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ORIGINAL RESEARCH ARTICLE

Sacubitril/valsartan improves cardiac function in Chinese patients with heart failure: a real-world study

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Abstract

Aims Sacubitril/valsartan significantly reduced heart failure (HF) hospitalization and cardiovascular mortality in a randomized controlled trial. However, little is known about real-world efficacy and safety of sacubitril/valsartan in Chinese patients with HF with reduced ejection fraction (HFrEF). We aimed to evaluate whether sacubitril/valsartan could improve cardiac function in Chinese patients with HFrEF in a tertiary hospital in China.

Methods and results Patients with HFrEF receiving sacubitril/valsartan in our hospital between January 2018 and January 2020 were recruited in the present study. We retrospectively collected and analysed all clinical parameters at baseline and during follow-up. A total of 100 consecutive patients (73% male) with HFrEF were recruited in the present study. During a median follow-up period of 365 days [interquartile range (IQR), 346–378], a pronounced improvement of cardiac function was achieved. New York Heart Association classification was significantly improved ($P < 0.001$), and median N-terminal pro-B-type natriuretic peptides level significantly decreased from 3003 pg/mL (IQR, 1513–5404) to 2039 pg/mL (IQR, 921–3955) ($P = 0.010$). Mean left ventricular ejection fraction increased from 31 ± 6% to 38 ± 10% ($P < 0.001$) and median left ventricular end-diastolic diameter reduced from 63 mm (IQR, 59–67) to 60 mm (IQR, 55–68) ($P = 0.001$). Mean pulmonary arterial systolic pressure decreased significantly from 49 ± 13 mmHg to 44 ± 12 mmHg ($P < 0.001$) and median right ventricular end-diastolic diameter reduced from 23 mm (IQR, 21–26) to 22 mm (IQR, 20–25) ($P = 0.030$). After treatment with sacubitril/valsartan, mean estimated glomerular filtration rate significantly decreased (from 88.8 ± 22.4 mL/min to 71.8 ± 27.3 mL/min, $P < 0.001$). Median serum creatinine and median blood urea nitrogen levels significantly increased [from 0.9 mg/dL (IQR, 0.8–1.0) to 1.1 mg/dL (IQR, 0.9–1.3), $P < 0.001$, and from 6.8 mmol/L (IQR, 5.5–8.9) to 8.0 mmol/L (IQR, 6.6–10.3), $P = 0.002$, respectively]. The proportion of patients with chronic kidney disease Stage 3/4 increased significantly from 8% to 39% ($P < 0.001$).

Conclusions In Chinese patients with HFrEF, sacubitril/valsartan treatment was associated with a pronounced improvement of cardiac function, but might be prone to a decrease in blood pressure and deterioration in renal function.

Keywords Sacubitril/valsartan; HFrEF; Real-world study; NT-proBNP; Echocardiographic parameters

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Introduction

In the PARADIGM-HF trial, sacubitril/valsartan reduced the primary composite outcome of heart failure (HF) hospitalization or cardiovascular mortality by 20%, as compared with enalapril.[1] According to this study, updated evidence-based guidelines for the treatment of HF provided Class I, level of evidence B recommendation to replace renin-angiotensin system blockers by sacubitril/valsartan in patients with chronic symptomatic HF with reduced ejection fraction (HFrEF) despite optimal treatment.[2,3]

Although potential hurdles associated with the use of sacubitril/valsartan existed in real-world scenario,[4] data from real-life studies seemed to confirm convincing beneficial results of randomized controlled trial. For instance, improved left ventricular ejection fraction (LVEF) and New York Heart

Association (NYHA) classification,[5,6] reverse remodelling,[7] and reduced costs of hospitalization[8] have been demonstrated in real-world observational studies. However, there is a paucity of real-world clinical data on the effects of sacubitril/valsartan on Chinese patients with HFrEF since it was approved by China Food and Drug Administration (CFDA) in 2017.

In this analysis, we aimed to investigate the characteristics and evolution of clinical parameters of a real-world cohort of Chinese patients with HFrEF receiving sacubitril/valsartan, hereby offering valuable information for clinicians when prescribing sacubitril/valsartan.

Methods

Study population

All chronic HF patients prescribed sacubitril/valsartan between January 2018 and January 2020 in a single tertiary hospital (Shandong Province, China) were identified using the computerized database of clinical management system. The inclusion criteria for the current study consists of (i) age ≥18 years, (ii) symptomatic HF defined as NYHA Class II–IV, (iii) LVEF ≤40% by echocardiography. The exclusion criteria for the current study consists of (i) patients lost to any follow-up after initiation of sacubitril/valsartan, (ii) age <18 years old, (iii) LVEF >40% by echocardiography, (iv) HF primarily resulting from right ventricular failure, pericardial disease, or congenital heart disease.

A total of 25 patients were excluded from this study after applying both the inclusion and exclusion criteria. Fifteen patients with LVEF >40% and one patient with right ventricular failure were excluded. Additionally, nine patients were excluded due to insufficient clinical parameters at follow-up. Finally, 100 consecutive patients were included in this study.

Up-titration of sacubitril/valsartan

There was no specific schedule of sacubitril/valsartan up-titration in this retrospective study. In clinical practice, the initial dose of sacubitril/valsartan was decided by physicians according to blood pressure at baseline. As a result, the initial dose of sacubitril/valsartan was not always the lowest one. If tolerated by the patient during follow-up, up-titration was performed every 2 weeks until the maximum tolerated dose of sacubitril/valsartan was achieved.

Study variables

Baseline demographics, aetiology of HF, blood pressure, presence of co-morbidities, baseline laboratory values, chronic kidney disease (CKD) stage, NYHA classification, echocardiographic data, and treatments for HF at baseline and during follow-up were retrospectively collected and analysed. Baseline data were collected from inpatient records before prescribing sacubitril/valsartan, and follow-up data were gathered from outpatient records at least 6 months after prescribing sacubitril/valsartan in order to have a substantial time frame of sacubitril/valsartan use. The study protocol was approved by the institutional review board.

Statistics

Continuous data were presented as mean ± standard deviation if normally distributed or as median (interquartile range, IQR) if not normally distributed. Normality was assessed by the Kolmogorov–Smirnov test. Categorical variables were expressed as percentages. The Student's *t*-test or the Mann–Whitney *U* test was used for comparisons between continuous data; χ^2 test was used for comparisons between categorical data. Comparison of mean ± standard deviation from published literature was performed using the summary independent sample *t*-test. A two-tailed *P* value <0.05 was considered to be statistically significant. All the statistical analyses were performed using the SPSS Statistics 19.0 software (Chicago, IL, USA).

Results

Comparison of baseline characteristics between this real-world study and PARADIGM-HF sacubitril/valsartan arm

From January 2018 to January 2020, a total of 100 consecutive patients were identified according to the aforementioned criteria. Baseline characteristics of enrolled patients are shown in *Table 1*. Briefly, age, gender, HF aetiology, and systolic blood pressure (SBP) were similar between this study and the PARADIGM-HF study. Regarding co-morbidities, patients in our study were less likely to have atrial fibrillation (21% vs. 36%, $P = 0.002$) and hypertension (53% vs. 71%, $P < 0.001$) but more likely to have stroke (14% vs. 8.5%, $P = 0.030$) than patients in PARADIGM-HF study. We also noticed a lower percentage of prior hospitalization for HF (46.0% vs. 62.3%, $P = 0.001$), higher baseline mean LVEF (31 ± 6% vs. 29 ± 6%, $P < 0.001$), and much worse NYHA classification (III/IV) (77.0% vs. 23.9%, $P < 0.001$). In addition, patients in the present study were more often treated with aldosterone antagonist (97% vs. 54%, $P < 0.001$) and loop diuretic (95% vs. 80%, $P < 0.001$) but with lower rate of cardiac resynchronization therapy (CRT) use (4.0% vs. 21.8%, $P < 0.001$) than those in PARADIGM-HF study.

Table 1 Baseline characteristics of enrolled patients

Variable	Total population (n = 100)
Demographics	
Mean age, years	62 ± 14
Male, *n* (%)	73 (73%)
Northern Chinese Han, *n* (%)	99 (99%)
Active smoker, *n* (%)	54 (54%)
Alcohol drinking, *n* (%)	59 (59%)
Prior hospitalization for HF, *n* (%)	46 (46%)
HF aetiology, *n* (%)	
Ischaemic	62 (62%)
Non-ischaemic	38 (38%)
Blood pressure	
Mean SBP, mmHg	124 ± 17
Mean DBP, mmHg	77 ± 12
Co-morbidities, *n* (%)	
Atrial fibrillation	21 (21%)
Hypertension	53 (53%)
Diabetes	28 (28%)
Stroke	14 (14%)
Pulmonary infection	18 (18%)
Dyslipidaemia	18 (18%)
Anaemia	9 (9%)
Median number of co-morbidities	2 (1–3)
Laboratory values	
Mean potassium, mmol/L	4.1 ± 0.5
Median NT-proBNP, pg/mL	3003 (1513–5404)
Median serum creatinine, mg/dL	0.87 (0.76–1.02)
Mean eGFR, mL/min	88.8 ± 22.4
Median eGFR, mL/min	88 (73–105)
Median BUN, mmol/L	6.8 (5.5–8.9)
CKD stage, *n* (%)	
Stage 1	46 (46%)
Stage 2	46 (46%)
Stage 3	8 (8%)
NYHA classification, *n* (%)	
Class II	23 (23%)
Class III	42 (42%)
Class IV	35 (35%)
Echocardiography data	
Mean LVEF, %	31 ± 6
Median LVEDD, mm	63 (59–67)
Median LAD, mm	48 (44–51)
Median RVEDD, mm	23 (21–26)
Median IVST, mm	10 (9–11)
Mean PASP, mmHg	49 ± 13
Treatments for heart failure, *n* (%)	
Beta-blocker	87 (87%)
Aldosterone antagonist	97 (97%)
Loop diuretic	95 (95%)
Digoxin	27 (27%)
Anticoagulant	23 (23%)
Statins	79 (79%)
Aspirin	62 (62%)
P2Y12 antagonist	30 (30%)
Metformin	22 (22%)
Amiodarone	6 (6%)
Amlodipine	4 (4%)
CRT	4 (4%)

BUN, blood urea nitrogen; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimating glomerular filtration rate; HF, heart failure; IVST, interventricular septum thickness; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptides; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; RVEDD, right ventricular end-diastolic diameter; SBP, systolic blood pressure.

Dose titration of sacubitril/valsartan at baseline and during follow-up

The starting dose of sacubitril/valsartan was 12/13 mg twice daily in 39 patients (39%), 24/26 mg twice daily in 60 patients (60%), and 49/51 mg twice daily in one patient (1%). During follow-up, the high dose of sacubitril/valsartan (49/51 mg twice daily) was achieved in 31 patients (31%) in the present study. However, 10 patients (10%) received dose de-escalation because of drop in SBP after the initiation of sacubitril/valsartan. *Figure 1A* shows dose titration of sacubitril/valsartan at baseline and during follow-up.

Clinical parameters at baseline and during follow-up

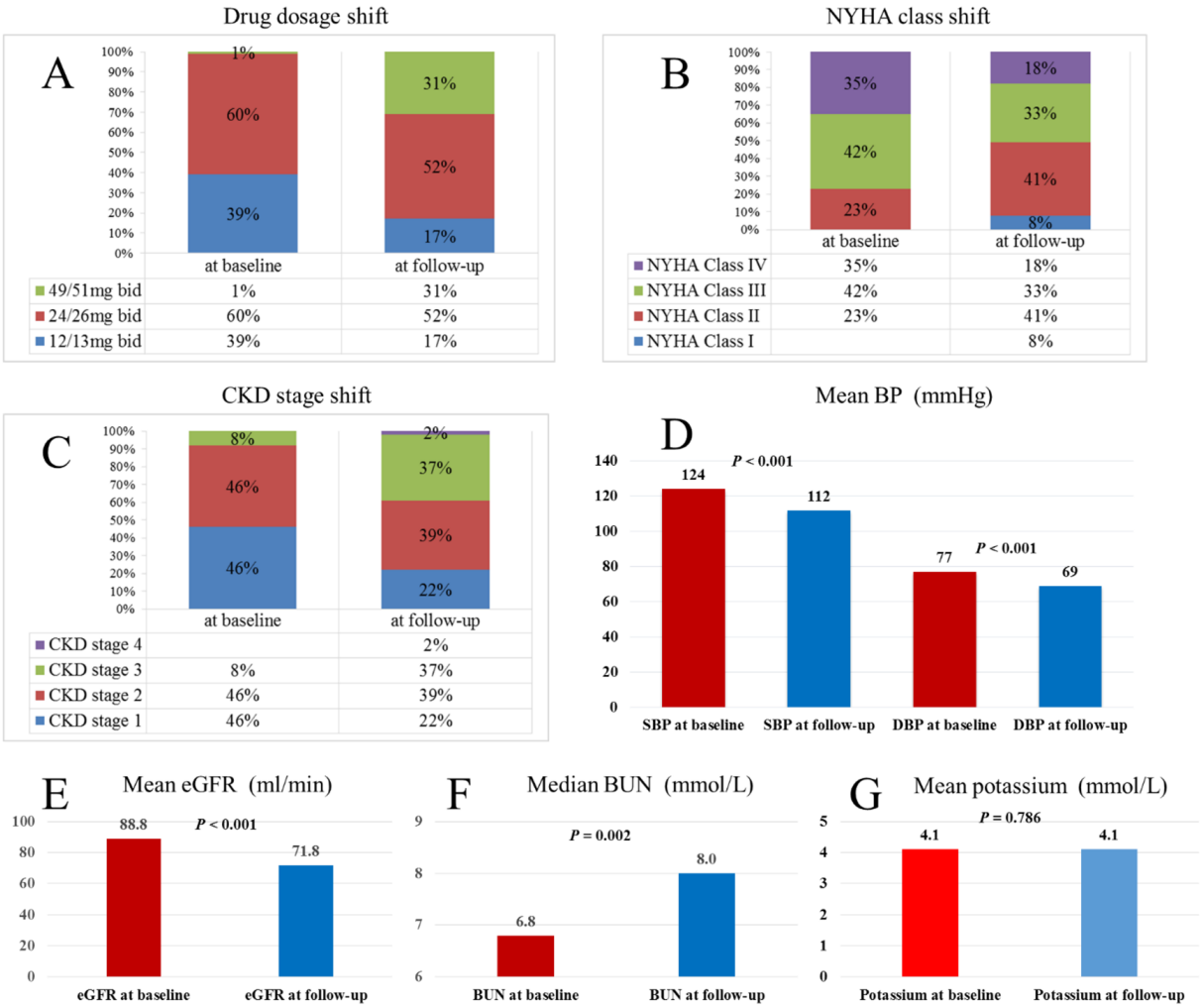
During a median follow-up period of 365 days (IQR, 346–378), unplanned hospitalization for HF occurred in 20 patients (20%), and no patients died. *Table 2* illustrates comparative analysis of the clinical parameters at baseline and during follow-up.

After treatment with sacubitril/valsartan, median N-terminal pro-B-type natriuretic peptides (NT-proBNP) level and mean and median estimating glomerular filtration rate (eGFR) level (*Figure 1E*) were significantly decreased, but median serum creatinine level and median blood urea nitrogen (BUN) level (*Figure 1F*) were significantly increased ($P < 0.05$ for all comparisons). At baseline for the present study, 46 (46%), 46 (46%), and 8 (8%) of the 100 patients had CKD Stage 1, CKD Stage 2, and CKD Stage 3, respectively. During follow-up, 51 patients (51%) reported worsening CKD stage, 35 patients (35%) reported no change, and 14 patients (14%) improved their CKD stage. Finally, the proportion of patients with CKD Stage 3/4 increased significantly from 8% to 39% ($P < 0.001$; *Figure 1C*).

During follow-up, 48 (48%) patients improved their NYHA classification, 43 (43%) patients reported no change and 9 (9%) patients reported worsening NYHA classification. Finally, the proportion of patients in NYHA Class III/IV decreased significantly from 77% to 51% after treatment with sacubitril/valsartan ($P < 0.001$; *Figure 1B*).

Moreover, significant improvements in a series of echocardiographic parameters were also observed during follow-up. Mean LVEF improved from 31 ± 6% to 38 ± 10% ($P < 0.001$). Median left ventricular end-diastolic diameter decreased from 63 mm (IQR, 59–67) to 60 mm (IQR, 55–68) ($P = 0.001$). Median right ventricular end-diastolic diameter decreased from 23 mm (IQR, 21–26) to 22 mm (IQR, 20–25) ($P = 0.030$). Mean pulmonary arterial systolic pressure decreased from 49 ± 13 to 44 ± 12 mmHg ($P < 0.001$). However, median left atrial diameter and median interventricular septum thickness were not significantly influenced by sacubitril/valsartan.

Figure 1 Longitudinal changes of drug dose (A), NYHA class (B), CKD stage (C), mean BP (D), mean eGFR (E), median BUN (F), and mean potassium (G) at baseline and during follow-up. BP, blood pressure; BUN, blood urea nitrogen; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimating glomerular filtration rate; NYHA, New York Heart Association; SBP, systolic blood pressure.



After treatment with sacubitril/valsartan, both systolic and diastolic blood pressure significantly decreased (*Figure 1D*). Strikingly, a drop of 11.3 ± 18.2 mmHg in SBP was noticed, which was significantly more pronounced in comparison with the 3.2 ± 0.4 mmHg drop seen in PARADIGM-HF ($P < 0.001$). Mean potassium did not change significantly during follow-up (*Figure 1G*). Over the entire treatment period, hypotension (SBP $<$ 100 mmHg) occurred in 15 patients, and serum potassium level of more than 5.5 mmol/L occurred only in two patients. None of these adverse events led to drug withdrawal.

Discussion

To the best of our knowledge, this is the first study to investigate the performance of sacubitril/valsartan in Chinese patients with HFrEF in a real-world clinical setting. The most striking findings of this analysis are that patients achieved a pronounced improvement of cardiac function with more favourable NYHA classification, significantly decreased median NT-proBNP level, and beneficial echocardiographic changes after treatment with low doses of sacubitril/valsartan. In addition, sacubitril/valsartan was well tolerated without drug withdrawal over the entire treatment period.

Differences between this real-world study and PARADIGM-HF study were also observed. Patients with much worse NYHA classification were enrolled into our cohort, and they were more often treated with aldosterone antagonist and loop diuretic but with lower rate of CRT use than those in PARADIGM-HF study. This could be explained that cost of CRT was too high for patients in China, and therefore, medical therapy has been the main option for Chinese patients with HF. Furthermore, all selected patients in the trial

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Table 2 Comparisons of clinical parameters between baseline and follow-up

Variable	Baseline (n = 100)	Follow-up (n = 100)	P value
Blood pressure			
Mean SBP, mmHg	124 ± 17	112 ± 14	<0.001
Mean DBP, mmHg	77 ± 12	69 ± 7	<0.001
Laboratory values			
Mean potassium, mmol/L	4.1 ± 0.5	4.1 ± 0.5	0.786
Median NT-proBNP, pg/mL	3003 (1513–5404)	2039 (921–3955)	0.010
Median serum creatinine, mg/dL	0.9 (0.8–1.0)	1.1 (0.9–1.3)	<0.001
Mean eGFR, mL/min	88.8 ± 22.4	71.8 ± 27.3	<0.001
Median eGFR, mL/min	88 (73–105)	67 (52–88)	<0.001
Median BUN, mmol/L	6.8 (5.5–8.9)	8.0 (6.6–10.3)	0.002
CKD stage, n (%)			<0.001
Stage 1/2	92 (92%)	61 (61%)	
Stage 3/4	8 (8%)	39 (39%)	
NYHA classification, n (%)			<0.001
Class I/II	23 (23%)	49 (49%)	
Class III/IV	77 (77%)	51 (51%)	
Echocardiography data			
Mean LVEF, %	31 ± 6	38 ± 10	<0.001
Median LVEDD, mm	63 (59–67)	60 (55–68)	0.001
Median LAD, mm	48 (44–51)	46 (42–53)	0.539
Median RVEDD, mm	23 (21–26)	22 (20–25)	0.030
Median IVST, mm	10 (9–11)	10 (9–11)	0.339
Mean PASP, mmHg	49 ± 13	44 ± 12	<0.001

BUN, blood urea nitrogen; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimating glomerular filtration rate; IVST, interventricular septum thickness; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptides; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; RVEDD, right ventricular end-diastolic diameter; SBP, systolic blood pressure.

experienced run-in period to ensure an acceptable side-effect profile of sacubitril/valsartan at target doses, which was a clear difference from our real-world study.[1] As a result, tolerability of sacubitril/valsartan was unpredictable at baseline in this study, which might affect adherence of patients and up-titration of sacubitril/valsartan during follow-up.

In the PARADIGM-HF, large proportion of patients (74.76%) achieved target dose of sacubitril/valsartan (97/103 mg twice daily) at the last assessment.[1,9,10] However, the proportion of patients who received target dose of sacubitril/valsartan would probably be lower in a real-world setting. In a cohort study in Canada, only 55% of patients received sacubitril/valsartan at a maximum dose of 49/51 mg twice daily, and the others received much lower doses.[5] In another real-world study, Martens *et al*. reported that only 11% of patients received a dose of sacubitril/valsartan 97/103 mg twice daily, 38% of patients received a dose of 49/51 mg twice daily, and 51% of patients received a dose of 24/26 mg twice daily.[4] In the current study, only 31 patients (31%) received sacubitril/valsartan at a maximum dose of 49/51 mg twice daily at the final assessment. Several real-world studies observed that changes in SBP after treatment with sacubitril/valsartan might affect dose titrating.[4,11] In our study, due to drop in SBP, 46 patients (46%) did not undergo dose up-titration of sacubitril/valsartan, and of these, 10 patients received dose de-escalation. Noteworthily, Senni *et al*. reported that if sacubitril/valsartan was titrated gradually, the target dose of 97/103 mg twice daily could be achieved and maintained in a high percentage of patients (~80%) with low SBP (100–110 mmHg).[12] This gives us a hint that establishing scheduled drug-escalation programmes for physicians might be helpful to achieve the maximum tolerated dose of sacubitril/valsartan in Chinese patients with HFrEF.

Although the proportion of patients who achieved the maximum dose of sacubitril/valsartan (49/51 mg twice daily) in our study was lower compared with other studies,[4,5] beneficial effect of sacubitril/valsartan with respect to improvement of cardiac function was still significant. After initiation of sacubitril/valsartan, NYHA classification significantly improved in the present study ($P < 0.001$). This observation preliminarily suggested that the effective dose of sacubitril/valsartan in Chinese HF population might be lower than that in Western population, which needed more evidence to prove.

As a neprilysin substrate, plasma B-type natriuretic peptide (BNP) level increased with neprilysin inhibition by sacubitril/valsartan, but plasma NT-proBNP (not a neprilysin substrate) level was not affected.[13] Therefore, NT-proBNP has been preferred and recommended as an indicator for evaluating the efficacy of sacubitril/valsartan.[14] In the current study, the median NT-proBNP level decreased significantly from 3003 pg/mL (IQR, 1513–5404) to 2039 pg/mL (IQR, 921–3955) (P = 0.010) at follow-up, which appeared to be consistent with the results in other real-world studies.[15–19]

For patients with HFrEF, reverse remodelling is an important treatment goal. In previous studies, left ventricular (LV) reverse remodelling could be evaluated with several echocardiographic parameters, which including improved LVEF and reduced LV size.[20] In the current study, LV reverse

remodelling was confirmed in terms of both improved mean LVEF (from 31 ± 6% to 38 ± 10%, $P < 0.001$) and reduced median LV end-diastolic diameter (from 63 to 60 mm, $P = 0.001$). The degree of improvement appeared to be consistent with the results in other real-world studies.[21–23] In addition, echocardiographic parameters of right ventricular function were also improved after sacubitril/valsartan therapy in our study. Mean pulmonary arterial systolic pressure decreased significantly from 49 ± 13 mmHg at baseline to 44 ± 12 mmHg at follow-up ($P < 0.001$). Median right ventricular end-diastolic diameter reduced from 23 mm (IQR, 21–26) to 22 mm (IQR, 20–25) ($P = 0.030$). A real-world study in Italy showed similar results about the benefit of sacubitril/valsartan on right ventricular function improvement.[24]

Regarding safety, sacubitril/valsartan showed good tolerability in the PARADIGM-HF trial. Fewer patients discontinued the study drug because of hypotension or abnormal laboratory values.[1] Previous real-life studies also observed similar results. Cosentino *et al*. discovered sacubitril/valsartan was well tolerated with stable blood pressure if correctly titrated, with no need for drug withdrawal and/or dose tapering.[6] Martens *et al*. reported that hypotension was the main reason for no further up-titration of sacubitril/valsartan (50%), but no discontinuation of sacubitril/valsartan occurred.[4] Likewise, 15 patients (15%) occurred hypotension (SBP < 100 mmHg), and two patients (2%) had serum potassium level of more than 5.5 mmol/L in our study, but no patients stopped sacubitril/valsartan over the entire treatment period.

A further important finding in our study is deterioration of kidney function in Chinese HFrEF population in terms of significantly decreased mean and median eGFR as well as significantly increased median serum creatinine level and median BUN level after treatment with sacubitril/valsartan. These unfavourable effects observed with sacubitril/valsartan on renal outcomes might be explained by reduced blood pressure and blockade of the renin-angiotensin system.[1,25] Noteworthily, different with our study, renal function did not change significantly after sacubitril/valsartan treatment in several recent real-life studies.[1,26,27] Moreover, a recent meta-analysis showed that sacubitril/valsartan significantly reduced the risk of renal deterioration in patients with HF compared with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (odds ratio 0.77, 95% confidence interval 0.61–0.97, $P = 0.020$).[28] Currently, underlying mechanisms of renal effects of sacubitril/valsartan were still unclear. Therefore, frequent evaluation of renal function is necessary for patients with sacubitril/valsartan.

Limitations

Several limitations should be addressed in the present study. First, the design was a single-centre retrospective observational survey. Second, a relatively small number of patients were recruited in the current study. More extensive studies are needed to evaluate the effect of sacubitril/valsartan. Third, biplane Simpson's method in our study was 2D-echocardiographic assessment, which was not as accurate as 3D-echocardiography or magnetic resonance imaging for volumetric analysis. Fourth, data on duration of the HFrEF and time on medical therapy prior to commencing sacubitril/valsartan were missing in the present study, so it is hard to distinguish the effects of sacubitril/valsartan from other potentially recently started medical therapy. Finally, the impact of patients' socio-economic status for the prescription of sacubitril/valsartan was not measured in this study. Sacubitril/valsartan treatment was not covered by our national health insurance before 1 January 2020. Therefore, the impact of high drug cost on treatment decision might exist in our study.

Conclusions

In this real-world study, sacubitril/valsartan treatment was associated with a pronounced improvement of cardiac function with more favourable NYHA classification, significantly decreased median NT-proBNP level, and beneficial echocardiographic changes, without remarkable adverse events. More interestingly, the effective dose of sacubitril/valsartan in Chinese HFrEF population might be lower than that in Western population. However, in the present study, dose titration of sacubitril/valsartan in Chinese HFrEF population was still difficult due to drop in SBP and significant deterioration of kidney function. Encouragingly, improved understanding of the effective dose and susceptibility to side effects in the Chinese population would help establish a tailored up-titration regime, with particular attention to renal function and blood pressure.

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Conflict of interest

All the authors declare no conflict of interest.

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