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Systematic Review of Cardiovascular Benefits and Safety of Sacubitril-Valsartan in End-Stage Kidney Disease

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Introduction: Patients with end-stage kidney disease (ESKD) frequently develop heart failure, contributing to high mortality. Limited data exist on cardiovascular benefits and safety of sacubitril-valsartan in this population. Our systematic review aims to evaluate the efficacy and safety of sacubitril-valsartan versus standard care in patients with ESKD who are on dialysis.

Methods: We conducted a search in Embase, MEDLINE, and Cochrane databases to identify relevant studies and assessed outcomes using random-effect model and generic inverse variance approach.

Results: Analysis of 12 studies involving 799 eligible patients with ESKD revealed improvement in left ventricular ejection fraction (LVEF) with sacubitril-valsartan compared to a control group with pooled mean difference (MD) 6.58% (95% confidence interval [CI]: 1.86, 11.29). LVEF significantly improved in patients with LVEF <50% (heart failure with reduced ejection fraction [HFrEF] and heart failure with moderately reduced ejection fraction [HFmrEF]) with MD 12.42% (95% CI: 9.39, 15.45). However, patients with LVEF >50% (heart failure with preserved ejection fraction [HFpEF]) did not exhibit statistically significant effect, MD 2.6% (95% CI: 1.15, 6.35). Sacubitril-valsartan significantly enhanced LVEF in patients with HFrEF, with MD 13.8% (95% CI: 12.04, 15.82). Safety analysis indicated no differences in incidence of hyperkalemia (pooled odds ratio [OR] 0.72; 95% CI: 0.38, 1.36) or hypotension (pooled risk ratio [RR] 1.03; 95% CI: 0.36, 2.98). No cases of angioedema were reported. However, safety analysis relies on evidence of limited robustness due to the observational nature of the studies.

Conclusion: Our systematic review suggests that sacubitril-valsartan benefits patients with ESKD with HFrEF and HFmrEF by improving LVEF without increasing the risk of hyperkalemia, hypotension, or angioedema compared to standard care. However, safety analysis based on observational studies inherently has limitations for establishing causal relationships.

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ESKD affects a significant number of individuals in the United States, with nearly 786,000 people requiring renal replacement therapy.[1] Patients with ESKD face numerous challenges, including an elevated risk of cardiovascular complications.[2] Among these complications, heart failure plays a prominent role and is a major contributor to the high mortality rates observed in this population. The prevalence of heart failure in patients with ESKD is alarmingly high, ranging from 20% to 50% depending on the population studied and the diagnostic criteria used, surpassing that of the general population.[3–5] The coexistence of ESKD and heart failure creates a complex clinical scenario, posing substantial challenges for both patients and health care providers.

The etiology of heart failure in patients with ESKD is multifactorial.[6] Traditional risk factors such as hypertension, diabetes mellitus, and ischemic heart disease are prevalent in this population and contribute to the development and progression of heart failure.[7] In addition, nontraditional risk factors, including uremic toxins, volume overload, anemia, and mineral and bone disorders, further contribute to the pathophysiology of heart failure in patients with ESKD.[8] The presence of heart failure in patients with ESKD has significant

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implications for their prognosis and outcomes.[9] It is well-established that heart failure in this population is associated with a higher risk of hospitalizations, cardiovascular events, and mortality.[10] Furthermore, patients with ESKD who have heart failure often experience reduced quality of life, increased health care utilization, and higher healthcare costs.[11,12] Consequently, the management of heart failure in patients with ESKD is crucial to improve their outcomes and overall well-being.

In recent years, sacubitril-valsartan, a novel therapeutic agent, has emerged as a promising treatment option for heart failure.[13,14] It combines sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor blocker. Sacubitril-valsartan has demonstrated superior efficacy compared to traditional renin-angiotensin-aldosterone system inhibitors in patients with HFrEF in the general population.[14,15] The PARADIGM-HF trial has provided compelling evidence for the clinical benefits of sacubitril-valsartan in reducing mortality and hospitalizations among patients with HFrEF.[14] Consequently, this therapeutic approach has been incorporated into all major guidelines[16,17] and plays a fundamental role in the management of HFrEF. However, the use of sacubitril-valsartan in patients with ESKD who are on dialysis remains relatively unexplored. These patients are often excluded from clinical trials due to their unique characteristics and the challenges associated with conducting research in this population. As a result, the existing evidence regarding the efficacy and safety of sacubitril-valsartan in patients with ESKD is limited, creating a critical knowledge gap that needs to be addressed. Therefore, we conducted a systematic review and meta-analysis adhering to methodological standards to examine the existing literature and address the following clinical question: What is the efficacy and safety of sacubitril-valsartan compared to conventional treatment patients with ESKD who are on dialysis?

METHODS

This systematic review was conducted in accordance with a predefined protocol that was registered at the International Prospective Register of Systematic Reviews (ID: CRD42023393793. The reporting of this review follows the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2021 checklist (Supplementary Table S1), ensuring transparency and completeness in reporting the review process and findings.[18]

Eligibility criteria

Randomized clinical trials and observational studies were eligible for inclusion if they reported efficacy and/or safety of sacubitril-valsartan in patients with ESKD who are on dialysis, including peritoneal dialysis (PD) and/or hemodialysis (HD). Efficacy was defined as follows: (i) change of LVEF, (ii) heart failure hospitalizations, (iii) all-cause hospitalizations, (iv) all-cause mortality, and (v) cardiovascular mortality. Safety was defined as follows: (i) hypotension, (ii) hyperkalemia, and/or (iii) angioedema. We excluded studies that reported advanced kidney disease or chronic kidney disease with no separate analysis of patients with ESKD. We excluded case reports, reviews, thesis, books, editorials, author responses, letters, comments, conference abstracts, guidelines, letters, notes, book chapters, surveys, protocols/registries (ongoing studies) with no available results.

Information sources and search strategies

A comprehensive search of several databases was performed on January 30, 2023. No date limits for the search were applied. Animal studies were excluded. No language restrictions were applied. Databases searched (and their content coverage dates) were Ovid MEDLINE(R) (1946+ including epub ahead of print, in-process, and other nonindexed citations), Ovid Embase (1974+), Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Cochrane Database of Systematic Reviews (2005+), Web of Science Core Collection via Clarivate Analytics (1975+), and Scopus via Elsevier (1970+).

The design and execution of the search strategies were a collaborative effort involving a medical librarian and the study investigators. Controlled vocabulary, along with the inclusion of relevant keywords, was employed to enhance the precision of the searches. Detailed information regarding the specific search terms utilized and their method of combination is provided in Supplementary Table S2.

Study selection

Two independent reviewers (MC and PK) conducted a thorough screening of all retrieved references to determine their inclusion based on the study title and abstract. Full-text articles were obtained unless both reviewers unanimously agreed that an abstract did not meet the eligibility criteria. Each full-text report was independently assessed to determine its final inclusion in the study. In the event of any disagreements regarding the inclusion of full-text articles, a consensus was reached through discussion. To measure the agreement on the inclusion of full-text articles, we employed the κ statistic.

Data collection and analysis

Data extraction was performed using a standardized form to capture relevant information from the included studies. This included recording study identifiers such

as author names, publication locations, and years. We also extracted study characteristics such as study design, sample size, and inclusion/exclusion criteria. Participant characteristics, including demographic data, comorbidities, type of heart failure and its definition, as well as the type of dialysis, were documented. Detailed descriptions of the intervention, including the dose and duration of sacubitril-valsartan administration, were recorded. Lastly, we collected data on study outcomes of interest, such as changes in LVEF, heart failure hospitalizations, all-cause hospitalizations, all-cause mortality, cardiovascular mortality, and safety outcomes (hypotension, hyperkalemia, and angioedema). Two reviewers (MC and PK) independently performed the data extraction, and any discrepancies were resolved through consensus. In cases where consensus could not be reached, a third reviewer adjudicated the disagreement. To ensure the completeness of data, we also reached out to the authors of the studies to request any missing or additional information.

OUTCOMES

The outcomes of interest in this systematic review were the MD in LVEF between baseline and after sacubitril-valsartan treatment. In addition, we assessed the OR or RR for various outcomes, including heart failure hospitalization, hospitalization due to all causes, all-cause mortality, cardiovascular mortality, hypotension, hyperkalemia, and angioedema, comparing the sacubitril-valsartan group to the control group. For the classification of heart failure subtypes, we followed the criteria outlined in the American Heart Association/American College of Cardiology guidelines.[19] This included categorizing heart failure patients as having HFrEF defined as LVEF $<40\%$, HFmrEF as LVEF of 40% to 50%, and HFpEF as LVEF $>50\%$. By utilizing these outcome measures and classification criteria, we aimed to assess the effectiveness and safety of sacubitril-valsartan in treating heart failure patients with different ejection fraction profiles compared to the control group.

Data synthesis and statistical analysis

We extracted mean and SD for continuous outcomes directly or calculated from relevant reported statistical results. Because some of the included studies reported medians with interquartile ranges instead of mean and SD, the approach recommended by Wan *et al.*[20] and Luo *et al.*[21] was used to estimate mean and SD from medians and interquartile ranges. We did not impute missing data. Multiple reports from the same cohort were never included in the same analysis.

Effect estimates were derived and consolidated using a random-effect model and the generic inverse variance approach. The random-effect model was chosen to account for potential heterogeneity across the included studies. The generic inverse variance approach was applied to calculate the pooled MD, OR, RR, and their corresponding CIs for the outcomes of interest. This statistical analysis aimed to provide a comprehensive and robust assessment of the efficacy and safety of sacubitril-valsartan in patients with ESKD who are on dialysis.

Because we aimed to analyze the change of continuous variables (LVEF) at baseline and after the intervention, we used the approach that incorporates this specific study design. We used the generic inverse variance method to calculate MD. In cases where studies reported continuous outcomes at baseline and after a specific follow-up time, a single measurement of MD was created by subtracting the final mean from the baseline mean. If SD for the changes were not available, we employed approaches recommended by Follmann *et al.*[22] and by Abrams *et al.*[23] to impute the missing SD values. To estimate the correlation coefficient, we relied on studies that provided considerable details on the data. In situations where either the baseline or final SD or change of SD was unavailable, we conducted sensitivity analysis by testing different correlation coefficients.

In addition, the I^2 statistic was calculated to assess the heterogeneity of effect size among the included studies. The I^2 statistic quantifies the percentage of total variation across studies that is due to heterogeneity rather than chance. A value greater than 50% suggests substantial heterogeneity, a range of 25% to 50% indicates moderate heterogeneity, and a value below 25% suggests low heterogeneity. By evaluating the I^2 statistic, the degree of heterogeneity among the studies included in the meta-analysis was assessed. To explore potential sources of heterogeneity, we performed prespecified subgroup analyses, including comparisons of LVEF changes in patients with ESKD with baseline LVEF $<50\%$ versus $>50\%$. Sensitivity analyses were conducted by serially excluding each study to evaluate the impact of individual studies on the pooled estimates (RR, OR, or MD). Forest plots were used to visualize variability within studies and incorporate it into the standard meta-analysis statistics.

All statistical analyses, including the calculation of the I^2 statistic and the construction of the funnel plot, were performed using RevMan software (version 5.4.1; Cochrane, London, United Kingdom). These statistical techniques allowed for the evaluation of heterogeneity among studies and the potential impact of publication bias on the overall results of the meta-analysis.

Risk of bias assessment

Risk of bias assessment was conducted by 2 independent reviewers (MC and PK) using the Cochrane Collaboration risk assessment tools[24] specifically designed for nonrandomized studies. Any disagreements that arose during the assessment process were resolved through consensus. To evaluate potential publication bias, we assessed funnel plots for asymmetry. Funnel plots provide a graphical representation of study precision against the effect size and can help identify potential publication bias if there is a skewed distribution of studies.

Grading the quality of evidence studies

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[25] approach to evaluate and assess the overall quality of evidence for each outcome included in our study. The GRADE approach is a widely recognized and accepted framework for systematically assessing the quality of evidence in systematic reviews and meta-analyses. It takes into account several factors, including study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias, to determine the overall quality of evidence. By applying the GRADE approach, we were able to provide an objective and transparent evaluation of the certainty and reliability of the evidence supporting the outcomes examined in our study. The GRADE assessment allows readers to gauge the confidence they can place in the findings and the subsequent strength of the recommendations based on the available evidence.

RESULTS

Our search strategy yielded a total of 122 potentially relevant articles. After a thorough screening process, 86 articles were excluded based on predetermined criteria, leaving us with 36 articles for full-length review. During this stage, 24 articles were further excluded because they did not meet our inclusion criteria. Ultimately, a total of 12 studies involving 799 patients with ESKD met the eligibility criteria and were included in the final analysis (Figure 1). The agreement between the reviewers involved in the article screening process was high, with a κ statistic of 0.82, indicating a

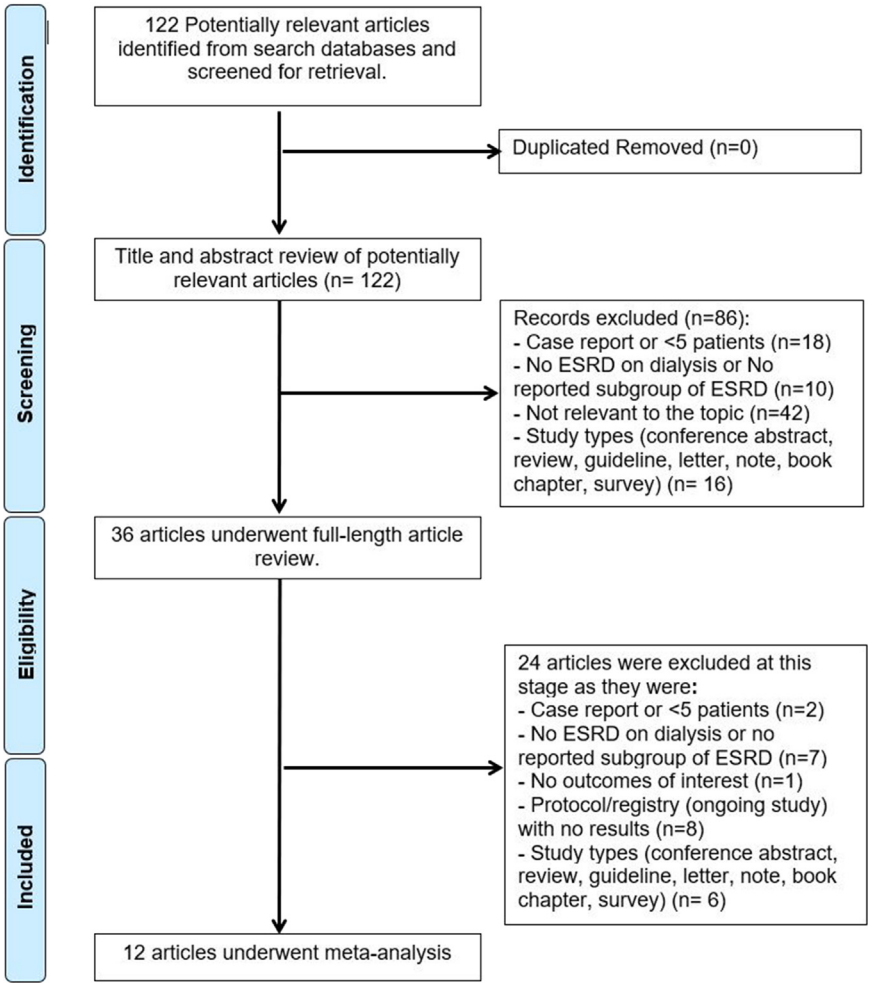

Figure 1. Search methodology and selection process. ESRD, end-stage renal disease.

strong level of consensus. For further details regarding the characteristics of the included studies, please refer to Table 1.

Change of LVEF in patients with ESKD

Change of LVEF was evaluated in a total of 9 studies.[13,26–29,31–33,36] The duration of follow-up ranged from 3 to 18 months (refer to Table 1 for details). All of these studies were before and after studies and reported LVEF at baseline and after the intervention in the same group of patients. Mean change of LVEF was obtained by subtracting the postintervention mean from the baseline mean. However, none of the studies provided sufficient information to calculate the SDs for the changes in LVEF. Thus, we employed an approach recommended by Follmann *et al.*[22] and Abrams *et al.*[23] to impute the SD. The correlation coefficient was calculated based on the study by Hsiao *et al.*,[30] which reported all the necessary parameters for the calculation (Correlation coefficient = 0.24). However, it is worth noting that Hsiao *et al.*[30] included both patients with advanced CKD and patients with ESKD without a separate analysis of the change in LVEF, specifically in patients with ESKD. Therefore, we also conducted sensitivity analysis using different correlation coefficients; however, the difference in effect estimates derived from these correlation coefficients was minimal.

Overall, the meta-analysis of the change in LVEF among patients with ESKD showed a statistically significant improvement of 6.58% (95% CI: 1.86, 11.29; $P = 0.006$). However, there was a high level of heterogeneity ($I^2 = 98\%$) among the included studies (Figure 2). To explore the sources of heterogeneity, we performed a prespecified subgroup analysis based on the average LVEF at baseline. As shown in Figure 3, there was a significant difference between the groups with LVEF >50% and LVEF <50% ($P < 0.0001$). The pooled change in LVEF demonstrated a significant improvement with a MD of 12.42% (95% CI: 9.39, 15.45; $P < 0.00001$) among patients with LVEF <50%. Although the statistical heterogeneity was $I^2 = 61\%$ ($P = 0.05$), indicating a moderate level of heterogeneity, all studies showed a clinical improvement in LVEF.

For patients with LVEF >50%, the pooled effect size was not statistically significant, with an MD of 2.6% (95% CI: −1.15, 6.35; $P = 0.17$), and there was a high level of heterogeneity. It is noteworthy that Wang *et al.*[32] and Zhao *et al.*[36] included both patients with HFrEF and those with HFpEF without separate analysis of outcomes. However, because most included patients had LVEF >50%, the average LVEF at baseline was greater than 50% in both studies. Sensitivity analysis by removing these 2 studies did not significantly affect the MD and level of heterogeneity.

Change of cardiac function in patients with ESKD with HFpEF and HFrEF

In terms of cardiac function, only 3 studies[13,26,33] provided a separate analysis for patients with HFrEF. The results demonstrated a significant improvement in LVEF with sacubitril-valsartan treatment in this patient population, with a pooled MD of 13.93% (95% CI: 12.04, 15.82; $P < 0.00001$). There was low and statistically nonsignificant heterogeneity ($I^2 = 20\%$; $P = 0.29$) among these studies (Figure 4a).

On the other hand, when assessing patients with HFpEF, only 3 studies[28,29,31] provided sufficient information for analysis. The change in LVEF in this subgroup was minimal and not statistically significant. The pooled MD was 0.78% (95% CI: 0.02, 1.53; $P = 0.04$) (Figure 4b). Notably, there was significant heterogeneity among these 3 studies: Fu *et al.*[28] and Guo *et al.*[29] did not show a significant difference, whereas Ma *et al.*[31] reported a contradictory finding with an improvement in LVEF.

Unlike LVEF, which is widely used to quantify systolic function, there is no single criterion standard for diagnosing diastolic dysfunction using echocardiography. Various echocardiographic parameters can be assessed to evaluate diastolic function, including measures such as E/A ratio, deceleration time, E′ velocity, E/E′ ratio, and others. In the analysis of cardiac dysfunction and symptomatic improvement in patients with HFpEF, we attempted to investigate these other echocardiographic parameters. However, due to the considerable heterogeneity in the definition and reporting of these parameters across the included studies, it was not feasible to perform a pooled quantitative analysis for the change in these parameters of cardiac function in patients with HFpEF.

Heart failure hospitalization, all-cause hospitalization and all-cause mortality

Regarding heart failure hospitalizations, only the studies by Hsiao *et al.*[30] and Niu *et al.*[26] provided data that could be included in the meta-analysis. The pooled OR for heart failure hospitalizations was 1.45 (95% CI: 0.48, 4.42; $P = 0.51$), with moderate heterogeneity observed ($I^2 = 66\%$; $P = 0.08$) (Figure 5). For other outcomes, such as all-cause hospitalizations and all-cause mortality, the available data reported by the included studies was insufficient for conducting a meta-analysis. Hsiao *et al.*[30] reported no significant difference in all-cause mortality between patients on sacubitril-valsartan and those on angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers, with a hazard ratio of 0.93 (95% CI: 0.38, 2.31; $P = 0.844$) in patients on dialysis. Similarly, Niu *et al.*[26] reported no significant difference in all-cause hospitalizations, OR of 0.77 (95% CI: 0.25, 2.37; $P = 0.65$).

Table 1. Study Characteristics

First Author/Year of Publication	Country of the study	Year of Study	Study Design	Dose of Sacubitril /Valsartan	Follow-up Time	Number of Patients	Age, yrs	Male, *n* (%)	Dialysis Modality	Type of Heart Failure and LVEF of Included Patients	Comorbidities/ Medications (*n*)
Niu *et al.*,[26] 2022	Taiwan	2019	Case-control study	97 mg/103 mg twice daily	12 mo	49	Mean 60.96 (SD 12.09)	32 (78.5%)	HD (23 patients) and PD (16 patients)	HFrEF, LVEF <40%	Hypertension: $n = 23$, Diabetes: $n = 12$, CAD: $n = 13$. B-blocker: $n = 16$, CCB: $n = 5$, ACEI/ARB: $n = 0$, MCA: $n = 2$
Feng *et al.*,[27] 2022	China	2019–2020	Prospective, observational, self-controlled study	50–100 mg twice a day	18 mo	11	Median 50 (IQR 39–72)	5 (45%)	HD	HFrEF and HFmrEF, LVEF 40% and 40–50%	N/A
Fu *et al.*,[28] 2021	China	2018–2019	Retrospective, observational self-controlled study	50–100 mg twice a day	3–12 mo	21	Median 55 (IQR 38–61)	14 (67%)	PD	HFpEF, LVEF >50%	Hypertension: $n = 21$, Diabetes: $n = 5$, CAD: $n = 21$ B-blocker: $n = 11$, CCB: $n = 21$, ACEI/ARB: $n = 6$, Diuretic: $n = 10$
Guo *et al.*,[29] 2022	China	2019–2021	Retrospective, observational self-controlled study	200 mg twice a day	3–12 mo	247	Mean 45.8 (SD 13.7)	154 (62%)	HD	HFpEF, LVEF >50%	Hypertension: $n = 23$, Diabetes: $n = 12$, CAD: $n = 13$ B-blocker: $n = 185$, CCB: $n = 213$, ACEI/ ARB: $n = 221$, MCA: $n = 12$
Hsiao *et al.*,[30] 2022	Taiwan	2016–2018	Retrospective, observational cohort study	N/A	Period from the cohort entry date until the first occurrence of an outcome, day of mortality, the last outpatient visits or discharge date, the end of the study period or at 12th month, whichever occurred first	618	N/A	N/A	Nonspecified	HFrEF, LVEF<40%	N/A
Lee *et al.*,[13] 2020	Korea	2017–2019	Retrospective, observational self-controlled study	90 ± 43 mg/day at baseline and 123 ± 62 mg/day at last follow-up	Median 132 days, (IQR 77–132)	23	Mean 60 (SD 17)	20 (85%)	HD and PD	HFrEF, LVEF<35%	Hypertension: $n = 18$, Diabetes: $n = 89$, CAD: $n = 21$ B-blocker: $n = 23$, ACEI/ ARB: $n = 23$
Ma *et al.*,[31] 2023	China	2018–2021	Retrospective, observational cohort study	50 mg/time, twice/day, and gradually increased to 100 mg/time, twice/day	6–12 mo	99	Mean 52 (SD 13)	67 (56%)	PD	HFpEF, LVEF >50%	Diabetes: $n = 23$ B-blocker: $n = 40$, CCB: $n = 45$, Diuretic: $n = 35$
Wang *et al.*,[32] 2022	China		Prospective, observational, self-controlled study	50–100 mg/day	12 wks	18	Mean 53.6 (SD 14.5)	15 (83%)	HD	HFpEF and HFrEF, LVEF in 1 patient <40%, 3 patients 40%–50%, 15 patients >50%	CAD: $n = 2$, B-blocker: $n = 18$, CCB: $n = 16$, ACEI/ARB: $n = 18$
Lihua *et al.*,[33] 2021	China	2018–2019	Prospective, observational, self-controlled	135–308 mg /day	12 mo	110	Mean 52 (SD 14.8)	65 (59%)	HD	HFrEF, LVEF <40%	CAD: $n = 6$, B-blocker: $n = 41$, CCB: $n = 105$, ACEI/ARB: $n = 102$, MCA: $n = 12$, Diuretic: $n = 6$

(Continued on following page)

Table 1. (Continued) Study Characteristics

First Author/Year of Publication	Country of the study	Year of Study	Study Design	Dose of Sacubitril /Valsartan	Follow-up Time	Number of Patients	Age, yrs	Male, *n* (%)	Dialysis Modality	Type of Heart Failure and LVEF of Included Patients	Comorbidities/ Medications (*n*)
Wen *et al.*,[34] 2022	China	2020–2021	Retrospective, observational self-controlled study	50–200 mg/day	6 mo	54	Mean 50.9 (SD 14.6)	29 (53%)	HD	HFrEF, LVEF <40%	B-blocker: $n = 51$
Zhang *et al.*,[35] 2022	China	2020–2021	Retrospective, observational self-controlled study	100 mg twice a day	7 d	47	Mean 45.9 (SD 12.4)	28 (60%)	PD	Nonspecified	Hypertension: $n = 42$, Diabetes, $n = 10$ ACEI/ARB: $n = 27$, Diuretic: $n = 12$
Zhao *et al.*,[36] 2022	China	2019–2021	Retrospective, observational cohort study	100 mg twice a day	3 mo	122	Mean 49.13 (SD 15.4)	75 (75%)	HD	Nonspecified	Hypertension: $n = 69$, Diabetes: $n = 17$, CAD: $n = 13$

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; d, day; HD, hemodialysis; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection; IQR, interquartile range; LVEF, left ventricular ejection fraction; MCA, mineralocorticoid antagonist; mo, month; PD, peritoneal dialysis.

Safety of sacubitril-valsartan in patients with ESKD

The safety of sacubitril-valsartan in patients with ESKD was assessed in several studies. Regarding the development of hyperkalemia, 8 studies provided data for analysis. The proportion of patients with ESKD who developed hyperkalemia while taking sacubitril-valsartan was 0.076 (48 of 545). In addition, 3 studies compared the number of hyperkalemia events between the sacubitril-valsartan and the control group, yielding a pooled OR of 0.72 (95% CI: 0.38, 1.36; $P = 0.31$), with no heterogeneity observed ($I^2 = 0\%$; $P = 0.94$) (Figure 6a).

In terms of hypotension as a safety event, 5 studies reported on its development. The proportion of patients who developed hypotension while taking sacubitril-valsartan was 0.63 (20 of 275). Only 2 studies compared the number of hypotension events between the sacubitril-valsartan group and the control group, resulting in pooled RR of 1.03 (95% CI: 0.36, 2.98; $P = 0.95$), with no heterogeneity observed ($I^2 = 0\%$; $P = 0.55$) (Figure 6b).

None of the 5 included studies, comprising a total of 426 patients with ESKD receiving sacubitril-valsartan, reported the development of angioedema as a safety event.

Effect of dialysis modalities

To assess the potential impact of dialysis modality on changes in LVEF and safety events among patients with ESKD receiving sacubitril-valsartan, we conducted subgroup analyses on studies that specifically included patients on HD or PD. Three studies by Fu *et al.*,[28] Ma *et al.*,[31] and Zhang *et al.*[35] exclusively enrolled patients on PD. However, Niu *et al.*[26] and Lee *et al.*[13] included patients on both PD and HD but did not report outcomes separately for each modality; thus, they were excluded from the subgroup analysis. Unfortunately, data from Zhang *et al.*[35] was not sufficient for the analysis of LVEF changes. As depicted in Supplementary Figure S1, our analysis revealed no significant difference between the HD and PD groups ($P = 0.76$). It is noteworthy that the 2 studies included in the PD subgroup focused on patients with HFpEF, whereas the HD subgroup comprised patients with both HFrEF and HFpEF. To account for this discrepancy, we performed a subgroup analysis for patients with an average LVEF >50%. In Supplementary Figure S2 illustrates that there was no significant difference in LVEF changes between patients on HD and PD ($P = 0.5$).

We also attempted to conduct a safety analysis based on the 3 studies that exclusively enrolled patients on PD. However, data for hyperkalemia and hypotension

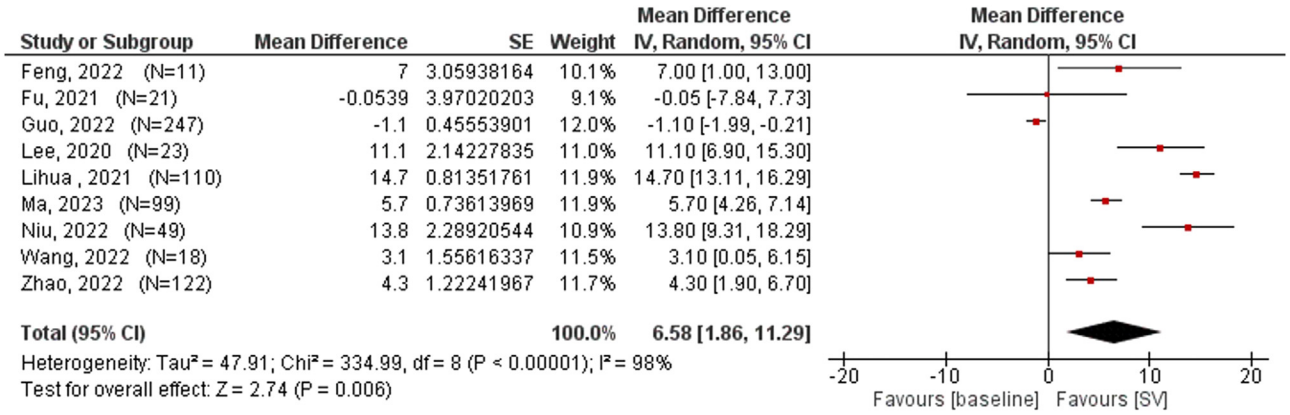

Figure 2. Change of left ventricular ejection fraction in patients with end-stage kidney disease. CI, confidence interval.

was scarce, with only 1 study available for each modality (Ma *et al.*[31] for PD and Zhao *et al.*[36] for HD), which precluded a subgroup analysis.

Risk of bias

The study quality and risk of bias were assessed across different domains, as shown in Figure 7. Furthermore, there was no evidence of publication bias observed through the visual assessment of funnel plot (Figure 8).

Summary of findings and recommendations

The quality of evidence for the assessed outcomes varied based on the GRADE criteria. For the overall change of LVEF, as well as the change of LVEF in patients with an average baseline LVEF >50% and in patients with HFpEF, the quality of evidence was rated as very low. This indicates that there are significant limitations in the available studies, such as risk of bias, inconsistency, imprecision, or indirectness, which result in a high degree of uncertainty in the findings. On the other hand, despite the fact that all of the studies were observational, the quality of evidence for the change of LVEF in patients with LVEF <50% and in patients with HFrEF was rated as high due to very strong association and large effect size. This suggests that there is a higher level of confidence in the findings for these specific subgroups.

Regarding the safety events, including hyperkalemia, hypotension, and angioedema, the quality of evidence was also rated as very low. This implies that the available studies suffer from limitations, and there is a high degree of uncertainty in the estimates of safety outcomes.

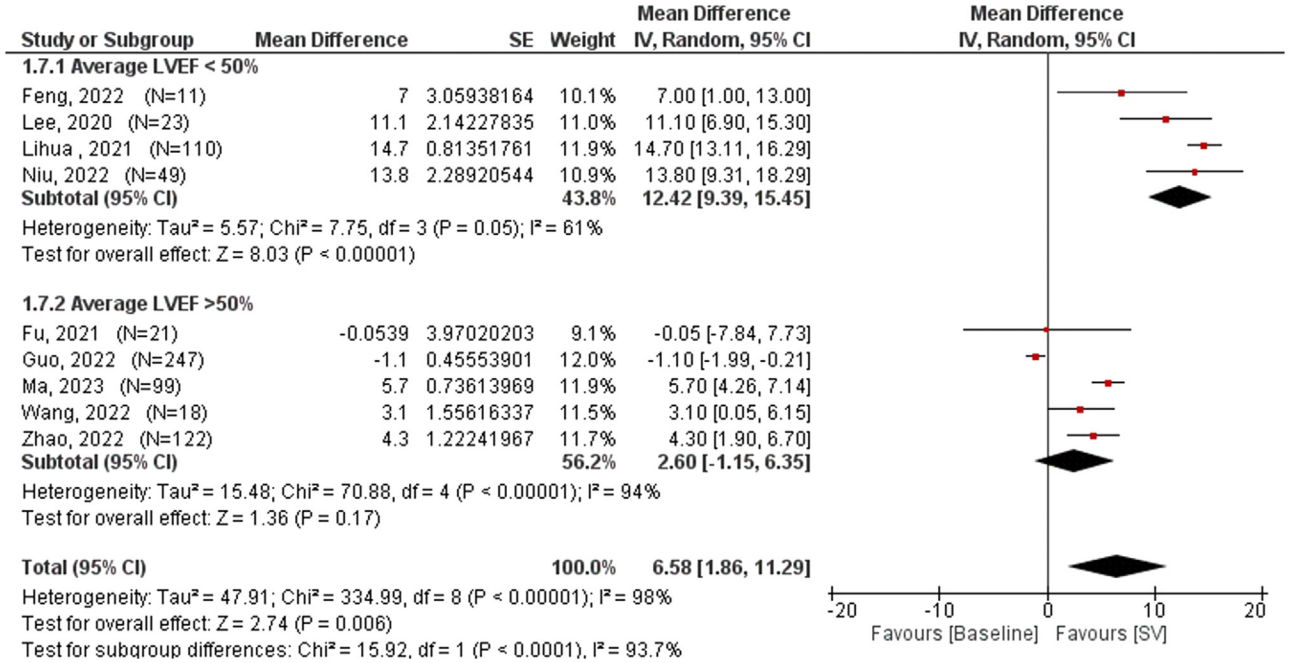

Figure 3. Subgroup analysis, change of left ventricular ejection fraction (LVEF) in patients with end-stage kidney disease with LVEF >50% versus LVEF <50%. CI, confidence interval.

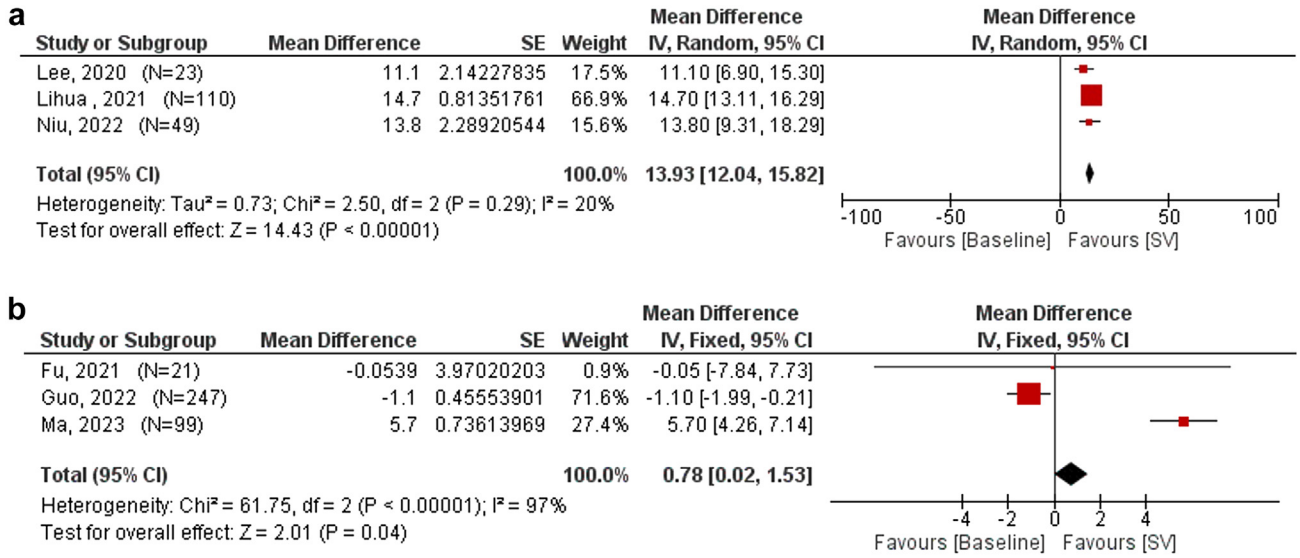

Figure 4. (a) Change of left ventricular ejection fraction in patients with HFrEF. (b) Change of left ventricular ejection fraction in patients with HFpEF. HFpEF, heart failure with preserved ejection. CI, confidence interval.

DISCUSSION

Our systematic review and meta-analysis summarized the potential benefits of sacubitril-valsartan in patients with ESKD with different types of heart failure. The findings highlight the potential efficacy of sacubitril-valsartan in this patient population, particularly among those with HFrEF. Considering the high prevalence of heart failure and its associated adverse outcomes[3–5] among patients with ESKD undergoing dialysis and limited available data concerning the cardiovascular benefits and safety of sacubitril-valsartan in this specific patient group, this review provides significant importance.

Subgroup analysis to explore the varying effects of sacubitril-valsartan among patients with HFrEF, HFmrEF, and HFpEF showed significant differences between these subgroups. Notably, the most substantial improvement in LVEF was observed in patients with LVEF below 50% (HFrEF and HFmrEF). These results indicate that sacubitril-valsartan may have a more pronounced effect in patients with reduced ejection fraction and emphasize the importance of considering the baseline cardiac function of patients with ESKD when determining the appropriateness of sacubitril-valsartan therapy. In the past decade, several new treatment strategies for heart failure have emerged.

Conversely, in patients with LVEF above 50% (HFpEF), the effect of sacubitril-valsartan was not statistically significant. The complex nature of defining HFpEF, which involves multiple echocardiographic and symptomatic criteria, suggests that the improvement or change in cardiac function may not solely depend on an increase in LVEF. In addition, the pathophysiological mechanisms underlying HFpEF differ from those of HFrEF. Despite the very low quality of evidence, our findings align with the results of the PARAGON-HF trial,[37] which also failed to find a significant benefit of sacubitril-valsartan in patients with HFpEF.

Another marker that is frequently used for evaluation of HFpEF is NT-proBNP. We tried to examine the potential prognostic value and diagnostic utility of serum natriuretic peptides BNP or NT-proBNP in patients with HFpEF. Overall, all 3 included studies demonstrated a reduction in NT-proBNP levels among patients with HFpEF. However, estimating the true effect size was challenging due to the skewed data and the influence of kidney failure on NT-proBNP concentrations. It is important to note that kidney failure can independently affect NT-proBNP concentrations, and the use of NT-proBNP for managing or diagnosing heart failure in these patients is not recommended.[38]

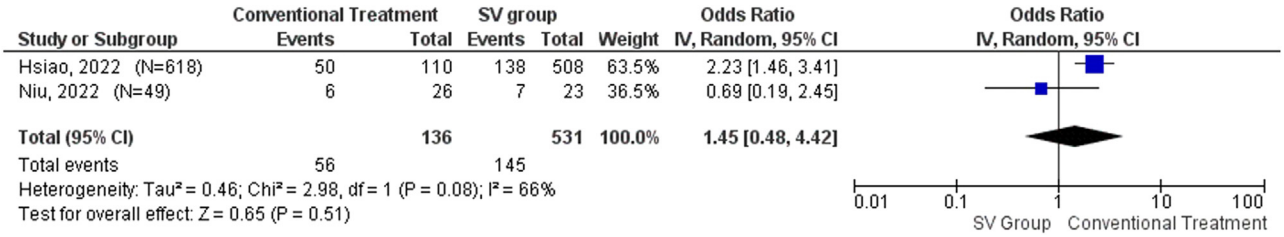

Figure 5. Heart failure hospitalizations in patients with heart failure with reduced ejection and end-stage kidney disease. CI, confidence interval.

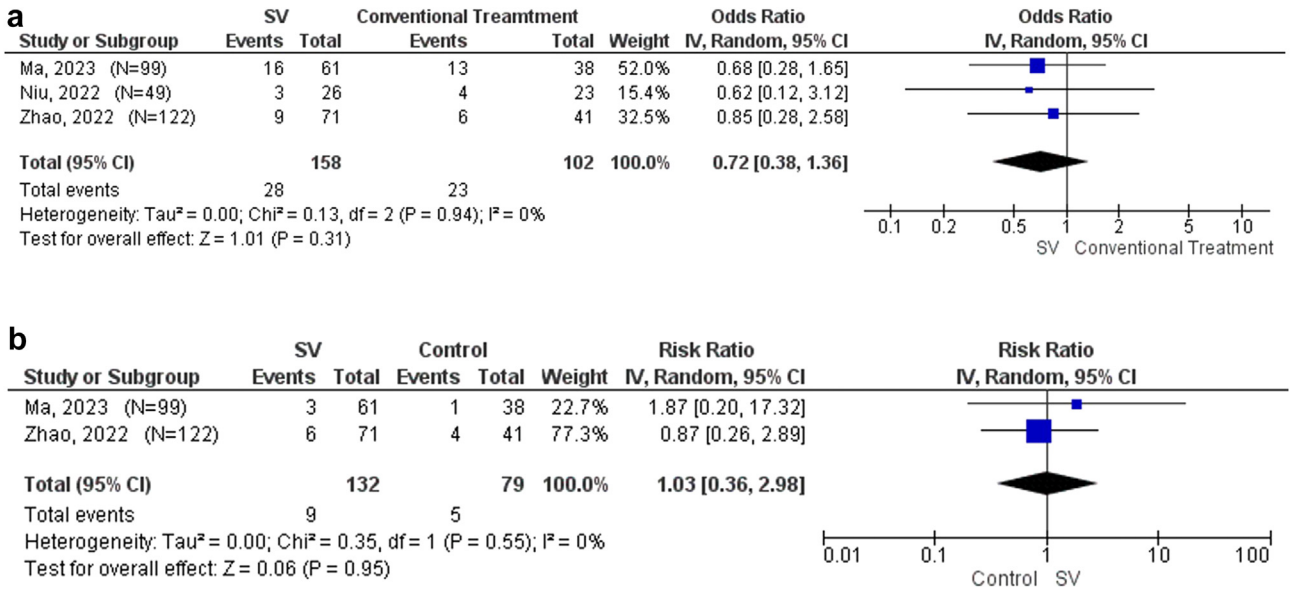

Figure 6. (a) Hyperkalemia in patients with end-stage kidney disease on sacubitril-valsartan compared to control group on standard of care. (b) Hypotension in sacubitril-valsartan group compared to control group. CI, confidence interval.

Therefore, we did not consider it clinically relevant to report a pooled estimate of the change in NT-proBNP levels in patients with ESKD.

The available data from the studies included in our analysis provided limited information on heart failure hospitalizations, all-cause hospitalizations, and all-

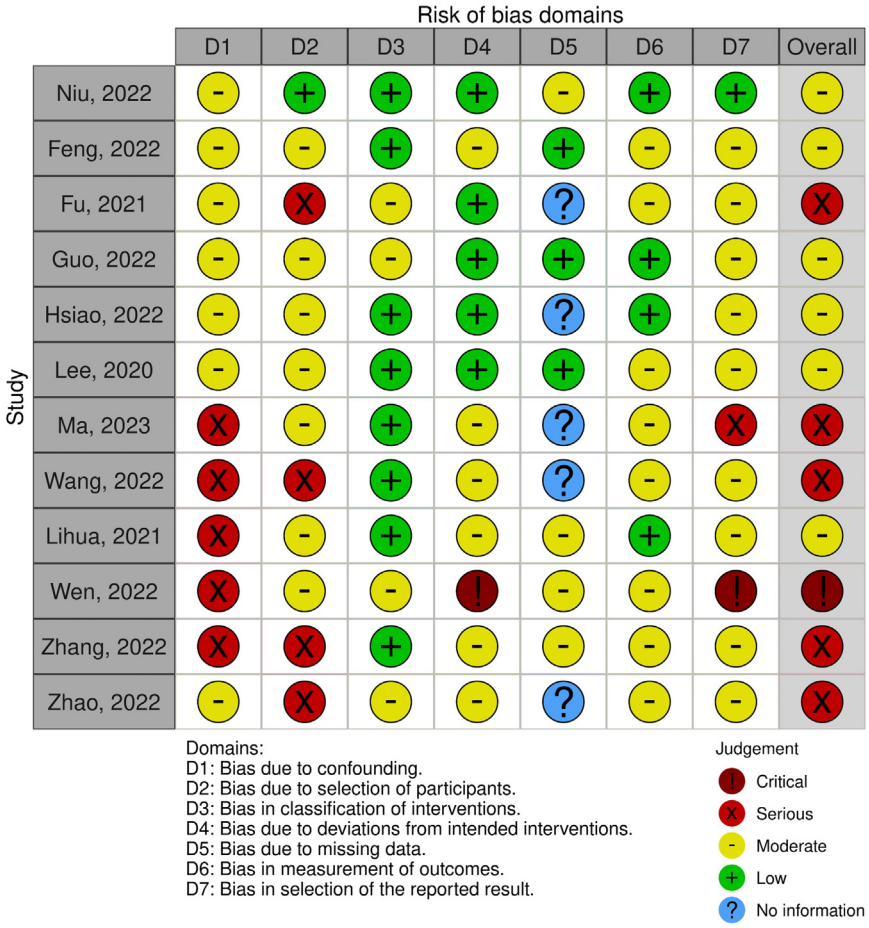

Figure 7. Risk of bias assessment.

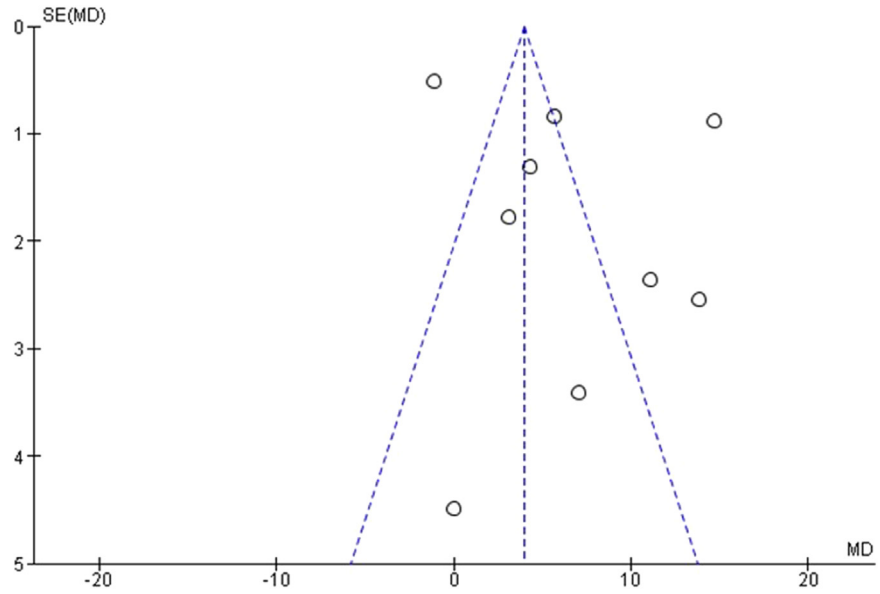

Figure 8. Publication bias.

cause mortality outcomes. Although sacubitril-valsartan was found to be associated with significant benefits in general population with heart failure,[15,39,40] there is significant knowledge gap regarding the impact of sacubitril-valsartan on heart failure hospitalizations, all-cause hospitalizations, and all-cause mortality in patients with ESKD.

The effect of dialysis modality on sacubitril-valsartan outcomes is an intriguing aspect of our review. Our subgroup analysis, which categorized studies into PD and HD patient groups, provides some insight into this matter. Although the number of studies in the PD subgroup was limited, our analysis indicated no significant difference in the change of LVEF between patients on PD and those on HD. However, it is important to note that the PD subgroup mainly consisted of patients with HFpEF, whereas the HD subgroup included both HFpEF and HFrEF patients. This disparity in patient populations may have influenced our findings. Further research with larger and more homogenous patient groups is needed to draw more definitive conclusions regarding the impact of dialysis modality on sacubitril-valsartan efficacy. In terms of safety, our study indicated a favorable side effect profile of sacubitril-valsartan in patients with ESKD, because there was no significant difference in the occurrence of hyperkalemia, hypotension, or angioedema compared to the control group. Hyperkalemia is a known concern when inhibiting the renin-angiotensin-aldosterone system, particularly in patients with kidney disease. However, it has been observed that the addition of a neprilysin inhibitor, such as sacubitril/valsartan, to patients already receiving renin-angiotensin-aldosterone system inhibitors does not significantly increase the risk of hyperkalemia. A meta-analysis conducted in patients with HFrEF revealed that the incidence of hyperkalemia was lower in patients receiving angiotensin receptor/neprilysin inhibitor treatment compared to those receiving angiotensin-converting enzyme inhibitors.[41] This suggests that the addition of neprilysin inhibition may not further contribute to hyperkalemia risk in this patient population. The certainty of evidence of these findings was very low, mainly due to the observational nature of the studies and the risk of bias. Close monitoring of adverse effects is still warranted, and further research is needed to establish the safety profile of sacubitril-valsartan in this specific population.

Our systematic review and meta-analysis have several limitations, primarily from the characteristics of the included studies. These limitations include heterogenicity in outcome measurements, differences in the definitions of HFrEF and HFpEF, heterogeneity in dialysis modalities (with some studies including only patients on PD and others including both PD and HD), and variations in the dosing of sacubitril-valsartan across different studies. A critical observation to underscore is that all the studies in our analysis were conducted in Asian countries. This geographic concentration introduces a potential limitation in the generalizability of our findings to populations beyond this region. Future research endeavors should be attentive to this limitation, emphasizing the inclusion of diverse geographical areas to ensure comprehensive insights. Furthermore, within population of patients with ESKD who are undergoing dialysis, potential confounding factors, particularly changes in volume status, may exist. These fluctuations have the potential to significantly impact clinical outcomes and may interact with the mechanisms of

sacubitril-valsartan. Although we acknowledge the possibility of these confounders, it is imperative to highlight that the included studies did not provide comprehensive data on volume status management, making it impossible for us to directly assess its impact. A notable limitation is that a proportion of the study population received PD and might have residual kidney function. This particular subgroup could have introduced confounding in safety analysis, especially hyperkalemia. Unfortunately, due to the scarcity of data available for this specific subgroup, we were unable to perform a formal subgroup analysis for hyperkalemia, further underscoring the limitations of our study.

Given the limitations in the quality of the available literature, it is essential to emphasize the critical need for future prospective research. Despite the valuable insights gained from our meta-analysis, the necessity for prospective investigations remains of utmost importance in establishing a more robust evidence base for the utilization of sacubitril-valsartan in patients with ESKD on dialysis. Future research should proactively consider and account for potential confounding factors, including changes in volume status and the effects of different dialysis modalities, to advance our understanding of this therapeutic intervention.

In conclusion, our systematic review and meta-analysis based on the currently available data indicate that sacubitril-valsartan, when compared to standard care, may hold potential benefits for patients with ESKD who are on dialysis, particularly those with HFrEF and HFmrEF, in terms of improving LVEF. Moreover, it is suggested that the use of sacubitril-valsartan in this patient population may not be associated with an increased risk of hyperkalemia, hypotension, or angioedema. However, it is crucial to acknowledge the limitations of the included studies, the low quality of evidence, and the observed heterogeneity when interpreting these results. Further research, including well-designed clinical trials, is warranted to establish the efficacy and safety of sacubitril-valsartan in patients with ESKD undergoing dialysis.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Subgroup analysis: change of left ventricular ejection fraction in patients with end-stage kidney disease after sacubitril valsartan in hemodialysis and peritoneal dialysis patients.

Figure S2. Subgroup analysis: change of left ventricular ejection fraction after sacubitril-valsartan in patients with ESKD with average EF >50%-hemodialysis and peritoneal dialysis.

Table S1. Preferred reporting items for systematic reviews and meta-analyses 2021 checklist.

Table S2. Actual search strategies.

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