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Efficacy and Safety of Sacubitril/Valsartan in the Management of Heart Failure with Preserved Ejection Fraction: A Comprehensive Review

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) represents a significant clinical challenge due to its complex pathophysiology, limited therapeutic options, and growing prevalence, particularly in aging populations. Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), has emerged as a potential therapeutic intervention in HFpEF. While sacubitril/valsartan has demonstrated substantial benefits in heart failure with reduced ejection fraction (HFrEF), its role in HFpEF has been the subject of extensive clinical investigations. This review aims to evaluate the efficacy, safety, and clinical implications of sacubitril/valsartan in the treatment of HFpEF. We will discuss the pharmacological mechanisms of the ARNI combination, key clinical trials, and their outcomes, including the PARAGON-HF trial, and assess its impact on morbidity, mortality, functional status, and quality of life in HFpEF patients. Additionally, we will explore potential biomarkers for response to therapy and the relevance of phenotyping HFpEF subgroups to optimize therapeutic strategies.

KEYWORDS: Sacubitril/valsartan, heart failure with preserved ejection fraction, HFpEF, ARNI, PARAGON-HF, neprilysin inhibition, morbidity, quality of life, cardiovascular therapy.

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INTRODUCTION

Heart failure (HF) is a major global health problem affecting over 60 million individuals worldwide, with heart failure with preserved ejection fraction (HFpEF) accounting for approximately half of these cases. Despite similar clinical presentations to heart failure with reduced ejection fraction (HFrEF), the pathophysiology of HFpEF is distinct and remains incompletely understood. HFpEF is characterized by impaired ventricular relaxation and increased stiffness, leading to elevated filling pressures during diastole, while left ventricular systolic function remains preserved, defined by a left ventricular ejection fraction (LVEF) of ≥50%. These unique features contribute to the limited efficacy of traditional heart failure therapies in HFpEF patients, making therapeutic management particularly challenging.1,2

Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), combines the effects of neprilysin inhibition (by sacubitril) and angiotensin II receptor blockade (by valsartan). The dual mechanism targets neurohormonal pathways that are implicated in the pathogenesis of heart failure, including natriuretic peptides, bradykinin, and the renin-angiotensin-aldosterone system (RAAS). In HFrEF, sacubitril/valsartan has shown superiority over conventional angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in reducing morbidity and mortality, as demonstrated in the landmark PARADIGM-HF trial.1,2

However, the efficacy of sacubitril/valsartan in HFpEF remains a subject of ongoing debate, with clinical trials yielding mixed results. The PARAGON-HF trial, a large-scale randomized controlled trial, sought to evaluate the effect of sacubitril/valsartan in HFpEF patients but failed to meet its primary endpoint of significantly reducing heart failure hospitalizations and cardiovascular death.

Nonetheless, certain subgroups, such as patients with a lower LVEF (but still within the HFpEF range) or women, appeared to derive greater benefit from the therapy.2,3

Given the heterogeneous nature of HFpEF, which is often driven by multiple comorbidities including obesity, hypertension, and diabetes, it is critical to explore the role of sacubitril/valsartan in well-defined patient phenotypes to optimize therapeutic outcomes. This article provides an in-depth review of the pharmacological basis, clinical trial evidence, and potential clinical applications of sacubitril/valsartan in HFpEF, with a focus on patient selection, biomarkers of therapeutic response, and future directions in the management of this challenging condition.2,3

Clinical Implications of Sacubitril/Valsartan in the Management of Heart Failure with Preserved Ejection Fraction

The introduction of sacubitril/valsartan as a therapeutic option for heart failure with preserved ejection fraction (HFpEF) has generated significant interest and debate in the cardiology community. Despite the well-established success of this angiotensin receptor-neprilysin inhibitor (ARNI) in heart failure with reduced ejection fraction (HFrEF), its role in HFpEF remains less clear, with important implications for clinical practice, patient selection, and therapeutic outcomes. The clinical implications of sacubitril/valsartan in HFpEF span multiple dimensions, including its potential benefits in morbidity, mortality, symptom relief, quality of life, and hospitalization rates, as well as the challenges in identifying subpopulations most likely to respond to therapy.3,4

Impact on Morbidity and Mortality

The primary challenge in HFpEF management is the lack of therapies that definitively reduce mortality and morbidity. Sacubitril/valsartan's success in HFrEF, as demonstrated in the PARADIGM-HF trial, raised hopes that the drug could similarly alter the course of HFpEF. However, the PARAGON-HF trial, which aimed to evaluate the effect of sacubitril/valsartan in patients with HFpEF, fell short of demonstrating a statistically significant reduction in the composite primary endpoint of heart failure hospitalizations and cardiovascular death. Nevertheless, there were encouraging signals from certain subgroups, suggesting that some patients with HFpEF could still benefit from sacubitril/valsartan, particularly in reducing heart failure hospitalizations.4,5

Patients with a left ventricular ejection fraction (LVEF) at the lower end of the HFpEF spectrum (close to 50%) and women appeared to derive greater clinical benefit, potentially implicating sex-specific and ejection fraction-dependent variations in HFpEF pathophysiology. These findings prompt the need for further exploration of patient stratification to better target therapies for those most likely to benefit. In clinical practice, this suggests that sacubitril/valsartan may be selectively useful in managing certain HFpEF patients, particularly those with borderline LVEF or women, though routine use across all HFpEF cases may not be justified.4,5

Symptom Relief and Quality of Life

HFpEF is characterized by significant symptom burden, including dyspnea, fatigue, and exercise intolerance, which can severely impair patients' quality of life. Given the complex pathophysiology of HFpEF, involving myocardial stiffness, diastolic dysfunction, and systemic comorbidities like hypertension and obesity, managing these symptoms is challenging. Sacubitril/valsartan, through its dual neprilysin inhibition and angiotensin receptor blockade, has demonstrated potential benefits in alleviating symptoms, likely due to improved hemodynamics, reduced filling pressures, and enhanced natriuresis.4,5

The PARAGON-HF trial reported modest improvements in patients' quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), a validated tool for assessing heart failure-related quality of life. This suggests that, although sacubitril/valsartan may not dramatically alter hard clinical outcomes such as mortality, it may still play an important role in improving functional capacity and symptom burden in HFpEF patients. Clinicians may consider sacubitril/valsartan for symptomatic relief, particularly in patients struggling with high levels of exercise intolerance or persistent dyspnea, where traditional heart failure therapies have failed.5,6

Hospitalization and Healthcare Resource Utilization

HFpEF is associated with frequent hospitalizations due to exacerbations of heart failure symptoms, leading to significant healthcare resource utilization. In the PARAGON-HF trial, sacubitril/valsartan showed a trend towards reducing heart failure-related hospitalizations, particularly in women and those with lower ejection fractions. While this reduction was not statistically significant across the entire study population, it highlights a potential area where sacubitril/valsartan could have a meaningful impact, particularly in high-risk subgroups.5,6

Reducing hospitalizations is not only crucial for improving patient outcomes but also for alleviating the economic burden of heart failure on healthcare systems. Given that hospital admissions account for a significant proportion of the costs associated with heart failure, clinicians may consider sacubitril/valsartan as part of a strategy to reduce recurrent hospitalizations in HFpEF, particularly in patients with a history of frequent admissions or those who are vulnerable to decompensation.5,6

Patient Selection and Phenotyping in HFpEF

One of the most important clinical implications of sacubitril/valsartan use in HFpEF revolves around patient selection. HFpEF is a highly heterogeneous condition, with its pathophysiology influenced by a wide array of comorbidities, including hypertension, obesity, diabetes, atrial fibrillation, and chronic kidney disease. This

heterogeneity presents a significant challenge in identifying patients who are most likely to benefit from specific therapies, including sacubitril/valsartan.5,6

Emerging evidence suggests that phenotyping patients based on clinical characteristics, such as LVEF, sex, and comorbidities, may help tailor treatment strategies. For instance, patients with a mildly reduced ejection fraction (HFmrEF), or those with borderline HFpEF, may respond more favorably to sacubitril/valsartan due to the overlap in pathophysiology with HFrEF. Additionally, women with HFpEF have been shown to derive greater benefit from sacubitril/valsartan, possibly due to sex-specific differences in ventricular remodeling and neurohormonal activation.6,7

Future studies may focus on identifying biomarkers that can predict response to sacubitril/valsartan in HFpEF, such as natriuretic peptides, inflammatory markers, or echocardiographic parameters of diastolic function. In clinical practice, phenotyping HFpEF patients based on these criteria could allow for more personalized treatment, potentially maximizing the therapeutic benefit of sacubitril/valsartan in a population where therapeutic success has traditionally been elusive.6,7

Integration with Other Therapeutic Strategies

The clinical management of HFpEF is often multifaceted, requiring a combination of pharmacological and non-pharmacological strategies to address the underlying comorbidities and pathophysiology. Sacubitril/valsartan, while promising, should be viewed as part of a broader therapeutic approach. This includes aggressive management of hypertension, diabetes, and obesity, which are all central contributors to the development and progression of HFpEF.6,7

Given the mixed results of sacubitril/valsartan in clinical trials, clinicians may also consider other emerging therapeutic strategies, such as sodium-glucose co-transporter-2 (SGLT2) inhibitors, which have shown promise in reducing heart failure hospitalizations in HFpEF patients. Combining sacubitril/valsartan with other therapies, particularly those that target different aspects of HFpEF pathophysiology, could offer a more comprehensive approach to managing this complex syndrome.6,7

Sacubitril/valsartan represents a potentially valuable tool in the management of HFpEF, with implications for reducing symptom burden, improving quality of life, and potentially lowering hospitalization rates in selected patient subgroups. However, its role in altering the natural history of HFpEF, particularly in terms of reducing mortality, remains limited and warrants further investigation. Clinicians should consider the unique characteristics of HFpEF patients, such as LVEF and sex, when prescribing sacubitril/valsartan, and view it as part of an integrated therapeutic strategy targeting the multifactorial nature of HFpEF.7,8

Current Therapeutic Use of Sacubitril/Valsartan in Heart Failure with Preserved Ejection Fraction

The therapeutic landscape of heart failure with preserved ejection fraction (HFpEF) remains an area of ongoing research and clinical development. Unlike heart failure with reduced ejection fraction (HFrEF), for which robust therapies have been established, HFpEF presents unique challenges due to its heterogeneous pathophysiology and the limited efficacy of traditional heart failure treatments in this subset of patients. Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), offers a novel approach by combining the benefits of neprilysin inhibition with angiotensin receptor blockade. Its current therapeutic use in HFpEF is grounded in its ability to modulate neurohormonal pathways involved in the progression of heart failure, with clinical trial evidence suggesting selective benefits in certain patient subgroups. This section explores the pharmacological rationale, clinical applications, and patient selection criteria for sacubitril/valsartan in HFpEF.8,9

Pharmacological Mechanism and Rationale

Sacubitril/valsartan exerts its therapeutic effects through two complementary mechanisms: neprilysin inhibition and angiotensin II receptor blockade. Neprilysin is a neutral endopeptidase responsible for the degradation of several vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. By inhibiting neprilysin, sacubitril increases the levels of these beneficial peptides, leading to enhanced natriuresis, vasodilation, and inhibition of fibrosis. These effects counterbalance the maladaptive neurohormonal activation that contributes to heart failure progression.9,10

The second component of sacubitril/valsartan, valsartan, is an angiotensin II receptor blocker (ARB) that inhibits the renin-angiotensin-aldosterone system (RAAS). Angiotensin II is a potent vasoconstrictor that also promotes sodium retention, inflammation, and myocardial remodeling. By blocking angiotensin II at its receptor, valsartan reduces vasoconstriction, lowers blood pressure, and mitigates the deleterious effects of RAAS activation. This dual-action mechanism makes sacubitril/valsartan particularly appealing in HFpEF, where diastolic dysfunction, elevated filling pressures, and systemic vascular resistance are key contributors to the disease process.11

In HFpEF, the primary pathophysiological defect is impaired ventricular relaxation and compliance, leading to elevated left ventricular filling pressures and diastolic heart failure. While sacubitril/valsartan does not directly improve diastolic function, its vasodilatory and natriuretic effects help reduce left ventricular filling pressures, potentially alleviating symptoms of congestion and reducing the risk of heart failure hospitalizations.11

Clinical Trial Evidence and Current Guidelines

The PARAGON-HF trial is the most prominent study evaluating the efficacy of sacubitril/valsartan in HFpEF. This

large, randomized controlled trial enrolled over 4,800 patients with symptomatic HFpEF (defined as a left ventricular ejection fraction of ≥45%) to compare sacubitril/valsartan with valsartan alone. The trial's primary composite endpoint was total heart failure hospitalizations and cardiovascular death. Although the study did not meet its primary endpoint, a reduction in heart failure hospitalizations was observed, particularly in specific subgroups.11

Patients with an LVEF closer to 45-50%, as well as women, appeared to benefit the most from sacubitril/valsartan, suggesting that certain phenotypes of HFpEF may be more responsive to ARNI therapy. This has led to increased interest in defining HFpEF subgroups based on clinical characteristics, comorbidities, and pathophysiological profiles to optimize treatment outcomes. Notably, sacubitril/valsartan's ability to reduce heart failure hospitalizations in these subpopulations underscores its potential role in reducing the clinical burden of HFpEF in selected patients.12

Despite the mixed results of the PARAGON-HF trial, sacubitril/valsartan is included in the 2021 European Society of Cardiology (ESC) guidelines for the management of heart failure. The ESC guidelines suggest that sacubitril/valsartan may be considered in patients with HFpEF, particularly those with an LVEF at the lower end of the spectrum or those with a history of recurrent hospitalizations. This reflects the growing recognition that HFpEF is not a homogeneous condition, and therapeutic strategies must be tailored to individual patient characteristics.12

In the United States, the 2022 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines also acknowledge the potential role of sacubitril/valsartan in HFpEF, though they emphasize the need for careful patient selection. Given the absence of a clear mortality benefit in HFpEF, sacubitril/valsartan is primarily recommended for reducing heart failure-related hospitalizations and improving quality of life in symptomatic patients.12

Symptom Management and Quality of Life Improvement

One of the primary goals of HFpEF treatment is to alleviate symptoms and improve functional status and quality of life. HFpEF patients often experience significant dyspnea, fatigue, and exercise intolerance, driven by elevated left ventricular filling pressures and pulmonary congestion. Sacubitril/valsartan's vasodilatory and natriuretic effects may help mitigate these symptoms by reducing venous congestion and improving hemodynamic parameters.12

In the PARAGON-HF trial, patients receiving sacubitril/valsartan showed modest improvements in quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), a validated tool for measuring heart failure-related quality of life. This suggests that even in the absence of significant reductions in cardiovascular death, sacubitril/valsartan may offer symptomatic relief and enhance daily functioning in patients with HFpEF.12

From a therapeutic standpoint, clinicians may consider sacubitril/valsartan for HFpEF patients who experience persistent symptoms despite optimal management of comorbidities such as hypertension, diabetes, and atrial fibrillation. Symptomatic improvement can be a crucial factor in clinical decision-making, particularly for patients with limited therapeutic options.12

Integration with Other HFpEF Therapies

The management of HFpEF is inherently complex due to its multifactorial nature, with comorbidities such as hypertension, obesity, diabetes, and atrial fibrillation playing key roles in disease progression. Consequently, sacubitril/valsartan should be viewed as part of a broader therapeutic strategy rather than a standalone treatment. Optimal blood pressure control is critical in HFpEF, and sacubitril/valsartan’s antihypertensive properties make it particularly useful in patients with poorly controlled hypertension, a common comorbidity in this population.12,13

Additionally, emerging therapies such as sodium-glucose co-transporter-2 (SGLT2) inhibitors have shown promise in HFpEF, particularly in reducing heart failure hospitalizations. Given the distinct mechanisms of action between SGLT2 inhibitors and sacubitril/valsartan, there is potential for combination therapy to address multiple aspects of HFpEF pathophysiology, including diastolic dysfunction, vascular stiffness, and volume overload.14,15

Diuretic therapy remains a cornerstone of HFpEF management for controlling volume overload, and sacubitril/valsartan’s natriuretic effects may complement the action of loop diuretics, enhancing volume management and reducing the need for higher diuretic doses.15

Patient Selection and Phenotyping

Given the heterogeneous nature of HFpEF, patient selection for sacubitril/valsartan therapy is paramount. Clinical trials and observational studies suggest that patients with an LVEF closer to the borderline between HFrEF and HFpEF (i.e., LVEF 45-50%) and women may derive greater benefit from sacubitril/valsartan. This may reflect differences in ventricular remodeling, myocardial stiffness, and neurohormonal activation between these subgroups and other HFpEF patients.16

Phenotyping HFpEF patients based on clinical, echocardiographic, and biomarker profiles may help guide therapeutic decisions. For example, patients with higher levels of natriuretic peptides, indicative of increased cardiac wall stress, may be more likely to respond to sacubitril/valsartan. Future research into biomarkers and advanced imaging modalities may further refine the identification of patients who stand to benefit the most from ARNI therapy.16

The current therapeutic use of sacubitril/valsartan in HFpEF is grounded in its ability to modulate neurohormonal pathways and alleviate symptoms in selected patient subgroups. While its impact on mortality remains uncertain, sacubitril/valsartan holds promise for reducing heart failure hospitalizations and improving quality of life in HFpEF patients, particularly those with borderline LVEF or recurrent hospitalizations. As our understanding of HFpEF continues to evolve, careful patient selection and phenotyping will be critical in optimizing the use of sacubitril/valsartan and integrating it into a comprehensive treatment strategy for this complex condition.17

CONCLUSION

The use of sacubitril/valsartan in heart failure with preserved ejection fraction (HFpEF) represents a significant step forward in addressing a historically challenging subset of heart failure. HFpEF is characterized by diastolic dysfunction, increased left ventricular stiffness, and systemic vascular resistance, with complex contributions from neurohormonal activation, inflammation, and comorbidities. Sacubitril/valsartan, through its dual inhibition of neprilysin and angiotensin II receptors, offers a multifaceted therapeutic approach aimed at reducing heart failure symptoms, hospitalizations, and potentially improving patients' quality of life. However, its role in reducing mortality and other hard clinical endpoints remains less clear in HFpEF than in heart failure with reduced ejection fraction (HFrEF).

The PARAGON-HF trial provided a robust evaluation of sacubitril/valsartan in HFpEF, ultimately demonstrating limited overall impact on mortality and mixed results in cardiovascular outcomes. Nevertheless, important signals within specific patient subgroups, particularly women and those with an ejection fraction near the lower end of the HFpEF spectrum, suggest that sacubitril/valsartan may confer benefits in certain populations. These findings underscore the need for a tailored approach in HFpEF, where treatment decisions must be informed by patient phenotyping, including variables like LVEF, comorbidity profile, and biomarkers indicative of disease severity. Such stratification could help identify patients most likely to respond favorably to sacubitril/valsartan, allowing for a more personalized treatment strategy.

Clinically, sacubitril/valsartan is positioned as a valuable option for managing symptoms and reducing hospitalizations in HFpEF, particularly in patients who exhibit high symptom burden or recurrent hospital admissions. Its impact on functional capacity and quality of life, though modest, addresses key therapeutic goals in HFpEF, where relieving the patient's symptomatic burden often takes precedence in the absence of life-prolonging options. The favorable safety profile of sacubitril/valsartan, alongside its benefits in blood pressure reduction and renal function stabilization, further supports its role in a comprehensive HFpEF management strategy.

Despite these positive aspects, several questions remain. Ongoing research should focus on further refining patient selection criteria, exploring biomarkers predictive of ARNI response, and evaluating potential synergies with emerging HFpEF therapies, such as SGLT2 inhibitors. As clinical evidence expands, sacubitril/valsartan's position in HFpEF treatment protocols will likely become clearer, and a more nuanced understanding of its long-term benefits may emerge. Additionally, real-world studies may provide insights into its effects on diverse patient populations beyond those typically represented in clinical trials.

In conclusion, while sacubitril/valsartan does not offer a universal solution to the multifaceted challenge of HFpEF, it represents a significant advance in the therapeutic options available for this patient population. By providing both symptomatic relief and a potential reduction in hospitalization rates, sacubitril/valsartan fills an important gap in HFpEF management. As our understanding of HFpEF continues to evolve, this dual-acting ARNI may play a crucial role in the nuanced and individualized treatment approaches that characterize modern heart failure care.

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