RENAL FAILURE
2024, VOL. 46, NO. 1, 2349135
https://doi.org/10.1080/0886022X.2024.2349135

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CHRONIC KIDNEY DISEASE AND PROGRESSION



# The role of sacubitril/valsartan in abnormal renal function patients combined with heart failure: a meta-analysis and systematic analysis

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**ABSTRACT**

**Aims:** This study aimed to investigate the efficacy and safety of sacubitril/valsartan in abnormal renal function (eGFR < 60 ml/min/1.73m$^2$) patients combined with heart failure based on randomized controlled trials (RCTs) and observational studies.

**Methods:** The Embase, PubMed and the Cochrane Library were searched for relevant studies from inception to December 2023. Dichotomous variables were described as event counts with the odds ratio (OR) and 95% confidence interval (CI) values. Continuous variables were expressed as mean standard deviation (SD) with 95% CIs.

**Results:** A total of 6 RCTs and 8 observational studies were included, involving 17335 eGFR below 60 ml/min/1.73m$^2$ patients combined with heart failure. In terms of efficacy, we analyzed the incidence of cardiovascular events and found that sacubitril/valsartan significantly reduced the risk of cardiovascular death or heart failure hospitalization in chronic kidney disease (CKD) stages 3–5 patients with heart failure (OR: 0.65, 95%CI: 0.54–0.78). Moreover, sacubitril/valsartan prevented the serum creatinine elevation (OR: 0.81, 95%CI: 0.68–0.95), the eGFR decline (OR: 0.83, 95% CI: 0.73–0.95) and the development of end-stage renal disease in this population (OR:0.73, 95%CI:0.60–0.89). As for safety outcomes, we did not find that the rate of hyperkalemia (OR:1.31, 95%CI:0.79–2.17) and hypotension (OR:1.57, 95%CI:0.94–2.62) were increased in sacubitril/valsartan group among CKD stages 3–5 patients with heart failure.

**Conclusions:** Our meta-analysis proves that sacubitril/valsartan has a favorable effect on cardiac function without obvious risk of adverse events in abnormal renal function patients combined with heart failure, indicating that sacubitril/valsartan has the potential to become perspective treatment for these patients.

**ARTICLE HISTORY**
Received 5 December 2023
Revised 25 March 2024
Accepted 2 April 2024

**KEYWORDS**
Sacubitril/valsartan; chronic kidney disease; heart failure; meta-analysis; randomized controlled trials; observational studies

## Introduction

Chronic kidney disease (CKD) is a global health problem with an increased risk of cardiovascular disease [1,2], often manifested as heart failure [2,3]. Moreover, studies have documented that concomitant heart failure is associated with elevated morbidity and mortality of patients with CKD stages 3–5 [3–5]. However, in these special patients, the management of heart failure remains a huge challenge, potentially due to adverse drug reactions and their limited response to conventional therapies [6]. So, it is imperative to explore new therapeutic strategies for abnormal renal function patients combined with heart failure.

In recent years, sacubitril/valsartan has been confirmed to ameliorate the prognosis of heart failure through vasodilatation, diuresis, natriuresis and anti-remodeling [2] by simultaneously restraining natriuretic peptides degradation and renin-angiotensin-aldosterone system (RAAS) activation [7]. Current clinical guidelines also have recommended sacubitril/valsartan for patients with heart failure [8,9] to mitigate the risk of cardiovascular death [10]. However, these guidelines primarily pertain to patients with normal renal function. Whether sacubitril/valsartan is safe and effective in patients with impaired renal function, especially in advanced kidney disease, is still unclear.

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/0886022X.2024.2349135.

**Systematic review registration:** [https://inplasy.com/inplasy-2023-12-0037/], identifier [INPLASY2023120037].

Some randomized controlled trials (RCTs) once suggested that CKD stage 3 patients with heart failure might have received renal and cardiovascular benefits from sacubitril/valsartan [11–13]. But these results are unsystematic and incomplete because they have to be extrapolated from subgroup analyses, as well as lack of safety outcomes. Additionally, patients with CKD at stage 4 or higher were excluded from RCTs investigating the effects of sacubitril/valsartan; however, they were included in several observational studies. One of the observational studies involving 49 patients with eGFR < 15 mL/min/1.73m$^2$ concomitant with heart failure demonstrated that sacubitril/valsartan effectively enhanced cardiac function without eliciting significant adverse effects [14]. But the findings of another observational study including 1039 patients with CKD stages 3–5 and heart failure indicated that, after a duration of 12 months, the sacubitril/valsartan group exhibited a higher incidence of adverse drug reactions than control group [15]. It follows that these observational studies have inconsistent conclusions, small sample sizes and short follow-up periods, leading to a bias when assessing the effect of sacubitril/valsartan in CKD stages 4–5 patients with heart failure.

Previously, our research team has completed a study on the effect of sacubitril/valsartan in patients with CKD, while mainly emphasizing patients with CKD stage 3 and only including RCTs [16]. Consequently, to evaluate the efficacy and safety of sacubitril/valsartan in a broader population and the real-world clinical practice, we conducted this meta-analysis on patients with CKD stages 3–5 combined with heart failure, based on both RCTs and observational studies.

## Materials and methods

This meta-analysis was conducted in compliance with the Preferred Reporting Items for Reporting Systematic Reviews and Meta-analyses (PRISMA) statement [17].

## Search strategy

Online databases including the Cochrane Library, Embase and PubMed were searched by Yang and Jin for relevant studies published as of December 9th, 2023, using the following terms: 'sacubitril valsartan', 'sacubitril and valsartan', 'sacubitril/valsartan', 'sakubitril valsartan', 'entresto', 'neprilysin inhibitor', 'LCZ696', 'LCZ-696', 'AHU377', 'ARNI', 'angiotensin receptor neprilysin inhibitor', 'angiotensin receptor neprilysin blocker'. Details were provided in the **Supplementary Materials**. Disagreements were solved through consulting with the third reviewer (Xu).

## Study selection

Two reviewers (Yang and Cheng) screened all titles, abstracts and full texts, as well as ultimately determined the inclusion of studies by the consensus. Any disagreements were referred to the third researcher (Bai) for advice. The following inclusion criteria were required for eligible literature:

a. Participants: the population of trial contained abnormal renal function (eGFR < 60 ml/min/1.73m$^2$) patients combined with heart failure;
b. Intervention: the experimental group used sacubitril/valsartan;
c. Comparisons: the control group without sacubitril/valsartan;
d. Outcomes: cardiovascular events or safety outcomes were available;
e. Study design: the number of patients with CKD and heart failure was definite or can be calculated; the type of study was RCT or observational study.

We identified and excluded studies which met at least one of the following criteria: (a) repeated literature; (b) title or content not relevant to our meta-analysis; (c) animal or cell trial; (d) article not published in English; (e) did not meet the inclusion criteria; (f) review, case, report, new, meta-analysis, conference abstract, letter, erratum or comment.

## Data extraction and quality assessment

We extracted the following information from the eligible trials: the trial name, number of patients, baseline eGFR, drug names and doses, duration of treatment, efficacy outcomes (the incidence of cardiovascular death or hospitalization for heart failure) and safety outcomes (changes in renal function; the incidence of hyperkalemia and hypotension). Discrepancies were addressed by consensus with a third author (Xu).

The bias of RCTs was assessed using the Cochrane risk of bias (ROB) tool according to 5 items: according to random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attribution bias), and selective reporting (reporting bias) and other bias [17].

In addition, the Risk of bias in Studies of Non-randomized Interventions Scale (ROBINS-I) was used to evaluate the quality of observational studies in 6 aspects: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, bias in selection of the reported results [18]. These assessments were done by two reviewers (Cheng and Yang) separately. Conflicts were resolved by the third investigator (Jin).

## Statistical analysis

All statistical analysis in this meta-analysis were performed on Review Manager 5.3. Quality assessment of observational studies and funnel plot of cardiovascular events was drawn

by RStudio 4.1.3. Dichotomous variables were described as event counts with the odds ratio (OR) and 95% confidence interval (CI) values. Continuous variables were expressed as mean ± standard deviation (SD) with 95% CIs. The heterogeneity of studies was assessed with the Q test, $I^2$ statistic and forest maps. Heterogeneity was low when $I^2$ was less than 25%, moderate when $I^2$ was between 25% and 50% and high when $I^2$ was greater than 50%. When $I^2$ was less than 50%, heterogeneity was considered acceptable. We chose a fixed-effects model when $I^2$<50%, otherwise the random-effects model was picked. Funnel plots and Egger's test were used to assess publication bias if at least ten studies were included. There is no missing data in the included articles, and we have received all answers from studies.

## Results

### Literature search results

Using our search strategy, we retrieved 10128 studies from target databases, removed 2854 duplicate records and further screened 1125 full texts for eligibility. Finally, six RCTs [11–13,19–21] and eight observational studies [14,15,22–27], involving a total of 17335 CKD stages 3–5 patients with heart failure, were included (Cohen's kappa = 0.832, $p < 0.01$, the consistency of literature search is strong). The flow diagram of literature searching and screening was detailed in the Figure 1.

### Baseline characteristics and quality assessment of included studies

As specified in Table 1, the characteristics of the included studies were summarized. A total of 17335 CKD stages 3–5 patients with heart failure were involved in our meta-analysis.

In terms of RCTs, three of the them compared sacubitril/valsartan with angiotensin converting enzyme inhibitor (ACEI) [12,19,21], two of them compared sacubitril/valsartan with angiotensin receptor blocker (ARB) [11,13], and the last one compared the sacubitril/valsartan with routine treatment of heart failure which contained ACEI or ARB [20]. The duration of treatment ranged from 8 weeks to 35 months. Regarding observational studies, patients in the experimental group received sacubitril/valsartan, while the control group did not receive sacubitril/valsartan. The period of therapy ranged from 6.9 to 15 months.

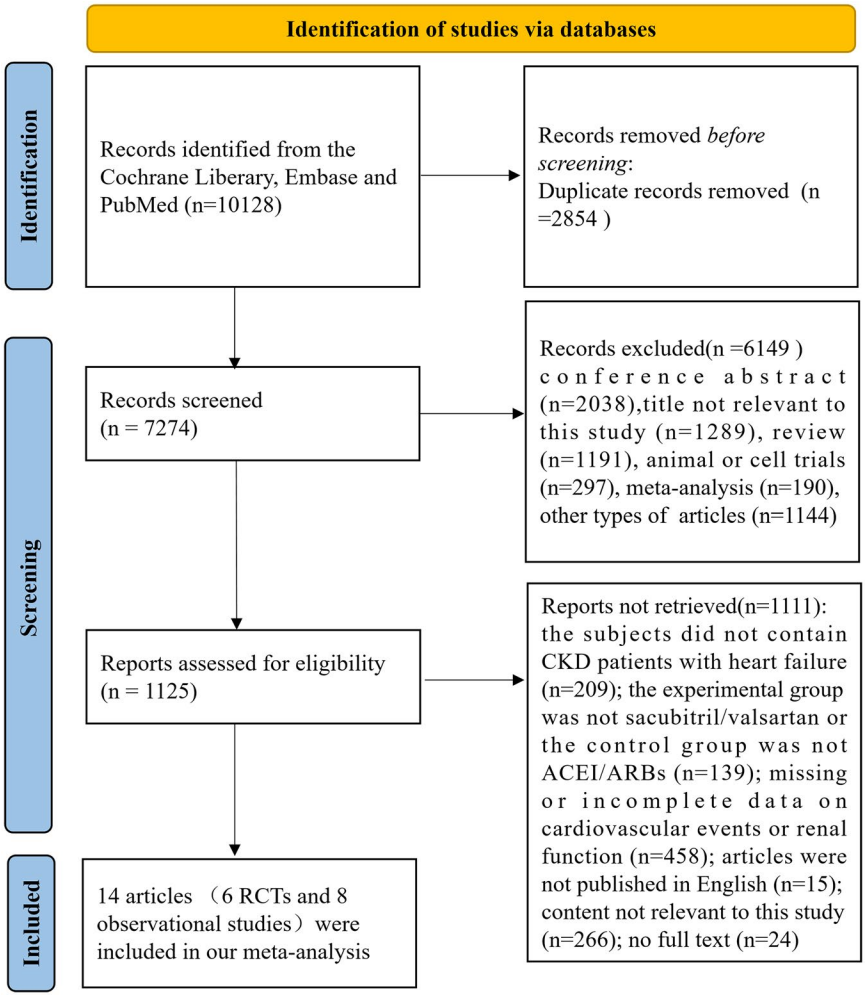


Figure 1. PRISMA 2020 flow diagram.

**Table 1.** Baseline characteristic of included studies.

| First author | Publication year | Country | Type of research | Sample | Baseline eGFR | Type of heart failure | Average for LVEF value (%), mean (SD) | | Dosage of medicine | | Duration of Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Control group | Experimental group | Control group | Experimental group | |
| Mc Causland et al. [11] | 2020 | America | RCT | 2341 | 30–60 ml/min/1.73m$^2$ | Heart failure with preserved ejection fraction | 57.8 (7.7) | 58.2 (7.8) | Valsartan 160mg/bid | Sacubitril/valsartan 97/103mg/bid | Median 35 months |
| Berg et al. [12] | 2021 | America | RCT | 455 | 30–60 ml/min/1.73m$^2$ | Heart failure with reduced ejection fraction | LVEF ≤ 40% | | Enalapril 10mg/bid | Sacubitril/valsartan 97/103mg/bid | 8 weeks |
| Damman et al. [19] | 2018 | America | RCT | 2745 | 30–60 ml/min/1.73m$^2$ | Heart failure with reduced ejection fraction | 30 (6) | | Enalapril 10mg/bid | Sacubitril/valsartan 97/103mg/bid | Median 27 months |
| Tsutsui et al. [21] | 2021 | Japan | RCT | 137 | 30–60 ml/min/1.73m$^2$ | Heart failure with reduced ejection fraction | 27.7 (5.5) | 28.6 (5.1) | Enalapril 10mg/bid | Sacubitril/valsartan 200mg/bid | 6 months |
| Voors et al. [13] | 2015 | America | RCT | 125 | 30–60 ml/min/1.73m$^2$ | LVEF ≥45% (heart failure with preserved ejection fraction) | LVEF ≥ 45% | | Valsartan 160mg/bid | Sacubitril/valsartan 200mg/bid | 36 weeks |
| Sheng et al. [20] | 2023 | China | RCT | 160 | <15 ml/min/1.73m$^2$ | NYHA II-IV | – | – | routine treatment of HF | Sacubitril/valsartan 100mg/bid | 6 months |
| Chang et al. [22] | 2019 | China | Observational study | 102 | <30 ml/min/1.73m$^2$ | Heart failure with reduced ejection fraction | LVEF ≤ 40% | | Standard heart failure management | Sacubitril/valsartan 112.5 ± 58.7 mg/qd | 15 months |
| Chen et al. [24] | 2021 | China | Observational study | 4040 | <60 ml/min/1.73m$^2$ | Heart failure with reduced ejection fraction | LVEF < 40% | | ACEI/ARBs | Sacubitril/valsartan | 11.8 months |
| Tan et al. [27] | 2021 | America | Observational study | 4109 | 15-60 ml/min/1.73m$^2$ | Heart failure with reduced ejection fraction | LVEF < 45% | | ACEI/ARBs | Sacubitril/valsartan | 7.8 months |
| Hsiao et al. [15] | 2022 | China | Observational study | 1039 | <30 ml/min/1.73m$^2$ | Heart failure with reduced ejection fraction | LVEF < 40% | | ACEI/ARBs | Sacubitril/valsartan | 6.9 months |
| Chang et al. [23] | 2023 | China | Observational study | 510 | <30 ml/min/1.73m$^2$ | Heart failure with reduced ejection fraction | 29.8 (7.4) | 29.8 (7.2) | Without sacubitril/ valsartan | Sacubitril/valsartan 143 ± 84mg/qd | 12 months |
| Niu et al. [14] | 2022 | China | Observational study | 49 | <15 ml/min/1.73m$^2$ | Heart failure with reduced ejection fraction | 35.73 (4.21) | 31.31 (5.53) | Conventional treatment | Sacubitril/valsartan 97/103mg/bid | 12months |
| Guo et al. [25] | 2022 | China | Observational study | 247 | <15 ml/min/1.73m$^2$ | Heart failure with preserved ejection fraction | 59.6 (6.3) | 56.8 (5.4) | ACEI/ARBs | Sacubitril/valsartan 200mg/bid | Median 8.5 months |
| Lee et al. [26] | 2023 | China | Observational study | 1276 | Creatinine clearance < 60 ml/min/1.73m$^2$ | Heart failure with reduced ejection fraction | 27.58 (5.90) | 27.41 (5.62) | ACEI/ARBs | Sacubitril/valsartan | 12months |

SD: standard deviation; RCT: randomized controlled trial; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; NYHA: New York Heart Association.

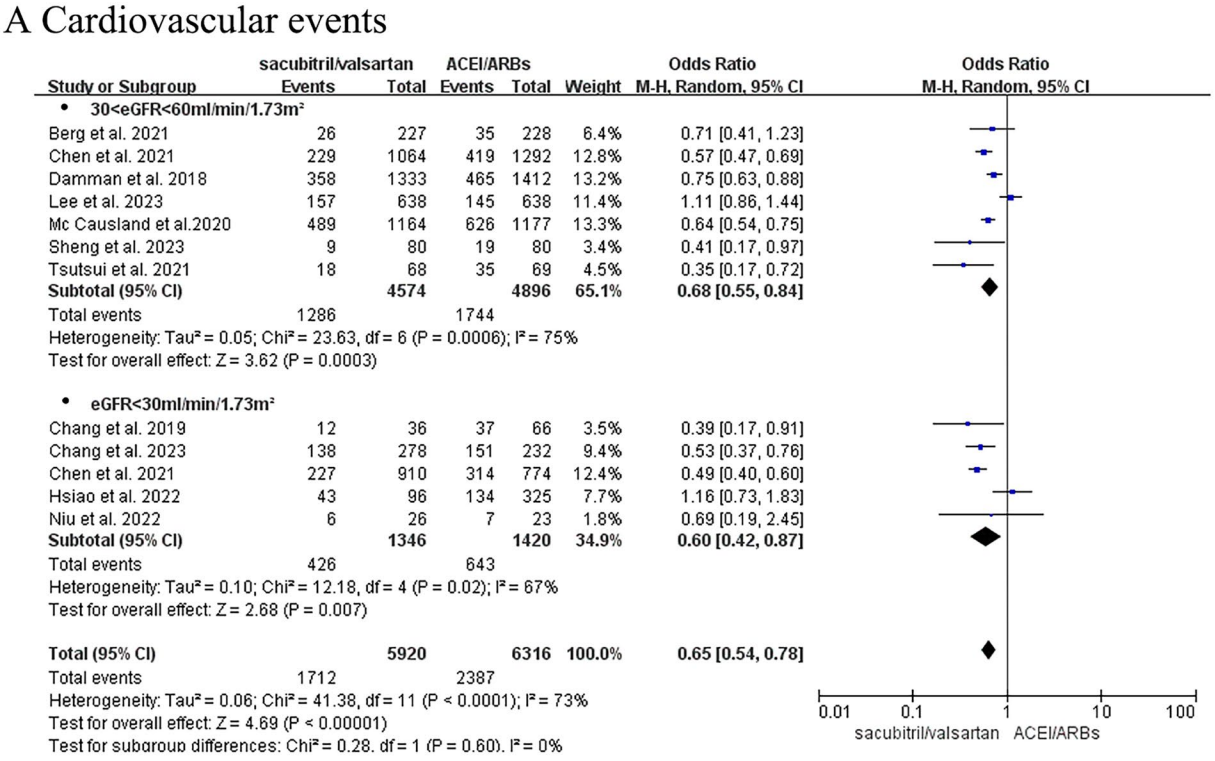


**Figure 2.** Results of cardiovascular events. (A) Forest plot showing the difference in cardiovascular events between sacubitril/valsartan and control group. (B) Funnel plot of cardiovascular events. Note: Berg et al. defined cardiovascular events as a composite of cardiovascular death or rehospitalization for heart failure [12]; Chen et al. described cardiovascular events as rehospitalization for heart failure and all-cause death [24]; Damman et al. Chang et al. Hsiao et al. Lee et al. and Tsutsui et al. described cardiovascular events as cardiovascular death or heart failure hospitalization [15,19,21–23,26]; Mc Causland et al. defined cardiovascular events as a composite of total (first and recurrent) hospitalizations for heart failure and death from cardiovascular causes; In Sheng et al.'s research, cardiovascular events were regarded as the rehospitalization of patients due to acute myocardial ischemia, HF, thromboembolic or hemorrhagic stroke, arrhythmia, and peripheral vascular disease [20]; Niu et al. regarded cardiovascular events as hospitalization because of cardiovascular diseases [14].

The average dosage of sacubitril/valsartan in most studies was 100 mg/bid or 200 mg/bid. And the mean dose of sacubitril/valsartan in two studies conducted by Chang et al. was 112.5 ± 58.7 mg/qd [22] and 143 ± 84mg/qd [23], respectively.

Based on the ROB tool, all included RCTs were of high quality (Supplementary figure 1). According to the ROBINS-I tool, eight observational studies were assessed as having a relatively low risk of bias in six areas (Supplementary figure 2).

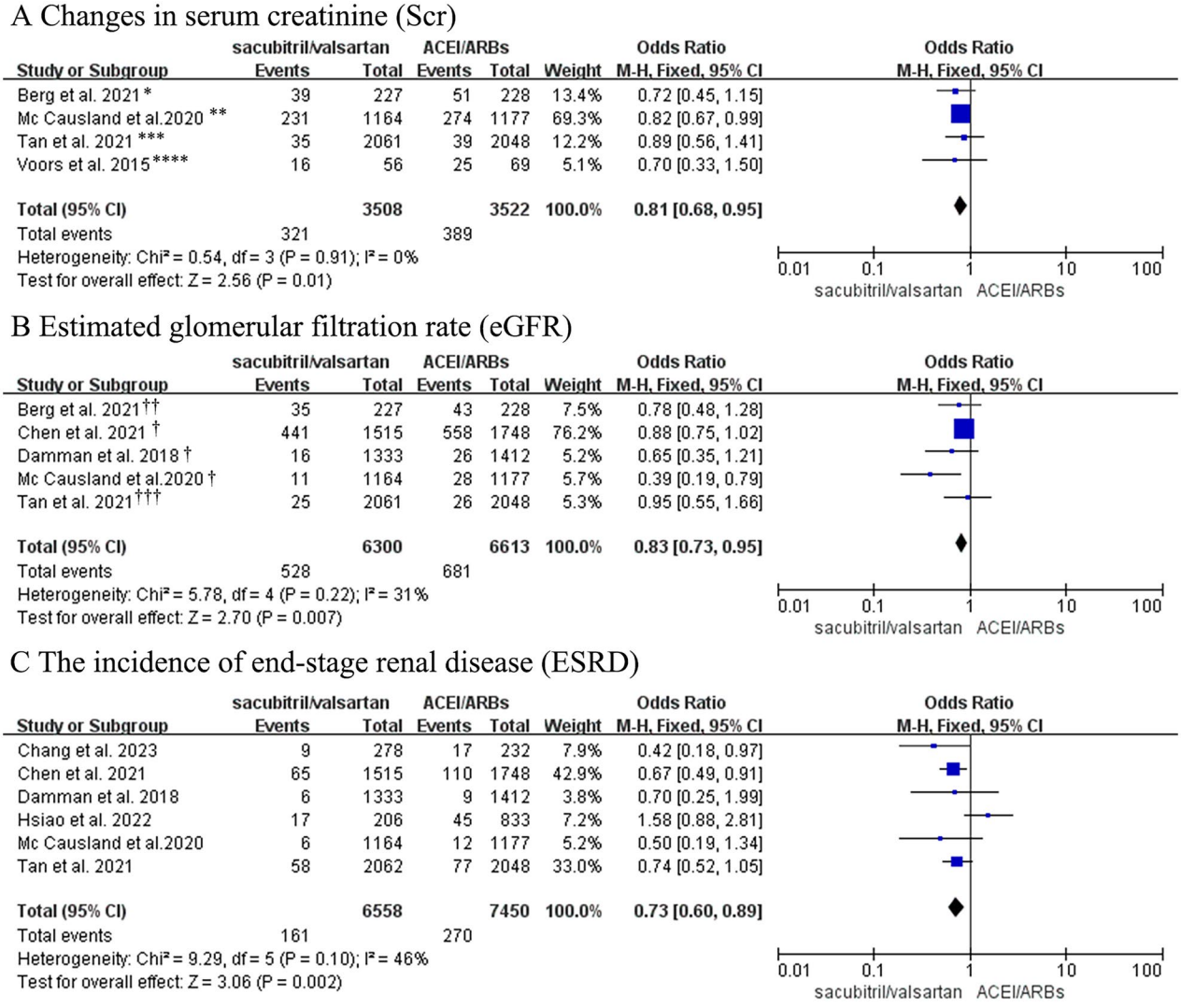


Figure 3. Results about cardiovascular events. (A) Forest plot about changes in Scr. (B) Forest plot regarding changes in eGFR. (C) Meta-analysis of the incidence of ESRD in CKD stages 3–5 patients with heart failure. *Berg et al. defined the change of Scr as an increase in serum creatinine of at least 0.5 mg/dL; **Mc Causland et al. were described the change of Scr as elevated serum creatinine ≥ 2.0 mg/dL; *** Tan et al. described the change of Scr as doubling of serum creatinine; ****Voors et al. defined the change of Scr as >0.3 mg/dL increase in creatinine in combination with an increase of more than 25% in serum creatinine between two time points. †In the Chen's study, the PARADIGM-HF trial and the PARAGON-HF trial, eGFR level declined >50% from baseline; ††In the Berg et al.'s trial, eGFR level declined >25% from baseline; †††In the Tan's study, eGFR level declined >30% or more from baseline.

### *Cardiovascular events*

A total of five RCTs and five observational studies described cardiovascular events (cardiovascular death or heart failure hospitalization). Compared with control group, sacubitril/valsartan treatment reduced the incidence of cardiovascular events in CKD stages 3–5 patients with heart failure (12236 patients, OR: 0.65, 95%CI: 0.54–0.78, $p<0.00001$, $I^2$=73%, Figure 2A). Additionally, subgroup analysis based on CKD stage showed that even patients with eGFR below 30 mL/min/1.73m$^2$ were able to derive cardiovascular benefits from sacubitril/valsartan (OR: 0.60, 95%CI: 0.42–0.87, $p=0.007$, $I^2$=67%, Figure 2A). Both funnel plot (Figure 2B) and Egger's test ($p=0.602$) did not show significant publication bias. Overall, sacubitril/valsartan exhibited cardioprotective effects in abnormal renal function patients combined with heart failure.

### *Renal events*

#### *Changes in serum creatinine (scr)*

Three RCTs and one observational study, involving 7030 CKD stages 3–5 patients with heart failure, analyzed the changes in serum creatinine. The pooled outcomes indicated that the risk of Scr elevation was obviously decreased in the sacubitril/valsartan group (OR: 0.81, 95% CI: 0.68–0.95, $p=0.01$, $I^2$=0%, Figure 3A).

#### *Estimated glomerular filtration rate (eGFR)*

Three RCTs and two observational studies reported the data on the incidence of eGFR reduction. As shown in Figure 3B, CKD stages 3–5 patients with heart failure in the sacubitril/valsartan group had a slower eGFR decline compared with

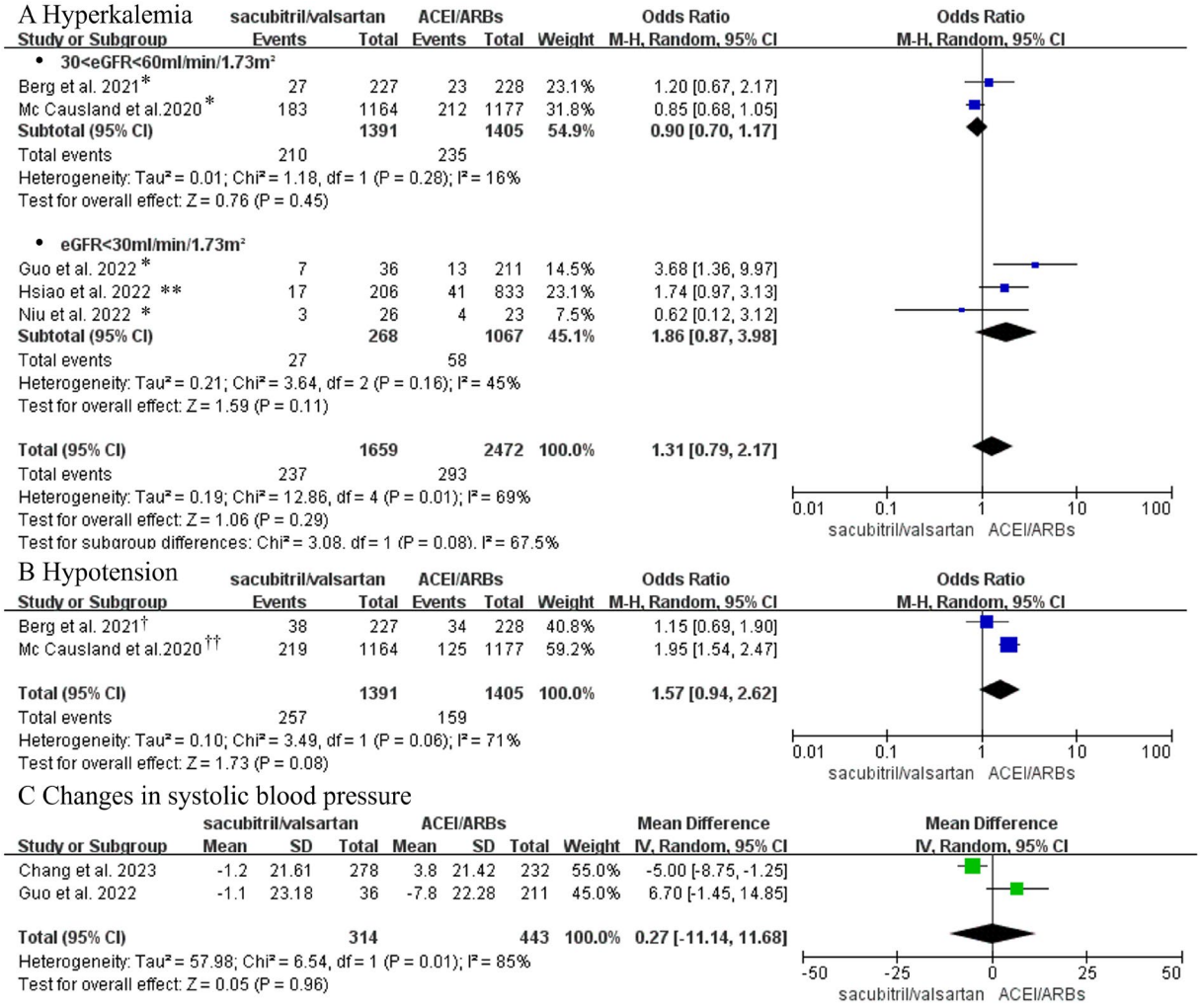


Figure 4. (A) Forest plot of the incidence of hyperkalemia. (B) Meta-analysis of the incidence of hypotension in CKD stages 3-5 patients with heart failure. (C) Forest plots of changes in blood pressure. *Hyperkalemia was defined as potassium > 5.5 mmol/L in these studies; ** Hyperkalemia was defined as potassium > 6mmol/L in Hsiao's study. †Berg et al. regarded hypotension as symptomatic hypotension; ††Hypotension in the Mc Causland et al.'s trial was regarded as SBP < 100 mmHg.

the control group (OR: 0.83, 95% CI: 0.73–0.95, $p = 0.007$, $I^2$=31%, Figure 3B).

### *The incidence of end-stage renal disease (ESRD)*

The incidence of ESRD was provided in two RCTs and four observational studies which contained 14008 CKD stages 3–5 patients with heart failure. Compared with control group, patients receiving sacubitril/valsartan had a lower incidence of ESRD (OR:0.73, 95%CI:0.60–0.89, $p = 0.002$, $I^2$=46%, Figure 3C).

To sum up, these findings indicated that sacubitril/valsartan might attenuate the progression of kidney function in abnormal renal function patients combined with heart failure.

### *Hyperkalemia*

Meta-analysis of two RCTs and three observational studies (with a total of 4131 CKD 3–5 stages patients with heart failure) showed that the risk of hyperkalemia in the sacubitril/valsartan group was comparable to that in the control group (OR: 1.31, 95% CI: 0.79–2.17, $p = 0.29$, Figure 4A), but with high heterogeneity ($I^2$=69%). To explore the source of heterogeneity, subgroup analysis was performed according to eGFR level, which illustrated a decrease in heterogeneity with no change in the conclusions (OR: 0.90, 95% CI: 0.70–1.17, $p = 0.45$, $I^2$=16%; OR: 1.86, 95% CI: 0.87–3.98, $p = 0.11$, $I^2$=45%, Figure 4A). In summary, sacubitril/valsartan might not increase the risk of hyperkalemia among abnormal renal function patients combined with heart failure.

### *Changes in blood pressure*

Regarding the changes in blood pressure, we applied dichotomous and continuous variables to perform the meta-analysis, respectively. Two RCTs consisting of 2796 CKD 3 stage patients with heart failure provided information about the incidence of hypotension (dichotomous variable). The results

showed that sacubitril/valsartan did not increase the risk of hypotension (OR:1.57, 95%CI:0.94–2.62, $p = 0.08$, $I^2 = 71\%$, Figure 4B).

Moreover, the pooled analysis of two observational studies involving 757 CKD 4–5 stages patients with heart failure indicated no statistically significant difference in systolic blood pressure between the two groups after follow-up (continuous variable, MD = 0.27 mmHg, 95% CI: −11.14–11.68, $p = 0.96$, Figure 4C).

Above all, we believed that the treatment with sacubitril/valsartan might not influence blood pressure in abnormal renal function patients combined with heart failure.

## Discussion

In the current study, we conducted a meta-analysis for the first time by combining RCTs and observational studies to comprehensively evaluate the efficacy and safety of sacubitril/valsartan in abnormal renal function patients with heart failure. With respect to efficacy, we found that sacubitril/valsartan significantly reduced the rate of cardiovascular death or heart failure hospitalization and the risk of kidney function worsening among eGFR below 60 mL/min/1.73m$^2$ patients with heart failure. As for safety outcomes, the risk of hyperkalemia and hypotension was not increased in patients receiving sacubitril/valsartan. To sum up, data from our study showed an apparent cardioprotective effect and good tolerability of sacubitril/valsartan, which could provide favorable evidence for the clinical management of abnormal renal function patients combined with heart failure.

It is clear that sacubitril/valsartan concurrently inhibits neprilysin and RAAS, thereby exerting effects on sympathetic tone alleviating, vasodilation, natriuresis, and diuresis [28,29]. Thus, sacubitril/valsartan has an absolute cardiovascular protective effect on heart failure patients with normal renal function [30,31]. For heart failure patients with abnormal renal function, a meta-analysis by Kang et al. revealed that the sacubitril/valsartan group reduced NT-proBNP levels, indicating the positive effect on cardiovascular system [32]. But this article focused on patients with CKD stage 3 and involved only three original studies. Based on this, our meta-analysis further included patients with CKD stages 4–5 and more relevant researches. Similar to the above study, we also found cardiovascular benefits of sacubitril/valsartan in CKD stages 3–5 patients with heart failure. To be specific, sacubitril/valsartan decreased risk of cardiovascular death or heart failure hospitalization. In summary, sacubitril/valsartan could improve cardiovascular prognosis in abnormal renal function patients combined with heart failure.

Theoretically, because of RAAS inhibition, sacubitril/valsartan can cause dilation of the efferent arterioles, subsequently leading to a decrease in glomerular pressure and eGFR [33]. However, our previous study [16] on patients with CKD stage 3 did not observe a significant reduction in eGFR among patients treated with sacubitril/valsartan. In the present meta-analysis, we further assessed the renal impact of sacubitril/valsartan on patients with lower eGFR based on RCTs and real-world observational studies. Consistently, the findings demonstrated that sacubitril/valsartan could effectively prevent the deterioration of renal function. This may be related to the increase in renal perfusion after improvement of heart failure by sacubitril/valsartan [14,25]. Furthermore, with the extension of follow-up (ranged from 8 weeks to 35 months), sacubitril/valsartan also revealed a favorable long-term prognosis for kidney function.

Hyperkalemia is a potentially fatal side effect of sacubitril/valsartan in patients with CKD [34]. But, the latest RCT involving CKD patients without heart failure found no statistical difference in hyperkalemia events between the sacubitril/valsartan and the control group [35]. Our meta-analysis, focusing on CKD patients combined with heart failure, also did not discover a trend of increased risk of hyperkalemia after sacubitril/valsartan treatment. Collectively, these findings indicated that sacubitril/valsartan may be safe for abnormal renal function patients combined with heart failure.

Previous studies found that in heart failure patients with normal kidney function, hypotension (SBP < 90mmHg) was more frequent in sacubitril/valsartan group than ACEI/ARBs [21]. Mechanistically, the use of sacubitril/valsartan in patients with renal impairment may increase the risk of hypotension, because the metabolism of sacubitril is dependent on renal function [33]. However, our results showed that sacubitril/valsartan did not exert a marked impact on blood pressure alterations among eGFR below 60 mL/min/1.73m$^2$ patients with heart failure. Generally, apart from RAAS overactivation and volume overload, several hormones such as endothelin [36] and thromboxane [37,38] also play a role in the development of hypertension in CKD patients. But these hormones are not inhibited by sacubitril-valsartan, which may explain why the incidence of hypotension in CKD stages 3–5 patients with heart failure receiving sacubitril/valsartan has not increased. Noteworthily, recent studies have demonstrated a dose-dependent effect of sacubitril/valsartan on anti-hypertension [39–41]. In clinical practice, the risk of hypotension may elevate with the increase in dosage of the drug. Thus, it is crucial to customize personalized therapy for individuals based on fluctuations in blood pressure.

There were several limitations in our study. First, our meta-analysis included several observational studies which lacked the experimental random allocation to assess outcomes accurately. But the risk of bias was relatively low in these observational studies, which meant that confounding factors were controlled to some extent. Second, some outcomes defined differently in these trials, but very slightly. Third, RCTs about the role of sacubitril-valsartan in patients with eGFR < 30 mL/min/1.73m$^2$ are still rare, and further large-scale RCTs should be carried out to validate above results.

## Conclusions

Our meta-analysis proves that sacubitril/valsartan has a favorable effect on cardiac function without obvious risk of adverse events in abnormal renal function patients combined

with heart failure, indicating that sacubitril/valsartan has the potential to become perspective treatment for these patients.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Funding

This work was supported by the Hebei Provincial Specialty Capacity Building and Specialty Leader Training Project ([2018]674), the Hebei Provincial Excellent Talents in Clinical Medicine Training Project ([2019]139), the Hebei Province Medical Technology Tracking Project (GZ2020013), the Hebei Clinical Medical Research Centre Project (20577701D), and the project of the Hebei Provincial Excellent Health Talents and High-Quality Development of Public Hospitals ([2022]180).

## Data availability statement

All data generated or analyzed during this study are included in this article or Supplementary files.

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