Am J Transl Res 2021;13(11):12114-12128
www.ajtr.org /ISSN:1943-8141/AJTR0130582

Review Article

The efficacy and safety of Sacubitril/Valsartan in the treatment of chronic heart failure: a meta-analysis

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Received January 22, 2021; Accepted September 6, 2021; Epub November 15, 2021; Published November 30, 2021

Abstract: Objective: A meta-analysis of the studies involving Sacubitril/Valsartan in chronic heart failure was performed to compare the efficacy and safety of Sacubitril/Valsartan with traditional drug therapy in chronic heart failure. Methods: We searched databases from PubMed, EMBASE, the Cochrane Library, Web of Science, and clinicaltrials.gov for studies published between 2010 and 2020 that reported efficacy and safety following Sacubitril/Valsartan administration. Results: Ten studies enrolling 1689 patients were included. Sacubitril/Valsartan outperformed traditional medicine (especially the Non-ARNI group) in terms of blood pressure, biomarkers and cardiac reverse remodeling indices, with striking changes in left ventricular ejection fraction, systolic blood pressure. Sacubitril/Valsartan showed significant benefit in renal function in patients with chronic heart failure. Conclusions: Compared with traditional drugs, Sacubitril/Valsartan significantly improved echocardiography, vital signs and biomarkers of patients with chronic heart failure, and reduced the incidence of hyperkalemia, renal dysfunction and other adverse reactions. Further large sample trials are needed in the future to determine the long-term effects of Sacubitril/Valsartan on efficacy and safety in patients with chronic heart failure.

Keywords: Chronic heart failure, Sacubitril/Valsartan, cardiac reverse remodeling, meta-analysis

Introduction

Chronic Heart Failure (CHF) is a complex clinical syndrome in which ventricular filling or ejection function is continuously impaired due to structural or functional abnormality of the heart, which is also the terminal stage of various cardiac disorders. The number of heart failure patients worldwide had reached 23 million and was increasing by 2 million per year, and the 5-year mortality of heart failure was much higher than that of most cancers [1]. In recent decades, heart failure has been considered as a chronic and spontaneous progressive disease, and the activation of different neuroendocrine systems leads to cardiac remodeling, which is a key factor in the development of heart failure (HF) [2, 3]. The sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS) and natriuretic peptide system (NPS) are the three predominant neuroendocrine systems, that might play a favorable or unfavorable role in the pathophysiology of heart failure. As the first angiotensin receptor-neprilysin inhibitor (ARNI), Sacubitril/Valsartan can block angiotensin II receptor and inhibit neprilysin enzyme through RAAS and NPS, respectively.

In the leading study (PARADIGM-HF trial), Sacubitril/Valsartan was shown to be superior to enalapril in reducing mortality, hospitalization rates and blood pressure of heart failure patients (LVEF≤40%) [4]. T The recently published PARAGON-HF trial results indicate that Sacubitril/valsartan may benefit patients with LVEF ranging from 45% to 57% (median) [5]. Myocardial fibrosis is an important pathophysiological mechanism underlying the development of HF. Sacubitril/Valsartan significantly decreased some biomarkers (associated with profibrotic signaling), which may contribute to improved outcomes [6]. Compared to enalapril, Sacubitril/Valsartan resulted in an early and

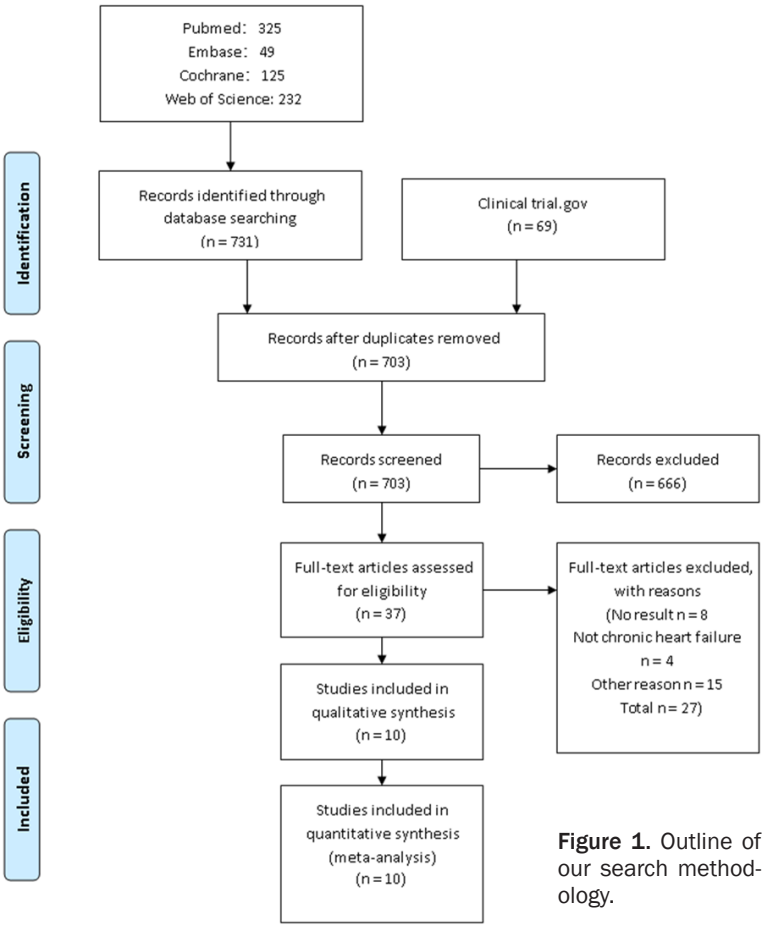

Figure 1. Outline of our search methodology.

sustained reduction in biomarkers of myocardial wall stress and injury (N-terminal pro-B-type natriuretic peptide and troponin) [7]. The concentration of NT-proBNP correlated with the extent of reversal of ventricular remodeling [8], and a recent study confirmed the involvement of Sacubitril/Valsartan in the above relationship [9]. In this context, we performed a systematic meta-analysis of the latest studies in the field of Sacubitril/Valsartan to compare the effects of other drugs with ARNI on CHF outcomes.

Methods

Literature retrieval

A systematic literature review was conducted for studies published in the English language from 2000 through to 2020 by searching PubMed, EMBASE, the Cochrane Library, Web of Science, and clinicaltrials.gov databases. The research subjects included "angiotensin receptor-neprilysin inhibitor", "heart failure", "chronic heart failure", "Sacubitril/Valsartan", "angiotensin receptor antagonists" and "angiotensin-converting enzyme inhibitor" (see the **Multimedia Appendix 1**).

Inclusion and exclusion criteria

All controlled studies involving the treatment of chronic heart failure with Sacubitril/Valsartan were included. Case reports were excluded. Included studies must meet the following criteria: (1) Adult patients aged 18 years old or over), (2) designed to compare the effects of ACEI/ARB with ARNI in the CHF population, (3) reported at least one of the primary outcomes or secondary outcomes: Vital signs (systolic blood pressure, diastolic blood pressure, heart rate), Echocardiography (left ventricular ejection fraction, left ventricular end-systolic dimension, left ventricular end-diastolic dimension, left atrial dimension, peak e-wave velocity/peak a-wave velocity ratio), Biomarkers (N-terminal pro-brain natriuretic peptide) and Safety (all-cause mortality, death from cardiovascular causes, angioedema, hyperkalemia, symptomatic hypotension, renal dysfunction).

Data extraction and quality evaluation

All the titles and abstracts of the literature were initially screened by two authors (Dai Hengfen and Zheng Caiyun) independently. Then, the two authors analyzed the full text respectively. Any disagreements were resolved by discussion and mutual consensus, or where agreement could not be reached, by arbitration with a third author (Huang Jungao). The researchers used a literature data extraction table to extract the required data, and other researchers confirmed the accuracy and authenticity of the data. The contents extracted included study information (study subject, author, date), baseline characteristics of study subjects (sample size, median age, sex ratio, heart failure type), control group, outcome indicators and adverse reactions after follow-up.

Table 1. Basic characteristics of included studies of the meta-analysis

Study	Study Design	Interventions	Category	Patients (N)	Age (year, Mean ± SD)	Women (%)	Outcomes	Follow-up (months)
Solomon 2012 [19]	RCT	ARNI Valsartan	HFpEF	301	71.1±9.1	56.5	ECG, Biomarkers, Safety	3 and 9
McMurray 2014 [4]	RCT	ARNI Enalapril	HFrEF	8399	63.8±11.4	21.8	Safety	27
Kang 2018 [20]	RCT	ARNI Valsartan	HFrEF	118	62.6±11.2	39.0	ECG, Safety	12
Gao 2019 [21]	RCT	ARNI Valsartan	HFrEF	120	70.3±7.3	26.7	ECG, Biomarkers, Safety	2
Solomon 2019 [5]	RCT	ARNI Valsartan	HFpEF	4796	72.7±8.4	51.7	Safety	35
Martens 2018 [22]	Prospective Observation	ARNI Non-ARNI	HFrEF	125	66.0±10.0	19.0	Vital Signs, ECG	4.2
Romano 2019 [14]	Prospective Observation	ARNI ACEI/ARB	HFrEF	205	59.0±10.0	15.0	Vital Signs, ECG, Biomarkers	10.5
Bayard 2019 [23]	Prospective Observation	ARNI Non-ARNI	HFrEF	41	70.0±10.0	24.4	ECG	3
El-Battrawy 2019 [24]	Prospective Observation	ARNI Non-ARNI	HFrEF	59	66.8±12.1	NR	Vital Signs, ECG, Biomarkers	12
Spannella 2019 [25]	Longitudinal Observational	ARNI Non-ARNI	HFrEF	84	65.4±11.3	32.1	Vital Signs, ECG	6 and 12

Vital Signs: including Systolic Blood Pressure, Diastolic Blood Pressure, Heart rate; ECG: echocardiography indicators including LVEF, LVES, LVED, LA and E/A ratio; Biomarkers: mainly refers to the NT-proBNP; Safety: including All-cause mortality, Death from cardiovascular causes, Angioedema, Hyperkalemia, Symptomatic hypotension, Renal dysfunction.

The quality of included randomized controlled trials was assessed using the Cochrane risk bias tool of the Cochrane system [10], and the quality of other studies (including retrospective cohort studies and prospective observational studies) were appraised using the Newcastle-Ottawa quality assessment scale [11].

Sensitivity analyses

Meta-analyses were conducted using Cochrane's Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and R programming language, version 3.6.3 (R Foundation for Statistical Computing, Guangzhou, China) with included literatures. Chi-square test was used to assess heterogeneity and I^2 was used for quantitative analysis. $P \geq 0.05$ and $I^2 \leq 50\%$ were considered to have no heterogeneity and a fixed-effects model was used. If $P < 0.05$ and $I^2 > 50\%$, the random-effects model was used, and then subgroup analysis was conducted to determine the cause of heterogeneity.

Results

Literature search results and baseline characteristics

Seven hundred and thirty-one articles were retrieved from different databases, along with 69 articles on clinical trial.gov. for a total of 800 articles. After removing the repeated studies, the remaining 703 articles were screened. 37 qualified articles with full text were read, 27 articles were excluded, 10 articles were included. Among the 10 literatures, there were 5 RCTs and 5 cohort studies. A total of 1689 patients were included. The system search results are shown in **Figure 1**. The baseline characteristics are presented in **Table 1**.

Quality assessment and publication bias

The quality of included randomized controlled trials was evaluated using the Cochrane systematic evaluation method, and other studies were evaluated using the Newcastle-Ottawa scale (**Figure 2** and **Table 2**). Funnel plots did not show significant publication bias (**Figure 3**).

Efficacy endpoints

LVEF: Ten studies provided data on LVEF. Meta-analysis was conducted according to different drugs in the control group, and there was no significant difference and high heterogeneity in the Valsartan group, while there was a significant difference in the non-ARNI and ACEI/ARB groups (Valsartan group: mean difference [MD] =2.47, 95% CI -2.57 to 7.50, I^2=95%, P=0.34; Non-ARNI group: mean difference [MD] =3.12,

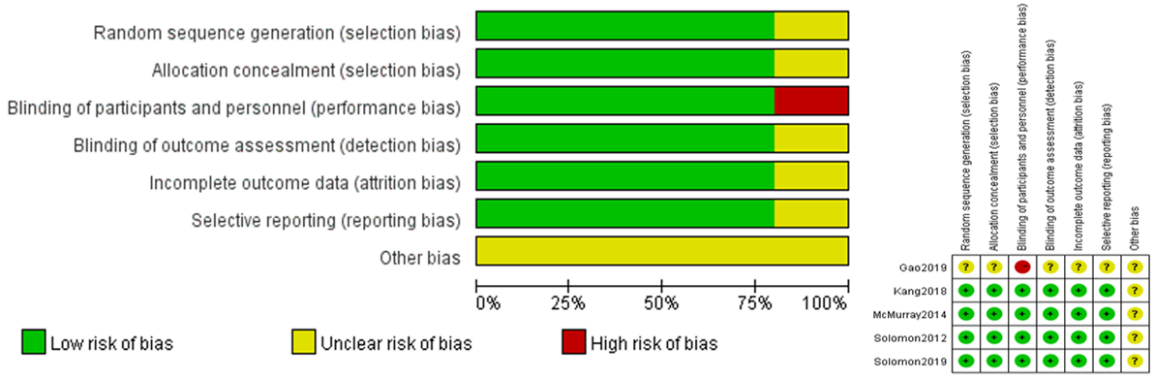

Figure 2. Quality evaluation of RCTs.

Table 2. Quality evaluation of other types of literature

Study	Representativeness of the exposed cohort	Selection of the non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total
Martens 2018	1	1	1	1	1	1	1	1	7
Romano 2019	1	1	1	1	1	1	1	1	8
Bayard 2019	1	1	1	1	1	1	1	1	8
El-Battrawy 2019	1	1	1	1	1	1	1	1	8
Spannella 2019	1	1	1	0	1	1	1	1	7

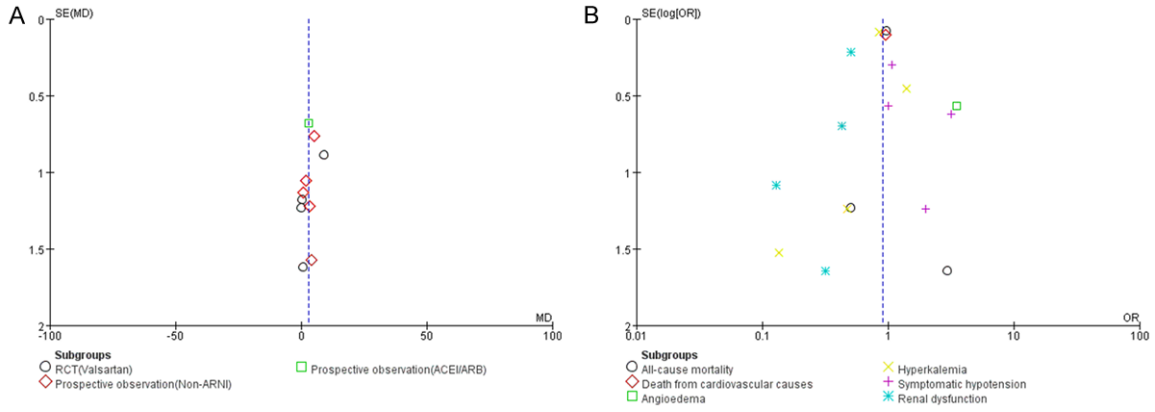

Figure 3. Funnel plot estimating publication bias. A. Left ventricular ejection fraction (LVEF). B. Safety (all-cause mortality, death from cardiovascular causes, angioedema, hyperkalemia, symptomatic hypotension and renal dysfunction).

95% CI 1.40 to 4.84, I^2=68%, *P*<.01; ACEI/ARB group: mean difference [MD] =3.00, 95% CI 1.67 to 4.33, *P*<.01), as shown in **Figure 4**.

Subgroup analysis of gender, age, follow-up time and sample size: Subgroup analysis of gender showed that the difference between the ARNI group and the control group was not related to gender, as shown in **Figure 5**.

Subgroup analysis of age showed that the difference between the ARNI group and the control group was not related to age, as shown in **Figure 6**.

Subgroup analysis of follow-up time (FU) showed that the difference between the ARNI group and the Valsartan group was not affected by follow-up time. Compared with the Non-ARNI

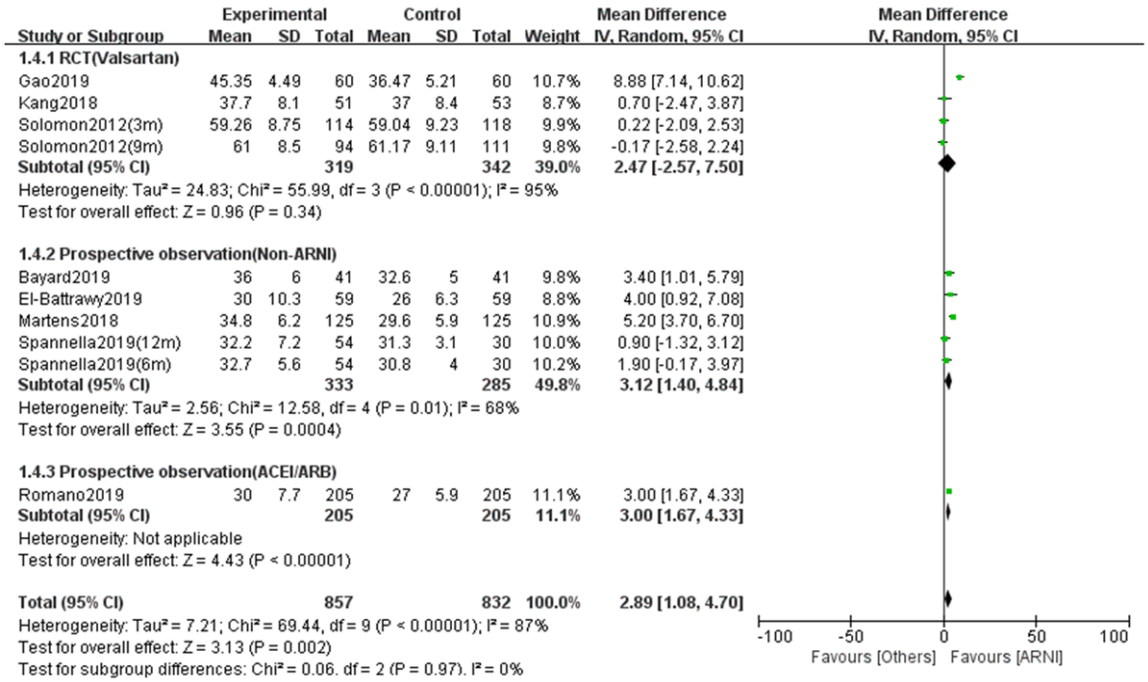

Figure 4. Forest plots for effect of Sacubitril/Valsartan on LVEF.

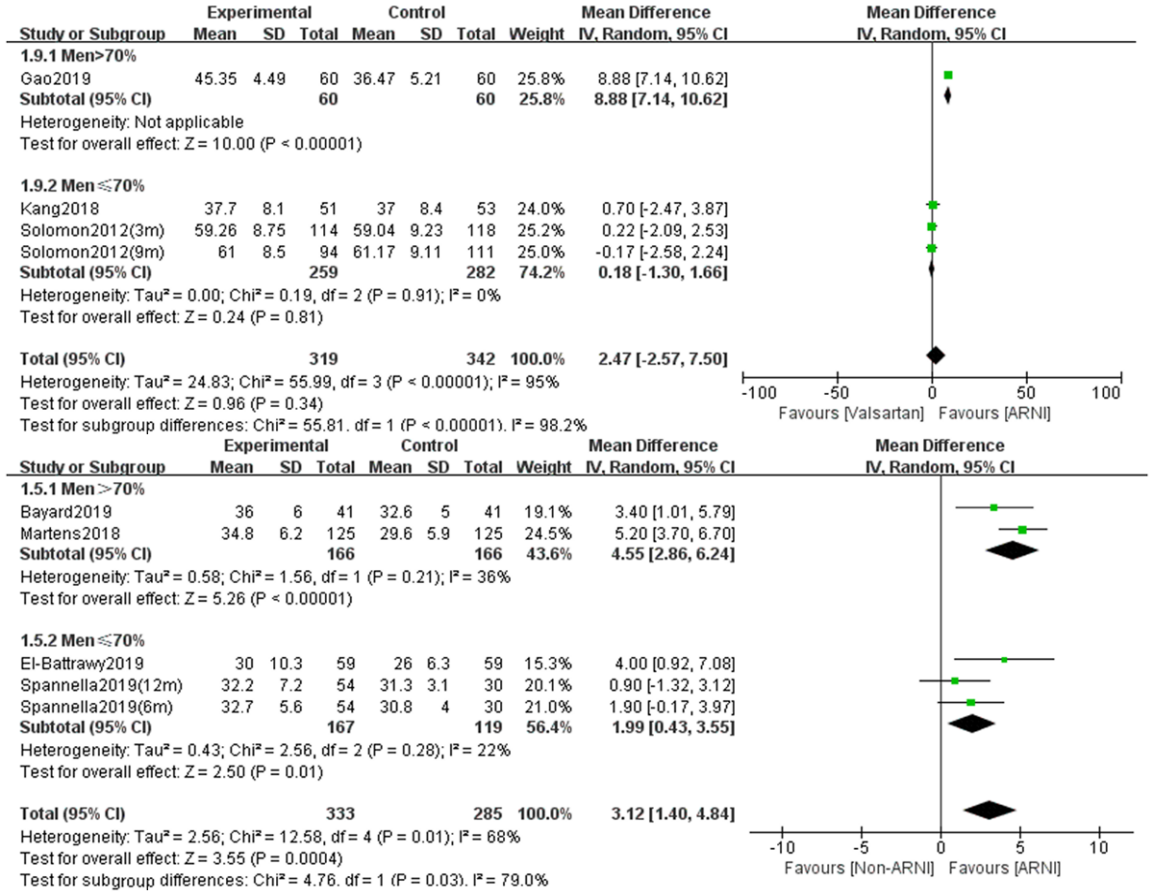

Figure 5. Subgroup analysis of gender in the improvement of LVEF in chronic heart failure with Sacubitril/Valsartan.

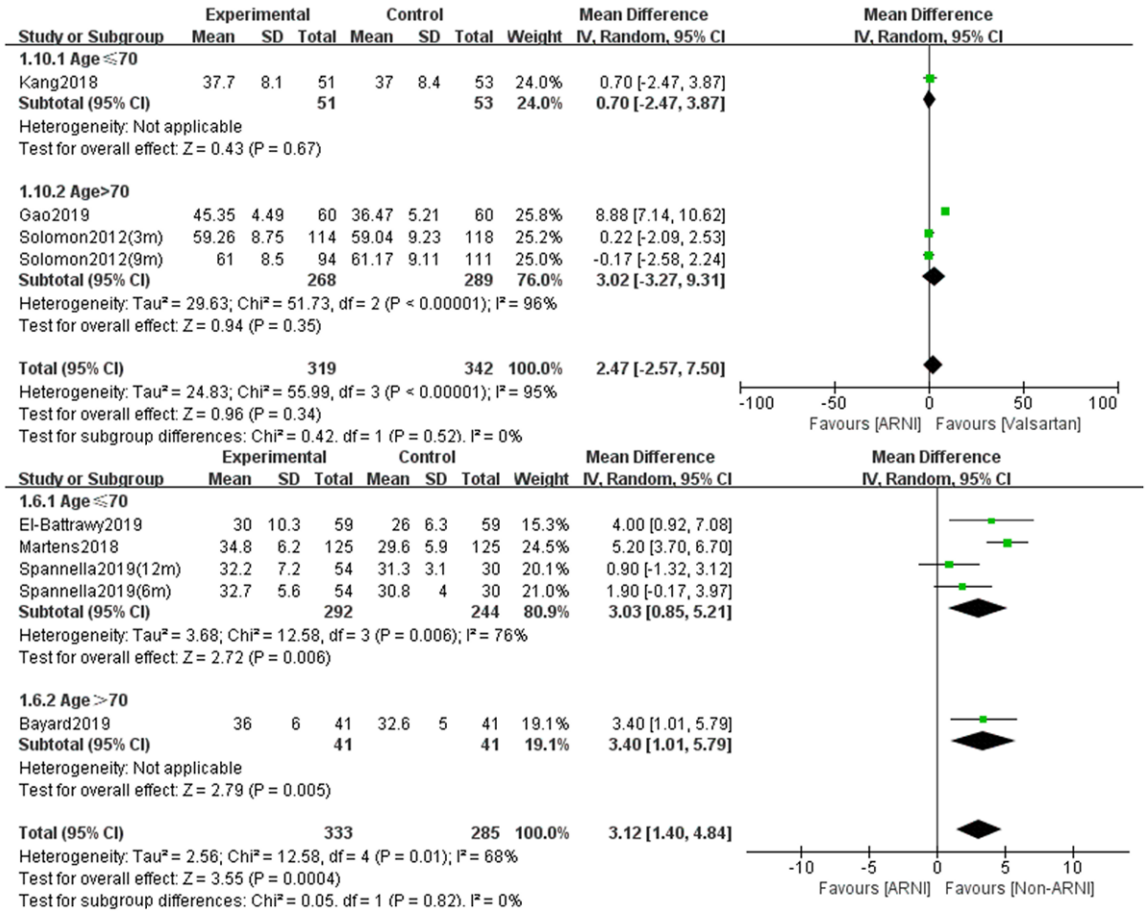

Figure 6. Subgroup analysis of age in the improvement of LVEF in chronic heart failure with Sacubitril/Valsartan.

group, the ARNI group had a better outcome in FU≤9 M population, and there was no significant difference in FU>9 M population. (FU≤9 M: mean difference [MD] =3.60, 95% CI 1.54 to 5.67, I^2=70%, P<.01; FU>9 M: mean difference [MD] =2.26, 95% CI -0.76 to 5.27, I^2=61%, P=0.14), as shown in **Figure 7**.

Subgroup analysis of sample size showed that the difference between the ARNI group and the control group was not related to sample size, as shown in **Figure 8**.

Other echocardiography indices: Other echocardiography indices mainly include LVES(D), left ventricular end-systolic dimension; LVED(D), left ventricular end-diastolic dimension; LA(D), left atrial dimension; E/A ratio. Through the meta-analysis, the ARNI group was superior to the Valsartan group of LA and LVED, and with significant differences. Compared with the Non-ARNI group there was no significant difference, as shown in **Figure 9**.

Vital signs: For vital signs including SBP, DBP and HR, meta-analysis results showed that the ARNI group was superior to the Non-ARNI group in SBP and HR, and there was no significant difference on DBP, as shown in **Figure 10** (SBP: mean difference [MD] =-3.65, 95% CI -6.80 to -0.49, I^2=23%, *P*<0.05; DBP: mean difference [MD] =-2.76, 95% CI -6.81 to -1.30, I^2=73%, *P*=0.18; HR: mean difference [MD] =-4.15, 95% CI -6.67 to -1.63, I^2=0%, *P*<0.01).

Safety endpoints

Major adverse reactions: The main safety endpoints include all-cause mortality, death from cardiovascular causes, angioedema, hyperkalemia, symptomatic hypotension, renal dysfunction. The adverse reactions of angioedema and symptomatic hypotension in the control group were less than those in the intervention group; There was a significant difference between the Sacubitril/Valsartan group and the traditional treatment group in renal dys-

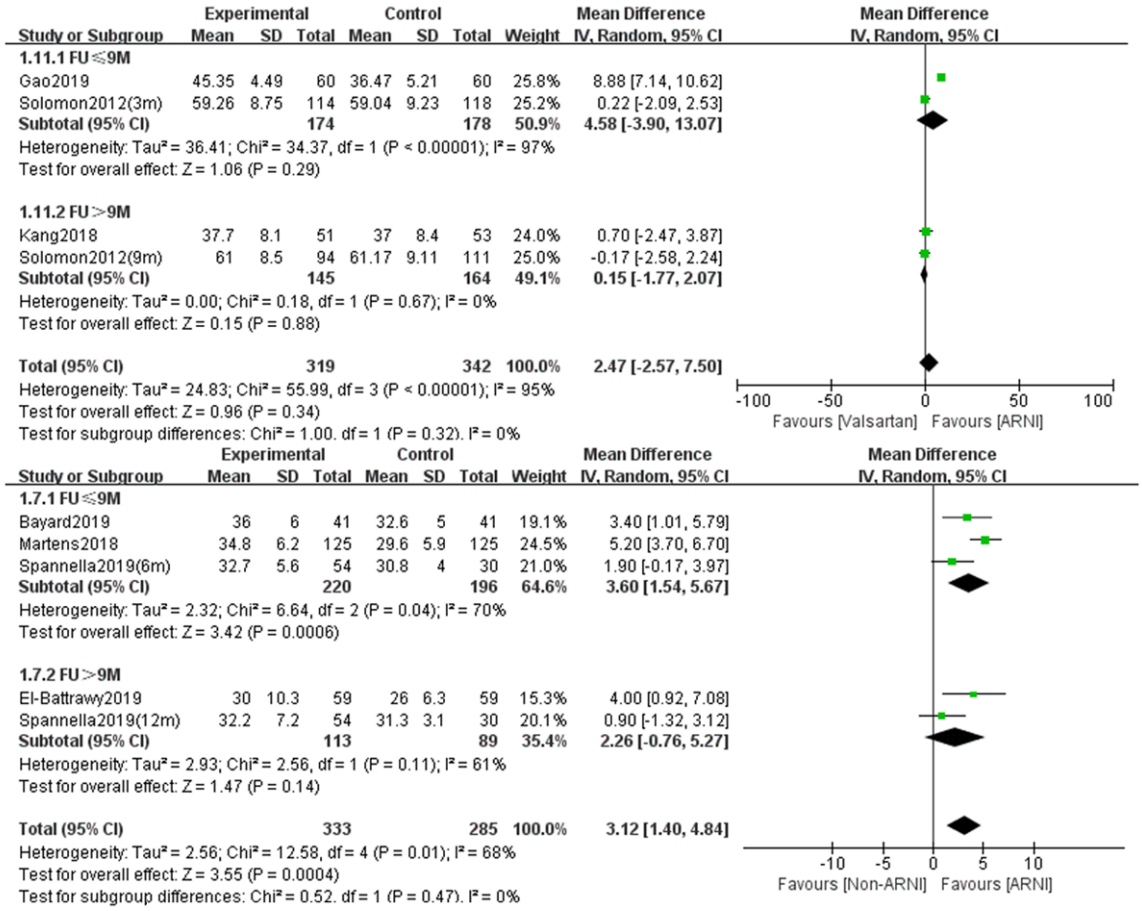

Figure 7. Subgroup analysis of follow-up time in the improvement of LVEF in chronic heart failure with Sacubitril/Valsartan.

function, and no significant difference in all-cause mortality, death from cardiovascular causes and symptomatic hypotension, as shown in **Figure 11**.

Other adverse reactions: Other adverse reactions include cerebral infarction, heart failure deterioration and rehospitalization, most of the studies had no significant differences in results, as shown in **Figure 12**.

Discussion

This study provided the latest systematic meta-analysis of assessing the effects of Sacubitril/Valsartan on LVEF, echocardiographic index, vital signs, biomarkers, and adverse reactions in patients with chronic heart failure. Compared with ACEIs/ARBs, all indicators of heart failure patients treated with Sacubitril/Valsartan showed significant improvement. Sacubitril/valsartan took effect one month after starting treatment, and the study's follow-up period ranged from 1 to 35 months. Subgroup analysis was used to address heterogeneity in LVEF and observed that gender, age, and follow-up time may contribute to differences in LVEF benefits. Sacubitril/Valsartan has a significant effect on the echocardiography index of CHF patients, including LVES, LVED. There was no significant difference in LA and E/A ratio. Both ACEIs and ARBs are recognized as essential agents for the treatment of chronic heart failure, with beneficial effects in reversing ventricular remodeling and reducing cardiovascular mortality. Therefore, as a unique combination of neprilysin inhibitor and ARB, Sacubitril/Valsartan has a reasonable effect on reversing ventricular remodeling and lowering blood pressure. Ventricular remodeling is a major underlying mechanism for CHF progression. Previous studies using assessments, of LVEF, LVESD, LVEDD, E/A ratio, or LA, had demonstrated that

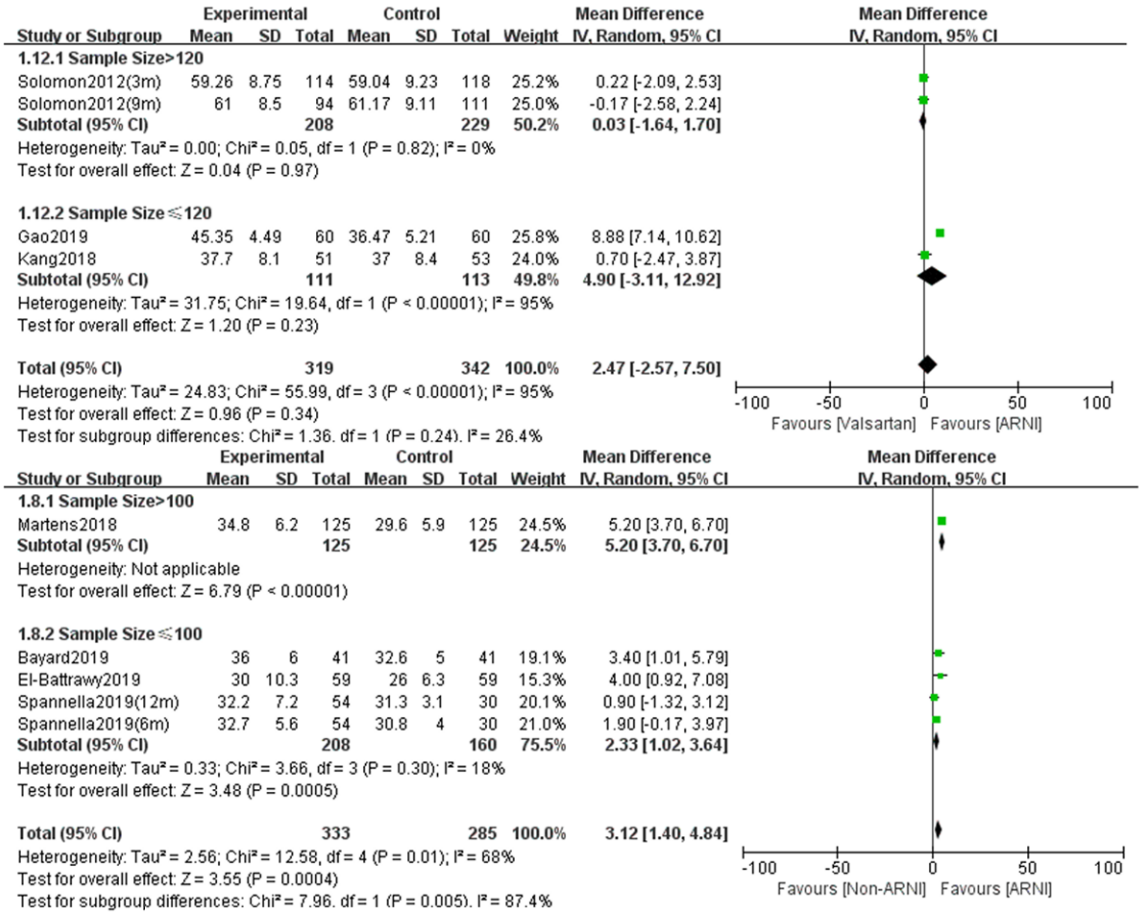

Figure 8. Subgroup analysis of sample size in the improvement of LVEF in chronic heart failure with Sacubitril/Valsartan.

left ventricular reverse remodeling is a dynamic process and could take many years to achieve [12, 13]. Recovery of left ventricular function is an important treatment goal for CHF, especially HFrEF. A prospective observational study of HFrEF patients indicated that the use of Sacubitril/Valsartan may produce "hemodynamic recovery" by reducing left ventricular filling pressure, mitral regurgitation from moderate to severe grade, and pulmonary artery systolic pressure, which associated with a reduction in NT-proBNP may ameliorate functional class capacity [14]. NT-proBNP is an epoch-making and specific marker for the determination of HF, which has been confirmed that the concentration of NT-proBNP was closely associated with left ventricular size and function [4]. And a greater reduction in NT-proBNP was associated with more extensive reverse remodeling and a better prognosis in HFrEF patients [8]. Results of the latest meta-analysis focused on cardiac reverse remodeling showed that patients with NT-proBNP reduction following Sacubitril/Valsartan initiation are more likely to experience reverse cardiac remodeling [15].

In terms of safety, compared with the traditional treatment group (the Non-ANRI group, the Valsartan group and the ACEI group), the number of events related to all-cause mortality and death from cardiovascular causes of Sacubitril/Valsartan group was reduced, but there was no significant difference. On the contrary, there were significant differences in the incidence of renal insufficiency. Serum potassium stability and renal function in patients with heart failure may benefit from Sacubitril/Valsartan. But for angioedema and symptomatic hypotension, the control group was superior to the intervention group. Sacubitril is associated with cardiomyocyte cell death, hypertrophy, and impaired myocardial contractility by a

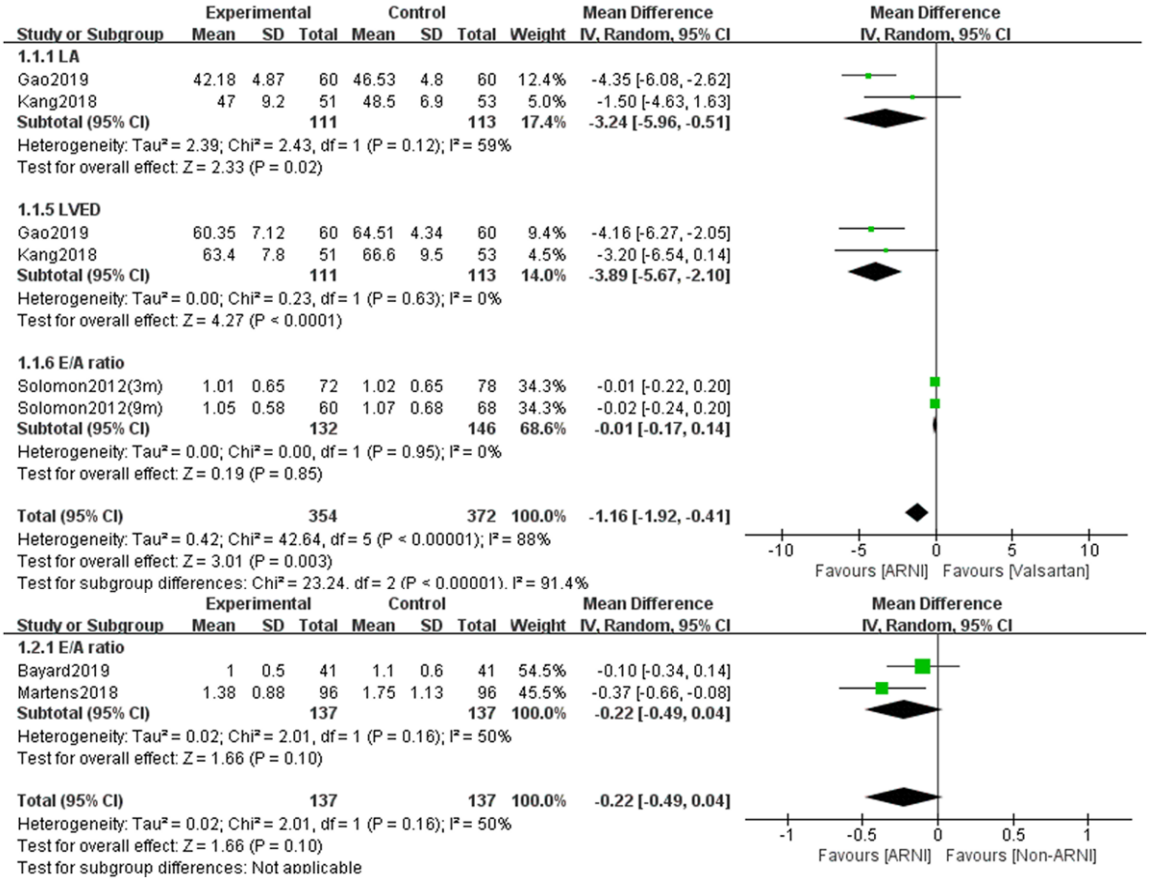

Figure 9. Forest plots for effect of Sacubitril/Valsartan on other echocardiography indices.

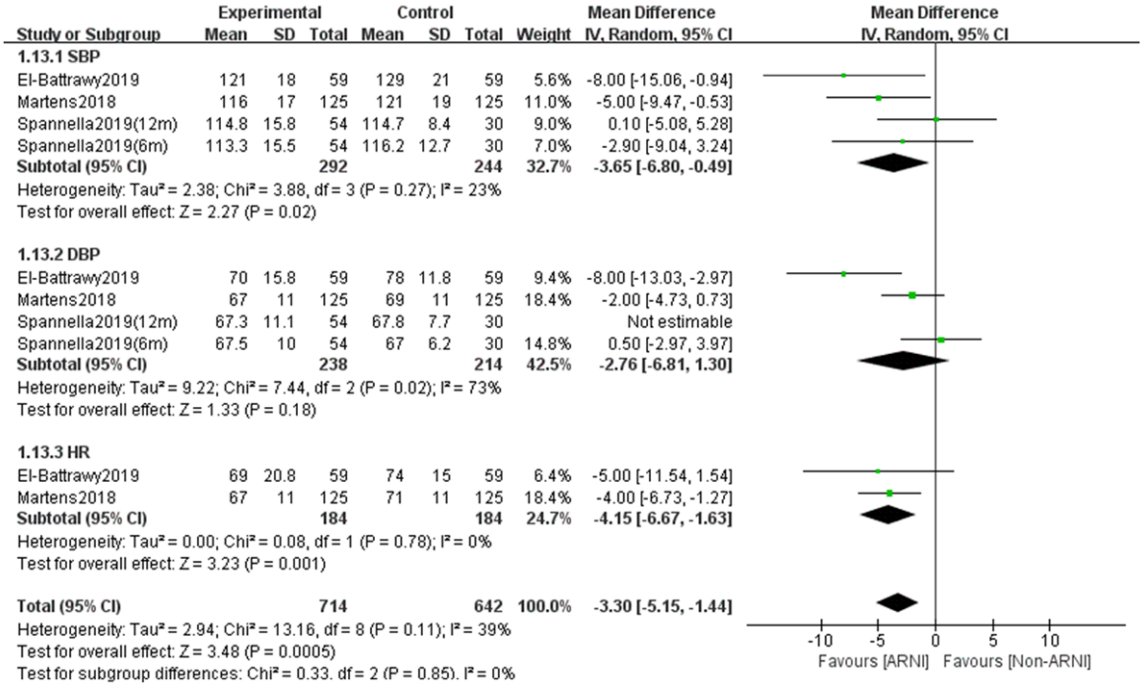

Figure 10. Forest plots for effect of Sacubitril/Valsartan on vital signs.

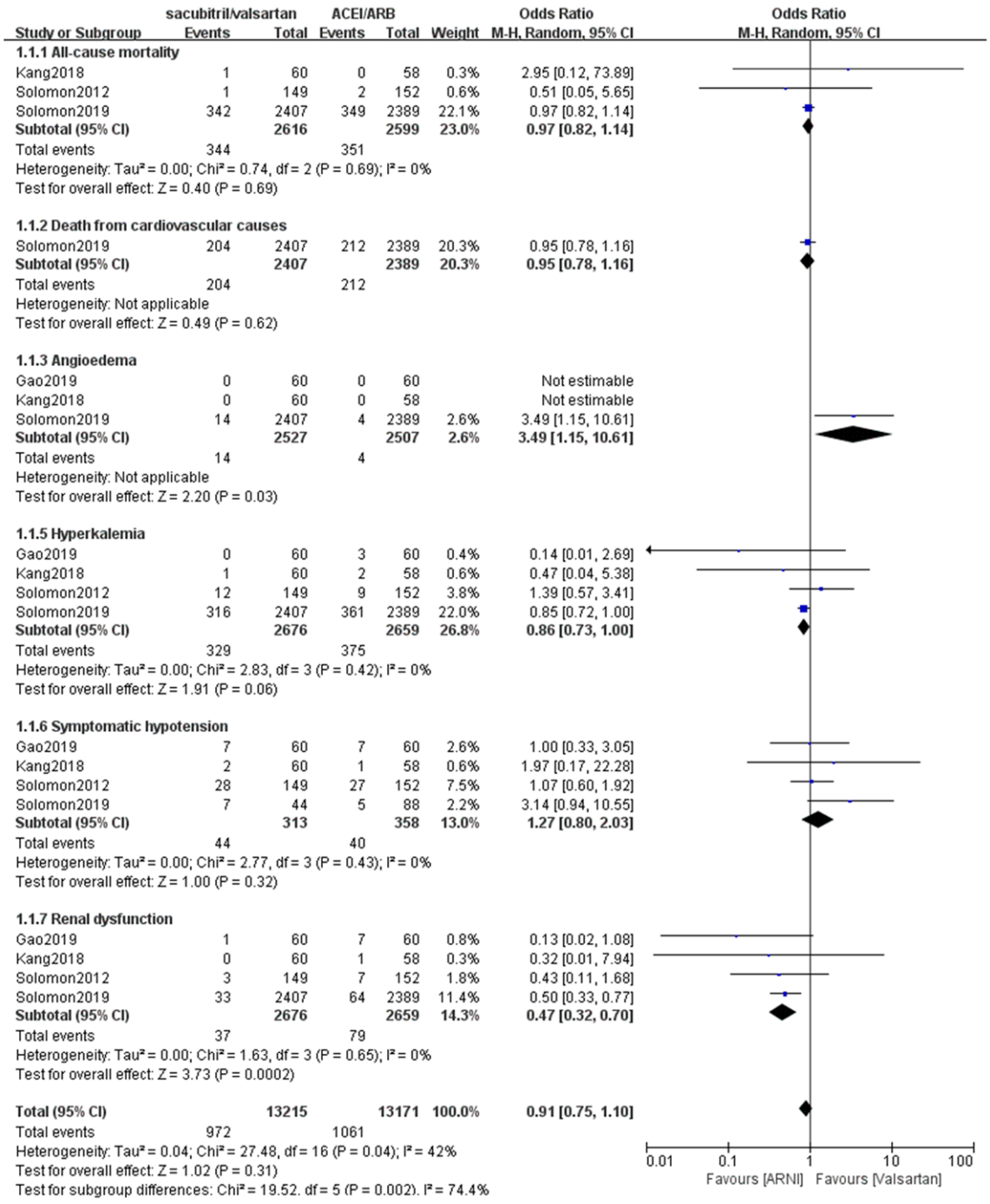

Figure 11. Forest plot of major adverse reactions.

systems biology approach, valsartan mainly blocks the AT1 receptor mechanistically [16]. Improved ventricular remodeling may be one of the mechanisms by which Sacubitril/Valsartan reduces cardiovascular and all-cause mortality, so Sacubitril/Valsartan has an advantage over ACEIs/ARBs in terms of therapeutic safety. Sacubitril/Valsartan sodium tablet is a salt compound crystal formed by the combination of Sacubitril and Valsartan in a ratio of 1:1 molar mass [17]. Because of its special crystal structure, it may be more susceptible to anaphylaxis, known as angioedema. Sacubitril/Valsartan is a precursor drug, which can be

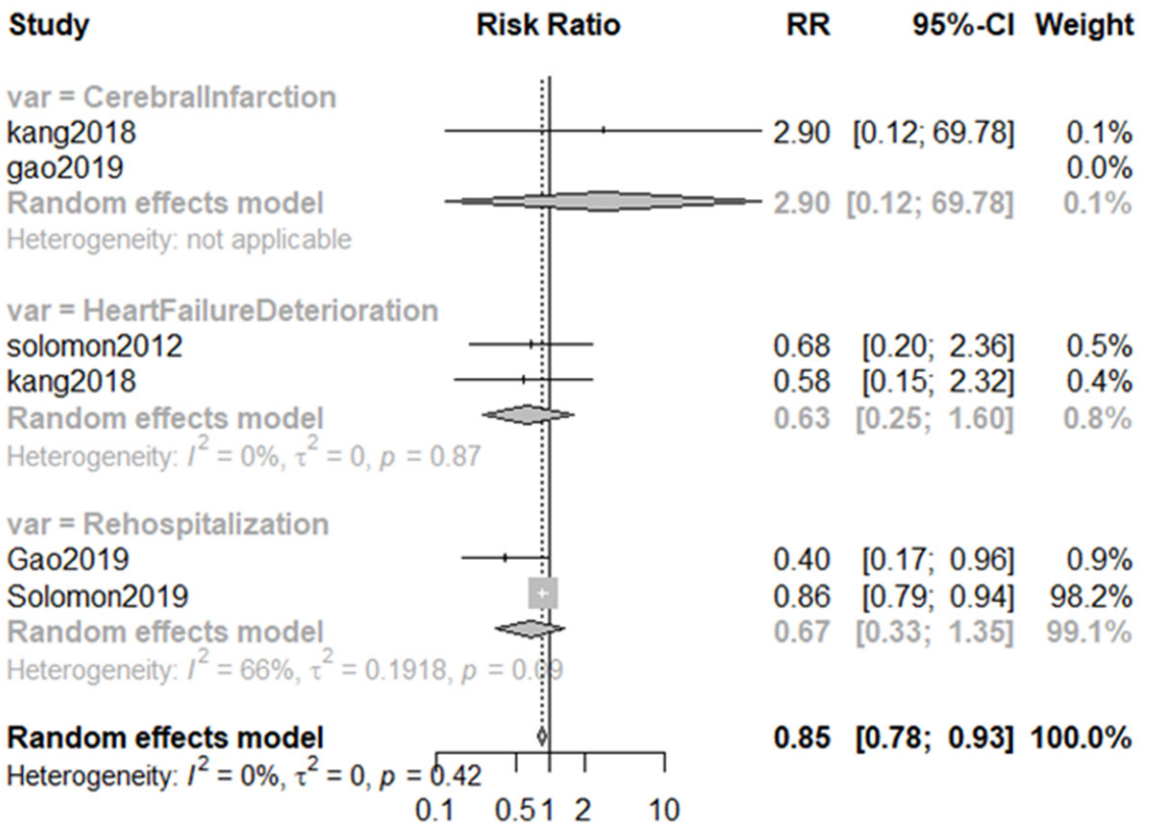

Figure 12. Forest plot of other adverse reactions.

metabolized into active enkephalinase inhibitor LBQ657 and valsartan in vivo [18], valsartan mainly blocks the AT1 receptor mechanistically to lower blood pressure.

Study limitations: the current meta-analysis included mainly observational studies, while RCT studies were few. Because randomized controlled trials have strict inclusion criteria, there is an observation phase prior to randomization to ensure patient tolerability. This suggests that randomized controlled trials may include healthier patients than observational studies. In addition, in observational studies, some patients may have received ACEIs/ARBs before receiving Sacubitril/Valsartan, and indicators of cardiac remodeling such as LVEF may have progressed from HFrEF to HFmrEF or HFpEF. Therefore, we need more and better RCTs in the future to focus on the efficacy and safety of Sacubitril/Valsartan. At the same time, some of the observational study may have unpredictable factors, so the interpretation of the results should be cautious. In addition, the sample size of some studies was not statistically controlled, and uneven changes in outcome indicators and follow-up time may have influenced the results.

Conclusions

This meta-analysis confirmed that Sacubitril/Valsartan could improve cardiac remodeling regardless of gender, age, sample size and follow-up time, and improve the patient's vital signs. For safety, Sacubitril/Valsartan can reduce renal insufficiency, but for angioedema and symptomatic hypotension, it showed no difference with the traditional intervention group.

The results of the current study suggest that if patients are treated with Sacubitril/Valsartan as early as possible, they may benefit more from the reversal of cardiac remodeling. Further studies on the long-term effects of Sacubitril/Valsartan on patients with CHF are needed to clarify the relationship between cardiac remodeling and long-term clinical outcomes, as well as the safety of the drug.

Acknowledgements

This study was supported by the Startup Fund for Scientific Research, Fujian Medical University (Grant number: 2020QH1346) and Fuzhou Health and Family Planning Science and Technology Innovation Platform Construction Project (2018-S-wp1).

Disclosure of conflict of interest

None.

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Pubmed

#1 Search (((((((LCZ696[Title/Abstract]) OR LCZ-696[Title/Abstract]) OR sacubitril[Title/Abstract]) OR sacubitril-valsartan [Title/Abstract]) OR entresto[Title/Abstract]) OR endopeptidase[Title/Abstract]) OR neutral endopeptidase[Title/Abstract]) OR neprilysin[Title/Abstract] OR Angiotensin receptor neprilysin inhibitor
#2 Search (((“Angiotensin-Converting Enzyme Inhibitors”[Mesh]) OR ((((((((((((((((Angiotensin Converting Enzyme Inhibitors[Title/Abstract]) OR Inhibitors, Kininase II[Title/Abstract]) OR Kininase II Antagonists[Title/Abstract]) OR Kininase II Inhibitors[Title/Abstract]) OR Angiotensin I-Converting Enzyme Inhibitors[Title/Abstract]) OR Angiotensin I Converting Enzyme Inhibitors[Title/Abstract]) OR Antagonists, Angiotensin-Converting Enzyme[Title/Abstract]) OR Antagonists, Angiotensin Converting Enzyme[Title/Abstract]) OR Antagonists, Kininase II[Title/Abstract]) OR Inhibitors, ACE[Title/Abstract]) OR ACE Inhibitors[Title/Abstract]) OR Inhibitors, Angiotensin-Converting Enzyme[Title/Abstract]) OR Enzyme Inhibitors, Angiotensin-Converting[Title/Abstract]) OR Inhibitors, Angiotensin Converting Enzyme[Title/Abstract]) OR Angiotensin-Converting Enzyme Antagonists[Title/Abstract]) OR Angiotensin Converting Enzyme Antagonists[Title/Abstract]) OR Enzyme Antagonists, Angiotensin-Converting[Title/Abstract]))) OR ((“Angiotensin Receptor Antagonists”[Mesh]) OR (((((((Antagonists, Angiotensin Receptor[Title/Abstract]) OR Receptor Antagonists, Angiotensin[Title/Abstract]) OR Angiotensin Receptor Blockers[Title/Abstract]) OR Receptor Blockers, Angiotensin[Title/Abstract]) OR Angiotensin II Receptor Antagonists[Title/Abstract]) OR Angiotensin II Receptor Blockers[Title/Abstract]) OR angiotensin receptor antagonist[Title/Abstract]))
#3 #1 and #2

EMBASE

#1 ‘sacubitril plus valsartan’/exp OR ‘lcz696’:ti,ab OR ‘lcz-696’:ti,ab OR ‘entresto’:ti,ab OR ‘sacubitril-valsartan’:ti,ab OR ‘sacubitril’:ti,ab OR ‘endopeptidase’:ti,ab OR ‘neutral endopeptidase’:ti,ab OR ‘neprilysin inhibitor’:ti,ab
#2 ‘dipeptidyl carboxypeptidase inhibitor’/exp OR ‘angiotensin converting enzyme inhibitors’:ti,ab OR ‘kininase ii inhibitors’:ti,ab OR ‘angiotensin i-converting enzyme inhibitors’:ti,ab OR ‘angiotensin i-converting enzyme inhibitors’:ti,ab OR ‘antagonists, angiotensin-converting enzyme’:ti,ab OR ‘antagonists, angiotensin converting enzyme’:ti,ab OR ‘inhibitors, ace’:ti,ab OR ‘ace inhibitors’:ti,ab OR ‘inhibitors, angiotensin-converting enzyme’:ti,ab OR ‘enzyme inhibitors, angiotensin-converting’:ti,ab OR ‘inhibitors, angiotensin converting enzyme’:ti,ab OR ‘angiotensin-converting enzyme antagonists’:ti,ab OR ‘angiotensin converting enzyme antagonists’:ti,ab OR ‘angiotensin receptor antagonist’/exp OR ‘antagonists, angiotensin receptor’:ti,ab OR ‘receptor antagonists, angiotensin’:ti,ab OR ‘angiotensin receptor blockers’:ti,ab OR ‘receptor blockers, angiotensin’:ti,ab OR ‘angiotensin ii receptor antagonists’:ti,ab OR ‘angiotensin ii receptor blockers’:ti,ab OR ‘angiotensin receptor antagonists’:ti,ab
#3 #1 and #2

The Cochrane Library search strategy

#1 MeSH descriptor: [Heart Failure, Systolic] explode all trees
#2 ((cardi*):ti,ab,kw OR (myocardi*):ti,ab,kw OR (heart):ti,ab,kw) AND ((failure):ti,ab,kw OR (dysfunction):ti,ab,kw)
#3 (“heart failure with reduced ejection fraction”):ti,ab,kw OR #1 OR #2
#4 (LCZ696):ti,ab,kw OR (sacubitril-valsartan):ti,ab,kw OR (sacubitril):ti,ab,kw OR (LCZ-696):ti,ab,kw OR (entresto):ti,ab,kw OR (endopeptidase):ti,ab,kw OR (neutral endopeptidase):ti,ab,kw OR (neprilysin inhibitor):ti,ab,kw
#5 #3 and #4

Web of Science search strategy

#1 (TS=(LCZ696 OR entresto OR “sacubitril-valsartan” OR “neprilysin inhibitor”))
#2 (TS=(heart OR myocardi* OR cardio* OR cardia*))

#3 (TS=(failure OR dysfunction))
#4 #2 AND #3
#5 (TS=("systolic heart failure" OR "heart failure with reduced ejection fraction" OR "ventricular dysfunction"))
#6 #4 OR #5
#7 #1 AND #6