Sacubitril-valsartan in Heart Failure With Preserved Ejection Fraction Following Acute Coronary Syndrome

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Research Article

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Abstract

Background

It was indicated that sacubitril-valsartan could improve the clinical prognosis in specific phenotype of heart failure with preserved ejection fraction (HFpEF) patients compared with valsartan. However, there is lack of evidence of the comparative effectiveness in HFpEF patients following acute coronary syndrome (ACS). The aim of this study was to evaluate whether the selection between sacubitril-valsartan and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) in HFpEF after ACS confered a prognostic benefit.

Methods

Using a propensity score matching of 1:2 ratio, this retrospective claims database study compared sacubitril-valsartan prescription (n=85) and ACEI/ARB therapy (n=170) in patients with HFpEF following ACS. Cox regression analysis was performed to assess the association between treatment and composite endpoints (all-cause mortality or hospitalization for heart failure).

Results

With a follow-up of 2 years, 52 patients (20.4%) either died from any cause or were hospitalized for heart failure, in which 10 patients (11.8%) with prescribed with sacubitril-valsartan and 42 patients (24.7%) treated with ACEI/ARB (P=0.016). Sacubitril-valsartan therapy was beneficial in N-terminal Pro-B-type natriuretic peptid (NT-proBNP) reduction as well as left ventricular ejection fraction (LVEF) change. And Cox proportional hazards regression model revealed that sacubitril-valsartan prescription (HR 0.473, 95% CI: 0.233-0.961, P=0.038) was associated with a reduced risk of the occurrence of composite endpoints.

Conclusion

Long-term sacubitril-valsartan exposure was associated with protective effects in terms of the incidence of cardiovascular events in patients with HFpEF following ACS.

Background

Although several therapies have been shown to improve survival among patients with heart failure with preserved ejection fraction (HFrEF), no agents have been proven to improve survival among patients with heart failure with reduced ejection fraction (HFpEF)[1,2]. A wide range of clinical risk factors for HFpEF, such as older age, female sex, history of hypertension, diabetes, obesity, atrial fibrillation (AF) and coronary artery disease, etc., have been identified[3]. Therefore, HFpEF patients have highly variable underlying cardiac structural and functional abnormalities, and the heterogeneous pathophysiology of HFpEF contributes to the difficulty exploring effective treatments[4]. Recently, the phenotypic diversity of HFpEF has been acknowledged, and it is suggested that specific HFpEF phenotypes could be identified that might benefit from certain treatments[5-9].

Previous studies have proposed that different phenotypes of HFpEF encompass distinct clinical features and outcomes[5-9], our previous study also identified 3 phenogroups of HFpEF based on clinical features using clustering analyze, characterized clinical outcomes and response to medical therapy among these phenotypic groups. And we identified that phenogroup 3 was accompanied with a higher burden of ischaemic heart disease (IHD) and type 2 diabetes mellitus (T2DM), and worse clinical outcomes[10]. More importantly, it was indicated that angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) use was associated with a lower risk of 5-year all-cause mortality or composite endpoints in this phenogroup, instead of the other phenogroups[10]. PARAGON-HF trial indicated that sacubitril-valsartan prescription was more effective on the primary composite outcome in specific population of HFpEF than valsartan[11]. The primary objective of this retrospective propensity score-matched cohort study is to determine whether long-term sacubitril-valsartan prescription confers a prognostic benefit in patients with HFpEF after acute coronary syndrome (ACS).

Methods

Study design and patient enrollment

The data analyzed in this study were obtained from our heart failure (HF) cohort study as previous described[10,12]. HFpEF was defined by clinical feature of HF with left ventricular ejection fraction (LVEF) greater than or equal to 45%[11]. Recruitment occurred where the patient was either in the hospital for a primary diagnosis of HFpEF (the assessment was performed following stabilization of the acute HF) or in the outpatient setting within 3 months of an episode of decompensated HF (requiring hospitalization or treatment in an outpatient setting). All enrolled patient had a history of ACS before the diagnose of HFpEF, which was classified in ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTE-ACS), according to current clinical practice guidelines[13-15]. Inclusion criteria also comprised age within 18 to 80 years old, NYHA class II-IV. Major exclusion criteria included HF history prior to ACS, atrial fibrillation, chronic obstructive pulmonary disease (COPD), infiltrative cardiomyopathy (sarcoid, amyloid) any time in past, active myocarditis, severe valve disease, cardiomyopathy, pericardial constriction, life expectancy < 1 year following consent date, pregnancy or nursing and severe liver and kidney dysfunction. Pharmacy claims were used to estimate sacubitril-valsartan exposure over two-year rolling windows. Discontinuation was defined as an interruption in prescription for sacubitril-valsartan that lasted for at least 30 consecutive days. Only patients that continued their sacubitril-valsartan were considered eligible to participate. Patients without baseline and follow-up echocardiographic data were also excluded. The study protocol was approved by the local ethics committee, and informed consent was obtained from all patients.

Propensity score matching was performed to avoid selection biases resulting from non-random assignment in this retrospective study. The 23 clinically relevant baseline variables included in the matching process were age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), estimated glomerular filtration rate (eGFR), body mass index (BMI), ratio of hypertension and T2DM, stroke, smoking, dyslipidemia, coronary lesion, PCI history, NYHA class, ACS category, statin, dual-anti

platelet-therapy (DAPT), spironolactone, beta-blockers, NT-proBNP, LVEF, left atrium diameter (LAD) and E/E'. The sacubitril-valsartan group was matched at a 1:2 ratio to the ACEI/ARB group.

Follow-up data and clinical outcomes

Follow-up information was obtained from a comprehensive medical record database[10,12]. Analyses were conducted to compare the composite endpoints (all-cause mortality or HF hospitalization) during 2 years of prescription with sacubitril-valsartan versus ACEI/ARB-based therapy. Most of the patients visited our outpatient clinic at least every 1 month. However, if the patients did not appear at their scheduled clinic, they were interviewed by telephone every 3 months.

Statistical analysis

Statistical analysis was performed using SPSS Statistical Software, version 22.0 (SPSS Inc., Chicago, IL, USA) and R Statistical Software, Version 3.0.1 (the R Foundation for Statistical Computing). Arithmetic means ± standard deviations were calculated for quantitative variables while qualitative variables were given as frequency and percentage (%). For quantitative variable analysis, t-test and one-way ANOVA test, if appropriate, were used. A two-sided chi square test was used to compare qualitative variables. Univariate and multivariate Cox regression analyses of relevant variables were performed to identify predictors for composite endpoints. All predictors with a significance of $P < 0.10$ in the univariate analysis were entered into the multivariate model. Relative risks are expressed as odds ratios (HR) with 95% confidence intervals (CIs). Freedom from composite endpoints at 2 years was analyzed with Kaplan-Meier statistics, with difference between groups assessed using the log-rank test. All values were two-tailed, and a P-value <0.05 was considered statistically significant.

Results

Study population

From January 1, 2018 to December 31, 2018, on the basis of the inclusion and exclusion criteria, we included a total of 835 patients with HFpEF following ACS, in which 93 patients have medical records of sacubitril-valsartan prescription, while 742 patients with ACEI/ARB treatment. And 25 patients who did not have continuous prescription of sacubitril-valsartan or ACEI/ARB were excluded from analyses. The final study population comprised 85 patients with sacubitril-valsartan therapy and 725 patients with ACEI/ARB therapy. After propensity score matching, a total of 85 patients receiving sacubitril-valsartan and 170 patients with ACEI/ARB treatment were enrolled. Table 1 demonstrated the demographic and baseline characteristics of the two groups. After propensity score matching, the two treatment groups were well balanced for baseline demographic, comorbidities, clinical and echocardiographic characteristics.

Beneficial effects of sacubitril-valsartan in clinical outcomes

After a follow-up of 2 years, the composite endpoints occurred in 10 patients (11.8%) of the sacubitril-valsartan group and 42 patients (24.7%) of the ACEI/ARB group (P= 0.016). Kaplan-Meier plots for the composite endpoints were presented in Figure 1, sacubitril-valsartan prescription markedly decreased the occurrence of composite endpoints compared with ACEI/ARB (P =0.018). For multivariate Cox regression analysis, variables with P<0.10 (age, T2DM, BMI, eGFR, LVEF, NT-proBNP, ACS category, beta-blocker prescription, sacubitril-valsartan exposure and spironolactone treatment) from univariate Cox regression analysis were entered into the multivariate Cox regression model. The result showed that sacubitril-valsartan exposure (HR 0.473, 95% CI: 0.233–0.961, P =0.038) or the higher LVEF level (HR 0.222,95% CI: 0.051–0.959, P = 0.044) was associated with a reduced risk of the occurrence of composite endpoints, and the higher NT-proBNP level (HR 1.523, 95% CI: 1.054–2.201, P =0.025) was associated with an increased risk of the occurrence of composite endpoints (Table 2). Additionally, 9 patients in the sacubitril-valsartan group and 36 patients in the ACEI/ARB group suffered from HF phenotype transition (shifted to HFrEF, LVEF<40%) (P=0.037). At the end of follow-up, the NT-proBNP level (1250±516 pg/ml vs 1478±686 pg/ml, P<0.001) was lower and LVEF (54.2±3.4% vs 52.9±4.2% P<0.001) was higher significantly in the sacubitril-valsartan group than that of ACEI/ARB group.

Adverse events

No difference of SBP/DBP reduction was found between the two groups during the follow-up. Patients in sacubitril-valsartan group were not more likely to have hypotension as well as less likely to have increases in the creatinine and potassium levels than those in ACEI/ARB group.

Discussion

Our study compared the effectiveness of sacubitril-valsartan versus ACEI/ARB therapy in patients with HFpEF following ACS, and the results showed that sacubitril-valsartan led to a significantly lower rate of all-cause mortality or hospitalization for HF. Besides, sacubitril-valsartan also markedly decreased the NT-proBNP level and was beneficial for an improved LVEF.

HFpEF is recognized as a heterogeneous syndrome that is thought to be driven by a range of comorbidities, and the diversity of patients may partly explain the failure to demonstrate clinical efficacy of ACEI/ARB, beta-blockers and spironolactone in randomized control trials[3]. Our previous study also showed that these three treatments were not associated with improved clinical outcomes in the whole HFpEF cohort[12]. It was suggested that the strategy “one size fits all” should be avoided and distinct HFpEF phenogroup might require different therapeutic approaches. Recent advances in the management of ACS have significantly reduced the likelihood of in-hospital mortality. However, the occurrence of HF in survivors of ACS, which requires readmission with high mortality and an increasing prevalence, has recently emerged as a critical clinical problem. It was reported that the predominant subtypes of HF after acute myocardial infarction were HF with mid-range ejection fraction (HFmrEF) and HFpEF, or HF with non-reduced ejection fraction[16]. HFpEF patients with coronary artery disease (CAD) are at higher risk of all-cause mortality and sudden death when compared with those without CAD. And it was found that IHD

conferred an approximate 20% increase in the risk of major adverse renal and cardiovascular events (MARCE) for patients with HFpEF[16]. Our previous study also indicated that IHD was an independent risk factor for LVEF deterioration and worse clinical outcomes in HFpEF patients[12]. Therefore, it is suggested the need to create specific interventions for this sub-population.

Recently, our results indicated that patients with HFpEF and IHD might benefit from long-term ACEI/ARB prescription[12]. Another study also demonstrated the differences in medical therapy among different HFpEF subgroups. In-hospital beta-blocker treatment was significantly associated with a reduction in in-hospital mortality only in HFpEF patients with hypertension, whereas in-hospital diuretic treatment was significantly associated with better outcome only in HFpEF patients without hypertension[17]. In recent PARAGON-HF trial[11,18,19], the effects of sacubitril-valsartan were compared with those of valsartan in HFpEF patients, and the primary outcome was a composite of HF hospitalization and cardiovascular death. Although treatment with sacubitril-valsartan did not result in a significantly lower rate of total hospitalizations for HF and death from cardiovascular causes among HFpEF patients (P=0.059), sub-analyses suggested beneficial effects in female patients and those with an LVEF between 45% and 57%. Hence, it was indicated that sacubitril-valsartan might be more effective than valsartan in specific phenotype of HFpEF.

In the present study, in order to reduce the heterogeneity of HFpEF, we enrolled the HFpEF patients after ACS and excluded patients with atrial fibrillation and COPD, just like the phenotype 3 in our previous study[10]. Our result showed that sacubitril-valsartan treatment was superior to ACEI/ARB in terms of all-cause mortality or HF hospitalization in HFpEF patients following ACS. Furthermore, it was also indicated that sacubitril-valsartan exerted a marked reduction in NT-proBNP level. PARAGON-HF trial[20] indicated that sacubitril-valsartan consistently decreased NT-proBNP by 19% relative to valsartan and patients who demonstrated the greatest reduction in NT-proBNP had the best subsequent outcomes.

Currently, HF patients are typically classified into HFpEF, HFmrEF or HFrEF on the basis of LVEF. However, LVEF is not necessarily static, as LVEF can worsen over time owing to progressive heart disease, or it can improve in response to HF treatment or reversal of the underlying pathogenesis[21]. Recent studies suggest that the changes of LVEF during follow-up might be associated with clinical prognosis[22,23]. Our previous study indicated that patients with HF with deteriorated LVEF had higher mortality, whereas patients with HF with improved LVEF had lower mortality[12]. Our present study further explored the effects of sacubitril-valsartan on LVEF change and HF transition. It was found that sacubitril-valsartan prescription was favorable for an improved LVEF.

The present study has several limitations. First, the present study was a retrospective analysis, with all the inherent problems of such a design in proving causality. Second, not all comorbid diseases and conditions associated with mortality could be evaluated, although we tried to include as many potential risk factors as possible. Certain risk or beneficial factors for prognosis were not recorded and analyzed, including data on left atrial volume and pulmonary capillary wedge pressure. Finally, it is also possible that the number of patients was not sufficiently large enough to identify all possible risk factors.

Conclusions

The present study demonstrated that HFpEF after ACS could benefit from sacubitril-valsartan treatment in term of all-cause mortality or hospitalization for HF, NT-proBNP level and LVEF change. Elucidation of the pathophysiological mechanisms behind these findings might lead to more effective individualized therapeutic strategies for HFpEF patients.

Declarations

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Authors' contributions

Professor J.F.Z. and J.G. designed the study; Z.H.H. and J.G. collected and analyzed the data and wrote the manuscript. C.Q.W. reviewed and edited the manuscript. All authors approved the final version of the paper.

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Availability of data and material

The datasets analyzed in the study can be obtained from the corresponding author on reasonable request.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Ninth People's Hospital affiliated to Shanghai Jiao Tong University School of Medicine.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Tables

Table 1 Baseline characteristics before and after propensity score matching

	before PSM			after PSM		
	Sacubitril-Valsartan (n=85)	ACEI/ARB (n=725)	P	Sacubitril-Valsartan (n=85)	ACEI/ARB (n=170)	P
age	70.5±7.0	69.8±6.9	0.377	70.5±7.0	70.2±7.0	0.747
sex(female)	27(31.8%)	240(33.1%)	0.804	27(31.8%)	56(32.9%)	0.850
BMI	25.3±2.3	25.1±2.3	0.448	25.3±2.3	25.0±2.3	0.287
hypertension	62(72.9%)	542(74.8%)	0.716	62(72.9%)	128(75.3%)	0.684
T2DM	24(28.2%)	216(29.8%)	0.706	24(28.2%)	42(24.7%)	0.544
dyslipidemia	55(64.7%)	490(67.6%)	0.592	55(64.7%)	115(67.6%)	0.639
stroke	5(5.9%)	36(5.0%)	0.608	5(5.9%)	9(5.3%)	1.000
STEMI/ NSTE-ACS	21(24.7%)/ 64(75.3%)	182(25.1%)/ 543(74.9%)	0.936	21(24.7%)/ 64(75.3%)	42(24.7%)/ 128(75.3%	1.000
multivessel	29(34.1%)	282(38.9%)	0.391	29(34.1%)	61(35.9%)	0.781
hemoglobin	12.1±1.5	12.2±1.6	0.583	12.1±1.5	12.2±1.3	0.583
eGFR	60.9±10.9	62.2±12.3	0.351	60.9±10.9	61.9±11.9	0.516
NT-proBNP	2130±1095	1875±926	0.020	2130±1095	1980±1025	0.206
NYHA II/III/IV	29/42/14	252/363/107	0.914	29/42/14	65/82/23	0.735
SBP	136.5±12.6	132.9±10.2	0.003	136.5±12.6	134.2±10.8	0.131
DBP	76.2±7.3	75.3±7.8	0.311	76.2±7.3	75.5±7.9	0.495
HR	81.2±9.6	80.9±10.2	0.796	81.2±9.6	81.0±10.3	0.881
PCI	62(72.9%)	543(74.9%)	0.695	62(72.9%)	126(74.1%)	0.841
DAPT	53(62.4%)	472(65.1%)	0.615	53(62.4%)	107(62.9%)	0.927
beta-blocker	63(74.1%)	519(71.6%)	0.623	63(74.1%)	124(72.9%)	0.841
spironolactone	24(28.2%)	188(25.9%)	0.648	24(28.2%)	46(27.1%))	0.843
statin	79(92.9%)	688(94.9%)	0.441	79(92.9%)	160(94.1%)	0.715
LVEF	53.5±3.2	55.2±3.9	0.0001	53.5±3.2	54.3±4.5	0.118
LAD	42.2±4.5	41.9±4.2	0.537	42.2±4.5	42.0±4.2	0.727
E/e'	13.9±2.9	13.2±2.5	0.017	13.9±2.9	13.5±2.7	0.278

Data are presented as mean±SD or number (%) of subjects. PSM: propensity score matching; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; BMI: body mass index; T2DM: type 2 diabetes mellitus; STEMI: ST-segment elevation myocardial infarction; NSTE-ACS: non-ST-segmentel elevation acute coronary syndrome; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal Pro-B-type natriuretic peptide; NYHA: New York Heart Association functional class; SBP:systolic blood pressure; DBP:diastolic blood pressure; HR: heart rate; PCI : percutaneous coronary intervention; DAPT: CABG: coronary artery bypass graft; DAPT: Dual-anti platelet-therapy; LVEF: left ventricular ejection fraction; LAD:left atrium diameter; E/e': mitral Doppler early velocity/mitral annular early velocity.

Table 2 Multivariable cox analysis for composite endpoints

	HR	95% CI	P value
age	1.004	0.967-1.043	0.825
T2DM	1.581	0.865-2.888	0.136
BMI	1.015	0.894-1.153	0.816
eGFR	0.977	0.949-1.005	0.110
LVEF	0.222	0.051-0.959	0.044
sacubitril-valsartan	0.473	0.233-0.961	0.038
beta-blocker	0.857	0.459-1.601	0.629
spironolactone	0.536	0.256-1.121	0.097
NT-proBNP category	1.523	1.054-2.201	0.025
ACS category	1.501	1..811-2.779	0.196

T2DM: type 2 diabetes mellitus; BMI: body mass index; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal Pro-B-type natriuretic peptide; ACS: acute coronary syndrome.

Figures

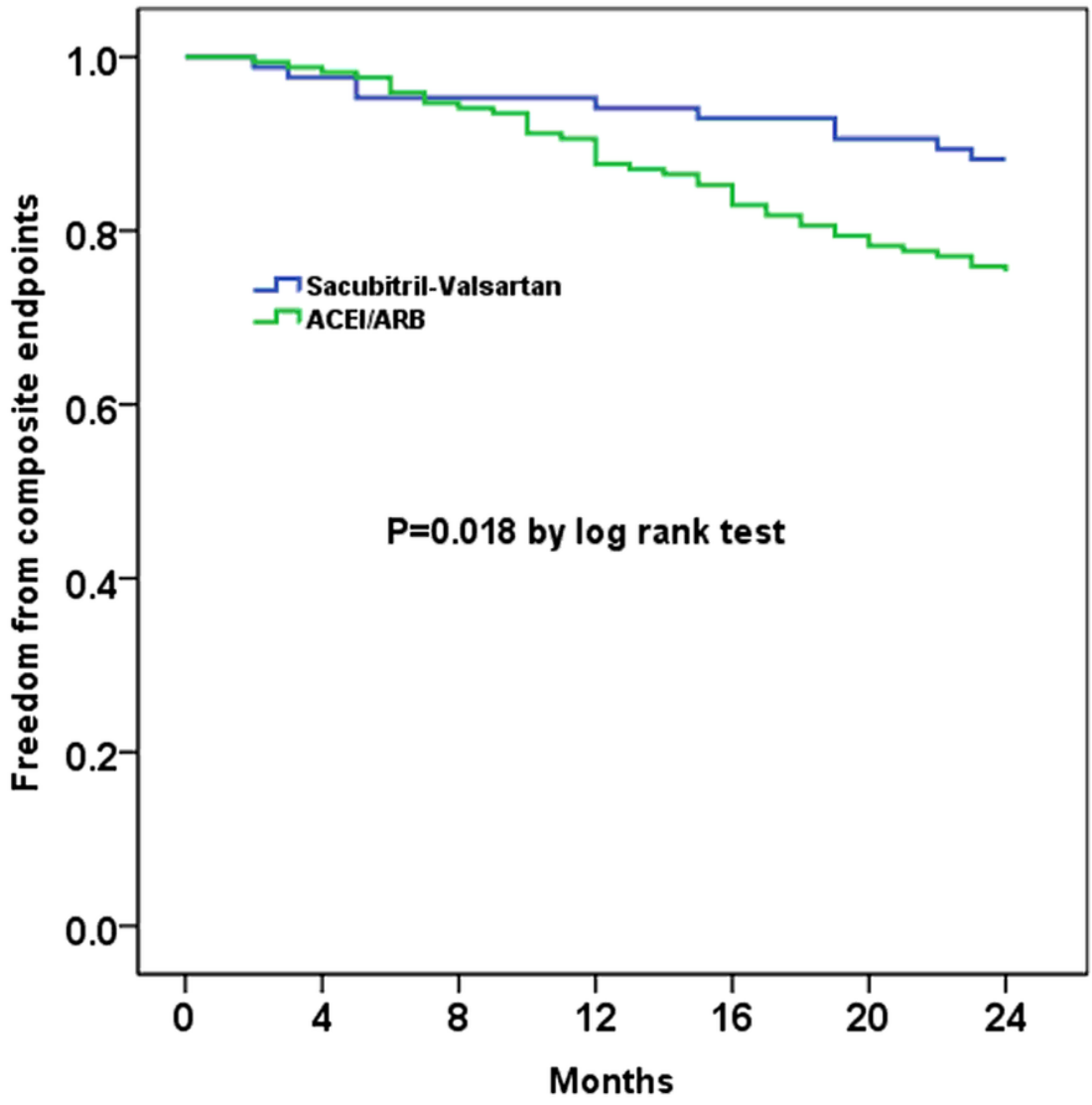

Figure 1

Kaplan-Meier curves of freedom from composite endpoints. The numbers at the bottom of the figure are “number at risk”.