



Impact of sacubitril/valsartan on echo parameters in heart failure patients with reduced ejection fraction a prospective evaluation

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ABSTRACT

Background: Sacubitril/valsartan has been shown to improve mortality and reduce hospitalizations in patients with heart failure (HF) with reduced ejection fraction (HFrEF). Although the physiological action mechanisms of sacubitril/valsartan are well described, its effects on left ventricular (LV) remodelling and other echocardiographic (echo) parameters have not been prospectively studied.

Objective: The aim of this prospective study was to: McMurray et al. (2012) [1] evaluate if sacubitril/valsartan impacts LV remodelling based on echo parameters; Ponikowski et al. (2016) [2] identify the predictive factors of sacubitril/valsartan response or intolerance.

Methods: From May 2017 to September 2018, 52 HF patients were prospectively enrolled using PARADIGM-HF criteria: Class II, III, or IV HF; ejection fraction (EF) of 40% or less; hospitalized for HF within the previous 12 months. Echo evaluation was performed before initiating sacubitril/valsartan and 3 months after optimal dose adjustment. Based on previous studies, patients with (absolute) improvement in left ventricular ejection fraction (LVEF) $\geq 5\%$ were considered significant sacubitril/valsartan responders.

Results: The 52 patients completing the study were characterized by age: 70 ± 10 years; gender: 11 women; aetiology: idiopathic in 20 and ischaemic in 32; NYHA Class: II in 17 and III in 35; LVEF: $32 \pm 5\%$; NTProBNP: 1805 ± 1914 pg/mL. The final population comprised 41 pts (79%), as 11 (21%) did not tolerate sacubitril/valsartan therapy. Under sacubitril/valsartan, several echo parameters significantly improved: LVEF from 32.6 ± 5 to $36 \pm 6\%$ ($p < 0.0001$); LVES volume from 117 ± 40 to 108 ± 46 mL ($p = 0.0051$); SEV from 59 ± 12 to 64 ± 13 ($p = 0.0061$); LVEDD from 60 ± 4 to 57 ± 5 mm ($p = 0.0002$); mean right ventricular systolic pressure (RVSP) from 39 ± 10 to 32 ± 8 ($p = 0.0001$). No significant modifications were observed concerning LV diastolic parameters or RV echo parameters. Sacubitril/valsartan echo responders ($n = 18/41$; 42%) had less severe LV remodelling, as shown by LVEDV: 144 ± 37 vs. 193 ± 47 mL, $p = 0.0009$; LVESV: 96 ± 28 vs. 133 ± 42 mL; $p = 0.003$; LVTDD: 61 ± 4 vs. 57 ± 5 mm; $p = 0.02$; significant mitral regurgitation: 6/18 (33%) vs. 16/23 (69%), $p = 0.02$; no diastolic LV or RV parameters impacted sacubitril/valsartan response. Predictors of sacubitril/valsartan intolerance were baseline creatinine level: 137 ± 99 vs. 100 ± 24 , $p = 0.03$; LVEF: 29 ± 6 vs. $33 \pm 5\%$; $p = 0.04$.

Conclusions: In HFrEF patients, sacubitril/valsartan significantly improves LV systolic remodelling, without any significant effects on LV diastolic or RV systolic echo parameters. Sacubitril/valsartan responders exhibit both less severe LV remodelling and less significant mitral regurgitation. Accordingly, sacubitril/valsartan could be used as soon as possible in HFrEF patients in order to limit LV remodelling, while precluding non-response or intolerance.

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1. Introduction

The treatment of chronic heart failure with reduced LVEF (HFrEF) using angiotensin-converting enzyme (ACE) inhibitors is well-established, with angiotensin receptor blockers (ARBs) as a safe and proven alternative [1,2]. A new therapeutic class of agents acting on the renin angiotensin aldosterone system (RAAS) and neutral endopeptidase system has been developed, known as angiotensin receptor

Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced LVEF; RV, right ventricular; Res, responders; TTE, trans-thoracic echocardiography; ARNI, angiotensin receptor neprilysin inhibitors; ARBs, angiotensin receptor blockers.

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neprilysin inhibitors (ARNI) [2–4]. The first in class is LCZ696, which is a molecule that combines valsartan (ARB) and sacubitril (neprilysin inhibitor) within a single substance. In the PARADIGM-HF trial, HFrEF patients assigned to LCZ696 (sacubitril/valsartan) had a substantially lower rate of hospitalization for HF and mortality compared to enalapril [3]. By inhibiting neprilysin, the degradation of natriuretic peptides (NPs), bradykinin, and other peptides is slowed down. High circulating A-type natriuretic peptide (ANP) and BNP levels exert physiologic effects through both binding to NP receptors and augmented generation of cGMP, thereby enhancing diuresis, natriuresis, myocardial relaxation, and anti-remodelling [2,5]. ANP and BNP also inhibit renin and aldosterone secretion. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention, as well as myocardial hypertrophy [2,5]. Owing to these specific physiopathological mechanisms, the clinical outcome proves more favourable compared to ACE; surprisingly, only very few data exist regarding the impact of sacubitril/valsartan on echocardiographic (echo) parameters, particularly LV remodelling [6–8]. Moreover, very few data are currently available concerning both sacubitril/valsartan echo responses and sacubitril/valsartan tolerance [2,3]. Accordingly, this prospective study sought to: (1) evaluate the impact of sacubitril/valsartan on echo parameters; and (2) assess the predictive factors of sacubitril/valsartan response or intolerance.

2. Methods

The study was approved by our Institutional Committee on Human Research. No extramural funding was employed to support this work. The authors are solely responsible for study design and conduct, study analyses, drafting and editing of the paper, as well as its final editorial content.

2.1. Patient selection

From June 2017 to September 2018, 52 CHF patients were prospectively enrolled. PARADIGM HF criteria were applied for patient inclusion [3]. Eligibility requirements at screening comprised an age of at least 18 years, New York Heart Association (NYHA) Class II, III, or IV symptoms, and ejection fraction of 40% or less. Patients were required to have been hospitalized for HF within the previous 12 months. Patients not taking any ACE inhibitor or ARB were considered for participation, or those having taken a stable dose of beta-blocker, ACE inhibitor, or ARB for at least 4 weeks. Exclusion criteria comprised symptomatic hypotension, systolic blood pressure of <100 mmHg, estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m² of body surface area, serum potassium level of >5.2 mmol/L at screening, angioedema history, or unacceptable side effects under ACE inhibitor or ARB treatment. Other exclusion criteria were as follows: correctable valvulopathy; acute coronary syndrome within <3 months; recent coronary revascularization within the last 3 months, or planned revascularization. Based on previous studies, an (absolute) improvement in LVEF ≥ 5% was considered to be a significant response to sacubitril/valsartan [9,10].

2.2. Study procedures

To minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition, ACE inhibitors were withheld for at least 36 h before initiating sacubitril/valsartan. Combined treatment with ACE inhibitor (or ARB) and sacubitril/valsartan was contraindicated. Patients underwent a clinical examination, 12 lead electrocardiography (ECG), trans-thoracic echocardiography (TTE), and Doppler evaluation prior to sacubitril/valsartan initiation. The same measurements were repeated at 3 months. Functional evaluation was conducted using NYHA classification.

2.3. Echocardiography measurements

TTE was performed by one observer (GB) blinded to the patient's status. Conventional TTE was systematically performed 24–72 h prior to sacubitril/valsartan introduction using a commercially available system (Vivid E9, GE Healthcare, France) and repeated 3 months after optimal sacubitril/valsartan treatment [11–13].

2.3.1. Left echo evaluation

Left ventricular systolic function was evaluated on two-dimensional echocardiography imaging of the left ventricle (LV). We measured LV dimensions (LVEDD, LVESD, SWT, and PWT) using M-mode with the parasternal long axis view at the papillary muscle level, and thereafter the biplane (modified Simpson's) method to measure LVEDV and LVESV. LVEF was calculated as $LVEDV - LVESV / LVEDV\%$. The transmitral pulsed-wave Doppler was recorded, with peaks of both *E* and *A* waves assessed and *E/A* ratio and *E* wave deceleration time calculated. Offline color-coded tissue Doppler imaging was carried out using the apical four-chamber view by placing the sample volume over the septal and lateral mitral annuli, with early diastolic velocity (*E'*) and late diastolic velocity (*A'*) then computed. The average *E'* velocities at the septal and lateral mitral annuli were estimated, and the *E/E'* ratio was calculated. Accordingly, LV diastolic dysfunction was graded in each patient according to the guidelines. LA maximum volume index (mL/m²) was evaluated in apical four- and two chambers. Mitral regurgitation was evaluated by traditional echocardiographic markers.

2.3.2. Right echo evaluation

A two-dimensional apical four-chamber view was applied to visualize the right ventricle (RV) volume and contractility. Percentage RV area change was calculated by dividing the difference in RV area between the end-diastolic and end-systolic phases by end-diastolic RV area. The endomyocardial contour was traced from the tricuspid annulus along the free wall to the apex, then back to the annulus, along the interventricular septum. Trabeculation, tricuspid leaflets, and chords were included in the chamber. M-mode images were employed to obtain tricuspid annular plane systolic excursion (TAPSE), as previously reported. In short, the M-mode cursor was oriented to the junction of the tricuspid valve plane with the RV free wall, and the total displacement of the tricuspid annulus from end-diastole to end-systole was computed. Calculation of the right ventricular performance index (MPI) was assessed by pulsed Doppler. By pulsed Doppler the tricuspid valve closure opening time (TCO) encompasses isovolumic contraction time, ejection time (ET), and isovolumic relaxation time. Pulsed-wave Doppler tissue was used to assess the longitudinal velocity of excursion termed RV *S'* or systolic excursion velocity. *S'* < 10 cm/s was the cut-off value of abnormal RV function suspicion. The pressure gradient between the RV and right atrium during systole was measured using the simplified Bernoulli equation [10].

2.4. Statistical analysis

All clinical variables were assessed at the time of inclusion. The echo parameters were evaluated just prior to sacubitril/valsartan initiation by one operator (GB) blinded to the patients' status and repeated after 3 months of optimal sacubitril/valsartan treatment. Continuous variables were expressed as mean ± SD or median with interquartiles, as appropriate. Comparisons between the patient groups were performed for continuous variables using unpaired Student's *t*-test or Mann-Whitney test, as appropriate. Categorical variables were compared using Chi-squared or Fisher's exact tests, as appropriate. A probability value of *p* < 0.05 was considered statistically significant. All analyses were performed using StatView®5.0 (StatView IV, Abacus Concept, Berkeley, CA, USA).

3. Results

3.1. Population

The 52 patients completing the study were characterized by age: 70 $\pm$ 10 years; gender: 11 women; cardiomyopathy aetiology: idiopathic in 20 and ischaemic in 32; NYHA Classes: II in 17 and III in 35; LVEF: 32 $\pm$ 5%; NTProBNP: 1805 $\pm$ 1914 pg/mL (Table 1). The final population comprised 41 pts (79%), given that 11 pts. (21%) did not tolerate sacubitril/valsartan therapy (Table 2). No difference was evidenced between ischaemic and dilated parameters at baseline. The maximal dosage (200 mg) with sacubitril/valsartan was obtained in 31/41 pts (75.6%) and in the resting population studied 10/41 pts (24.4%) the mean dosage was 100 mg a day. The optimal dosage did not influence the echo response in our study or reduction in left ventricular remodelling/mitral regurgitation ($p = 0.8$). No patients suffered from cutaneous reactions to the drug.

3.1.1. Echo remodelling under sacubitril/valsartan therapy (Table 3)

No difference between both groups was evidenced as to clinical parameters and risk factors. Under sacubitril/valsartan therapy, several echo parameters significantly improved: LVEF from 32.6 $\pm$ 5 to 36 $\pm$ 6% ($p < 0.0001$); LVES volume from 117 $\pm$ 40 to 108 $\pm$ 46 mL ($p = 0.0051$); LVES from 59 $\pm$ 12 to 64 $\pm$ 13 ($p = 0.0061$); LVEDD (60 $\pm$ 4 to 57 $\pm$ 5 mm; $p = 0.0002$); right ventricular systolic pressure (RVSP) from 39 $\pm$ 10 to 32 $\pm$ 8 ($p = 0.0001$). No significant modifications were observed in terms of LV diastolic function parameters or RV echo parameters.

3.1.2. Echo responders (Table 4)

Sacubitril/valsartan echo responders ($n = 18/41$; 42%) exhibited less severe LV remodelling: LVEDV 144 $\pm$ 37 vs. 193 $\pm$ 47 mL ($p = 0.0009$); LVESV 96 $\pm$ 28 vs. 133 $\pm$ 42 mL ($p = 0.003$); LVEDD 61 $\pm$ 4 to 57 $\pm$ 5 mm ($p = 0.02$); less significant mitral regurgitation 6/18 (33%) vs. 16/23 (69%) ($p = 0.02$). Moreover, no LV diastolic function or RV parameters were impacted by sacubitril/valsartan response.

3.1.3. Sacubitril/valsartan intolerance

Eleven pts (21%) did not tolerate sacubitril/valsartan therapy. Factors of sacubitril/valsartan intolerance were significantly associated with baseline creatinine level (137 $\pm$ 99 vs. 100 $\pm$ 24; $p = 0.03$) and LVEF (29 $\pm$ 6 vs. 33 $\pm$ 5%; $p = 0.04$). No RVEcho parameters influenced sacubitril/valsartan tolerance. The type of cardiomyopathy aetiology also did not influence the sacubitril/valsartan response or intolerance.

Table 1
Population characteristics.

	Study population ($n = 52$)
Age (yr.)	70 $\pm$ 10
Gender (% women)	11/52 (21%)
Hypertension	32/52 (61.5%)
Diabetes mellitus	18/52 (34.6%)
Tobacco smoking	10/52 (19.2%)
Cholesterol	24/52 (46%)
Structural Heart Disease Idiopathic Ischaemic	20 (61.5%) 32 (38.5%)
NYHA Class II NYHA Class III	17 (33%) 35 (67%)
LVEF (%)	32 $\pm$ 5
LVED volume (mL)	176 $\pm$ 56
LVES volume (mL)	121 $\pm$ 47
LVED diameter (mm)	60 $\pm$ 5
LVES diameter (mm)	50 $\pm$ 8
IVT (cm ²)	16 $\pm$ 0.3
Cardiac index output (L/min/m ²)	2.3 $\pm$ 0.3
Systolic pulmonary pressure (mmHg)	37 $\pm$ 10
Mitral insufficiency ($\geq$ II Grade) (%)	28/52 (54%)

LVEF: left ventricular ejection fraction; IVT: integral velocity time; LVED: left ventricular end-diastolic; LVES: left ventricular end-systolic.

Table 2
Final population characteristics.

	Study population ($n = 41$)
Age (yr.)	70 $\pm$ 10
Gender (% women)	10/41 (24.4%)
Hypertension	24/41 (58.5%)
Diabetes mellitus	14/41 (34.1%)
Tobacco smoking	7/41 (17%)
Cholesterol	20/41 (49%)
Structural Heart Disease Idiopathic Ischaemic	17 (41.5%) 24 (58.5%)
NYHA Class II NYHA Class III	14 (34%) 27 (66%)
LVEF (%)	33 $\pm$ 5
LVEDV (mL)	172 $\pm$ 50
LVESV (mL)	117 $\pm$ 41
LVEDD (mm)	60 $\pm$ 5
LVESD (mm)	49 $\pm$ 7
IVT (cm ²)	16.5 $\pm$ 0.3
Cardiac index output (L/min/m ²)	2.3 $\pm$ 0.3
Systolic pulmonary pressure (mmHg)	39 $\pm$ 10
Mitral insufficiency ($\geq$ II Grade) (%)	22/41 (54%)
Echo responders	18/41 (44%)

LVEF: left ventricular ejection fraction; IVT: integral velocity time; LVED: left ventricular end diastolic; LVES: left ventricular end systolic.

4. Discussion

4.1. Major findings

In the PRADIGM-HF trial, sacubitril/valsartan reduced by 20% cardiovascular mortality or hospitalization for HF in HFrEF patients [3], leading to FDA approval of sacubitril/valsartan in 2015, and HF guideline modification in 2017 [14]. Despite a significant morbi-mortality improvement in HFrEF patients, only very few data were available concerning the LCZ696 impact on echo LV remodelling [7,8]. This prospective study demonstrated that sacubitril/valsartan exerted an additional favourable action on LV remodelling and RV systolic pressure in HFrEF patients, who had previously been treated by ACE inhibitors. Moreover, our study results revealed that sacubitril/valsartan responders displayed both less severe LV remodelling and less significant mitral regurgitation.

4.2. Sacubitril/valsartan benefits

Composite angiotensin receptor-neprilysin inhibition represents a novel pharmacological strategy for managing HFrEF patients. Neprilysin is a membrane-bound endopeptidase that hydrolyses atrial, brain, and C-type natriuretic peptides and other endogenous vasodilator peptides, such as adrenomedullin and bradykinin, thereby being a major tool for eliminating these peptides [15]. Accordingly, inhibition of

Table 3
Comparison between sacubitril/valsartan before and after sacubitril/valsartan.

Population ($n = 41$)	Before treatment	After sacubitril/valsartan	P value
LVEF (%)	32.6 $\pm$ 5	36 $\pm$ 6	<0.0001
LVEDV (mL)	172 $\pm$ 49	166 $\pm$ 58	0.1
LVTSD (mL)	117 $\pm$ 40	108 $\pm$ 46	0.005
LVES (mL)	59 $\pm$ 12	64 $\pm$ 13	0.006
LVTDD (mm)	60 $\pm$ 4	57 $\pm$ 5	0.0002
LVTSD (mm)	49 $\pm$ 7	48 $\pm$ 5	0.2
IVT	16.5 $\pm$ 3	17.6 $\pm$ 3	0.01
E/A	1.1 $\pm$ 0.6	1 $\pm$ 0.5	0.4
Cardiac index output (L/min/m ²)	2.3 $\pm$ 0.4	2.4 $\pm$ 0.5	0.09
Systolic pulmonary pressure (mmHg)	39 $\pm$ 10	32 $\pm$ 8	0.0001
RVEDD (mm)	31 $\pm$ 4	31 $\pm$ 4	0.9
BDRV diameter (mm)	41 $\pm$ 6	41 $\pm$ 6	0.9
TAPSE (mm)	18 $\pm$ 4	18 $\pm$ 4	0.2
RVFS (%)	36 $\pm$ 6	38 $\pm$ 6	0.8

LVEF: left ventricular ejection fraction; IVT: integral velocity time; LVED: left ventricular end diastolic; LVES: left ventricular end systolic; RV fractional shortening (%RVFS).

Table 4
Comparison between sacubitril/valsartan responders and non-responders.

	Resp + (n = 18)	Resp (-) (n = 23)	P value
Age (yr.)	72 ± 11	69 ± 9	0.4
Gender (% female)	6/18 (33%)	4/23 (17%)	0.2
LVEF (%)	34 ± 4	36 ± 2	0.15
LVEDV (mL)	144 ± 37	193 ± 48	0.0009
LVESV (mL)	96 ± 28	133 ± 42	0.003
LVEDD (mm)	57 ± 5	61 ± 4	0.01
LVESD (mm)	48 ± 5	50 ± 9	0.36
IVT	16 ± 4	17 ± 3	0.4
E/A	1.2 ± 0.7	1 ± 0.6	0.5
Cardiac Index Output (L/min/m ²)	2.4 ± 0.4	2.3 ± 0.3	0.25
Systolic pulmonary pressure (mmHg)	36 ± 8	41 ± 11	0.2
RVEDD (mm)	30 ± 4	31 ± 4	0.4
BDRV diameter (mm)	41 ± 6	41 ± 5	0.9
TAPSE (mm)	19 ± 3	17 ± 4	0.2
RVFS (%)	36 ± 6	36 ± 6	0.9
Mitral regurgitation	6/18	16/23	0.01

LVEF: left ventricular ejection fraction; IVT: integral velocity time; LVED: left ventricular end diastolic; LVES: left ventricular end systolic; RV fractional shortening (%RVFS).

neprilysin, which is a neutral endopeptidase, results in increased levels of natriuretic peptides, with several potential benefits like natriuretic effects and vasodilatation [16]. Dual RAAS and neprilysin inhibition translates into decreased angiotensin-II-mediated hypertrophy or fibrosis, along with beneficial antiproliferative and antihypertrophic effects [15,16]. Generally, natriuretic peptides are secreted in response to excessive plasma volume and left ventricular filling pressure, features that are commonly found in HF patients. These agents thus contribute to the regulation of sodium and water balance, blood volume, arterial blood pressure, and sympathetic inhibition [15,16]. Neprilysin inhibition represents an alternative strategy that works by preventing the breakdown of endogenous natriuretic peptides [15,16]. While the combination of ACE and neprilysin inhibitors had already been tested, it was initially found to be associated with an abnormal risk of angioedema due to abnormal increases in bradykinin levels [16]. This, therefore, led to discontinuing the clinical development of the tested drug [17]. In order to prevent the angioedema risk, LCZ696 was designed, as based on the simultaneous blocking of both RAAS and neprilysin systems [15,16]. The striking clinical benefits of LCZ696 were demonstrated in the PARADIGM HF study, reflected by a significant reduction in the primary composite end point of cardiovascular death or HF hospitalization, along with a 16% reduction in the risk of death from any cause [3]. Subanalyses demonstrated that the benefits were not affected by the patients' risk factors, such as age, race, comorbidities, or prior use of ACE inhibitors or mineralocorticoid receptor antagonists (MRAs) [3]. While the clinical benefits of sacubitril/valsartan are well demonstrated, thereby supporting the efficiency of the anticipated underlying physiological mechanisms, its additional effects on tissue remodelling are not yet well-established. Indeed, LV remodelling is a major mechanism of underlying disease progression in HFrEF patients [18]. The clinical benefits of sacubitril/valsartan, according to the underlying multiple physiopathological mechanisms, could be varied and multiple. So far, the potent additional reverse remodelling effect of sacubitril/valsartan has been investigated in the PRIME prospective study [7]. This recent prospective randomized study has demonstrated that an angiotensin receptor neprilysin inhibitor is more effective in improving functional mitral regurgitation associated with heart failure than an angiotensin receptor blocker. The authors found that in comparison with valsartan, sacubitril/valsartan further reduces the effective regurgitant orifice area, left ventricular end-diastolic volume index, left atrial volume index, and the ratio of mitral in-flow velocity to mitral annular relaxation velocity (E/E') [7]. No benefit was observed in LVEF but the authors excluded the more severe patients with LVEF ≤ 25% and only patients with significant mitral regurgitation [7]. One retrospective study also observed an additional impact of sacubitril/valsartan on LVEF and LV

dimensions at 3 months [8]. This latter study, however, was an observational trial using a retrospective study design [8]. Our study employed a prospective design to assess the impact of sacubitril/valsartan on LV remodelling. As reported in the Results section, the impact of sacubitril/valsartan on LV remodelling proved highly favourable. We demonstrated that LVEF significantly improved (+3.6% in absolute value), which is likely accounted for by a significant reduction in LVES volume. Consequently, the reverse remodelling did not only impact LVEF, but exerted, likewise, a positive effect on systolic pulmonary pressure, most probably due to sacubitril's underlying physiological effects.

4.3. Identification sacubitril/valsartan responders

The extent of the sacubitril/valsartan effect was studied in a pre-defined HFrEF population, and consequently, the expected potential response was based on clinical and echo criteria [3]. While several other clinical factors have been studied, such as age, race, co-morbidities, as well as lower dosage, these factors had no impact on the sacubitril/valsartan effect [3,19]. While the clinical benefits of sacubitril/valsartan have been clearly demonstrated, the magnitude of the treatment response may differ depending on other parameters like echo parameters. For this specific reason, we sought to further determine the clinical or echo factors that may interfere with LVEF improvement. Based on previous studies, an absolute improvement in LVEF ≥ 5% was considered clinically relevant, thus defining sacubitril/valsartan responders [8,9]. Our study found that sacubitril/valsartan echo responders exhibited less severe LV remodelling as reflected by lower LVEDV (144 ± 37 mL) and lower LVESV (96 ± 28 mL) compared to non-responders (Table 3). Moreover, sacubitril/valsartan responders had less significant mitral regurgitation compared to non-responders. No LV diastolic function or RV parameters were revealed to influence sacubitril/valsartan response. Till now no effect was evidenced concerning the effect of sacubitril/valsartan and diastolic parameters in the literature, we are still waiting for the PARAGON-HF trial results. These results proveclinically relevant, providing evidence for using LCZ696 at an earlier time in HFrEF patients, prior to the occurrence of severe LV remodelling impending LV function recovery.

4.4. Sacubitril/valsartan tolerance

In the PARTADIGM-HF study, sacubitril/valsartan was discontinued in 17.8% of pts (n = 746). During the run-in period, 12% of pts withdrew from the study, because of adverse events, such as cough (most frequently), hyperkalaemia, renal dysfunction, or hypotension [3]. In our study, sacubitril/valsartan intolerance was observed in 21% of pts. The factors that significantly influenced sacubitril/valsartan tolerance were serum creatinine levels and more-severely altered LVEF. This last point further emphasises the benefit of using sacubitril/valsartan at an early disease stage and this, in an effort to prevent drug intolerance.

4.5. Therapeutic implications

Echo LV remodelling under sacubitril/valsartan had not been well studied before and to our knowledge, only one prospective study was previously published [19]. Our study found that a significant LVEF improvement is to be expected when using LCZ696, even in patients already treated with ACE inhibitors. Consequently, LV improved remodelling under sacubitril/valsartan may be accounted for by an additional effect of neprilysin inhibition by means of natriuretic peptides. This complementary effect of natriuretic peptides improves LV function, as clearly demonstrated in our study. Moreover, sacubitril/valsartan beneficial response on LV function may prove to be even more significant when the drug is administered at an early disease stage. Indeed, we demonstrated that LV function improvement was higher in the patient subset exhibiting lower LV dilatation. Therefore, the discussion as to whether sacubitril/valsartan should be administered earlier in the

disease course is now open, and further clinical studies must be conducted to find appropriate answers to this debate.

4.6. Study limitations

Due to the small sample size and the absence of control group ($n = 52$), these data should be interpreted cautiously until confirmed by suitably-powered clinical trials that are undoubtedly needed. Several other echo factors may likewise affect sacubitril/valsartan responses, such as diastolic parameters. Due to the absence of sinus rhythm in 12/41 (29.3%) pts., our analysis was not sufficiently powered to answer this question. Of note is that impact of RV function is likewise difficult to analyse given that a sufficiently high number of pts with right ventricular dysfunction was lacking for such an analysis. Concerning echo sacubitril/valsartan echo responders, it might be necessary to verify this result in a bigger cohort in order to acknowledge if there is a cut-off point for LVEF from which an improvement of HFrEF is only based on symptomatic therapy instead of pathomorphological myocardial improvement.

5. Conclusions

In HFrEF patients, sacubitril/valsartan significantly improves the LV systolic remodelling, without any significant effect on LV diastolic or RV systolic echo parameters. Sacubitril/valsartan responders displayed less severe LV remodelling and less significant mitral regurgitation. Accordingly, sacubitril/valsartan could be used at an earlier time in HFrEF patients in order to further limit LV remodelling.

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