

Original Research Article

Comparative renoprotection: Sacubitril/valsartan versus ACEI or ARB - A systematic review and meta-analysis

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Abstract

Purpose: To evaluate the renoprotective effect of sacubitril/valsartan (Sac/Val) against angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB).

Methods: Following PRISMA guidelines, a thorough search of PubMed, Embase, Web of Science, and Cochrane Library was performed up to May 18, 2023. Eligibility criteria included prospective, randomized, controlled trials comparing sac/Val and ACEI/ARB with regard to renal outcomes. Data extraction and quality assessment were undertaken independently by two reviewers. Fixed or random effects models were used depending on the heterogeneity among studies. Subgroup analyses were performed based on the presence or absence of heart failure.

Results: Eleven trials with varied patient populations and clinical settings were included. The meta-analysis revealed that Sac/Val exhibited a significantly reduced risk of renal function decline compared to ACEI/ARB (Risk Ratio (RR) = 0.86, 95 % Confidence Interval (CI) (0.78, 0.96), $p = 0.016$). Subgroup analysis showed that the renoprotective effect was significant in patients with heart failure (RR = 0.84, 95 % CI (0.75, 0.94), $p = 0.011$), but not in non-heart failure patients (RR = 1.04, 95 % CI (0.80, 1.37), $p = 0.66$).

Conclusions: This systematic review and meta-analysis suggest that Sac/Val confers substantial renoprotective effect compared with ACEI/ARB, particularly among heart failure patients. However, further research is required to elaborate on the full potential of Sac/Val as a nephroprotective agent.

Keywords: Sacubitril/Valsartan, Renoprotective effect, Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, Systematic review, Meta-analysis

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INTRODUCTION

Long-term deterioration of renal function is a debilitating factor in the prognosis and survival rate of patients across a spectrum of diseases. This holds particularly true for cardiovascular illnesses, such as heart failure (HF), where renal dysfunction often interplays with cardiac

conditions, propelling each other in a cyclic pattern of mutual exacerbation [1,2]. Moreover, as renal impairment progresses, it escalates the risk of cardiovascular diseases, intensifying the severity and complexity of patient conditions. The chronic kidney disease (CKD) patient population is highly susceptible to cardiovascular complications. A significant concern is the decline

in glomerular filtration rate, which intensifies the risk of cardiovascular illness and death, resulting in a generally poor prognosis [3,4]. This scenario becomes especially challenging with the advent of worsening renal function (WRF), which has emerged as a substantial hurdle to current treatment paradigms focused on prolonging patient survival. Over the years, advancements in pharmacological interventions designed to protect the kidneys have been relatively stagnant. This leaves an unmet clinical need for the development of novel drugs capable of strengthening renal protection [5].

Sacubitril/Valsartan (Sac/Val), which has gained substantial affirmation for its therapeutic benefits in HF, is being investigated for potential applications across other clinical areas. Its mechanism of action involves inhibiting the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, while concurrently enhancing the natriuretic peptide (NP) system [1]. The augmented NP system contributes to salutary cardiovascular and renal effects, serving as an ideal adjunctive therapeutic target to RAAS and sympathetic nervous system inhibition [6]. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) have been traditionally employed for renal protection. These agents mitigate the progression of renal diseases by lowering blood pressure and reducing proteinuria. As a result, they help preserve renal function and delay the progression of renal disease. However, the use of ACEI/ARB is fraught with potential pitfalls, such as decreased renal perfusion and elevated serum creatinine levels, which paradoxically exacerbate renal dysfunction [7]. This limitation has stymied the widespread application of these agents in renal disease management.

Interestingly, emerging research suggests that Sacubitril/Valsartan, which also possesses RAAS-inhibitory properties, may provide protective benefits to renal function, thereby slowing down the progression of renal disease [8,9]. Interestingly, emerging research suggests that Sacubitril/Valsartan, which also possesses RAAS-inhibitory properties, may provide protective benefits to renal function, thereby slowing down the progression of renal disease [10]. Therefore, the potential role of Sacubitril/Valsartan in renal protection remains inconclusive and necessitates further examination.

To address this clinical conundrum, the current meta-analysis aims to analyze existing randomized controlled trials (RCTs) to investigate the renoprotective effects of Sacubitril/Valsartan

compared to ACEI/ARB. It is anticipated that this systematic examination will enhance understanding of the comparative renoprotective capabilities of these agents and consequently facilitate the identification of new therapeutic strategies for managing renal diseases.

METHODS

Search strategy

In conducting this systematic review and subsequent meta-analysis, the criteria outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was followed [11]. To ensure a comprehensive literature search, four digital databases, namely PubMed, Embase, Web of Science, and Cochrane Library were searched, without imposing any temporal restrictions to ensure maximum inclusivity. The search was conducted on May 18, 2023. The syntax and terminologies necessary to accommodate the unique linguistic requirements of each database were used. In PubMed, specific search strategy included the following keywords: (sacubitril valsartan) or sacubitril or entresto or LCZ696 OR HU377 or (angiotensin receptor neprilysin inhibitor) or (neprilysin inhibitor). Language constraints were not applied to avoid potential biases and enhance the comprehensiveness of the findings. In addition to electronic search, a manual examination of the reference sections of pertinent articles was carried out to identify any additional relevant records, thereby ensuring that the search strategy was as exhaustive and inclusive as possible.

Inclusion criteria

They had to be prospective, randomized, controlled trials; control group should receive ACEI/ARB intervention, while study group should receive sacubitril/valsartan intervention; all studies must provide data on renal adverse events, either as secondary endpoints or adverse reactions; if a study involving the same population is published more than once, the study with the largest sample size or the most recently published study is selected.

Exclusion criteria

Duplicate publications; studies with incomplete, unclear, or inconsistent outcome data; studies of suboptimal quality or those lacking primary data; and case reports, opinion pieces, commentaries, and narrative reviews were excluded from this search.

Data extraction

The literature screening and data extraction processes were independently performed by two separate evaluators to minimize potential bias and errors. In case of disagreements arising during these processes, a resolution was sought through discussions between the involved reviewers. Where consensus was not reached, a third reviewer was consulted to mediate the dispute. The data fields extracted encompass: the authors of the study, the year of publication, the sample size, estimated glomerular filtration rate (eGFR), creatinine (Cr), ejection fraction (EF), New York Heart Association Functional Classification (NYHA), the outcome indicators measured, and any reported adverse reactions or events. In instances where the desired data was not included in the published report, the original investigators were contacted via email to solicit the unpublished data.

Quality assessment

The evaluation of the methodological quality of the studies incorporated in this review was undertaken using the Cochrane Collaboration's risk of bias tool [12]. This process was independently conducted by two reviewers who assessed several aspects, including the generation of random sequences, allocation concealment, blinding of participants and staff, handling of incomplete outcome data, selectivity in reporting, and the presence of any other potential biases. Each category was classified according to its associated risk of bias, as being of either high, unclear, or low risk. In cases where there was discordance in the assessments of the two reviewers, a consensus was reached via deliberation or, if necessary, by invoking the opinion of a third reviewer.

Statistical analyses

The heterogeneity between studies was assessed using chi-square statistics and quantified by the I^2 value. When the I^2 value was less than 50 % and the corresponding p -value was more than or equal to 0.10, it indicated that there was no significant heterogeneity. In such cases, the fixed-effect model was employed to compute the combined effect size. In contrast, when the I^2 value was equal to or more than 50 %, or the corresponding P -value was less than 0.10, it suggested significant heterogeneity. Subgroup analysis or sensitivity analysis was performed to identify and eliminate potential causes of heterogeneity. In the presence of statistical heterogeneity alone, the random-effects model was used to calculate the

combined effect size. Results were extracted from each study and presented as RR with 95 % CI for dichotomous variables. Publication bias was assessed for meta-analyses with 10 or more eligible studies using the symmetry of the funnel plot and Egger's test. All statistical tests were two-sided, and a P -value of less than 0.05 was deemed statistically significant. Data were analyzed using Stata version 17 (StataCorp, College Station, TX, USA).

RESULTS

Search results and study selection

Upon conducting an initial search of the electronic databases, a total of 986 relevant literature sources were identified. After eliminating redundant literature, reviewing titles and abstracts, and applying rigorous inclusion and exclusion criteria, a total of 23 relevant studies were identified. Subsequently, 12 studies were excluded from further analysis. Ultimately, a total of eleven articles were incorporated [9,10,13-21]. Figure 1 displays the process and outcomes of the literature screening.

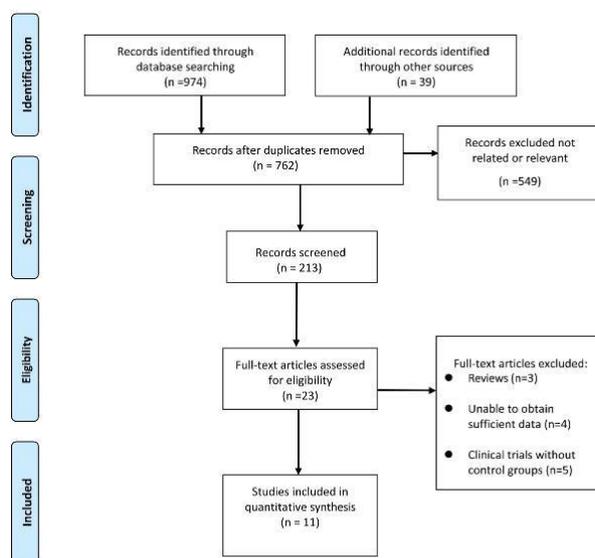


Figure 1: Selection process of included studies

Study characteristics

The studies included in this meta-analysis were conducted from 2015 to 2021, providing a comprehensive and recent insight into the topic. A total of 11 trials were analyzed, comprising a substantial sample size that ranged from 114 to 8442 patients. Across the studies, the patient's age was typically similar, ranging around the mid to late 60s, but with some variations. The percentage of male participants in the study population varied significantly, ranging from 48 %

to 86 %. The definition of renal function decline differed between studies but included criteria such as an increase in SCr, a percentage decrease in eGFR, end-stage renal disease, kidney failure death, and acute kidney injury. The inclusion criteria generally encompassed various stages of heart failure as classified by the NYHA, varying degrees of EF, and other specific conditions like hypertension, LV hypertrophy, LA enlargement, and high NT-proBNP levels. The follow-up duration in the included studies primarily ranged from weeks to months, with the longest follow-up period being 33.9 months and the shortest being 8 weeks. The control group drug was majorly Enalapril, but some studies also used Valsartan, Irbesartan, and Olmesartan (Table 1).

Results of quality assessment

An assessment of bias susceptibility was undertaken within multiple realms among the 11 incorporated studies for this meta-analysis. Five studies showcased a minimized bias risk across all sections, reflecting an elevated degree of methodological precision. However, it was identified that 20 % of the studies were susceptible to a heightened risk of bias in the areas of random sequence generation and blinding of participants. This raises the possibility that the potential for performance bias could have affected the outcomes of these studies. Moreover, an increased risk of bias was found due to selective reporting in approximately 15 % of the randomized controlled trials included. This implies that the risk of partial or selective outcome reporting may have influenced the cumulative findings of these studies (Figure 2).

Results of meta-analysis

The results from the meta-analysis suggest a significant renoprotective role of Sacubitril/Valsartan compared to ACEI/ARBs. The homogeneity among the included studies was satisfactory ($p = 0.188$, $I^2 = 26.9 \%$), therefore, a fixed effects model was used to consolidate effect sizes. Notably, Sacubitril/Valsartan was associated with a significantly lower risk of renal function deterioration compared to ACEI/ARBs (RR = 0.86, 95 % CI (0.78, 0.96), $p = 0.016$) (Figure 3).

Subgroup analysis based on the presence or absence of heart failure

The studies included in this analysis also showed good homogeneity, hence a fixed effects model was adopted. The results suggested that in patients with HF, Sacubitril/Valsartan significantly

reduced the risk of kidney function deterioration compared to ACEI/ARBs (RR = 0.84, 95 % CI (0.75, 0.94), $p = 0.011$). However, in non-HF patients, Sacubitril/Valsartan did not significantly decrease this risk (RR = 1.04, 95% CI (0.80, 1.37), $p = 0.66$) (Figure 4).

Subgroup analysis based on the type of heart failure

The included studies showed good homogeneity ($p > 0.05$). Thus, a fixed effects model was utilized. In patients with HFpEF, Sacubitril/Valsartan significantly reduced the risk of kidney function deterioration (RR = 0.87, 95 % CI (0.78, 0.97), $p = 0.026$). However, in patients with HFrEF, although Sacubitril/Valsartan was associated with a reduced risk, this reduction was not statistically significant (RR = 0.91, 95 % CI (0.75, 1.10), $p = 0.36$) (Figure 5).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
DAMMAN K et al. 2018	+	+	+	+	+	+	+
DESAI A S et al. 2019	+	+	+	+	+	+	+
HAYNES R et al. 2018	+	+	+	+	+	+	+
KANG D H et al. 2019	+	+	+	+	+	+	+
NCT01870739 2016	+	+	+	+	+	+	+
OUTSTEP-HF 2019	+	+	+	+	+	+	+
PIESKE B et al. 2021	+	+	+	+	+	+	+
SOLOMON S D et al. 2019	+	+	+	+	+	+	+
TSUTSUI H et al. 2021	+	+	+	+	+	+	+
VELAZQUEZ E J et al. 2019	+	+	+	+	+	+	+
VOORS A A et al. 2015	+	+	+	+	+	+	+

Figure 2: The quality assessment of included studies was conducted using the Cochrane Collaboration's risk of bias tool. In the figure, red indicates high risk, and green indicates low risk

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

Author	Year	No. of patients	Age (years)	Male (%)	Definition of renal function decline	Inclusion criteria	Follow-up duration	Control group drug
Tsutsui <i>et al</i>	2021	223	69.0±9.7 vs 66.7±10.9	192 (86)	SCr≥2.0 mg/dL	NYHA II-IV, EF≤35%	33.9 months	Enalapril
Pieske <i>et al</i>	2021	2566	73±8.4 vs 72±8.6	1265 (49)	25%↓eGFR decrease	NYHA II-IV, EF>40% HF, visible LV hypertrophy or LA enlargement, and accompanied by ↑NT-proBNP	24 weeks	Enalapril/Valsartan
Velazquez <i>et al</i>	2019	881	61(5171) vs 63(5472)	635 (72.1)	SCr≥0.5 mg/dL increase (≥44 μmol/L), 25% decrease in eGFR	Hemodynamically stable, ADHF and EF≤40%	8 weeks	Enalapril
Kang <i>et al</i>	2019	118	64.7±10.2 vs 60.5±11.8	72 (61)	SCr≥2.5 mg/dL	NYHA II -III and EF between 25-50% in functional MR	12 months	Valsartan
Solomon <i>et al</i>	2019	4822	72.7±8.3 vs 72.8±8.5	2317 (48)	End-stage renal disease, kidney failure death, or 50%↓eGFR	NYHA II-IV, EF≥45%	26 months	Valsartan
DESAI <i>et al</i>	2019	464	67.8±9.8 vs 66.7±8.5	355 (77)	35%↓eGFR, SCr≥ 0.5 mg/dL increase and 25%↓eGFR	Hypertension; EF≤40% NYHA I-III	12 weeks	Enalapril
OUTSTEP-HF Damman <i>et al</i>	2019 2018	621 8442	66.89±10.74 vs 63.8±11.5 vs 63.8±11.3	487(79) 6567 (78)	eGFR decrease or SCr increase End-stage renal disease, 50%↓eGFR or >30 mL/min/73m ² decrease	NYHA II and LVEF≤40% NYHA II-IV, EF≤40%	12 weeks 27 months	Enalapril Enalapril
Haynes <i>et al</i>	2018	414	62.0±14.1 vs 63.6±13.4	298 (72)	25%↓eGFR	eGFR≥45 and <60 mL/min/1.73 m ² and uACR> 20; or eGFR≥20 and <45mL/min/1.73 m ²	12 months	Irbesartan
NCT01870739	2016	114	60.5±7.8 vs 59.2±13.1	77 (68)	Acute kidney injury	SBP≥140 mmHg and < 180 mmHg and elevated brachial artery pressure (≥50 mmHg)	52 weeks	Olmesartan
Voors <i>et al</i>	2015	301	70.9±9.4 vs 71.2±8.9	152 (57)	SCr≥0.5 mg/dL or >25% increase	NYHA II-III, HFpEF, EF>45%	3 months	Valsartan

Note: eGFR, estimated glomerular filtration rate; SCr, serum creatinine; uACR, urine albumin to creatinine ratio; SBP, systolic blood pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; ADHF, acute decompensated heart failure; MR, mitral regurgitation. ↑, increase; ↓, decrease

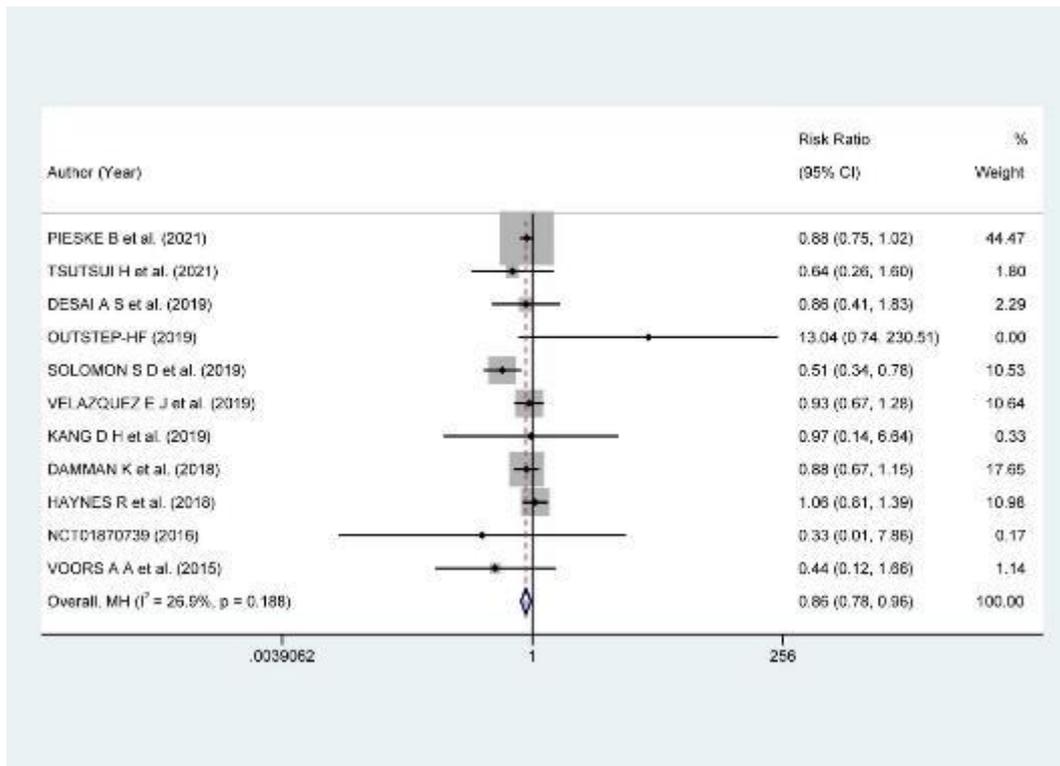


Figure 3: Meta-analysis of the renoprotective effects of Sacubitril/Valsartan compared to ACEI/ARB

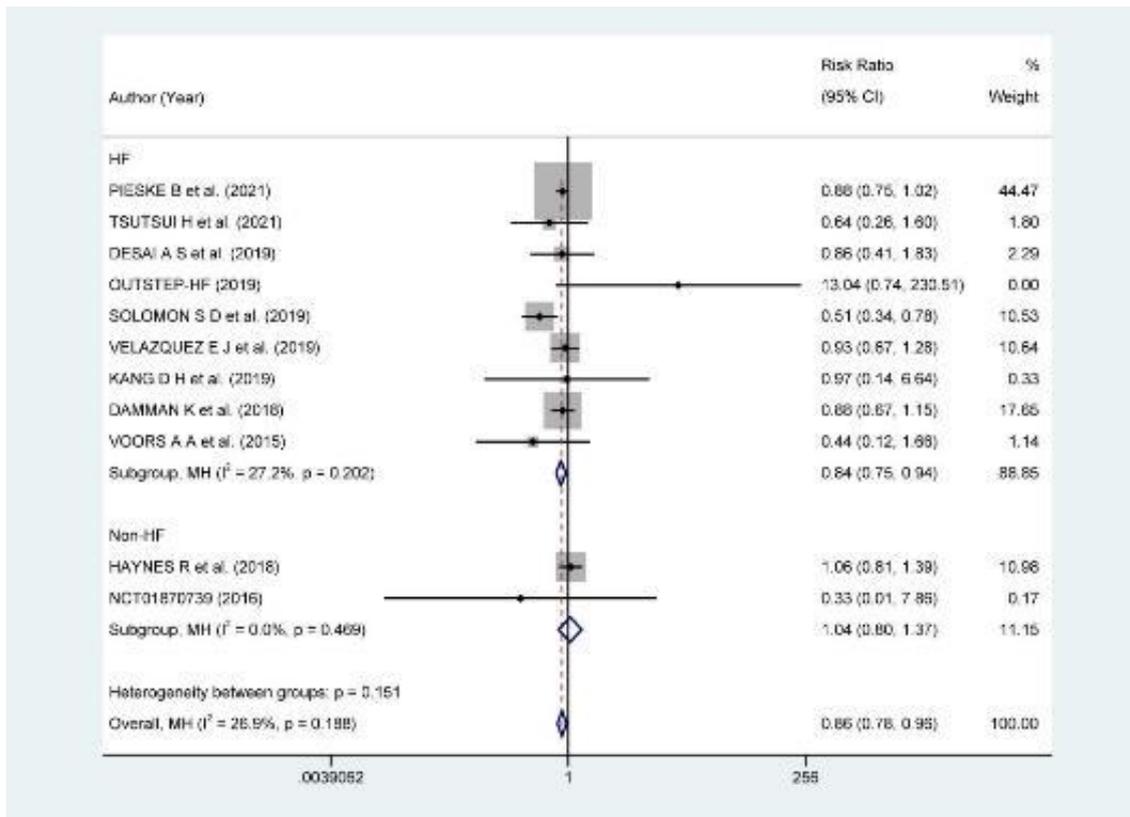


Figure 4: Subgroup meta-analysis of the renoprotective effects of Sacubitril/Valsartan compared to ACEI/ARB based on the presence or absence of Heart Failure

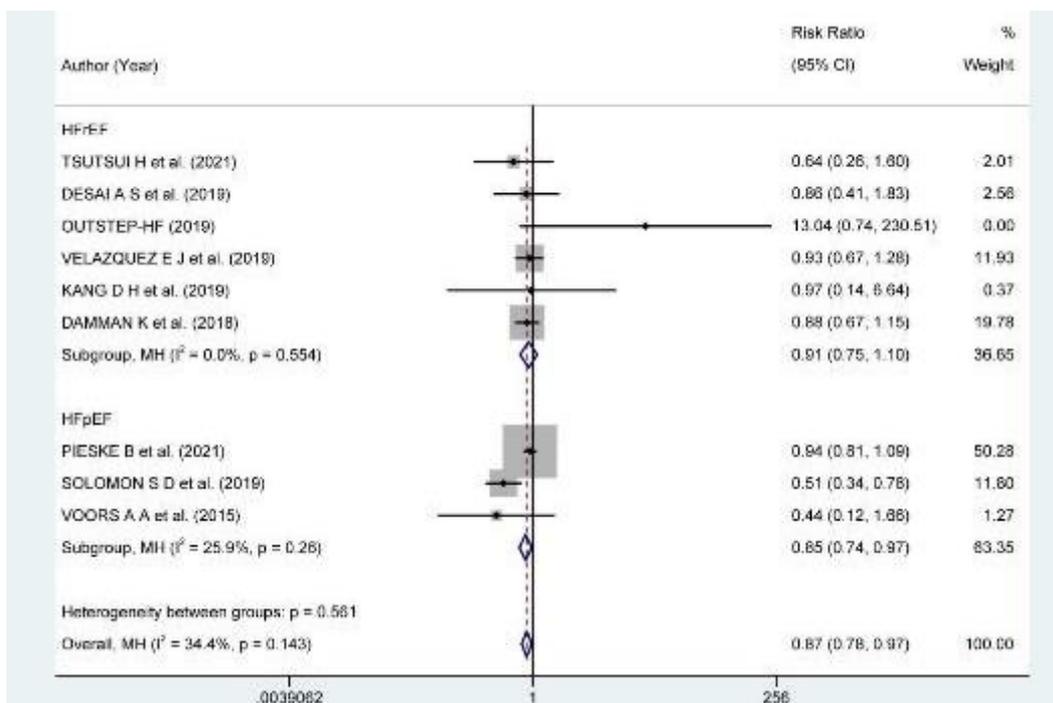


Figure 5: Subgroup meta-analysis of the renoprotective effects of Sacubitril/Valsartan compared to ACEI/ARB based on the type of Heart Failure

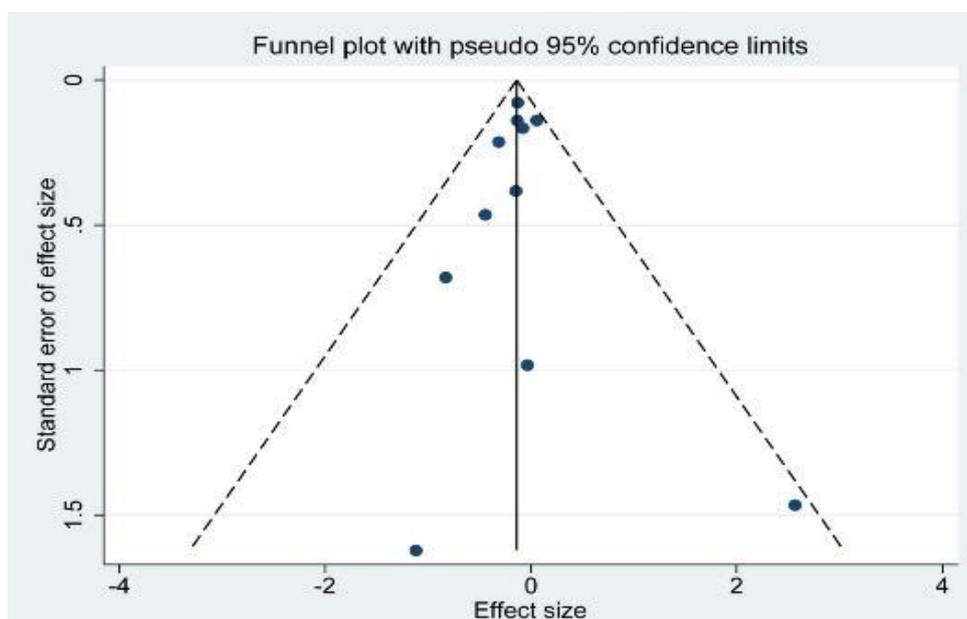


Figure 6. Funnel plot for publication bias in all included studies

Publication bias

The funnel plots generated from the gathered studies demonstrated symmetry, indicating no substantial publication bias (Figure 6). Furthermore, Egger’s linear regression test, conducted for various variables, did not reveal any significant publication bias ($p > 0.05$ for all variables). This supports the robustness of this meta-analytic findings and enhances the reliability and validity of the results.

DISCUSSION

Sacubitril/Valsartan (Sac/Val) possesses a unique mechanism of action that capitalizes on the beneficial effects of natriuretic peptides (NP) and angiotensin receptor blockers. The dual-action model of Sac/Val enhances the levels of NP, which plays a crucial role in regulating intravascular volume in response to high blood volume and pressure. These peptides promote

natriuresis (excretion of sodium in urine) and vasodilation. This effect leads to an increase in the second messenger cyclic guanosine monophosphate (cGMP), which subsequently triggers the dilation of afferent arterioles [1]. Consequently, the estimated glomerular filtration rate (eGFR) is improved, resulting in significant enhancement of renal blood flow and overall kidney function. Simultaneously, Sac/Val acts by inhibiting the RAAS, a crucial pathway involved in renal disease progression and cardiovascular disorders. Valsartan, an integral part of Sac/Val, is an angiotensin receptor blocker that specifically blocks angiotensin II type I receptors [22]. This blockade action disrupts the adverse effects of angiotensin II, which includes vasoconstriction, salt and water reabsorption, and aldosterone release. By impeding angiotensin II-dependent aldosterone release, Sac/Val effectively minimizes fluid retention and the deleterious effects of aldosterone on the cardiovascular system [23,24].

A meta-analysis suggested that a combination of neprilysin and RAAS inhibitors protects kidney function more effectively than ACEI/ARB [25]. Preclinical studies [6,7] on Sacubitril/Valsartan (Sac/Val) have indicated its potential to ameliorate kidney function in chronic kidney disease (CKD). These studies suggest that Sac/Val has the ability to attenuate oxidative stress, inflammation, and fibrosis markers, which are associated with CKD. When compared to RAAS inhibitors, Sac/Val delayed the changes in renal function in nephrectomized rats, leading to increased diuresis, decreased proteinuria, and a more substantial reduction in the histological markers associated with CKD progression. Clinical trials such as PARAGON-HF [16] and PARAMOUNT [13] have provided evidence of the renal benefits associated with Sacubitril/Valsartan (Sac/Val) compared to Valsartan alone in heart failure patients with heart failure with preserved ejection fraction (HFpEF). These trials demonstrated a significant reduction in the risk of renal events with Sac/Val treatment. In contrast, the UK HARP-III trials [10] evaluated the medium-term effects of Sac/Val on kidney function and its impact on cardiovascular biomarkers but found no significant differences between Sac/Val and irbesartan in renal protection among CKD patients, with 8 % heart failure at baseline.

This study revealed that compared to ACEI/ARB, Sac/Val offered significant renal protection, with a relative risk reduction of 11 % in the decline of renal function. Subgroup analysis revealed that Sacubitril/Valsartan (Sac/Val) led to a 13 % relative risk reduction in renal function decline in

patients with heart failure (HF). However, in patients without HF, its effects were comparable to those of ACE inhibitors/angiotensin receptor blockers (ACEI/ARBs). Sac/Val resulted in a 15 % relative risk reduction in renal function decline in HFpEF patients, whereas the difference was not statistically significant in HFrEF.

The renal protective effects of Sac/Val might be primarily due to its efficacy in improving cardiac function in HF patients, reflecting the different determinants of renal disease progression in non-HF (especially CKD) and HF populations. Several studies suggest that worsening renal function (WRF) may have a weaker association with mortality in heart failure with preserved ejection fraction (HFpEF), compared to those with mid-range ejection fraction (mid-EF) and reduced ejection fraction (HFrEF) [26]. This implies that the association between WRF and mortality may vary across different ejection fraction categories in heart failure. In HFpEF, renal dysfunction may not directly reflect the worsening state of heart failure. Conversely, in HFrEF, renal dysfunction may be closely associated with progressive HF, and while it may be less frequent, it is associated with significantly higher risk once it occurs [27].

Limitations of this study

This meta-analysis does have certain limitations that should be acknowledged. First, the analysis was constrained by the availability of data, with only 11 studies meeting the inclusion criteria. The primary clinical trials that were considered in this analysis were conducted in patients with heart failure (HF), with renal parameters as secondary endpoints. It is important to note that these trials may not fully illuminate the complete renal protective potential of Sacubitril/Valsartan (Sac/Val). Further studies specifically designed to evaluate the renal effects of Sac/Val as a primary outcome in different patient populations, including those without HF, are warranted to provide a more comprehensive understanding of its renal protective properties. Secondly, the non-HF subgroup analysis was limited due to only two studies fitting inclusion criteria in this study. This resulted in a small participant pool and a narrow spectrum of disease types studied. In contrast, the heart failure (HF) subgroup included a larger patient population, which may introduce bias in the overall findings of this analysis. It is important to consider this potential bias when interpreting the results, as the larger HF subgroup might have had a greater influence on the overall conclusions. Future studies should aim to include a more balanced representation of different patient populations to minimize such biases and provide a more accurate assessment of the renal

protective potential of Sacubitril/Valsartan (Sac/Val). Lastly, the dosage and timing of the medication administration in most studies were largely determined by HF treatment protocols, which might not align with the optimal therapeutic parameters for renal protection. The use of ACEI/ARB for renal preservation often requires higher dosages, and as such, the administration as per HF treatment protocols may not reach the effective therapeutic dose and timing for kidney treatment.

CONCLUSION

This systematic review and meta-analysis suggest that Sac/Val confers substantial renoprotective effect when compared with ACEI/ARB, particularly among heart failure patients. However, more extensive research is required to further elucidate the full potential of Sac/Val as a nephroprotective agent.

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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