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Impact of sacubitril/valsartan on implantable defibrillator eligibility in heart failure: a real-world experience

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Abstract. – OBJECTIVE: Current guidelines recommend an implantable cardiac defibrillator (ICD) in patients with symptomatic heart failure and reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] ≤35%) despite ≥3 months of optimal medical therapy. Recent observations demonstrated that sacubitril/valsartan induces beneficial reverse cardiac remodeling in eligible HFrEF patients. Given the pivotal role of LVEF in the selection of ICD candidates, we sought to assess the impact of sacubitril/valsartan on ICD eligibility and its predictors in HFrEF patients.

PATIENTS AND METHODS: We retrospectively evaluated 48 chronic HFrEF patients receiving sacubitril/valsartan and previously implanted with an ICD in primary prevention. We assumed that ICD was no longer necessary if LVEF improved >35% (or >30% if asymptomatics) at follow-up.

RESULTS: Over a median follow-up of 11 months, sacubitril/valsartan induced a significant drop in LV end-systolic volume (-16.7 ml/m², *p*=0.023) and diameter (-6.8 mm, *p*=0.022), resulting in a significant increase in LVEF (+3.9%, *p*<0.001). As a consequence, 40% of previously implanted patients resulted no more eligible for ICD at follow-up. NYHA class improved in 50% of the population. A dose-dependent effect was noted, with higher doses associated to more reverse remodeling. Among patients deemed no more eligible for ICD, lower NYHA class (odds ratio (OR) 3.73 [95% CI 1.05; 13.24], *p*=0.041), better LVEF (OR 1.23 [95% CI 1.01; 1.48], *p*=0.032) and the treatment with the intermediate or high dose of sacubitril/valsartan (OR 5.60 [1.15; 27.1], *p*=0.032) were the most important predictors of status change.

CONCLUSIONS: In symptomatic HFrEF patients, sacubitril/valsartan induced beneficial cardiac reverse remodeling and improved NYHA class. These effects resulted in a significant reduction of patients deemed eligible for ICD in primary prevention.

Key Words:
Sacubitril/valsartan, Heart failure, Implantable cardioverter defibrillator, Reverse remodeling, Echocardiography.

Introduction

Ventricular remodeling is a major determinant in the progression of heart failure with reduced ejection fraction (HFrEF)[1]. It usually occurs as a consequence of maladaptive activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) secondary to myocardial injury. Pathologic left ventricular (LV) remodeling consists of changes in cardiac geometry (increased LV volumes) and function (reduced LV ejection fraction, LVEF) and is associated with a higher risk for cardiovascular events. Indeed, it represents an important target for heart failure (HF) therapy[2]. Several clinical studies and a recent meta-analysis have demonstrated the beneficial effect on LV remodeling of different classes of drugs in HFrEF patients. In particular, renin-angiotensin system (RAS) inhibitors, mineralocorticoid receptor antagonists and betablockers have been demonstrated to significantly mitigate or reverse LV remodeling, paralleled by a reduction in HF hospitalization and mortality[3].

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In HFrEF patients that remain symptomatic and exhibit a residually depressed cardiac function (LVEF ≤35%) despite ≥3 months of optimal medical therapy (OMT), current guidelines recommend to implant a cardioverter defibrillator (ICD) in order to reduce the risk of sudden cardiac death (SCD) and all-cause mortality[4].

Sacubitril/valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI) that provides the concurrent modulation of natriuretic peptides system and inhibition of the angiotensin (AT_1) receptor. In the PARADIGM-HF trial, sacubitril/valsartan significantly lowered rates of cardiovascular death or HF hospitalization and improved functional status compared with enalapril in symptomatic ambulatory HFrEF patients[5]. Explanation of ARNI benefits remains elusive, but a systems biology model suggested reverse remodeling to be one plausible mechanism[6]. Recently, several reports[7-10] showed that sacubitril/valsartan enhances cardiac reverse remodeling and improves New York Heart Association (NYHA) class to a greater degree than RAS blockers alone. However, none of these studies specifically focused on the effect of ARNI-induced LVEF improvement on ICD eligibility.

Given the pivotal role of LVEF in the selection of ICD candidates among HFrEF patients, we sought to assess the impact of sacubitril/valsartan on ICD eligibility and its potential clinical predictors in this setting.

Patients and Methods

Study Population

We retrospectively evaluated patients with chronic (>6 months) HFrEF (LVEF <35%), on OMT and previously implanted with an ICD before sacubitril/valsartan availability on the market (2009-2015). All patients were followed-up in the last year at the HF outpatient clinic of our institution. Sacubitril/valsartan was prescribed as part of medical treatment optimization and according to the Italian reimbursement criteria: (1) symptomatic HF defined as NYHA class II-IV; (2) LVEF ≤35% measured by echocardiography; (3) pre-treatment with a maximum tolerated dose of RAS inhibitors (angiotensin converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARB]) for at least 4 weeks. Patients with reversible cardiac dysfunction or the need for simultaneous initiation of another therapy (i.e., cardiac resynchronization therapy) that may induce reverse remodeling were excluded. Sacubitril/valsartan was initiated and progressively uptitrated every 2-4 weeks to the maximally tolerated dose as in routine clinical practice. Physical examination with NYHA class evaluation at baseline (before sacubitril/valsartan starting dose) and at follow-up was recorded. All echocardiographic examinations performed within 30 days from clinical visit were analyzed (EchoPAC station; GE Healthcare, UK) by the same operator blinded to other patient details according to current recommendations[11,12]. We assumed that ICD was no longer necessary for primary prevention of sudden cardiac death if LVEF improved >35% (or more than 30% in asymptomatic patients) at follow-up echocardiography.

The study was approved by the Local Ethical Committee (Ethics Committee ASL-RMB) and is in accordance with the Declaration of Helsinki. All patients signed written informed consent.

Statistical Analysis

Data are presented as mean ± standard deviation or as median and interquartile ranges [IQR] if not normally distributed. Skewness was tested using the Shapiro-Wilk normality test. Variables not normally distributed were log-transformed before the analysis. Logistic and linear regressions were performed to assess associations and outcome predictors. Continuous variables were compared with the Student's *t*-test, paired *t*-test, ANOVA-test, Mann-Whitney U-test or Kruskal-Wallis test when appropriate. Categorical values were compared with the Pearson χ^2-test or Fisher's exact test when appropriate. Ten biplane LVEF measurements (5 at baseline and 5 at follow-up) were randomly selected and measured twice by the same operator blinded to other patient details. The intra-operator reproducibility of LVEF was assessed using the Bland-Altman method. The level of statistical significance was set at a 2-sided *p*-value <0.05. All analyses were performed using JMP pro 15.0 statistical software (SAS Institute, Inc., Cary, North Carolina).

Results

Patients' Characteristics

A total of 55 patients was considered suitable for the analysis. Of these, 7 patients (13%) developed side effects (symptomatic hypotension in 4 cases, worsening renal function in 1 case, hyperkaliemia in 2 cases) related to sacubitril/

valsartan treatment (all on 24/26 mg dose) and discontinued the drug before planned follow-up. Therefore, a total of 48 patients were included in the final analysis. In this cohort, 18 (38%) patients were treated with the 24/26 mg dose, 17 (35%) with the 49/51 mg dose and 13 (27%) with the 97/103 mg dose. During the observation period none of the patients experienced significant adverse events necessitating dose reduction or drug discontinuation.

Baseline clinical characteristics are summarized in Table I. Patients were predominantly males (89%), with a mean age of 66.6 ± 8.9 years and a body mass index of 28.4 ± 4.3 kg/m^2. At enrolment, 46% of study participants were in NYHA Class II and 52% in NYHA class III. The median NTproBNP was 1027 [879; 1560] pg/mL, the mean plasma potassium 4.5 ± 0.4 mmol/L and the glomerular filtration rate (eGFR) 83.6 ± 29.6 mL/min/1.73m^2. HF etiology was mainly ischemic (63%). At baseline, echocardiography showed a mean LVEF of 30.0 ± 3.8%. The mean LV end-diastolic (LVEDVI) and end-systolic (LVESVI) volume index were 103.5 ± 17.0 mL/m^2 and 76.4 ± 17.8 mL/m^2, respectively. Optimized guidelines-recommended medical therapy was extensively used. Approximately 80% of patients was treated with mineralocorticoid receptor

Table I. Baseline characteristics.

Clinical characteristics	
Age, years	66.6 ± 8.9
Male, n. (%)	43 (89)
Body mass index, kg/m^2	28.4 ± 4.3
NYHA class, n (%)	
- II	22 (46)
- III	25 (52)
- IV	1 (2)
Systolic blood pressure, mmHg	131 ± 14
Diastolic blood pressure, mmHg	81 ± 10
Heart failure aetiology, n (%): Ischemic; non-ischemic	30 (63); 18 (37)
Diabetes mellitus, n (%)	17 (35)
Dyslipidaemia, n (%)	33 (69)
Hypertension, n (%)	41 (85)
Atrial fibrillation, n (%)	19 (40)
Laboratory examinations	
Hemoglobin, gr/dL	13.7 ± 1.5
Sodium, mmol/L	141.5 ± 1.9
Potassium, mmol/L	4.5 ± 0.4
eGFR, mL/min/1.73 m^2	83.6 ± 29.6
NTproBNP, ng/L	1027 [879; 1560]
Echocardiography	
LV end-diastolic diameter, mm	64.2 ± 8.9
LV end-systolic diameter, mm	57.1 ± 6.7
LV end-diastolic volume index, mL/m^2	103.5 ± 17.0
LV end-systolic volume index, mL/m^2	76.4 ± 17.8
LV ejection fraction, %	30.0 ± 3.8
Left atrial volume, mL/m^2	55.5 ± 27.6
LV mass index, gr/m^2	140.7 ± 36.3
E/Em ratio	12.8 ± 4.7
Mitral regurgitation, n (%): 0-1; 2-3	33 (69); 15 (31)
Tricuspid regurgitation, n (%): 0-1; 2-3	40 (83); 8 (17)
Pulmonary artery systolic pressure, mmHg	36.9 ± 10.3
Tricuspid annular plane systolic movement, mm	20.9 ± 4.1
Therapy	
Furosemide, n (%)	38 (79)
ACEi or ARB, n (%)	48 (100)
ACEi/ARB therapy duration, months	41.6 ± 22.1
MRA, n (%)	38 (79)
Betablocker, n (%)	48 (100)

Abbreviations: ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blockers; eGFR – estimated glomerular filtration rate; LV – left ventricle; MRA – mineralocorticoid receptor antagonist; NTproBNP - N-terminal pro b-type natriuretic peptide; NYHA – New York Heart Association.

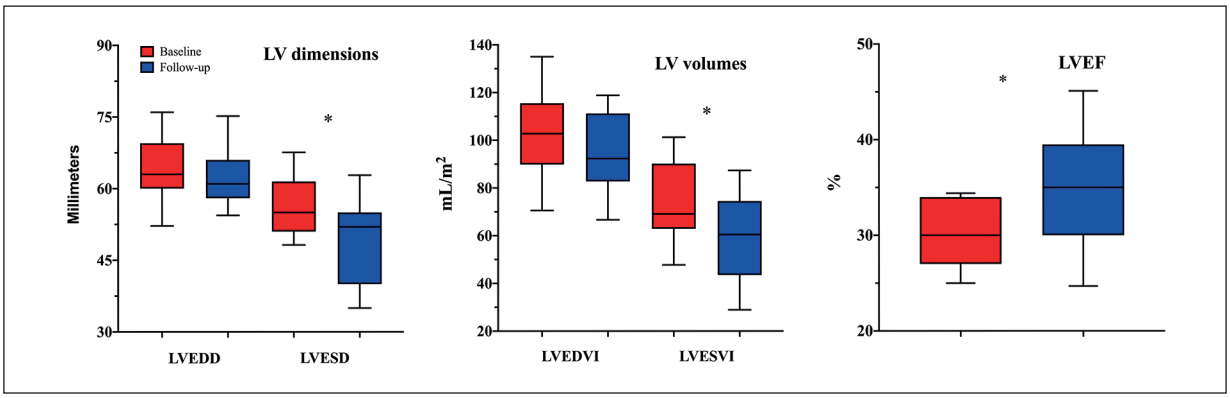

Figure 1. Left ventricular volumes, dimensions and systolic function at baseline (*red box*) and follow-up (*blue box*). Abbreviations: LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LVEDVI – left ventricular end-diastolic volume index; LVESVI – left ventricular end-systolic volume index; LVEF – left ventricular ejection fraction. Box and whiskers are median and 10-90% percentiles. Asterisk stands for *p*-value <0.05.

antagonist (MRA) and was taking loop diuretics, while all of them were on beta-blockers and ACEi or ARB. The mean time on ACEi or ARB before sacubitril/valsartan initiation was 41.6 ± 22.1 months.

At follow-up, systolic and diastolic blood pressure dropped on average 6.1 and 3.9 mmHg, respectively. Concurrently, potassium level increased of 0.1 mmol/L and eGFR declined of 1.9 ml/min/m^2 (**Supplementary Table I**).

Sacubitril/Valsartan Effect: Measurements and Correlates

The median time between sacubitril/valsartan initiation and the follow-up echocardiogram was 11 [interquartile range 6-14] months. Sacubitril/valsartan induced a significant drop in LV end-systolic volume (-16.7 ml/m^2, p=0.023) and diameter (-6.8 mm, p=0.022). A trend toward reduction in LV end-diastolic volume (-13.7 ml/m^2, p=0.097) and diameter (-1.9 mm, p=0.060) was also showed. The improvement in volumetric remodeling resulted in a significant increase in LVEF (+3.9%, p<0.001) (Figure 1). In particular, LVEF improved in 62% (N=30) of the entire population, remained unchanged in 19% (N=9) and worsened in another 19% (N=9). Sacubitril/valsartan showed a dose-dependent impact on LV systolic function, with higher dosages significantly associated with larger LVEF improvement (Figure 2). Baseline clinical and echocardiographic characteristics were similar across different doses of ARNI, with the exception of younger age and higher eGFR, that were significantly more prevalent on higher doses of the drug (**Supplementary Table II**). We did not observe any significant change in terms of left atrial volume index (LAVI; p=0.197), LV mass index (LVMI; p=0.371), diastolic dysfunction grade (p=0.769), pulmonary artery systolic pressure (p=0.116) and visually graded mitral (p=0.570) and tricuspid (p=0.09) regurgitation after initiation of sacubitril/valsartan (**Supplementary Table III**).

At follow-up, NYHA class significantly improved from baseline (p<0.001) (Figure 3A). Sacubitril/valsartan induced a dose-dependent effect on NYHA functional status, with higher

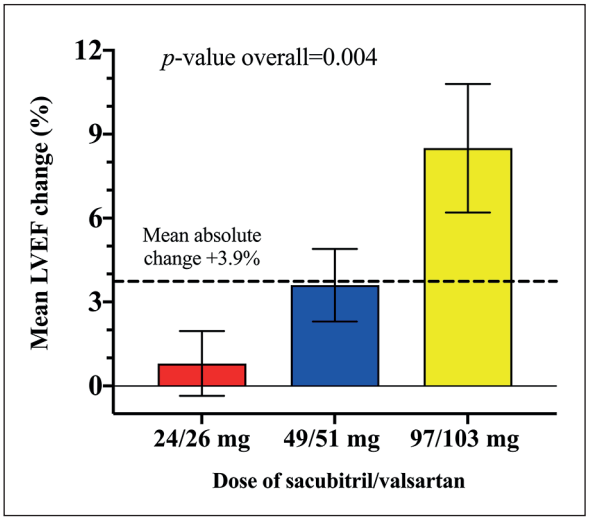

Figure 2. LVEF absolute change from baseline to follow-up according to sacubitril/valsartan dosing strata (24/26 mg bid, N=18; 49/51 mg bid, N=17; 97/103 mg bid, N=13). Dashed line represents the mean absolute change in LVEF in the overall population; *p*-value indicate general *p*-value of ANOVA-test.

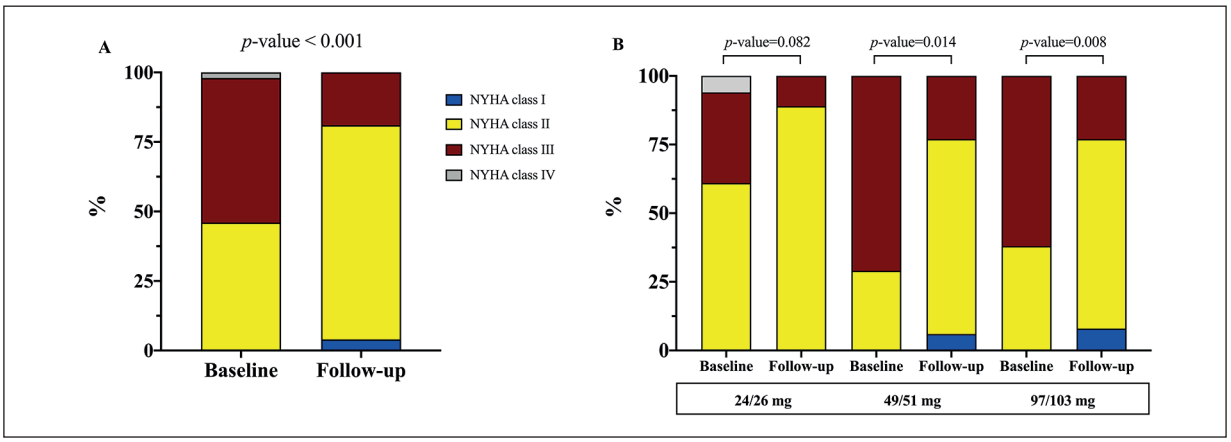

Figure 3. Effect of sacubitril/valsartan treatment on NYHA class change from baseline to follow-up in **(A)** the overall population and **(B)** according to sacubitril/valsartan dosing strata (24/26 mg bid, N=18; 49/51 mg bid, N=17; 97/103 mg bid, N=13).

doses significantly leading to larger improvement (Figure 3B). Overall, 24 (50%) patients reported an improvement (46% of 1 NYHA class; 4% of ≥2 NYHA class), 20 (42%) reported no change and 4 (8.0%) reported a worsening of their NYHA functional status. NYHA class and LVEF improved concurrently in HF patients not indicated anymore for ICD implantation (R^2=0.19, p=0.028).

The effect of ARNI treatment on LV reverse remodeling indexes (change in LVEF and LVESVI) strongly impacted on evaluation for ICD eligibility at follow-up. After sacubitril/valsartan treatment, 40% (N=19) of patients previously implanted with an ICD did not meet anymore the eligibility criteria (Figure 4A), with a higher impact on patients treated with the intermediate and full dose of the drug (Figure 4B). LVEF improvement was significantly associated with a lower NYHA class (II *vs.* III; R^2=0.32, p=0.025) and a dose of sacubitril/valsartan higher than 24/26 mg twice a day (R^2=0.36, p=0.011), but not with age, HF aetiology, gender or comorbidities (Table II). None of the patients died or were hospitalized for cardiovascular causes during the follow-up period.

Finally, the intra-operator reliability for echocardiographic biplane LVEF measure was good (mean difference ± SD: 0.20 ± 2.62%) (**Supplementary Figure 1**).

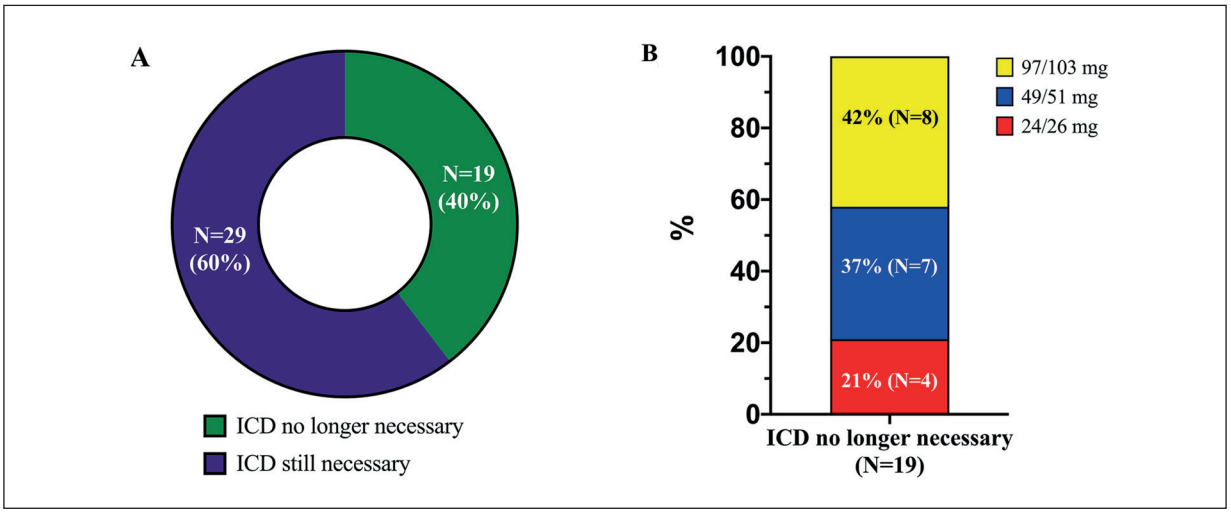

Figure 4. **(A)** Impact of sacubitril/valsartan on eligibility for implantable cardioverter defibrillator (ICD) at follow-up. **(B)** Patients no longer indicated for ICD implantation according to sacubitril/valsartan dosing strata.

Table II. Variables associated with left ventricular ejection fraction (LVEF) change.

Parameter	Correlation coefficient [95% CI]	*p*-value
Age, years-0.185 [-0.446; 0.103]	0.206	
Sex, male 0.108 [-0.181; 0.380]	0.464	
Body surface area, m^2	-0.142 [-0.418; 0.157]	0.349
NYHA class, II *vs.* III	0.321 [0.041; 0.555]	0.025
Systolic blood pressure, mmHg	0.076 [-0.212; 0.353]	0.604
HF aetiology, ischemic *vs.* non-ischemic	-0.072 [-0.349; 0.216]	0.626
Diabetes mellitus, (Yes *vs.* No)	0.136 [-0.153; 0.404]	0.355
Hypertension, (Yes *c* No)	-0.113 [-0.385; 0.176]	0.443
Atrial fibrillation, (Yes *vs.* No)	0.121 [-0.168; 0.392]	0.409
Potassium, mmol/L	-0.014 [-0.361; 0.335]	0.936
eGFR, mL/min/1.73 m^2	0.197 [-0.101; 0.464]	0.193
NTproBNP, ng/L	0.202 [-0.139; 0.502]	0.243
LVEDVI, mL/m^2	-0.439 [-0.837; 0.263]	0.204
LVESVI, mL/m^2	-0.436 [-0.836; 0.266]	0.207
Baseline LVEF, %	-0.034 [-0.315; 0.252]	0.817
LV mass index, gr/m^2	-0.079 [-0.374; 0.230]	0.617
MRA, (Yes *vs.*No)	-0.062 [-0.340; 0.226]	0.675
ACEi/ARB therapy duration, months	-0.103 [-0.422; 0.238]	0.554
Sacubitril/valsartan dose, >24/26 mg bid	0.364 [0.089; 0.587]	0.011

Abbreviations: ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blockers; bid – bis in die; eGFR – estimated glomerular filtration rate; MRA – mineralocorticoid receptor antagonist; NTproBNP - N-terminal pro b-type natriuretic peptide; NYHA – New York Heart Association; LV – left ventricular; LVEDVI – left ventricular end-diastolic volume index; LVESVI – left ventricular end-systolic volume index.

Predictors of LVEF Improvement

Among patients deemed not more eligible for ICD implantation at follow-up visit, the main reason was LVEF increase rather than NYHA class improvement alone. Predictors of eligibility status change were a lower NYHA class (class II *vs.* III, odds ratio (OR) 3.73 [95% CI 1.05; 13.24], p=0.041), a better LVEF (OR 1.23 [95% CI 1.01; 1.48], p=0.032) and a dose of sacubitril/valsartan higher that 24/26 mg twice a day (OR 5.60 [1.15; 27.1], p=0.032). On the contrary, indexes classically associated with improved reverse remodeling, such as younger age, female gender, non-ischemic etiology, and sinus rhythm, did not impact on change of ICD eligibility (Table III).

Table III. Predictors of change in ICD eligibility at follow-up.

Parameter	Odds ratio [95% CI]	Likelihood, χ^2	*p*-value
Age, years	0.95 [0.89; 1.02]	1.48	0.223
Sex, male	0.98 [0.14; 6.50]	0.01	0.983
NYHA class, II *vs.* III	3.73 [1.05; 13.24]	4.16	0.041
HF aetiology, ischemic vs non-ischemic	1.16 [0.33; 4.05]	0.06	0.813
Diabetes mellitus, (Yes *vs.* No)	0.91 [0.24; 3.39]	0.02	0.885
Atrial fibrillation, (Yes *vs.* No)	2.47 [0.74; 8.16]	2.19	0.135
eGFR, mL/min/1.73 m^2	1.02 [0.99; 1.05]	2.28	0.131
NTproBNP, ng/L	1.88 [0.53; 6.64]	0.85	0.327
LVEDVI, mL/m^2	0.93 [1.05; 1.08]	1.51	0.219
LVESVI, mL/m^2	0.90 [0.76; 1.06]	2.99	0.083
Baseline LVEF, %	1.23 [1.01; 1.48]	5.66	0.032
Sacubitril/valsartan dose, > 24/26 mg bid	5.60 [1.15; 27.1]	5.02	0.032

Abbreviations: bid – bis in die; eGFR – estimated glomerular filtration rate; HF – heart failure; ICD – implantable cardiac defibrillator; NTproBNP – N-terminal pro b-type natriuretic peptide; NYHA – New York Heart Association; LVEF – left ventricular ejection fraction; LVEDVI – left ventricular end-diastolic volume index; LVESVI – left ventricular end-systolic volume index.

Discussion

In this retrospective study of patients with chronic HFrEF previously treated with a maximum tolerated dose of ACEi or ARB and implanted with an ICD in primary prevention, sacubitril/valsartan induced incremental LV reverse remodeling and NYHA functional class improvement. These effects were dose-dependent and resulted in a change of ICD eligibility in 40% of the studied population.

Neurohormonal blockade with ACEi, ARB, beta-blockers and MRA is the cornerstone of current medical therapy for HFrEF[4]. These drugs have been demonstrated to reduce morbidity and mortality[13-17] through the antagonism of two main regulatory pathways that are pathologically hyperactivated in HF patients: the RAAS and the SNS[18]. Both RAAS and SNS are responsible not only for vasoconstriction and sodium and water retention, but also for cardiac hypertrophy, fibrosis and cell death, that lead in turn to adverse ventricular remodeling[18]. Pharmacological modulation of these systems in HFrEF patients has been demonstrated to induce beneficial effects on LV size and function[19-22]. A growing body of evidence[23-25] shows that sacubitril/valsartan have beneficial effects on LV reverse remodeling both in animal models and in humans[7,10]. Recently, two prospective studies specifically investigated this topic. Martens et at[9] demonstrated that switching from a RAS-blocker to ARNI had beneficial effects on both systolic and diastolic function at 4 months follow-up, with a mean LVEF increase of 5%. Concurrent improvement in NYHA class was also reported. Similarly, Januzzi et al[8] showed that sacubitril/valsartan treatment significantly improved markers of cardiac volume and function at 12 months in a large HFrEF cohort, with a mean LVEF increase of 9.4%. In a recent metanalysis of twenty studies enrolling 10.175 patients, ARNI showed a beneficial impact on reverse remodeling indexes (LVEF, LV volumes and diameters) and functional capacity in patients with HFrEF[26]. Confirming these data, we found a significant improvement in LV systolic function and size and a concurrent improvement in NYHA functional status after sacubitril/valsartan treatment. It should be noted that, differently from the abovementioned studies[8,9], we were not able to demonstrate a concurrent significant reduction in LAVI, LVMI, diastolic function and visual assessed mitral regurgitation degree. Moreover, we recorded a lower magnitude of LVEF improvement compared to previous observations with a similar follow-up duration (i.e., PROVE-HF study)[8]. Considering the dose-dependent effect of ARNI, the main reason for these differences might be related to the lower use of the target dose of sacubitril/valsartan in our population (27%) compared to other studies (i.e., 65% in the PROVE-HF).

We showed that ARNI significantly impacted on change in LVESV, but not in LVEDV (we recorded only a trend in reduction). This response was not unexpected since it has been shown also for other HFrEF therapies. Namely, after initiation of RAAS antagonists or a beta-blocker the systolic volume often drops more than the diastolic, resulting in an improved LVEF[22,27-29]. Mechanistically, the beneficial effect on reverse remodeling of sacubitril/valsartan could be due to a combination of direct cellular effects and hemodynamic changes induced by neprilysin inhibition. In fact, on one hand the vasodilatory, natriuretic, and diuretic effect of ARNI is responsible for a reduction of afterload and preload, allowing the LV to work on a more favourable Frank-Starling curve[5,30]. Concurrently, sacubitril is implicated in attenuating apoptosis and impaired myocyte contractility, leading in turn to peculiar antifibrotic properties[6,31].

In our study sacubitril/valsartan induced a significant response in terms of LVEF improvement. As a consequence, 40% of HFrEF patients previously implanted with a defibrillator resulted to no longer fulfil eligibility criteria for primary prevention. This might have a dramatic impact not only on patients' life, but also on public health. In fact, model-based health economic analysis showed that the health benefits associated with ARNI treatment are cost-effective when compared with enalapril or ICD implantation[32,33]. Our study suggests that the cost-saving of sacubitril/valsartan therapy could be also higher than previously showed, since it might substantially reduce ICD implantations for SCD prevention according to the current HF guidelines criteria[4]. In addition, recent observational data showed that cardiac reverse remodeling induced by ARNI is associated with a lower incidence of ventricular arrhythmias in HFrEF patients[34], potentially further increasing the beneficial effect of this drug on SCD prevention.

We found that a lower NYHA class, a better LVEF and a higher dose of sacubitril/valsartan were able to predict a change in ICD eligibility after ARNI treatment. In the PARADIGM-HF

trial, a nominally significant interaction between baseline NYHA class and the effect of sacubitril/valsartan treatment was observed for the composite primary endpoint (improved outcomes with NYHA class I-II; p=0.03; without adjustment for multiple comparisons)[5]. If the demonstrated LV reverse remodeling induced by ARNI could contribute to this benefit is still matter of debate. In the PROVE-HF study, the subgroup of patients with new-onset HF showed the better improvement in LVEF (12.8% [95% CI, 11.05% to 14.5%]; p<0.001), demonstrating the strong impact on LV remodeling of early sacubitril/valsartan intervention[8]. This concept is consistent with current guidelines[35] and is based on several published evidence showing that timely interventions are associated with improved outcomes[36, 37]. LVEF is a core criterium for ICD eligibility in HFrEF patients. A recent analysis from the PARADIGM-HF trial (LVEF ≤40%; n=8.399) showed that sacubitril/valsartan was effective at reducing cardiovascular death and HF hospitalization throughout all the investigated LVEF spectrum[38]. In our study a higher baseline LVEF was a predictor of cardiac reverse remodeling. It is probably that patients with a better LV systolic function at baseline (closer to the LVEF decision threshold of 35%) might experience more frequently the loss of ICD eligibility at follow-up even with small LVEF improvements. Finally, we showed that only a dose of sacubitril/valsartan higher than 24/26 mg twice a day was able to predict reverse remodeling. Other studies[8,9] demonstrated a response gradient across ARNI dosages, although a beneficial change in LV remodeling parameter was recorded also with the lower dose. This is not unexpected since also other HF therapies showed a dose-dependent effect. In the Metoprolol CR/XL Randomized Intervention Trial in Heart failure (MERIT-HF)[39] and in the Carvedilol Or Metoprolol European Trial (COMET)[40] patients unable to achieve target dose of the study drug experienced greater excess of cardiovascular events compared with those successfully titrated. In another study[27] investigating the effect of spironolactone in HF patients, those who achieved the full dose of the drug had the greatest benefit in terms of LVEF and peak VO_2 improvement. Altogether, these observations added further biologic plausibility to our findings.

Our results further increase the current body of evidence demonstrating the importance of medical treatment optimization before referring HF patients for device or advanced therapies. In particular, we demonstrated that sacubitril/valsartan significantly improved LV reverse remodeling. As a consequence of increased LVEF, a consistent part of HFrEF patients in our cohort was deemed not more eligible for ICD implantation.

Limitations

This study has several limitations. It is observational, single-group, open-label design with a small sample size. This was not a placebo-controlled trial but instead a retrospective analysis of a real-world population, and therefore causality cannot be addressed. We cannot completely exclude those concurrent pharmacological treatments had a role in determining results. However, patients were optimally treated before initiation of sacubitril/valsartan and those with a recent diagnosis of HF or a short disease-course (< 6-month duration) were excluded. The lack of a control group precludes a direct comparison of sacubitril/valsartan patients to those on OMT. Nevertheless, patients are unlikely to achieve further significant benefits if they failed to have significant reverse remodeling within the first 6 months of OMT. The retrospective design of the study did not allow to evaluate reverse remodeling at a predefined time interval, but only at clinically scheduled follow-up. A consistent percentage of our population did not reach the target dose of the study drug. This suggest that our analysis might understate the actual response in terms of reverse remodeling, which could be even higher. A recent study[34] reported that sacubitril/valsartan treatment was associated with a lower degree of ventricular arrhythmias, resulting in less ICD-interventions. Since we did not collect data about arrhythmic events in the follow-up period, we can only speculate on this effect in our cohort. However, it has been postulated that the antiarrhythmic action of sacubitril/valsartan might be related to cardiac reverse remodeling, adding plausibility to a possible effect also in our population. Finally, although we explored at each visit the patients' adherence to treatment, due to the observational nature of the study we do not have a controlled assessment of this parameter.

Conclusions

In symptomatic HFrEF patients treated with optimal medical therapy and implanted with an ICD in primary prevention, switching from an

ACEi or ARB to sacubitril/valsartan was associated with beneficial cardiac reverse remodeling and improved NYHA functional class. These effects were dose-dependent and resulted in a change of ICD eligibility in 40% of the studied population. Adequately powered and controlled clinical trials are needed to validate these results.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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