating toward target dose, as tolerated, independent of clinical signs and symptoms. During the first several years following publication and regulatory approval (in the days before publication of the first HF clinical practice

guideline) (9), adoption of this life-saving treatment was slow. There remained a lingering perception that ACEi were third-line treatments for hypertension and that their presumed onerous adverse event profile demanded much caution when considering prescribing them. At that time, it required a large and prolonged educational effort for providers to accept the notion of initiating or changing treatment on the basis of new data, rather than on the basis of a worsening of the patient's condition. The same reluctance continues today regarding driving to the target dose in the absence of worsening symptoms, despite evidence that dose makes a difference, again, regardless of clinical worsening (10).

Regardless of the magnitude of a clinical trial treatment effect, concern about trial design and gaps in knowledge may provide clinicians and payers rationale, justified or not, to avoid prescribing or covering expensive new treatment options. The good news is that such concerns may motivate manufacturers to reduce the price. The bad news is that they may have an adverse effect on patient outcomes. Although providers appropriately retain the prerogative of deciding the appropriate treatment for an individual patient, resolution of questions regarding the principal trial result will improve clinician decision making. The analysis by Solomon et al. (3) has helped to eliminate 1 rationale for delaying a change to sacubitril/valsartan, namely, that waiting until the patient deteriorates does not diminish overall treatment benefit. This analysis provides strong evidence that the paradigm shift driven by PARADIGM-HF is equally applicable to patients regardless of HF hospitalization history.

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