Research Letter

PARAGON-HF Clinical Trial Eligibility in a Population of Patients Hospitalized With Heart Failure

PARAGON-HF (prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin receptor blocker global outcomes in heart failure with preserved ejection fraction [HFpEF]) missed its primary endpoint of reducing total hospitalizations and cardiovascular death in patients with HFpEF. The data suggest a modest treatment effect of sacubitril/valsartan compared with valsartan alone and a heterogeneous response to treatment, with potential benefit in subgroups.[1] It remains to be seen how the population of patients with HFpEF enrolled in trials compares to those encountered in clinical practice.[2] *PARAGON-HF* baseline characteristics showed a higher prevalence of comorbidities compared with other HFpEF study participants.[3] There has, however, been no comparison on how the *PARAGON-HF* trial enrollees compare to patients with HFpEF in US-wide clinical practice.

Our aim: 1) determine eligibility for *PARAGON-HF* amongst patients in a contemporary, US-wide HFpEF sample ("All-HFpEF"); 2) determine potential eligibility for sacubitril/valsartan using a minimal set of criteria most relevant to clinical practice ("Broad-criteria" cohort); and 3) compare long-term outcomes between cohorts.

Methods

The study population included patients from the GWTG−HF (Get with the Guidelines−Heart Failure) registry. GWTG−HF is a contemporary registry established by the American Heart Association, and includes a diverse cohort of patients hospitalized for HF or who developed HF symptoms during hospitalization.[4] The initial study population (All-HFpEF) consists of all patients discharged alive in GWTG-HF between January 2006 and June 2018 with left ventricular ejection fraction >40% on quantitative assessment or normal/mild dysfunction if based on qualitative assessment. Next, we derived 2 separate groups by applying: 1) *PARAGON-HF* inclusion/exclusion criteria ("*PARAGON-HF* eligible"), and 2) a set of clinically relevant criteria (Broad-criteria; (Fig. 1). The Broad-criteria represent a minimal set of inclusion and exclusion criteria, attempting to understand the number of patients with HFpEF encountered in clinical practice for whom clinicians might consider sacubitril/valsartan. Data on all-cause mortality and HF-readmission rate 1-year post index discharge were obtained by linking GWTG-HF (age ≥65) with the Medicare Part A inpatient fee-for-service claims between 2006 and 2015.

Results

Total of 106,440 patients in GWTG-HF met our definition of All-HFpEF. *PARAGON-HF* inclusion criteria were met by 85,924 patients (80.7%), with a final cohort of patients with HFpEF meeting both the *PARAGON-HF* inclusion/exclusion criteria being N=10,961 (10.3%; Fig. 1). In contrast, 75,846 (71.3%) patients with HFpEF in GWTG-HF met the Broad-criteria.

"*PARAGON-HF* eligible" patients tended to be older than the Broad-criteria or All-HFpEF cohorts (mean age in years: 78.7 vs 75.1 vs 74.7), with similar proportion of women (59.7% vs 58.6% vs 59.6%), and generally lower rates of comorbid disease (coronary artery disease: 48.4% vs 44.8% vs 46.1%; diabetes: 41.0% vs 45.7% vs 48.7% and renal insufficiency: 8.0% vs 11.2% vs 22.7%).

Among the Center for Medicare and Medicaid Services-linked patients (27.9% of All-HFpEF), the 1-year all-cause mortality was 25.5% (N=885) for *PARAGON-HF* eligible versus 31.1% (N=6334) for Broad-criteria versus 33.7% (N=9511) for All-HFpEF (log rank test $P < .001$). HF-readmission rate at 1 year was 22.8% in the *PARAGON-HF* eligible cohort versus 25.1% in Broad-criteria versus 26.7% in All-HFpEF (Gray's test $P < .001$).

Discussion

In a contemporary, US-wide cohort of patients hospitalized for HF, 10.3% met *PARAGON-HF* inclusion and exclusion criteria. Minimizing inclusion and exclusion criteria, increased potential eligibility for the use of sacubitril/valsartan to 71.3% of all patients with HFpEF. Baseline characteristics and clinical outcomes at 1 year indicate a lower risk profile of *PARAGON-HF* eligible patients compared with patients with HFpEF encountered in clinical practice.

Despite a modest treatment effect that did not reach statistical significance in the overall in *PARAGON-HF* cohort, some secondary endpoints and subgroups such as women and lower left ventricular ejection fraction derived a modest benefit.[1] Future prospective trials in HFpEF will need to determine which population derives the greatest benefit from sacubitril/valsartan. Notwithstanding the strong evidence of clinical benefit in patients with heart failure with

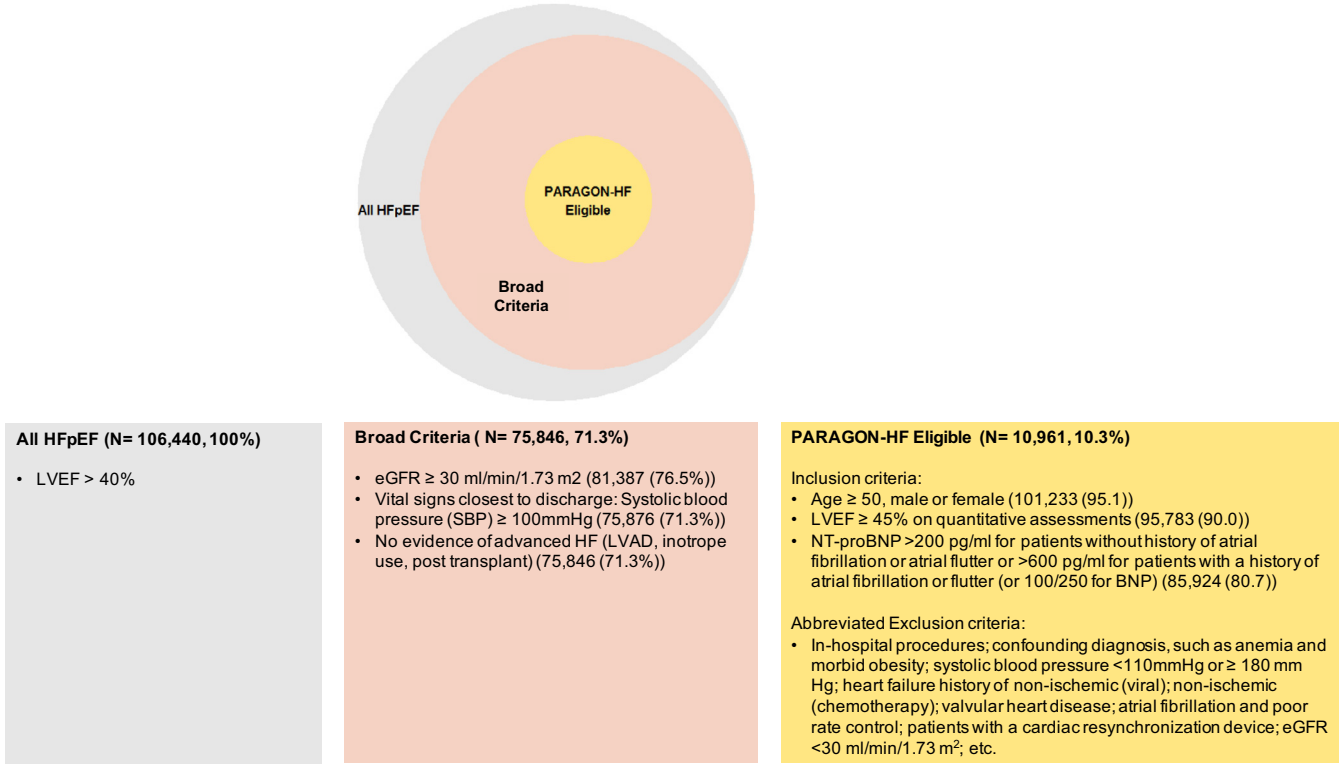

Fig. 1. Patients with HFpEF in GWTG-HF and a subset of patients meeting Broad-criteria and *PARAGON-HF* criteria. BNP, brain natriuretic peptide; eGFR, estimated glomerular ejection fraction, LVAD, left ventricular assist device; LVEF, left ventricular rejection fraction.

reduced ejection fraction, adoption of sacubitril/valsartan remains low.[5] Given marked differences between an US-wide clinical population and *PARAGON-HF*, and the known heterogeneity of HFpEF, careful consideration of the eligible HFpEF population is warranted. Despite surrogate[6] and clinical outcome data[1] it may be important to characterize responders to therapy before its application in HFpEF.

Whereas *PARAGON-HF* primarily enrolled outpatients, GWTG-HF was comprised of hospitalized patients, indicative of a higher risk population. The hospital setting is important to identify potentially eligible patients and optimize medications prior to discharge. The outcome analysis utilized only Medicare patients and is not representative of the entire population. Additionally, although *PARAGON-HF* used echocardiographic criteria beyond EF to increase HFpEF specificity, this was unavailable in GWTG-HF.

Overall, in our analysis there are differences in HFpEF patient characteristics for those studied in *PARAGON-HF* compared with those encountered in a US-wide clinical practice, with only 10.3% of the studied population with HFpEF meeting inclusion/exclusion criteria for *PARAGON-HF*.

Disclosures

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Sabina Sayeed, MA[1,**]
Marat Fudim, MD, MHS[1,2,**]
Adam D. Devore, MD, MHS[1,2]
Haolin Xu, MS[3]
Roland A. Matsouaka, PhD[3]
Paul A. Heidenreich, MD[4]
Clyde W. Yancy, MD[5]
Gregg C. Fonarow, MD[6]
Adrian F. Hernandez, MD, MHS[1,2,*]

[1]*Duke Clinical Research Institute, Durham, North Carolina*
[2]*Division of Cardiology, Duke University Medical Center, Durham, North Carolina*
[3]*Department of Biostatistics and Bioinformatics, Duke University, Durham, North Carolina*
[4]*Division of Cardiology, Veterans Affairs Palo Alto Healthcare System, Palo Alto, California*
[5]*Division of Cardiology, Northwestern University, Chicago, Illinois*
[6]*Ahmanson-UCLA Cardiomyopathy Center, University of California, Los Angeles, Medical Center, Los Angeles, California*

E-mail address: adrian.hernandez@duke.edu (A.F. Hernandez).

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