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Clinical characteristics, prescription patterns, and persistence associated with sacubitril/valsartan adoption

A STROBE-compliant study

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Abstract

Sacubitril/valsartan (sac/val) was launched in China in 2018; however, the adoption of sac/val in real-world clinical practice has yet to be described.

This study aimed to analyze real-world treatment patterns of sac/val using data from 3 tertiary hospitals in China.

A non-interventional, retrospective cohort study of patients with Heart failure (HF) prescribed sac/val from 3 tertiary hospitals in China between January 1, 2018 and June 30, 2020 was conducted. The analysis included sac/val dose titration patterns and persistence during 6 months post-index.

A total of 267 patients were included, with a mean age of 63.9 ± 13.1 years. At index, 27% of patients were prescribed sac/val 12/13 mg b.i.d., 63.7% were prescribed 24/26 mg b.i.d., 4.5% were prescribed the target dose of 49/51 mg b.i.d., and 4.8% were not prescribed according to the recommended dose. During the 6 months post-index, 8.3% of patients had only 1 dose titration record. Good therapeutic persistence was observed across sac/val doses, and only 15.7% of patients discontinued sac/val during the 6 months post-index.

In China, the majority of patients prescribed sac/val are not initiated on the recommended dose nor up-titrated according to drug instruction. Notably, good persistence with sac/val is observed in the real-world cohort study.

Abbreviations: HF = heart failure, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, sac/val = sacubitril/valsartan, SBP = systolic blood pressure.

Keywords: dose titration, heart failure, persistence, prescription, sacubitril/valsartan

1. Introduction

Heart failure (HF) is a major public health challenge owing to its impact on mortality, morbidity, and economic burden.[1–4] The prevalence of HF in China in 2019 was estimated at approximately 1.3%,[5] and hospitalization is a major driver of HF treatment cost, which is consequently associated with substantial costs to the healthcare system.[6] Although the discovery and optimized use of pharmacotherapies that improve outcomes such as those targeting the renin-angiotensin-aldosterone system,[7] the 5-year mortality and rates of hospitalization remain poor.[8] Therefore, identification and development of novel pharmacological therapies remain paramount to improving outcomes in HF.

Sacubitril/valsartan (sac/val), a first-in-class dual action molecule of the neprilysin inhibitor sacubitril and the angiotensin II type 1 receptor blocker valsartan, demonstrated a 20% reduction in the primary outcome of cardiovascular death or HF hospitalization (HR, 0.80; 95% CI, 0.73–0.87) in PARADIGM-HF study.[9] As a result, sac/val was approved by the Food and Drug Administration and European Medicines Agency and received a Class I recommendation in the European and US HF guidelines.[10,11] However, several studies have shown that treatment patterns of sac/val under real-world conditions were different with the PARADIGM-HF study,[12–17] which might affect prescription of sac/val in clinical practice.

Sac/val was launched in China in 2018, however, the adoption of sac/val in real-world clinical practice has yet to be described. Therefore, the purpose of this study was to describe prescription patterns of sac/val in clinical practice using data from 3 tertiary hospitals in China. This study also aimed to evaluate possible factors associated to persistence of sac/val after index.

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2. Materials and methods

2.1. Study design

We carried out a non-interventional, retrospective cohort study of patients with HF from 3 tertiary hospitals in China. The full study period was between January 1, 2018 and June 30, 2020, giving a minimum of 6 months of follow-up after sac/val initiation.[18]

2.2. Study population

HF patients aged ≥18 years who were prescribed sac/val at least once between January 1, 2018 and January 30, 2020 were included in the study. For each individual, the index date was defined as the date of their first recorded sac/val prescription.

2.3. Sac/val dose and titration patterns

Sac/val dose and titration patterns were analyzed during the 6 months after index. Key outcomes included individual dose at index and titration patterns during the 6 months after index.

2.4. Sac/val persistence

Sac/val persistence was assessed using the direct-reporting method (by asking the patient, "Are you still persistent with therapy with sac/val?").[19] All patients were contacted by telephone during the 6 months after index to determine sac/val persistence.

2.5. Statistical analysis

Continuous variables are expressed as mean ± standard deviation if normally distributed or median (inter-quartile range) if not normally distributed. Normality was checked by the Shapiro–Wilk statistic. Categorical data were expressed as numbers and percentages and compared with Pearson's χ^2 test or Fisher exact, when appropriate. Continuous variables were compared with Student *t* test, Mann–Whitney *U* test, and paired *t*-test, when appropriate. Univariate and multivariate logistic regression were used to assess predictors of sac/val persistence in the 6 months after initiation. Statistical Significance was considered if *P* value <.05. Statistics were performed using SPSS version 21 (IBM, Chicago, IL).

2.6. Ethics statement

Only aggregated, anonymized patient data were used in these analyzes. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Shandong First Medical University, Tengzhou Central People's Hospital, and Xintai People's Hospital.

3. Results

3.1. Baseline patient demographics and characteristics

In total, 267 patients were enrolled into the study between January 1, 2018 and January 30, 2020. The patient demographics and characteristics are shown in Table 1. The mean age of these patients was 63.9 ± 13.1 years and more than two-thirds of the study population (69.7%) were male. The mean systolic blood pressure (SBP) was 120 ± 18 mmHg, and 75.6% of patients were New York Heart Association (NYHA) Class III/IV. The mean left ventricular ejection fraction (LVEF) was 36.7% ± 10.2% in these patients, and the proportion of patients with ejection fraction (EF) ≤40% was 61.4%. Patients in the present study were predominantly male, had a higher LVEF, had a lower SBP, and had a higher NYHA class than those in the PARADIGM-HF trial. The most frequently recorded comorbidities were ischaemic heart disease and hypertension, which were recorded in 69% and 45% of patients, respectively (Table 1). Patients were less likely to have atrial fibrillation, hypertension and diabetes but more likely to have stroke and ischaemic heart disease than patients in PARADIGM-HF study. Use of cardiovascular medications was high: 92.5%, 81.3%, and 89.1% of patients had received prescriptions for aldosterone antagonists, beta-blockers, and loop diuretics, respectively.

Table 1

Demographics and clinical characteristics of enrolled patients at index.

Variable	Patients in the present study (n = 267)	PARADIGM-HF sac/val arm (n = 4,187)	*P* value
Demographics			
Age, yr	63.9 ± 13.1	63.8 ± 11.5	.891
Male, n (%)	186 (69.7)	3308 (79)	<.001
Prior hospitalization for HF, n (%)	159 (59.6)	2607 (62.3)	.376
Blood pressure			
SBP, mmHg	120 ± 18	122 ± 15	.037
NYHA class, n (%)			<.001
Class I	7 (2.6)	180 (4.3)	
Class II	50 (18.7)	2998 (71.6)	
Class III	104 (38.9)	969 (23.1)	
Class IV	98 (36.7)	33 (0.8)	
Missing	8 (3)	7 (0.2)	
Mean LVEF, %	36.7 ± 10.2	29 ± 6.1	<.001
LVEF class, n (%)			
LVEF ≤40%	164 (61.4)	NA	
LVEF >40%	70 (26.2)	NA	
LVEF Missing	33 (12.4)	NA	
Co-morbidities, n (%)			
Atrial fibrillation	67 (25.1)	1517 (36.2)	<.001
Ischaemic heart disease	185 (69.3)	1818 (43.4)	<.001
Hypertension	122 (45.7)	2969 (70.9)	<.001
Diabetes	65 (24.3)	1451 (34.7)	.001
Stroke	33 (12.4)	355 (8.5)	.029
Medication use at index, n (%)			
Beta-blocker	217 (81.3)	3899 (93.1)	<.001
Aldosterone antagonist	247 (92.5)	2271 (54.2)	<.001
Loop diuretics	238 (89.1)	3363 (80.3)	<.001
Digoxin	82 (30.7)	NA	
Lipid-lowering drugs	186 (69.7)	NA	
Antiplatelet medications	184 (68.9)	NA	

Sac/val = sacubitril/valsartan, HF = heart failure, SBP = systolic blood pressure, NYHA = New York Heart Association, LVEF = left ventricular ejection fraction.

3.2. Sac/val dose at index and treatment patterns

At index, 27% of patients were prescribed sac/val 12/13 mg b.i.d., 63.7% were prescribed 24/26 mg b.i.d., 4.5% were prescribed the target dose of 49/51 mg b.i.d., and 4.8% were not prescribed according to the above dose pattern.

In total, only 23 patients (8.3%) had 1 dose titration record during the 6 months post-index. Moreover, any titration efforts attempted on these patients was done prior to discharge, and the mean time to dose titration was 6 ± 2 days. Among 254 patients

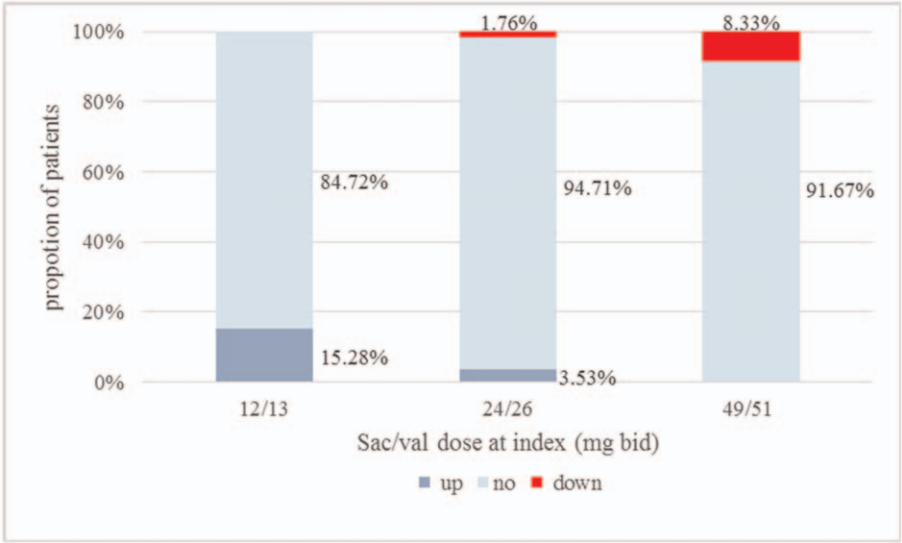

Figure 1. Titration patterns during the 6 months post-index, stratified by sac/val dose at index. sac/val = sacubitril/valsartan.

prescribed sac/val according to the recommended dose, only 2.5% of patients were up-titrated during this period, and down-titration was observed in 1.5% of patients. Of the patients who were prescribed 12/13 mg b.i.d. or 24/26 mg bid at index, 15.3% and 3.5% were up-titrated, respectively. Of the patients who were prescribed 24/26 mg b.i.d. or 49/51 mg b.i.d. at index, 1.76% and 8.33% were down-titrated, respectively. No titration was observed in 84.72%, 94.71%, and 67% of patients who were prescribed 12/13 mg b.i.d., 24/26 mg b.i.d, and 49/51 mg b.i.d. (Fig. 1).

3.3. Sac/val persistence

Overall, 225 of the 267 patients (84.3%) were persistent with sac/val in the 6 months after index, and only 42 patients (15.7%) discontinued sac/val. The univariate and multivariate predictors of 6-month medication persistence are shown in Table 2. Adjusting for potential confounders, better persistence was observed in patients with LVEF ≤40% and those having prior hospitalization for HF.

4. Discussion

Our study has 4 main findings:

1. real-world patients exhibit baseline characteristics of more pronounced disease severity in comparison with patients in PARADIGM-HF study;
2. 27% of patients received the lowest dose of sac/val (12/13 bid);
3. 87.3% of all patients stay on their initial dose in the 6 months post-index; and
4. the estimated persistence with sac/val at 6 months was high across all doses.

Although sac/val has convincingly proven its benefit in reducing HF hospitalization and cardiovascular mortality in PARADIGM-HF, patients with severe symptomatic HF were underrepresented in this trial.[9,20] Our findings showed that patients prescribed sac/val in real world are more likely to have a higher NYHA classification and a lower baseline LVEF than patients enrolled in the PARADIGM-HF trial, which supported those observations in several recent real-world studies.[13,17,21,22] The present study and the other real-world studies conformably indicate that patients in real-world clinical practice have more severe HF than those enrolled in PARADIGM-HF.[13,17,21,22]

Similar to other real-world studies,[13,17,23,24] the majority of patients (63.7%) were prescribed the sac/val dose of 24/26 mg b.i.d. at index despite this dose being suggested for special populations; those with moderate hepatic impairment, moderate to severe renal impairment, SBP ≥100 mmHg to 110 mmHg, or patients not currently taking or taking a low dose of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.[25,26] Notably, 27% of patients were prescribed sac/val 12/13 mg b.i.d. at index in this study, and so low initial dose has not been reported in previous real-world studies of sac/val.[13,17,23,24] In the present study, reasons for low initial dose of sac/val were hypotension (SBP < 100) (n = 15, 20.8%), older age (age ≥70) (n = 28, 38.9%) and poor heart function (LVEF ≤70) (n = 38, 52.8%). Additionally, 87.3% of patients remained the initial dose during the 6 months post-index. The proportion of patients with no record of dose change in this study is also higher than that in other real-world studies of sac/val.[15,17] Due to the lack of medication prescription experience, physicians are reluctant to titrate up the dose without specific reasons might be a possible cause. Moreover, the effective dose of sac/val in Chinese HF population with smaller body size may be lower than that in Western population.[27] However, because of retrospective study, this viewpoint needs more evidence to prove.

Sac/val persistence (84.3%) at 6 months post-index were found to be high and in line with those observed in other real-world studies.[15,28] Better persistence was observed in patients with LVEF ≤40% and those having prior hospitalization for HF, which could be due to the fact that these patients are with more pronounced disease severity and need long-term treatment to prevent aggravation of HF.

Table 2

The univariate and multivariate analyses of predictors of 6-month medication persistence.

	Continuation (n = 225)	Discontinuation (n = 42)	Crude *P* value	Adjusted *P* value
Demographics				
Age, yr	63.7 ± 13.1	65.4 ± 13.1	.439	.254
Male, n (%)	161 (71.6)	25 (59.5)	.119	.252
Prior hospitalization for HF, n (%)	142 (63.1)	17 (40.5)	.006	.003
Blood pressure				
SBP, mmHg	120.6 ± 17.8	122.8 ± 18.6	.462	.281
NYHA classification, n (%)			.688	NA
Class I/ II	47 (20.9)	10 (23.8)		
Class III/ IV	171 (76.0)	31 (73.8)		
LVEF classification, n (%)			<.001	.009
LVEF ≤40%	157 (69.8)	6 (14.3)		
LVEF >40%	54 (24.0)	17 (40.5)		
Co-morbidities, n (%)				
Atrial fibrillation	57 (25.3)	10 (23.8)	.834	.392
Ischaemic heart disease	157 (69.8)	28 (66.7)	.688	.677
Hypertension	108 (48.0)	14 (33.3)	.080	.057
Diabetes	55 (24.4)	14 (33.3)	.227	.716
Stroke	27 (12.0)	6 (14.3)	.679	.329
Medication use at index, n (%)				
Beta-blocker	186 (82.7)	31 (73.8)	.177	.118
Aldosterone antagonist	208 (92.4)	39 (92.9)	1.000	.325
Loop diuretics	202 (89.8)	36 (85.7)	.437	.271
Digoxin	68 (30.2)	14 (33.3)	.688	.518
Lipid-lowering drugs	158 (70.2)	28 (66.7)	.645	.655
Antiplatelet medications	158 (70.2)	26 (61.9)	.285	.105

Sac/val = sacubitril/valsartan, HF = heart failure, SBP = systolic blood pressure, NYHA = New York Heart Association, LVEF = left ventricular ejection fraction.

The main strength of this study lies in that clinical characteristics, prescription patterns, and persistence associated with sac/val adoption in real-world clinical practice in 3 tertiary hospitals in China was described in detail. These findings will offer a larger cardiology audience valuable information when prescribing sac/val. However, several limitations should be mentioned. First, the overall number of patients in this study is relatively small. Second, the data source includes patients in 3 hospitals in China, and findings in other populations may be different. Third, due to the unavailability of enough data on clinical parameters such as NYHA class, LVEF and eGFR, statistical methods such as logistic regression could not be performed to further explore the potential associations between baseline parameters and persistence. Finally, if costs may have influenced prescription of sac/val was not analyzed in the present study.

5. Conclusion

In this multi-center cohort study, patients exhibit baseline characteristics of more pronounced disease severity. Twenty seven percentages of patients are initially prescribed the lowest dose of sac/val (12/13 mg b.i.d.) and 87.3% of all patients stay on their initial dose in the 6 months post-index. Medication persistence during 6 months post-index were high. Further research is required to explore the reasons for the lack of up-titration, and educational efforts to promote up-titration should be intensified.

Author contributions

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Funding acquisition: Wenwen Chen.
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