Clinical efficacy of combined sacubitril/valsartan and the Chinese herbal preparation, Qili Qiangxin Capsules on reverse cardiac remodeling in patients with heart failure with reduced ejection fraction

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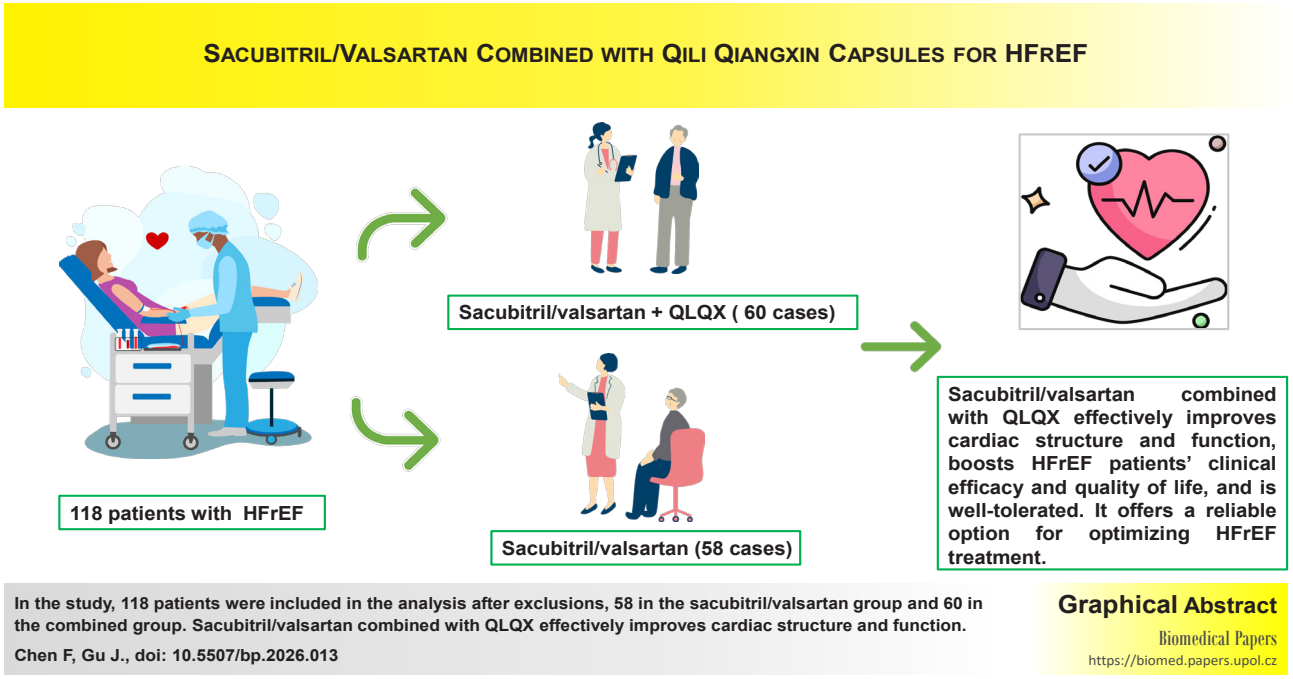
Background. Heart failure with reduced ejection fraction (HFrEF) is mainly characterized by cardiac remodeling. Sacubitril/valsartan and Qili Qiangxin Capsules (QLQX a Chinese patent medicine, commonly used for the treatment of CHF with wide acceptance in Chinese patients), each benefit HFrEF alone, however, further high-quality clinical evidence is needed to confirm their combined effect on reversing cardiac remodeling.
Objective. To study the role of sacubitril/valsartan plus QLQX in reversing cardiac remodeling in HFrEF patients, and provide evidence for optimizing HFrEF treatment.
Methods. 124 HFrEF patients were admitted to our hospital from Feb 2023 to Apr 2025. After exclusions, 118 were analyzed and divided by treatment (per electronic records) into two groups: sacubitril/valsartan (58 cases) and sacubitril/valsartan + QLQX (combined group, 60 cases). Primary outcomes included left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular global longitudinal strain (GLS), and serum N-terminal pro-brain natriuretic peptide (NT-proBNP). Secondary outcomes included serum cardiac troponin I (cTnI), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), clinical efficacy, 6-minute walking test (6MWT), Minnesota Living with Heart Failure Questionnaire (MLHFQ), and adverse events.
Results. The combined group showed significantly greater improvements in LVEF and absolute GLS (all $P<0.001$), greater reductions in LVEDD ($P=0.026$), LVESD ($P=0.039$) and NT-proBNP ($P=0.020$) than the monotherapy group. The combined group had greater reductions in CRP ($P=0.003$), TNF-α ($P<0.001$) and cTnI ($P<0.001$), a higher total clinical effective rate ($P=0.008$), a greater increase in 6MWT ($P=0.025$) and a greater decrease in MLHFQ score ($P<0.001$) than the monotherapy group. Adverse event incidence did not differ significantly between groups ($P=0.431$).
Conclusion. Sacubitril/valsartan combined with QLQX effectively improves cardiac structure and function, boosts HFrEF patients' clinical efficacy and quality of life, and is well-tolerated. It offers a reliable option for optimizing HFrEF treatment.



In the study, 118 patients were included in the analysis after exclusions, 58 in the sacubitril/valsartan group and 60 in the combined group. Sacubitril/valsartan combined with QLQX effectively improves cardiac structure and function.
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Key words: heart failure with reduced ejection fraction, cardiac remodeling, sacubitril/valsartan, Qili Qiangxin Capsules, combined therapy

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INTRODUCTION

Various cardiovascular diseases progress to a terminal stage known as heart failure (HF), which is distinguished by inadequate circulatory perfusion and systemic-pulmonary circulatory congestion. Such characteristics stem from myocardial systolic and diastolic dysfunction. It has become a major public health issue threatening human health worldwide[1,2]. Based on differences in left ventricular ejection fraction (LVEF) and changes after treatment, HF is classified into heart failure with reduced ejection fraction (HFrEF), heart failure with improved ejection fraction (HFimpEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF) (ref.[3]). Epidemiological data show that the global prevalence of HFrEF is on a continuous upward trend[1,4]. Cardiac remodeling serves as the core pathological basis for the occurrence and development of HFrEF. Its essence is a process of structural and functional remodeling resulting from the imbalance of compensatory mechanisms activated by the body after myocardial injury. It is mainly manifested as a vicious cycle involving ventricular cavity enlargement, myocardial hypertrophy, myocardial fibrosis, and decreased systolic function[5]. When the myocardium is damaged due to factors such as ischemia and excessive load, long-term compensation leads to the enlargement of left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD), resulting in eccentric hypertrophy[6]. Meanwhile, angiotensin (Ang) secreted by the renin-angiotensin-aldosterone system (RAAS) can activate fibroblasts and promote collagen deposition; norepinephrine released by sympathetic nerve excitation accelerates myocardial cell apoptosis, further aggravating ventricular dilatation and worsening systolic and diastolic dysfunction[7].

Centered on breaking the pathological vicious cycle, reversing cardiac remodeling, and improving prognosis, the treatment of HFrEF has formed a comprehensive system with pharmacotherapy as the cornerstone and non-pharmacological interventions as supplements. It focuses on key links in the pathological process, such as neuroendocrine activation and ventricular remodeling[8]. Sacubitril/valsartan, as the first angiotensin receptor-neprilysin inhibitors (ARNI), is a fixed-dose combination of sacubitril and valsartan in a 1:1 ratio. On one hand, valsartan can specifically block the angiotensin type 1 (AT1) receptor of Ang , inhibit the excessive activation of RAAS, and reduce myocardial hypertrophy and fibrosis. On the other hand, sacubitril can inhibit the activity of neprilysin, reduce the degradation of natriuretic peptides in the body, and enhance the diuretic and vasodilatory. This dual mechanism synergistically improves cardiac structure and function[9]. The PARADIGM-HF study[10] found that as opposed to the group receiving enalapril, the ARNI group reduced the risk of heart failure hospitalization by 21% (ref.[10]) and the risk of all-cause mortality by 16% (ref.[10]) in HFrEF patients, alongside notably improved quality of life and good safety characteristics. Subsequent PIONEER-HF study[11] supplemented and confirmed the functional efficacy of ARNI in patients with acute decompensated HF. Although the PARADISE-MI study[12] showed that early ARNI treatment in individuals suffering from acute myocardial infarction did not provide more significant clinical benefits than angiotensin-converting enzyme inhibitors (ACEI), with the extension of the follow-up period, the longer the treatment duration, the greater the benefits in ARNI.

Based on the concepts of holism and syndrome differentiation and treatment, traditional Chinese medicine has demonstrated advantages in the treatment of HFrEF. Qiliqiangxin Capsule (QLQX) comprises a combination of 11 Chinese herbal medicines. These have the effects of replenishing qi, activating blood circulation, promoting diuresis, and relieving edema[13,14]. In a systematic review focusing on chronic heart failure (CHF) (ref.[15]), 7 preclinical studies revealed that QLQX had the ability to enhance myocardial remodeling (LVEDD: SMD = −1.04, 95%CI: −1.39, −0.70; LVEF: SMD = 1.20, 95%CI: 0.97, 1.43; NT-proBNP: SMD = −2.15, 95%CI: −3.60, 0.71) (ref.[15]). In conclusion, QLQX has potential mechanisms of action on myocardial cell apoptosis and cardiac function, and exhibits notable clinical adjuvant efficacy and safety.

Focusing on indicators related to cardiac remodeling, this study aims to explore the clinical efficacy of sacubitril/valsartan combined with QLQX in reversing cardiac remodeling for patients who have HFrEF, clarify the key mechanisms underlying their synergistic effects, and comprehensively evaluate the efficacy and safety of the combined therapy. Its specific goals include: providing an evidence-based protocol for integrated traditional Chinese and Western medicine treatment of HFrEF in clinical practice; promoting the upgrading of the cardiac remodeling assessment system and improving the accuracy of determining remodeling reversal; offering mechanistic references for the synergistic intervention of traditional Chinese and Western medicine in cardiovascular diseases; laying a foundation for subsequent studies on target compatibility and dosage optimization of combined traditional Chinese medicine and modern drugs; and facilitating the transition of heart failure treatment from symptom control to pathological reversal.

MATERIALS AND METHODS

General information

According to the electronic medical record data, 124 patients with HFrEF received hospitalization in our hospital from February 2022 to April 2025. 6 patients were excluded, with the specific reasons being incomplete data in 4 patients, severe aortic stenosis in 1 patient, and implantation of a pacemaker device [implantable cardioverter-defibrillator (ICD)] in 1 patient. Finally, 118 patients were included for data analysis. Based on the recorded different treatment regimens, they were divided into two groups: the sacubitril/valsartan group (58 cases) and the sacubitril/valsartan combined with QLQX group (combined group, 60 cases). See Fig. 1.

Inclusion criteria

(1) Meeting the diagnostic criteria for HFrEF specified in the 2024 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure[14]; (2) Aged 18–75 years; (3) New York heart association-functional classification (NYHA-FC) II–IV; (4) Presence of cardiac remodeling confirmed by echocardiography; (5) Significantly elevated NT-proBNP levels[16].

Exclusion criteria

(1) Severe valvular heart disease; (2) Acute decompensated heart failure; (3) Cardiac diseases such as congenital heart disease, restrictive cardiomyopathy, and hypertrophic cardiomyopathy; (4) Severe arrhythmia; (5) Hepatic or renal insufficiency; (6) Active infection or malignant tumor;(7) Allergy to any component of sacubitril/valsartan or QLQX, or a history of angioedema; (8) Participation in other clinical trials and use of investigational drugs within the past 1 month, or planned use of unapproved cardiovascular drugs during the study period; (9) Pregnant or lactating women; (10) Psychiatric illness or cognitive impairment[17].

Treatment regimens

According to the electronic medical record data of the patients, both groups received in-hospital basic treatment, including cardiotonic therapy, diuretic therapy, oxygen therapy, low-salt diet, vasoactive drug therapy, and treatment for underlying diseases.

Sacubitril/Valsartan Group: Patients orally took Sacubitril/Valsartan Sodium Tablets (Entresto, Novartis Singapore Pharmaceutical Manufacturing Private Ltd., Singapore, Approval No.: HJ20170363, Specification: 100 mg), 50 mg orally twice daily, Blood pressure, heart rate and renal function were closely monitored during medication. For patients with no obvious adverse reactions, the dose was gradually titrated to the target dose of 100 mg orally twice daily every 2 to 4 weeks, while those who could not tolerate the target dose were maintained on the maximum tolerated dose. The treatment course was 6 months.

Combined Group: In addition to oral administration of Sacubitril/Valsartan Sodium Tablets, patients also took QLQX (Shijiazhuang Yiling Pharmaceutical Co., Ltd., China, Specification: 0.3 g, Approval No.: Z20040141), 4 capsules each dose, three times per day. The treatment course was 6 months[18].

Blood Pressure Control Thresholds: During the titration and maintenance treatment phases, the lower limit of blood pressure control was defined as a systolic blood pressure (SBP) ≥ 90 mmHg and a diastolic blood pressure (DBP) ≥ 60 mmHg. In cases of SBP < 90 mmHg or the occurrence of hypotensive symptoms such as dizziness and fatigue, titration was immediately suspended; the dosage was reduced to the last well-tolerated level if necessary. Titration eligibility was re-evaluated only after blood pressure recovered above the predefined threshold and clinical symptoms resolved.

Standard Anti-Heart Failure Treatment Regimen: Patients in both groups received standardized background therapy in accordance with the 2024 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure. First-line basic medications included β-blockers (metoprolol sustained-release tablets/bisoprolol), mineralocorticoid receptor antagonists (MRAs; spironolactone 20 mg once daily, for patients with normal renal function), and sodium-glucose cotransporter 2 inhibitors (SGLT2is; dapagliflozin 10 mg once daily or empagliflozin 10 mg once daily, for patients without contraindications). The types of the aforementioned medications, initial dosages, and

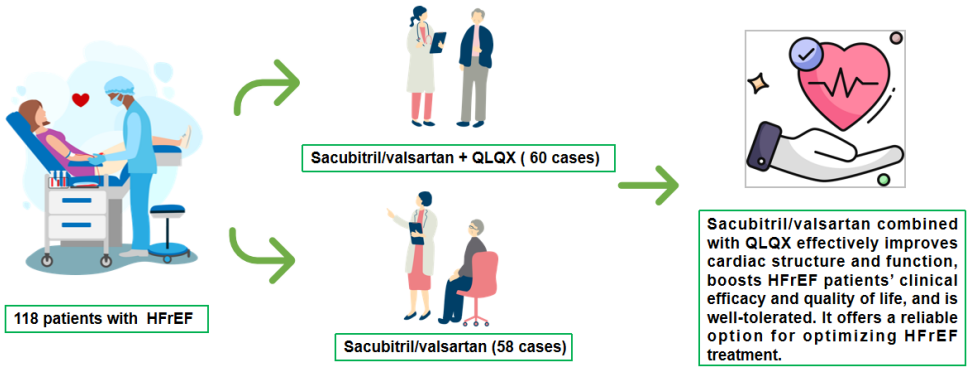

Fig. 1. Sacubitril/Valsartan combined with Qili Qiangxin capsules for HFrEF.
QLQX, Qili Qiangxin capsules; SAS, severe aortic stenosis; ICD, implantable cardioverter defibrillator. The figure shows that 118 were included in the analysis after exclusions, 58 in the sacubitril/valsartan group and 60 in the combined group. Sacubitril/valsartan combined with QLQX effectively improves cardiac structure and function.

titration strategies were well balanced and consistent between the two groups. Patients with irregular use of basic anti-heart failure drugs or significantly different medication regimens were excluded from the study.

Ethical statement

All protocols of this study were strictly in line with the Declaration of Helsinki and had obtained official approval from Chongqing Seventh People's Hospital's Medical Ethics Committee. The personal information of all participants was de-identified, and real names were replaced with unique identification codes to link electronic medical records and research data. Research data, such as biochemical indicators and echocardiographic findings, were stored on the hospital's dedicated server.

Outcome measures

Primary outcome measures

Ventricular structure and function indicators

LVEF, LVEDD, LVESD, and GLS were measured using a color Doppler ultrasound system (Consona NT, Mindray, China, No. 20222060077).

Heart failure biomarkers

5 mL of fasting venous blood from patients was collected in EDTA anticoagulant tubes. The blood samples spun at 3000 rpm for 10 minutes using a centrifuge (Microfuge® 20R, Beckman, USA), after which the serum fraction was separated. NT-proBNP was measured using a Human NT-proBNP ELISA Kit (sensitivity: 11.5 pg/mL, Cat. No. ab263877, Abcam, UK).

Secondary outcome measures

Inflammatory factors and myocardial injury markers

Venous blood collection and processing were performed in the same manner as described in Section 2.6.1.2. Serum cardiac troponin I (cTnI) was measured using a Human Cardiac Troponin I ELISA Kit (sensitivity: 4.4 pg/mL, Cat. No. ab200016, Abcam, UK); Human CRP ELISA Kit (sensitivity: 5.36 pg/mL, Cat. No. ab260058, Abcam, UK) was used for measuring C-reactive protein (CRP); and Human TNF-α ELISA Kit (sensitivity: 4.32 pg/mL, Cat. No. ab181421, Abcam, UK) was used for measuring tumor necrosis factor-α (TNF-α).

Clinical efficacy

Markedly Effective: NYHA functional class improved by 2 grades or more within 6 months, and the main symptoms basically resolved within 6 months;

Effective: NYHA functional class improved by 1 grade within 6 months, and the main symptoms were alleviated within 6 months;

Ineffective: No improvement in NYHA functional class and no relief of main symptoms within 6 months[18].

6-Minute Walking Test (6MWT)

The patient walks as hard as possible for 6 min on a specific flat walking ground. After the test, the maximum distance walked was recorded[19].

Minnesota Living with Heart Failure Questionnaire (MLHFQ)

There are 21 items and 3 domains (physical domain, emotional domain, and other domains) in MLHFQ. Higher scores are indicative of a poorer quality of life (total score: 0–105) (ref.[20]). The weighted kappa coefficient for each item of the MLHFQ ranges from 0.4 to 0.84, and the internal consistency Cronbach's α coefficient is 0.88 (ref.[21]).

Adverse events

Adverse events associated with sacubitril/valsartan during treatment included hypotension, gastrointestinal reactions, and dizziness. Adverse events associated with QLQX included gastrointestinal reactions and dry mouth[18,22].

Sample size calculation method

Yao et al.[18] analyzed HF patients about the curative effect of QLQX combined with sacubitril/valsartan. The LVEF before treatment was (36.98 ± 2.25)% (ref.[18]), and after treatment, it was (42.08 ± 3.24)% (ref.[18]). From these data, the estimated Cohen's d was 0.54. Based on this value, with a significance level (α) of 0.05 and a statistical power (1-β) of 80%, the calculated sample size was 55 cases per group, resulting in a total sample size of 110 cases (using G*Power 3.1.9.7 software). Taking into account the potential data loss in retrospective studies, a total of 118 patients were included in this study, with 58 cases in the sacubitril/valsartan group and 60 cases in the combined group, to ensure the stability of the results.

Statistical methods

Statistical analysis of patients' baseline data and outcome measures was performed using SPSS 27 software. Potential confounders that may affect the study outcomes in Table 1 were included in the regression model, and Logistic regression analysis was used to control for confounding factors. To assess the normal distribution of continuous data, the Shapiro-Wilk test was applied. If the data conformed to a normal distribution, they were expressed as mean±SD; independent samples t-test was used for comparisons between groups, and paired t-test was used for comparisons within the same group before and after treatment. For continuous data with non-normal distribution, they were expressed as M(IQR), and the Mann-Whitney U test was used for between-group comparisons. Categorical data were presented as n(%) and used the Chi-Square test. All data results used $P<0.05$ as the threshold to determine a statistical difference.

RESULTS

Comparison of clinical data between the two groups

As shown in the baseline data in Table 1, there were no statistically significant differences between the two groups in demographic characteristics, heart failure-related baseline indicators, vital signs, lifestyle habits, and

use of baseline anti-heart failure medications (all $P>0.05$). The between-group balance was favorable. Odds ratios (OR) and their 95% confidence intervals (95% CI) also indicated no significant differences between the two groups. This suggests that the confounding effects of most potential confounders were effectively eliminated between the two groups, providing a reliable basis for the subsequent fair comparison of treatment outcome measures.

Comparison of ventricular structure and function indicators

The ventricular structure and function indicators-LVEF, LVEDD, LVESD, and GLS-were compared between the two groups (Table 2). After treatment, LVEF and the absolute value of GLS increased (all $P<0.05$), while LVEDD and LVESD decreased (all $P<0.05$). When comparing the data before and after treatment, the increases in LVEF and the absolute value of GLS in the combined group were more significant (95%CI: −5.69, −3.07, $P<0.001$; 95%CI: −3.54, −2.24, $P<0.001$), and the decreases in LVEDD and LVESD were also more significant (95%CI: 0.15, 2.40, $P=0.026$; 95%CI: 0.06, 2.22, $P=0.039$). Results revealed that after treatment, patients in both groups exhibited enhanced left ventricular systolic function, and myocardial remodeling and myocardial injury were reversed. Moreover, the combination of sacubitril/valsartan and QLQX achieved a better therapeutic effect.

Table 1. Baseline data [mean±SD, n(%)].

Variables	Sacubitril/Valsartan Group (n=58)	Combined Group (n=60)	*P*	OR	OR for 95%CI
Age (years)	47.03±8.36	47.88±7.82	0.570	1.02	0.96,1.08
BMI (kg/m^2)	23.98±1.60	24.04±1.55	0.835	1.03	0.81,1.31
Height (cm)	167.48±8.11	168.57±8.58	0.480	1.01	0.98,1.04
Weight (kg)	68.03±8.79	68.93±9.04	0.587	1.01	0.97,1.05
Gender n (%)					
Male n (%)	32 (55.2)	34 (56.7)	0.870	0.93	0.43,2.00
Female n (%)	26 (44.8)	26 (43.3)			
LVEF (%)	32.37±3.71	33.07±3.73	0.308	1.05	0.99,1.11
NYHA-FC n (%)					
II n (%)	20 (34.5)	21 (35.0)	0.997	1.01	0.52,1.96
III n (%)	32 (55.2)	33 (55.0)			
IV n (%)	6 (10.3)	6 (10.0)			
Previous HF hospitalization n (%)	22 (37.9)	23 (38.3)	0.964	0.98	0.49,1.96
SBP (mmHg)	114.62±10.41	115.90±10.45	0.507	1.01	0.98,1.04
DBP (mmHg)	70.72±6.50	71.88±6.56	0.337	1.03	0.98,1.08
HR (bpm)	71.40±7.43	72.35±7.17	0.479	1.02	0.98,1.06
Previous history of HF n (%)	53 (91.4)	59 (98.3)	0.086	0.18	0.02,1.51
Smoking history n (%)	21 (36.2)	20 (33.3)	0.743	1.14	0.55,2.35
Alcohol drinking history n (%)	18 (31.0)	20 (33.3)	0.789	0.90	0.41,1.96
Basic anti-HF medications n (%)					
β-blockers n (%)	55 (94.8)	56 (93.3)	0.550	1.892	0.345,10.361
MRA (spironolactone) n (%)	52 (89.7)	53 (88.3)	0.664	1.325	0.387,4.536
SGLT2i n (%)	50 (86.2)	51 (85.0)	0.725	1.228	0.362,4.169

BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA-FC, New York heart association-functional classification; HF, heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; OR, Odds Ratio; 95%CI, 95% confidence interval; MRA, Mineralocorticoid Receptor Antagonist; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitor.

Table 2. Comparison of ventricular structural and functional indicators [mean±SD].

Variables	Time	Sacubitril/Valsartan Group (n=58)	Combined Group (n=60)	Difference 95%CI	*P*	Effect size
LVEF (%)	Before treatment	32.37±3.71	33.07±3.73	−2.06,0.65	0.308	−0.189
	After treatment	36.52±3.55*	40.90±3.64*	−5.69,−3.07	<0.001	−1.219
LVEDD (mm)	Before treatment	58.08±3.11	58.05±3.19	−1.12,1.18	0.960	0.009
	After treatment	52.95±3.02*	51.68±3.14*	0.15,2.40	0.026	0.414
LVESD (mm)	Before treatment	49.11±3.02	49.11±3.11	−1.12,1.11	0.993	−0.002
	After treatment	43.84±2.95*	42.71±2.97*	0.06,2.22	0.039	0.384
The absolute value of GLS (%)	Before treatment	13.77±1.65	14.03±1.69	−0.87,0.35	0.395	−0.157
	After treatment	15.77±1.76*	18.66±1.79*	−3.54,−2.24	<0.001	−1.626

$P<0.05$ vs. before treatment; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; GLS, left ventricular global longitudinal strain.

Comparison of heart failure biomarkers

After treatment, the NT-proBNP levels decreased in both groups (all $P<0.05$), additionally, the reduction in NT-proBNP levels was more notable in the combined group relative to the sacubitril/valsartan group (95%CI: 22.21, 254.81, $P=0.020$) (Table 3). This indicates that heart failure was improved in patients of both groups after treatment, and the combination of sacubitril/valsartan and QLQX achieved a better effect in improving heart failure.

Comparison of inflammatory factors and myocardial injury markers

The myocardial injury marker cTnI and the inflammatory factors CRP and TNF-α were compared between the two groups (Table 4). After treatment, cTnI, CRP, and TNF-α levels decreased in both groups (all $P<0.05$), and the reductions in these three indicators were more notable in the combined group than in the monotherapy group (95%CI: 0.009, 0.017, $P<0.001$; 95%CI: 0.57, 2.70, $P=0.003$; 95%CI: 0.62, 2.20, $P<0.001$). This suggests that after treatment, myocardial injury was improved and inflammatory levels were reduced in patients of both groups; meanwhile, the combination therapy of sacubitril/valsartan and QLQX achieved a better effect in improving myocardial injury and reducing inflammatory levels.

Comparison of clinical efficacy

The clinical efficacy of patients in the two groups was statistically analyzed. See Table 5. In the sacubitril/valsartan monotherapy group, 16 patients achieved a "markedly effective" response and 25 patients achieved an "effective" response, with an overall effective rate of 70.7%. In the combined group, 32 patients achieved a "markedly effective" response and 22 patients achieved an "effective" response, with an overall effective rate of 90%. The clinical efficacy of sacubitril/valsartan combined with QLQX was significantly better than that of sacubitril/valsartan monotherapy ($P=0.008$).

Comparison of 6MWT results

After treatment, the 6MWT distance was prolonged in both groups (all $P<0.05$). The prolongation of 6MWT distance in the combined group was more significant (95%CI: −38.21, −2.67, $P=0.025$) as opposed to sacubitril/valsartan monotherapy. This indicates that the cardiopulmonary compensation capacity during exercise was improved and the cardiac function status was enhanced in patients of both groups after treatment, and the combined use achieved a better therapeutic effect (Table 6).

Comparison of MLHFQ scores

After treatment, the MLHFQ scores decreased in both groups (all $P<0.05$), and the decrease in MLHFQ scores was more significant in the combined group (95%CI: 4.76, 9.42, $P<0.001$) (Table 7). This points to the fact that the quality of life of patients in the two groups was enhanced after receiving treatment, and the combined medication resulted in a more significant improvement in quality of life.

Table 3. Comparison of NT-proBNP [mean±SD].

Variables	Time	Sacubitril/Valsartan Group (n=58)	Combined Group (n=60)	Difference 95%CI	*P*	Effect size
NT-proBNP (pg/mL)	Before treatment	1838.10±415.16	1897.17±434.19	−214.05,95.92	0.452	−0.139
	After treatment	1455.34±307.15*	1316.83±329.83*	22.21,254.81	0.020	0.434

*$P<0.05$ vs. before treatment; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 4. Comparison of cTnI, CRP and TNF-α [mean±SD].

Variables	Time	Sacubitril/Valsartan Group (n=58)	Combined Group (n=60)	Difference 95%CI	*P*	Effect size
cTnI (ng/mL)	Before treatment	0.078±0.015	0.082±0.016	−0.010,0.002	0.156	−0.263
	After treatment	0.060±0.012*	0.047±0.011*	0.009,0.017	<0.001	0.762
CRP (mg/L)	Before treatment	15.00±3.71	15.54±3.78	−1.91,0.82	0.432	−0.145
	After treatment	11.87±2.99*	10.24±2.85*	0.57,2.70	0.003	0.561
TNF-α (pg/mL)	Before treatment	12.33±2.49	12.71±2.51	−1.29,0.53	0.412	−0.152
	After treatment	10.01±2.11*	8.60±2.23*	0.62,2.20	<0.001	0.648

*$P<0.05$ vs. before treatment; cTnI, serum cardiac troponin I; CRP, C reactive protein; TNF-α, tumor necrosis factor-α.

Table 5. Comparison of clinical efficacy [n (%)].

Variables	Sacubitril/Valsartan Group (n=58)	Combined Group (n=60)	*P*	Effect size
Marked effect n (%)	16 (27.6)	32 (53.3)	-	-
Effective n (%)	25 (43.1)	22 (36.7)	-	-
Ineffective n (%)	17 (29.3)	6 (10.0)	-	-
Overall effective n (%)	41 (70.7)	54 (90.0)	0.008	−0.244

Comparison of adverse events

See Table 8. During the treatment period, among patients taking sacubitril/valsartan, 6 cases experienced hypotension, 4 cases had gastrointestinal reactions, and 3 cases had dizziness. In the group taking the combination therapy, the adverse events included 4 cases of hypotension, 4 cases of gastrointestinal reactions, and 2 cases of dry mouth. No notable difference was found between the two groups with regard to the incidence of adverse events (22.4% vs. 16.7%, *P*=0.431).

DISCUSSION

The core mechanisms of HFrEF are characterized by myocardial cell apoptosis, myocardial fibrosis, ventricular cavity enlargement, and decreased systolic function, which ultimately lead to progressive deterioration of cardiac function[23]. Currently, as a representative drug of ARNI, sacubitril/valsartan has become the cornerstone of HFrEF treatment. It achieves hemodynamic improvement and inhibition of myocardial remodeling through dual inhibition of RAAS and neprilysin[24]. As a representative Chinese patent medicine for the integrated traditional Chinese and Western medicine treatment of heart failure, QLQX can activate blood circulation and dredge collaterals, promote diuresis and relieve edema". Modern pharmacological studies have confirmed that it can regulate inflammatory responses, improve myocardial energy metabolism, and inhibit myocardial fibrosis[25]. The following is an in-depth discussion of the results, combined with mechanisms, existing studies, and research limitations.

In this study after treatment, the increase in LVEF in the combined group was higher than that in the monotherapy group; the reduction ranges of LVEDD and LVESD in the combined group were greater than those in the monotherapy group; also, the increase in absolute GLS was more marked in the combined group. These findings suggest that the combined therapy has a more significant role in promoting the recovery of ventricular systolic function and reverse remodeling. The combined group exhibited larger declines in NT-proBNP and cTnI, this points to the fact that the combined therapy can more effectively reduce ventricular load and inhibit myocardial injury. Also, the reduction in inflammatory factors was greater in the combined group; the total clinical effective rate of the combined group was higher than that of the monotherapy group; and the prolongation range of 6MWT distance and the decrease range of MLHFQ score in the combined group were both better than those in the monotherapy group. No notable difference was identified in the total incidence of adverse events between the two groups, and neither group had severe adverse reactions nor treatment discontinuation events. This indicates that the combined therapy does not increase safety risks and has good tolerance.

From the perspective of traditional Chinese medicine theory, the core pathogenesis of Heart Failure with HFrEF lies in "yang-qi deficiency and decline, internal obstruction of static blood, and internal retention of fluid-dampness". QLQX is composed of Huangqi, Fuzi, Danshen, Tinglizi, and other Chinese herbs. Among them, Huangqi and Fuzi replenish qi and warm yang to invigorate cardiac yang; Danshen and Honghua activate blood circulation and dredge collaterals to improve microcirculation; Tinglizi and Zexie promote diuresis and relieve edema to reduce fluid-dampness retention. This formulation conforms to the traditional Chinese medicine

Table 6. Comparison of 6MWT [mean±SD].

Variables	Time	Sacubitril/Valsartan Group (n=58)	Combined Group (n=60)	Difference 95%CI	*P*	Effect size
6MWT (m)	Before treatment	277.07±50.11	283.92±51.50	−25.38,11.69	0.466	−0.135
	After treatment	358.86±49.23*	379.30±48.25*	−38.21,−2.67	0.025	−0.419

**P*<0.05 vs. before treatment; 6MWT, 6 min walking test.

Table 7. Comparison of MLHFQ Score [mean±SD].

Variables	Time	Sacubitril/Valsartan Group (n=58)	Combined Group (n=60)	Difference 95%CI	*P*	Effect size
MLHFQ Score (scores)	Before treatment	44.07±7.63	45.30±7.77	−4.04,1.58	0.387	−0.160
	After treatment	35.17±5.87*	28.08±6.85*	4.76,9.42	<0.001	1.110

**P*<0.05 vs. before treatment; MLHFQ, Minnesota living with heart failure questionnaire.

Table 8. Comparison of adverse events [n (%)].

Variables	Sacubitril/Valsartan Group (n=58)	Combined Group (n=60)	*P*	Effect size
Hypotension n (%)	6 (10.3)	4 (6.7)	-	-
Gastrointestinal reactions n (%)	4 (6.9)	4 (6.7)	-	-
Dizziness n (%)	3 (5.2)	/	-	-
Xerostomian (%)	/	2 (3.3)		
Total n (%)	13 (22.4)	10 (16.7)	0.431	0.073

therapeutic principle of "treating both the root cause and symptoms"[26]. From the perspective of modern pharmacology, the active components of QLQX exert effects through multiple targets: (1) Inhibiting the transforming growth factor-β1 (TGF-β1)/Smad signaling pathway to reduce collagen deposition and suppress myocardial fibrosis; (2) Downregulating the activity of the nuclear factor-κB (NF-κB) pathway to decrease the release of inflammatory factors such as TNF-α and CRP, thereby alleviating myocardial inflammatory injury[27]; (3) Improving myocardial mitochondrial function to enhance ATP production and relieve myocardial energy metabolism disorders; (4) Inhibiting the expression of myocardial cell apoptosis-related proteins to reduce myocardial cell loss[28]. A 2024 animal study on rats showed that QLQX may exert an effect on ventricular remodeling. The results demonstrated downregulated levels of NT-proBNP (P<0.01) (ref.[29]) and cTnI (P<0.05) (ref.[29]), along with an increased LVEF (P<0.05) (ref.[29]). This mechanistic study provides experimental support for the decreases in NT-proBNP and cTnI, as well as the increase in LVEF observed in the combined group of this study, indicating that QLQX is not merely an adjuvant in the combined therapy but participates in reversing cardiac remodeling through clear molecular mechanisms. On the one hand, sacubitril/valsartan blocks AT1 receptor, inhibiting myocardial hypertrophy, myocardial fibrosis, and ventricular cavity enlargement caused by excessive activation of RAAS (ref.[30]). On the other hand, it inhibits the degradation of natriuretic peptides by neprilysin, increasing endogenous natriuretic peptide levels to enhance diuretic and vasodilatory effects and reduce ventricular preload. Meanwhile, it activates the guanylate cyclase-cyclic guanosine monophosphate (GC-cGMP) pathway to inhibit myocardial cell apoptosis[30,31]. The advantages of the combined therapy in this study are in three aspects. (1) Anti-fibrotic effect: sacubitril/valsartan primarily inhibits RAAS-mediated collagen synthesis, while QLQX can suppress the activity of matrix metalloproteinases (MMPs) to reduce collagen degradation imbalance. The two agents synergistically decrease the myocardial collagen volume fraction (CVF), promoting the reduction of LVEDD and LVESD (ref.[32]). (2) Anti-inflammatory effect: sacubitril/valsartan inhibits NF-κB activation by increasing natriuretic peptide levels, while QLQX directly downregulates the phosphorylation level of NF-κB p65. Together, they enhance the anti-inflammatory actions, and alleviate myocardial inflammatory injury, laying a foundation for the recovery of LVEF. (3) Myocardial cell protection: sacubitril/valsartan improves myocardial hemodynamics, and QLQX enhances mitochondrial function. The two agents synergistically reduce myocardial cell apoptosis and improve myocardial contractile efficiency. This synergistic effect is particularly significant in the improvement of the absolute value of GLS. As a more sensitive indicator of myocardial function than LVEF, GLS suggests that the combined therapy can reverse occult myocardial injury-an effect difficult to achieve with monotherapy[33].

The inclusion of the absolute value of GLS in the core assessment system of this study is crucial for overcoming the limitations of previous research. The absolute value of GLS measures myocardial longitudinal contractile function via speckle-tracking echocardiography, which can capture subtle improvements in myocardial function even when LVEF has not yet changed significantly. It is therefore particularly suitable for evaluating subclinical cardiac remodeling. A 2023 study published in the European Heart Journal pointed out that an increase of ≥2% (ref.[34]) in the absolute value of GLS following treatment in HFrEF patients can cut the risk of HF rehospitalization by 25% (ref.[34]), and this study further confirms the positive impact of GLS on prognosis[34]. Chronic inflammation is a core driver of the progression of cardiac remodeling in HFrEF. TNF-α can induce myocardial cell apoptosis and promote myocardial fibrosis, while CRP exacerbates myocardial injury by activating the complement system. In this study, the decreases in TNF-α and CRP in the combined group were greater. On one hand, sacubitril/valsartan inhibits the release of inflammatory factors by increasing natriuretic peptide levels; on the other hand, tanshinone IIA in QLQX can directly inhibit NF-κB pathway and reduce the transcription of inflammatory factors[35]. This synergistic anti-inflammatory effect not only improves the myocardial microenvironment but also reduces vascular endothelial injury and further alleviates ventricular load, which is also an important reason for the more significant prolongation of 6MWT distance in the combined group. The combined group achieved a higher total clinical effective rate, and the decrease in MLHFQ score was more significant, indicating that the therapeutic benefits have been transformed from improvements in objective indicators to enhancements in patients' subjective perceptions. From a mechanistic perspective, the increase in LVEF and the reduction in LVEDD alleviate pulmonary congestion and relieve dyspnea; the prolongation of 6MWT reflects improved exercise tolerance, enabling patients to complete daily activities; and the decrease in inflammatory factors mitigates systemic symptoms such as weakness and fatigue. These factors collectively contribute to the improvement in quality of life[35,36].

This study breaks through the limitation of previous combined therapy studies that mostly focused on conventional indicators such as LVEF and NT-proBNP. It incorporates the absolute value of GLS into the core assessment system, as the absolute value of GLS can sensitively capture subtle improvements in occult myocardial function. Meanwhile, the study also includes inflammatory factors (CRP, TNF-α), myocardial injury indicators (cTnI), exercise tolerance (6MWT), and quality of life (MLHFQ) to form a multi-dimensional assessment system. This system comprehensively reflects the efficacy of the combined therapy and provides a reference for indicator design in subsequent studies. Based on the pathological characteristics of HFrEF patients, the combined treatment regimen designed in this study not only adheres to the principle of targeted inhibition of RAAS and inflammatory pathways in modern medicine but also embodies the advantage of holistic regulation in traditional Chinese medicine. It thus provides high-quality

clinical evidence for the integrated traditional Chinese-Western medicine treatment of HFrEF. In current clinical practice, some HFrEF patients cannot tolerate full-dose ARNI treatment due to poor tolerance. However, the addition of QLQX can improve efficacy without increasing safety risks, offering a better treatment option for such patients[35].

This study is a retrospective study, with data derived from the medical record, and has the following limitations: (1) selection bias: all included patients were inpatients, which may have led to the omission of outpatients with mild symptoms and thus insufficient representativeness of the sample; (2) inadequate control of confounding factors: although baseline data were balanced using statistical methods, there may still be unmeasured confounding factors that affect the results; (3) short observation period: the observation period of this study was 6 months, which only evaluated short-term efficacy without obtaining long-term prognosis data. Therefore, the long-term efficacy of the combined therapy requires further investigation; (4) lack of subgroup analysis: this study did not conduct subgroup analysis, so it was impossible to determine the optimal population for the combined therapy. In response to the limitations of this study, future research can be carried out in the following aspects: (1) conduct multi-center, large-sample, double-blind randomized controlled trials to enhance the reliability and generalizability of the results; (2) perform subgroup analysis to clarify the applicable population of the combined therapy among patients with different baseline characteristics; (3) carry out drug dose exploration studies to optimize the dose regimen of the combined therapy, thereby further improving its efficacy and tolerability.

CONCLUSION

Through retrospective analysis, this study confirms that the combination of sacubitril/valsartan and QLQX can effectively reverse cardiac remodeling in HFrEF, improve clinical efficacy and quality of life, and exhibits good safety. This result provides a more optimal integrated Traditional Chinese and Western medicine treatment regimen for HFrEF patients and lays a foundation for subsequent studies.

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Ethic Approval and consent to participate/informed consent: All protocols of this study were strictly in line with the Declaration of Helsinki and had obtained official approval from Chongqing Seventh People's Hospital's Medical Ethics Committee. (Approval number: 2025–003). We secured a signed informed consent form from every participant.

Data availability statement: The data supporting the findings of this study can be obtained from the corresponding author, upon request.

Declaration of generative AI and AI-assisted technologies: None.

REFERENCES

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res 2023;118(17):3272-87. doi: 10.1093/cvr/cvac013
2. Greene SJ, Bauersachs J, Brugts JJ, Ezekowitz JA, Lam CSP, Lund LH, Ponikowski P, Voors AA, Zannad F, Zieroth S, Butler J. Worsening heart failure: Nomenclature, epidemiology, and future directions: JACC review topic of the week. J Am Coll Cardiol 2023;81(4):413-24. doi: 10.1016/j.jacc.2022.11.023
3. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart failure with mid-range or mildly reduced ejection fraction. Nat Rev Cardiol 2022;19(2):100-16. doi: 10.1038/s41569-021-00605-5
4. Zamorano JL, Gonzalez Leal A. Advances in heart failure management. Med Clin (Barc) 2024;163(1):32-39. doi: 10.1016/j.medcli.2023.12.026
5. Shou J, Huo Y. Changes of calcium cycling in HFrEF and HFpEF. Mechanobiol Med 2023;1(1):100001. doi: 10.1016/j.mbm.2023.100001
6. Rashid AM, Khan MS, Fudim M, DeWald TA, DeVore A, Butler J. Management of heart failure with reduced ejection fraction. Curr Probl Cardiol 2023;48(5):101596. doi: 10.1016/j.cpcardiol.2023.101596
7. Shi L, Huang L, Yin E, Deng J, Du X. Effect of pueraria on left ventricular remodelling in HFrEF: A systematic review and meta-analysis. PLoS One 2023;18(12):e0295344. doi: 10.1371/journal.pone.0295344
8. Sinagra G, Pagura L, Stolfo D, Fabris E, Savarese G, Rapezzi C, Ferrari R, Merlo M. Combining new classes of drugs for HFrEF: from trials to clinical practice. Eur J Intern Med 2021;90:10-15. doi: 10.1016/j.ejim.2021.05.017
9. Fisher MM, Outhred A, Bowey CJ. Can clinical anaphylaxis to anaesthetic drugs be predicted from allergic history? Br J Anaesth 1987;59(6):690-2. doi: 10.1093/bja/59.6.690
10. Matsumoto S, Shen L, Henderson AD, Bohm M, Desai AS, Kober L, Lefkowitz MP, Packer M, Rouleau JL, Solomon SD, Swedberg K, Vaduganathan M, Vardeny O, Voors AA, Zile MR, Jhund PS, McMurray JJV. Asymptomatic vs symptomatic hypotension with sacubitril/valsartan in heart failure and reduced ejection fraction in PARADIGM-HF. J Am Coll Cardiol 2024;84(18):1685-700. doi: 10.1016/j.jacc.2024.08.012
11. Berg DD, Samsky MD, Velazquez EJ, Duffy CI, Gurmu Y, Braunwald E, Morrow DA, DeVore AD. Efficacy and safety of sacubitril/valsartan in high-risk patients in the PIONEER-HF trial. Circ Heart Fail 2021;14(2):e007034. doi: 10.1161/CIRCHEARTFAILURE.120.007034
12. Shah AM, Claggett B, Prasad N, Li G, Volquez M, Jering K, Cikes M, Kovacs A, Mullens W, Nicolau JC, Kober L, van der Meer P, Jhund PS, Ibram G, Lefkowitz M, Zhou Y, Solomon SD, Pfeffer MA. Impact of sacubitril/valsartan compared with ramipril on cardiac structure and function after acute myocardial infarction: The PARADISE-MI

echocardiographic substudy. Circulation 2022;146(14):1067-81. doi: 10.1161/CIRCULATIONAHA.122.059210
13. Wang T, Hou B, Qin H, Liang J, Shi M, Song Y, Ma K, Chen M, Li H, Ding G, Yao B, Wang Z, Wei C, Jia Z. Qili Qiangxin (QLQX) capsule as a multi-functional traditional Chinese medicine in treating chronic heart failure (CHF): A review of ingredients, molecular, cellular, and pharmacological mechanisms. Heliyon 2023;9(11):e21950. doi: 10.1016/j.heliyon.2023.e21950
14. Chinese Society of Cardiology CMA. Chinese guidelines for the diagnosis and treatment of heart failure 2024. Chin J Cardiol 2024;52(3):235-75. doi: 10.3760/cma.j.cn112148-20231101-00405
15. Xing X, Guo J, Mo J, Li H, Zhang H, Shao B, Wang Y, Li H, Wang J, Leung CL, Jiang Y, Yin W, Chen H, He Q. Qili Qiangxin capsules for chronic heart failure: A GRADE-assessed clinical evidence and preclinical mechanism. Front Cardiovasc Med 2022;11(9):1090616. doi: 10.3389/fcvm.2022.1090616
16. Robles-Mezcua A, Januzzi JL, Pavon-Moron FJ, Rodriguez-Capitan J, Lopez-Garrido MA, Cruzado-Alvarez C, Robles-Mezcua M, Gutierrez-Bedmar M, Couto-Mallon D, Rueda-Calle EC, Barreiro-Perez M, Sanchez PL, Gomez-Doblas JJ, Jimenez-Navarro MF, Garcia-Pinilla JM. Effects of sacubitril/valsartan on cardiac remodeling in heart failure with reduced ejection fraction: An integrated study of molecular biomarkers and imaging techniques. Biomed Pharmacother 2025;183:117874. doi: 10.1016/j.biopha.2025.117874
17. Shaddy R, Burch M, Kantor PF, Solar-Yohay S, Garito T, Zhang S, Kocun M, Mao C, Cilliers A, Wang X, Canter C, Rossano J, Wallis G, Menteer J, Daou L, Kusa J, Tokel K, Dilber D, Xu Z, Xiao T, Halnon N, Daly KP, Bock MJ, Zuckerman W, Singh TP, Chakrabarti M, Levitas A, Senni M, Grutter G, Kim GB, Song J, Lee HD, Chen CK, Sanchez-de-Toledo J, Law Y, Wanitkun S, Cui Y, Anjos R, Mese T, Bonnet D, Investigators P-H. Sacubitril/valsartan in pediatric heart failure (PANORAMA-HF): A randomized, multicenter, double-blind trial. Circulation 2024;150(22):1756-66. doi: 10.1161/CIRCULATIONAHA.123.066605
18. Yao J, Liu D. Clinical effect of Qili Qiangxin capsule combined with sacubitril-valsartan in patients with chronic heart failure. J Healthc Eng 2022;23(2022):8598806. doi: 10.1155/2022/8598806
19. Khan MS, Anker SD, Friede T, Jankowska EA, Metra M, Pina IL, Coats AJ, Rosano G, Roubert B, Goehring UM, Dorigotti F, Comin-Colet J, Vanveldhuisen DJ, Filippatos GS, Ponikowski P, Butler J. Minimal clinically important differences in 6-minute walk test in patients with HFrEF and iron deficiency. J Card Fail 2023;29(5):760-70. doi: 10.1016/j.cardfail.2022.10.423
20. Zhao D, Zhang Y, Yong Y, Wang L, Liu J. Vericiguat combined with "new quadruple" therapy enhances cardiac function and life quality in patients with heart failure: a single-center prospective study. Front Cardiovasc Med 2024;11(11):1476976. doi: 10.3389/fcvm.2024.1476976
21. Edwards JJ, O'Driscoll JM. Exercise training in heart failure with preserved and reduced ejection fraction: A systematic review and meta-analysis. Sports Med Open 2022;8(1):76. doi: 10.1186/s40798-022-00464-5
22. Chen W, Chang H, Wang X, Wang Y, Liu Y, Wang D. The efficacy and safety of a Qiliqiangxin capsule combined with sacubitril/valsartan in the treatment of chronic heart failure: A systematic review and meta-analysis. Evid Based Complement Alternat Med 2023;3(2023):2701314. doi: 10.1155/2023/2701314
23. Mohammadnezhad G, Azadmehr B, Mirheidari M, Yousefi N. Cost-effectiveness analysis of dapagliflozin in the management of heart failure with reduced ejection fraction (HFrEF): a systematic review. Cost Eff Resour Alloc 2022;20(1):62. doi: 10.1186/s12962-022-00396-7
24. Rajzer P, Biegus J. Sacubitril/valsartan in a wide spectrum of heart failure patients (from mechanisms of action to outcomes in specific populations). Heart Fail Rev 2025;30(2):387-405. doi: 10.1007/s10741-024-10471-1
25. Wu N, Chi J, Cai H, Hu J, Lai Y, Lin C, Kang L, Sun J, Huang J, Li M, Xu L. Traditional Chinese medication qili qiangxin capsule protects against myocardial ischemia-reperfusion injury through suppressing autophagy via the phosphoinositide 3-kinase/protein kinase B/forkhead box O3 axis. J Ethnopharmacol 2025;337(Pt 1):118821. doi: 10.1016/j.jep.2024.118821
26. Hao J, Wang M, Wu Q, Song T, Hao Y, Chang L, Hou Y, Jia Z. Deciphering the molecular mechanisms of QLQX capsules in heart failure: A multi-omics perspective. Phytomedicine 2025;25(143):156828. doi: 10.1016/j.phymed.2025.156828
27. Ashrafizadeh M. Cell death mechanismsin human cancers: Molecular pathways, therapy resistanceand therapeutic perspective. J Can Biomol Therap 2024;1(1):17-40. doi: 10.62382/jcbt.v1i1.13
28. Packer M. Qiliqiangxin: A multifaceted holistic treatment for heart failure or a pharmacological probe for the identification of cardioprotective mechanisms? Eur J Heart Fail 2023;25(12):2130-43. doi: 10.1002/ejhf.3068
29. Sun M, Liu C, Gao K, Xu X, Chen K, Qiu L, Wang X. Qili Qiangxin capsule attenuates myocardial fibrosis by modulating collagen homeostasis post-infarction in rats. PLoS One 2024;19(9):e0310897. doi: 10.1371/journal.pone.0310897
30. Campanile A, Visco V, De Carlo S, Ferruzzi GJ, Mancusi C, Izzo C, Mongiello F, Di Pietro P, Virtuoso N, Ravera A, Bonadies D, Vecchione C, Ciccarelli M. Sacubitril/valsartan vs. standard medical therapy on exercise capacity in HFrEF patients. Life (Basel) 2023;13(5):1174. doi: 10.3390/life13051174
31. Grewal PK, Abboud A, Myserlis EP, Goldschmidt ME, Butler J, Skopicki HA, Kalogeropoulos AP. Sacubitril/valsartan and cognitive outcomes in heart failure with reduced ejection fraction. JACC Adv 2023;2(4):100372. doi: 10.1016/j.jacadv.2023.100372
32. Raphael DM, Liu Z, Jin Z, Cui X, Han D, He W, Shangguan J, Shen D. Effects of sacubitril/valsartan on clinical symptoms, echocardiographic parameters, and outcomes in HFrEF and HFmrEF patients with coronary heart disease and chronic kidney disease. Curr Med Res Opin 2021;37(7):1071-78. doi: 10.1080/03007995.2021.1908243
33. Pastore MC, Mandoli GE, Giannoni A, Benfari G, Dini FL, Pugliese NR, Taddei C, Correale M, Brunetti ND, Carluccio E, Mengoni A, Guaricci AI, Piscitelli L, Citro R, Ciccarelli M, Novo G, Corrado E, Pasquini A, Loria V, Degiovanni A, Patti G, Santoro C, Moderato L, Malagoli A, Emdin M, Cameli M, Collaborators D-AC, Rosa G, Magnesa M, Mazzeo P, De Carli G, Bellino M, Iuliano G, Casciano O, Binno S, Canepa M, Tondi S, Cicoira M, Mega S. Sacubitril/valsartan reduces indications for arrhythmic primary prevention in heart failure with reduced ejection fraction: insights from DISCOVER-ARNI, a multicenter Italian register. Eur Heart J Open 2022;2(1):oeab046. doi: 10.1093/ehjopen/oeab046
34. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A. Corrigendum to: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2021;42(48):4901. doi: 10.1093/eurheartj/ehab670
35. He L, Liu Y, Yang K, Zou Z, Fan C, Yao Z, Dai Y, Li K, Chen J, Yao X. The discovery of Q-markers of Qiliqiangxin capsule, a traditional Chinese medicine prescription in the treatment of chronic heart failure, based on a novel strategy of multi-dimensional "radar chart" mode evaluation. Phytomedicine 2021;82:153443. doi:0.1016/j.phymed.2020.153443
36. Pelaia C, Armentaro G, Volpentesta M, Mancuso L, Miceli S, Caroleo B, Perticone M, Maio R, Arturi F, Imbalzano E, Andreozzi F, Perticone F, Sesti G, Sciacqua A. Effects of sacubitril-valsartan on clinical, echocardiographic, and polygraphic parameters in patients affected by heart failure with reduced ejection fraction and sleep apnea. Front Cardiovasc Med 2022;5(9):861663. doi: 10.3389/fcvm.2022.861663