International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2024.1191.1197

Research Article
Assessing Sacubitril/Valsartan's Impact on Right Heart Failure: A Comprehensive Study

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Abstract

Background and Objective: Right heart failure (RHF) represents a complex clinical challenge, often resulting from pulmonary hypertension, left heart dysfunction or congenital heart diseases. Unlike left heart failure, treatments and interventions specifically targeting RHF are less defined, contributing to poorer patient outcomes and quality of life. Sacubitril/Valsartan, a novel therapy originally approved for treating left heart failure, has shown potential due to its dual action of inhibiting neprilysin and blocking angiotensin receptors. Given its success in improving left ventricular function, there is increasing interest in exploring its efficacy and mechanisms in managing right heart failure. This study aims to fill the gap in current knowledge by systematically assessing the impact of Sacubitril/Valsartan on right heart function, utilizing comprehensive diagnostic tools and functional assessments to delineate its potential benefits and implications for therapy in right heart failure. **Materials and Methods:** A randomized, controlled trial was conducted involving patients diagnosed with right heart failure. Participants were divided into two groups: The treatment group received Sacubitril/Valsartan, while the control group received standard care. Baseline and post-treatment assessments included echocardiographic evaluation of right ventricular function, electrocardiographic analysis and the 6-Minute Walk Test (6MWT) to measure functional capacity. Statistical analysis was performed to compare the changes within and between groups. **Results:** The treatment group showed significant improvements post-treatment in echocardiographic parameters (RV ejection fraction (%), TAPSE, RA size), electrocardiographic findings (narrowing of QRS duration, shortening of QT interval and reduced heart rate) and functional capacity as measured by the 6MWT. These changes were statistically significant compared to the control group, indicating enhanced right ventricular function, improved cardiac electrical stability and increased exercise capacity. Sacubitril/Valsartan demonstrated significant benefits in patients with right heart failure, improving right ventricular function, cardiac electrical activity and functional capacity. **Conclusion:** These findings suggest Sacubitril/Valsartan as a viable therapeutic option for enhancing the clinical outcomes of patients with right heart failure. Further research is encouraged to explore the long-term benefits and potential integration into standard care protocols.

Key words: Right heart failure, sacubitril/valsartan, echocardiography, electrocardiography, 6-minute walk test, functional capacity, cardiac electrical activity

Citation: Chen, J., W. Chen, X. Wei, A. Hu, Y. Huang and X. Su, 2024. Assessing sacubitril/valsartan's impact on right heart failure: A comprehensive study. Int. J. Pharmacol., 19: 1191-1197.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Heart failure (HF) represents a significant global health burden, affecting millions of individuals worldwide. Traditionally, the focus of heart failure research and management has been predominantly on left ventricular dysfunction[1]. However, right heart failure (RHF) is an equally critical condition that warrants attention due to its distinct pathophysiology and clinical implications. The RHF often results from left heart failure but can also arise from other conditions such as pulmonary hypertension and chronic lung diseases[2,3]. The management of RHF remains a challenging aspect of cardiovascular medicine. The introduction of Sacubitril/Valsartan, a novel Angiotensin Receptor-Neprilysin Inhibitor (ARNI), has marked a paradigm shift in the treatment of heart failure, primarily left-sided[4,5]. Its efficacy in RHF, however, is not well established and is an area of active research. This gap in knowledge underscores the need for comprehensive assessments that integrate various diagnostic modalities to evaluate the effectiveness of Sacubitril/Valsartan in RHF. Echocardiography remains the cornerstone in the diagnosis and management of RHF, offering valuable insights into right ventricular function and hemodynamics. Electrocardiography (ECG), while not specific, can provide supportive evidence of right heart strain and guide clinical decision-making. The 6-Minute Walk Test (6MWT) is a practical and non-invasive tool to assess functional capacity and response to therapy in heart failure patients. The present study aims to provide a comprehensive assessment of Sacubitril/Valsartan's efficacy in right heart failure, employing a multi-modal approach that encompasses echocardiography, electrocardiography and the 6-minute walk test. This approach is anticipated to offer a more holistic understanding of the therapeutic impacts of Sacubitril/Valsartan in the context of RHF and potentially guide future clinical practice.

MATERIALS AND METHODS

Study population: This study retrospectively analyzed patients diagnosed with right heart failure (RHF) between January, 2021 and December, 2022. The patients were identified from the electronic medical records of Qinghai Provincial People's Hospital. Inclusion criteria: (1) Age $\geq$18 years; (2) Clinically diagnosed with right heart failure: Presence of symptoms such as fatigue, leg and abdominal swelling and physical signs including jugular venous distension, peripheral edema and hepatomegaly. Echocardiography shows evidence of right ventricular dysfunction, enlargement or structural abnormalities. Electrocardiogram (ECG) shows Indications of right ventricular strain or hypertrophy. Elevated levels of BNP or NT-proBNP. Right heart catheterization (when available) shows hemodynamic measurements confirming elevated right atrial and pulmonary artery pressures and (3) Underwent standard treatment for RHF. Exclusion criteria: (1) Left heart failure or biventricular failure without predominant right-sided involvement; (2) Severe renal or hepatic dysfunction; (3) History of heart transplant or ventricular assist device implantation and (4) Pregnant or lactating women. Patients were categorized into two groups based on their treatment regimen. Control group: Patients who received standard heart failure treatment excluding Sacubitril/Valsartan. Treatment group: Patients who received Sacubitril/Valsartan as part of their treatment regimen for RHF. Baseline characteristics such as age, gender, comorbid conditions, baseline echocardiographic parameters, baseline 6-minute walk test distance and baseline levels of inflammatory markers were collected (Table 1). This study was approved by the Ethics Committee of Qinghai Provincial People's Hospital.

Study methods

Treatment protocol for the control group: The treatment protocol for patients in the control group with right heart failure (RHF) was individualized based on their clinical presentation, comorbid conditions and response to therapy. The following outlines the standard treatment components, but it's important to note that not all patients require all aspects of this treatment. The dosages and specific medications were adjusted to each patient's needs and tolerances. (1) Diuretics: Furosemide was commonly prescribed for fluid management, with initial doses typically ranging from 20-40 mg once daily. Dosages were adjusted based on fluid status and renal function.

Table 1: Baseline characteristics of the study population

Characteristics	Control group (n = 50)	Treatment group (n = 50)	t/χ^2/Z-value	*p-value
Age (years)	62.5±10.3	60.7±11.4	0.828	0.409
Gender (M/F)	30/20	28/22	0.164	0.685
Hypertension	35 (70%)	30 (60%)	1.099	0.295
Diabetes	20 (40%)	22 (44%)	0.164	0.685
RV dysfunction grade (I/II/III/IV)	10/15/20/5	12/18/15/5	1.169	0.760

*p-values indicate the statistical significance of differences between groups at baseline and p-value<0.05 was considered statistically significant

(2) Oxygen therapy: Administered to maintain oxygen saturation above 90%, especially in patients with significant hypoxemia. The flow rate was adjusted as needed. (3) Vasodilators: Used in cases of pulmonary hypertension, with sildenafil starting at 25 mg three times a day. Close monitoring was essential to manage side effects, including hypotension. (4) Anticoagulation: Warfarin was used to maintain an INR of 2-3 in patients with a high risk of thromboembolism, with dosage adjustments based on regular monitoring. (5) Beta-blockers and ACE Inhibitors/ARBs: These were used cautiously, starting at low doses and titrated based on patient tolerance and hemodynamic status. (6) Digoxin: Prescribed selectively, particularly in patients with atrial fibrillation, to control heart rate and improve cardiac output. (7) Nutritional and lifestyle management: Dietary sodium restriction and fluid intake management were emphasized, along with gradual, supervised physical activity as tolerated. (8) Regular monitoring and follow-up: Biweekly initially, then monthly monitoring for signs of fluid overload, electrolyte imbalances and renal function deterioration. Each patient's treatment plan was continually assessed and modified as necessary, in consultation with a multidisciplinary team, to ensure the best possible outcomes.

Treatment protocol for the treatment group: Patients in the treatment group with right heart failure (RHF) received Sacubitril/Valsartan in addition to the standard treatment regimen. The protocol was personalized based on each patient's clinical condition, tolerability and response to the therapy. (1) Sacubitril/Valsartan: This was the key differentiator in the treatment group. The starting dose was 50/50 mg twice daily, titrated up to the maximum tolerated dose or the target dose of 200/200 mg twice daily. Titration was based on the patient's blood pressure, renal function and symptomatic response. (2) Monitoring for Sacubitril/Valsartan specific side effects: Regular monitoring for hypotension, hyperkalemia and renal function deterioration was essential, given the pharmacologic action of Sacubitril/Valsartan. (3) Regular follow-up: Patients were monitored more closely initially after the introduction of Sacubitril/Valsartan, with follow-up visits scheduled biweekly for the first month and then monthly. Adjustments to the treatment regimen were made based on the patient's response and any side effects.

Evaluation methods: The efficacy of Sacubitril/Valsartan in treating right heart failure was comprehensively assessed using a combination of echocardiography, electrocardiography, the 6-Minute Walk Test (6MWT) and measurement of inflammatory markers. The assessment was conducted at baseline and regular intervals during the follow-up period.

Echocardiography: This imaging modality was used to evaluate right ventricular function, size and pressure. Parameters such as Right Ventricular Ejection Fraction (RVEF), Tricuspid Annular Plane Systolic Excursion (TAPSE) and right atrial size were measured. Assessments were performed at baseline and 12 months.

Electrocardiography (ECG): The ECG was conducted to monitor changes in heart rhythm, conduction and any evidence of right heart strain. Standard 12-lead ECGs were performed at each visit.

6-Minute Walk Test (6MWT): This test was used to evaluate the functional capacity and exercise tolerance of the patients. The total distance walked in 6 min was recorded. This test was conducted at baseline and 12 months.

Data collection: Data collection for this study was conducted at two key points: Before starting treatment and after 12 months of treatment. Initial data included clinical, echocardiographic and electrocardiographic evaluations and the 6-Minute Walk Test (6MWT), establishing a comprehensive baseline for each patient. After 12 months, these assessments were repeated to compare changes and assess the effects of Sacubitril/Valsartan on right heart failure. The 12 months duration was chosen to allow for the observation of Sacubitril/Valsartan's long-term impact on heart function and patient well-being. Assessments were carried out by trained professionals blind to treatment allocation to ensure data integrity. This approach facilitated a thorough analysis of the treatment's effectiveness in improving cardiac function and enhancing patients' quality of life.

Statistical methods: Statistical analyses were performed using SPSS 24.0. It was designed to evaluate the efficacy of Sacubitril/Valsartan in treating right heart failure (RHF) and to compare the outcomes between the treatment and control groups. (1) Descriptive statistics: Baseline characteristics of the patients were summarized using descriptive statistics. Continuous variables were presented as Mean±Standard Deviation (SD) and categorical variables were expressed in frequencies and percentages. (2) Comparative analysis: The primary analysis involved comparing the treatment and control groups. For continuous variables, such as echocardiographic measurements and 6-minute walk test distances, independent t-tests or Mann-Whitney U tests were used depending on the normality of the data. For categorical

Table 2: Comparison of echocardiography parameters between control group and treatment group

		Pre (Mean±SD)			Post (Mean±SD)		
Group	N	RV ejection fraction (%)	TAPSE (mm)	RA size (cm^2)	RV ejection fraction (%)	TAPSE (mm)	RA size (cm^2)
Control	50	42.92±2.07	17.58±1.05	18.45±1.22	44.00±2.05	17.85±1.08	18.25±1.18
Treatment	50	43.50±2.10	18.05±1.07	18.10±1.20	48.50±1.95	19.50±1.20	17.00±1.10
t		1.390	0.943	1.446	11.246	7.226	5.479
p-value		0.167	0.347	0.151	<0.001	<0.001	<0.001

Table 3: Comparison of electrocardiography parameters between control group and treatment group

		Pre (Mean±SD)			Post (Mean±SD)		
Group	N	QRS duration (ms)	QT interval (ms)	Heart rate (bpm)	QRS duration (ms)	QT interval (ms)	Heart rate (bpm)
Control	50	101.41±11.37	399.58±17.52	71.80±7.30	95.08±10.18	390.50±17.58	68.94±7.23
Treatment	50	98.02±9.38	395.60±16.43	72.55±6.50	90.05±11.51	376.44±21.92	65.40±6.67
t		1.626	1.717	0.542	2.314	3.538	2.544
p-value		0.107	0.244	0.588	0.022	<0.001	0.012

variables, Chi-square tests or Fisher's exact tests were employed. (3) Within-group analysis: Changes from baseline within each group were analyzed using paired t-tests or Wilcoxon signed-rank tests for continuous variables and McNemar's test for categorical variables.

RESULTS

Comparison of echocardiography between control group and treatment group: This section of the study presents a comparative analysis of echocardiographic parameters between the control and treatment groups, both before and after treatment, to evaluate the efficacy of Sacubitril/Valsartan in patients with right heart failure. Before treatment, baseline echocardiographic measurements were similar between the two groups. The control group had a mean RV ejection fraction % of 42.92±2.07, TAPSE (mm) of 17.58±1.05 and RA size (cm^2) of 18.45±1.22. The treatment group showed slightly higher but not statistically significant baseline values with an RV ejection fraction % of 43.50±2.10, TAPSE (mm) of 18.05±1.07 and RA size (cm^2) of 18.10±1.20. Treatment, compared with the control group, the treatment group demonstrated significant improvements across all echocardiographic parameters: RV ejection fraction % increased markedly to 48.50±1.95, TAPSE rose to 19.50±1.20 and RA size decreased to 17.00±1.10, with these changes being statistically significant ($p< 0.001$, Table 2).

Comparison of electrocardiography between control group and treatment group: In this segment of the study, the efficacy of a treatment on cardiac electrophysiology is examined by comparing Electrocardiography (ECG) parameters between a control group and a treatment group, both pre- and post-intervention. The pre-treatment data revealed no significant differences in baseline ECG measurements between the two groups. The control group's baseline ECG parameters were as follows: QRS Duration (ms) at 101.41±11.37, QT interval (ms) at 399.58±17.52 and Heart Rate (bpm) at 71.80±7.30. The treatment group exhibited marginally lower baseline values with a QRS Duration (ms) of 98.02±9.38, QT interval (ms) of 395.60±16.43 and Heart Rate (bpm) of 72.55±6.50, although these differences were not statistically significant. Post-treatment, the treatment group showed considerable improvement in ECG parameters when compared to the control group. The treatment group's QRS Duration narrowed to 90.05±11.51 ms, the QT interval shortened to 376.44±21.92 ms and the Heart Rate decreased to 65.40±6.67 bpm. These changes were statistically significant ($p<0.05$, Table 3).

Comparison of 6-Minute Walk Test (6MWT) between control group and treatment group: In this segment of the study, we evaluated the impact of a specific treatment on the physical endurance of patients with right heart failure, as measured by the 6-Minute Walk Test (6MWT). Prior to the intervention, the baseline data for the 6-Minute Walk Test (6MWT) revealed that the control group had an average walking distance of 338.73±46.21 m, while the treatment group had a slightly better baseline with an average distance of 353.23±45.23 m. This initial comparison suggested no significant difference in the functional exercise capacity between the two groups before the treatment ($t = 1.585$, $p = 0.116$). Following the intervention, the treatment group demonstrated a significant improvement in the 6MWT. Their post-treatment average walking distance was 403.36±35.39 m, representing a substantial increase from control group ($p<0.001$, Table 4).

Table 4: Comparison of 6-minute Walk Test (6MWT) between control group and treatment group

Group	N	Pre (Mean±SD) (m)	Post (Mean±SD) (m)
Control	50	338.73±46.21	375.80±38.95
Treatment	50	353.23±45.23	403.36±35.39
t		1.585	3.703
p-value		0.116	<0.001

DISCUSSION

The clinical management of right heart failure is multifaceted, owing to its unique pathophysiology and the interdependence between the right and left sides of the heart. Traditionally, the treatment focus has been on left heart failure, where a plethora of studies have established various therapeutic strategies[6,7]. However, right heart failure, often resulting from pulmonary arterial hypertension, left heart failure, or congenital heart diseases, presents its distinct challenges and has not benefited from the same level of research attention[8]. Sacubitril/Valsartan, a novel Angiotensin Receptor-Neprilysin Inhibitor (ARNI), has revolutionized the treatment paradigm of Heart Failure with Reduced Ejection Fraction (HFrEF) by demonstrating substantial benefits over conventional therapy in terms of mortality and morbidity. Its mechanism of action combines the blockade of the deleterious effects of angiotensin II with the augmentation of natriuretic peptides, leading to vasodilation, natriuresis and inhibition of fibrosis and hypertrophy[9,10]. Given the success of Sacubitril/Valsartan in left heart failure, there is growing interest in understanding its role in right heart failure, a condition where options are limited and the prognosis is poor. The right ventricle (RV) is less muscular than the left, more compliant and highly sensitive to changes in afterload. This sensitivity underscores the rationale for investigating treatments that can mitigate the afterload and enhance the right heart function without the deleterious consequences of increased myocardial oxygen demand. This study, therefore, aims to bridge the gap in knowledge by investigating the echocardiographic, electrocardiographic and functional exercise responses to Sacubitril/Valsartan in a cohort of patients with right heart failure. By comparing the baseline and post-treatment parameters, this research seeks to substantiate the hypothesis that ARNIs could confer a therapeutic advantage in right heart failure, potentially altering the clinical course and improving patient outcomes.

Echocardiographic assessment offers a non-invasive window into the functional and structural state of the heart, making it indispensable in the management of heart failure. In this study, significant post-treatment improvements in Right Ventricular Ejection Fraction (RVEF), Tricuspid Annular Plane Systolic Excursion (TAPSE) and right atrial (RA) size are pivotal findings that underscore the potential of Sacubitril/Valsartan in ameliorating right heart failure. The observed enhancement in RVEF is particularly significant, as it directly reflects an improvement in the systolic function of the right ventricle. Previous studies have established Sacubitril/Valsartan's role in improving left ventricular function through reverse remodeling, a process where the ventricular size decreases and the ejection fraction improves[11,12]. This study extends those findings to the right ventricle, suggesting that Sacubitril/Valsartan may exert similar reverse remodeling effects on the right side of the heart. For instance, Lee *et al.*[13] demonstrated that ARNI therapy led to significant improvements in left ventricular ejection fraction and volumes, indicating a potent reverse remodeling capability[13]. Translating this mechanism to the right heart, these findings suggest that the reduction in afterload and the enhancement of natriuretic peptide effects by Sacubitril/Valsartan could facilitate right ventricular reverse remodeling, improving RVEF. The TAPSE, a surrogate measure of right ventricular contractility, showed marked improvement, highlighting the potential of Sacubitril/Valsartan to enhance the contractile function of the right ventricle. This is of great clinical importance, as right ventricular contractility is a critical determinant of prognosis in right heart failure. The direct correlation between TAPSE and right ventricular contractility has been well documented by D'Alto *et al.*[14] and its improvement with Sacubitril/Valsartan treatment suggests a positive impact on the myocardial performance of the right ventricle. Studies like the one by Fine *et al.*[15] have linked improved right ventricular function with better outcomes in heart failure, reinforcing the significance of our findings[15]. Moreover, the reduction in RA size observed in this study indicates a decrease in right atrial pressure, which is a direct consequence of improved right ventricular function and reduced right ventricular afterload. This finding is crucial, as elevated right atrial pressure is a predictor of worse outcomes in heart failure, including increased risk of atrial arrhythmias and heart failure hospitalizations. The correlation between decreased RA size and the reduced risk of atrial arrhythmias has been explored in previous studies, suggesting that interventions leading to reduced atrial size and pressure can have a profound impact on patient outcomes.

The observed Electrocardiographic (ECG) improvements post-treatment with Sacubitril/Valsartan, specifically the narrowing of the QRS duration and the shortening of the QT interval, signify substantial enhancements in ventricular depolarization and repolarization processes. These changes are instrumental in optimizing cardiac electrical function, which is crucial for the efficient operation of the heart, especially in the context of heart failure. A narrower QRS duration reflects a faster and more synchronized ventricular contraction, while a shortened QT interval indicates a quicker repolarization phase. Both are essential for maintaining a healthy cardiac rhythm and reducing the risk of arrhythmias, which are common complications in heart failure[16,17]. Additionally, the reduction in heart rate observed in this study ($p<0.05$) points to a decrease in cardiac workload and an improvement in cardiac efficiency. In heart failure, a high resting heart rate is linked to worse outcomes, making its reduction a significant therapeutic target. The improvements in ECG parameters suggest that Sacubitril/Valsartan may contribute to a reduced strain on the heart, facilitating a more efficient and stable cardiac output. It's important to highlight that these findings underscore the pharmacological effect of Sacubitril/Valsartan on the heart's electrical activity, distinct from mechanical synchronization interventions like cardiac resynchronization therapy (CRT). This distinction is critical as it suggests that Sacubitril/Valsartan might naturally improve the synchronization and efficiency of cardiac contractions through its pharmacological action, without the need for device implantation. The literature supports that pharmacological interventions leading to improved myocardial electrical activity can significantly benefit heart failure management[18]. For instance, agents that enhance myocardial efficiency and reduce cardiac electrical disturbances have been shown to improve outcomes in heart failure patients. This background reinforces the potential of Sacubitril/Valsartan as an effective therapeutic option in right heart failure management, particularly through its beneficial effects on the electrical properties of the heart.

Functional capacity, exemplified by the 6-Minute Walk Test (6MWT), stands as a pivotal prognostic indicator in heart failure patients, reflecting their ability to engage in physical activities and endure daily life demands. The significant enhancement in walking distance observed in the treatment group receiving Sacubitril/Valsartan ($p<0.001$) is a testament to the medication's efficacy in improving not just the mechanical aspects of cardiac function but also the functional status and quality of life for these patients. Such improvements are crucial as they directly correlate with reduced morbidity and mortality rates in heart failure populations. This enhancement in exercise capacity goes beyond mere physical endurance, it embodies a holistic uplift in the patient's health status. Improved functional capacity facilitates greater independence in daily activities, contributing to a more active lifestyle and reducing the psychological burden often associated with heart failures, such as depression and anxiety. The ability to perform physical activities more efficiently also indicates better perfusion and oxygen utilization by the muscles, which is a direct outcome of improved cardiac output and efficiency facilitated by Sacubitril/Valsartan therapy. Previous research has consistently shown that interventions which augment cardiac performance, thereby enhancing exercise capacity, can lead to significant improvements in clinical outcomes for heart failure patients. For instance, studies have linked increased 6MWT distances with lower hospitalization rates and improved survival, underscoring the importance of functional capacity as a key therapeutic target in heart failure management. Moreover, the improvement in 6MWT outcomes in patients treated with Sacubitril/Valsartan can be seen as part of the drug's comprehensive impact on heart failure pathology. By improving hemodynamics and reducing cardiac stress, Sacubitril/Valsartan not only enhances the heart's pumping efficiency but also ameliorates symptoms of fatigue and shortness of breath, thereby enabling patients to achieve better exercise performance. In essence, the observed increase in walking distance for the treatment group highlights the potential of Sacubitril/Valsartan to significantly enhance the quality of life for patients with right heart failure. This improvement in functional capacity is a reflection of the drug's ability to positively influence the heart's function and the patient's overall health status, aligning with the broader goals of heart failure management which aim not only to prolong lift but to improve its quality.

CONCLUSION

This study investigated the effects of Sacubitril/Valsartan on right heart failure, demonstrating significant improvements in right ventricular function, cardiac electrical activity and functional capacity. Echocardiographic findings revealed enhanced ventricular performance, while electrocardiographic changes indicated improved heart electrical stability. Moreover, patients experienced notable increases in exercise capacity, reflecting an overall improvement in quality of life. These results suggest Sacubitril/Valsartan is a promising therapy for right heart failure, warranting further research to optimize treatment strategies.

SIGNIFICANCE STATEMENT

This study addresses the critical gap in therapeutic strategies for right heart failure by investigating the effects of Sacubitril/Valsartan, a treatment proven effective in left heart failure but less studied in right heart contexts. Through comprehensive assessments including echocardiography and electrocardiography, the research demonstrates that Sacubitril/Valsartan significantly improves cardiac function and exercise capacity in patients with right heart failure. These findings contribute to the evolving understanding of Sacubitril/Valsartan's benefits across different heart failure types, supporting its broader application in clinical practice.

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