Effects of sacubitril-valsartan on heart failure patients with mid-range ejection fractions: A systematic review and meta-analysis

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Aim: The effect of sacubitril-valsartan (ARNI) in heart failure (HF) patients with mid-range ejection fractions (HFmrEF) remains unclear. This study aimed to investigate the effects of ARNI in HFmrEF patients.

Methods: From inception to 15 February 2022, articles were searched via PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Whip, and Wanfang databases. Left ventricular functions, indicators related to HF, quality of life score, 6-Minute Walk Test, total effective rate, mortality, readmission rate, and adverse events were the outcomes. Relative risk (RR), weighted mean difference (WMD), and 95% confidence interval (CI) were used to evaluate the outcomes. The heterogeneity test was conducted for each indicator and measured by I² statistics. Subgroup analysis was performed regarding the type of study and duration of treatment.

Results: Sixteen studies involving 1,937 patients were included in this study. Our results showed ARNI was likely to improve left ventricular function by increasing the left ventricular ejection fraction (LVEF) (WMD: 2.36, 95%CI: 1.09–3.62), stroke volume (WMD: 16.80, 95%CI: 11.38–22.21), and left ventricular short-axis shortening rate (WMD: 16.80, 95%CI: −2.48 to −1.13), left atrial diameter (WMD: 2.23, 95%CI: −2.83 to −1.63), C-reactive protein level (WMD: −1.40, 95%CI: −2.62 to −0.18), and N-terminal-pro B-type natriuretic peptide level (WMD: −494.92, 95%CI: −641.34 to −348.50). ARNI has a higher total effective rate (RR: 1.15, 95%CI: 1.08–1.21), Kansas City cardiomyopathy questionnaire (WMD: 4.13, 95%CI: 3.46–4.81), and 6-Minute Walk Test (WMD: 51.35, 95%CI: 26.99–75.71) compared with angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). In addition, ARNI decreased the readmission rate (RR: 0.54, 95%CI: 0.43–0.68) (all p < 0.05). Nevertheless, there were no significant differences in the adverse outcomes.

Conclusion: This meta-analysis suggests ARNI may be an effective strategy with which to improve the left ventricular function, quality of life, and reduce the readmission rate in HFmrEF patients. However, long-term clinical studies with
large samples are still needed to further explore the efficacy and safety of ARNI compared with ACEI or ARB in the HFmrEF population.

**KEYWORDS**

sacubitril-valsartan, median ejection fraction, heart failure, systematic review, meta-analysis

**Introduction**

Heart failure (HF) is a clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood (Bozkurt et al., 2021). HF with mid-range ejection fraction (HFrEF) with left ventricular ejection fraction (LVEF) ranging from 40 to 49% is a category of HF (McDonagh et al., 2022). HFrEF is a hemodynamic state in which heart cannot meet the circulatory demands of the body, or at the expense of increased left ventricular filling pressure (Ye et al., 2022). The incidence of HFrEF accounts for 10–20% of the population with HF (Ponikowski et al., 2016a; Srivastava et al., 2020). HFrEF is associated with notable morbidity and mortality (Rickenbacher et al., 2017). Consequently, it is essential to find therapies for HFrEF patients.

Substantial evidence has indicated that angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) could improve the partially attenuate left ventricular (LV) dilation and remodeling in HF, however, the morbidity and mortality of HF patients remain unacceptably high (Asgar et al., 2015; Zhang et al., 2020). In recent years, angiotensin receptor nephrilysin inhibitor (ARNI) also named sacubitril-valsartan demonstrated to reduce mortality and morbidity of HF and is now a new recommended treatment option for symptomatic reduced ejection fraction (HFrEF) according to the recommendations from the American College of Cardiology (ACC), and the European Society of Cardiology (ESC) (Maddox et al., 2021; McDonagh et al., 2022). ARNI mainly focuses on inhibiting the activity of nephrilysin to decrease the degradation of natriuretic peptides, stimulate vasodilation and diuresis, and reduce myocardial fibrosis and hypertrophy, which has shown clinical benefits in HF with HFrEF (Pascale-Figal et al., 2021). Nevertheless, there are currently limited studies comparing the effects of ARNI and traditional ACEI/ARB drugs on patients with HFrEF. There are differences in LVEF, epidemiological characteristics, and pathogenesis of patients with different types of HF, so it is necessary to seek optimal treatment for HFrEF patients (Xin et al., 2019). Furthermore, the efficacy and safety of ARNI in patients with HF are still controversial (Zhang et al., 2020). Hence, a meta-analysis to assess and compare the ARNI and traditional ACEI/ARB drugs on HFrEF patients is needed.

Herein, we performed a meta-analysis to evaluate the potential clinical benefits and safety of ARNI in HFrEF patients in which ARNI was compared with ACEI/ARB drugs.

**Methods**

This meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines without registry.

**Data sources and search strategy**

Databases including PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Whip, and Wanfang were searched without any restrictions from inception to 15 February 2022. The search strategy from the PubMed consisted of the following keywords: “Sacubitril Valsartan” OR “sacubitril and valsartan sodium hydrate drug combination” OR “sacubitril valsartan sodiumhydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “trisodium (3-(1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-3′-methyl-2′-(pentanoyl(2′-tetrazol-5-ylate)biphenyl-4′-ylmethyl)amino)butyrate) hemipentahydrate” OR “sacubitril and valsartan drug combination” OR “sacubitril valsartan drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination” OR “sacubitril-valsartan sodium hydrate drug combination”. The specific search strategy was the combination of keywords as follows: appropriate search strategy.

**Selection criteria**

Inclusion criteria based on the PICOS principles were: 1) Populations: Patients diagnosed with HFrEF; 2) intervention:
ARNI as the observation group; 3) comparators: ACEI or ARB as the control group; 4) outcomes: left ventricular function, indicators related to HF, quality of life score, 6-Minute Walk Test (6-MWT), total effective rate, mortality, readmission rate, and adverse events; 5) study design: Randomized controlled trials (RCTs) or cohort studies 6) studies published in English and Chinese.

The exclusion criteria were as follows: 1) animal experiments; 2) case reports, meta-analyses, reviews, and letters.

Data extraction and quality assessment

Two investigators (Jianbin Qin and Weijian Wang) initially screened studies based on abstracts and reviewed the full text according to eligibility criteria. The final qualification for inclusion depended on the agreement between the two reviewers. Any differences should be resolved through consultation with the third reviewer (Ping Wei). The following data were extracted from each included study: basic characteristics of studies (authors, publication year, country, study design), characteristics of patients (sample size, gender, age), ARNI and ACEI/ARB treatments (dosage and duration of treatment), study design, Randomized controlled trials (RCTs) or cohort studies, and adverse events; 5) study design: Randomized controlled trials (RCTs) or cohort studies 6) studies published in English and Chinese.

The exclusion criteria were as follows: 1) animal experiments; 2) case reports, meta-analyses, reviews, and letters.

Variables and outcomes assessment

According to ESC guidelines, the diagnostic criteria for HFrEF in this study was a LVEF of 40–49% (Ponikowski et al., 2016b).

The primary outcomes were left ventricular functions including left ventricular ejection fraction (LVEF), left ventricular end diastolic dimension (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular septal thickness (DVST), left atrial diameter (LAD), stroke volume (SV), left ventricular short axis shortening rate (FS), C-reactive protein (CRP) level. The second outcomes were 1) indicators related to HF including N-terminal-pro brain natriuretic peptide (NT-proBNP), soluble suppression of tumorigenesis-2 (sST2), growth differentiation factor-15 (GDF-15); 2) quality of life score including Minnesota heart failure scale score (MHHQL), and The Kansas city cardiomyopathy Questionnaire (KCCQ); 3) 6-MWT; 4) total effective rate; 5) mortality including 1-year mortality, and cardiac death; 6) readmission rate; 7) adverse events including HF worsen, malignant arrhythmia, renal function deterioration, hyperkalemia, hypotension, angioedema, serum creatinine (SCr) level. LVEF was calculated as end-diastolic minus end-systolic volume divided by end-diastolic volume (Panza et al., 2019). The normal range of LVEDD was 35–56 mm, LVESD was 20–40 mm, and LAD was 27–40 mm (Yang et al., 2018). Quality of life was assessed by the MHHQL and KCCQ. MHFQ is a 21-item disease specific instrument with scores varying from 0 to 5 and a summary score varying from 0 to 105, the highest score representing the worst health-related quality of life (Napier et al., 2018). The KCCQ was a 23-item, self-administered questionnaire that quantifies physical function, symptoms, social function, self-efficacy, and quality of life for patients with HF. The higher the score, the better the quality of life (Green et al., 2000). The total effective rate was assessed in 3 outcomes: 1) significantly effective: after treatment, the symptoms of HF were significantly improved, the LVEF was significantly increased, and the cardiac function grade was decreased to >; 2) effective: after treatment, the symptoms of HF were relieved, and LVEF was reduced, and the cardiac function grade has decreased by >1; 3) no curative effect: after treatment, the symptoms of HF and LVEF did not improve or even worsened (Xiangjie Liu, 2021). Readmission rate referred to the ratio of hospital readmission due to HF to follow-up. Hypotension was defined as blood pressure < 90/60 mm Hg (McMurray et al., 2014). Deterioration of renal function was defined as a relative increase of serum creatinine ≥25% or an increase of serum creatinine ≥0.3 mg/dl (1 mg/dl = 88.4 μmol/L) from baseline (Bhatt et al., 2018). Hyperkalemia referred to blood clear potassium > 5 mmol/L during the follow-up period (Akinlade et al., 2014). The angioedema was angionecrotic edema, also known as giant urticaria, which involves deep layers of skin, including subcutaneous tissues, as well as airway mucosa, and is manifested as localized non-pitting edema occurring in local tissues (Zuberbier et al., 2018).

Statistical analysis

Relative risk (RR) was used as an effect indicator for categorical data. Continuous data were analyzed by calculating weighted mean difference (WMD), and the effect size was expressed by 95% confidence intervals (CIs). Heterogeneity of effects across trials was evaluated by I² tests for heterogeneity. When the heterogeneity statistic I² ≥ 50%, random-effects model analysis was performed, otherwise, fixed-effects model analysis was applied. p < 0.05 was considered statistically significant. When the difference was statistically significant and I² ≥ 50%, subgroup analysis was performed regarding the type of study and duration of treatment. Sensitivity analysis was performed for all outcomes. Begg’s test was examined to evaluate the potential for publication bias. When publication bias occurred, the “cut-and-fill method” was adopted to adjust publication bias. Software...
Stata 15.1 (Stata Corporation, College Station, TX, United States) was used for statistical analysis.

Results

Literature search and characteristics of studies

A total of 5,408 studies were identified in the initial literature search. By removing duplicates, 3,287 articles were retrieved. After screening for titles and abstracts, 34 articles were left. Finally, 16 studies (Wang, 2019; Cunfang Chen et al., 2020; He Wen et al., 2020; Pengfei Ma, 2020; Rong Liu et al., 2020; Dongruil Xu and Liu, 2021; Man Gao et al., 2021, Meixian Chen et al., 2021; Mi, 2021; Wu Yi et al., 2021; Xiangjie Liu, 2021; Xinxin Guo, 2021; Yongyue Zhou, 2021; Xiang Li, 2021; Ye et al., 2022; Lr Liana Tumasyan et al., 2019) were included in this study, involving 6 cohort studies and 10 RCTs. A total of 1,937 patients participated in the study, including 913 in the experimental group and 1,024 in the control group. There were 3 low-quality articles and 13 high-quality articles included. The flow chart of study selection is shown in Figure 1. The basic characteristics of included studies are presented in Table 1. The data of each outcome before and after treatment between the observation group and control group are presented in Table 2.

![Flow chart of study selection and patient's collection](image-url)
### TABLE 1 Basic characteristics of included studies.

| Author     | Year | Country | Study design | Groups | Drugs                                      | Duration of treatment (months) | Sample size [n (%)] | Age (years, mean ± SD) | Male/Female [n (%)] | Diabetes | Outcomes | Quality |
|------------|------|---------|--------------|--------|-------------------------------------------|-------------------------------|---------------------|------------------------|---------------------|-----------|----------|---------|
| Wang 2019  | China | RCT     | ARNI         |         | Sacubitril valsartan, the initial dose is 50 mg once, bid, in the later stage, it is increased according to the patient’s tolerance, specifically every 2–4 weeks, until it reaches a stable 200 mg once, bid | 3                             | 48                  | 55.9 ± 5.4             | 35/13               | NA        | NT-proBNP, LVEF, Scr, total effective rate | 5       |
| Tumasyan 2019 | Armenia | RCT | ACEI/ARB | ACEI/ARB | ARNI Sacubitril/valsartan, 200 mg, bid Ramipril Ramipril 10 mg/Valsartan 160 mg, bid | 12                            | 48                  | 57.5 ± 4.3             | 37/11               | NA        | 1-year mortality, readmission rate | 3       |
| Liu 2020 | China | Retrospective cohort | ARNI         |         | Sacubitril valsartan, from the minimum dose of 25.0 mg/time, orally bid, gradually increased to the maximum tolerated dose of 200.0 mg/time, orally bid Benazepril Benazepril hydrochloride, from the minimum dose of 2.5 mg/time, orally once a day, gradually increased to the maximum tolerated dose of 10 mg/time, orally once a day | 1                             | 20                  | 61.75 ± 13.04          | 16/4                | NA        | NT-proBNP, LVEF, LVESD, LAD | 4       |
| Wen 2020 | China | RCT | ARNI         |         | Sacubitril valsartan, 100 mg, bid | 6                             | 41                  | 55 ± 7                 | 28/13               | 11         | Total effective rate, NT-proBNP, GDF-15, sST2, LVEF, FS, 6-MWT, quality of life, readmission rate, adverse events | 4       |
| Ma 2020 | China | Retrospective cohort | ARNI         |         | Valsartan Valsartan, 80 mg, bid | 3                             | 41                  | 53 ± 6                 | 25/16               | 8          | Total effective rate, NT-proBNP, LVEDD, DVST, LAD, LVEF, quality of life | 5       |
| Chen 2020 | China | RCT | ARNI         |         | Analapril Analapril tablets, 5 mg/time, bid | 6                             | 50                  | 64.37 ± 8.45           | 28/22               | NA        | NT-proBNP, LVEF, LVEDD, cardiac death, readmission rate | 5       |

(Continued on following page)
| Author       | Year | Country | Study design | Groups | Drugs                                                                 | Duration of treatment (months) | Sample size | Age (years, mean ± SD) | Male/Female | Diabetes | Outcomes | Quality |
|--------------|------|---------|--------------|--------|-----------------------------------------------------------------------|--------------------------------|-------------|------------------------|-------------|----------|----------|---------|
| Mi           | 2021 | China   | RCT          | ARNI   | Sacubitril valsartan, 25 mg/time, bid; then gradually increased to 200 mg/time, bid | 1                              | 53          | 69.5 ± 9.6             | 31/22       | 18       | LVEF, LVESD, LVEDD | 4       |
| Xu           | 2021 | China   | RCT          | ARNI   | Sacubitril valsartan, 50 mg, bid, according to the disease and tolerance, the dose is doubled every 2–4 weeks until 100 mg, bid | 6                              | 49          | 66.6 ± 13.6            | 32/17       | 11       | NT-proBNP, sST2, CRP, SCr, LVEDD, DVT, LAD, LVEF, 6-MWT, readmission rate, cardiac death, adverse events | 6       |
| Gao          | 2021 | China   | Prospective cohort | ARNI   | Sacubitril valsartan, start with a low dose of 50 mg and gradually increase to a target dose of 200 mg according to the patient’s condition and blood pressure tolerance, bid | 12                             | 43          | 61 ± 11                | 22/21       | 7        | NT-ProBNP, 6-MWT, readmission rate, 1-year mortality | 4       |
| Guo          | 2021 | China   | RCT          | ARNI   | Sacubitril valsartan, 100 mg/tablet, 100 mg/time, bid | 12                             | 58          | 68.25 ± 4.30           | 38/20       | 25       | NT-proBNP, LVEF, LVEDD | 5       |
| Li           | 2021 | China   | RCT          | ARNI   | Valsartan, 80 mg/tablet, 80 mg/d | 12                             | 58          | 67.70 ± 3.72           | 41/17       | 22       | Total effective rate, LVEF, FS, quality of life, readmission rate, adverse events | 6       |
| Wu           | 2021 | China   | Retrospective cohort | ACEI/ARB | Sacubitril valsartan | 3                              | 95          | 69.32 ± 7.72           | 64/31       | NA       | NT-proBNP, LVEF, LVEDD | 5       |
|              |      |         |              | ACEI   | ACEI                                                                  |                                | 99          | 71.42 ± 7.69           | 44/44       | NA       |                                 |         |

(Continued on following page)
| Author | Year | Country | Study design | Groups | Drugs | Duration of treatment (months) | Sample size [n (%)] | Age (years, mean ± SD) | Male/Female [n (%)] | Diabetes | Outcomes | Quality |
|--------|------|---------|--------------|--------|-------|--------------------------------|---------------------|------------------------|---------------------|----------|----------|---------|
| Liu    | 2021 | China   | Retrospective cohort | ARB   | ARB   | 3                              | 84                  | 70.56 ± 6.86           | 54/30               | NA       | LVEF, LVEDD, DVST, LAD, quality of life, total effective rate, adverse cardiac events | 7       |
|        |      |         |              | ARNI  | Sacubitril valsartan, the initial dose is 50 mg each time, bid, and it is increased by 1 time after 2–4 days until the target dose is 200 mg each time, bid, a course of 3 months, a total of 1 course of treatment | | | | | | | |
|        |      |         |              | Enalapril | Enalapril, 5 mg, bid, a course of 3 months, a total of 1 course of treatment | 52                  | 62.63 ± 6.85           | 30/22               | NA       | | |
| Zhou   | 2021 | China   | RCT          | ARNI  | Sacubitril valsartan, initial dose 50 mg/time, bid, dose increase every 2–4 weeks times, the maximum dose is 200 mg/time, bid | 100                 | 68.88 ± 10.16          | 64/36               | 39       | NT-proBNP, LVEF, LVEDD, LAD, total effective rate | 4       |
|        |      |         |              | Benazepril | Benazepril hydrochloride, starting at 2.5 mg/d and gradually increasing to 10 mg/d | 100                 | 69.81 ± 9.54           | 61/39               | 32       | | |
| Chen   | 2021 | China   | RCT          | ARNI  | Sacubitril valsartan, starting from 50 mg/time, bid, it is also doubled or halved every 2 weeks, and titrated to the maximum tolerated dose (target dose of 200 mg/time, bid) | 59                  | 60.5 ± 12.6            | 37/22               | 14       | LVEF, SV, 1-year mortality, readmission rate, renal function deterioration, hyperkalemia | 6       |
|        |      |         |              | Candesartan | Candesartan, starting from 4 mg, once a day, doubling or halving the dose every 2 weeks, and gradually titrating to the maximum tolerated dose according to the patient’s tolerance (target dose: 16 mg/time, once a day) | 56                  | 60.4 ± 12.7            | 38/21               | 19       | | |
| Ye     | 2022 | China   | Retrospective cohort | ARNI  | Sacubitril valsartan, 50 mg/starting dose 25 mg, bid, gradually increasing to the target dose according to the blood pressure of the patients | 84                  | 62.29 ± 12.82          | 52/32               | 84       | LVEF, LVEDD, readmission rate | 7       |
|        |      |         |              | Valsartan | Valsartan, 80mg, qd | 86                  | 63.49 ± 11.61          | 56/30               | 86       | | |

Notes: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; HF, heart failure; HFrEF, heart failure with mid-range ejection fraction; NA, not available; RCT, randomized controlled trial; SD, standard deviation; bid, twice a day; qd, every day; CAD, coronary atherosclerotic heart disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; DVST, diastolic ventricular septal thickness; LAD, left atrial diameter; CRP, C-reactive protein; Scr, serum creatinine; SV, stroke volume; FS, left ventricular short axis shortening rate; GDF-15, growth differentiation factor-15; sST2, soluble suppression of tumorigenesis-2; 6-MWT, 6-min walking distance trial.
TABLE 2 Left ventricular function outcomes before and after treatment between sacubitril-valsartan and ACEI/ARB group.

| Outcomes | Author     | Year | Controls | Controls | Observation group | Observation group | Control group | Control group |
|----------|------------|------|----------|----------|-------------------|-------------------|---------------|---------------|
|          |            |      | Sample   | Sample   | Before treatment  | After treatment   | Before treatment| After treatment|
|          |            |      | [n (%)]  | [n (%)]  | (mean ± SD)       | (mean ± SD)       | (mean ± SD)   | (mean ± SD)   |
| Left ventricular function | Fanhao Ye | 2022 | Valsartan | 84 | 44.69 ± 4.6 | 54.76 ± 4.24 | 86 | 44.64 ± 4.42 | 49.28 ± 3.47 |
| LVEF (%) | Yi Wu_a    | 2021 | ACEI     | 95 | 43.23 ± 2.9 | 44.88 ± 7.07 | 99 | 44.05 ± 2.82 | 46.7 ± 5.06  |
|          | Yi Wu_b    | 2021 | ARB      | 95 | 43.23 ± 2.9 | 44.88 ± 7.07 | 84 | 44.09 ± 2.67 | 47.09 ± 5.39 |
|          | Yi Wu_c    | 2021 | ACEI     | 95 | 43.23 ± 2.9 | 45.08 ± 7.77 | 99 | 44.05 ± 2.82 | 49.28 ± 5.38 |
|          | Yi Wu_d    | 2021 | ARB      | 95 | 43.23 ± 2.9 | 45.08 ± 7.77 | 84 | 44.09 ± 2.67 | 50.77 ± 6.02 |
|          | Xiangjie Liu | 2021 | Enalapril | 53 | 44.23 ± 1.08 | 55.37 ± 4.06 | 52 | 44.29 ± 1.05 | 51.05 ± 3.94 |
|          | Yongyue Zhou_a | 2021 | Benazepril | 93 | 44.28 ± 2.49 | 45.36 ± 2.67 | 92 | 44.47 ± 2.54 | 45.16 ± 2.85 |
|          | Yongyue Zhou_b | 2021 | Benazepril | 93 | 44.28 ± 2.49 | 47.52 ± 2.72 | 92 | 44.47 ± 2.54 | 46.09 ± 2.84 |
|          | Yongyue Zhou_c | 2021 | Benazepril | 93 | 44.28 ± 2.49 | 50.34 ± 2.71 | 92 | 44.47 ± 2.54 | 47.95 ± 2.63 |
|          | Guokun Wang | 2019 | ACEI/ARB | 48 | 42.6 ± 2.5  | 52.3 ± 3.5   | 48 | 41.8 ± 3.1   | 46.5 ± 2.4   |
|          | Meixian Chen | 2021 | Candesartan | 57 | 43.5 ± 2.1  | 49 ± 6       | 56 | 43.8 ± 2.3   | 43.8 ± 7.4   |
|          | Rong Liu    | 2020 | Benazepril | 20 | 44.1 ± 2.73 | 48.75 ± 6.77 | 20 | 44.8 ± 2.84 | 50.95 ± 7.42 |
|          | Xiang Li_a  | 2021 | ACEI/ARB | 103 | 43.82 ± 2.81 | 45.09 ± 2.99 | 100 | 44.03 ± 2.83 | 44.48 ± 3.89 |
|          | Xiang Li_b  | 2021 | ACEI/ARB | 103 | 43.82 ± 2.81 | 51.27 ± 5.18 | 100 | 44.03 ± 2.83 | 46.49 ± 4.2  |
|          | Xiang Li_c  | 2021 | ACEI/ARB | 103 | 43.82 ± 2.81 | 57.15 ± 4.07 | 100 | 44.03 ± 2.83 | 48.74 ± 3.93 |
|          | He Wen      | 2020 | Valsartan | 41 | 44.6 ± 3.4  | 51.2 ± 3.8   | 41 | 43.9 ± 1.9   | 49.5 ± 2.8   |
|          | Pengfei Ma  | 2020 | Enalapril | 50 | 44.3 ± 1.2  | 55.41 ± 4.13 | 50 | 44.12 ± 1.17 | 51.19 ± 4.02 |
|          | Cunfang Chen_a | 2020 | ACEI/ARB | 45 | 42.8 ± 2.3  | 44.7 ± 3.1   | 45 | 43.1 ± 2.2   | 44.2 ± 3     |
|          | Cunfang Chen_b | 2020 | ACEI/ARB | 45 | 42.8 ± 2.3  | 47.3 ± 3.1   | 45 | 43.1 ± 2.2   | 45.6 ± 2.5   |
|          | Cunfang Chen_c | 2020 | ACEI/ARB | 45 | 42.8 ± 2.3  | 52.8 ± 3.5   | 45 | 43.1 ± 2.2   | 46.5 ± 3.1   |
|          | Hong Mi     | 2021 | Benazepril | 30 | NA ± NA    | 64.58 ± 8.14 | 30 | NA ± NA    | 58.13 ± 7.32 |
|          | Dongrui Xu  | 2021 | Enalapril | 49 | 43.9 ± 3.2  | 53.2 ± 4.1   | 49 | 43 ± 2.8    | 45.6 ± 3.4   |
|          | Xinxin Guo  | 2021 | Valsartan | 58 | 45.15 ± 3.9 | 51.2 ± 2.05  | 58 | 46.1 ± 3.35 | 49.05 ± 2.92 |

LVEDD (mm)  Fanhao Ye 2022 Valsartan 84 51.52 ± 6.2 47.26 ± 4.71 | 86 | 50.05 ± 5.62 | 50.12 ± 5.62 |
| Yi Wu_a | 2021 ACEI | 95 | 56.86 ± 7.2 | 55.5 ± 8.21 | 99 | 55.43 ± 6.21 | 52.49 ± 7.04 |
| Yi Wu_b | 2021 ARB | 95 | 56.86 ± 7.2 | 55.5 ± 8.21 | 84 | 55.46 ± 7.66 | 53.72 ± 7.69 |
| Yi Wu_c | 2021 ACEI | 95 | 56.86 ± 7.2 | 50.34 ± 7.34 | 99 | 55.43 ± 6.21 | 50.93 ± 6.65 |
| Yi Wu_d | 2021 ARB | 95 | 56.86 ± 7.2 | 50.34 ± 7.34 | 84 | 55.46 ± 7.66 | 50.81 ± 7.55 |
| Xiangjie Liu | 2021 Enalapril | 53 | 60.25 ± 5.97 | 47.53 ± 4.31 | 52 | 60.31 ± 5.92 | 52.27 ± 5.13 |
| Yongyue Zhou_a | 2021 Benazepril | 93 | 55.28 ± 7.14 | 53.89 ± 5.31 | 92 | 56.16 ± 6.98 | 55.19 ± 6.48 |
| Yongyue Zhou_b | 2021 Benazepril | 93 | 55.28 ± 7.14 | 51.98 ± 6.31 | 92 | 56.16 ± 6.98 | 54.17 ± 5.87 |
| Yongyue Zhou_c | 2021 Benazepril | 93 | 55.28 ± 7.14 | 47.84 ± 7.31 | 92 | 56.16 ± 6.98 | 52.14 ± 5.26 |

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TABLE 2 (Continued) Left ventricular function outcomes before and after treatment between sacubitril-valsartan and ACEI/ARB group.

| Outcomes | Author | Year | Controls | Sample size [n (%)] | Before treatment (mean ± SD) | After treatment (mean ± SD) | Sample size [n (%)] | Before treatment (mean ± SD) | After treatment (mean ± SD) |
|----------|--------|------|----------|---------------------|-----------------------------|-----------------------------|---------------------|-----------------------------|-----------------------------|
| LVESD (mm) | Rong Liu | 2020 | Benazepril | 20 | 54.15 ± 5.54 | 55 ± 5.36 | 20 | 54.55 ± 7.67 | 55.15 ± 6.06 |
| DVST (mm) | Xiangjie Liu | 2021 | Enalapril | 53 | 12.16 ± 1.48 | 8.98 ± 0.86 | 52 | 12.22 ± 1.53 | 10.32 ± 1.07 |
| LAD (mm) | Xiangjie Liu | 2021 | Enalapril | 53 | 44.56 ± 4.08 | 34.18 ± 3.15 | 52 | 44.36 ± 4.12 | 36.77 ± 3.44 |
| SV (ml) | Meixian Chen | 2021 | Candesartan | 57 | 80 ± NA | 91.9 ± 15.8 | 56 | 75.9 ± NA | 75.1 ± 13.5 |
| FS (%) | Xiang Li_a | 2021 | ACEI/ARB | 103 | 22.21 ± 2.73 | 22.67 ± 1.69 | 100 | 22.35 ± 1.86 | 22.46 ± 2.28 |
| SCr (μmol/L) | Guokun Wang | 2019 | ACEI/ARB | 48 | 78.8 ± 6.2 | 95.3 ± 5.8 | 48 | 77.9 ± 7.3 | 86.2 ± 5.7 |
| CRP (μg/ml) | Dongrui Xu | 2021 | Eenalapril | 49 | 9.6 ± 7.8 | 3.1 ± 2.3 | 49 | 9.6 ± 8.1 | 4.5 ± 3.7 |

Indicators related to heart failure

| Author | Year | Controls | Sample size [n (%)] | Before treatment (mean ± SD) | After treatment (mean ± SD) |
|--------|------|----------|---------------------|-----------------------------|-----------------------------|
| Yi Wu_a | 2021 | ACEI | 95 | 3397.03 ± 4951.87 | 2469.07 ± 4830.57 | 99 | 2103.18 ± 2460.54 |

(Continued on following page)
Left ventricular function

LVEF (%)

A total of 14 studies were included to evaluate the effect of ARNI on LVEF. The heterogeneity test results showed $I^2 = 95.6\%$, therefore, the random effect model was used. The result demonstrated that LVEF levels were significantly improved in patients with HFmrEF in the ARNI group ($WMD: 2.36, 95\%CI: 1.09$ to $3.63, p < 0.001$) (Table 3; Figure 2A). Subgroup analysis based on study type showed that LVEF levels were significantly higher in patients with HFmrEF in the ARNI group compared with ACEI or ARB group in the RCT study ($I^2 = 95.3\%, WMD: 3.58, 95\%CI: 2.22$ to $4.93, p < 0.001$) (Table 3; Figure 2B). However, in cohort studies, there was no difference in LVEF levels between the ARNI group and the ACEI or ARB group.
TABLE 3 Efficacy and safety of sacubitril-valsartan treatment in HFmrEF patients.

| Outcomes                  | WMD (95%CI)       | p       | I² |
|---------------------------|-------------------|---------|----|
| **Left ventricular fraction** |                   |         |    |
| LVEF (%)                  | 2.36 (1.09, 3.63) | <0.001  | 95.6|
| Study design              |                   |         |    |
| RCT                       | 3.58 (2.22, 4.93) | <0.001  | 95.3|
| Cohort                    | -0.18 (-3.37, 3.00) | 0.911   | 96.2|
| Duration of treatment (months) |                   |         |    |
| 1                         | -0.05 (-1.21, 1.11) | 0.927   | 74.5|
| 3                         | 1.15 (-1.39, 3.70) | 0.374   | 96.1|
| 6                         | 4.53 (2.39, 6.66) | <0.001  | 93.4|
| 12                        | 5.31 (2.22, 8.3)  | 0.001   | 96  |
| LVEDD (mm)                | -2.48 (-3.83, -1.13) | <0.001  | 84.9|
| Study design              |                   |         |    |
| RCT                       | -3.45 (-5.11, -1.80) | <0.001  | 79.3|
| Cohort                    | -1.29 (-3.36, 0.89) | 0.247   | 88.5|
| Duration of treatment (months) |                   |         |    |
| 1                         | 0.52 (-1.41, 2.46) | 0.595   | 66.8|
| 3                         | -2.90 (-4.58, -1.22) | 0.001  | 75.1|
| 6                         | -6.34 (-8.88, -3.81) | <0.001  | 73.6|
| 12                        | -2.57 (-3.54, -1.60) | <0.001  | 0   |
| LVEDD (mm)                | -0.19 (-2.14, 1.77) | 0.853   | 0   |
| DVST (mm)                 | -2.03 (-4.39, 0.33) | 0.091   | 99  |
| Study design              |                   |         |    |
| RCT                       | -0.50 (-0.94, -0.06) | 0.024   | NA  |
| Cohort                    | -2.80 (-5.82, 0.23) | 0.07    | 99.2|
| LAD (mm)                  | -2.23 (-2.83, -1.6) | <0.001  | 21.8|
| FS (%)                    | 2.054 (0.25, 3.86) | 0.025   | 95.9|
| Duration of treatment (months) |                   |         |    |
| 1                         | 0.21 (-0.34, 0.76) | 0.457   | NA  |
| 6                         | 2.06 (0.82, 3.29)  | 0.001   | 74.5|
| 12                        | 3.96 (3.25, 4.67)  | <0.001  | NA  |
| Indicators related to heart failure |                   |         |    |
| NT-proBNP (ng/L)          | -494.92 (-641.34, -348.50) | <0.001  | 93.9|
| Study design              |                   |         |    |
| RCT                       | -623.33 (-812.19, -434.47) | <0.001  | 93.3|
| Cohort                    | -239.93 (-244.47, -235.40) | <0.001  | 0   |
| Duration of treatment (months) |                   |         |    |
| 1                         | -181.53 (-403.67, 40.62) | 0.109   | 12  |
| 3                         | -407.60 (-664.02, -271.17) | <0.001  | 92.7|
| 6                         | -774.37 (-961.72, -587.03) | <0.001  | 83.3|
| 12                        | -226.31 (-369.67, -82.95) | 0.002   | 0   |
| sST2 (pg/ml)              | -7.40 (-14.35, -0.44) | 0.037   | 85.6|
| Quality of life score     |                   |         |    |
| MHIQFL                    | -10.13 (-20.61, 0.34) | 0.058   | 98.4|
| Study design              |                   |         |    |
| RCT                       | -0.70 (-2.30, 0.90)  | 0.39    | NA  |
| Cohort                    | -14.92 (-16.79, -13.04) | <0.001  | 0   |
| KCCQ                      | 4.13 (3.46, 4.81)   | <0.001  | 0   |

(Continued in next column)

TABLE 3 (Continued) Efficacy and safety of sacubitril-valsartan treatment in HFmrEF patients.

| Outcomes                  | WMD (95%CI)       | p       | I² |
|---------------------------|-------------------|---------|----|
| Mortality                 |                   |         |    |
| 1-year mortality          | 0.69 (0.38, 1.27)  | 0.23    | 0   |
| Cardiac death             | 0.62 (0.26, 1.46)  | 0.272   | 0   |
| Readmission rate          | 0.54 (0.43, 0.68)  | <0.001  | 0   |
| Adverse events            |                   |         |    |
| Renal function deterioration | 0.57 (0.26, 1.23)  | 0.151   | 0   |
| Hypotension               | 0.71 (0.36, 1.39)  | 0.311   | 0   |
| SCr (μmol/L)              | -0.62 (-2.05, 19.81) | 0.953   | 92.4|
| Duration of treatment (months) |                   |         |    |
| 3                         | 9.10 (6.80, 11.40) | <0.001  | NA  |
| 6                         | -11.80 (-22.87, -0.73) | 0.037   | NA  |

Notes: HFmrEF: heart failure with mid-range ejection fraction; WMD: weighted mean difference; RR: relative risk; CI: confidence interval; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular end-systolic diameter; LVESD: diastolic ventricular septal thickness; LAD: left atrial diameter; SY: stroke volume; FS: left ventricular short axis shortening rate; CRP: C-reactive protein; NT-proBNP: N-terminal pro brain natriuretic peptide; sST2: soluble suppression of tumorigenesis-2; MHIQFL: Minnesota heart failure scale score; KCCQ: The Kansas city cardiomyopathy questionnaire; 6-MWT: 6-Minute Walk Test; Scr: serum creatinine.

(WMD: -0.18, 95%CI: -3.37 to 3.00, p = 0.91). According to the duration of treatment subgroup analysis, there was no difference in LVEF between the two groups at 1 and 3 months of treatment (p > 0.05). At 6 and 12 months of treatment, the LVEF level of the ARNI group was higher than that of the control group, with the WMD being 4.53 (95%CI: 2.39 to 6.66, p < 0.001) in 6 months, and being 5.31 (95%CI: 2.22 to 8.39, p = 0.001) in 12 months, respectively (Table 3; Figure 2C).

**LVEDD (mm)**

The LVEDD between the ARNI group and ACEI or ARB group was assessed in 9 studies. The random effect model results suggested that LVEDD in ARNI group was lower than that in the control group after treatment (WMD: -2.48, 95%CI: -3.83 to -1.13, p < 0.001) (Table 3; Figure 3A). Subgroup results based on RCTs also showed a similar result (I² = 79.3%, WMD: -3.45, 95%CI: -5.11 to -1.80, p < 0.001) (Table 3; Figure 3B). In term of the subgroup analysis of duration of treatment, there was no difference in LVEDD between the two groups after 1 month of treatment (p > 0.05). At 3 (WMD: -2.90, 95%CI: -4.58 to -1.22, p = 0.001), 6 (WMD: -6.34, 95%CI: -8.88 to -3.81, p < 0.001) and 12 months of treatment (WMD: -2.37, 95%CI: -3.54 to -1.20, p < 0.001), LVEDD in the ARNI group was lower than that in the control group (Table 3; Figure 3C).
LVESD (mm)

A total of two studies were included to evaluate the LVESD after treatment between ARNI and ACEI or ARB groups. The fixed-effect model indicated no statistically significant difference in LVESD between ARNI and ACEI or ARB treatment (WMD: −0.19, 95%CI: −2.14 to 1.77, p = 0.85) (Table 3).

DVST (mm)

A total of 3 studies assessed DVST after treatment. The random-effect model indicated ARNI was not superior to ACEI or ARB treatment in DVST (I² = 99%, WMD: −2.03, 95%CI: −4.39 to 0.33, p = 0.091). However, according to the study type analysis, DVST was lower in the ARNI group than ACEI or ARB group. (WMD: −0.50, 95%CI: −0.94 to −0.06, p = 0.024) (Table 3).

LAD (mm)

Five studies investigate LAD between ARNI and ACEI or ARB treatment. ARNI showed a greater decrease in LAD (I² = 21.8%, WMD: −2.23, 95%CI: −2.83 to −1.63, p < 0.001) (Table 3; Figure 4).

SV (ml)

Meixian Chen et al. (2021) studied the effect of ARNI vs. candesartan on stroke output of patients, and the results showed that SV in the experimental group was higher than that in the control group (WMD: 16.80, 95%CI: 11.39 to 22.22, p < 0.001).

FS (%)

Two articles were included to investigate FS, and the difference in heterogeneity test results showed I² = 95.9%, so the random effect model was used for analysis. The result demonstrated that FS after ARNI treatment was higher than
FIGURE 4
Forest plot of LAD between sacubitril-valsartan and ACEI or ARB.

FIGURE 5
Forest plot of FS between sacubitril-valsartan and ACEI or ARB.
ACEI or ARB treatment (WMD: 2.05, 95%CI: 0.25 to 3.86, \( p = 0.025 \)) (Table 3; Figure 5).

CRP (\( \mu \text{g/ml} \))
A study Dongrui Xu and Liu (2021) by Xu et al. investigated the effect of ARNI VS enalapril on CRP in HFmrEF patients. The results indicated that CRP in the ARNI group was lower than that in the control group (WMD: \(-1.40, 95\% \text{CI: } -2.62 \text{ to } -0.18, p = 0.024 \)) (Table 3; Figure 5).

Indicators related to HF

NT-proBNP (ng/L)
Ten studies were used to investigate the NT-proBNP level after treatment. A random effect model was used for analysis. ARNI could significantly reduce patients’ NT-proBNP (WMD: \(-494.92, 95\% \text{CI: } -641.34 \text{ to } -348.50, p < 0.001 \)) (Table 3 Figure 6A). Based on the subgroup analysis of study type, whether in RCT study (\( I^2 = 93.3\% \), WMD: \(-623.33, 95\% \text{CI: } -705.95 \text{ to } -540.70, p < 0.001 \)).
−812.19 to −434.47, \( p < 0.001 \)) or cohort study (\( I^2 = 0.0\% \), WMD: −239.93, 95\%CI: −244.47, −235.40, \( p < 0.001 \)), patients treated by ARNI had lower NT-proBNP (Table 3; Figure 6B). According to the subgroup analysis of the duration of treatment, there was no statistical difference in NT-proBNP between the two groups (\( p > 0.05 \)) after 1 month of treatment. After 3 months (WMD: −467.60, 95\%CI: −664.02 to −271.17, \( p < 0.001 \)), 6 months (WMD: −774.37, 95\%CI: −961.72 to −587.03, \( p < 0.001 \)) and 12 months (WMD: −226.31, 95\%CI: −369.67 to −82.95, \( p = 0.002 \)) of treatment, nT-proBNP in the ARNI group was lower than that in the control group (Table 3; Figure 6C).

sST2 (pg/ml)

Two studies assessed the sST2 after treatment between ARNI and ACEI or ARB groups. The random effect model analysis showed that sST2 in the ARNI group was lower than that in ACEI or ARB group (WMD: −7.40, 95\%CI: −14.35 to −0.44, \( p = 0.037 \)) (Table 3; Figure 7).

GDF-15 (pg/ml)

He Wen et al. (2020) studied the effect of ARNI vs valsartan on the growth and transformation factor of GDF-15 in HFmrEF patients. The results showed no statistical difference between the two groups of GDF-15 (WMD: −66.00, 95\%CI: −912.55 to 780.55, \( p = 0.879 \)).

Quality of life score

MHFQL

Three studies used MHFQL to evaluate the effects of ARNI and ACEI or ARB on quality of life. Random effects model analysis showed no difference in MHFQL between the two groups (WMD: −10.13, 95\%CI: −20.61 to 0.34, \( p = 0.058 \)) (Table 3).

KCCQ

A total of 1 study containing 3 groups of data were included to assess quality of life through KCCQ. A higher quality of life was found in HFmrEF patients using ARNI (WMD: 4.13, 95\%CI: 3.46 to 4.81, \( p < 0.001 \)) (Table 3).

6-MWT (m)

Three articles were included to assess 6-MWT. The fixed-effect model results showed that the treatment of ARNI significantly increased 6-MWT in HF patients with HFmrEF (\( I^2 = 5.1\% \), WMD: 51.35, 95\%CI: 26.99 to 75.71, \( p < 0.001 \)) (Table 3).

Total effective rate

Total effective rate was evaluated in 6 studies, and the heterogeneity test results indicated \( I^2 = 0.0\% \), so fixed-effect model was used. The total effective rate of ARNI was higher than that of ACEI or ARB (RR: 1.15, 95\%CI: 1.08 to 1.21, \( p < 0.001 \)) (Table 3).

Mortality

1-year mortality

The 1-year mortality was assessed in 3 studies. We use the fixed-effect model to combine analysis, and the results showed that there was no difference in 1-year mortality between the ARNI and ACEI or ARB treatments groups (RR: 0.69, 95\%CI: 0.38 to 1.27, \( p = 0.230 \)). The incidence of cardiac death was 0.04 after the ARNI treatment and 0.06 in the ACEI or ARB treatment (Table 3).

Cardiac death

Four studies evaluated cardiac death after the ARNI and ACEI or ARB treatments. The fixed-effect model results showed the ARNI was no better than ACEI or ARB in decreasing cardiac death (RR: 0.62, 95\%CI: 0.26 to 1.46, \( p = 0.272 \)). The incidence of cardiac death was 0.04 after the ARNI treatment and 0.06 in the ACEI or ARB treatment (Table 3).

Readmission rate

A total of 9 articles examined the effects of ARNI and ACEI or ARB on readmission rates. Our combined results indicated that the use of ARNI was associated with a greater reduction in readmission rates than the ACEI or ARB (RR: 0.54, 95\%CI: 0.43 to 0.68, \( p < 0.001 \)) (Table 3; Figure 8).

Adverse events

Worsening HF and malignant arrhythmia

Xiangjie Liu (2021) evaluated the effects of ARNI on cardiac function and short-term prognosis in HFmrEF patients and found that the incidence of worsening HF and malignant arrhythmia in ARNI was not statistically significant compared with enalapril maleate tablets in the control group.

Hyperkalemia

A study by Meixian Chen et al. (2021) found that the incidence of hyperkalemia in ARNI and the control group was not statistically significant.

Angioedema

A clinical study (Xiang Li, 2021) evaluating the efficacy and safety of ARNI in the treatment of patients with HFmrEF has reported that the incidence of angioedema in ARNI was not statistically significant compared with the control group.
Renal function deterioration

Four studies evaluated renal function deterioration. The result demonstrated that the incidence of renal function deterioration between ARNI treatment and ACEI or ARB treatment was not significantly different (RR: 0.57, 95%CI: 0.26 to 1.23, \( p = 0.151 \)) (Table 3).

Hypotension

The hypotension was assessed in 2 articles. Our result indicated no difference between ARNI treatment and ACEI or ARB treatment in hypotension (RR: 0.71, 95%CI: 0.36 to 1.39, \( p = 0.31 \)) (Table 3).

SCr (\( \mu \text{mol/L} \))

SCr was assessed before and after treatment in two studies, and the results of the random-effect model showed no difference in SCr between the ARNI and ACEI or ARB groups after treatment (I\(^2\) = 92.4%, WMD: −0.62, 95%CI: −21.05 to 19.81, \( p = 0.953 \)) (Table 3).

Sensitivity analysis and publication bias

Sensitivity analysis was performed through sequentially excluded individual studies to assess the stability of the results. The sensitivity analysis result demonstrated that our findings are trustworthy. Begg’s test was used to evaluate the publication bias for outcomes with ≥9 articles. According to the results, LVEF (Z = 0.74, \( p = 0.460 \)), LVEDD (Z = 0.86, \( p = 0.392 \)), NT-proBNP (Z = 1.44, \( p = 0.149 \)), readmission rate (Z = 0.52, \( p = 0.602 \)) did not have publication bias.

Discussion

Unlike HFrEF patients, the treatment for HFmrEF patients was still symptom-based and empiric, without definitive strategies for this entity (Nie et al., 2021). Despite previous studies finding that ACEI and ARB might improve the symptoms and functional capacity of the non-HFrEF patient, they did not reduce morbidity and mortality (Solomon et al., 2012). This meta-analysis evaluating the effects of ARNI on HFmrEF patients compared with ACEI/ARB drugs demonstrated that compared with ACEI or ARB, ARNI was likely to improve left ventricular function by increasing the LVEF, SV, and FS, decreasing LVEDD, LAD, CRP, AND NT-proBNP. The ARNI had a higher total effective rate and KCCQ and 6-MWT. In addition, ARNI decreased the readmission rate.
ARNI, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan (Tillman et al., 2019), is the first drug indicated to be superior to enalapril in reducing mortality for patients with HF and shows the potential to improve the left ventricular function of patients with HF (Solomon et al., 2016). In this study, compared with ACEI or ARB, ARNI could significantly increase the LVEF and FS, with a decreasing NT-proBNP. LVEF and FS reflect left ventricular systolic function, while NT-proBNP can reflect the ventricular volume and ventricular wall tension, both of which can evaluate the severity of HF (Newton et al., 2009). The increase of NT-proBNP and the decrease of LVEF and FS could reflect the increase in adverse events among patients with HF (Vaskova et al., 2020). A study (Xiang Li, 2021) by Li et al. showed that with the prolongation of treatment time, the NT-proBNP of the two groups showed a gradual downward trend, while the LVEF and FS showed an upward trend, however, the effect of the ARNI group was more obvious. The reduction in NT-ProBNP may indirectly reflect that ARNI could rapidly decrease the left ventricular pressure and volume overloads and improve the left ventricular function in HFrEF patients compared with ACEI or ARB (Nie et al., 2021). sST-2 is produced by cardiomyocytes and fibroblasts when they are in a state of stress or injury and can be derived from large blood vessels and myocardial microvascular endothelial cells (Pascual-Figal and Januzzi, 2015). sST-2 can early predict myocardial fibrosis and ventricular remodeling and is an independent predictor of the prognosis of HF (Gaggin et al., 2014). The decreased degree of sST-2 in the ARNI group was more obvious than that in the control group after treatment, indicating that ARNI had obvious advantages in reducing the severity of HFmrEF (Dongruil Xu and Liu, 2021). ARNI has the dual effect of inhibiting enkephalinase and ARB (Wachter et al., 2020). On the one hand, ARNI can inhibit enkephalinase and increase peptides (such as natriuretic peptides) degraded by enkephalinase level, play the role of improving left ventricular function and play the role of improving the left ventricular function of patients with HF, treatment with ARNI has also been reported to be associated with a higher rate of symptomatic hypotension (Zhang et al., 2020). Even though we did not find an increase in hypotension with ARNI, the safety of ARNI still needs more RCTs to be evaluated. The mortality of HFmrEF patients is another matter of concern. Hobbs et al. (2007) showed that the 5-year mortality rate of HFmrEF patients was as high as 26%. Although our findings showed that there was no difference in reducing mortality between ARNI and traditional anti-HF drugs, the 1-year mortality rate was significantly lower with ARNI than with ACEI/ARB. In a double-blind trial, ARNI was effective in reducing cardiovascular mortality in patients with HFrEF (McMurray et al., 2014). In conclusion, compared with ACEI/ARB drugs, ARNI is not worse in terms of safety in HFmrEF patients.

Quality of life is another key criterion to assess the treatment effect on HF patients. A previous study suggested that the proportion of patients with an improvement of 5 points in the KCCQ score was higher in the ARNI group (Solomon et al., 2019), which is consistent with our findings. The 6 MWT, a method to detect functional compensatory ability, is widely used in the clinical evaluation of cardiopulmonary diseases before and after therapeutic intervention (Lin et al., 2021). Our study demonstrated that the ARNI had a higher 6-MWT compared with ACEI/ARB. A study assessing the early effects of ARNI on exercise tolerance in patients with HF/HFmrF found that ARNI improved exercise tolerance, peak VO\(_2\) and ventilatory efficiency at 6.2 months of follow-up (Vitale et al., 2019). Giallauria et al. found that ARNI therapy improves autonomic function, functional capacity, and ventilation (Giallauria et al., 2020). In clinical practice, ARNI can be considered a drug for HFmrEF patients, however, further studies are needed to better elucidate the underlying mechanisms of this functional improvement. Despite the efficacy and safety of ARNI in the treatment of patients with HF, a study (Oh et al., 2022) by Oh et al. dimentated that earlier use of ARNI was related to better clinical outcomes and earlier left ventricular reverse remodeling; remodeling of left atrial was less prominent in the later use group implying delayed response in diastolic function. The timing of initiation of ARNI therapy in patients with HF needs further investigation.

The use of ARNI in cardiac devices treated patients has also been investigated. The study by Sardu et al. (2022) evaluating the effects of ARNI in cardiac resynchronization therapy with defibrillator (CRTd) non-responders found that at 1 year of follow-up, ARNI-users had a higher increase of LVEF Fand 6 MWT along with a more significant reduction of left ventricular end-systolic volume (LVEVs) compared to non-ARNI users. This evidence implied that ARNI-based therapies increase the probability of anti-remodeling effects of CRTd. In addition, the study by Sardu et al. (2018) found that ST2 protein may be used as valid monitoring biomarker, and as a predictive biomarker in failing heart internal cardioverter defibrillator (ICD) patients affected by metabolic syndrome. More studies
are needed to explore the effect of ARNI on the use of cardiac devices in patients with HFrEF.

Financial status may be particularly important given the high cost of the newer therapy ARNI approach; the high prevalence of geriatric diseases in elderly patients with HF, caregiver support may be particularly important in an era of the increasing complexity of pharmacologic regimens (Sumarsono et al., 2020). In addition, the elderly HF population is highly heterogeneous, with different pathophysiological mechanisms, the frequent presence of other chronic diseases, and functional and cognitive impairments that can significantly affect the utility and value of diagnostic research and therapeutic interventions (Francis et al., 2014; Gorodeski et al., 2018). However, most of the included studies were lacking in information on patients’ backgrounds, future studies still need to examine the use of ARNI in old patients with HFrEF.

There are several limitations to this meta-analysis. First, the results should be interpreted with caution given the limited number of included RCTs, and the small sample size. Second, due to the limitation of the included literature, we could not analyze the patients with a history of chronic diseases and drug history, which might have produced confounding bias for the evaluation. Third, in order to have a better understanding of the long-term benefit and potential side effects of ARNI on HFrEF patients, longer duration studies are needed. Future RCTs with larger sample sizes and longer-duration are needed to confirm our findings.

Conclusion

This study evaluated the effects of ARNI on HFrEF patients compared with ACEI/ARB drugs, and found that ARNI may be an effective and safe strategy with which to improve the left ventricular function and quality of life, reduce readmission rate in HFrEF. In the future, more well-designed trials are needed to confirm these findings and investigate whether ARNI has a clear benefit in patients with HFrEF.

Author contributions

JQ and JY designed the study. JQ wrote the manuscript. WW, PW, PH, and RL collected, analyzed and interpreted the data. JY critically reviewed, edited and approved the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by Scientific Research Project of Guangxi Health Commission (No. 20211971).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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