

Predictors of sacubitril/valsartan high dose tolerability in a real world population with HFrEF

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Abstract

Aims The angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan (Sac/Val) demonstrated to be superior to enalapril in reducing hospitalizations, cardiovascular and all-cause mortality in patients with ambulatory heart failure and reduced ejection fraction (HFrEF), in particular when it is maximally up-titrated. Unfortunately, the target dose is achieved in less than 50% of HFrEF patients, thus undermining the beneficial effects on the outcomes. In this study, we aimed to evaluate the role of Sac/Val and its titration dose on reverse cardiac remodelling and determine which echocardiographic index best predicts the up-titration success.

Methods and results From January 2020 to June 2021, we retrospectively identified 95 patients (65.6 [59.1–72.8] years; 15.8% females) with chronic HFrEF who were prescribed Sac/Val from the HF Clinics of 5 Italian University Hospitals and evaluated the tolerability of Sac/Val high dose (the ability of the patient to achieve and stably tolerate the maximum dose) as the primary endpoint in the cohort. We used a multivariable logistic regression analysis, with a stepwise backward selection method, to determine the independent predictors of Sac/Val maximum dose tolerability, using, as candidate predictors, only variables with a *P*-value < 0.1 in the univariate analyses. Candidate predictors identified for the multivariable backward logistic regression analysis were age, sex, body mass index (BMI), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), dyslipidaemia, atrial fibrillation, systolic blood pressure (SBP), baseline tolerability of ACEi/ARBs maximum dose, left ventricle global longitudinal strain (LVGLS), LV ejection fraction (EF), tricuspid annulus plane systolic excursion (TAPSE), right ventricle (RV) fractional area change (FAC), RV global and free wall longitudinal strain (RVGLS and RV-FW-LS). After the multivariable analysis, only one categorical (ACEi/ARBs maximum dose at baseline) and three continuous (younger age, higher SBP, and higher TAPSE), resulted significantly associated with the study outcome variable with a strong discriminatory capacity (area under the curve 0.874, 95% confidence interval (CI) (0.794–0.954) to predict maximum Sac/Val dose tolerability.

Conclusions Our study is the first to analyse the potential role of echocardiography and, in particular, of RV dysfunction, measured by TAPSE, in predicting Sac/Val maximum dose tolerability. Therefore, patients with RV dysfunction (baseline TAPSE <16 mm, in our cohort) might benefit from a different strategy to titrate Sac/Val, such as starting from the lowest dose and/or waiting for a more extended period of observation before attempting with the higher doses.

Keywords Heart failure; ARNI; Neprilysin inhibitors; Right ventricular function; Sacubitril valsartan

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Introduction

In the PARADIGM-HF trial, the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan (Sac/Val) was demonstrated to be superior to enalapril in reducing hospitalizations for worsening heart failure (HF), cardiovascular mortality, and all-cause mortality in patients with ambulatory heart failure and reduced ejection fraction (HFrEF).¹ Because the PARADIGM-HF trial required dose titration up to a target dose (97/103 mg) before randomization, little evidence is available regarding low (24/26 mg) and middle (49/51 mg) doses in a real-world setting. It has been recently shown that the 97/103 or 49/51 mg dose is associated with lower mortality or hospitalization rate for HF in patients receiving Sac/Val compared with the 24/26 mg dose group.² In addition, in a post hoc analysis of the PARADIGM-HF trial, patients who had a reduction to the low or middle dose of Sac/Val showed a significantly higher risk of cardiovascular death or re-hospitalization for HF, when compared with those who maintained the target dose.³ Unfortunately, the target dose is currently achieved in less than 50% of HFrEF patients.^{4,5} Therefore, it be helpful to identify variables able to predict which patients are likely to reach maximal up-titration. To date, some clinical variables, such as blood pressure, renal function, and patients' volume status, can predict the tolerability of high dose Sac/Val.^{6,7} Other than clinical variables, some echocardiographic parameters may be associated with Sac/Val target dose achievement. Indeed, recent studies have shown that the beneficial effects of Sac/Val are related to its ability to promote reverse remodelling and improve exercise tolerance, cardiopulmonary functional capacity and autonomic function.^{8–10}

The present study aims to evaluate the role of Sac/Val and its titration dose on cardiac reverse remodelling and determine which echocardiographic index best predicts the up-titration success.

Methods

From January 2020 to June 2021, we retrospectively selected patients with chronic HFrEF. They were prescribed with Sac/Val, according to the European Society of Cardiology guidelines¹¹ from the HF Clinics of 5 Italian University Hospitals (University Hospital of Salerno, Riuniti Hospital of Foggia, Monaldi Hospital and Federico II University of Naples, and University of Messina). Informed consent was obtained from all participants.

Exclusion criteria for the current study included (i) concomitant initiation of a therapy known to induce reverse remodelling (e.g. Cardiac Resynchronization Therapy [CRT]) during the study follow-up or in the previous 6 months; (ii) echocardiographic images of low quality that do not allow

for reliable offline assessment; (iii) any change of home medications in the 2 weeks before Sac/Val initiation and any change of other neurohormonal blockers (e.g. beta-blockers and mineral-corticoid receptor antagonists) doses during the follow-up. From clinical records, we collected data on demographics (age and gender), medical history (presence of co-morbidities and HF aetiology), ongoing treatments with other medications, clinical characteristics (blood pressure-BP, heart rate-HR, NYHA functional class), and echocardiographic results, immediately before starting Sac/Val treatment (baseline) and after 6 months from dose optimization, with doses being up-titrated every 2 weeks after initiation. We selected only patients where Sac/Val up-titration was attempted to avoid therapeutic inertia, even for a limited period.

The presence of chronic kidney disease (CKD) was defined by a glomerular filtration rate of less than 60 mL/min per 1.73 m² (using the last serum creatinine value available at the time of enrolment). The ischaemic aetiology of the HF syndrome was defined as a previous history of myocardial infarction and/or prior revascularization through percutaneous and/or surgical procedures.

Patients had no history of malignancy and/or severe renal/hepatic impairment. According to the above criteria, we identified 95 patients with HFrEF.

All investigations were carried out according to the principles of the Helsinki Declaration. For this study, the primary endpoint was tolerability of Sac/Val high dose in the cohort, defined as the ability of the patient to achieve and stably tolerate the maximum dose during the follow-up. Concerning our primary endpoint, the study cohort has been divided into two groups: patients who reached the maximum dose versus patients who did not. Our secondary outcome was a measure of patients' response to Sac/Val, defined by the occurrence of the left ventricle (LV) reverse remodelling within 6 months.

According to previous studies,^{12–14} we considered LV reverse remodelling as an improvement of LV ejection fraction (EF) to 45% or a reduction in LV end-systolic volume (ESV) of 15% from baseline. About the occurrence of LV reverse remodelling, we classified our study population into two main groups (responders vs. not responders).

Echocardiographic measurements

Echocardiographic examinations were performed with a 3.5 MHz monoplane ultrasound probe of Vivid E-9 (GE-Vingmed Ultrasound, Horten, Norway), according to international guidelines.¹⁵ All parameters were analysed offline by two expert operators blinded to clinical data. Left ventricular ejection fraction (LVEF) was calculated by the Simpson biplane method according to the following formula: LVEF = [left ventricular end-diastolic volume

(LVEDV)-LV end-systolic volume (LVESV)]/LVEDV \times 100 as mean of two measures in four and two apical chambers. Mitral E and A velocities, E/A ratio, tissue Doppler analysis of mitral annular E' velocity, and mitral E/e' ratio were measured. Additionally, the diameter of the inferior vena cava and its respiratory variation was measured in the subcostal view and used to estimate right atrial pressure. Peak systolic pulmonary artery pressure (sPAP) was estimated by adding right atrial pressure to the systolic tricuspid regurgitation gradient.

Right ventricular (RV) systolic parameters were also estimated, assessed by calculating the tricuspid annulus plane systolic excursion (TAPSE)¹⁶ and the RV fractional area change (FAC), calculated as (RV end-diastolic area – end-systolic area)/RV end-diastolic area \times 100.¹⁵ Tricuspid annular S' velocity (RVs') was measured using pulsed-wave tissue Doppler.¹⁶

RV function was assessed using an off-axis apical 4-chamber view for better visualization of RV.

LV and RV strain analyses were also performed with 2D strain software EchoPAC (GE Healthcare) using high frame rate acquisitions (>40 frames per second) of the apical four-chamber, two-chamber and long-axis view for the LV global longitudinal strain (LVgLS), and the off-axis apical 4-chamber view both for the RV free wall (RV-FW-LS) and for RV global longitudinal strain (RVgLS), as outlined in consensus documents.^{17,18}

Statistical analysis

Continuous variables were expressed as median (interquartile range [IQR]) and compared using the Student's *t*-test (for normally distributed variables) or Wilcoxon–Mann–Whitney test (for non-normally distributed variables). Normality was checked with the Kolmogorov–Smirnov and the Shapiro–Wilk statistic. When appropriate, categorical data were summarized as percentage and compared using χ^2 test or Fisher's exact test. Paired samples *t*-test was performed to assess changes in continuous echocardiographic data between baseline and 6 months follow-up. Using a stepwise backward selection method, a multivariable logistic regression analysis was employed to determine the independent predictors of Sac/Val maximum dose tolerability, using covariates with a *P*-value <0.1 in the univariate analyses. Based on clinical judgement, we forced gender and the presence of CKD in the model. To assess the presence of multicollinearity, the variance inflation factor (VIF) was determined, and a value between 5 and 10 was considered indicative of multicollinearity.¹⁹ Baseline TAPSE and RVs' were highly correlated, and we chose to analyse only the TAPSE contribution in the final model, being the most routinely used parameter to describe RV function. We assessed linearity for continuous covariates

concerning log odds of our primary outcome. We verified that the final model was a good fit by using the Hosmer–Lemeshow test and the C-statistic. Rates of missing values among candidate variables were <4%: TAPSE, RVgLS, and RV-FW-LS: 3.2%, and LVgLS: 2.1%. No imputation has been realized in our study.

Due to the small sample size, to reduce the risk of overfitting, we performed an internal validation by bootstrapping 1000 samples of the original study group, as previously described.²⁰ As estimated in the bootstrap sample, the model was evaluated in both the bootstrap sample and the original one. The performance in the bootstrap sample represents an estimation of the apparent performance, and the performance in the original sample represents test performance. The difference between these performances is an estimation of the optimism in the apparent performance. This difference was averaged to obtain a stable estimate of the optimism.

To give a potential role in clinical practice to our final logistic regression model, each continuous predictor variable was converted to a categorical variable based on values above or below the optimal cutoff for each variable, defined as the highest value of Youden's J index (sensitivity + specificity – 1) on receiver-operator characteristic (ROC) curve analysis for that variable in the cohort.²¹ These categorical variables were then re-entered into a multivariable logistic regression model to determine their relative contribution to the final model results. For all tests, a *P* value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 23.0 (SPSS Inc., Chicago, Illinois) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The baseline characteristics of the study population are reported in *Table 1*. The median age was 65.6 years [59.1–72.8], and most patients were males (80, 84.2%). Hypertension was reported in 82.1% of cases, dyslipidaemia in 66.3%, and ischaemic aetiology of HF in 40%. At the time of recruitment, almost all of the patients were in NYHA class II (58%) or III (41%). Non-cardiovascular co-morbidities were significantly detected, with chronic obstructive pulmonary disease (COPD) in 25.3% of patients, and CKD in 44.2%.

Furosemide was prescribed in almost 78% of cases (at a mean dose of 53.2 \pm 73.2 mg), mineralocorticoid receptor antagonist (MRA) in 75%, beta-blockers in 98%, and ivabradine in 9.5%.

At 6 months from dose optimization of Sac/Val, 37.9% of the population was taking the highest dose of Sac/Val, 27.4% the intermediate dose and 34.7% the lowest dose.

Table 1 Baseline characteristics of study population ($n = 95$)

Clinical variables	
Age, years	65.6 [59.1–72.8]
Female, N (%)	15 (15.8)
BMI, kg/m^2	27 [24.5–30.8]
BSA, m^2	1.86 [1.76–2]
SBP, mmHg	115 [110–130]
DBP, mmHg	70 [60–80]
HR, b.p.m.	68 [61–78]
Hypertension, N (%)	78 (82.1)
Dyslipidaemia, N (%)	63 (66.3)
Diabetes, N (%)	35 (36.8)
Ischaemic aetiology, N (%)	38 (40)
Smoking, N (%)	17 (17.9)
ICD, N (%)	38 (40)
CRT-D, N (%)	18 (18.9)
CKD, N (%)	42 (44.2)
Atrial fibrillation, N (%)	40 (42.1)
COPD, N (%)	24 (25.3)
Obesity, N (%)	30 (31.6)
NYHA II, N (%)	55 (57.9)
NYHA III, N (%)	39 (41)
Pharmacological treatment	
Beta-blockers, N (%)	93 (97.9)
MRA, N (%)	71 (74.7)
Furosemide, N (%)	74 (77.9)
Patients on maximum dose of ACEi/ARBs, N (%)	36 (37.9)
Ivabradine, N (%)	9 (9.5)

BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy defibrillator; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; MRA, mineralocorticoid receptor antagonist; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

The main reasons for failure to tolerate the highest Sac/Val dose were: symptomatic hypotension (39 patients, 41%); impairment of renal function (decline in estimated

glomerular filtration rate (eGFR) of 30% or greater; 6 patients, 6.3%); gastrointestinal symptoms (12 patients, 12.6%); and others (2 patients, 2.1%).

Effects of Sac/Val on clinical and echocardiographic parameters at follow-up

The main variation of clinical, haemodynamic, and echocardiographic parameters at follow-up are reported, in *Figures 1, 2*, and *Table 2*, respectively. A significant reduction of both systolic (SBP) and diastolic blood pressure (DBP) at follow-up was observed (*Figure 1A,B*), together with a trend in HR reduction (*Figure 1C*). Conversely, a significant improvement in NYHA functional class was reported (NYHA II: from 58% to 74%; NYHA III: from 41% to 14%; *Figure 2*); notably, 11 patients (12%) showed NYHA class I, at follow-up (*Figure 2*).

After 6 months, both LV and RV function significantly improved (*Table 2*): LVEF significantly increased from 28.8% [22.2–33] to 35% [29–40]; ($P < 0.001$). LVESV significantly decreased from 135 mL [108–180] to 114 mL [83–166] ($P < 0.001$), and sPAP decreased from 35 mmHg [28.7–48.5] to 31.5 mmHg [23–42.2] ($P < 0.001$). Moreover, both LV and RV strain analysis showed a significant improvement (LVgLS from -7.4% [-9.8 ; -5.6] to -9.15% [-12.5 ; -7.1], $P < 0.001$; RVgLS from -13.3% [-17.1 ; -8.9] to -15.6% [-19 ; -11.5], $P < 0.001$; RV-FW-LS from -17.7% [-21.3 ; -12.7] to -20% [-23.5 ; -15.2], $P < 0.001$).

In patients who achieved the maximum dose of Sac/Val, we observed some differences in baseline clinical and haemodynamic parameters (*Table 3*) and in the magnitude of improvement of some LV and RV echocardiographic parameters (*Table 4*). Patients who tolerated the maximum dose of Sac/Val also showed a positive trend in term of LV

Figure 1 Reduction of SBP (A, $P = 0.001$), DBP (B, $P = 0.008$) and HR (C, $P = 0.09$) at follow-up. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

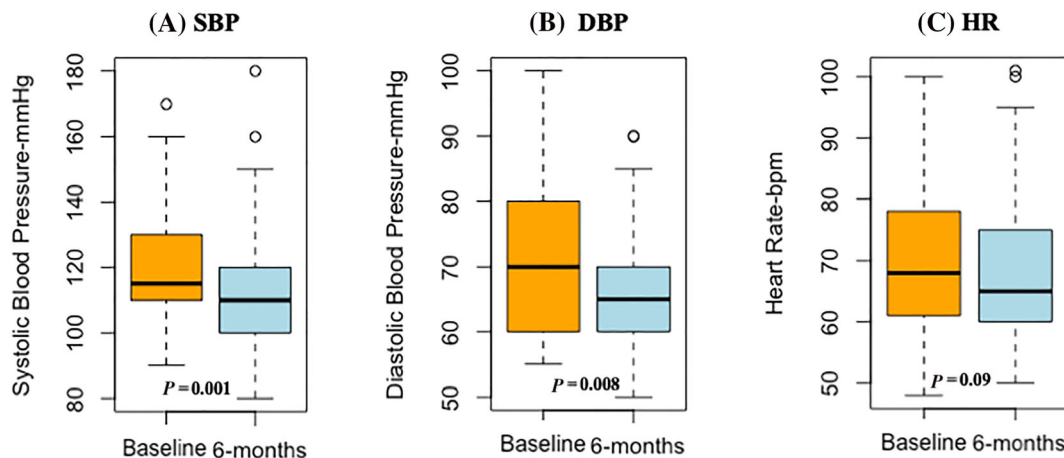
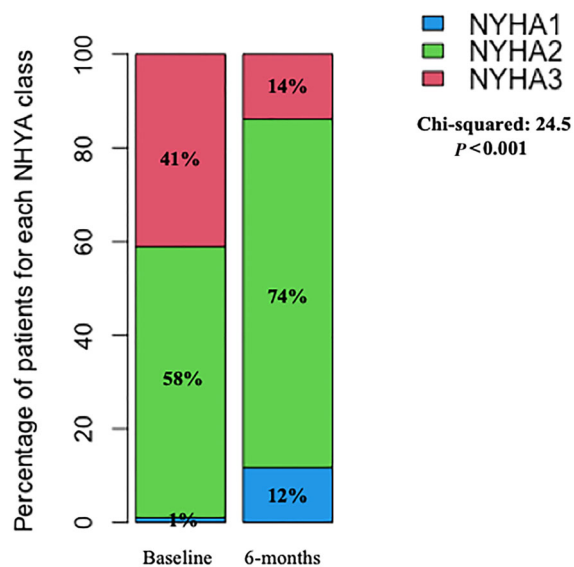


Figure 2 Changes of NYHA class from baseline to 6 months in patients treated with Sac/Val ($P < 0.001$). NYHA, New York Heart Association.

Bar graphs showing the changes of NYHA class from baseline to 6 months in patients treated with Sacubitril/Valsartan



reverse remodelling (Figure 3), and of a NYHA class <3 at follow-up (Supporting Information, Figure S1).

Determinants of the maximum dose tolerability: univariate and multivariable analysis

Univariable regression analysis between baseline characteristics and the primary outcome variable is shown in the Supporting Information, Table S1.

Candidate predictors for the multivariable backward logistic regression analysis were selected as outlined in the Methods section. When we entered the following variables: age, sex, body mass index-BMI, CKD, COPD, dyslipidaemia, atrial fibrillation, SBP, baseline tolerability of ACEi/ARBs maximum dose, LVgLS, LVEF, TAPSE, FAC, RVgLS, and RV-FW-LS in the multivariable model, only one categorical (ACEi/ARBs maximum dose at baseline), and three continuous (younger age, higher SBP, and higher TAPSE) resulted significantly associated with the study outcome variable (Supporting Information, Table S2). The final regression model demonstrated a strong discriminatory capacity [area under the curve 0.874, 95% confidence interval (CI) 0.794–0.954]. Differences between observed and expected probabilities were small, indicating good calibration ($P = 0.695$, using the Hosmer–Lemeshow statistic). After adjustment for optimism, our final risk prediction model was able to discriminate patients achieving the highest dose of Sac/Val from those unable to tolerate the target dose, with a consistent C statistics of 0.853. The three continuous variables associated with the primary study endpoint in the final model were converted into categorical ones, as outlined in the Methods section, and re-entered in a binary logistic regression model, to show the contribution of each term in the determination of the primary outcome (Table 5).

Discussion

This study shows that the PARADIGM-HF target dose of Sac/Val is achieved in about 38% of HFrEF patients during the 6 month follow-up. Compared with patients enrolled in the PARADIGM-HF trial,¹ our patients demonstrated a similar age and prevalence of co-morbidities, but higher rankings on the NYHA classification and higher rates of implanted cardiac devices (albeit similar values of LVEF). Moreover, patients of

Table 2 Changes in echocardiography 6 months after initiation of Sac/Val treatment ($n = 95$)

	Baseline	6 months	<i>P</i>
LVEDV, mL	186 [158–233]	172 [142–227]	<0.001
LVESV, mL	135 [108–180]	114 [83–166]	<0.001
LVEF, %	28.8 [22.2–33]	35 [29–40]	<0.001
LVgLS, %	−7.4 [−9.8; −5.6]	−9.15 [−12.5; −7.1]	<0.001
E/ <i>e</i> ' ratio	14 [11–19]	12 [8–16]	<0.001
Basal RVD, mm	38 [34–44.7]	37 [34–43]	0.001
RVgLS, %	−13.3 [−17.1; −8.9]	−15.6 [−19; −11.5]	<0.001
RV-FW-LS, %	−17.7 [−21.3; −12.7]	−20 [−23.5; −15.2]	<0.001
FAC, %	35 [30–42]	39 [34–46]	<0.001
TAPSE, mm	18 [15–20]	18.5 [17–22]	<0.001
RV <i>s</i> ', cm/s	10.4 [8.8–12]	11 [9–14]	<0.001
sPAP, mmHg	35 [28.7–48.5]	31.5 [23–42.2]	<0.001

LVEDV, left ventricle end-diastolic volume; LVESV, left ventricle end-systolic volume; LVEF, left ventricular ejection fraction; LVgLS, left ventricular global longitudinal strain; E, early-wave transmitral diastolic velocity; *e*'_r, early-diastolic velocity at tissue Doppler imaging; RVD, right ventricle diameter; RVgLS, right ventricular global longitudinal strain; RV-FW-LS, right ventricular free wall longitudinal strain; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; RV*s*'_r, tricuspid annular *S*'_r velocity; sPAP, pulmonary artery systolic pressure. We have reported in bold the statistically significant *P*-value.

Table 3 Baseline clinical and haemodynamic characteristics in relation to the Sac/Val dosage

	Maximum dose not reached, <i>n</i> = 59	Maximum dose reached, <i>n</i> = 36	<i>P</i>
Age, years	69.4 [62.5–74.5]	59.7 [49.3–66.4]	0.002
Female, <i>N</i> (%)	10 (16.9)	5 (13.9)	0.69
BMI, kg/m ²	27.5 [25.1–30.8]	25.5 [23–28.8]	0.07
SBP, mmHg	110 [110–120]	122.5 [110–133.7]	0.047
DBP, mmHg	65 [60–70]	72.5 [62.5–80]	0.016
HR, b.p.m.	70 [61–80]	66.5 [61.2–75]	0.89
Hypertension, <i>N</i> (%)	50 (84.7)	28 (77.8)	0.39
Dyslipidaemia, <i>N</i> (%)	43 (72.9)	20 (55.6)	0.08
Diabetes, <i>N</i> (%)	22 (37.3)	13 (36.1)	0.91
Ischaemic aetiology, <i>N</i> (%)	26 (44.1)	12 (33.3)	0.3
Smoking, <i>N</i> (%)	10 (16.9)	7 (19.4)	0.9
ICD, <i>N</i> (%)	21 (35.6)	17 (47.2)	0.75
CRT-D, <i>N</i> (%)	13 (22)	5 (13.9)	
CKD, <i>N</i> (%)	28 (47.5)	14 (38.9)	0.41
Atrial fibrillation, <i>N</i> (%)	32 (54.2)	8 (22.2)	0.009
COPD, <i>N</i> (%)	19 (32.2)	5 (13.9)	0.046
Obesity, <i>N</i> (%)	19 (32.2)	11 (30.6)	0.87
NYHA II, <i>N</i> (%)	34 (57.6)	21 (58.3)	0.73
NYHA III, <i>N</i> (%)	24 (40.7)	15 (41.7)	

BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy defibrillator; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association. We have reported in bold the statistically significant *P*-value.

Table 4 Change in echocardiographic parameters at 6 months, in relation to the Sac/Val dosage

Δ -Change in echocardiography ^a	Maximum dose not reached, <i>n</i> = 59	Maximum dose reached, <i>n</i> = 36	<i>P</i>
Δ LVEDV, mL	−9 [−32.6; 11]	−20 [−32; −5]	0.054
Δ LVESV, mL	−15.6 [−38; −6]	−25.5 [−33.7; −13.5]	0.037
Δ LVgLS, %	−1.5 [−2.9; −0.6]	−2 [−2.7; −1.1]	0.2
Δ LVEF, %	5 [3–9.4]	7.75 [5.25–11]	0.032
Δ E/ <i>e</i> ' ratio	−2 [−4; 0]	−2.4 [−5; −1.1]	0.13
Δ Basal RVD, mm	−2 [−3; 0.5]	−1 [−3; 0]	0.72
Δ RVgLS, %	−1 [−3.6; −0.27]	−1.9 [−2.9; −0.95]	0.52
Δ RV-FW-LS, %	−1 [−4.6; −0.07]	−2 [−3.4; −0.5]	0.22
Δ FAC, %	4 [2–5]	4.75 [2–6]	0.27
Δ TAPSE, mm	1 [0.5–2.5]	2 [1–3]	0.2
Δ RVs', cm/s	1 [0.35–2]	1.5 [1–3]	0.05
Δ sPAP, mmHg	−5 [−13.5; 1.25]	−5 [−10; 0]	0.57

LVEDV, left ventricle end-diastolic volume; LVESV, left ventricle end-systolic volume; LVgLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; E, early-wave transmitral diastolic velocity; *e*'_r, early-diastolic velocity at tissue Doppler imaging; RVD, right ventricle diameter; RVgLS, right ventricular global longitudinal strain; RV-FW-LS, right ventricular free wall longitudinal strain; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; RVs', tricuspid annular S' velocity; sPAP, pulmonary artery systolic pressure. We have reported in bold the statistically significant *P*-value.

^a Δ -Change in echocardiography: follow-up - baseline value.

the PARADIGM-HF trial were selected a priori to tolerate the maximum tested dose.¹

Because little information is available about the titration and tolerability of maximal doses of Sac/Val in clinical practice for HFrEF patients, these findings still emphasize the issue of appropriate Sac/Val dose titration in a real-world setting. Due to emerging data indicating that higher doses of Sac/Val are associated with improved outcomes,²² investigations on mechanisms related to dose titration in the community are eagerly awaited.

To the best of our knowledge, our study is the first to analyse the potential role of echocardiography in predicting Sac/Val maximum dose tolerability. Indeed, previous studies

designed to test the association with the achievement of the highest Sac/Val doses focused only on clinical variables, such as, demographic characteristics, BP and concomitant medication.^{6,23}

Accordingly, we showed that age, baseline SBP and baseline tolerability of ACEi/ARBs maximum dose, are critical determinants of Sac/Val target dose achievement. Baseline SBP is, of course, the primary determinant for achieving of higher Sac/Val dose. In our cohort, a significant reduction in BP was observed during follow-up, and hypotension still represents, in several observational studies, the main determinant of ineffective up-titration.²⁴ Elderly patients are frailer, with a higher co-morbidity burden and, therefore, more prone to

Figure 3 The distribution of patients with left ventricular reverse remodelling (responder) in relation to Sac/Val dosage reached after 6 months ($P = 0.053$).

Bar graphs showing the distribution of patients with LV reverse remodeling (responder) in relation to the Sacubitril/Valsartan dosage reached after 6 months

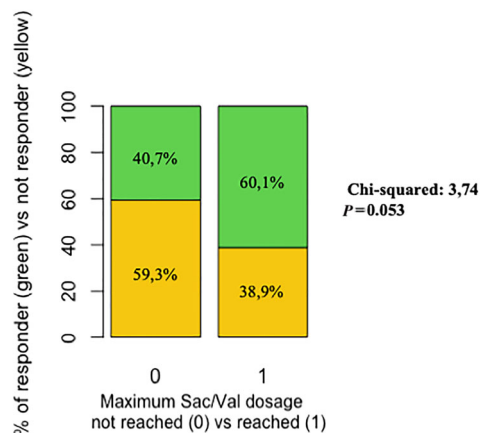


Table 5 Multivariable predictive model of reaching maximum recommended dose of Sac/Val

Variables	Odds ratio	95% confidence interval	p
Age ≥ 60 years	0.202	0.06–0.675	0.009
SBP ≥ 125 mmHg	2.942	1.021–8.480	0.046
Baseline TAPSE ≥ 16 mm	3.744	1.054–13.3	0.041
ACEi/ARBs maximum dose at baseline	3.496	1.289–9.481	0.014

SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers. We have reported in bold the statistically significant P -value.

adverse effects during up-titration, compared with the selected trial population.⁷ Finally, as expected, the baseline tolerability of ACEi/ARBs maximum dose plays a key role in achieving of Sac/Val target dose, in line with previous literature findings.⁶

About the echocardiography role, we confirmed the ability of Sac/Val to improve, during follow-up, several parameters related to both LV and RV function.^{25–27} This information is lacking in the PARADIGM-HF trial because the study design did not include patients with echocardiographic follow-up. We also showed an improvement in NYHA class during the follow-up and a trend towards a better clinical improvement in patients with positive reverse remodelling during Sac/Val treatment.^{28,29}

The analysis of potential baseline echocardiographic contributors to Sac/Val maximum dose tolerability showed

that RV baseline function, as measured by TAPSE, predicts the ability to reach the Sac/Val target dose. Although the role of RV function in the prognostic definition of patients with HFrEF has been previously elucidated,^{30,31} its potential effect on appropriate drug management for patients with HFrEF remains undetermined. It has been recently reported that, in patients with HFrEF, Sac/Val is associated with the improvement of the RV function.^{32,33} However, in both studies, Sac/Val target dose was under-represented. In 163 patients enrolled by Masarone and colleagues,³³ Sac/Val was administered at a dose of 24/26 mg twice daily in 102 patients (62.5%) and at a dose of 49/51 mg twice daily in the remaining 61 patients (37.5%), while in a more recent work by Yang and collaborators,³² 22 patients (27%) were treated with 49/51 mg twice daily, 56 patients (68%) with 24/26 mg twice daily, and 4 patients (5%) were managed with a very low dose of 12/13 mg twice daily. From a clinical point of view, a low dose of Sac/Val can be still effective³⁴; therefore, it could be argued that patients with RV dysfunction (baseline TAPSE < 16 mm, in our cohort) still need to be considered for Sac/Val treatment and, even, for possible up-titration, possibly with a different follow-up timing and dose modification pattern, to maximize the Sac/Val up-titration process.

However, in patients with significant bi-ventricular dysfunction, uncertainties about the fine management of this drug need to be elucidated by assessing the exact mechanisms linked to an improvement of RV function.^{35–37}

Study limitations

Several limitations should be acknowledged, limiting the generalization of results. The study's retrospective nature and the relatively small sample size and the absence of a control group treated with ACEi/ARBs limit definitive conclusions. In addition, although several baseline information has been collected, some specific variables might be missed, with a potential influence on the final multivariable model results. Nonetheless, even of small size, our study is developed in a real-world context and provided a multicentre collection of the data from several outpatient clinics for HF, supporting our findings' relevance.

Conclusions

The present study shows a significant improvement of both RV and LV function during Sac/Val treatment in patients with HFrEF, with evidence of a positive effect on LV remodelling. Baseline RV dysfunction may be associated with poor maximum Sac/Val up-titration, suggesting different approach in this cohort. More extensive studies are encouraged to generate and validate, both internally and externally, specific

models able to predict the tolerability to the Sac/Val maximum dose.

Conflict of interest

Carlo Gabriele Tocchetti has received funding from Amgen and personal fees from VivaLyfe and is listed as an inventor on two heart failure patents. Valeria Visco, Ilaria Radano, Alfonso Campanile, Amelia Ravera, Angelo Silverio, Daniele Masarone, Giuseppe Pacileo, Michele Correale, Pietro Mazzeo, Giuseppe Dattilo, Francesco Giallauria, Alessandra Cuomo, Valentina Mercurio, Paola Di Pietro, Albino Carrizzo, Rodolfo Citro, Gennaro Galasso, Carmine Vecchione, and Michele Ciccarelli declare no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The distribution of patient with NYHA class of 3 and less than 3, in relation to the Sac/Val dosage reached after 6 months. NYHA: New York Heart Association.

Table S1. Univariable associations between baseline predictors and the ability in reaching maximum recommended dose of Sac/Val.

Table S2. Multivariable predictive model of reaching maximum recommended dose of Sac/Val before dichotomization of the main continuous predictors.

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