EDITORIALS

PARAGON-HF — Why We Do Randomized, Controlled Clinical Trials

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Patients with heart failure and preserved ejection fraction have high morbidity and mortality, as well as reduced quality of life, and there are no approved therapies. The complex pathophysiological mechanisms contributing to this condition have made therapeutic development difficult. The PARAMOUNT (Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blocker] on Management of Heart Failure with Preserved Ejection Fraction) trial,[1] a phase 2 trial of sacubitril–valsartan (a combination angiotensin receptor–neprilysin inhibitor) as compared with valsartan alone in patients with heart failure with preserved ejection fraction, showed a significant reduction in natriuretic peptide levels at 12 weeks. PARADIGM-HF (Prospective Comparison of ARNI with ACEI [angiotensin-converting–enzyme inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial),[2] a trial of sacubitril–valsartan as compared with enalapril in patients with heart failure with reduced ejection fraction, showed a 20% lower risk of hospitalization for heart failure or death from cardiovascular causes in a time-to-event analysis, which led to the hope that sacubitril–valsartan could become the first drug to show a clinical benefit in patients with heart failure with preserved ejection fraction.

Solomon et al.[3] report in this issue of the *Journal* the results of a landmark trial, PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction), which compared sacubitril–valsartan with valsartan alone in patients with heart failure with preserved ejection fraction. The trial included patients who were 50 years of age or older and who had signs and symptoms of heart failure, an ejection fraction of 45% or higher, and elevated natriuretic peptide levels. A total of 4822 patients (51% of whom were women) in 43 countries underwent randomization after a single-blind run-in period. After a median of 35 months, there were 894 primary events (hospitalizations for heart failure and deaths from cardiovascular causes) in the sacubitril–valsartan group and 1009 primary events in the valsartan group (rate ratio, 0.87; 95% confidence interval [CI], 0.75 to 1.01; P=0.06). The incidence of death from cardiovascular causes was 8.5% in the sacubitril–valsartan group and 8.9% in the valsartan group (hazard ratio, 0.95; 95% CI, 0.79 to 1.16). There were 690 hospitalizations for heart failure in the sacubitril–valsartan group and 797 in the valsartan group (rate ratio, 0.85; 95% CI, 0.72 to 1.00). Quality of life and New York Heart Association functional class were improved in the sacubitril–valsartan group. Among the prespecified subgroups, there were interactions suggesting benefit in patients with lower ejection fraction and in women.

Often, when a clinical trial does not meet its primary end point, we learn more from the secondary analyses than with a successful intervention. In the PARAGON-HF trial, there are several important lessons. The suggestion of benefit with sacubitril–valsartan in the cohort of patients with mildly reduced ejection fraction is consistent with findings from the CHARM (Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity)–Preserved trial of candesartan[4] and the TOPCAT (Treatment of Preserved

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Cardiac Function Heart Failure with an Aldosterone Antagonist) trial of spironolactone.[5] Data from biomarker and proteomic profiling provide biologic support for clinical phenotypic overlap as a continuum between heart failure with reduced ejection fraction and heart failure with preserved ejection fraction.[6] The finding of a suggested benefit with sacubitril–valsartan in women was unexpected. Women have smaller hearts than men, and perhaps the dose of medication was pharmacologically higher. The differences in adipose-tissue distribution between men and women may result in a higher state of inflammation, neurohormonal activation, and adverse hemodynamic exercise response in women.[7] In future studies of heart failure with preserved ejection fraction, prospective stratification according to ejection fraction (40 to 50% vs. >50%) and sex should be considered.

Nonetheless, the overall findings of the PARAGON-HF trial are clearly quite different from those of PARADIGM-HF. Two important observations may help to explain the divergent results. The baseline natriuretic peptide levels were approximately 77% higher in PARADIGM-HF than in the PARAGON-HF trial. If indeed the drug reduces adverse cardiac remodeling reflected by reduction in natriuretic peptide levels, this mechanism may be less important in patients with heart failure with preserved ejection fraction than in patients with heart failure with reduced ejection fraction. Soluble neprilysin reduces the favorable effects of natriuretic peptides, and levels of soluble neprilysin have been shown to be elevated and to be linearly related to morbidity and mortality among patients with heart failure with reduced ejection fraction.[8] However, it has been shown that patients with heart failure with preserved ejection fraction have lower circulating neprilysin levels than do persons without heart failure.[9] Thus, a neprilysin inhibitor may be less effective without elevations of this substrate.

Several other issues should be considered in interpreting the findings of the PARAGON-HF trial. The comparator valsartan may have had a potential beneficial effect, as did candesartan in the CHARM-Preserved trial. Thus, it was an ambitious goal to believe that sacubitril–valsartan could be superior to valsartan by a relative 22%, as predicted in the power calculation. The clinical events committee used strict criteria for adjudicating hospitalizations for heart failure, which may have reduced event counts owing to insufficient documentation. As in the CHARM-Preserved trial, when primary end-point events in the PARAGON-HF trial were determined by the investigator rather than by the clinical events committee, the P value was below rather than above 0.05. Finally, despite the P value of 0.06 for the primary end point, the rate ratio (0.87) suggests the possibility that a larger trial might have shown a significant benefit.

Of course, the totality of evidence must be carefully considered when evaluating the results of a trial. In this trial, the investigators set a high bar for success and identified some signals suggestive of benefit, despite a neutral result for the primary end point. As we continue to learn from these data, we should be grateful to the investigators and patients for their commitment to this landmark endeavor.[10]

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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