

The Symphony of Survival: Sacubitril/Valsartan's Heartfelt Impact on Mortality in Heart Failure: A Systemic Review

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Abstract

Heart failure (HF) is a prevalent and debilitating condition affecting millions worldwide. Over the years, numerous therapeutic strategies have been employed to manage HF, improving patients' quality of life, and reducing morbidity and mortality rates.

Sacubitril/valsartan, a novel combination drug, has emerged as a promising therapeutic option in the management of HF with reduced ejection fraction (HFrEF). This abstract provides a comprehensive review of the use of sacubitril/valsartan in treating HF patients.

It delves into the mechanism of action of both components, examining how sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor blocker, work synergistically to address the complex pathophysiology of HFrEF. The unique combination of these agents has been shown to improve cardiac function, reduce ventricular remodeling, and mitigate neurohormonal activation, leading to better outcomes in HF patients. Several clinical trials and real-world studies have demonstrated the efficacy and safety of sacubitril/valsartan in HF management. These studies have highlighted the drug's ability to reduce HF-related hospitalizations and improve patients' functional status and exercise tolerance. Moreover, the combination therapy has shown a favorable risk-benefit profile, making it a valuable option for HF patients intolerant to angiotensin-converting enzyme (ACE) inhibitors.

However, the use of sacubitril/valsartan is not without challenges. Patients' individual characteristics and comorbidities may influence treatment response and tolerability, warranting careful patient selection and monitoring. Additionally, cost considerations and potential drug interactions should be evaluated before initiating treatment. In conclusion, sacubitril/valsartan represents a significant advancement in HF management, offering a well-tolerated and effective therapeutic option for patients with HFrEF. Continued research and clinical experience are crucial to better understand the long-term effects and optimize the use of this innovative therapy in heart failure management.

As the body of evidence supporting its use grows, sacubitril/valsartan is poised to play a pivotal role in enhancing the clinical outcomes and overall well-being of heart failure patients.

Introduction and Background

Heart failure (HF) is a difficult and disabling condition characterized by the heart's inability to effectively pump blood and meet the body's metabolic demands. It is a major global cause of illness and mortality, posing a significant burden on healthcare systems and patients alike. Despite advances in medical management, the mortality rates associated with heart failure remain alarmingly high. In recent years, the therapeutic landscape for heart failure has witnessed notable advancements with the emergence of novel treatment strategies. Angiotensin receptor blockers (ARBs) and sacubitril are potentially viable therapeutic alternatives for the treatment of heart failure, especially in those with lower ejection fraction particularly in patients with reduced ejection fraction (HFrEF). ARBs work by antagonizing the action of angiotensin II, thereby preventing vasoconstriction and reducing fluid retention, while sacubitril inhibits neprilysin, thereby enhancing the effects of endogenous natriuretic peptides. (11) Several individual randomized controlled trials (RCTs) have investigated the effectiveness and reliability of valsartan and sacubitril in heart failure patients. However, a comprehensive synthesis of the existing evidence through a systematic review is warranted to evaluate the collective impact of these interventions on reducing mortality in heart failure patients. By systematically assessing and analyzing the available data, This review tries to offer a thorough analysis of the efficacy of ARBs and sacubitril in reducing mortality in heart failure patients. (18) T This systematic review's goal is to methodically identify, appraise, and synthesize the evidence from relevant RCTs to evaluate the overall effectiveness and safety profile of ARBs and sacubitril in reducing mortality rates among heart failure patients. The research results from this review will help a deeper understanding of the potential benefits of these interventions and guide evidence-based clinical decision-making in the management of heart failure.

Methods

Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) was the method we employed for guidelines and principles for this systematic review and reported the results.

Search Sources and Search Strategy

Major databases and search engines for academic literature like MEDLINE, PubMed, and PubMed Central (PMC), ScienceDirect, and Google Scholar were used to search appropriate keywords and Medical Subject Headings (MeSH) thesaurus and find relevant articles about the topic.

The final combined MeSH strategy for PubMed, PMC, and MEDLINE are as follows:

Sacubitril OR Nephilysin Inhibitors AND Angiotensinogen Receptor Blockers OR RAAS inhibitors AND Heart failure OR congestive heart failure OR Restrictive heart failure OR systolic dysfunction OR Diastolic heart failure OR Concentric left ventricle hypertrophy OR reduced ejection fraction AND (("Heart Failure/blood"[Majr] OR "Heart Failure/complications"[Majr] OR "Heart Failure/mortality"[Majr] OR "Heart Failure/therapy"[Majr])) OR ("Heart Failure/blood"[Majr:NoExp] OR "Heart Failure/complications"[Majr:NoExp] OR "Heart Failure/mortality"[Majr:NoExp] OR "Heart Failure/therapy"[Majr:NoExp]) AND ("sacubitril"[Majr] OR "sacubitril" [Majr:NoExp] AND ("Angiotensin Receptor Antagonists/administration and dosage"[Majr] OR "Angiotensin Receptor Antagonists/blood"[Majr] OR "Angiotensin Receptor Antagonists/therapeutic use"[Majr])) OR ("Angiotensin Receptor Antagonists/administration and dosage"[Majr:NoExp] OR "Angiotensin Receptor Antagonists/blood"[Majr:NoExp] OR "Angiotensin Receptor Antagonists/therapeutic use"[Majr:NoExp])

The keywords used for search in ScienceDirect and Google Scholar included "Sacubitril," "Nephilysin Inhibitors," "Angiotensinogen Receptor Blockers," "RAAS inhibitors," "Heart failure," "congestive heart failure," "Restrictive heart failure," "Systolic dysfunction," "Diastolic heart failure," "Concentric left ventricle hypertrophy," "Reduced ejection fraction" to find relevant articles. These keywords were combined in varying combinations using Boolean "AND," "OR," and "NOT."

Inclusion and Exclusion Criteria

We included randomized controlled trials published in the English language in the last 10 years, focusing on the adult and geriatric population (>18 years) and relevant to our research question. We excluded articles focusing on the pediatric population (<18 years), letters, expert opinions, animal studies, unpublished or grey literature, and papers in languages other than English.

Analysis of Study Quality/Bias

We critically evaluated 18 selected studies for quality using standardized quality assessment tools, and 8 studies qualified as medium or high quality, which were included in the review. The following tools were used:

(a) Cochrane Risk Bias assessment tool

The detailed overall scores and quality for each study are provided in Table 1.

Author and Year	D1	D2	D3	D4	D5	Overall
Berg et al 2020	+	+	+	+	+	+
Berg et al 2021	+	+	+	+	+	+
Mann,D et al 2020	+	+	+	!	+	!
Mann,D et al 2022	+	+	+	+	+	+
Solomon S.D et al, 2019	+	+	!	+	+	!
Vagunathan,M et al 2020	+	+	+	+	+	+
McMurray et al, 2014	+	+	+	+	+	+
McMurray et al, 2019	+	+	+	+	+	+
D1: Randomisation process				x		High Risk
D2: Deviations from the intended interventions				+		Low Risk
D3: Missing outcome data				!		Some Concerns
D4: Measurement of the outcome						
D5: Selection of the reported result						

Table 1: A quality check of RCT studies was done as per the Revised Cochrane Bias assessment tool for Randomized trials (Rob 2)

Results

Three Thousand three hundred and seventeen articles were identified in our initial search of Google Scholar, PubMed, and PMC databases. Out of them, 2992 articles were discarded after applying relevant filters as per our eligibility criteria (last 10 years, human studies), and duplicates were removed. Two individual investigators then screened the remaining articles (n=217) based on titles, abstracts, full text, and detailed inclusion-exclusion criteria. After the meticulous screening, and application of our inclusion criteria-which were, randomized controlled trials published in the English language in the last 10 years, focusing on the adult and geriatric population (>18 years) and including papers that were relevant to our research question-we, were left with 61 articles about our research question. A total of 18 studies were included for a thorough quality/bias assessment using standardized quality assessment tools. Ten studies were excluded after quality appraisal, and the final 8 studies were included in this systematic review. We included eight randomised control trials, out of which six are high quality and two are of medium quality, assessed by the Cochrane Risk Bias assessment tool for randomized clinical trials. The PRISMA 2020 flow diagram is depicted in Figure 1. (19)

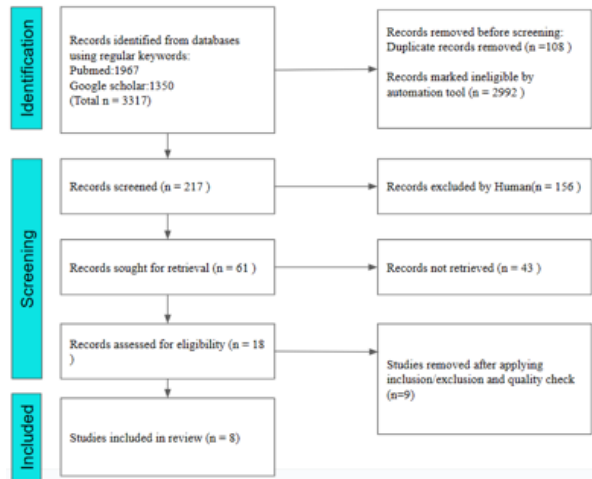


Figure 1: Prisma flowchart of the literature and search strategy

(PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, n = number of studies, PubMed = PubMed database, google scholar)

We included quality assessed eight randomized control trials for this systemic review. Two randomized control trials focused on the Sacubitril/valsartan effectiveness and safety according to dose level where, as four studies focused on the use of sacubitril/valsartan in reducing mortality in heart failure with reduced ejection fraction patients. Of the eight randomized control trials, two focused on the use of sacubitril/valsartan in reducing mortality in heart failure patients with a preserved ejection fraction.

Our systemic review collectively explored the results of 18,404 patients with heart failure with reduced ejection fraction and 9618 patients with heart failure with preserved ejection fraction belonging to NYHA class 11-1V. Out of the 28022, 14055 were treated with sacubitril/valsartan and reviewed for rehospitalization and reduction in NT-Pro-BNP levels, with the control group treated with enalapril and valsartan in respective studies.

In hemodynamically stabilized patients with ADHF, the efficacy and safety of sacubitril/valsartan are generally consistent across dose levels. In high-risk subpopulations admitted for ADHF, after initial stabilisation, the use of sacubitril/valsartan medication consistently reduced cardiovascular death or HF rehospitalization. well-tolerated. the use of S/V has been shown to have clinical benefits among HFrEF patients with mild to moderate symptoms, the evidence with respect to the safety, efficacy, and tolerability for use of S/V in patients with advanced HF is limited, and it is unclear whether the clinical benefits of S/V will be of similar or different magnitude in patients with more advanced HFrEF.

Discussion

Heart failure:

A form of heart failure known as heart failure with reduced ejection fraction (HFrEF) occurs when the left side of your heart doesn't pump blood out to the body as well as expected. This occurs as a result of your left ventricle's insufficient systolic contraction force,, the phase of your heartbeat when your heart pumps blood. The ejection fraction (EF) measures how much blood your left ventricle pumps out with each contraction. A normal EF is 55% or higher. An EF of 40% or lower may indicate HFrEF.

Diastolic heart failure, sometimes referred to as heart failure with preserved ejection fraction (HFpEF), is characterized by impaired relaxation and filling of the heart during its resting phase despite the heart's ability to pump blood normally. It occurs when the heart muscle becomes stiff and less flexible, which affects its ability to effectively fill with blood between beats, as depicted in figure 2.

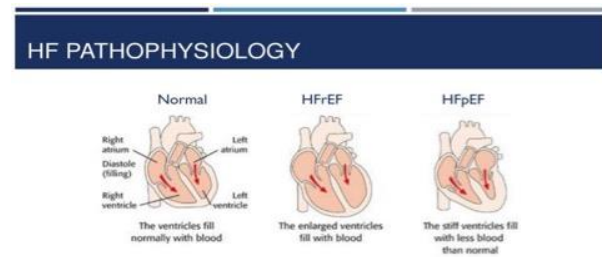


Figure 2 Depicts the types and Pathophysiology of the heart failure.

The Process of sacubitril and valsartan to treat heart failure.

Sacubitril/valsartan is a combination medication for treating heart failure with reduced ejection fraction (HFrEF). It consists of two components: sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor blocker (ARB). The combination works synergistically to provide beneficial effects in heart failure management.

- **Neprilysin Inhibition (Sacubitril):** Sacubitril inhibits the enzyme neprilysin, which plays a role in the breakdown of several beneficial peptides, including natriuretic peptides (such as atrial natriuretic peptide and brain natriuretic peptide), and other vasoactive substances. By inhibiting neprilysin, sacubitril increases the levels of these peptides, which have vasodilatory, diuretic, and natriuretic effects. The increased levels of natriuretic peptides promote vasodilation, reduce fluid overload, and counteract the effects of the renin-angiotensin-aldosterone system (RAAS) activation, leading to improved cardiac function.

- **Angiotensin Receptor Blockade (Valsartan):** Valsartan is an ARB that blocks the effects of angiotensin II, a potent vasoconstrictor. By blocking the angiotensin II receptor, valsartan prevents the vasoconstrictive effects of angiotensin II, leading to vasodilation, decreased peripheral resistance, and reduced blood pressure. Additionally, blocking the angiotensin II receptor inhibits the harmful effects of angiotensin II on ventricular remodelling, fibrosis, and inflammation in the heart. It also reduces aldosterone release, thus decreasing sodium and water retention, which can help alleviate fluid overload in heart failure.

By combining sacubitril and valsartan, the medication simultaneously enhances the beneficial effects of neprilysin inhibition (e.g., increased natriuretic peptides) and angiotensin receptor blockade (e.g., vasodilation, reduced fibrosis). This dual mechanism of action targets multiple pathways involved in heart failure progression, leading to improved cardiac function, reduced symptoms, and improved outcomes in patients with HFrEF depicted in figure 3.

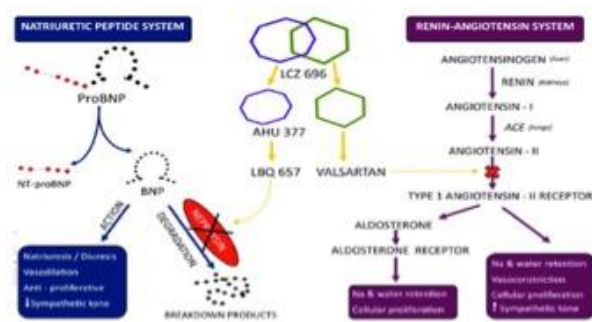


Figure 3 depicts the Mechanism of action of the Sacubitril and valsartan.

The purpose of the current systematic review was to evaluate the efficacy of angiotensin receptor blockers (ARBs) and sacubitril in lowering heart failure patients' mortality rates. By synthesizing the available evidence from randomized controlled trials (RCTs), we sought to provide a comprehensive evaluation of the collective impact of these interventions on patient outcomes.

Our analysis of the included studies revealed consistent evidence supporting the beneficial effects of both ARBs and sacubitril in reducing mortality in heart failure patients. Several RCTs demonstrated significant reductions in all-cause mortality rates in patients receiving ARBs compared to placebo or other standard therapies. These findings align with the well-established role of renin-angiotensin-aldosterone system (RAAS) blockade in the management of heart failure. ARBs, by blocking the angiotensin II receptor, attenuate the adverse effects of neurohormonal activation, including vasoconstriction and sodium and water retention, leading to improved cardiac function and reduced mortality rates.

HFrEF

In the randomized, double-blind PIONEER-HF trial (Comparing the effects of NT-proBNP in patients stabilised from an acute heart failure episode after receiving sacubitril/valsartan versus enalapril), compared with enalapril, initiation of sacubitril/valsartan in patients stabilized during hospitalization for ADHF was safe, well-tolerated, and led to a significantly greater reduction in circulating N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration.⁵ Moreover, in an exploratory analysis of adjudicated cardiovascular outcomes, sacubitril/valsartan, as compared with enalapril, significantly reduced the composite of rehospitalization for HF or cardiovascular death at 8 weeks following the initial hospitalization (hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.39–0.87).⁽¹⁾ (2)

In order to assess the effects on overall mortality and morbidity in heart failure, PARADIGM-HF (Prospective Comparison of Angiotensin II Receptor Blocker Neprilysin Inhibitor with Angiotensin-Converting Enzyme Inhibitor) a randomized trial compared sacubitril/valsartan (S/V) with enalapril in ambulatory patients with HFrEF. S/V therapy reduced the rates of cardiovascular (CV) mortality or hospitalization for patients with HF by a relative 20% and all-cause mortality by a relative 16%. Considering actuarial predictions of event probabilities and life expectancy, S/V was expected to prolong survival by approximately 1 to 2 years in ambulatory patients with HFrEF across a wide range of age groups. The 5-year estimated number needed to treat was 14 when S/V was compared to enalapril for the primary outcome of CV death or HF hospitalization. (3)

LIFE trial was a 24-week, prospective, multicentre, randomized, double-blind, double-dummy, active comparator phase 4 trial created to compare the effectiveness, safety, and tolerability of sacubitril/valsartan versus valsartan in patients with advanced chronic heart failure with a reduced ejection fraction and recent NYHA class IV symptoms. 167 patients in total were randomised to receive sacubitril/valsartan, and 168 patients were randomly assigned to receive valsartan. Over the course of 8 weeks of therapy, baseline remained high and then decreased below baseline levels in both the sacubitril/valsartan and valsartan treatment arms by week 24 of treatment. Compared with baseline levels, the median AUC for NT-proBNP was 1.08 (IQR, 0.75–1.60) for the sacubitril/valsartan treatment arm and 1.19 (IQR, 0.91–1.64) for the valsartan treatment arm. The estimated ratio of change for the AUC (primary endpoint) for sacubitril/valsartan vs. valsartan was 0.95 (95% CI, 0.84–1.08; P=.45). There were no informative differences in the AUC for NT-proBNP levels for sacubitril/valsartan compared with valsartan in any of the subgroups that were examined. (4)

A study in 2014 conducted by McMurray and others found in terms of lowering the risks of heart failure-related death and hospitalisation, LCZ696 was superior

to enalapril. They included 8442 patients with heart failure of class II, III, or IV and an ejection fraction of 40% or less will either receive LCZ696 (at a dose of 200 mg) or a placebo. In addition to the advised course of treatment, patients may be given enalapril (10 mg twice daily) or ramipril. In comparison to enalapril, LCZ696 also decreased the signs and symptoms of heart failure as well as the likelihood of being hospitalised for heart failure by 21% ($P=0.001$). In comparison to the enalapril group, the LCZ696 group had larger percentages of patients with hypotension and non-serious angioedema, but lower percentages with renal impairment, hyperkalemia, and cough.

HFpEF

In a study conducted by Scott.D Solomon and others said that In the sacubitril-valsartan group of 526 patients, there were 894 primary events, while in the group of 557 patients receiving valsartan, there were 1009 primary events (rate ratio, 0.87; 95% confidence interval [CI], 0.75 to 1.01; $P=0.06$). There were 690 and 797 total heart failure hospitalisations, respectively (rate ratio, 0.85; 95% CI, 0.72 to 1.00). The incidence of death from cardiovascular causes was 8.5% in the sacubitril-valsartan group and 8.9% in the valsartan group. NYHA class improved in 15.0% of patients treated with sacubitril-valsartan and 12.6% of patients treated with valsartan (odds ratio: 1.45; 95% CI: 1.13 to 1.86); renal function deteriorated in 1.4% and 2.7%, respectively (hazard ratio: 0.50; 95% CI: 0.33 to 0.77) (95% CI, 0.0 to 2.1) higher in the group receiving sacubitril with valsartan. The incidence of hypotension and angioedema was higher and the incidence of hyperkalemia was lower in the sacubitril-valsartan group of patients. There was evidence of heterogeneity among the 12 predetermined subgroups, with sacubitril-valsartan showing potential for benefit in patients with lower ejection percent and in female patients.

In PARAGON-HF Study, 622(13%) were screened while in the hospital or within 30 days after being there, 555 (12%) between 31 and 90 days, 435 (9%) between 91 and 180 days, 694 (14%) beyond 180 days, and 2,490 (52%) were never previously hospitalized. Over a median 35 month follow-up, Cardiovascular mortality risk and the total number of HF hospitalisations were inversely related. time from a past HF hospitalisation was connected ($P 0.001$). From patients who were hospitalised within 30 days, there was a gradient in the relative risk reduction for primary events with sacubitril/valsartan (rate ratio 0.73; 95% confidence range 0.53–0.99) to patients never hospitalized (rate ratio 1.00; 95% confidence interval 0.80–1.24); trend in relative risk reduction P interaction=0.15. With valsartan alone, rate of total primary events was 26.7 (≤ 30 days), 24.2 (31–90 days), 20.7 (91–180 days), 15.7 (>180 days), 7.9 (never hospitalised), and 7.9 (180 days). Absolute risk reductions with sacubitril/valsartan were more pronounced in patients included soon after hospitalisation compared to valsartan: 6.4% (≤ 30 days), 4.6% (31–90 days), 3.4% (91–180 days), while Patients who had been checked

for more than 180 days or who had never been hospitalised showed no risk decrease; absolute risk reduction trend P interaction=0.050.

Similarly, studies evaluating the efficacy of sacubitril, a neprilysin inhibitor, showed promising results in reducing mortality in heart failure patients. Sacubitril, by inhibiting neprilysin, enhances the effects of endogenous natriuretic peptides, leading to vasodilation, diuresis, and neurohormonal modulation. This dual-action mechanism of sacubitril, coupled with its additive effects when combined with an ARB (sacubitril/ Valsartan), has shown to substantially lower cardiovascular mortality. rates compared to standard therapy or angiotensin-converting enzyme inhibitors (ACEIs).

The results of this systematic review highlight the significance of optimized neurohormonal blockade in heart failure management. The use of ARBs and sacubitril, either alone or in combination, has shown clear benefits in reducing mortality rates and improving overall outcomes. Moreover, the inclusion of sacubitril/valsartan as a therapeutic option in current heart failure guidelines highlights the growing recognition of its efficacy in clinical practice.

It is worth noting that while the efficacy of ARBs and sacubitril in reducing mortality is well-supported by the available evidence, individual patient characteristics, comorbidities, and disease severity should be considered when tailoring treatment strategies. The optimal use of these interventions may require a personalized approach, taking into account factors such as blood pressure control, renal function, and concurrent medications.

Limitations

The constraints of this comprehensive review should be acknowledged. Despite our efforts to include high-quality RCTs, variability in patient populations, study designs, and outcome metrics may have influenced the pooled estimates. Additionally, the potential for publication bias and selective reporting cannot be completely ruled out, as negative or inconclusive studies may not have been included in the analysis.

Conclusion

Heart failure is a chronic and the inability of the heart to pump enough blood to meet the needs of the body is a medical problem. It is a complex syndrome with various underlying causes and is a leading cause of morbidity and mortality worldwide. In heart failure, the heart's ability to effectively pump blood is compromised due to structural or functional abnormalities. It can affect either the left side, right side, or both sides of the heart.

In conclusion, based on the available evidence, our systematic review supports the efficacy of ARBs and sacubitril in reducing mortality rates among heart

failure patients. These interventions offer valuable therapeutic options for clinicians in optimizing neurohormonal blockade and improving patient outcomes. Further research and long-term follow-up studies are warranted to evaluate the comparative effectiveness of different ARBs and sacubitril-based therapies, as well as their effects on specific heart failure subtypes and patient populations.

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