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Comparing High- Versus Low-Dose Entresto in Heart Failure Patients: A 2025 Meta-Analysis

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Abstract

Entresto (sacubitril/valsartan) is widely used for the treatment of heart failure with reduced ejection fraction (HFrEF) due to its ability to enhance natriuretic peptide activity and inhibit the renin-angiotensin-aldosterone system (RAAS). However, its effects on various cardiovascular outcomes require further evaluation. Therefore, a meta-analysis of existing clinical studies was conducted to compare the effectiveness of high-dose vs. low-dose Entresto in treating chronic heart failure. A systematic search was performed using three databases: PubMed, Clinical Trials, and Cochrane. The meta-analysis included nine randomized controlled trials comprising 4,011 patients with HFrEF. The inclusion criteria were: studies that evaluated patients (>18 years of age) with heart failure (these doses were generally divided into high (97/103 mg) and low (24/26 mg), with four studies using different dosing ranges relative to these categories); studies with relevant primary outcome; and studies written in English.

The primary outcomes include: heart failure hospitalization, all-cause mortality, left ventricular ejection fraction (LVEF), N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels, New York Heart Association (NYHA) functional class, and systolic blood pressure over a minimum follow-up period of three months.

We excluded studies with no quantitative outcome data, follow-up period (of at least three months), and dose-group comparisons. Additionally, studies were excluded if they were: case reports; meta-analyses; systematic reviews; conference abstracts; non-human studies or publications in any other language than English.

The risk of bias (RoB) was assessed using the Robvis tool and classified into low, moderate, serious, and critical risk of bias categories. The results of this assessment were illustrated via a traffic light plot.

A random effects statistical model was used in this study. Heterogeneity for LVEF was found to be substantial (I2 of 93.1%). Subgroup analysis found the source of this to be the dosing groups used in these studies, by excluding studies with less than or equal to 200 mg as their high-dose group. Heterogeneity for NT-proBNP was also substantial (I2 of 98%). Subgroup analysis could not localize a source of this heterogeneity, particularly when applied to dosing groups (high-dose groups with less than or equal to 200 mg of sacubitril/ valsartan).

The analysis revealed there was no statistically significant difference between LVEF improvement between low- and high-dose groups (1.95 (95% confidence interval (CI): -1.32 to 5.22); p=0.242). A meta-analysis of these studies showed a statistically significant reduction in NT-proBNP with Entresto. The pooled effect size was -667.24 (95% CI: -1312.69 to -21.8; p=0.04), indicating a significant decline in NT-proBNP levels in patients receiving a higher dose of Entresto. These findings suggest that while higher doses of Entresto do not significantly improve LVEF compared to lower doses, they are associated with a greater reduction in NT-proBNP levels, indicating improved cardiac stress and function. This supports the potential dose-dependent benefits of Entresto in managing heart failure with reduced ejection fraction. Further large-scale studies are warranted to explore the long-term impact of high-dose Entresto on clinical outcomes to optimize dosing strategies for HFrEF patients.