

Reviewers Comments

Reviewer 2

Although the paper has improved, I stand by my original conclusion: top few patients, and nothing new.

Responses

Dear Reviewer,

Thank you for your thoughtful and constructive review of our manuscript, "Impact of Sacubitril/Valsartan on Cardiac Reverse Remodeling in Patients with Heart Failure Undergoing Cardiac Resynchronization Therapy." We sincerely appreciate your positive feedback on the manuscript's clarity and the insightful suggestions for its improvement. Below, we provide a detailed point-by-point response.

The following improved version of the Study Limitations section will be included in revised manuscript: "Several important limitations of our study must be acknowledged. First, the observational, non-randomized design introduces potential for selection bias and unmeasured confounding, despite our statistical adjustments for known prognostic factors. The treatment decision was made by the treating physicians, and while the baseline difference in ACEI/ARB use is inherent to studying sacubitril/valsartan, residual confounding cannot be ruled out. Second, the single-center setting and modest sample size limit the generalizability of our findings. Although the study was sufficiently powered to detect the large effect sizes observed in our primary reverse remodeling endpoints, it lacked the statistical power for robust subgroup analyses or to detect smaller, clinically relevant differences. A post-hoc calculation indicates a power of approximately 68% ($\alpha=0.05$) for the primary response comparison, which is below the conventional 80% threshold. This underscores the need for validation in larger trials. Third, the 12-month follow-up period was adequate to assess reverse remodeling but is too short to evaluate long-term clinical outcomes such as cardiovascular mortality or sustained reductions in heart failure hospitalization. Notably, hard clinical endpoints were rare in our cohort, with only one hospitalization event per group, rendering our study profoundly underpowered for such comparisons. Finally, the proposed mechanistic explanations for the observed benefits, particularly those involving electrophysiological substrate modification, remain speculative and are derived from associations. Confirmation requires dedicated basic science and invasive electrophysiological studies. We explicitly state that our findings should be interpreted as generating a promising hypothesis regarding improved reverse remodeling and clinical response at one year. They do not constitute evidence of long-term mortality benefit, which must be established in future, large-scale, multicenter randomized controlled trials with extended follow-up."