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Influence of Aging on Outcomes of Sacubitril/Valsartan in Hypertensive Patients with Heart Failure: A Multicenter Retrospective Study

ABSTRACT

Background: The aim of this study was to investigate the influence of aging on the effectiveness and tolerance of sacubitril/valsartan (sac/val) among hypertensive patients complicated with heart failure in a real-world setting.

Methods: This multicenter, retrospective study included patients (≥18 years old) admitted with a diagnosis of hypertension and heart failure, starting sac/val therapy between January 2020 and December 2021 from 3 medical centers. Patients were grouped by the cutoff age of 65 years. Outcomes were collected 31-365 days after the initiation of sac/val and were compared in a matched cohort after 1:1 propensity score matching (PSM).

Results: A total of 794 patients were finally analyzed. Blood pressure and cardiac functions improved significantly compared with values at baseline. There were 269 patients in each cohort (<65 years and ≥65 years) after PSM. After PSM, the incidence of hyperuricemia and hypotension in the elderly patients (≥65 years) was significantly higher than in those <65 years of age. Kaplan–Meier estimate suggested that the cumulative incidence of new or recurrent cardiovascular events increased significantly at the age of ≥65 years after the point of 3 months (log-rank $P = .00087$).

Conclusion: Sac/val benefited patients in both cohorts by improving blood pressure and cardiac function. Elderly patients (≥65 years) were susceptible to hypotension, low diastolic blood pressure, hyperuricemia, and underwent cardiac-related readmissions more frequently.

Keywords: Outcome, aging, heart failure, hypertension, sacubitril/valsartan

ORIGINAL INVESTIGATION

Chengchun Zuo[1*]
Xiaoye Li[1*]
Yingyun Guan[2*]
Linlin Fan[1]
Jing Li[1]
Dan Tian[1]
Can Chen[1]
Xiaoyu Li[1]
Zhichun Gu[3]
Chi Zhang[3]
Xiaolan Bian[2]
Qianzhou Lv[1]

[1]*Department of Pharmacy, Zhongshan Hospital, Fudan University, Shanghai, China*
[2]*Department of Pharmacy, Ruijin Hospital School of Medicine, Shanghai Jiaotong University, Shanghai, China*
[3]*Department of Pharmacy, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China*

Corresponding author:
Qianzhou Lv
✉ 13916088938@163.com

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*These authors have contributed equally to this work.

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INTRODUCTION

The prevalence of hypertension and heart failure (HF) is increasing worldwide, contributing to an increasing incidence of unexpected cardiovascular events and mortality, thereby placing a heavy medical burden on the society. The majority of patients diagnosed with HF in Asia are accompanied by hypertension.[1] The link between hypertension and HF could be mainly attributed to hypertrophy, changes in the renin–angiotensin–aldosterone system (RAAS) and myocardial insult. Hypertension is strongly associated with HF, especially in the elderly,[2] which could be attributed to myocardial stiffness and multiple comorbidities with aging.[3] Elderly HF patients are more susceptible to treatment-resistant hypertension. Hence, it seems necessary to control resistant hypertension among the elderly to improve clinical outcomes.[4]

As an angiotensin receptor–neprilysin inhibitor, sacubitril/valsartan (sac/val) is superior to other types of antihypertensive agents because its mechanism covers both the natriuretic peptide system and RAAS,[5] showing a promising role in improving cardiovascular outcomes.[6] Sac/val has been found to be efficacious in the treatment of resistant hypertension, renal hypertension, and systolic hypertension in elderly Asian patients.[7-9] Additionally, a cost-utility meta-analysis based on different populations in China revealed that sac/val was cost-effective for hypertension treatment under a high willing-to-pay threshold.[10]

Approximately 20% of patients discontinued sac/val in the run-in phase because of adverse events, and hypotension occurred most frequently.[11] In addition, a single-center retrospective study focusing on patients with hypertension and HF in China found that a history of atrial fibrillation or chronic kidney disease, and high baseline levels of serum creatinine, uric acid, and N-terminal pro B-type natriuretic peptide (NT-proBNP) might lead to the discontinuation of sac/val due to intolerance.[12] However, there is limited evidence on these populations, especially the elderly. Hence, we conducted a multicenter study to explore the influence of aging on the clinical outcomes of sac/val in hypertensive patients combined with HF.

METHODS

Study Design and Patient Selection

In this multicenter, observational, retrospective real-world study, clinical information was obtained from the electronic medical record (EMR) systems. The study population comprised patients (≥18 years old) admitted with a diagnosis of hypertension and HF (or cardiac insufficiency, with the New York Heart Association (NYHA class II-IV, NT-proBNP >300 pg/mL), newly receiving sac/val therapy between January 2020 and December 2021 from 3 medical centers. Individuals were excluded if their systolic blood pressure (SBP) was <110 mm Hg or >180 mm Hg on admission, information after initiating sac/val during a 12-month follow-up period was not attainable, they discontinued sac/val therapy within 31 days, or they took angiotensin-converting enzyme inhibitors (ACEI) within 36 hours or angiotensin-receptor blockers (ARB) within 24 hours before starting sac/val. To investigate the impact of aging, the study population was divided into 2 cohorts: patients aged <65 years and patients aged ≥65 years. The date of data collection was 31 January 2022.

Data Collection

All information on the medical history of patients was collected from the EMR. Demographic data included gender, age, history of smoking, and alcohol. Clinical data included blood pressure, diagnosis on admission, dosage of sac/val (maximum tolerated dosage), concomitant medication use, and results of laboratory tests as well as echocardiographic parameters. Baseline SBP and diastolic blood pressure (DBP) referred to the values obtained on admission. Laboratory indicators included electrolytes, liver function (alanine aminotransferase (ALT), aspartate aminotransferase (AST), kidney function (estimated glomerular filtration rate (eGFR) serum creatinine, and uric acid), and myocardial markers (NT-proBNP). Laboratory results were obtained at baseline and after initiation of sac/val. Echocardiographic parameters were obtained by echocardiography 31-365 days after receiving sac/val. The maximum tolerated dosage of sac/val was adjusted from the initial levels by senior physicians according to the effectiveness and tolerance of each patient.

Definitions of Outcomes

The primary outcomes measured were data on the improvement of blood pressure, laboratory indicators, and cardiac biomarkers, as well as the proportion of participants achieving the target threshold of echocardiographic parameters 31-365 days after the initiation of sac/val. Secondary outcomes included the frequencies of adverse events, the proportion of patients discontinuing sac/val due to intolerable adverse events, and the incidence of first or recurrent cardiovascular events within 12 months. Cardiovascular events were defined as emergency admissions, unplanned visits, or hospitalizations due to acute HF, myocardial infarction, or stroke.

In terms of adverse events, hypotension and dizziness were self-reported by patients; abnormal serum creatinine referred to values above the upper limit of normal or those increasing up to 20% from baseline; hyperuricemia was defined as values of serum uric acid above the upper limit of normal laboratory reference values (female: 357 μmol/L; male: 428 μmol/L), and hyperkalemia referred to serum potassium concentration exceeding 5.5 mmol/L.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 19.0; IBM, Armonk, NY, USA). Comparisons of normally distributed values between the 2 groups were analyzed by *t*-test, and the Wilcoxon rank sum test was applied for the non-normally distributed data. Normally distributed data were reported as mean ± SD (SD), while non-normally distributed data were reported as median and interquartile range (IQR). Categorical data were presented as frequencies and percentages and were compared by the chi-squared test. A two-tailed *P* value <.05 was considered statistically significant.

To eliminate confounding factors and control for consistent baseline levels between the 2 cohorts, the patients were matched by age-stratified analysis using propensity score matching (PSM). Each patient aged <65 years was matched with a patient aged ≥65 years. Control variables were SBP and DBP on admission, gender, renal insufficiency, number of hypertensive drug classes, and the maximum tolerated dosage. Frequencies of cardiovascular events between the 2 age groups (<65 years vs. ≥65 years) were estimated by the Kaplan–Meier (K-M) curve.

RESULTS

Participants

A total of 1150 patients diagnosed with hypertension and HF (or cardiac insufficiency, with the NYHA class II-IV), receiving

HIGHLIGHTS

- Elderly patients were susceptible to hypotension after sacubitril/valsartan therapy.
- Laboratory indicators should be monitored when taking sacubitril/valsartan.
- Intolerance made the elderly patients easily undergo rehospitalization for cardiac events.
- Dosage of sacubitril/valsartan should be up-titrated cautiously for the elderly patients.
- Prompt treatments for adverse events are in need to improve tolerance.

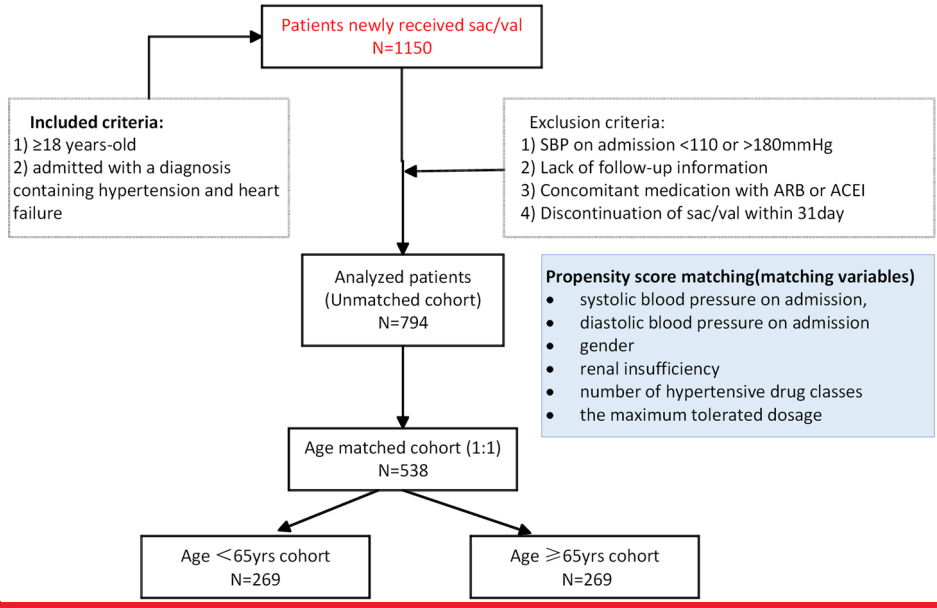

Figure 1. Study flowchart. SBP, systolic blood pressure; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

sac/val from the 3 centers were collected. The inclusion process of the 794 patients who were finally analyzed is presented in Figure 1. The characteristics of all participants are shown in Supplementary Table 1. After 1:1 PSM, there were 269 patients in each cohort (aged <65 years and ≥65 years). Baseline characteristics before and after 1:1 age-matched PSM are summarized in Table 1. Before matching, there were significant differences in baseline DBP, gender, renal insufficiency, and maximum tolerated dose between the 2 groups ($P < .05$). Patients aged ≥65 years had lower DBP on admission, and a higher proportion were receiving a maximum tolerated dosage of ≤200 mg/day. In addition, the proportion of male patients was higher in the <65 years cohort. No significant difference was found in the parameters after matching between the 2 cohorts.

Effectiveness Outcomes

Compared with the median values at baseline, the blood pressure, and NT-proBNP values decreased significantly after treatment in the 2 cohorts ($P < .001$) (Table 2). After PSM, there was no difference in the proportions of patients achieving the target threshold of blood pressure and LAD between the 2 groups. Compared with patients in the group aged <65 years (Table 3), the percentage of patients reaching the target values of NT-proBNP (42.2% vs. 23.9%, $P < .001$) and left ventricular ejection fraction (56.9% vs. 47.2%, $P = .025$) was lower at the age group of ≥65 years. Interestingly, the difference in NT-proBNP levels from baseline to those obtained 31-365 days after taking sac/val was similar [Median (IQR): 606 (52.2-2180) vs. 769 (0-2330), $P = .999$]. Notably, patients in the ≥65 years cohorts had significantly

Table 1. Baseline Characteristics of Participants Before and After Propensity Score Matching

	Unmatched Cohorts			Matched Cohorts		
Parameters	**<65 (n = 346)**	**≥65 (n = 448)**	***P***	**<65 (n = 269)**	**≥65 (n = 269)**	***P***
Baseline clinic SBP, median (IQR), mm Hg	136 (121-153)	135 (122-149)	.475	135 (120-152)	136 (122-148)	.819
Baseline clinic DBP, median (IQR), mm Hg	80.0 (72.0-91.0)	76.0 (68.0-85.0)	**<.001**	79.0 (70.0-89.0)	78.0 (70.0-87.0)	.568
Gender (males), n (%)	303 (87.6%)	300 (67.0%)	**<.001**	227 (84.4%)	226 (84.0%)	.906
Number of antihypertensive drugs						
1	15 (4.3%)	20 (4.5%)	.25	11 (4.1%)	10 (3.7%)	.976
2	83 (24.0%)	107 (23.9%)		71 (26.4%)	69 (25.7%)	
3	192 (55.5%)	270 (60.3%)		147 (54.6%)	152 (56.5%)	
4	56 (16.2%)	51 (11.4%)		40 (14.9%)	38 (14.1%)	
Renal insufficiency*	104 (30.3%)	180 (41.5%)	**.001**	92 (34.2%)	86 (32.0%)	.582
Maximum tolerated dose						
≥200 mg/day	165 (47.7%)	164 (36.6%)	**.002**	114 (42.4%)	110 (40.9%)	.726
<200 mg/day	181 (52.3%)	284 (63.4%)		155 (57.6%)	159 (59.1%)	

We have reported in bold the statistically significant *P* value.
DBP, diastolic blood pressure; IQR, interquartile range; sac/val, sacubitril/valsartan; SBP, systolic blood pressure.
*Renal insufficiency referred to estimated glomerular filtration rate (eGFR) at baseline <60 mL/min/1.73 m².

Table 2. Changes in Blood Pressure and Cardiac Biomarkers 31-365 Days After Sac/Val Therapy

	Before sac/val (794)	After sac/val (794)	Difference (794)	*P*
Systolic BP, median (IQR), mm Hg	135 (121-151)	123 (111-136)	11 (0-25.5)	**<.001**
Diastolic BP, median (IQR), mm Hg	78 (70-88)	72 (64-80)	6 (−2 to 16)	**<.001**
NT-proBNP, median (IQR), pg/mL	1939 (858-4930)	748 (259-2342)	648 (0-2156)	**<.001**

We have reported in bold the statistically significant *P* value.
DBP, diastolic blood pressure; IQR, interquartile range; NT-proBNP, N-terminal pro B-type natriuretic peptide; sac/val, sacubitril/valsartan; SBP, systolic blood pressure.

higher NT-proBNP levels at baseline. Additionally, DBP showed a greater decline among patients in the group aged ≥65 years than the others, resulting in significantly lower levels after sac/val treatment.

After PSM, the Kaplan–Meier analysis illustrated that the cumulative incidence of new or recurrent cardiovascular events increased significantly in the ≥65 years age group after 3 months (log-rank *P* = .00087) (Figure 2).

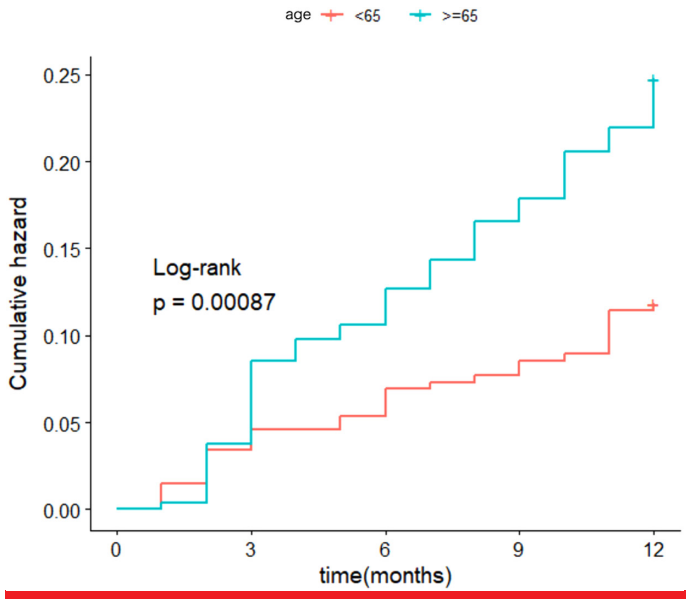

Figure 2. Kaplan–Meier analysis for the cumulative incidence of cardiovascular events among 2 age groups (red, <65 years; blue, ≥65 years); *P* < .05 indicates statistical significance.

Safety Outcomes

In terms of safety concerns, adverse events reported during the follow-up period mainly included dizziness, hypotension, elevated creatinine, hyperuricemia, and hyperkalemia. As shown in Table 4, the incidence of hyperuricemia was significantly higher among patients aged ≥65 years than those aged <65 years (17.1% vs. 24.9%, *P* = .026). Notably, the incidence of hypotension in elderly patients (≥65 years) was significantly higher than in those aged <65 years (21.9% vs. 8.6%, *P* < .001). Moreover, among people experiencing hypotension, 54% (32/59) of patients in the ≥65 years age group had reduced LVEF (range: 25%-38%), while 9% (2/23) of those aged <65 years had reduced LVEF (range: 25%-30%).

DISCUSSION

The impact of aging on the effectiveness and tolerance of sac/val in patients with hypertension and HF in the real world has been rarely studied. The novelty of our study lies in assessing the differences in effectiveness and safety outcomes between subgroups of patients stratified by the cutoff point of 65 years of age, and reminding physicians

Table 3. Effectiveness Outcomes After Propensity Score Matching

	<65 (n = 269)	≥65 (n = 269)	*P*
Difference of variables			
Baseline SBP, median (IQR), mm Hg	135 (120-152)	136 (122-148)	.819
SBP after sac/val, median (IQR), mm Hg	124 (110-138)	125 (110-136)	.748
Difference of SBP, median (IQR), mm Hg	11.0 (0-24.0)	10.0 (0-27.0)	.957
Baseline DBP, median (IQR), mm Hg	79.0 (70.0-89.0)	78.0 (70.0-87.0)	.568
DBP after sac/val, median (IQR), mm Hg	74.0 (66.0-84.0)	70.0 (61.0-77.0)	**<.001**
Difference of DBP, median (IQR), mm Hg	4.00 (−4.00 to 14.0)	9.00 (1.00-18.0)	**<.001**
NT-proBNP at baseline, median (Q1-Q3), pg/mL	1500 (536-4100)	2120 (1100-5330)	**.002**
NT-proBNP after treatment, median (Q1-Q3), pg/mL	476 (171-1360)	1060 (373-2880)	**<.001**
Difference of NT-proBNP values, median (Q1-Q3), pg/mL	606 (52.2-2180)	769 (0-2330)	.999
Treatment target			
BP achieving target	201 (74.7%)	216 (80.3%)	.121
LAD achieving target	67 (24.9%)	72 (26.8%)	.622
LVEF achieving target	153 (56.9%)	127 (47.2%)	**.025**
NT-proBNP achieving target	105 (42.2%)	61 (23.9%)	**<.001**

Target threshold of BP: clinical BP <140/90 mm Hg; target threshold of LAD: ≤40 mm; target threshold of LVEF: ≥50%; target threshold of NT-proBNP <300 ng/mL. We have reported in bold the statistically significant *P* value.
BP, blood pressure; DBP, diastolic blood pressure; IQR, interquartile range; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; sac/val, sacubitril/valsartan; SBP, systolic blood pressure.

Table 4. Safety Outcomes After Propensity Score Matching

	<65 Years Old (n = 269)	≥65 Years Old (n = 269)	*P*
Hypotension	23 (8.6%)	59 (21.9%)	**<.001**
Increased creatinine	14 (13.9%)	16 (11.3%)	.545
Hyperuricemia	46 (17.1%)	67 (24.9%)	**.026**
Hyperkalemia	6 (2.2%)	5 (1.9%)	.761
Dizzy	2 (0.7%)	2 (0.7%)	1.000
Other ADRs	9 (3.3%)	11 (4.1%)	.649
Withdrawal due to intolerance	9 (3.3%)	8 (3.0%)	.805

We have reported in bold the statistically significant *P* value.

to increase the dose cautiously and to prevent and manage adverse reactions promptly.

The main finding of this multicenter retrospective study is that a greater decline in DBP, higher incidence of hyperuricemia and hypotension, and more cardiovascular events were reported among the elderly patients (≥ 65 years) when compared with those aged <65 years.

A retrospective study by Umehara et al[13] suggested that the high frailty severity and low LVEF might act synergistically to cause physical deterioration and an increase in readmissions among HF patients.[13] Advancing age was associated with frailty.[14,15] The underlying reason for the increasing prevalence of frailty with aging might be associated with degenerative disease and reduced reserve function of certain organs in the elderly. In addition, evidence showed that frailty was closely associated with cardiovascular events.[16] Patients aged ≥65 years had higher NT-proBNP values, and a lower proportion of them achieved the target goal of LVEF (≥50%) in the present study. Similar to previous statistics,[17] the incidence of new or recurrent cardiovascular events was remarkably elevated among the elderly patients (≥65 years) compared with the others (<65 years). Also, elevated NT-proBNP was present in elderly patients without HF, and the application of other echocardiographic parameters was recommended for the assessment of cardiovascular function in future research.[18]

Another published study found that the benefits of sac/val for the elderly increase with age, even considering the discontinuation and switching rates observed in the real world.[19] Nevertheless, it is necessary to clarify the factors leading to intolerance. It had been previously reported that the median age of the intolerance group was higher than those reaching the maximum tolerated dose (73.4 years vs. 69.1 years).[20] In this study, the proportion of elderly patients discontinuing sac/val due to intolerance in the ≥65 years age group was not significantly different from those aged <65 years. The exclusion of patients who discontinued sac/val within 31 days might result in no difference in the tolerance between the 2 subgroups. Moreover, starting with a lower dose and prolonging the period to reach the standard dose is favorable for improving patient tolerance.[21]

Previous studies identified a high prevalence of isolated systolic hypertension and isolated diastolic hypotension in older adults due to the stiffening of large arteries with aging.[22,23] In accordance with previous findings, patients in the age group of ≥65 years in the current study had lower DBP after taking sac/val, and the decline range between values before and after therapy was significantly larger than those ≤65 years of age. Moreover, our results showed that the older patients (≥65 years) were more susceptible to hypotension compared with the other group. The PARADIGM-HF trial also found that approximately 1 in 5 patients aged ≥75 years experienced hypotension.[24] Noticeably, remarkably low DBP might increase the risk of myocardial infarction caused by coronary under perfusion.[25] Moreover, we found that the susceptibility of older patients (≥65 years) to hypotension might also be related to low LVEF, which was similar to a previous study.[26] Even if a higher dose of sac/val could lead to more reductions in HF admissions,[27] clinicians preferred a low strength of sac/val in the elderly population and monitored with caution.[28] Consistent with previous observations, before PSM, the significantly lower median maximum tolerated dose of sav/val was observed in the age group ≥65 years in the current study.

Though evidence showed the benefit of sac/val in reducing uric acid due to its role in increasing urinary uric acid excretion,[29] this study found that elderly patients ≥65 years were more susceptible to hyperuricemia after receiving sac/val, potentially contributing to worse cardiovascular outcomes in the subgroup.[30] Urate-lowering therapy was recommended in elderly patients with hyperuricemia after antihypertensive therapy.[30] An epidemiological research confirmed older age as a significant factor for the prevalence of hyperuricemia in China, increasing from 60 years of age and peaking after 70 years of age.[31] Another survey conducted in the United States also identified the increasing prevalence of hyperuricemia with age, among those aged ≥65 years.[32]

Study Limitations

The study has some limitations. First, the results might be biased by selecting 65 years of age as the cutoff point between the 2 age-stratified groups and the retrospective nature of the study. Secondly, clinical events among patients lacking follow-up information were not analyzed, thus data on adverse events and cardiovascular events might have been underestimated. Thirdly, this study did not perform a frailty assessment and failed to confirm the association of frailty with effectiveness and safety of sac/val in the age-stratified subgroups. Fourthly, data on right ventricular function were not available in this study, which might also affect the tolerability of sac/val therapy in HF patients.[33] Further prospective studies with larger sample sizes and longer follow-up periods are required to examine the impact of frailty on clinical outcomes of sac/val in Chinese patients with hypertension and HF.

CONCLUSION

Sac/val benefited patients from both cohorts in improving blood pressure and cardiac function. However, older patients (≥65 years) were found to be susceptible to hypotension, low DBP, and hyperuricemia, and were more likely to undergo readmissions due to new or recurrent cardiovascular events. Therefore, it is necessary to up-titrate the dosage cautiously

for elderly patients, closely monitor the laboratory indicators, and promptly administer treatment for the corresponding adverse reactions.

Ethics Committee Approval: The retrospective study was approved by the Medical Ethics Committee of Zhongshan Hospital (ethical approval number: B2022-105; date: February 28, 2022).

Informed Consent: Written informed consent was not required because this retrospective analysis was limited to information from the electronic medical records collected as part of the routine treatment by clinicians.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C. Zuo, X.L., Y.G., D.T.; Design – C. Zuo, X.L., Y.G., L.F., J.L., Xiaoyu L.; Supervision – X.B., Q.L.; Resource – Xiaoyu L., Z.G., X.B., Q.L.; Materials – C. Zuo, X.L., Y.G.; Data Collection and/or Processing – C. Zuo, L.F., J.L., D.T., C.C., C. Zhang; Analysis and/or Interpretation – C.C., Z.G., C. Zhang; Literature Review – L.F., J.L., D.T., C.C., C. Zhang; Writing – C. Zuo, X.L., Y.G.; Critical Review – Xiaoyu L., Z.G., X.B., Q.L.

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

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Supplementary Table 1. Baseline Characteristics of all Analyzed Participants before Matching

Characteristics	Variables	n=794
Dosage of sac/val	Initiative dosaige, mg, median (IQR)	100 (50~150)
	Maximum tolerated dosage	
	≥200, n (%)	329 (41.4%)
	<200, n (%)	465 (58.6%)
Demographic information	Age, years, median (IQR)	67 (56~75)
	Gender	
	Male, n (%)	603 (75.9%)
	Female, n (%)	191 (24.1%)
	History of smoking, n (%)	283 (35.6%)
	History of alcohol, n (%)	126 (15.9%)
Blood Pressure	SBP on admission, mm Hg, median (IQR)	135 (121~151)
	DBP on admission, mm Hg, median (IQR)	78 (70~88)
Laboratory results	ALT, U/L, median (IQR)	21.0 (14.0~30.0)
	AST, U/L, median (IQR)	22.0 (17.0~29.0)
	Creatinine, μmol/L, median (IQR)	93.0 (77.0~127)
	Uric acid, μmol/L, median (IQR)	398 (317~497)
	eGFR, ml/min/1.73 m^2, median (IQR)	69.7 (47.0~86.6)
	serum Potassium, mmol/L, median (IQR)	4.00 (3.70~4.30)
	NT-proBNP, pg/ml, median (IQR)	1940 (858~4930)
Co-morbidities	Dyslipidemia, n (%)	53 (6.7%)
	Diabetes, n (%)	307 (38.7%)
	Atrial fibrillation, n (%)	215 (27.1%)
	CAD, n (%)	441 (55.5%)
	After stent, n (%)	243 (30.6%)
	Liver insufficiency, n (%)	22 (2.8%)
	History of stroke/TIA, n (%)	100 (12.6%)
Co-medication	CCB, n (%)	209 (26.3%)
	β blocker, n (%)	658 (82.9%)
	Diuretics, n (%)	568 (71.5%)
	Statins, n (%)	546 (68.8%)
	Oral antiplatelet drugs, n (%)	495 (62.3%)

sac/val, sacubitril/valsartan; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NT-proBNP, N-terminal pro B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; TIA, transient ischaemic attack; CCB, calcium channel blocker.