META-ANALYSIS

Effectiveness and Safety of Sacubitril/Valsartan in Heart Failure with Preserved Ejection Fraction: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective • Heart failure with preserved ejection fraction (HFpEF) is a prevalent and clinically significant condition characterized by limited treatment options. In this context, the objective of this meta-analysis is to evaluate the effectiveness of sacubitril/valsartan compared to angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in managing HFpEF..

Methods • A systematic search of relevant studies was conducted in PubMed, Embase, Web of Science, and Cochrane Library. Randomized controlled trials comparing sacubitril/valsartan to ACEIs or ARBs in HFpEF patients were included. Inclusion criteria: LVEF>45%, NYHA II-IV, Sac/Val vs ACEI/ARB, RCTs, treatment duration >3 months, sample size ≥25 per group. Exclusion criteria: Animal studies, unclear/missing data, poor quality, case studies/expert opinions.Hospitalization for heart failure and cardiovascular mortality were the primary outcomes, while the additional results included mortality from all causes, improvement of NYHA class, modifications in NT-proBNP, and with LVEF.

Results • Sacubitril/valsartan substantially reduced heart failure hospitalization rates compared to ACEIs and ARBs, according to a total of six studies involving 5,201 participants (Relative Risk, 0.78; 95% CI, 0.65 to 0.85; P = .001). Nonetheless, there were no significant improvements in mortality due to cardiovascular disease (Relative Risk, 0.94; 95% CI, 0.79-1.12; P = .563). Sacubitril/valsartan did not affect total mortality from all causes significantly (Relative Risk, 0.95; 95% CI, 0.84-1.09; P = .453), but it did enhance NYHA classification (Relative Risk, 1.25; 95% CI, 1.10-1.43; P = .001). NT-proBNP levels decreased substantially (Weighted Mean Difference, -266.67; 95% CI, -525.86 to -7.47), whereas there had been little major shift in LVEF (Weighted Mean Difference, 1.49; 95% CI, -1.33 to 4.21; P = .342).

Conclusions • Sacubitril/valsartan may provide superior benefits in reducing heart failure hospitalization rates, NT-proBNP levels, and improving NYHA classification in patients with HFpEF compared to ACEIs and ARBs. Sacubitril/valsartan might be considered as a preferred treatment option for HFpEF patients due to its benefits in reducing heart failure hospitalization rates and improving symptom severity. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

As a result of different electrical, anatomical, or physiological disorders, heart failure (HF) causes impaired ventricular expansion and/or ejection, resulting in inadequate output from the heart to meet the metabolic demands of the tissues in the body.[1] This syndrome is characterized by congestion in the pulmonary and/or circulation throughout the body, inadequate blood perfusion to organs and tissues, and common symptoms including dyspnea, fatigue, and fluid retention. Heart failure has become one of the greatest hazards to human health due to the prevalence of cardiovascular diseases. in the year 2016, the European Society about Cardiology (ESC) recommendations over HF categorized patients with a left ventricular ejection fraction (LVEF) above fifty percent as having cardiac disease via preserved ejection fraction (HFpEF).[2] Previous reports suggested that the prevalence of HFpEF was comparable to that of HFrEF, but with the aging of the population, especially the increase of hypertension, diabetes, and obesity, the prevalence of HFpEF has an increasing trend. A study in the United States showed that HFpEF increased from 45% to 55% between 1987 and 2001.[1] A study in Japan showed that

the proportion of hospitalized patients with HFpEF increased from 50.6% in 2000-2004 to 68.7% in 2006-2010.[2]

HFpEF is a heterogeneous syndrome that includes impaired diastolic efficiency and elevated end-diastolic ventricular pressure, whereas LVEF remains normal or near-normal and is, therefore, also known as diastolic heart failure (DHF).[3] HFpEF is characterized by preserved or near-normal LVEF, indicating that the heart's pumping function is relatively preserved during systole. However, impaired diastolic filling and relaxation lead to elevated pressures within the heart chambers during diastole, resulting in symptoms and signs of heart failure. Thus, HFpEF is commonly referred to as diastolic heart failure (DHF), distinguishing it from heart failure with reduced ejection fraction (HFrEF), where there is a significant decrease in LVEF and impaired systolic function. The prevalence of HFpEF has been increasing annually and now accounts for fifty percent of the heart failure population, making it the most prevalent form of heart failure.[4] Heart failure with preserved ejection fraction (HFpEF) poses significant challenges for clinicians due to the complexities in diagnosis, lack of targeted treatments for the multifactorial disease, limitations of current therapeutic options, and the need for individualized patient care. The heterogeneity of HFpEF patients implies a personalized and comprehensive management strategy involving a multidisciplinary team of healthcare professionals. Addressing these challenges requires continued research efforts to deepen our understanding of the underlying mechanisms of HFpEF and identify novel therapeutic targets.[5] With the increasing prevalence of obesity, diabetes, and hypertension, the incidence of HFpEF has increased. Current guidelines and evidence-based medicine have not identified effective treatments for HFpEF patients. Although angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), loop diuretics, beta-blockers, and calcium channel blockers have some therapeutic effects on HFpEF, their efficacy is not substantial, and there are still high rates of rehospitalization and mortality.[6]

Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI) class representative drug, is a combination of the angiotensin receptor antagonist valsartan and the neprilysin (NEP) inhibitor sacubitril in a 1:1 ratio.[7,8] Sacubitril/Valsartan (ARNI) is a promising medication for managing heart failure with preserved ejection fraction (HFpEF). By combining angiotensin receptor blockade and neprilysin inhibition, it addresses key pathophysiological mechanisms in HFpEF. The angiotensin receptor blockade helps reduce afterload, while neprilysin inhibition increases vasodilation, diuresis, and natriuresis, thus reducing preload. Though its efficacy in HFpEF is still being studied, clinical trials have shown potential benefits in reducing hospitalization rates. Further research is necessary to fully understand sacubitril/valsartan's role and its impact on mortality in HFpEF patients. Sacubitril/valsartan concentrates on suppressing neprilysin action to decrease the breaking down of natriuretic peptides, which promotes dilation along with diuresis and minimizes the development of myocardial fibrosis and hypertrophy. Sacubitril/valsartan has shown stronger anti-heart failure effects.[9] The PARAMOUNT-HF study comparing ARNI with ARB in HFpEF treatment revealed that sacubitril/valsartan could effectively reduce left atrial volume and significantly improve cardiac function in HFpEF patients.[10] However, the PARAGON-HF study comparing the overall outcomes of ARNI versus ARB treatment in HFpEF patients demonstrated that sacubitril/valsartan could not effectively improve long-term prognostic indicators, such as cardiovascular mortality, in HFPEF patients.[11]

There are limited large-scale studies on sacubitril/valsartan treatment for HFpEF patients, and the existing studies remain controversial regarding its efficacy and safety. Therefore, this meta-analysis aims to evaluate the impact of sacubitril/valsartan on key clinical outcomes in heart failure with preserved ejection fraction (HFpEF) patients. The specific objectives include assessing the effects of sacubitril/valsartan on hospitalization rates, mortality, exercise capacity, quality of life, and functional status in HFpEF patients. Additionally, the study aims to explore potential subgroup differences based on age, gender, comorbidities, and baseline characteristics. Through this analysis, we hope to provide valuable insights into the role of sacubitril/valsartan in managing HFpEF and inform future clinical practice and research.

MATERIALS AND METHODS

During the systematic review process and subsequent reporting of our results, we maintained adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Since the information utilized in this article was obtained from published sources, neither informed consent nor ethical approval was required. Two researchers systematically searched for relevant studies, independently determined their eligibility, collected information, and assessed the research's quality. The two researchers were required to come to an agreement and resolve any points of contention.

Search strategy

On January 6, 2023, a comprehensive search was conducted in four electronic databases (PubMed, Embase, Web of Science, and Cochrane Library) without any time restrictions. The search terms used were tailored to each database. The following keywords and MeSH terms were included: "heart failure with preserved ejection fraction," "sacubitril/valsartan," "angiotensin receptor-neprilysin inhibitor," "ARNI," "diastolic cardiac failure," "HFpEF," "HFnEF," "DHF." No language restriction was applied. Additionally, the reference lists of relevant articles were manually screened to identify any additional eligible studies.

Inclusion criteria

Studies included in the systematic review were required to meet the following criteria, with corresponding rationales

provided: Left Ventricular Ejection Fraction (LVEF) > 45%: This criterion was chosen to specifically focus on heart failure with preserved ejection fraction (HFpEF) patients, as defined by an LVEF above the established threshold. The objective was to ensure that the study population primarily consisted of HFpEF patients. Heart function classified as NYHA Class II-IV: The inclusion of patients with New York Heart Association (NYHA) class II-IV heart function aimed to target individuals with symptomatic HFpEF and varying degrees of functional impairment. By including these patients, the study aimed to capture a representative sample from the HFpEF population. Comparison between the sacubitril/valsartan group and ACEI or ARB group: This criterion aimed to examine the comparative effectiveness of sacubitril/valsartan against two commonly used medications, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), in managing HFpEF. The objective was to assess the specific impact of sacubitril/valsartan in relation to these standard treatment options. Randomized Controlled Trials (RCTs): RCTs were chosen to ensure a high level of evidence and minimize biases in treatment comparisons. Randomization helps distribute potential confounders between groups, enhancing the internal validity of the findings. Treatment duration of more than 3 months: A minimum treatment duration of more than 3 months was set to evaluate the medium to long-term effects of sacubitril/valsartan in HFpEF patients. This duration allowed for the assessment of sustained treatment benefits and potential adverse events. Sample size of at least 25 participants in each group: The minimum sample size requirement aimed to ensure an adequate number of participants in each treatment group for reliable statistical analysis and interpretation of the results.

Exclusion Criteria

The following exclusion criteria were applied to maintain the focus and quality of the systematic review: Animal studies: Excluding animal studies was necessary to maintain the relevance and applicability of the findings to human HFpEF patients. Studies with unclear data sources or missing data, where the authors cannot be contacted: Studies lacking clear data sources or inaccessible data could introduce uncertainty and hinder the assessment of methodological quality and data reliability. Studies with poor quality: Poor-quality studies may introduce biases or lack the necessary rigor to provide reliable evidence. By excluding such studies, the overall quality of the systematic review was enhanced. Case studies, commentary, opinions from experts, and narrative evaluations: These study types were excluded to maintain a focus on primary research and findings derived from rigorous research methodologies.

Data extraction

The process of data extraction involved independent review and cross-checking by two evaluators. Initially, the evaluators screened the abstracts and titles of identified papers, excluding clearly irrelevant literature. Subsequently, the evaluators thoroughly examined the full-text articles of potentially relevant studies to determine their eligibility for inclusion in the systematic review. Standardized Excel files were used to extract key information, including the first author's name, publication year, country, study design, demographic details, and details of control and intervention treatments (such as dose, frequency, duration, and mean follow-up time). Any discrepancies that arose during the data extraction process were resolved through discussion and consensus between the evaluators. Additionally, in cases where published reports did not provide the desired or complete data, contact was made with the original study investigators via email to request any unpublished data. This meticulous data extraction process aimed to ensure the reliability, accuracy, and comprehensiveness of the included studies' data, thus contributing to a robust systematic review..

Quality assessment

The possibility of bias in the included randomized controlled trials (RCTs) was evaluated using the revised Risk of Bias instrument (ROB 2), developed by the Cochrane Collaboration. Two independent examiners assessed several domains to determine the likelihood of bias in each study. These domains included the randomization process, allocation concealment, blinding of participants and personnel, completeness of outcome data, selective reporting, and other potential sources of bias. In the domain of randomization, the adequacy of the method used to generate random sequences was evaluated. Allocation concealment assessed whether the allocation sequence was adequately concealed from both participants and study personnel. Blinding of participants and personnel examined whether treatment allocation was adequately masked. The completeness of outcome data was assessed to identify any potential missing data. Selective reporting investigated the possibility of only reporting favorable or statistically significant results. Finally, the domain of other sources of bias considered additional factors that could introduce bias but were not covered explicitly in the previous domains. For each domain, the likelihood of bias was categorized as low, unclear/ambiguous, or high. Through the use of the ROB 2 instrument and assessment of these domains, the quality assessment aimed to identify any potential sources of bias in the included RCTs, strengthening the reliability and validity of the systematic review.

Statistical analyses

Using chi-square statistics and I^2 values, the heterogeneity between experiments was evaluated. Using the I^2 statistic, heterogeneity was assessed among the included studies. A value of 0% for I^2 between 30% and 60% are considered moderate heterogeneity, while values above 60% indicate substantial heterogeneity. We normalize the relative risk of each article and then combine them using random effects models. The reporting bias of meta-analyses is determined by employing the asymmetry

Table 1. Characteristics of studies included in the meta-analysis.

Author	Year	Study Design	Sample Size (ARNI)	Sample Size (control)	Male/Female (ARNI)	Male/Female (Control)	Drugs (ARNI)	Drug (Control)	Follow-up
Solomon et al	2012	RCT	149	152	64/85	67/85	Sacubitril-valsartan 200 mg, bid	Valsartan 160 mg bid	9 months
Solomon et al	2019	RCT	2407	2389	1166/1241	1148/1238	Sacubitril-valsartan 200 mg, bid	Valsartan 160 mg bid	35 months
Tumasyan et al	2019	RCT	27	56	NA	NA	Sacubitril-valsartan 200 mg, bid	Valsartan 160 mg bid, Ramipril 10 mg	12 months
Wang et al	2019	RCT	48	48	35/13	37/11	Sacubitril-valsartan 200 mg, bid	ACEI and ARB	12 months
Shi et al	2020	RCT	20	22	13/7	16/6	Sacubitril-valsartan 100 mg, bid	Valsartan 80 mg qd	3 months
Chen et al	2020	RCT	53	53	31/22	24/29	Sacubitril-valsartan 200 mg, bid	ACEI and ARB	6 months

Figure 1. Selection process of included studies

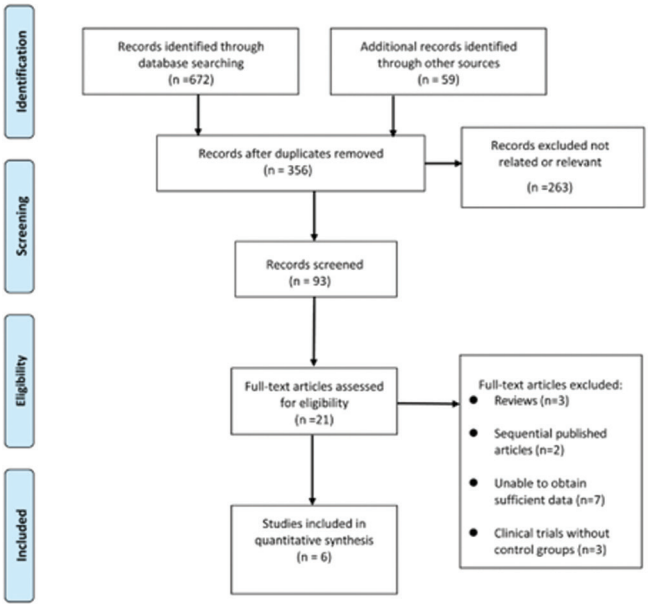
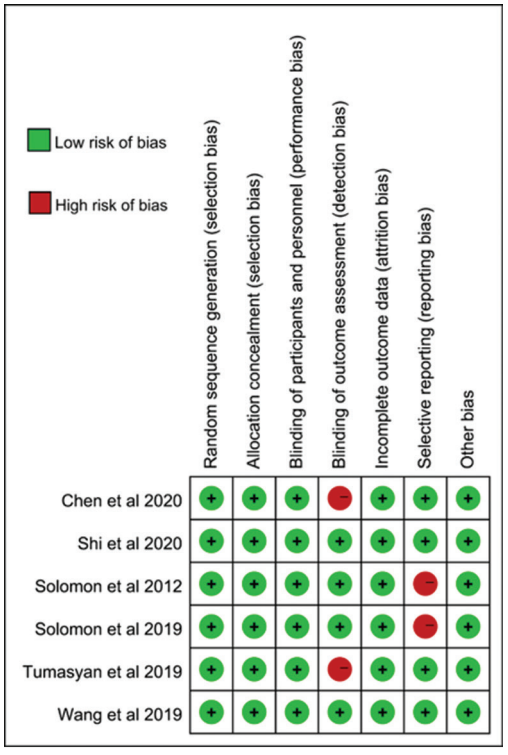


Figure 2. Quality assessment of included studies using Rob 2 tool. Red in figure indicates high risk, yellow represents unclear risk, and green means low risk.



of the funnel visualization and Egger's test. Publication bias refers to the selective publication of studies with significant or positive results. Funnel plots and Egger's test help detect and assess this bias, ensuring a more comprehensive and reliable representation of evidence in systematic reviews. If the funnel plot was asymmetrical, hypothetical negative unpublished studies were imputed to see whether publication bias significantly affected the impact estimates. A two-sided $P < .05$ was deemed highly significant in all statistical analyses. Data from RCTs meeting inclusion criteria were analyzed using Stata v 17 (StataCorp, College Station, TX, USA).

RESULTS

Search results and study selection

Initial results from a search of electronic databases revealed 731 relevant publications. After removing redundant literature, reading titles and abstracts, and screening rigorously according to criteria for inclusion and exclusion, 21 relevant studies were identified, and 15 were eliminated from further consideration. Six articles were finally included.[10,11,14-17] Figure 1 depicts the literature review process and results.

Study characteristics

The properties of the studies included in the present systematic review are presented in Table 1. The six aforementioned studies had a combined representative sample of 5,503 patients. They were disseminated between 2012 and 2020. The majority of fundamental characteristics of the study, including average age, gender and ethnic composition, medical history, NYHA classification, left cardiac ejection fraction, and initial treatment for heart failure, were distributed similarly among the sacubitril/valsartan cohort, the ACEI cohort, and the ARB cohort.

Results of quality assessment

The evaluation for bias risk in the six included studies was conducted throughout multiple domains. Two studies exhibited a low risk of bias across every category, indicating a high degree of methodological rigor. Nevertheless, 33.3% of the studies were determined to pose a high risk in bias in participant and staff blinding. This suggests that performance bias may have affected the results of these studies. In addition, 33.3% of the studies that included controlled studies exhibited an elevated likelihood of selective reporting bias. This suggests that incomplete or selective reporting of outcomes may have affected the aggregate findings of these investigations (Figure 2).

Figure 3. Forest plots of the effect of sacubitril/valsartan on the rate of heart failure hospitalization.

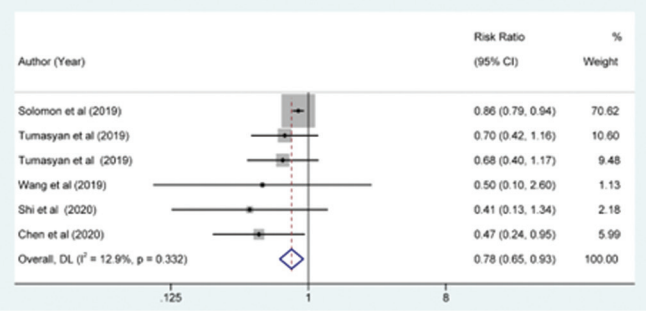


Figure 4. Forest plots of the effect of sacubitril/valsartan on the cardiovascular mortality.

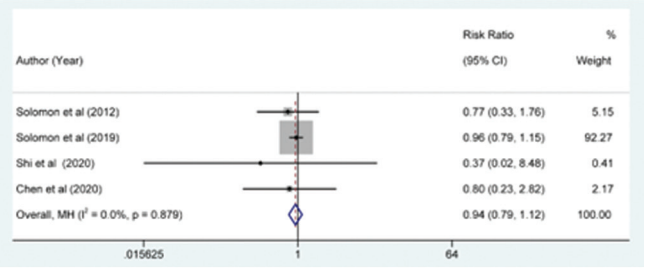


Figure 5. Forest plots of the effect of sacubitril/valsartan on the all-cause mortality.

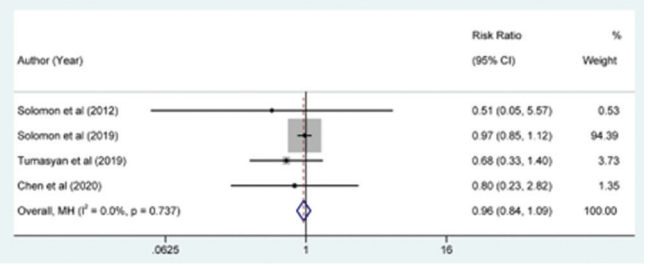


Figure 6. Forest plots of the effect of sacubitril/valsartan on the New York Heart Association class.

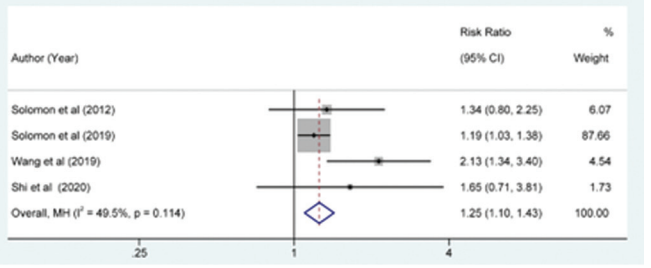


Figure 7. Forest plots of the effect of sacubitril/valsartan on the changes of NT-ProBNP.

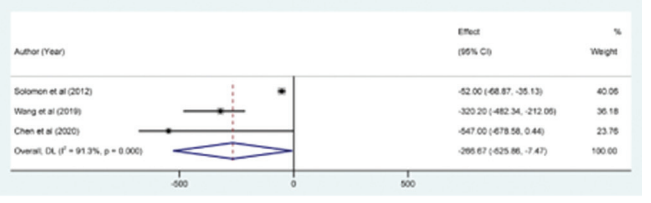
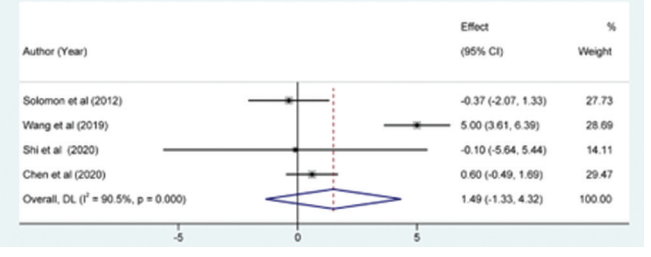


Figure 8. Forest plots of the effect of sacubitril/valsartan on the left ventricular ejection fraction (LVEF).



Primary Outcomes

Five studies containing an aggregate of 5201 patients reported heart failure hospitalization rates. There was no significant heterogeneity (I^2 = 12.9%; P = .332), so a model with fixed effects was used. The hospitalization rate for heart failure was markedly lower in the sacubitril/valsartan group than in the ACEI and ARB groups (RR, 0.78; 95% CI, 0.65 to 0.85; P = .001) (Figure 3). There was no significant heterogeneity (I^2 = 0%; P = .879) in four studies involving 5124 patients investigating cardiovascular mortality. Figure 4 demonstrates that sacubitril/valsartan could not significantly decrease cardiovascular mortality among individuals with hypertensive heart failure when compared with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

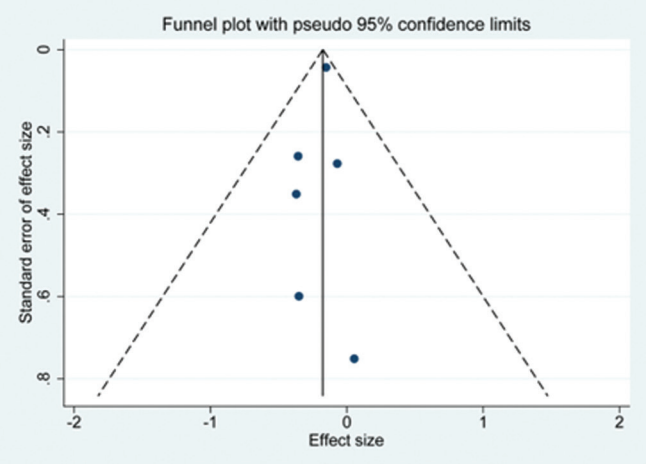
Secondary Outcomes

Four studies have reported total mortality. There was no significant heterogeneity (I^2 = 0%; P = .737), so a fixed-effects model was utilized for analysis. Figure 5 displays that the total mortality rate for all causes in the sacubitril/valsartan group was not significantly different from that of the ACEI and ARB groups (RR, 0.95; 95% confidence interval [CI], 0.85-1.09; P = .453). In addition, improvements in NYHA categories have been assessed in four separate investigations involving a total of X participants, and no substantial heterogeneity was detected (I^2 = 49.5%; P = .114). In comparison with inhibitors of angiotensin-converting enzymes as well as angiotensin receptor blockers, sacubitril/valsartan may improve NYHA classification in hypertensive heart failure patients (RR, 1.25; 95% CI, 1.10-1.40; P < .001) (Figure 6). Changes in NT-proBNP and LVEF were also observed. Both had significant heterogeneity (NT-proBNP: I^2 = 91.3%; P < .001; left ventricular ejection fraction: I^2 = 90.5%; P < .001) (Figure 7), and a random-effects model was employed. The results demonstrated that sacubitril/valsartan significantly reduced NT-proBNP levels (WMD, -266.67; 95% CI, -525.86 to -7.47; P < .05). However, it did not show a statistically significant increase in LVEF (WMD, 1.49; 95% CI, -1.33 to 4.32; P = .342) (Figure 8).

Publication bias

In view of the limited number of investigations, bias in publication was only evaluated for hospitalization for heart failure. The funnel plots constructed from the observed studies exhibited symmetry, indicating a balanced representation of studies across the range of effect sizes.

Figure 9. Funnel plot for publication bias in all included studies.



Importantly, the absence of significant publication bias in the funnel plots suggests that there is no evidence of selective reporting or suppression of studies with unfavorable outcomes (Figure 9).

DISCUSSION

HFpEF is a unique form of heart failure characterized by a preserved ejection fraction; however, its underlying mechanisms are not fully understood. As a result, there has been a lack of notable advancements in the management of HFpEF.[1] Managing heart failure with preserved ejection fraction (HFpEF) presents challenges due to its multifactorial nature, including diastolic dysfunction, endothelial dysfunction, and systemic inflammation. These complexities make targeted interventions complex. Diastolic dysfunction impairs ventricular relaxation and filling during diastole. Endothelial dysfunction affects vasodilation and vasoconstriction. Systemic inflammation exacerbates cardiac remodeling and can impact other organs. Clinical trials have had limited success in identifying effective therapies. Further research and personalized management strategies are needed for HFpEF. National and international guidelines classify Sacubitril/valsartan, which has a dual mechanism of action against heart failure, as a Class I medication for treating heart failure, a condition with reduced ejection fraction. Sacubitril/valsartan is a combination drug that acts through a dual mechanism to improve heart failure outcomes. Sacubitril is an inhibitor of neprilysin, an enzyme that degrades natriuretic peptides, which promote diuresis, natriuresis, and vasodilation. Valsartan, on the other hand, is an angiotensin II receptor blocker that reduces neurohormonal activation, which plays a role in heart remodeling and fibrosis. By inhibiting neprilysin and blocking the angiotensin II pathway, sacubitril/valsartan can enhance the activity of natriuretic peptides while reducing the detrimental effects of angiotensin II, leading to improved cardiac function and remodelling reversal. In patients with HFpEF, sacubitril/valsartan has shown promise in improving exercise capacity and reducing hospitalizations compared to standard of care. The efficacy of sacubitril/valsartan in managing heart failure with preserved ejection fraction (HFpEF) is a topic of ongoing debate within the academic community.[18] The present meta-analysis suggests that sacubitril/valsartan may be more effective than ACEIs and ARBs in mitigating heart failure symptoms and reducing the frequency of heart failure hospitalizations and NT-proBNP levels in individuals who have HFpEF. Nonetheless, the intervention fails to significantly improve cardiovascular mortality or all-cause mortality rates, nor does it reduce LVEF significantly. In addition, the administration of sacubitril/valsartan has been shown to decrease the incidence of hyperkalemia and elevated serum creatinine levels but does not appear to influence hypotension.

The management of patients with heart failure with preserved ejection fraction (HFpEF) currently relies on symptom-oriented and empirical approaches, lacking a conclusive strategy specifically addressing this condition. Prior research has indicated that ACE inhibitors and ARBs may enhance symptoms and functionality among individuals with HFpEF.[11] However, these medications do not appear to decrease morbidity and mortality. The natriuretic peptide system is primarily regulated by atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). In addition to possessing vasodilatory and diuretic properties, these hormones inhibit the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system.[19] In addition, they decompress the myocardium and reverse the heart's remodeling. The stimulation of the natriuretic neuropeptide structure has been identified as a crucial compensatory mechanism for abnormal systolic conformance along with relaxing among individuals with heart failure (HF) with preserved ejection fraction (HFpEF), thereby preventing volume and pressure imbalance. The defensive mechanism is probably compromised during the initial phases of HFpEF. Elevating the levels of active natriuretic peptides could potentially serve as a viable therapeutic approach for individuals with heart failure with preserved ejection fraction (HFpEF). Sacubitril/valsartan functions predominantly by suppressing neprilysin, which effectively stops the breakdown for ANP as well as BNP, thereby restoring the activity of the natriuretic peptide system.[8] Multiple studies suggest that sacubitril/valsartan may be preferable to ACE inhibitors (ACEIs) along with angiotensin receptor blockers (ARBs) for improving clinical results among individuals in heart failure alongside reduced ejection fraction (HFrEF).

Nevertheless, the precise function of the aforementioned factor in individuals with heart failure with preserved ejection fraction (HFpEF) remains uncertain. The present meta-analysis suggests that the administration of sacubitril/valsartan is associated with a significant reduction in hospitalization rates due to heart failure. However, it does not appear to significantly affect mortality rates related to cardiovascular events or all-cause mortality. The study of sacubitril/valsartan for individuals alongside a left ventricular ejection fraction of 45% demonstrated that hospitalization rates for heart failure did not improve

significantly. This study is considered the most extensive one conducted on the subject. Nevertheless, the aforementioned deduction is equivocal, and further analysis of subgroups reveals that individuals with left ventricular ejection fraction (LVEF) falling within the lower range (45%-57%) can certainly experience advantageous outcomes from the administration of sacubitril/valsartan. The observed variation may be associated with a more pronounced anomaly in the natriuretic peptide mechanism in heart failure patients and a decreased left ventricular ejection fraction. The NYHA classification is a crucial metric for evaluating the gravity of symptoms associated with heart failure. Improvement in NYHA classification reflects symptom relief and enhanced quality of life in HFpEF patients treated with sacubitril/valsartan. HFpEF imposes limitations on physical activity, and reducing dyspnea and fatigue improves daily living and overall well-being. Our study demonstrates significant NYHA classification improvements, indicating that sacubitril/valsartan may enhance quality of life for HFpEF patients. Based on the present meta-analysis, the findings of the PARAMOUNT trial indicate that sacubitril/valsartan can effectively enhance the NYHA classification after 36 weeks in comparison to ACEIs and ARBs.[10] The aforementioned advantage was similarly noted in the Paragon-HF clinical trial. The assessment of treatment efficacy in heart failure patients also encompasses the pivotal aspect of quality of life. The PARAMOUNT study did not yield any discernible intergroup disparities in the Kansas City Cardiomyopathy Questionnaire scores across all time intervals. 33% of patients who received sacubitril/valsartan and 29% of those who received valsartan alone had a 5-point increase when compared with their Kansas City Cardiomyopathy Questionnaire scores, according to the Paragon-HF study[11] In a separate study involving a group of individuals, it was discovered that the administration of sacubitril/valsartan led to a substantial decrease in the answers to the questions of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) among patients without heart failure with preserved ejection fraction (HFpEF).[20] The available evidence suggests that sacubitril/valsartan has the potential to enhance the symptoms and quality of life of patients with heart failure with preserved ejection fraction (HFpEF). Since neprilysin does not affect the proteolytic degradation of NT-proBNP, the fluctuating amount of NT-proBNP can indicate the decrease in left ventricular wall tension in patients receiving sacubitril/valsartan therapy. NT-proBNP levels serve as an indicator of left ventricular wall tension in HFpEF. Higher levels indicate increased tension and advanced disease, while decreasing levels suggest improved diastolic function and better outcomes. Monitoring NT-proBNP helps assess disease progression and treatment response, such as with sacubitril/valsartan. Persistent elevation or rising levels may signify inadequate response or worsening condition. NT-proBNP is a valuable biomarker for monitoring and managing HFpEF, providing insights into cardiac function and guiding therapeutic interventions.

This study has certain limitations, summarized as follows: 1) Some included studies have small sample sizes, which may introduce bias to some extent; 2) The diagnostic criteria for HFpEF have been updated to LVEF >50%, but some studies have not been updated, and the definition of HFpEF remains LVEF >45%. We used the criteria set by the study designers during the screening process; 3) It is challenging to control for other confounding factors such as age, comorbidities, follow-up time, etc. Therefore, some variables in different studies may lead to biases in the evaluation process. The limitations of varying diagnostic criteria and study characteristics can affect the generalizability of our findings. Our study's results have important clinical implications for HFpEF management, highlighting sacubitril/valsartan as an effective treatment option and emphasizing the importance of monitoring NT-proBNP levels. Future research should standardize diagnostic criteria, increase sample sizes, and explore long-term outcomes to optimize HFpEF care.

CONCLUSIONS

Sacubitril/valsartan has shown potential benefits in reducing heart failure hospitalization rates, NT-proBNP levels, and improving NYHA classification in HFpEF patients compared to ACEIs and ARBs. However, there are no significant effects on cardiovascular mortality, all-cause mortality, or LVEF changes. Further large-scale randomized controlled trials are needed to confirm these findings and explore the long-term effects of sacubitril/valsartan on HFpEF patients. The clinical relevance of these results lies in the potential improvement in patient care and outcomes, with reduced hospitalizations and improved quality of life. Future research should investigate other aspects of HFpEF management and design trials based on these findings. Implementing a patient-centered approach, sacubitril/valsartan can contribute to better NYHA classification and NT-proBNP levels, translating into enhanced patient experiences and outcomes. Multidisciplinary collaboration among cardiologists, nurses, and healthcare providers is crucial for the effective use of sacubitril/valsartan in HFpEF management. Limitations of the study include heterogeneity in diagnostic criteria and study characteristics, which may affect the generalizability of the findings. Future studies should address these limitations to ensure reliable and applicable results.

ETHICAL COMPLIANCE

Not applicable.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

YM and JY designed the study and performed the experiments, LQ and LW collected the data, YG and XZ analyzed the data, YM and JY prepared the manuscript. All authors read and approved the final manuscript.

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