IJC Heart & Vasculature 35 (2021) 100821

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Effects and clinical implications of sacubitril/valsartan on left ventricular reverse remodeling in patients affected by chronic heart failure: A 24-month follow-up

Carla Paolini [a,1], Giacomo Mugnai [a], Chiara Dalla Valle [a], Andrea Volpiana [a], Alessandra Ferraglia [a], Anna Chiara Frigo [b], Claudio Bilato [a,*]

[a] Division of Cardiology, West Vicenza General Hospitals, Arzignano-Vicenza, Italy
[b] Biostatistics, Epidemiology and Public Health Unit, Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy

ARTICLE INFO

Article history:
Received 12 April 2021
Received in revised form 10 May 2021
Accepted 3 June 2021

Keywords:
Reverse remodeling
Heart failure
Sacubitril/valsartan

ABSTRACT

Background: Compared to angiotensin inhibition, angiotensin-neprilysin "blockade" improves mortality and reduces hospitalizations in patients with heart failure (HF) with reduced ejection fraction (EF). Sacubitril/valsartan is known to influence left ventricular (LV) reverse remodeling with systolic function improvement, although underlying mechanisms remain partially unclear. Our objectives were to evaluate whether sacubitril/valsartan promotes LV remodeling and improves LV ejection fraction (LVEF) (above the 35% threshold by echocardiographic evaluation) and to identify predictors of reverse remodeling in a real-world setting.

Methods: New York Heart Association (NYHA) class II–III patients with EF $\leq$ 35% were consecutively enrolled. All patients were on optimal medical therapy on the initiation of sacubitril/valsartan therapy. Full clinical and multi-parametric echocardiographic evaluation, electrocardiogram, and laboratory tests were performed at baseline and after 3, 6, 12, and 24 months.

Results: In total, 69 patients were recruited from July 2016 to August 2018. Reverse remodeling was observed in 57.7% (30/52) of patients, occurring within 3, 6, 12, and 24 months in 2, 11, 13, and 4 patients, respectively. Twenty-four (46%) patients showed LVEF improvement above the threshold of 35% during follow-up, occurring in 1, 10, 9, and 4 patients within 3, 6, 12, and 24 months, respectively. Primitive dilated cardiomyopathy and female gender were identified as significant predictors of reverse remodeling. NYHA class was improved in both remodeling and non-remodeling patients.

Conclusion: Sacubitril/valsartan promotes favorable cardiac remodeling and significantly improves LVEF in a significant proportion of HF patients within 24 months, both in NYHA class II and III patients with HF.

1. Introduction

Despite advances in medical therapy, congestive heart failure (HF) remains a major cause of morbidity and mortality worldwide. Sacubitril/valsartan is the first-in-class angiotensin receptor-neprilysin inhibitor (ARNI) [1] recommended by guidelines to reduce morbidity and mortality in patients with symptomatic HF with reduced ejection fraction (HFrEF) [2]. However, the effects of sacubitril/valsartan on cardiac function are not yet fully understood. In particular, the mechanisms leading to the advantages of ARNI compared to angiotensin-converting enzyme inhibitors (ACEi) in terms of favorable outcomes remain unclear.

Recent studies have demonstrated a positive effect of sacubitril/valsartan on left ventricular (LV) reverse remodeling and the

Abbreviations: ACEi, Angiotensin-converting enzyme inhibitors; ARBs, Angiotensin II receptor blockers; ARNI, Angiotensin receptor-neprilysin inhibitor; CI, Confidence interval; CRT, Cardiac resynchronization therapy; ESC, European Society of Cardiology; GFR, Glomerular filtration rate; HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction; ICD, Implantable cardioverter-defibrillator; LA, Left atrium; LV, Left ventricular; LVEF, Left ventricular ejection fraction; MR, Mitral regurgitation; NYHA, New York Heart Association; OMT, Optimal medical therapy; OR, Odds ratio; RAAS, Renin-angiotensin-aldosterone system.

* Corresponding author at: Division of Cardiology, West Vicenza General Hospitals, Via del Parco 1, 36071 Arzignano-Vicenza, Italy.
E-mail address: claudio.bilato@aulss8.veneto.it (C. Bilato).

[1] Authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcha.2021.100821
2352-9067/

improvement of systolic function [3–5]. However, most of these observations as well as data on the efficacy of sacubitril-valsartan in HFrEF patients have come from clinical trials, whilst real-life observations are scarce. The objective of our study was to evaluate whether sacubitril/valsartan promotes LV remodeling and improves LV ejection fraction (LVEF) and to identify predictors of reverse remodeling in a real-world setting.

2. Methods

2.1. Patient population

HFrEF patients on optimal medical therapy (OMT) who started sacubitril/valsartan were consecutively enrolled at the Division of Cardiology, West Vicenza General Hospitals, Italy, according to the following criteria: 1) symptomatic HFrEF (≤35%) despite OMT as defined by the 2016 European Society of Cardiology (ESC) guidelines [2]; 2) New York Heart Association (NYHA) class II–III; 3) if cardiac resynchronization therapy (CRT) was present, only non-responder patients were enrolled.

All patients underwent a full clinical evaluation at baseline and 3, 6, 12, and 24 months of follow-up; this included an assessment of the NYHA class, recording of drug dose modification (in particular diuretics), electrocardiogram and laboratory testing, and multiparametric echocardiographic evaluation. Sacubitril/valsartan dosage was up-titrated to the maximum tolerated dose every two weeks.

This study complied with the Declaration of Helsinki. The research protocol was approved by the locally appointed ethics committee and informed consent was obtained by the patients.

2.2. Echocardiographic measurements

Echocardiographic analyses were performed in a left lateral decubitus position using Epiq 5 and CX 50 (Philips Medical Systems, Andover, MA, USA) by operators blinded to patient details. LV volumes and LVEF were calculated by Simpson's biplane method. Left atrium (LA) diameters were obtained from the optimized parasternal long axis. All measurements were acquired by the mean of 3 beats (for patients in sinus rhythm) or 5 beats (for patients in atrial fibrillation). Mitral regurgitation was evaluated by traditional echocardiographic markers. Reverse remodeling was defined by measuring LV end diastolic volume, LV end systolic volume and LVEF. In particular, according to previous studies [3], an absolute improvement in LVEF of 5% or more was considered to classify the patient as a responder to sacubitril/valsartan.

2.3. Laboratory tests

The glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [6] with creatinine traceable to isotope dilution mass spectrometry. The GFR was estimated at baseline and after 3, 6, 12, and 24 months of therapy with sacubitril/valsartan.

2.4. Statistical analysis

Categorical data are presented as percentages and numbers; normally distributed continuous data as mean ± standard deviation. Normal distribution was tested with the Kolmogorov-Smirnov test. Unpaired and paired Student's *t*-test was used, when appropriate, for comparison of normally distributed data. To compare non-continuous variables expressed as a proportion, the χ^2 test was used, when appropriate. Univariable and subsequent possible multivariable logistic regression modeling were performed. A probability value of $p < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Mac, Version 20.0, Chicago, IL, USA.

3. Results

In total, 69 patients were consecutively enrolled from July 2016 to August 2018. Among these, 3 patients died prematurely, 2 underwent orthotopic heart transplantation, and 1 patient was implanted by a left ventricular assist device. Sacubitril/valsartan was interrupted in 4 patients because of hypotension; 1 patient developed glottis edema, and another showed significant worsening of chronic renal failure. Five patients were lost during follow-up. Therefore, the analysis was made on a final population of 52 patients.

Table 1 summarizes the baseline characteristics of the 52 patients: the mean age was 69.5 ± 13.1 years and 42 (80.8%) patients were male. Twenty-four (46.2%) patients had primitive cardiomyopathy, 4 (7.7%) patients were hypertensive, while 17 (32.7%) patients had coronary artery disease; for the remaining 7 (13.5%) patients, the etiology of cardiomyopathy was valvular or post-actinic. Twenty-seven (51.9%) patients were in NYHA class II and 25 were in NYHA class III (49.1%). On average, LVEF was 28.5 ± 6.2%.

All patients were on OMT at the maximally tolerated dose. In particular, 96.2% of patients were on β-blockers (molecule, mean daily dose ± SD: metoprolol, 127.6 ± 69.2 mg; bisoprolol, 3.6 ± 2.4 mg; carvedilol, 19.9 ± 20.0 mg) and 94.2% on ACEi (molecule, mean daily dose ± SD: ramipril, 7.2 ± 3.2 mg; enalapril, 9.0 ± 7.2 mg) or Angiotensin II receptor blockers (ARBs) (four patients: valsartan 40 mg/day and 60 mg/day; losartan 50 mg/day; telmisartan 30 mg/day). Almost 90% of patients were on diuretics (furosemide) with a daily dose ranging from 25 mg to 375 mg. The maximal dosage (97/103 mg per day) of sacubitril/valsartan was reached in 30 out of 52 patients (57.7%). Sixteen patients had an implantable cardioverter-defibrillator (ICD) and 6 were on CRT.

Reverse remodeling was observed in 57.7% (30/52) of patients. Baseline characteristics of patients with and without reverse remodeling were mostly similar although blood pressure values and GFR levels were slightly better (albeit not significantly) in patients with reverse remodeling (Table 2).

NYHA class improved irrespective of the occurrence of LV reverse remodeling, as shown in Fig. 1. This is a known effect of ARNI therapy but the reasons why remain to be clarified. By the end of the 24-month follow-up, approximately 35–40% of patients were in NYHA class I with a substantial reduction of patients in NYHA class III. By contrast, a slight but significant worsening of renal function was observed. Indeed, creatinine serum levels increased from 1.17 ± 0.31 to 1.27 ± 0.40 mg/dL ($p = 0.01$) and GFR decreased from 61.0 ± 22.1 to 57.5 ± 19.6 mL/min/1.73 m^2 ($p = 0.02$) (Table 3).

LV end-diastolic volume decreased from 196.0 ± 58.0 mL at baseline to 160.2 ± 56.9 mL after 24 months of sacubitril/valsartan therapy ($p = 0.003$). Similarly, LV end-systolic volume decreased from 153.2 ± 47.5 mL to 112.5 ± 46.1 mL ($p = 0.003$), with a significant improvement in LVEF from 28.5 ± 6.2% to 38.2 ± 8.6% ($p < 0.00001$) (Fig. 2; Table 3). Compared with baseline, left atrial diameter was reduced at 24-months though not significantly ($p = 0.3$). Favorable remodeling of the LV was observed in more than half of the patients: 17 (63%) out of 27 patients with NYHA class II and 13 (52%) out of 25 NYHA class III patients had reverse remodeling.

A more favorable effect in terms of LV remodeling was observed in patients with less degree of mitral regurgitation (MR): 16 (62%) out of 26 patients with mild MR, 7 (58%) out of 12 patients with

Table 1
Baseline characteristics.

Patient characteristic	
Age (years)	69.5 ± 13.1
Males, n (%)	42 (80.8)
Systolic pressure (mm Hg)	126.5 ± 15.0
Diastolic pressure (mm Hg)	76.9 ± 9.8
Creatinine (mg/dL)	1.16 ± 0.31
GFR (mL/min/1.73 m^2)	61.0 ± 22.1
Left atrial diameter (mm)	81.5 ± 61.6
LVEDV (mL)	196.0 ± 58.0
Indexed LVEDV (mL/mq)	104.1 ± 35.8
LVESV (mL)	160.2 ± 56.9
Indexed LVESV (mL/mq)	84.4 ± 39.9
LVEF (%)	28.5 ± 6.2
Etiology of cardiomyopathy, n (%):	
- Ischemic	17 (32.7)
- Primitive	24 (46.2)
- Hypertensive	4 (7.7)
- Others	7 (13.5)
Arterial hypertension, n (%)	30 (57.7)
Diabetes, n (%)	11 (21.2)
Previous coronary artery bypass graft, n (%)	4 (7.7)
Previous percutaneous coronary intervention, n (%)	15 (28.8)
NYHA class, n (%):	
- III	27 (52)
- IV	25 (48)
Mitral regurgitation, n (%):	
- None	10 (19.2)
- Mild	26 (50)
- Moderate	12 (23.1)
- Severe	4 (7.7)
Drugs, n (%):	
- Beta blockers	50 (96.2)
- Previous ACEi	45 (86.5)
- Previous ARBs	4 (7.7)
- MRAs	28 (53.8)
- Amiodarone	9 (17.3)
Dosage of furosemide, n (%):	
- 25 mg	6 (11.5)
- 50 mg	18 (34.6)
- 75 mg	6 (11.5)
- 100 mg	6 (11.5)
- 125 mg	3 (5.8)
- 150 mg	3 (5.8)
- 175 mg	2 (3.8)
- 250 mg	3 (5.8)
- 375 mg	4 (7.7)
- Not	1 (1.9)
ICD, n (%)	16 (30.8)
CRT-D, n (%)	6 (11.5)

All data depicted as mean ± SD unless stated otherwise. ACEi = angiotensin converting enzyme inhibitors; ARBs = Angiotensin II receptor blockers; CRT-D = cardiac resynchronization therapy defibrillator; GFR = glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; MRAs = mineralocorticoid receptor antagonists; n = number; NYHA = New York Heart Association; SD = standard deviation.

moderate MR, and 1 out of 4 patients with severe MR experienced LV remodeling.

Most (87%) patients showed LV improvement within 1 year from initiation of therapy with sacubitril/valsartan: occurring in 2 (6.7%), 11 (36.7%), 13 (43.3%), and 4 (13.3%) patients within 3, 6, 12, and 24 months, respectively (Fig. 3). Furthermore, among the 30 subjects with favorable LV remodeling, LVEF crossed the threshold of 35% in 24 patients. Specifically, this occurred in 1 (4.2%) patient after 3 months of treatment, in 10 (41.7%) patients within 6 months, in 9 (37.5%) patients within 12 months, and in 4 (16.7%) patients within 24 months of treatment.

Among the 6 non-responder-to-CRT-D patients, LVEF showed a favorable remodeling (from 28.3 ± 5.6% to 37.5 ± 5.1%; + 9.3 ± 3.1%, mean ± SD) in 4 patients; in 1 patient, LVEF increased by 4% (from 26% to 30%), and, in another patient, decreased by 2% (from 32% to 30%).

Table 2
Baseline characteristics of patients with and without reverse remodeling.

Patient characteristic	Reverse remodeling (n = 30)	No Reverse remodeling (n = 22)	P-value[a]
Age (years)	68.3 ± 15.5	71.2 ± 8.8	0.4
Males, n (%)	21 (70)	21 (95)	**0.03**
Systolic pressure (mm Hg)	129.1 ± 17.0	122.4 ± 11.8	0.1
Diastolic pressure (mm Hg)	78.0 ± 10.3	74.5 ± 8.4	0.2
Creatinine (mg/dL)	1.03 ± 0.19	1.21 ± 0.42	0.1
GFR (mL/min/mq)	67.2 ± 22.5	53.8 ± 20.2	0.1
Left atrial diameter (mm)	49.3 ± 8.9	63.5 ± 45.1	0.2
LVEDV (mL)	196.5 ± 69.8	195.2 ± 38.8	0.9
LVESV (mL)	160.2 ± 56.9	153.3 ± 31.1	0.5
LVEF (%)	27.5 ± 6.1	29.4 ± 4.8	0.2
Arterial hypertension, n (%)	18 (60)	12 (55)	0.8
Diabetes, n (%)	6 (20)	5 (23)	1.0
Presence of atrial fibrillation, n (%)	10 (33)	11 (50)	0.2
Furosemide (mg per day)	66.9 ± 80.8	100.0 ± 82.4	0.1

[a] *p*-value < 0.05 considered statistically significant. All data depicted as mean ± SD unless stated otherwise. LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; n = number; SD = standard deviation.

To identify predictors of favorable remodeling response to sacubitril/valsartan treatment, a logistic regression analysis was performed using demographic, clinical, and echocardiographic variables. Only female gender and primitive cardiomyopathy were significant by univariate analysis, with significance maintained after multivariate analysis (odds ratio [OR] 10.30; 95% confidence interval [CI] 1.12–94.93; p = 0.04 for female gender, and OR 4.44; 95% CI 1.26–15.69; p = 0.02 for primitive cardiomyopathy) (Table 4).

During the 24-month follow-up no serious adverse events occurred in the 52 patients who completed the study.

4. Discussion

Prior to the 2014 publication of the PARADIGM-HF trial [1], international guidelines [2] recommended, as medical therapy for the management of HFrEF patients, β-blockers, ACEi/ARBs, and aldosterone antagonists in order to improve clinical outcomes and promote reverse LV remodeling. Nowadays, sacubitril/valsartan has been demonstrated to be superior to enalapril, in terms of reduction of cardiac death and hospitalization due to HF in HFrEF patients. Nevertheless, few clinical studies and/or case-series have reported data on LV function and LV reverse remodeling after sacubitril/valsartan therapy in a real-world setting.

Here we report the effects of sacubitril/valsartan in 52 consecutively enrolled patients treated for 24 months by evaluating clinical, laboratory, and echocardiographic parameters. Our results show a significant improvement of several reverse remodeling echocardiographic parameters in more than half of the patients, which mostly occurred within 1 year after ARNI therapy initiation. Notably, in 24 of 30 patients with favorable reverse remodeling, LVEF was also increased significantly from a clinical point of view (i.e., above the threshold of 35%).

To this regard, it is noteworthy that, according to current guidelines from both the ESC [2] and the American College of Cardiology [7], HFrEF patients are eligible for ICD implantation only if they

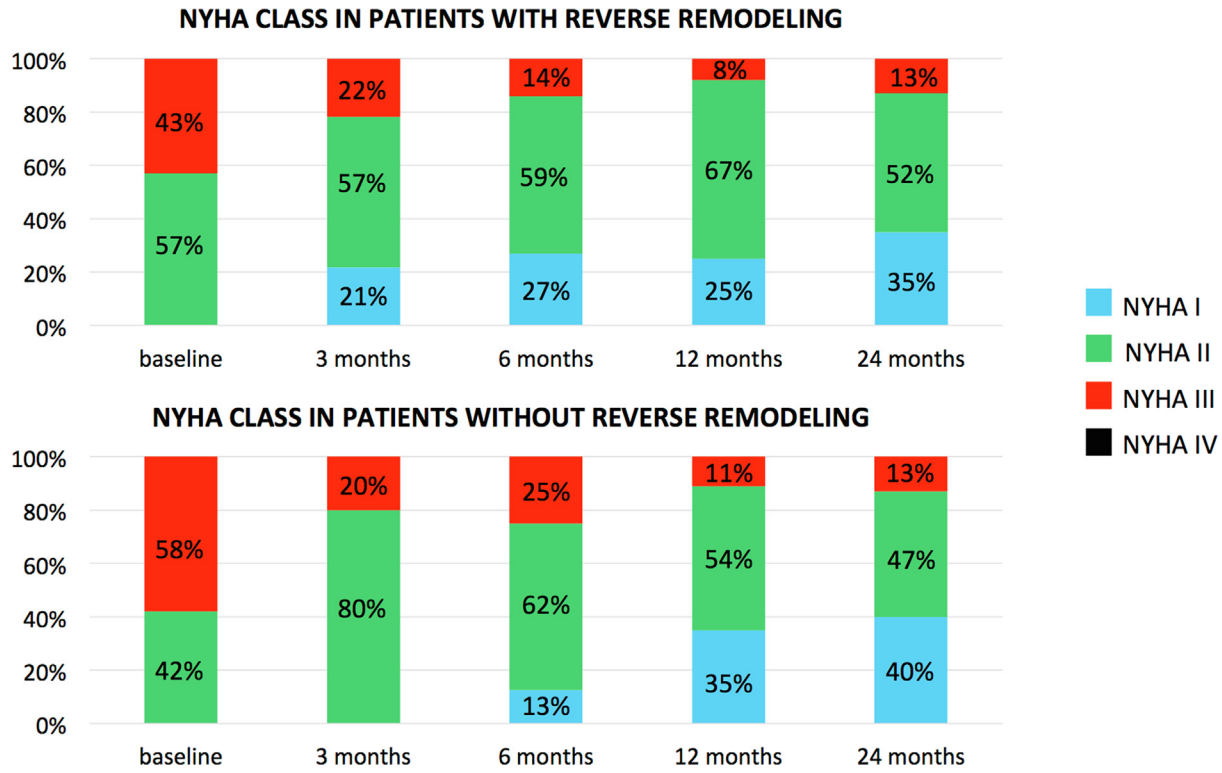

Fig. 1. New York Heart Association (NYHA) class improvement in patients with (top) and without (bottom) cardiac remodeling during the 24-month follow-up (at 3, 6, 12, and 24 months). Data are expressed as percentage of the two subgroups.

Table 3
Comparison between basal and post-treatment periods.

Variable	Pre-treatment	Post-treatment	P-value[a]	Mean delta
Systolic pressure (mm Hg)	126.2 ± 15.2	122.3 ± 17.2	0.06	−4.2 ± 11.8
Diastolic pressure (mm Hg)	76.5 ± 9.6	71.3 ± 10.1	0.001	−4.7 ± 9.9
Creatinine (mg/dL)	1.17 ± 0.31	1.27 ± 0.40	0.01	+0.14 ± 0.33
GFR (mL/min/1.73 m^2)	61.0 ± 22.1	57.5 ± 19.6	0.02	−6.2 ± 14.4
Left atrial diameter (mm)	56.5 ± 32.8	48.8 ± 9.1	0.3	−2.0 ± 8.7
LVEDV (mL)	196.0 ± 58.0	160.2 ± 56.9	0.003	−40.7 ± 58.1
LVESV (mL)	153.2 ± 47.5	112.5 ± 46.1	0.003	−51.3 ± 61.4
LVEF (%)	28.5 ± 6.2	38.2 ± 8.6	<0.00001	+9.8 ± 10.2
Furosemide (mg per day)	81.5 ± 82.3	79.9 ± 93.0	0.7	−3.5 ± 68.1
NYHA class, n (%):				
- II	0/52 (0)	19/52 (36.5)		
- III	27/52 (51.9)	26/52 (50.0)	<0.01	–
- IV	25/52 (48.1)	7/52 (13.5)		
	0/52(0)	0/52 (0)		

[a] *p*-value < 0.05 considered statistically significant. All data depicted as mean ± SD unless stated otherwise. GFR = glomerular filtration rate; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; n = number; NYHA = New York Heart Association; SD = standard deviation.

have good functional status with an expected survival of>1 year and with LVEF ≤ 35% despite 3 months of OMT. Our patients demonstrated a major rate of LV remodeling with an improvement of LVEF > 35% after 6–12 months of treatment, suggesting that sacubitril/valsartan might significantly reduce the number of candidates for ICD implantation or at least delay the time of implantation over the lifespan of the HFrEF patient.

Furthermore, as recently reported by Alhakak [8] in an analysis of 14,516 patients undergoing first-time ICD implantation for primary or secondary prevention from Danish nationwide registries, mortality rate was low within 1 year after implantation, although several important risk factors including dialysis, chronic renal disease, cancer, advanced age, and other comorbidities may increase 1-year mortality. In these subjects, therefore, the potential benefit of ICD should be carefully evaluated before implantation and sacubitril/valsartan might be considered in order to re-evaluate ICD implantation.

In our analysis, female gender and primitive dilated cardiomyopathy were identified as significant predictors of favorable LV remodeling and LVEF improvement. Sex differences in the cardiovascular system have been largely attributed to the effects of sex steroid hormones, such as estrogen and testosterone. Estrogens provoke rapid vasodilatation, reduce vessel-wall responses to injury, decrease the development of atherosclerosis, and prevent apoptosis in cardiac myocytes during heart failure [9,10]. Testosterone inversely influences myocardial remodeling after myocardial infarction and activates nuclear factor-κB, which contributes to the activation of inflammatory mechanisms [11–13].

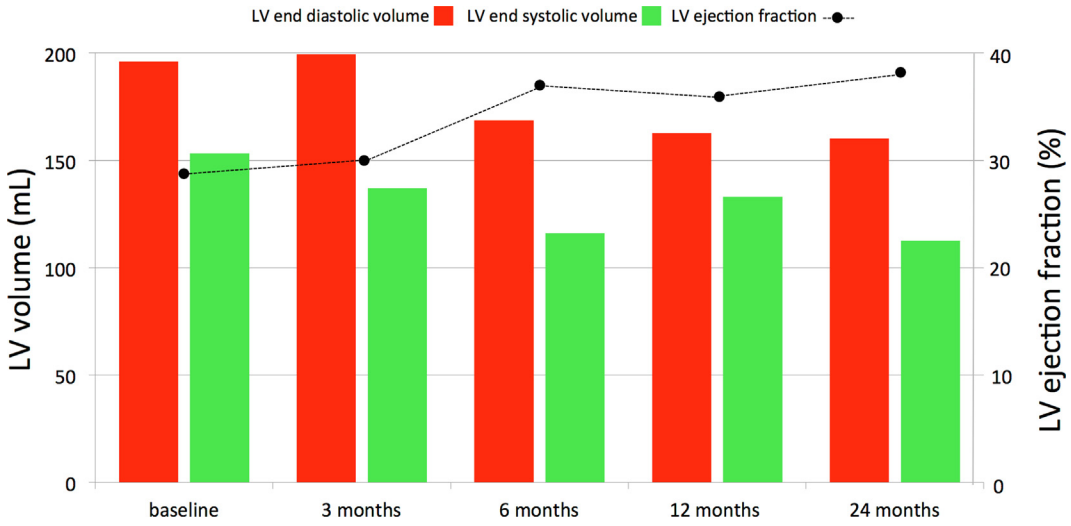

Fig. 2. Modification (mL) of left ventricular end-diastolic volume and end-systolic volume (bars) and of left ventricular ejection fraction (line) during the 24-month follow-up (at 3, 6, 12, and 24 months).

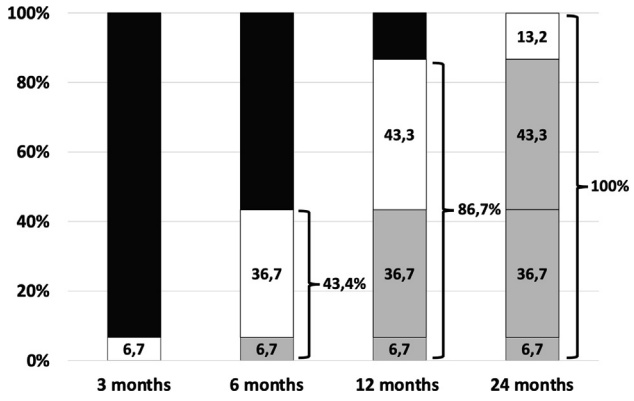

Fig. 3. Percentage of patients showing favorable left ventricular (LV) remodeling at the different time points (3, 6, 12, and 24 months) among the totality of individuals (n = 30) who displayed the improvement of LV function. White segments indicate patients with new evidence of LV positive reverse remodeling; grey segments show patients who already demonstrated the improvement of LV function in the previous assessments.

Sex-related differences in the gene expression within the ventricular myocardium of patients with idiopathic dilated cardiomyopathy have been reported [14]. Furthermore, several studies report that men with myocarditis or dilated cardiomyopathy have a greater induction of extracellular matrix proteins and/or fibrosis in the heart compared with women, including increased collagen and matrix metalloproteinase production [15,16]. Whether these differences play a role in the clinical and echocardiographic response to sacubitril/valsartan, however, remains to be clarified.

Worsening renal function has been associated with increased mortality in HF patients under inpatient or outpatient care: inhibitors of the renin-angiotensin-aldosterone system (RAAS) may reduce the GFR and thus may impair renal function, at least initially, however, they provide major clinical outcome benefits over the long-term [17–19]. In HF patients, worsening of the renal function depends on a heterogeneous variety of causes [20], and RAAS blockade improves clinical outcomes regardless of renal impairment [21]. On the other hand, compared with enalapril, sacubitril/-valsartan slows the rate of GFR decrease and also has favorable effects on renal outcomes in HFrEF [22]. In our patients both creatinine levels and GFR worsened at the follow-up, especially in the

Table 4
Univariate and multivariate logistic regression analysis for reverse remodeling.

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**P-value**[a]	**OR**	**95% CI**	**P-value**[a]
Age (years)	0.98	0.93–1.03	0.44			
Female gender	9.00	1.05–77.47	**0.04**	10.30	1.12–94.93	**0.04**
Primitive cardiomyopathy	4.00	1.22–13.14	**0.02**	4.44	1.26–15.69	**0.02**
Hypertension	1.25	0.41–3.80	0.69			
Diabetes	0.85	0.22–3.24	0.81			
Final dosage of 97/103 mg per day	2.40	0.77–7.44	0.13			
Baseline arterial systolic pressure	1.03	0.99–1.07	0.13			
Baseline arterial diastolic pressure	1.04	0.98–1.11	0.21			
LA diameter (mm)	0.96	0.89–1.04	0.32			
GFR (mL/mq/min)	1.03	0.99–1.07	0.12			
LVEDV (mL)	1.00	0.99–1.01	0.54			
LVESV (mL)	1.01	0.99–1.02	0.27			
LVEF (%)	0.93	0.84–1.04	0.21			
Furosemide dosage (mg per day)	0.99	0.99–1.01	0.17			
Presence of atrial fibrillation	0.50	0.16–1.55	0.23			

[a] *p*-value < 0.05 considered statistically significant. CI = confidence interval; GFR = glomerular filtration rate; LA = left atrial; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume; OR = odds ratio.

patients with favorable remodeling and who showed improvement in both NYHA class and LVEF. A possible contributing cause could have been that the dosage of furosemide was not substantially modified even in the patients who improved their functional and clinical status, due to an ambiguous "real-world related therapeutic inertia".

Recently, Castrichini et al. [23] demonstrated a consistent rate of left atrial reverse remodeling, defined as a decrease > 15% in the left atrium end-systolic volume, in patients treated with sacubitril/valsartan. By contrast, left atrial diameter was not significantly reduced in our study, hence we were unable to demonstrate an atrial reverse remodeling in the setting of real-world observation. However, a larger number of both patients and real-world observations might overturn this conclusion.

A major point of strength of our study is the relatively long term of follow-up. Indeed, to our knowledge, our study is among the longest observations in the setting of the real world. This aspect is noteworthy not only in terms of efficacy but also for the safety and tolerability of the ARNI therapy. Sacubitril/valsartan ameliorated NYHA class in most of the patients and was able to promote LV reverse remodeling and to improve LVEF in more than half of the treated patients, mostly within 12 months of therapy. On the other hand, among the overall population, 3 patients died prematurely, 2 underwent heart transplantation, 1 was implanted by left ventricular assist device, and adverse events occurred in 6 out of 69 individuals (8.7%). However, in the patients who completed the 24-month follow-up only 4 patients were hospitalized for HF recurrence, and only 1 patient was hospitalized within the first 4 months.

Finally, as reported in Table 2, the baseline characteristics of patients with and without reverse remodeling were mostly similar, with blood pressure values and GFR levels slightly improved albeit not significantly in patients with reverse remodeling. This could suggest that sacubitril/valsartan should be initiated earlier to maximize the beneficial effects of the ARNI therapy in terms of clinical outcomes as well as improvement of LV performance: further studies are needed to confirm this hypothesis.

4.1. Limitations

Some limitations of our study need to be acknowledged. This is a clinical registry in the real-world setting and, therefore, without a control population. The sample is relatively small, but with a non-negligible follow-up of 24 months. Because of the nature of the study, LVEF was quantified only by Simpson's biplane method and LA size only by measuring the diameter. Cardiac magnetic resonance was not available in our patients although we recognize that it could be useful to more precisely characterize the myocardial tissue and to investigate the effect of sacubitril/valsartan on LV fibrosis. Finally, sample plasmatic HF biomarkers such as brain natriuretic peptide were not systematically available for all the patients.

5. Conclusion

Treatment with sacubitril/valsartan improved LV performance and NYHA class in real-world HFrEF patients at the 2-year follow-up. This suggests that, in this patient population, sacubitril/valsartan should be implemented with a "the sooner the better" strategy, which might avoid or delay the time of ICD implantation.

Funding

Editorial assistance was unconditionally funded by Novartis Farma.

CRediT authorship contribution statement

Carla Paolini: Conceptualization, Data curation, Formal analysis. **Giacomo Mugnai:** Data curation, Formal analysis. **Chiara Dalla Valle:** Conceptualization, Data curation. **Andrea Volpiana:** Project administration, Software. **Alessandra Ferraglia:** Data curation. **Anna Chiara Frigo:** Formal analysis. **Claudio Bilato:** Conceptualization, Formal analysis, Funding acquisition, Resources, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Editorial assistance was provided by Melanie Gatt (PhD) an independent medical writer, on behalf of Health Publishing & Services Srl.

References

[1] J.J. McMurray, M. Packer, A.S. Desai, et al., Angiotensin-neprilysin inhibition versus enalapril in heart failure, N. Engl. J. Med. 371 (2014) 993–1004.
[2] P. Ponikowski, A.A. Voors, S.D. Anker, et al., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. J. Heart Fail. 18 (2016) 891–975.
[3] A. Almufleh, J. Marbach, S. Chih, et al., Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients, Am. J. Cardiovasc. Dis. 7 (2017) 108–113.
[4] G. Bayard, A. Da Costa, R. Pierrard, C. Romeyer-Bouchard, J.B. Guichard, K. Isaaz, Impact of sacubitril/valsartan on echo parameters in heart failure patients with reduced ejection fraction a prospective evaluation, Int. J. Cardiol. Heart Vasc. 25 (2019) 100418.
[5] A.S. Desai, S.D. Solomon, A.M. Shah, et al., Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial, JAMA (2019) 1–10.
[6] A.S. Levey, L.A. Stevens, C.H. Schmid, et al., A new equation to estimate glomerular filtration rate, Ann. Intern. Med. 150 (2009) 604–612.
[7] C.W. Yancy, M. Jessup, B. Bozkurt, et al., 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, Circulation 128 (2013) 1810–1852.
[8] A. Alhakak, L. Ostergaard, J.H. Butt, et al., Cause-specific death and risk factors of one-year mortality after implantable cardioverter-defibrillator implantation: a nationwide study, Eur. Heart. J. Qual Care Clin. Outcomes (2020), https://doi.org/10.1093/ehjqcco/qcaa074.
[9] M.E. Mendelsohn, R.H. Karas, The protective effects of estrogen on the cardiovascular system, N. Engl. J. Med. 340 (1999) 1801–1811.
[10] T. Simoncini, A.R. Genazzani, J.K. Liao, Nongenomic mechanisms of endothelial nitric oxide synthase activation by the selective estrogen receptor modulator raloxifene, Circulation 105 (2002) 1368–1373.
[11] O. Baltatu, C. Cayla, R. Iliescu, D. Andreev, M. Bader, Abolition of end-organ damage by antiandrogen treatment in female hypertensive transgenic rats, Hypertension 41 (2003) 830–833.
[12] M.A. Cavasin, Z.Y. Tao, A.L. Yu, X.P. Yang, Testosterone enhances early cardiac remodeling after myocardial infarction, causing rupture and degrading cardiac function, Am. J. Physiol. Heart Circ. Physiol. 290 (2006) H2043–H2050.
[13] A. Planavila, J.C. Laguna, M. Vazquez-Carrera, Nuclear factor-kappaB activation leads to down-regulation of fatty acid oxidation during cardiac hypertrophy, J. Biol. Chem. 280 (2005) 17464–17471.
[14] G.E. Haddad, L.J. Saunders, S.D. Crosby, et al., Human cardiac-specific cDNA array for idiopathic dilated cardiomyopathy: sex-related differences, Physiol. Genomics 33 (2008) 267–277.
[15] M.S. Cocker, H. Abdel-Aty, O. Strohm, M.G. Friedrich, Age and gender effects on the extent of myocardial involvement in acute myocarditis: a cardiovascular magnetic resonance study, Heart 95 (2009) 1925–1930.
[16] V. Regitz-Zagrosek, U. Seeland, Sex and gender differences in myocardial hypertrophy and heart failure, Wien. Med. Wochenschr. 161 (2011) 109–116.
[17] K. Damman, T. Jaarsma, A.A. Voors, et al., Both in- and out-hospital worsening of renal function predict outcome in patients with heart failure: results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH), Eur. J. Heart Fail. 11 (2009) 847–854.

[18] K. Damman, G. Navis, A.A. Voors, et al., Worsening renal function and prognosis in heart failure: systematic review and meta-analysis, J. Card Fail 13 (2007) 599–608.
[19] G.L. Smith, J.H. Lichtman, M.B. Bracken, et al., Renal impairment and outcomes in heart failure: systematic review and meta-analysis, J. Am. Coll. Cardiol. 47 (2006) 1987–1996.
[20] C. Ronco, M. Haapio, A.A. House, N. Anavekar, R. Bellomo, Cardiorenal syndrome, J. Am. Coll. Cardiol. 52 (2008) 1527–1539.
[21] H. Clark, H. Krum, I. Hopper, Worsening renal function during renin-angiotensin-aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction, Eur. J. Heart Fail. 16 (2014) 41–48.
[22] K. Damman, M. Gori, B. Claggett, et al., Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure, JACC Heart Fail 6 (2018) 489–498.
[23] M. Castrichini, P. Manca, V. Nuzzi, et al., Sacubitril/valsartan induces global cardiac reverse remodeling in long-lasting heart failure with reduced ejection fraction: standard and advanced echocardiographic evidences, J. Clin. Med. 9 (2020) 906.