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SHORT COMMUNICATION

Sacubitril/valsartan in patients with heart failure with reduced ejection fraction with end-stage of renal disease

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Abstract

Aims Sacubitril/valsartan (SV) reduced heart failure hospitalization and cardiovascular mortality compared with enalapril in the Prospective Comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure trial. However, this trial excluded patients with end stage of renal disease (ESRD); thus, the efficacy and safety of SV in heart failure with reduced ejection fraction (HFrEF) with ESRD remains uncertain.

Methods and results We retrospectively analysed the clinical and laboratory data of 501 HFrEF patients who administered with SV from March 2017 to April 2019 in a single tertiary university hospital. A total of 23 HFrEF patients with ESRD on dialysis [58.3% non-ischaemic heart failure; left ventricular ejection fraction (LVEF): 29.7 ± 4.4%] were included in this study. At baseline and follow-up visit, we evaluated cardiovascular biomarkers such as high-sensitive troponin T (hsTnT), soluble ST2 (sST2), echocardiographic parameters, and clinical and adverse events. The mean dose of SV was 90 ± 43 mg/day at baseline and 123 ± 62 mg/day at last follow-up (follow-up duration: median 132 days). The level of hsTnT was significantly reduced from 236.2 ± 355.3 to 97.0 ± 14.0 pg/mL (P = 0.002), and the sST2 level was significantly reduced from 40.4 ± 44.0 to 19.6 ± 14.1 ng/mL (P = 0.005). LVEF was significantly improved from 29.7 ± 4.4% to 40.8 ± 10.4% (P = 0.002). During the follow-up, up-titration, down-titration, and maintenance of SV dosing were observed in 7 (30%), 5 (21.7%), and 11 patients (47.8%), respectively. SV down-titration group had adverse events including symptomatic hypotension (systolic blood pressure $<$100 mmHg) (n = 4) and dizziness (n = 1), but they did not discontinue SV therapy.

Conclusions We found that SV could safely reduce the hsTnT and sST2 levels and improve LVEF in HFrEF patients with ESRD. As far as we know, this is the first study to show the efficacy and safety of SV in HFrEF with ESRD on dialysis. Larger prospective, long-term follow-up study should be warranted.

Keywords Sacubitril/valsartan; Heart failure with reduced ejection fraction patients; End-stage renal disease; Dialysis

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Introduction

Sacubitril/valsartan (SV) reduced heart failure (HF) hospitalization and cardiovascular mortality compared with angiotensin-converting enzyme inhibitor (ACE-I), enalapril in the Prospective Comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[1] But there are varying levels of evidence for guideline-directed medical therapies for HF in the chronic kidney disease (CKD) population, with a relative paucity of data especially in patients with advanced CKD (Stages 4 and 5) and end stage of renal disease (ESRD).[2] Several studies in heart failure with reduced ejection fraction (HFrEF), including PARADIGM-HF trial, suggest that SV can

slow the decline in kidney function compared with ACE-I/angiotensin receptor blocker (ARB). However, the PARADIGM-HF trial excluded patients with advanced CKD and ESRD, so the efficacy and safety of SV in these population remains uncertain. There were only two studies for evaluating SV in advanced CKD patients as far as we know. A previous study reported that SV could safely decrease blood pressure (BP) without a decline in kidney function in Japanese patients with hypertension and renal dysfunction (estimated glomerular filtration rate, 15 to 60 mL/min/1.73 m^2).[3] Recently published United Kingdom Heart and Renal Protection-III (UK HARP-III) trial showed that SV had similar

Table 1 Baseline characteristics, change in clinical parameters, cardiovascular biomarkers, and echocardiographic parameters before and after sacubitril/valsartan therapy according to heart failure aetiology

Variable	Ischaemic (*N* = 9)	Non-ischaemic (*N* = 14)	*P*-value*
Demographics			
Age (years)	67 ± 9	57 ± 20	0.208
Male, *n* (%)	9 (100)	11 (78.6)	0.266
Duration of heart failure (years)	5 ± 6	4 ± 5	0.899
Duration of dialysis (years)	6 ± 4	6 ± 5	0.464
Co-morbidities			
Atrial fibrillation, *n* (%)	1 (11.1)	2 (14.3)	0.825
Hypertension, *n* (%)	7 (77.8)	11 (78.6)	0.964
Diabetes, *n* (%)	8 (88.9)	3 (21.4)	0.002
Coronary artery disease, *n* (%)	8 (88.9)	3 (21.4)	0.002
Medications			
ACE-I or ARB, *n* (%)	9 (100)	14 (100)	>0.999
Beta-blocker, *n* (%)	9 (100)	14 (100)	>0.999
Ivabradine, *n* (%)	4 (44.4)	13 (92.9)	0.637
Clinical parameters			
Systolic BP (mmHg)			
Baseline	110 ± 43	109 ± 49	0.727
Follow-up	119 ± 24	112 ± 25	0.614
P-value (baseline vs. follow-up)	0.374	0.65	—
Diastolic BP (mmHg)			
Baseline	75 ± 23	88 ± 26	0.122
Follow-up	70 ± 22	81 ± 25	0.376
P-value (baseline vs. follow-up)	0.675	0.052	—
Heart rate (b.p.m.)			
Baseline	73 ± 10	76 ± 10	0.412
Follow-up	72 ± 10	74 ± 11	0.681
P-value (baseline vs. follow-up)	0.865	0.462	—
Cardiovascular biomarkers			
High-sensitive troponin T (pg/mL)			
Baseline	273.4 ± 421.1	111.5 ± 133.2	0.039
Follow-up	79.4 ± 29.5	97.2 ± 108.4	0.417
P-value (baseline vs. follow-up)	0.018	0.034	—
Delta hsTnT (%)	42.2 ± 29.8	13.5 ± 23.4	0.043
sST2 (ng/mL)			
Baseline	34.9 ± 4.1	48.4 ± 60.7	0.298
Follow-up	18.0 ± 2.6	15.7 ± 9.9	0.44
P-value (baseline vs. follow-up)	0.108	0.018	—
Delta sST2 (%)	47.6 ± 14.7	52.9 ± 23.1	0.569
Echocardiographic parameters			
LVEF (%)			
Baseline	29.7 ± 2.4	30.5 ± 4.9	0.179
Follow-up	39.6 ± 8.1	42.6 ± 12.0	0.817
P-value (baseline vs. follow-up)	0.018	0.009	—
Delta LVEF (%)	22.6 ± 14.4	23.0 ± 22.7	0.911

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; hsTnT, high-sensitive troponin T; LVEF, left ventricular ejection fraction; sST2, soluble ST2.
**P* value for ischaemic vs. non-ischaemic.

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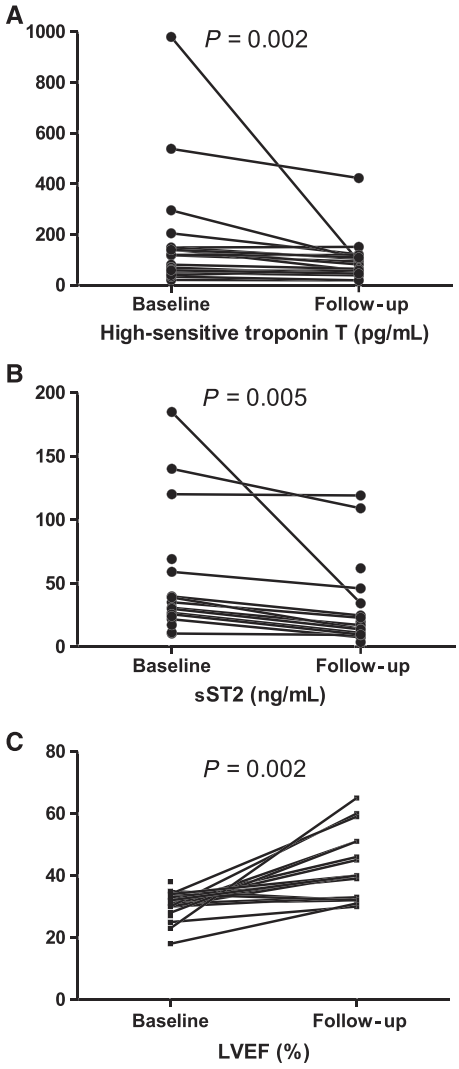
Figure 1 Change of (A) high-sensitive troponin T, (B) soluble ST2 (sST2), and (C) left ventricular ejection fraction (LVEF) after sacubitril/valsartan treatment.



beneficial effects on kidney function and albuminuria to irbesartan, but it had the additional effect of lowering BP and cardiac biomarkers [e.g. troponin I and N-terminal pro-brain natriuretic peptide (NT-proBNP)] in CKD patients (estimated glomerular filtration rate, 20 to 60 mL/min/1.73 m^2).[4]

Methods

We retrospectively analysed the clinical and laboratory data of 501 HFrEF patients who was prescribed with SV from March 2017 to April 2019 in a single tertiary university hospital. We enrolled the following inclusion criteria: age >18 years and left ventricular ejection fraction (LVEF) ≤35% in echocardiography and anuric ESRD on haemodialysis or peritoneal dialysis more than 6 months, and we excluded patients with cardiac resynchronization therapy. Eventually, 23 patients were included in this study. All patients were switched from ACE-I/ARB to SV, on top of guideline-directed medical therapies (beta-blocker 100%, ivabradine 52%). At baseline and follow-up visit, we evaluated cardiovascular biomarkers such as high-sensitive troponin T (hsTnT), soluble ST2 (sST2), echocardiographic parameters, and clinical and adverse events.

Results

Mean age was 60 ± 17 years old, and male is 85%. The main aetiology of HFrEF was non-ischaemic origin cardiomyopathy (58.3%). The median duration of HF and dialysis was 3 [interquartile range (IQR) 1–8] and 4 (IQR 3–6) years, respectively. The mean dose of SV was 90 ± 43 mg/day at baseline and 123 ± 62 mg/day at last follow-up (follow-up duration: median 132, IQR 77–132 days). *Table 1* demonstrated the change of clinical and echocardiographic parameters and biomarkers before and after SV treatment regarding HF aetiology (ischaemic vs. non-ischaemic). From baseline to follow-up, the hsTnT level was significantly reduced from 236.2 ± 355.3 to 97.0 ± 14.0 pg/mL (P = 0.002, *Figure 1A*), and the sST2 level was significantly reduced from 40.4 ± 44.0 to 19.6 ± 14.1 ng/mL (P = 0.005, *Figure 1B*). LVEF was significantly improved from 29.7 ± 4.4% to 40.8 ± 10.4% (P = 0.002, *Figure 1C*), and diastolic BP was significantly decreased from 76 ± 18 to 69 ± 14 mmHg (P = 0.043), but there was no significant difference in systolic BP (126 ± 16 vs. 121 ± 19 mmHg, P = 0.269). During the follow-up period, up-titration, down-titration, and maintenance of SV dosing were observed in 7 (30%), 5 (21.7%), and 11 patients (47.8%), respectively. SV down-titration group had adverse events including symptomatic hypotension (systolic BP <100 mmHg) (n = 4) and dizziness (n = 1), but they did not discontinue SV therapy. In addition, there were only two cases (10%) of HF hospitalization without cardiovascular mortality in our study population.

We analysed the effect of SV in terms of the aetiology of HF (ischaemic, n = 9 vs. non-ischaemic, n = 14). There was no significant difference in age, HF, and dialysis duration between two groups. The hsTnT level was significantly reduced in both groups. Interestingly, the hsTnT change was significantly greater in ischaemic HF than non-ischaemic HF group (−42% vs. −14%, P = 0.043). The sST2 level was significantly decreased only in non-ischaemic HF group, but the sST2 change was not significantly different between two groups. In addition, LVEF was significantly improved in both groups, but the LVEF change was similar between two groups (22.6% for ischaemic vs. 23.0% for non-ischaemic, P = 0.911).

Aims

However, there have been no studies about SV in ESRD patients until now. Therefore, we aimed to examine the effect and safety of SV in the treatment of HFrEF patients with ESRD.

Conclusions

To our knowledge, this is the first study that shows that SV could safely reduce the hsTnT and sST2 levels and improve LVEF in HFrEF patients with ESRD. In ESRD patients, cardiac biomarkers such as hsTnT and sST2 could be used for risk stratification.[5,6] The hsTnT level has been known to help identify patients at greater risk of cardiovascular mortality and sudden cardiac death, and the sST2 level had prognostic value, independently of renal function and dialysis.[7–12] The UK HARP-III trial showed that SV could decrease troponin T level compared with olmesartan in advanced CKD patients.[4] Recent PIONEER-HF trial also showed that SV could decrease the hsTnT and sST2 levels more, compared with ACE-I in acute decompensated HF.[13] These lines of recent findings are consistent with our findings in ESRD patients. In addition, the clinical implication of more decrease in the hsTnT level by SV treatment in ischaemic HF group should be confirmed and evaluated in further studies, although the post hoc analysis of the PARADIGM-HF trial showed similar adjusted clinical outcomes across HF aetiology.[14] NT-proBNP is a well-known surrogate marker in HF (especially for HFrEF), but it can be largely affected by dialysis timing and duration, so NT-proBNP is not appropriate for evaluating the SV effect in patients with ESRD.

In terms of safety, most common adverse event related to SV use was hypotension (systolic BP $<$100 mmHg), which occurred during or just after finishing haemodialysis. In our study, 17% and 4% patients experienced symptomatic hypotension and dizziness, respectively, so we down-titrated their SV dose. However, this down-titration of SV dose was not related to stopping SV therapy. Therefore, we suggest that we could use SV safely in HFrEF patients with ESRD. There have been only two studies for evaluating SV in advanced CKD patients but no studies in ESRD patients until now as far as we know. And two studies for advanced CKD patients were conducted in hypertensive patients (not HF patients), so our study may give small but potent clinical evidences for a new treatment option, SV for the patients with both heart and kidney failure.

Our study had some limitations. First, our study was not a randomized controlled trial (RCT) evaluating clinical outcomes like the PARADIGM-HF trial. Based on our findings, we suggest RCTs for comparing SV with ACE-I/ARB in terms of biomarkers, left ventricular reverse remodelling, and clinical outcomes in HFrEF patients with ESRD. There is an ongoing observation registry study (ClinicalTrials.gov Identifier: NCT03771729) that evaluate the clinical role of SV in advanced CKD patients as far as we know, and further prospective study regarding clinical outcomes should be warranted to support the clinical evidence of SV use in patients with advanced CKD and ESRD. Second, there have been no pharmacokinetic data of SV in ESRD patients with dialysis although a pharmacokinetic study using SV showed that renal dysfunction increased exposure to sacubitrilat (sacubitril metabolite), not sacubitril (prodrug) in three ESRD patients without dialysis.[15] Third, we analysed a small number of patients in Asian population. However, this is the first study to show the efficacy and safety of SV in HFrEF with ESRD on dialysis. Larger prospective, long-term follow-up study including RCT should be warranted.

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Conflict of interest

None declared.

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