Article

Impact of sacubitril/valsartan on indication of implantable cardioverter defibrillator, left ventricle ejection fraction and biomarkers: Data from a real life cohort in Heart Failure with reduced ejection fraction.

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Abstract: Background**:** our purpose is to assess the effectiveness and safety of sacubitril/valsartan (SV) in "real-world" patients with heart failure and reduced ejection fraction (HFrEF), including a broader spectrum of patients than those in clinical trials and evaluating variables not previously described in the literature. Methods: real-world study in HFrEF patients (N:204), both in and outpatients, who started SV between October 2017 and December 2018. We performed a prospective analysis with a 12-month follow-up. The study outcomes were effectiveness and safety, measured by individual parameters and combined endpoints, comparing the pre and post practice periods. Results: at the end of follow-up, an improvement of left ventricle ejection fraction (LVEF): 29.8% vs 33.7; p<0.0001, a decrease in NT-proBNP levels (3928 pg/mL vs 2902 pg/mL; p=0.012), number of hospital admissions (141 vs 35; p<0.0001) and percentage of patients with implantable cardioverter defibrillator (ICD) indication (79.9% vs 49.5%; p<0.0001) were observed. Of our population, 81.3% met a combined efficacy endpoint (defined by increase of LVEF, reduction of hospital admission or improvement in functional class). No differences were observed in parameters regarding safety. Conclusions: Sacubitril/valsartan has brought about a revolution in the therapeutic management of HFrEF patients and its use may raise questions about what is considered "optimal medical therapy" prior to implantation of cardiac devices.

Keywords: Heart failure with reduced ejection fraction; Real-life practice; Sacubitril/valsartan; Left ventricular ejection fraction recovery; Implantable cardioverter defibrillator

1. Introduction

Heart failure (HF) affects more than 23 million people around the world [1], it represents one of the main causes of cardiovascular morbidity and mortality, its prevalence increasing with age [2]. The latest clinical practice guidelines [3] classify HF into three groups according to left ventricular ejection fraction (LVEF): HF with reduced LVEF (<40%), mid-range LVEF (40-49%), and preserved LVEF (≥50%), resulting in different repercussions on therapeutic patient management.

HFrEF treatment comprises neurohormonal antagonists, including angiotensin converting enzyme inhibitors (ACEi) or angiotensinogen receptor blockers (ARB), beta-blockers (BB), and mineralocorticoid receptor antagonists (MRA), which have been shown to improve prognosis. Recently, sacubitril-valsartan (SV) has joined this therapeutic arsenal. This drug combines a neprilysin inhibitor and angiotensin II receptor antagonist (ARA II), resulting in an increase in natriuretic peptide levels, while inhibiting the effects of angiotensin II. SV has been shown to be superior to enalapril in reducing the risk of death and

hospitalization for HF [4]. The combination with the best efficacy on patient prognosis has proven to be ARNI+BB+MRA [5].

The SV efficacy has been demonstrated in several randomized clinical trials (RCT) that compared this combination to enalapril. The results of the PARADIGM-HF [4], in patients with chronic HFrEF, have revealed that SV significantly improves the prognosis of HFrEF patients in New York Heart Association (NYHA) Class II-IV, as compared to enalapril. In addition, SV was demonstrated to reduce long-term mortality, both overall and of cardiovascular origin, and the need of hospital readmission due to worsening HF. On the other hand, data from the PIONEER-HF [6] showed that SV reduces N-terminal pro-B type natriuretic peptide (NT-proBNP) levels and readmission rates compared to enalapril in acute HF. Finally, data from the PROVE-HF [7] have shown that there was a correlation between the reduction in NT-proBNP levels after SV therapy in HFrEF patients and several signs of reverse cardiac remodeling at one-year follow-up.

Based on the drug's prescribing information [8], SV administration is allowed if systolic blood pressure (SBP) ≥100mmHg, potassium level <5.4mmol/L, and estimated glomerular filtration rate (eGFR) >60mL/min/1.73m^2. Caution is warranted in the event of eGFR of 30-60mL/min/1.73m^2 and is definitely discouraged in end-stage renal disease. A few evidences have been reported in the literature supporting its use outside of these criteria [9].

The use of an implantable cardioverter-defibrillator (ICD) to avoid sudden cardiac death is indicated in patients with symptomatic HF (NYHA Class II/III) and LVEF ≤35% after ≥3 months of optimal medical therapy. SV treatment in patients with LVEF ≤35% has been associated with LVEF recovery and improvement in functional class [4,6,7]. This implies that a few patients that, prior to SV therapy, displayed an indication for an ICD based on the current guidelines [3] would no longer require such an ICD intervention. This paradigm opens an entirely new approach to prevent sudden death in HFrEF patients.

Despite these data, there is a gap in the scientific literature, since we do not have any clinical trial that evaluates the decrease in the indication of CDI through the use of SV. There is also no real life data on this fact.

This study sought to analyze SV effectiveness and safety in HFrEF patients in real-world clinical practice and evaluate its impact on other outcome measures, including the indication for ICD.

2. Materials and Methods

We performed a prospective study in real-world SV-treated patients with HFrEF. The study was carried out in one single center between 2017 and 2019 (Huelva University Hospital, a tertiary hospital). This center's heart failure unit (HFU) comprises three cardiologists and two nurses specialized in HF care HFU is considered the reference unit for a population of 550,000 people, with around 800 patients admitted yearly.

The study was conducted according with the Declaration of Helsinki, and approved by the ethics committee of the Juan Ramon Jimenez Hospital (Protocol Code 174, 02/09/2017). Written informed consent was obtained from all subjects involved in the study

2.1. Patients

All consecutive HFrEF patients attending the Huelva University Hospital who started SV treatment between October 2017 and December 2018 were included (N=204), regardless of whether they were in or outpatients. Figure 1 shows patients enrolment into the study. Definition of HF was consistent with that of the European Society of Cardiology guidelines [3], including presentation of typical HF symptoms that may be accompanied by HF signs caused by a structural or functional heart disease. HFrEF is defined by the presence of HF symptoms in a NYHA Class II, III, or IV patient, with LVEF <40%. The inclusion criteria for the study were: 1) adult patients (18 years old and over) that fulfilled the HF diagnosis; 2) LVEF <40% confirmed by echocardiography. The exclusion criteria

were: 1) patients with LVEF ≥40%; 2) HF due to right ventricular failure, pericardial disease, congenital heart disease or pulmonary hypertension, 3) concomitant dementia 4) clinical situations with a life-expectancy of <1 year; 4) potential follow-up difficulties. (Supplementary data, Table S1). 7 patients died to follow-up and 3 patients were lost to follow-up

2.2. Variables and measurements

Demographic data, baseline characteristics, medical history including prior treatments, NYHA functional class, LVEF, vital signs, and laboratory parameters before starting SV treatment were collected. The follow-up period was 12 months. Patients were evaluated within the first month after starting SV treatment depending on their individual needs, and then every three months until the end of the 12-month follow-up. The protocol for the follow-up visits comprised a medical examination, anamnesis of relevant clinical features, signs, and symptoms, medication, NYHA functional class, SV de-escalation or withdrawal, potential undesirable effects attributable to SV therapy (symptomatic hypotension, impaired renal function, hyperkalemia, or angioedema), blood testing, electrocardiogram (EKG), and treatment adjustment of treatments as necessary according to the clinical practice guidelines. An echocardiography was performed at 12 months or earlier in the case of worsening HF at the discretion of cardiologist.

2.3. Clinical outcomes

The study outcomes were effectiveness and safety, measured by individual parameters and combined endpoints, with pre- and post-practice data compared.

The effectiveness parameters applied were LVEF, NT-proBNP levels, indication for ICD, functional class, and number of hospitalizations. In addition, there was a combined endpoint including any of the following three criteria: increase in LVEF, reduction in hospital admissions, or improvement in functional class.

Regarding safety, data on creatinine, potassium, blood pressure, percentage of patients hat attained the maximum dose, and percentage of patients that discontinued treatment were recorded. The combined safety endpoint was defined by the absence of any of the following three criteria: hyperkalemia >5.5; creatinine > 2.5, and symptomatic hypotension.

2.4. Statistical analyses

A descriptive analysis was carried out using central tendency and dispersion measures, as well as frequency and percentage distribution for quantitative and qualitative variables, respectively. Possible differences in baseline characteristics between our cohort and that of the PARADIGM [5] clinical trial were analyzed using parametric or non-parametric tests depending upon the distribution of quantitative variables, and differences of proportions and Chi-squared test for the qualitative ones.

The comparison of individual effectiveness and safety parameters from baseline and 12 months after treatment initiation was carried out using tests for paired data like the paired Student's t-test and McNemar's test.

The association of effectiveness and safety with different subgroups was studied, using the odds ratio (OR) as an association measure. These analyzes were performed in the following subgroups: inpatient or outpatient; eGFR <30mL / >30mL/min/1.73m2; systolic blood pressure <= 100mmHg/>100mmHg; NYHA II v. NYHA III/IV. Statistical analysis was carried out using STATA Version 12 (Stata Corporation, College Station, TX).

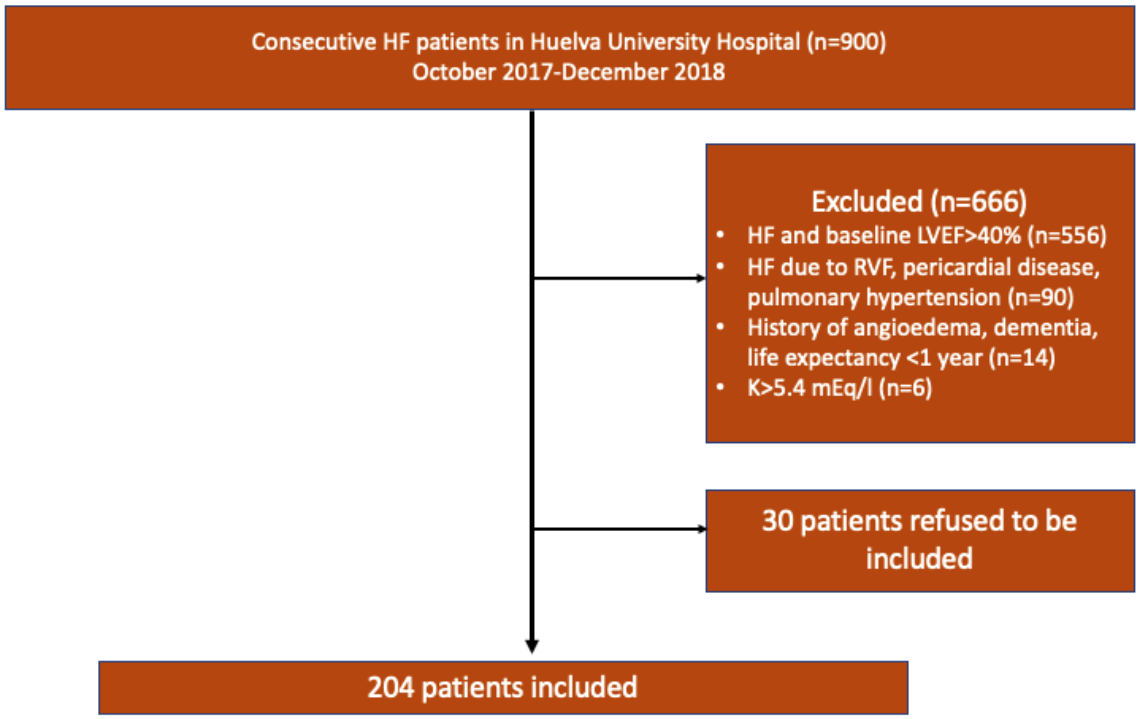
3. Results

3.1. Study cohort

The study cohort included 204 patients (Figure 1), who were mostly male (78%), with a mean age of 66 ± 11 years, median HF duration of 2.1 years, and average LVEF of 29.8 ±

6.3%. The most common etiology was ischemic (54%), followed by idiopathic (26%). The distribution of patients by functional NYHA class was: 63.3% Class II, 29.1% Class III, 6.5% Class I, and 1% Class IV. Median values (P25-P75) for NT-proBNP and SBP levels were 1803pg/mL (873-3864 pg/mL) and 120mmHg (110-135 mmHg), respectively, with mean values (± SD) for serum creatinine of 1.33 ± 1.45mg/dL. Concerning comorbidity, 47% of patients exhibited prior acute myocardial infarction, 71% hypertension, 39% diabetes, 65% dyslipidemia, and 38% atrial fibrillation (Table 1).

Figure 1. Flow chart of patients included in the study.



HF, heart Failure; LVEF, left ventricle ejection fraction; RVF, right ventricular failure

Table 1. Study cohort: baseline characteristics.

Variable	N	Value
Gender (male), n (%)	204	160 (78.4)
Age (years), mean ± SD	204	66.0 ± 11.2
Duration of heart failure, median (P_{25}-P_{75})	204	2.1 (0.5 – 6.7)
Number of hospitalizations, median (P_{25}-P_{75})	204	0 (0 - 1)
Heart rate, mean ± SD	204	65.8 ± 13.5
SBP (mm Hg), median (P_{25}-P_{75})	204	120 (110 – 135)
DBP (mm Hg), median (P_{25}-P_{75})	204	70 (60 – 80)
Comorbidities:		
• Hypertension, n (%)	203	144 (70.9)
• Hypercholesterolemia, n (%)	203	132 (65.0)
• Diabetes, n (%)	204	80 (39.2)
• Anemia, n (%)	204	22 (10.8)
• Previous atrial fibrillation, n (%)	204	77 (37.8)
• Previous percutaneous transluminal angioplasty, n (%)	204	96 (47.0)
• Smoking, n (%)		
- Ex-smoker	204	126 (61.8)
- Current smoker		18 (8.8)
• Ictus, n (%)	204	22 (10.8)
• Obesity, n (%)	204	42 (20.6)
• Chronic obstructive pulmonary disease, n (%)	204	42 (20.6)
• Obstructive sleep apnea, n (%)	204	11 (5.4)
• Previous myocardial infarction, n (%)	204	97 (47.6)
• Peripheral artery disease, n (%)	203	15 (7.4)

Variable	N	Value
• Dementia, n (%)	203	1 (0.5)
• Valvular prosthesis, n (%)	204	14 (6.9)
• Cardiomyopathy		
- Ischemic, n (%)	204	111 (54.4)
- Non-ischemic, n (%)	204	90 (44,1)
- Hypertensive, n (%)		4 (4.4)
- Tachycardia-induced, n (%)		6 (6.7)
- Valvular, n (%)		8 (8.9)
- Familiar, n (%)		6 (6.7)
- Idiopathic, n (%)		23 (25.6)
- Myocarditis, n (%)		2 (2.2)
• LVEF (%), mean ± SD	204	29.8 ± 6.3
• ACEI/ARB previous (%)		96,9
• Beta-blockers (%)		94,7
• MRA (%)		81,6
• Ivabradine (%)		37,5

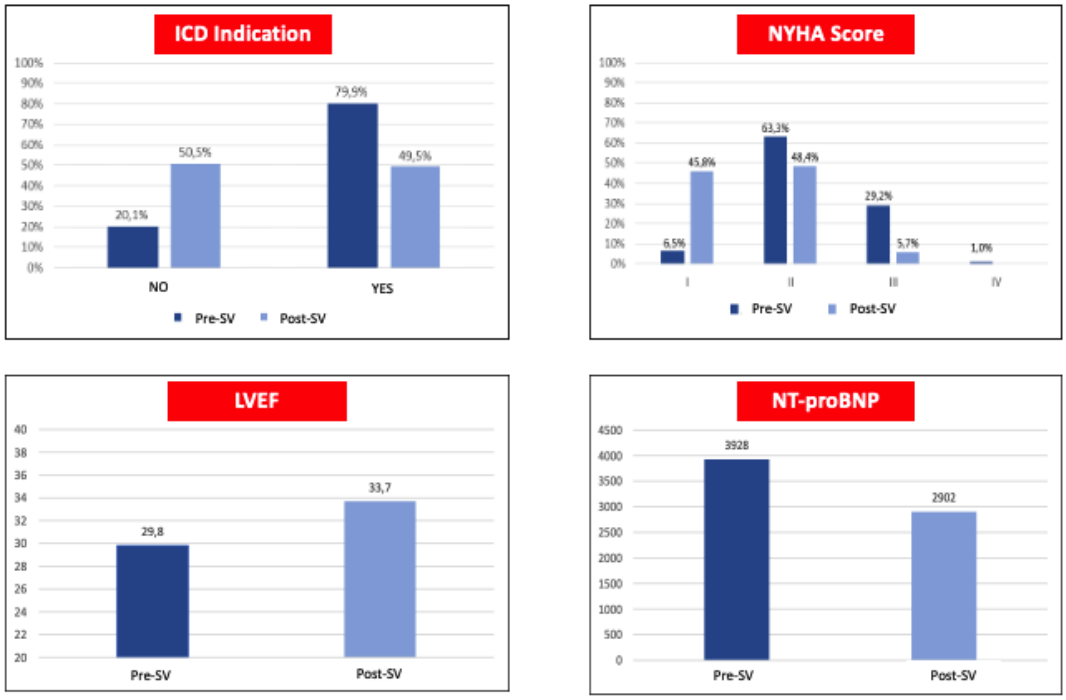
SD, standard deviation; SBP, systolic blood pressure; DBP, Diastolic blood pressure; LVEF, left ventricular ejection fraction; ACEI, Angiotensin-converting-enzyme inhibitors; ARB, Angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonist

The comparison with the PARADIGM data trial [5] showed that our study cohort patients were older and displayed worse kidney function, higher natriuretic peptides levels, and worse functional class (Supplementary data, Table S2).

3.2. Outcomes: Efficacy

Comparative efficacy parameters recorded before and after SV treatment have been illustrated in Figure 2. This illustration reveals a significant increase in LVEF (29.8% vs. 33.7%; p<0.0001), along with a marked decrease in patients with ICD indication (79.9% vs. 49.5%; p<0.0001), an important decrease in NT-proBNP levels (3928 vs. 2902 pg/mL; p=0.012), and a strong reduction in hospital admissions (141 vs. 35; p <0.0001). In addition, SV was shown to significantly improve patients' functional status, so that the percentage of Class I patients changed from 6% to 46%; Class II from 63% to 48%; Class III from 29% to 6% (Table 2).

Figure 2. Main efficacy parameters of the study



ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; NT-proBNP, N-terminal pro-B type natriuretic peptide.

Table 2. Efficacy: before-after sacubitril/valsartan and combined endpoint.

Individual efficacy parameter	**N**	**Baseline**	**After SV**	***p* value**
LVEF (%), mean ± SD	161	29.8 (6.4)	33.7 (8.0)	**<0.0001**
NT-proBNP (pg/mL), mean ± SD	146	3928 (6594)	2902 (6141)	**0.012**
HF admission, n	203	141	35	**<0.0001**
Loop diuretic (mg), mean ± SD	152	39.8 (31.5)	39.9 (36.1)	0.947
ICD indication, *n* (%)	204	163 (79.9%)	101 (49.5%)	**<0.0001**
NYHA Functional class, *n* (%)				
• I		13 (6.5%)	88 (45.8%)	
• II		126 (63.3%)	93 (48.4%)	**<0.0001**
• III		58 (29.1%)	11 (5.7%)	
• IV		2 (1.0%)	-	
Basal characteristics		**Combined efficacy endpoint**		***p* value**
		No (N=22)	**Yes (N=166)**	
Place where the treatment was started				
• Inpatients		20 (90.9%)	143 (86.1%)	0.744
• Outpatients		2 (9.1%)	23 (13.9%)	
Age (years)		67.0±13.9	66.0±10.9	0.687
Gender (male), n (%)		18 (81.8%)	128 (77.1%)	0.788
SBP, mean ± SD		120.7±16.6	122.8±21.3	0.660
Diabetes		4 (18.2%)	72 (43.4%)	**0.035**
Atrial fibrillation		12 (54.5%)	57 (34.3%)	0.065
Heart Failure duration (years), mean ± SD		6.2±6.1	4.2±5.0	0.087
Ischemic , n (%)		11 (50.0%)	90 (54.2%)	0.709
LVEF at diagnosis (%), mean ± SD		32.5±5.6	29.6±6.3	**0.040**
QRS duration (ms), mean ± SD		131.5±32.4	122.7±23.7	0.221
NT-proBNP (pg/mL), mean ± SD		1738±1506	4368±7065	0.100
NYHA Functional class, *n* (%)				
• I		1 (4.5%)	7 (4.3%)	
• II		21 (95.4%)	98 (60.5%)	**0.001**
• III		-	55 (33.9%)	
• IV		-	2 (1.2%)	

Nº of admissions	0.27±0.55	0.82±0.95	**0.009**
Creatinine (mg/dL), median (P_{25}-P_{75})	2.13±2.95	1.25±0.09	**0.009**
eGFR (CKD-EPI) (ml/min/1,73 m²), median(P_{25}-P_{75})	59.5±27.5	72.2±25.2	**0.028**
Loop diuretics, n (%)	15 (68.2%)	106 (64.2%)	0.716
Angiotensin-converting-enzyme inhibitors, n (%)		154 (93.3%)	0.367
Betablockers, n (%)	22 (100%)	154 (93.3%)	0.367
Ivabradine, n (%)	5 (22.7%)	52 (31.5%)	0.400
Mineralcorticoid receptors antagonists, n (%)	17 (77.3%)	136 (82.4%)	0.556

LVEF, left ventricular ejection fraction; SD, standard deviation; NT-proBNP, N-terminal pro-B type natriuretic peptide; HF, heart failure; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate (CKD-EPI formula).

The combined efficacy endpoint was defined by the presence of any of the following three criteria: increase in LVEF, reduction in hospital admissions, or improvement in functional class. The number of patients meeting any of these criteria was 84 (41%) for reduction in hospitalizations, 114 (60.6%) for improvement in functional class; 91 (56.5%) for improvement in LVEF. A total of 166 cohort patients (81.3%) met the combined efficacy endpoint.

Patients who met this combined endpoint had lower LVEF at diagnosis (29.6 vs. 32.5; p = 0.040), worse functional class (p = 0.001), higher number of hospitalizations (p = 0.009), higher frequency of diabetes (43% vs. 18%; p = 0.035), better renal function with lower creatinine levels (2.13 vs. 1.25; p = 0.009), and higher rate of glomerular filtration (72.2 vs. 59.5; p = 0.028) (Table 2).

Finally, subgroup analysis revealed that efficacy was significantly higher in patients who met the PARADIGM trial [5] criteria (OR=2.76; p=0.046), with decreased efficacy observed when basal glomerular filtration was <30 (OR=0.15; p=0.003).

3.3. Outcomes: Safety

Comparison of safety parameters recorded at baseline and at 12-month follow-up showed no significant difference in serum creatinine, potassium, and systolic blood pressure values. It should be noted that only 6% of patients discontinued treatment, and that 38% attained a final dose of 97/103 mg (Table 3).

The only differences observed between patients who met and those who did not meet the combined safety criteria were the lower concentration of NT-proBNP (3223 vs. 6070 pg/mL; p=0.013), lower functional class (p=0.024), and lower number of hospitalizations (0.63 vs. 0.96; p=0.037) (Table 3).

Table 3. Safety: before-after sacubitril/valsartan and combined endpoint.

SAFETY	**N**	**Before SV**	**After SV**	**p value**
Creatinine (mg/dL), mean (SD)	81	1.30 (1.53)	1.61 (2.24)	0.311
Potassium (mEq/L), mean (SD)	80	4.7 (4.6)	4.6 (4.5)	0.208
SBP (mm Hg), mean (SD)	82	120.6 (17.5)	117.8 (17.4)	0.152
Final dose				
• Retired			12 (6.1%)	
• 24/26 mg	198		34 (17.2%)	
• 49/51 mg			76 (38.4%)	
• 97/103 mg			76 (38.4%)	
Basal characteristics		**Combined safety endpoint**		***p* value**
		No (N=45)	**Yes (N=152)**	
Place where the treatment was started				
• Inpatients, n (%)		36 (80.0%)	134 (88.2%)	0.162
• Outpatients, n (%)		9 (20.0%)	18 (11.8%)	
Age (years), mean ± SD		65.8±9.9	66.1±11.4	0.871
Gender (male), n (%)		37 (82.2%)	119 (78.3%)	0.568
SBP, mean ± SD		123.4±21.6	122.6±20.8	0.837
Diabetes, n (%)		22 (48.9%)	56 (36.8%)	0.147
Atrial fibrillation, n (%)		16 (35.6%)	59 (38.8%)	0.692
HF duration (years),mean ± SD		4.4±4.7	4.2±5.1	0.792
Ischemic, n (%)		27 (60.0%)	83 (54.6%)	0.522

LVEF (%), mean ± SD	30.2±6.5	29.9±6.2	0.762
QRS duration (ms), mean ± SD	118.9±23.8	124.3±25.5	0.257
NT-proBNP (pg/mL), mean ± SD	6070±10144	3223±4861	**0.013**
NYHA Functional class, *n* (%)			
• I	3 (6.7%)	10 (6.8%)	
• II	21 (46.7%)	100 (68.0%)	**0.024**
• III	21 (56.7%)	35 (23.8%)	
• IV	-	2 (1.4%)	
Nº of admissions, mean ± SD	0.96±1.10	0.63±0.85	**0.037**
Creatinine (mg/dL), mean ± SD	1.70±2.11	1.24±1.21	0.072
eGFR (CKD-EPI) (ml/min/1,73 m²), mean ± SD	68.2±29.8	71.0±24.0	0.510
Starting dosage	1.42±0.54	1.55±0.62	0.203
Potassium (mEq/L) , mean ± SD	4.67±0.49	4.63±0.46	0.597
Criteria for ICD before the treatment, n (%)	33 (73.3%)	123 (80.9%)	0.271
Anemia, n (%)	7 (15.6%)	14 (9.2%)	0.226
Dementia, n (%)	-	1 (0.7%)	1.000
Angiotensin-converting-enzyme inhibitors, n (%)	41 (93.2%)	144 (94.7%)	0.713

SD, standard deviation; SBP, systolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate (CKD-EPI formula); ICD, implantable cardioverter defibrillator.

Subgroup analysis revealed that SV was safer in patients with glomerular filtration above 30mL/min/1.73m2 and better functional class, with OR of 0.27 (p=0.030) and 0.38 (p=0.007), respectively. There were no differences between inpatient and outpatient setting, regardless of blood pressure values or whether or not PARADIGM inclusion criteria were met.

4. Discussion

To our knowledge, this is one of the most comprehensive studies on SV in HFrEF patients carried out to date. The study included outpatients and inpatients, in addition to involving different efficacy and safety outcomes, some of which have not yet been studied in previously conducted clinical trials According to the results obtained, SV treatment for 12 months exerts the following effects: (i) clear reduction in ICD indication; (ii) increase in LVEF; decrease in NT-proBNP and readmission; rates; (iii) combined efficacy endpoint achieved in 81.3% of patients. In addition, SV has proven to be safe without resulting in creatinine concentration, potassium level, or SBP value changes, and with only a low discontinuation rate (6%).

Despite the observation that clinical trials are the first-choice tool for evaluating the efficacy of drugs, we should not forget that patients included in clinical trials are highly selected; generally, they do not represent real-life settings [10]. This underlines the relevance of conducting real-life studies like the one reported herein in order to enable us to assess their effectiveness in real-life patients across the entire disease spectrum. Indeed, our population also included older patients with more advanced heart disease and worse kidney function than previous SV clinical trials have done [4,6,7].

Different observational studies have been carried out on the SV use under real-life conditions. Table 4 provides a summary of the most relevant studies. Regarding efficacy endpoints, this drug has been shown to be effective in improving LVEF [11,12,13] and functional outcome by improving NYHA class [11,12,14,15], while reducing hospital admissions for worsening HF [12,14,15,16]. However, none of these studies have focused on changes in ICD indications following SV treatment.

The study's efficacy results showed that 81% of SV-treated patients attained the combined efficacy endpoint (defined by at least one of the following criteria: improvement in LVEF, better functional class, or fewer hospital readmissions. It must be stressed that although various studies have published efficacy results based on different parameters, none of them have used a combined measurement as in our case, which can be considered an estimate of overall drug efficacy. There is still little information in real life about the use

during hospitalization. We consider it highly relevant to note that in our study the efficacy and safety did not change according to the out or in-patient onset.

Advances made in HF management have enabled us to reduce sudden death in HFrEF patients, through implementing optimal medical therapy [17] and using various devices [18]. Despite these major advances made, more than one-third of all-cause mortality in contemporary clinical trials is still to be accounted for by sudden cardiac death [19]. ICD implantation has proven its long-term efficacy in preventing patients from sudden cardiac death [20], but approach has a high economic cost, and it is not devoid of serious harm [21,22]. The cost-effectiveness of ICD implantation for primary prevention in patients with a LVEF <40% and ischemic or non-ischemic heart disease has been previously analyzed [21]. These data have revealed that the mean lifetime cost of ICD was shown to be much higher. Accordingly, the cost of a 'no ICD strategy' was € 50 685 ± € 4604 versus € 86 759 ± € 3343 for an 'ICD strategy', although the ICD implantation strategy was cost-effective. Regarding complications, Van der Heijden et al. [22] showed that the 12-year ICD complication rate, with or without cardiac resynchronization therapy, was 20% (95% confidence interval [CI]: 18% -22%) for inappropriate shock, 6% (95% CI: 5% -8%) for device-related infection, and 17% (95% CI: 14% -21%) for lead failure. These study results underline that a decrease in ICD indications likely achieves significant cost saving and an improvement in HF patients' quality of life.

The reduction in ICD indications achieved in our study (79.9% prior to 49.5% at 12 months; p <0.00001) proves to be very interesting information. In an article published by El Battrawy et al. [23], SV failed to decrease ventricular arrhythmias after 12-month follow-up, whereas in a recent article by Rohde et al. [24], it is concluded that the benefit of such a reduction is greater in ICD users and non-ischemic cardiomyopathy patients. Nevertheless, no direct comparison between ICD use and SV addition has been published so far. Yet, in some studies, SV has been shown to effectively reduce ventricular tachycardia and ventricular fibrillation rates, while decreasing the number of ICD-delivered shocks [25,26]. Consequently, SV treatment may definitely turn out to be cost-effective versus ICD implantation [27].

On the other hand, our data show a reverse remodeling with improvement in LVEF (from 29.8 to 33.7%; p <0.0001); these results are similar to those published by Martens et al. [28]. The mean value of NT-proBNP was reduced (3928 to 2903pg/mL; p = 0.012), together with a marked improvement in functional class (40% remained asymptomatic after using SV), as described by Lau et al. [29].

Table 4. Main characteristics of real-life studies with sacubitril/valsartan.

Author	Patients (*n*)	NYHA class	LVEF(%)	Final dose SV	NYHA change	Final LVEF (%)	Loss of ICD indication	HF admissions
Esteban A[14]	427	II: 68% III:27%	29	Low 21% Mid 33% High 33%	Yes	33	N/A	Decrease
Chang HY[19]	466	II: 79%	27	N/A	N/A	N/A	N/A	Decrease
Lopez JC[17]	527	II: 63% III:30%	30	Low 27% Mid 35% High 36%	Yes	30	N/A	Decrease
Pharithi RB[15]	322	I: 10% II: 78% III:11%	28	Low 8% Mid 11% High 80%	Yes	32	N/A	N/A
González L[16]	250	N/A	31	N/A	N/A	36	N/A	N/A
Martens P[18]	201	II: 68% III: 31%	29	Low 33% Mid 42% High 25%	Yes	N/A	N/A	Decrease

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SV, sacubitril/valsartan; ICD, implantable. cardioverter defibrillator; HF, heart failure; N/A, non-available.

As for the drug's safety in our sample, neither worsening of creatinine or potassium values nor changes in SBP were observed. Not surprisingly, the drug discontinuation rate was only 6%.

The main limitation of the study resides in its observation nature, in addition to not dealing with a control group; does not make it possible to ensure that the observed response is due exclusively to the study drug. Also, a propensity score match between the present group of patients and those who did no receive SV in the historical control would have been more reliable for this scope. Another limitation is the heterogeneity of the study sample due to the lax inclusion/exclusion criteria and that, although it increases the external validity of the study, it will make it difficult to draw conclusions about specific groups of patients with more homogeneous characteristics, also for a limited sample size, due to the fact it was a unicenter register. Randomized studies involving a larger number of patients are re-quired to go deeper into this issue.

5. Conclusions

The results of this real-life study prove that SV treatment attains effectiveness in 88.3% of patients without any associated safety concerns. In addition, the improvement in left ventricle remodeling and reduction in ICD indications observed are likely to significantly impact patients' prognosis and quality of life, all of which at a lower cost.

Supplementary materials: supplementary data (including Table S1 and Table S2) is available online at "https://www.mdpi.com/XXX".

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