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SHORT COMMUNICATION

Left ventricular output indices and sacubitril/valsartan titration: role of stroke volume index

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Abstract

Aims This study aims to investigate the role of echocardiographically determined left ventricular output indices on sacubitril/valsartan titration in a cohort of outpatients with heart failure and reduced ejection fraction (HFrEF).

Methods and results We analysed 106 HFrEF patients who underwent echocardiography examination up to 1 week before starting treatment with sacubitril/valsartan. For each patient, a comprehensive list of clinical and laboratory parameters was collected, and stroke volume index (SVi), cardiac index, and flow rate were calculated. The primary endpoint was the occurrence of complete titration of sacubitril/valsartan. The secondary endpoint was the incidence of adverse events (hypotension and renal adverse events). Univariate and multivariate logistic regression were used to identify variables associated with the primary and secondary endpoints. Mean age of patients was 73.7 ± 10.4 years, 72 patients (71.7%) had ischaemic aetiology of HF, and mean ejection fraction was 29.4 ± 5.9%. At multivariate analysis, SVi [odds ratio (OR) 1.43 per 5 mL/m^2 increase, 95% confidence interval (CI) 1.03–1.97; P = 0.028], serum sodium (OR 1.18, 95% CI 1.02–1.37; P = 0.022), and haemoglobin (OR 1.73, 95% CI 1.25–2.40; P = 0.001) were found to be independent predictors of titration during follow-up. Multivariate analysis for the secondary endpoint showed SVi (OR 0.63 per 5 mL/m^2 increase, 95% CI 0.44–0.90; P = 0.012) and New York Heart Association Class III (OR 2.65, 95% CI 1.07–6.5; P = 0.034) to be associated with hypotension.

Conclusions Stroke volume index is positively associated with complete titration of sacubitril/valsartan. Patients with low SVi are more prone to experience hypotension during titration

Keywords Sacubitril; Valsartan; Entresto; HFrEF; Titration

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Background

Randomized clinical trials (RCTs) showed that sacubitril/valsartan exerts greater benefit than enalapril in patients with heart failure and reduced ejection fraction (HFrEF).[1–3] These two drugs have a comparable adverse event profile except for hypotension that occurs more frequently with sacubitril/valsartan and could explain its underuse in recent RCTs and registries.[4–6] In clinical practice, matching between arterial blood pressure (BP) values and symptomatic hypotension is not straightforward and patients with normal/low BP at baseline are often able to tolerate target doses of sacubitril/valsartan. BP is the result of interaction between left ventricular output (LVO), arterial elastance, and peripheral resistance.[7,8] We hypothesized that LVO is the main factor driving symptoms of hypotension and could predict sacubitril/valsartan titration better than BP.

Aims

The aim of this study was to assess the association between left ventricular output indices (LVOIs) assessed by echocardiography at baseline and the occurrence of complete titration of sacubitril/valsartan during follow-up. The association between LVOIs and adverse events was also evaluated.

Table 1 Baseline characteristics of the overall population and according to the achieving of complete titration

Variable	Overall	Incomplete titration	Complete titration	*P*-value
Patients, no.	106	44	62	
Age, years (SD)	73.7 (10.4)	76.4 (9.4)	71.6 (10.7)	**0.025**
Male sex, no. (%)	87 (82.1)	36 (81.8)	51 (82.3)	0.95
CV risk factors				
Hypertension, no. (%)	89 (84.0)	36 (81.8)	53 (85.5)	0.61
Diabetes, no. (%)	38 (35.8)	15 (34.1)	23 (37.1)	0.75
Physical features (SD)				
Systolic BP, mmHg (SD)	125.4 (14.7)	124 (14.9)	126.4 (14.5)	0.42
Diastolic BP, mmHg (SD)	74.7 (9.3)	73.2 (8.6)	75.7 (9.7)	0.16
Pulse pressure, mmHg (SD)	50.7 (10.6)	50.8 (9.6)	50.6 (11.4)	0.91
Heart rate, b.p.m. (SD)	67.9 (11.7)	68.8 (13.6)	67.2 (10.3)	0.51
BMI, kg/m^2 (SD)	27.5 (4.6)	27.0 (4.3)	27.8 (4.9)	0.44
Aetiology of HF				0.52
Ischaemic aetiology, no. (%)	76 (71.7)	33 (75.0)	43 (69.4)	
Non-ischaemic aetiology, no. (%)	30 (28.3)	11 (25.0)	19 (30.6)	
Comorbidities				
Chronic renal failure (eGFR $<$ 60 mL/min/1.72 m^2), no. (%)	66 (62.3)	33 (75.0)	33 (53.2)	**0.023**
Baseline laboratory analysis				
Serum sodium, mg/mL (SD)	140.5 (3.4)	139.7 (4.1)	141.0 (2.6)	0.075
Serum potassium, mg/mL (SD)	4.4 (0.6)	4.5 (0.5)	4.4 (0.6)	0.24
eGFR, mL/min/1.72 m^{2a} (SD)	54.0 (20.3)	49.0 (21.7)	57.6 (18.5)	**0.032**
Haemoglobin, g/dL (SD)	13.2 (1.6)	12.5 (1.4)	13.6 (1.6)	$<$**0.001**
Median BNP values, pg/mL (IQR)	412 (190–806)	603 (191–1019)	371 (156–553)	0.11
NYHA class, no. (%)				0.18
I	5 (4.7)	2 (4.5)	3 (4.8)	
II	68 (64.2)	24 (54.5)	44 (71.0)	
III	33 (31.1)	18 (40.9)	15 (24.0)	
Heart rhythm at baseline ECG, no. (%)				0.13
Sinus rhythm	50 (47.2)	19 (43.2)	31 (50.0)	
Atrial fibrillation/flutter	28 (26.4)	9 (20.5)	19 (30.6)	
Paced rhythm	28 (26.4)	16 (36.4)	11 (18.4)	
Echocardiogram				
LVEDVi, mL/m^2 (SD)	111.0 (42.5)	103.9 (36.1)	114.9 (45.6)	0.25
Ejection fraction, no. (%)	29.4 (5.9)	28.0 (6.5)	30.4 (5.3)	**0.044**
SV, mL (SD)	60.0 (17.0)	55.6 (14.5)	63.3 (18.3)	**0.02**
SVi, mL/m^2 (SD)	31.0 (7.9)	28.7 (7.0)	32.6 (8.1)	**0.011**
Cardiac index, L/min/m^2 (SD)	2.1 (**0.7**)	2.0 (**0.6**)	2.2 (**0.7**)	0.12
Flow rate, mL/min (SD)	215.4 (58.9)	203.8 (49.7)	223.6 (63.8)	0.10
PAPs, mmHg (SD)	43.7 (10.1)	45.3 (9.6)	42.4 (10.4)	0.34
Diastolic dysfunction[b], no. (%)				0.12
Grade I	24 (22.6)	8 (18.2)	16 (25.8)	
Grade II	22 (20.8)	14 (31.8)	8 (12.9)	
Grade III	30 (28.3)	14 (31.8)	16 (25.8)	
Undetermined	30 (28.3)	8 (18.2)	22 (35.5)	
Heart failure treatments				
Beta-blocker, no. (%)	96 (90.1)	40 (91.0)	56 (90.3)	0.92
MRAs, no. (%)	89 (84.0)	38 (86.4)	51 (82.3)	0.57
Loop diuretics, no. (%)	97 (91.5)	42 (95.5)	55 (88.7)	0.22
Median loop diuretics dose, mg/day[c] (IQR)	50 (25–75)	50 (25–100)	50 (25–75)	0.055
Loop diuretics preventive reduction, no. (%)	32 (30.2)	11 (25.0)	21 (33.9)	0.33
ICD/CRT-D, no. (%)	38 (35.8)	19 (43.2)	19 (30.6)	0.18
CRT-P/CRT-D, no. (%)	17 (16.0)	8 (18.2)	9 (14.5)	0.61

BMI, body mass index; BP, blood pressure; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; CV, cardiovascular; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEDVi, left ventricular end-diastolic volume index; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; PAPs, pulmonary artery pressures; SBP, systolic blood pressure; SV, stroke volume; SVi, stroke volume index.
Values are reported as mean and standard deviation (SD), number and percentage, or median and interquartile range (IQR). *P*-values $<$ 0.05 are reported in bold.
[a]The Modification of Diet in Renal Disease formula has been used.
[b]Loop diuretic doses are reported as furosemide equivalents.
[c]Patients with undermined status were excluded from this analysis.

Methods

Data sources and study population

We prospectively collected data of all patients prescribed sacubitril/valsartan for the first time, from 30 October 2019 to 18 September 2020. As per internal protocol, patients prescribed with sacubitril/valsartan were followed up at our outpatient clinic with scheduled clinical visits until full titration or dose stabilization. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and without any external funding. Patients were informed that their participation was voluntary, and all gave informed consent.

Outcomes

The primary outcome was the occurrence of complete titration of sacubitril/valsartan (97/103 mg twice daily) during follow-up. Secondary outcomes were (i) patient-reported symptoms of hypotension (defined as dizziness, weakness, or syncope with systolic BP lower than 90 mmHg) and (ii) renal adverse events [potassium levels greater than 5.5 meq/L or any drop of estimated glomerular filtration rate (eGFR) more than 50%].

Table 3 Multivariate logistic regression for predictors of primary outcome

Variable	OR (95% CI)	*P*-value
Age (years)	0.94 (10.88–1.01)	0.075
Serum sodium (mg/mL)	1.18 (1.02–1.37)	**0.022**
eGFR (mL/min/1.72 m^2)	1.03 (0.99–1.06)	0.14
Haemoglobin (g/dL)	1.73 (1.25–2.40)	**0.001**
NYHA Class III	0.45 (0.14–1.45)	0.18
Paced rhythm at baseline ECG	0.41 (0.11–1.48)	0.17
Ejection fraction (1-point %)	1.04 (0.94–1.16)	0.47
SVi (per 5 mL/m^2)	1.43 (1.03–1.97)	**0.028**

CI, confidence interval; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; OR, odds ratio; SVi, stroke volume index. *P*-values < 0.05 are reported in bold.

Table 2 Univariate logistic regression for predictors of primary outcome

Variable	OR (95% CI)	*P*-value
Patients, no.	106	
Age, years	0.95 (0.91–0.99)	**0.019**
Male sex, no. (%)	1.03 (0.38–2.82)	0.95
CV risk factors		
Hypertension	1.31 (0.46–3.71)	0.61
Diabetes	1.14 (0.51–2.56)	0.75
Physical features		
Systolic BP (mmHg)	1.01 (0.98–1.04)	0.41
Diastolic BP (mmHg)	1.03 (0.99–1.08)	0.16
Pulse pressure (mmHg)	1.00 (0.96–1.04)	0.91
Heart rate (b.p.m.)	0.98 (0.94–1.02)	0.25
BMI (kg/m^2)	0.99 (0.96–1.02)	0.49
Aetiology of HF		
Ischaemic aetiology	0.75 (0.32–1.80)	0.53
Baseline laboratory analysis		
Serum sodium (mg/mL)	1.12 (0.99–1.28)	0.081
Serum potassium (mg/mL)	0.64 (0.30–1.35)	0.24
eGFR (mL/min/1.72 m^2)	1.02 (1.00–1.05)	**0.036**
Haemoglobin (g/dL)	1.62 (1.22–2.16)	**0.001**
BNP (pg/mL)	0.71 (0.46–1.11)	0.14
NYHA Class III	0.46 (0.20–1.06)	0.069
Atrial fibrillation/flutter at baseline ECG	1.72 (0.69–4.27)	0.244
Paced rhythm at baseline ECG	0.42 (0.17–1.01)	**0.053**
Echocardiogram		
LVEDVi (mL/m^2)	1.01 (1.00–1.02)	0.25
Ejection fraction (%)	1.07 (1.00–1.15)	0.051
SV (per 5 mL)	1.15 (1.01–1.31)	**0.025**
SVi (per 5 mL/m^2)	1.38 (1.05–1.81)	**0.018**
Cardiac index (mL/min/m^2)	1.00 (1.00–1.00)	0.13
Flow rate (mL/min)	1.01 (1.00–1.01)	0.11
PAPs (mmHg)	0.97 (0.92–1.03)	0.33
Diastolic dysfunction (Grade III)	1.05 (0.42–2.63)	0.92
Loop diuretics preventive reduction	1.54 (0.65–3.64)	0.33

BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CI, confidence interval; CV, cardiovascular; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEDVi, left ventricular end-diastolic volume index; NYHA, New York Heart Association; OR, odds ratio; PAPs, pulmonary artery pressures; SV, stroke volume; SVi, stroke volume index. *P*-values < 0.05 are reported in bold.

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Echocardiographic examination

A comprehensive echocardiographic examination was performed using a GE Vivid S60 echocardiographic scanner (GE Healthcare, Milwaukee, WI, USA) equipped with a 3.5 MHz transducer. One expert physician performed all echocardiographic measures. Cardiac chamber dimension, left ventricular filling pressure and stroke volume, were calculated following the guidelines of American Society of Echocardiography and European Association of Cardiovascular Imaging.[9–11] Among LVOIs we focused on stroke volume index (SVi), cardiac index, and flow rate.

Statistical analysis

Baseline characteristics were summarized as means and standard deviations, medians, and interquartile ranges, or percentages. The effect of baseline characteristic on the occurrence of the primary endpoint was estimated using univariate logistic regression. Clinically relevant variables with *P*-value < 0.10 were added to the multivariate regression model. Furthermore, patients were divided by SVi tertiles, and the occurrence of primary and secondary outcomes was analysed accordingly. All the analyses were conducted using STATA Version 16.1 (College Station, TX, USA).

Results

Patients' characteristics

Patients' characteristics are reported in *Table 1*. The final study population consisted of 106 patients with a mean age of 73.7 ± 10.4 years. Seventy-two patients (71.7%) had ischaemic aetiology of HF with a mean ejection fraction of 29.4 ± 5.9%. The median visit number was two (interquartile range 2–3), and 93.4% of patients achieved stable dose of sacubitril/valsartan within four visits.

Primary outcome

The baseline characteristics of patients according to the occurrence of primary endpoint are shown in *Table 1*. At the univariate analysis, SV [odds ratio (OR) 1.15 per 5 mL increase, 95% confidence interval (CI) 1.01–1.31; *P* = 0.025], SVi (OR 1.38 per 5 mL/m^2 increase, 95% CI 1.05–1.81; *P* = 0.018), left ventricular ejection fraction (OR 1.07, 95%

Figure 2 Primary outcome according to SVi tertiles. SVi, stroke volume index.

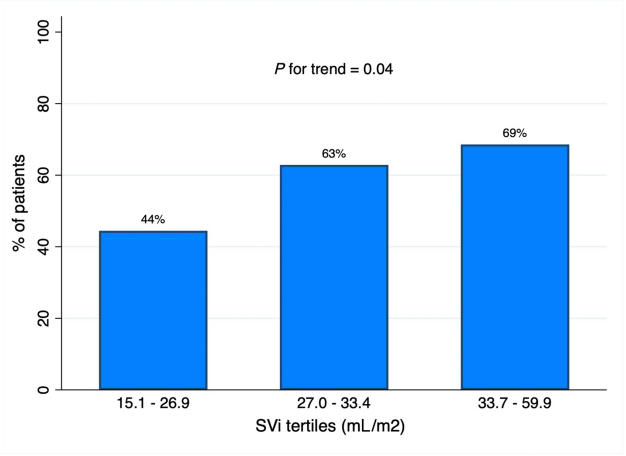
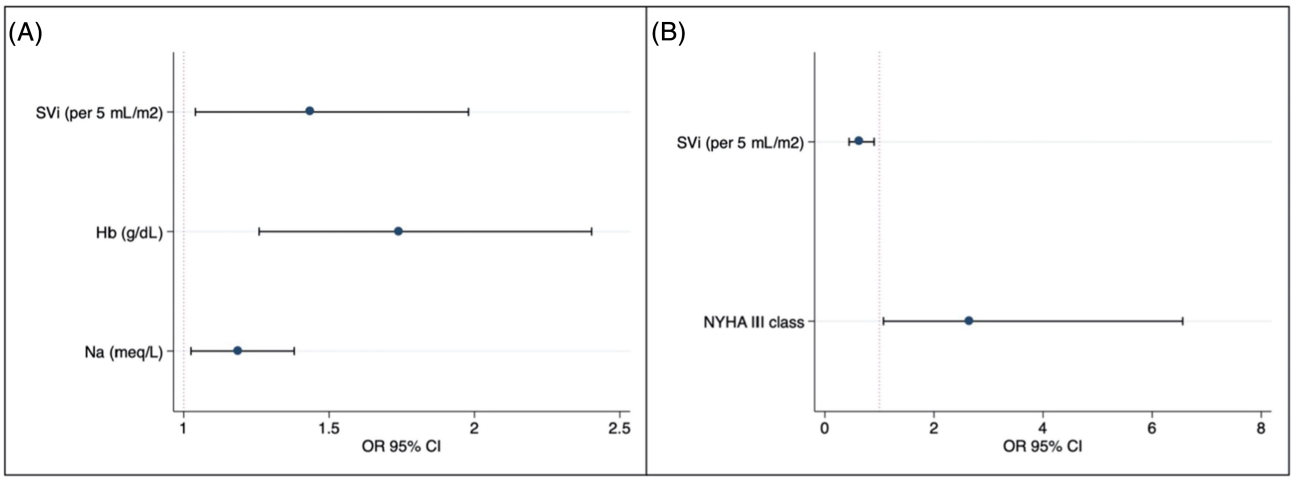


Figure 1 Odds ratio for primary outcome and hypotension at multivariate logistic regression. (A) Sacubitril/valsartan complete titration. (B) Occurrence of hypotension. CI, confidence interval; Hb, haemoglobin; NYHA, New York Heart Association; OR, odds ratio; SVi, stroke volume index.



CI 0.99–1.14; P = 0.051), eGFR (OR 1.02, 95% CI 1.00–1.05; P = 0.036), haemoglobin (OR 1.62, 95% CI 1.22–2.16; P = 0.001), and age (OR 0.95, 95% CI 0.91–0.99; P = 0.019) were predictors of complete titration (*Table 2*). At the multivariate analysis, SVi (OR 1.43 per 5 mL/m^2 increase, 95% CI 1.03–1.97; P = 0.028), haemoglobin level (OR 1.73, 95% CI 1.25–2.40; P = 0.001), and baseline serum sodium (OR 1.18, 95% CI 1.02–1.37; P = 0.022) remained independent predictors of outcome (*Table 3*; *Figure 1A*). We further analysed the occurrence of the primary outcome according to tertiles of SVi. The first SVi tertile ranged from 15.13 to 26.9 mL/m^2, the second tertile from 27.00 to 33.4 mL/m^2, and the third tertile from 33.7 to 59.9 mL/m^2. The primary outcome occurred in 16 (44.4%) patients in the first tertile, 22 (62.9%) in the second tertile, and 24 (68.6%) in the third tertile (*Figure 2*), P-value for trend = 0.04.

Secondary outcome

Forty (37.7%) patients experienced at least one adverse event. Twenty-six patients (25.2%) experienced symptomatic hypotension, 16 (17.5%) experienced an acute decrease of eGFR, and 18 (17.5%) experienced hyperkalaemia (*Table 4*). In a multivariate logistic regression model, SVi (OR 0.63 per 5 mL/m^2 increase, 95% CI 0.44–0.90; P = 0.012) and New York

Table 4 Secondary endpoints according to tertiles of stroke volume index

Adverse events *N* (%)	Overall	First tertile (n = 36)	Second tertile (n = 35)	Third tertile (n = 35)	P-value
Symptomatic hypotension	26 (25.2)	14 (39.9)	5 (14.3)	7 (20.0)	**0.041**
Acute decrease of eGFR	16 (17.5)	6 (16.7)	6 (17.1)	4 (11.4)	0.76
Hyperkalaemia	18 (17.5)	7 (19.4)	7 (20.4)	4 (11.4)	0.56

eGFR, estimated glomerular filtration rate.
Adverse events were reported as numbers and percentage. P-values < 0.05 are reported in bold.

Table 5 Univariate and multivariate analysis of predictor of symptomatic hypotension

Variable	Univariate analysis OR (95% CI), P-value	Multivariate analysis OR (95% CI), P-value
Patients, no.	106	
Age, years	1.02 (0.98–1.07), P = 0.33	—
Male sex, no. (%)	1.92 (0.51–7.19), P = 0.34	—
CV risk factors		
Hypertension	0.74 (0.23–2.35), P = 0.61	—
Diabetes	0.74 (0.29–1.91), P = 0.54	—
Physical features		
Systolic BP (mmHg)	0.99 (0.96–1.02), P = 0.36	—
Diastolic BP (mmHg)	0.96 (0.91–1.02), P = 0.16	—
Pulse pressure (mmHg)	1.00 (0.96–1.04), P = 0.96	—
Heart rate (b.p.m.)	1.00 (0.96–1.04), P = 0.84	—
BMI (kg/m^2)	1.02 (0.99–1.05), P = 0.29	—
Aetiology of HF		
Ischaemic aetiology	1.10 (0.41–2.96), P = 0.86	—
Baseline laboratory analysis		
Serum sodium (mg/mL)	0.90 (0.79–1.04), P = 0.15	—
Serum potassium (mg/mL)	1.26 (0.56–2.84), P = 0.58	—
eGFR (mL/min/1.72 m^2)	0.99 (0.97–1.02), P = 0.61	—
Haemoglobin (g/dL)	0.78 (0.59–1.04), P = 0.096	0.80 (0.59–1.09), P = 0.15
lnBNP (pg/mL)	1.02 (0.63–1.65), P = 0.93	—
NYHA Class III	3.00 (1.20–7.53), **P = 0.019**	2.65 (1.07–6.5), **P = 0.034**
Atrial fibrillation/flutter at baseline ECG	0.42 (0.13–1.36), P = 0.15	—
Paced rhythm at baseline ECG	1.70 (0.65–4.43), P = 0.28	—
Echocardiogram		
LVEDVi (mL/m^2)	1.01 (1.00–1.02), P = 0.28	—
Ejection fraction (%)	0.89 (0.83–0.97), **P = 0.005**	0.92 (0.85–1.00), P = 0.053
SVi (per 5 mL/m^2)	0.65 (0.46–0.91), **P = 0.012**	0.63 (0.44–0.90), **P = 0.012**
Cardiac index (mL/min/m^2)	1.00 (1.00–1.00), **P = 0.033**	—
Flow rate (mL/min)	0.99 (0.98–1.00), **P = 0.021**	—
PAPs (mmHg)	0.96 (0.90–1.03), P = 0.24	—
Diastolic dysfunction (Grade III)	0.86 (0.30–2.51), P = 0.79	—
Loop diuretics preventive reduction	1.24 (0.48–3.19), P = 0.65	—

BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CI, confidence interval; CV, cardiovascular; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEDVi, left ventricular end-diastolic volume index; NYHA, New York Heart Association; OR, odds ratio; PAPs, pulmonary artery pressures; SVi, stroke volume index. P-values < 0.05 are reported in bold.

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Heart Association Class III (OR 2.65, 95% CI 1.07–6.5; $P = 0.034$) were independent predictors of symptomatic hypotension (*Table 5*; *Figure 1B*). None of the LVOIs was a predictor of renal outcomes at univariate analysis.

Conclusions

Our study tested the hypothesis that LVOIs could predict sacubitril/valsartan complete titration and tolerability. Among LVOIs, SV and SVi were the only positively associated with complete titration of sacubitril/valsartan. These findings are consistent with a recent paper showing that SVi is the best comprehensive parameter of LVO.[12] Furthermore, SVi was inversely related to the occurrence of symptomatic hypotension. Arterial BP is generated by the interaction of LVO, peripheral resistance, and great vessel elastance. HFrEF patients usually have low LVO and increased peripheral resistance, mediated by neurohormonal response. This neurohormonal response is accountable for restoring a 'normal' BP even in a low cardiac output state. The treatment with sacubitril/valsartan, exerting many vasodilatory effects, could unmask the low output state reducing peripheral resistance and precipitating symptoms of hypotension in those with very low SVi and BP. In contrast with previous reports, systolic BP, age, and eGFR did not predict a successful drug titration in our cohort at multivariate analysis. Alongside with SVi, baseline haemoglobin level independently predicted titration. Haemoglobin level has well-known prognostic implication in HFrEF but, except for Pharithi *et al*.,[13] there are no studies highlighting its association with sacubitril/valsartan titration. In this study, however, the association was not confirmed after correction for other covariates. Finally, consistent with previous findings from Dashwood *et al*., also, baseline sodium level resulted to be an independent predictor of outcome at our multivariate analysis (*Table 2*).[14] This finding highlights the importance of reassessing and eventually adapting diuretic therapy while starting treatment with sacubitril/valsartan, to avoid hypovolaemia. The main finding of this analysis is that patients with low SVi are more prone to develop symptomatic hypotension while treated with sacubitril/valsartan. This should not be perceived as a deterrent to initiate and titrate sacubitril/valsartan therapy but should instead encourage physicians to correct modifiable factors in patients that struggle to tolerate the treatment.

We identified some limitations in our study. This was a monocentric study based on echocardiographic examinations performed at our institution. The echocardiographic examinations were not dedicated to our aim (despite performed by a standardized protocol and expert cardiologists), and some patients were excluded because of inadequate image quality or lacking pulsed-wave sampling at left ventricular outflow tract. Moreover, we supposed that in patients with low SVi, an increase in peripheral resistance is responsible for normal BP. *In vivo* assessment of peripheral resistance could support our findings but, unfortunately, we did not use this evaluation in our clinical routine.

Conflict of interest

The authors have nothing to declare.

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