Treatment Effects of Sacubitril/Valsartan Compared With Valsartan in Patients with Recent Hospitalization
Brief Title: PARAGON-HF Recent Hospitalization

Ankeet S. Bhatt, MD, MBA[1], Brian L. Claggett, Ph.D[1], Milton Packer, MD[2], Martin P. Lefkowitz, MD[3], Michael R. Zile, MD[4], John J.V. McMurray, MD[5], Scott D. Solomon, MD[1], and Muthiah Vaduganathan, MD, MPH[1]

[1]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA
[2]Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, Texas
[3]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey
[4]Medical University of South Carolina, Charleston and Ralph H. Johnston Veterans Administration Medical Center, Charleston, South Carolina
[5]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland

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Address for Correspondence:
Muthiah Vaduganathan, MD, MPH
Brigham and Women's Hospital
Division of Cardiovascular Medicine
75 Francis Street
Boston, MA 02115
Phone: (617) 525-7053
Email: mvaduganathan@bwh.harvard.edu

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Introduction

The Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial demonstrated sacubitril/valsartan modestly lowered total heart failure (HF) hospitalizations and cardiovascular death compared with valsartan in ambulatory HF patients with left ventricular ejection fraction (LVEF) ≥45%[1]. Treatment benefits were greater in patients with lower ejection fractions[2] and post-hoc analyses identified greater benefit in those with recent HF hospitalization.[3] That patients with recent HF hospitalization might be an important target population among individuals with heart failure and mildly reduced or preserved ejection fraction is underscored by the potential benefit of sotagliflozin in this population the SOLOIST-WHF trial.[4] Recently, the FDA expanded the indication for sacubitril/valsartan to encompass potentially all patients with chronic HF, although the revised label stated that benefits are most clearly evident in those with an LVEF below normal. In light of these observations, we conducted more detailed analyses of the treatment effects in patients with recent hospitalization in PARAGON-HF, including those with LVEF above the normal range.

Methods

The design and primary results of PARAGON-HF have been previously reported[1]. In brief, the study was a randomized assessment of sacubitril/valsartan vs. valsartan in HF patients with LVEF≥45%. Randomization during acute HF hospitalization was not permitted, however, screening was allowed once the patient had stabilized and returned to his/her pre-decompensation health status. The primary endpoint was the composite of total (first and recurrent) HF hospitalizations and cardiovascular death. We additionally evaluated total HF

hospitalizations and total worsening HF events (total HF hospitalization + urgent HF visits + cardiovascular death)[5]. For this analysis, we focused on patients with a recent hospitalization (≤30 days of trial screening) to mirror inclusion criteria for PARAGLIDE-HF (NCT03988634). As prespecified, higher LVEF was defined as >57% (median), while lower LVEF was defined as ≤57%.

The treatment effect of sacubitril/valsartan vs. valsartan was compared across higher and lower LVEF categories for patients with very recent hospitalization using a semiparametric proportional rates method and compared to those with more remote hospitalization[6]. Interaction testing was performed to determine effect modification by LVEF above or below the median. All statistical analyses were performed using STATA version 16.1 (StataCorp, College Station, Texas).

Results

Of the 4,796 validly randomized patients in PARAGON-HF, 622 (13%) had a very recent hospitalization (≤30 days). These patients had a mean age was 71.6±9.0 years, 54% were women, 81% were White, median LVEF was 57 (IQR:50-62)%. There were 214 events for the primary outcome in patients with very recent hospitalization.

In patients with very recent hospitalization, those with *higher* LVEF had absolute event rates for the primary endpoint of 27.4 (95% confidence interval [CI]: 20.0–37.7) per 100 patient-years for those randomized to valsartan compared with 21.3 (95% CI 15.6–29.3) for those randomized to sacubitril/valsartan [rate ratio (RR): 0.70 (95% CI 0.46–1.07)]. Among patients with *lower*

LVEF absolute incident event rates were 26.1 (95% CI 19.9–34.3) per 100 patient-years for valsartan and 19.2 (95% CI 12.6–29.1) per 100 patient-years for sacubitril valsartan [RR: 0.77 (95% CI 0.47–1.27)]; $p_{interaction}$ for treatment effect by LVEF ≤ vs. > trial median = 0.84 (**Figure**). There appeared to be greater variation in the treatment effect by LVEF in those with more remote hospitalization, though interaction assessments were not robust ($p_{interaction}$ range 0.05 to 0.12) (**Figure)**.

The point estimates for the treatment effects of sacubitril/valsartan vs. valsartan in patients with very recent hospitalization were similar between those with lower and higher LVEF for total HF hospitalizations [lower LVEF: RR 0.69 (95% CI 0.38–1.28) vs. higher LVEF: RR 0.71 (95% CI 0.45–1.10)]; $p_{interaction}$ for treatment effect by LVEF = 0.91 and for the composite of total worsening HF events (**Figure**).

Discussion

In this exploratory post-hoc analysis of PARAGON-HF, the treatment benefits of sacubitril/valsartan vs. valsartan potentially appeared stronger in patients with a recent hospitalization than in those with more remote or no hospitalization, with similar point estimates regardless of LVEF. Hospitalization for HF represents a seminal event in the disease progression and identifies patients at high risk for recurrent HF events. Neurohormonal activation may be more pronounced during periods of decompensation and early post-discharge. Similarly, recently hospitalized patients may have persistent subclinical congestion, enhancing the potential benefits of augmenting natriuretic peptides through neprilysin inhibition. In patients with HFrEF, sacubitril/valsartan resulted in a rapid improvement in neurohumoral markers and

clinical outcomes when initiated during acute HF hospitalization.[7] In a recent trial of sotagliflozin in patients with worsening of HF requiring hospitalization, treatment benefits were consistent across LVEF, including those with preserved LVEF.[4] In our study, the treatment heterogeneity by LVEF observed in PARAGON-HF[2] appeared less prominent in patients with very recent hospitalization, however, small group sizes resulting in wide confidence margins limit the ability of this study to provide definitive suggestion of benefit of sacubitril/valsartan among recently hospitalized patients with higher LVEF. Based on these hypothesis-generating trends, it is possible that the modifiable risk conferred by recent hospitalization may be large enough to mitigate other treatment modifiers and that the previously reported augmented treatment benefit of sacubitril/valsartan in recently hospitalized patients[3] may extend to these higher LVEF ranges.

The ongoing PARAGLIDE-HF study (NCT03988634) will assess the effects of sacubitril/valsartan vs. valsartan initiated in patients with LVEF>40% who are currently hospitalized with HF or ≤30 days from discharge; these patients are expected to most closely resemble those recently hospitalized in PARAGON-HF and may confirm our exploratory findings.

The limitations of this analysis should be noted. This analysis was post-hoc and non-prespecified and should be considered as hypothesis-generating. Interaction tests often lack statistical power, although relative and absolute risk reductions appeared qualitatively similar in higher and lower LVEF subgroups in those with very recent hospitalization. The subgroup of recently hospitalized patients that is the focus of this exploratory analysis was relatively small in the context of the

overall enrollment in PARAGON-HF and our findings require further confirmation in dedicated studies.

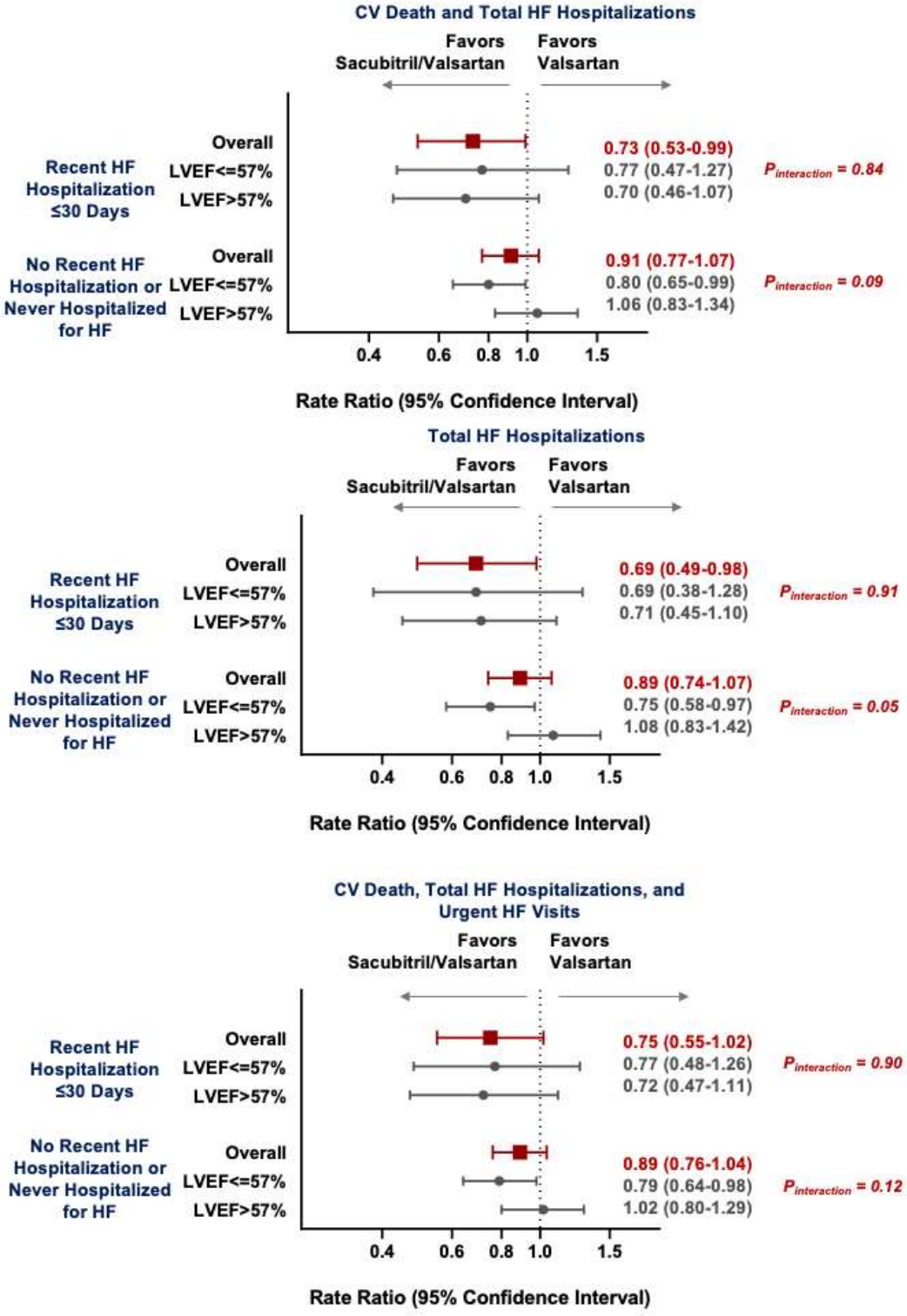
Conclusion

Patients with HFpEF with recent HF hospitalization, irrespective of specific LVEF, may derive benefit from sacubitril/valsartan vs. valsartan; this hypothesis will be further tested in the ongoing PARAGLIDE-HF trial.

References

1. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med 2019;381(17):1609–20.
2. Solomon SD, Vaduganathan M, L Claggett B, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation 2020;141(5):352–61.
3. Vaduganathan M, Claggett BL, Desai AS, et al. Prior heart failure hospitalization, clinical outcomes, and response to sacubitril/valsartan compared with valsartan in hfpef. J Am Coll Cardiol 2020;75(3):245–54.
4. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med 2021;384(2):117–28.
5. Vaduganathan M, Cunningham JW, Claggett BL, et al. Worsening Heart Failure Episodes Outside a Hospital Setting in Heart Failure with Preserved Ejection Fraction: The PARAGON-HF Trial. JACC Heart Fail 2021;
6. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. J Royal Statistical Soc B 2000;62(4):711–30.
7. Morrow DA, Velazquez EJ, DeVore AD, et al. Clinical Outcomes in Patients With Acute Decompensated Heart Failure Randomly Assigned to Sacubitril/Valsartan or Enalapril in the PIONEER-HF Trial. Circulation 2019;139(19):2285–8.

Figure: Treatment Response to Sacubitril/Valsartan vs. Valsartan by Recency of Hospitalization and Ejection Fraction



CI = confidence interv
LWYY = Lin, Wei, Ya