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ORIGINAL ARTICLE

Sacubitril/Valsartan in Real-Life Practice: Experience in Patients with Advanced Heart Failure and Systematic Review

Carles Moliner-Abós[1] · Mercedes Rivas-Lasarte[1] · Julia Pamies Besora[1] · Paula Fluvià-Brugues[1] · Eduard Solé-González[1] · Sonia Mirabet[1] · Laura López López[1] · Vicens Brossa[1] · Maria José Pirla[1] · Nuria Mesado[1] · Jesús Álvarez-García[1] · Eulàlia Roig[1]

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Abstract

Purpose Sacubitril/valsartan reduced heart failure (HF) admissions and cardiovascular mortality in the PARADIGM-HF trial. However, real-life studies are scarce comparing daily practice patients with those of the trial. The aim of our study was to analyze the efficacy and safety of the drug in an advanced heart failure cohort and to review systematically the previous real-life studies published to date.

Methods We performed a retrospective analysis of consecutive patients prescribed sacubitril/valsartan in a single tertiary HF clinic between September 2016 and February 2018. HF admissions before and after the initiation of the drug were assessed in a paired fashion. A systematic review of real-life studies published to date was also conducted.

Results Sacubitril/valsartan was started in 108 patients who were in a more advanced NYHA class and more frequently treated with mineral receptor antagonists, internal cardiac defibrillator, and cardiac resynchronization therapy than in the PARADIGM-HF trial. After a 6-month follow-up, we observed a significant reduction in the HF hospitalizations, median levels of NT-proBNP, and need for levosimendan ambulatory perfusion. Likewise, we found a significant improvement in mean LVEF and end diastolic left ventricle diameter. Regarding safety, sacubitril/valsartan was well-tolerated without any severe adverse effect.

Conclusion Sacubitril/valsartan in real-life is prescribed to a more advanced HF population, which could be responsible for the difficulties in reaching high doses of the drug. However, after a 6-month follow-up, sacubitril/valsartan significantly reduces HF hospitalization and induces cardiac reverse remodeling, without remarkable adverse events.

Keywords Sacubitril/valsartan · Heart failure · Real-life practice · Review

✉ Jesús Álvarez-García
jalvarezg@santpau.cat

Carles Moliner-Abós
cmoliner@santpau.cat

Mercedes Rivas-Lasarte
mrivasl@santpau.cat

Julia Pamies Besora
jpamiesb@santpau.cat

Paula Fluvià-Brugues
paulafluvia.girona.ics@gencat.cat

Eduard Solé-González
esoleg@santpau.cat

Sonia Mirabet
smirabet@santpau.cat

Laura López López
llopezl@santpau.cat

Vicens Brossa
vbrossa@santpau.cat

Maria José Pirla
mpirla@santpau.cat

Nuria Mesado
nmesado@santpau.cat

Eulàlia Roig
eroigm@santpau.cat

[1] Cardiology Department, Hospital de la Santa Creu i Sant Pau, IIB-SantPau, CIBERCV, Universidad Autónoma de Barcelona, Calle Sant Antoni Maria Claret 167, 08025 Barcelona, Spain

Introduction

Heart failure (HF) is a major public health problem, with an increasing incidence and prevalence [1], which implies a substantial health-care resource burden despite pharmacological progress in the last decades [2]. Within these new drugs, sacubitril/valsartan showed promising results in its pivotal study, the PARADIGM-HF trial [3], so it was approved in Europe in late 2015, and since then, it is being increasingly prescribed [4].

However, real-life patients often differ substantially compared to those in clinical trials [5, 6], and cohort studies have an important role in revealing drug performance in daily clinical practice and in generating new hypotheses. Until now, sacubitril/valsartan has specially been prescribed in a higher-risk profile population with more comorbidity and in more advanced condition [7–22]. Moreover, preliminary real-world data about the efficacy and tolerability of this drug is partially supported by improvement in functional class [8, 12, 15, 18–20] and cardiac remodeling [9, 10, 17, 18], and a reduction in HF readmissions [10, 16, 17, 19].

Hence, we conducted a study aimed to analyze the real-life patient clinical profile and explore the safety and efficacy of sacubitril/valsartan in a tertiary referral hospital. Furthermore, we compare our experience with previous reports about the initial use of sacubitril/valsartan.

Methods

Study Population

This is a retrospective cohort study of all consecutive patients attended at the HF clinic in a single tertiary referral center since September 2016 to February 2018 in which sacubitril/valsartan was introduced. The clinical criteria for initiating the drug were (i) symptomatic HF defined as New York Heart Association (NYHA) class II–IV, (ii) left ventricular ejection fraction (LVEF) $\leq 40\%$ measured by echocardiography, and (iii) pretreatment according to the current European Society of Cardiology guidelines (including ACEI or ARB) [23].

Study Variables

Data were collected using the electronic health record of the hospital. The following clinical variables were gathered at study inclusion and during the follow-up period: demographic and previous clinical history, NYHA functional class, systolic blood pressure, laboratory blood tests including NT-proBNP within the previous 30 days before sacubitril/valsartan initiation, ECG, echocardiography within the previous 6 months, and pharmacological and non-pharmacological treatment. In order to simplify the analysis of the HF pharmacological treatment baseline dose, we divided it into two groups: those who had a baseline dose > 50% of the advised dose according to the current European Society of Cardiology guidelines [23], and those who did not. Basal characteristics of the patients were compared to those in the PARADIGM-HF drug arm [3] using the published data available in the article or supplementary material.

Follow-up and Study Endpoints

After initiation of sacubitril/valsartan, the frequency of the follow-up visits was performed at the discretion of the attending cardiologist. Most patients visited the HF clinic every 2-4 weeks, with renal function and serum potassium determination, and clinical status check. Once the drug was up-titrated until maximum tolerated dose, a new determination of NT-proBNP and echocardiography was usually done. We used patients as their own control using a validated antecedent-incident analysis. The incident HF follow-up duration was calculated as the time from starting sacubitril/valsartan until the time of censoring: death, heart transplantation, or a 6-month complete period. Over a similar follow-up duration, the number of HF admissions before the initiation of sacubitril/valsartan was calculated. Thereafter, the number of previous HF admissions was compared with the number of incident HF hospitalizations.

The primary objective was to study the incidence of HF admission and the need for ambulatory administration of levosimendan or intravenous diuretic before and after treatment with sacubitril/valsartan.

Secondary objectives were to study other efficacy endpoints such as the change in NYHA class, NT-ProBNP levels, left ventricle remodeling and safety endpoints including dizziness or symptomatic low blood pressure, angioedema or severe allergic reactions, worsening of renal or electrolyte disturbances.

Statistical Analysis

Continuous variables were expressed as the mean ± standard deviation (SD) or as median (interquartile range). Continuous variables were compared with the Student's t test, log-rank test, or paired t test. Categorical variables were expressed as percentages and compared with the $\chi 2$ or Fisher's exact tests. To analyze the differences between the efficacy and safety endpoints before and after the initiation of sacubitril/valsartan, we used the McNemar's exact test for categorical variables and Wilcoxon matched-pairs signed-rank test or the Student's t test for paired samples whenever appropriate. A two-sided p value < 0.05 was considered statistically significant. All the analyses were performed using STATA software (v. 13.1).

Search Method

The aim of the systematic review was to select observational cohort studies reflecting real-life practice in sacubitril/valsartan use. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines [24]. A systematic literature search was performed in Pubmed on November 6, 2018 for studies published, with no data or language restriction. After duplicate deletion, two researchers (C.M. and M.R-L.) independently screened articles via title/abstract (sacubitril/valsartan). Full text examination was performed in duplicate across both authors, with a third author (J.A-G) moderating discrepancies.

Results

Comparison of Clinical Characteristics of the Study Population and Paradigm-HF Trial

A total of 108 patients began sacubitril/valsartan between September 2016 to February 2018. Table 1 compares the baseline clinical characteristics of our study population and the PARADIGM-HF drug arm. Briefly, our patients had a worse NYHA baseline class and a higher use of MRA, ICD, and CRT therapies than those from the trial.

Up-titration of Sacubitril/Valsartan

Table 2 summarizes the starting and final dose achieved of sacubitril/valsartan in our study population. Although in more than half of patients the drug was initiated at the lowest dose, it could be up-titrated to the maximum dose in nearly 50% of them. The most common limitations during the titration process were low systolic blood pressure and hyperkalemia.

Efficacy and Safety of Sacubitril/Valsartan

After a median follow-up period of 156 ± 51 days, eight patients were transplanted and eight died. In the 77 patients completing the 6-month follow-up, compared to period before treatment, there was a significant reduction of the HF admission (23 vs. 8%, $p < 0.05$) and the need of ambulatory perfusion of levosimendan (13 vs. 3%, $p < 0.05$) rates, without a change in the need for ambulatory intravenous diuretic administration (6 vs. 6%). In the same way, Fig. 1 illustrates the favorable NYHA functional class change of our patients at the end of the drug titration period. Moreover, a significant improvement of NT-proBNP levels and left ventricle

Table 1 Clinical characteristics of the study population and PARADIGM-HF trial

	Study population ($n = 108$)	PARADIGM-HF drug arm ($n = 4187$)	p value
Age, years, $\bar{x}$ (SD)	64 (11)	64 (11)	1.000
Males, *n* (%)	85 (79)	3308 (79)	0.939
Ischemic etiology, *n* (%)	59 (55)	2506 (60)	0.275
Atrial fibrillation, *n* (%)	42 (39)	1517 (36)	0.571
LVEF, $\bar{x}$ (SD)	30 (7)	30 (6)	1.000
NYHA functional class, *n* (%)			
II	65 (60)	2998 (72)	< 0.001
III	43 (40)	969 (23)	
Previous HF admission, *n* (%)	43 (40)	2607 (62)	< 0.001
NT-proBNP, ng/L, median (IQR)	1164 (698–3678)	1631 (885–3154)	< 0.001
Serum creatinine, mg/dL, $\bar{x}$ (SD)	1.1 (0.3)	1.1 (0.3)	1.000
Serum potassium, mmol, $\bar{x}$ (SD)	4.5 (0.5)	4.5 (0.5)	1.000
Systolic BP, mmHg, $\bar{x}$ (SD)	123 (19)	122 (15)	0.589
Beta-blockers, *n* (%)	105 (97)	3899 (93)	0.094
ACEI/ARB, *n* (%)	108 (100)	4185 (100)	1.000
MRA, *n* (%)	100 (93)	2271 (54)	< 0.001
ICD, *n* (%)	58 (54)	623 (15)	< 0.001
CRT, *n* (%)	20 (19)	292 (7)	< 0.001
Waiting list for heart transplantation	8 (7)	0	–

HF heart failure, $\bar{x}$ mean, *SD* standard deviation, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *ng* nanograms, *L* liter, *IQR* interquartile range, *mg* milligrams, *dL* deciliter, *mmol* milimoles, *BP* blood pressure, *mm* millimeters, *ACEI* angiotensin converter enzyme inhibitors, *ARB* aldosterone receptor blockers, *MRA* mineralocorticoed receptor antagonist, *ICD* implantable cardiac defibrillator, *CRT* cardiac resynchronization therapy

Table 2 Tolerability of sacubitril/valsartan in the study population after 6-month follow-up

	Study population ($N = 108$)
Initial dose, *n* (%)	
24/26 mg	57 (52.8)
49/51 mg	47 (43.5)
97/103 mg	4 (3.7)
Patients discontinuing the drug, *n* (%)	*17 (16)*
Reason for discontinuation, *n* (%)	
Others	6 (35.3)
Worsening HF	4 (23.5)
Costs related	4 (23.5)
Hyperkalemia	1 (5.9)
Symptomatic hypotension	1 (5.9)
Worsening renal function	1 (5.9)
Maximum tolerated dose in 91 patients, *n* (%)	
Less than 24/26 mg	1 (1.1)
24/26 mg	25 (27.5)
49/51 mg	20 (23.1)
97/103 mg	44 (48.3)
Reason for not achieving the higher dose mg, *n* (%)	
Symptomatic hypotension	30 (63.8)
Hyperkalemia	6 (12.8)
Not justified	5 (10.6)
Worsening renal function	3 (6.4)
Others	3 (6.4)

mg milligrams, *HF* heart failure

remodeling parameters were found when highest maximum tolerated dose of sacubitril/valsartan was achieved.

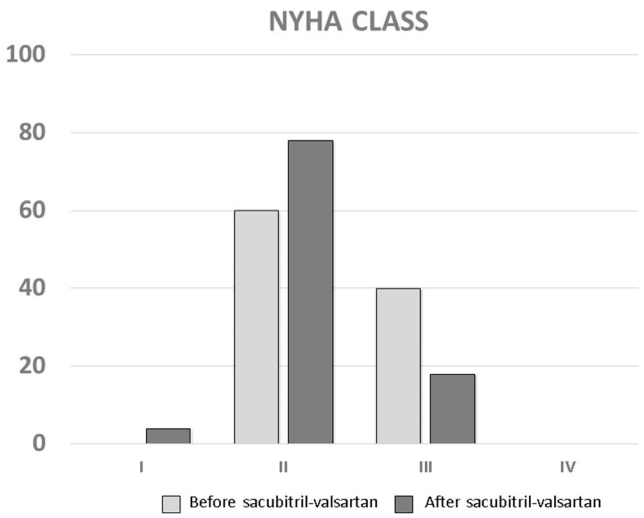

Fig. 1 NYHA class before and after the treatment with sacubitril/valsartan. Results are expressed in percentage of patients. NYHA, New York Heart Association

Regarding safety, a non-significant increase in serum potassium and creatinine was found with a slight decrease in systolic blood pressure. Sacubitril/valsartan had to be discontinued in 16% of the cohort, but no severe adverse effects were reported. Most of the patients stopped the treatment because of atypical complaints such as headache, diarrhea, or dizziness without reported hypotension. Table 3 summarizes the efficacy and safety events in our study population during the follow-up period.

Previous Real-Life Studies

We found 16 studies published to date including 5911 patients treated with sacubitril/valsartan in daily clinical practice. Figure 2 summarizes the searching process and Table 4 presents the main characteristics of the mentioned studies. Most of the patients included were males with a mean age of 68 years, from single-center experiences (56%). Six of those studies reported NYHA class change after the introduction of sacubitril/valsartan, but only four studies provided echocardiographic data or the impact on hospitalizations for HF.

Discussion

Main Findings

In a real-life cohort of patients with advanced HF from a tertiary center, sacubitril/valsartan showed a significant reduction in hospitalizations and seemed to have also a cardiac remodeling benefit after a short follow-up period, in spite of better baseline drugs and devices therapy. Furthermore, we did not observe any serious adverse effect and it was generally well tolerated.

Clinical Profile of the Patients in Real-life Clinical Practice

Sacubitril/valsartan has strongly demonstrated a greater reduction of cardiovascular death and HF hospitalizations than enalapril in symptomatic patients with HF and low left ventricular ejection fraction [3]. However, these impressive results were achieved after a carefully run-in phase and, thus, in a selected population, possibly far distinct from daily clinical practice [5, 6]. Table 4 resumes the main characteristics of the real-life studies conducted until now with this drug [7–22]. Most of them have shown that sacubitril/valsartan is nowadays initiated in older patients with a more advanced HF. In our cohort, despite a similar age, and lower levels of NT-proBNP, patients were in a more advanced functional class, with a high need for levosimendan ambulatory perfusions, and had a worse short-term prognosis with nearly 15% of mortality or heart transplantation. These findings could be explained because our center is a referral hospital for complex HF therapies and, therefore, we attend a more advanced HF population. In

Table 3 Efficacy and safety of sacubitril/valsartan in the study population after 6-month follow-up

	Before treatment ($n = 77$)	After treatment ($n = 77$)	p value
Efficacy			
HF admission, *n* %	18 (23)	6 (8)	0.017
Ambulatory iv diuretic, *n* %	6 (8)	6 (8)	1.000
Ambulatory iv levosimendan, *n* %	10 (13)	2 (3)	0.022
NT-proBNP, ng/L, median (IQR)	1113 (680–2541)	704 (410–2162)	0.046
LVEF, x̄ (SD) (37 pts)	32 (6)	37 (10)	0.003
EDDLV, mm, x̄ (SD) (40 pts)	63 (8)	60 (9)	0.011
Safety			
Serum potassium, mmol, x̄ (SD)	4.5 (0.5)	4.6 (0.5)	0.510
Serum creatinine, mg/dL, x̄ (SD)	1.09 (0.28)	1.12 (0.31)	0.105
eGFR, x̄ (SD)	69 (18)	68 (19)	0.224
Systolic BP, mmHg, x̄ (SD)	123 (16)	119 (20)	0.011

HF heart failure, *iv* intravenous, *ng* nanograms, *L* liter, *IQR* interquartile range, *LVEF* left ventricular ejection fraction, *x̄* mean, *SD* standard deviation, *EDDLV* end diastolic diameter left ventricle, *mm* millimeters, *mmol* milimoles, *mg* milligrams, *dL* deciliter, *eGFR* estimated glomerular filtration rate, *BP* blood pressure

relation to background treatment, our patients showed a higher proportion of mineraloid receptor antagonists and devices such as cardiac resynchronization or defibrillators than PARADIGM-HF population [3], reflecting perhaps that the drug was reserved for patients with already optimized treatment, according to the ESC guidelines [23].

In relation to the titration process, the initial dose was the lowest (50 mg/12 h) in a 53% of the patients and maximum doses of the drug (200 mg/12 h) were achieved in a similar proportion of them. The achieved daily mean sacubitril/valsartan dose was 139 mg in our study population, much lower than in PARADIGM-HF (375 mg/day) [3]. This could also be a consequence of having a more advanced HF population. Surprisingly, in a study conducted by the Catalan Institute of Health [4] in which data from the electronic prescription system and electronic health record was used to

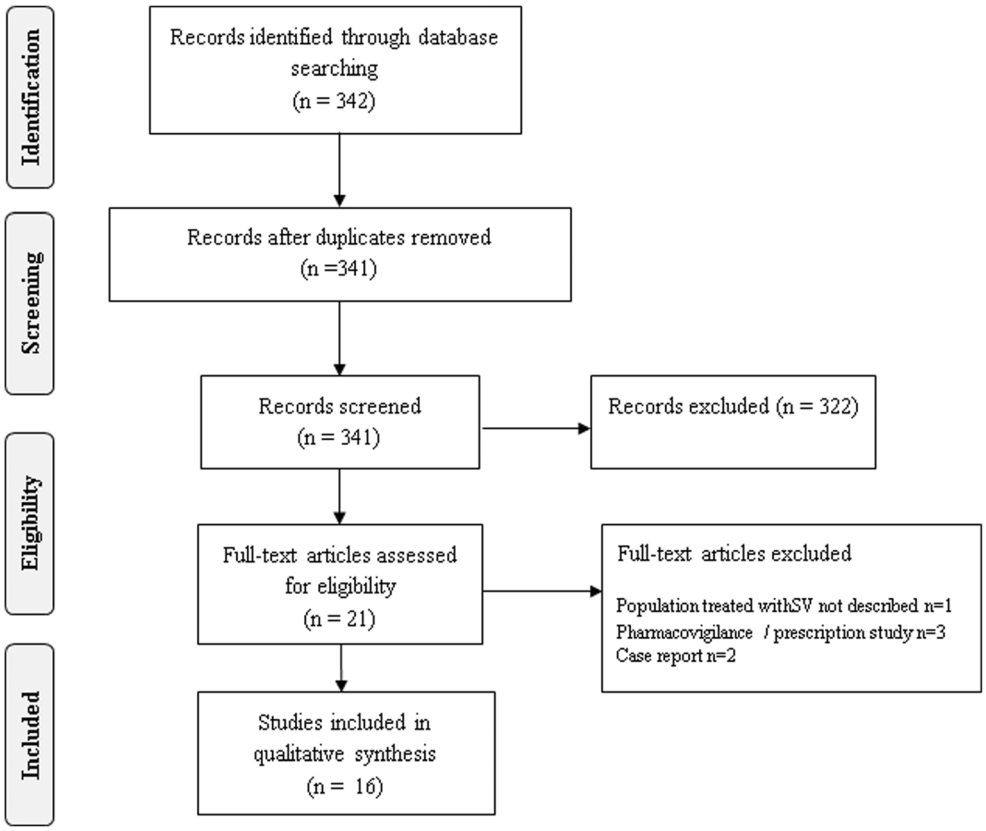

Fig. 2 Flow diagram of the search process. SV, sacubitril/valsartan

Table 4 Main characteristics of real-life studies with sacubitril/valsartan in chronological order

Author (ref)	Patients (*n*)	Study design	Males (%)	Age (y)	NYHA class	LVEF (%)	Final dose SV	Follow-up (m)	NYHA change	Echo data	HF admissions
Luo [7]	495	Multi-center	68	65 (55–77)	N/A		N/A	N/A	N/A	N/A	N/A
Kałużna-Oleksy [8]	28	Single-center	87	61 (16)	II 18% III 79%	25 (8)	Low 56% Mid 40% High 4%	3	Yes	N/A	N/A
Almufleh [9]	48	Single-center	79	70 (11)	Median NYHA II	26 (8)	Low-mid 45% High 55%	3	N/A	Yes	N/A
De Vecchis [10]	44	Single-center	71	76 (5.5)	IV 2%	38 (6)	High 80%	5	N/A	Yes	Yes
De Vecchis [11]	51	Multi-center	67	79 (2.4)	N/A	38 (4)	Low-mid 39%	N/A	N/A	N/A	N/A
Wachter [12]	1643	German admin database	67	73.1 (12.2)/ 68.9 (11.7)	I 3/1% II 25/33% III 57/58% IV 15/9%	N/A	Low 42% Mid 37% High 21%	12	Yes	N/A	N/A
Sangaralingham [13]	2244	Medicare data	69	67.6 (12)	N/A	N/A	High 24.5%	N/A	N/A	N/A	N/A
Pogge [14]	52	Single-center	75	69 (12)	II–III 100%	26 (8)	Low 6% Mid 7% High 87%	2	N/A	N/A	N/A
Martens [15]	120	Single-center	81	66 (11)	II 63% III 36%	26 (6)	N/A	3	Yes	N/A	N/A
De Vecchis [16]	68	Multi-center	49	78–79	N/A	35–38	Low 20 patients High 48 patients	5	N/A	N/A	Yes
Antol [17]	200	Medicare/Medicaid database	70	72 (12)	N/A	N/A	Low 45% Mid 38% High 1%	4	N/A	Yes	Yes
Martens [18]	125	Single-center	81	66 (10)	II 60% III 39%	30 (6)	Low 35% Mid 37% High 28%	4	Yes	Yes	N/A
Martens [19]	201	Single-center	82	68 (11)	II 68% III 31%	29 (8)	Low 33% Mid 42% High 25%	7	Yes	N/A	Yes
Rodil Fraile [20]	65	Single-center	68	79 (7)	III 25% IV 74%	37 (2)	Low 75% Mid-high 25%	10	Yes	N/A	N/A
Vicent [21]	427	Multi-center	70	68 (12)	II 70% III 24%	29 (7)	N/A	6	N/A	N/A	N/A
Laflamme [22]	100	Single-center	76	64 (11)	II 73% III 26%	26 (7)	Low 23% Mid 33% High 46%	1	N/A	N/A	N/A

Ref reference, *y* years, *NYHA* New York Heart Association, *LVEF* left ventricular ejection fraction, *SV* sacubitril/valsartan, *m* months, *HF* heart failure, *N/A* non-available

characterize Catalan population with sacubitril/valsartan, up to a 64.6% was being treated with the lowest dose of drug, which is much higher than the 24% we found at the end of the titration phase. This could be partially explained because this report concerns a cross-sectional study and it does not differentiate those patients that have been recently started with sacubitril/valsartan and those are still in the up-titration process. All the available data on real population shows a greater difficulty in the up-titration process than in PARADIGM-HF [8–14, 16–20, 22]. It is important to underline that the prognostic impact of sacubitril/valsartan seems especially relevant for those patients with higher dose in a daily clinical practice. However, the benefit over ACEI was maintained regardless of the achieved dose [19], which may prompt reconsideration of the optimal dose recommendation in current guidelines.

Performance of Sacubitril/Valsartan in a Real-Life Scenario

After a 6-month follow-up after initiation of sacubitril/valsartan, we observed a significant reduction in the HF hospitalizations, median levels of NT-proBNP, and need for levosimendan ambulatory perfusion. Similar to other studies [8, 12, 15, 18–20], we found a significant improvement in NYHA class. Moreover, we observed a significant improvement in the LVEF, and reduction in end diastolic diameter of left ventricle, suggesting that sacubitril/valsartan may result in a reverse cardiac remodeling, in line with what other studies have already shown [9, 16, 18, 19].

Compared to PARADIGM-HF, we found a higher dropout rate related to adverse events (18 vs. 11%, $p < 0.001$). The main reasons were atypical complaints, decompensated HF, or economic reasons. Only three cases discontinued sacubitril/valsartan because of moderate asymptomatic hyperkalemia, renal function deterioration, and symptomatic hypotension. Martens et al. reported no drop out in a 90-day follow-up [15]. In the same study, hypotension was the reason hindering up-titration in 50%, compared to a 63% of the cases in our study. Regarding hyperkalemia, it has been reported to be lower with sacubitril/valsartan than with ACEI [3]. Accordingly, in our cohort this only lead to sacubitril/valsartan discontinuation in one patient. However, incidence of mild hyperkalemia that hindered up-titration occurred in 12.6%. Differences with the PARADIGM-HF could be explained partially because in the trial the run-in phase led to a careful selection of patients less prone to hyperkalemia.

Clinical Implications

Until now, sacubitril/valsartan has been specially prescribed in a higher-risk profile population with more comorbidity and in more advanced condition. It should be noted that this drug is considered a paradigm change in the treatment of HF, combining successfully for first time a neurohormonal blocker (valsartan) with a promoter of a natural physiological pathway (sacubitril, through the enhancement of natriuretic peptides). Given the excellent results achieved in patients in NYHA class II and III [3] and in real daily practice [7–22], we should consider when to start it. In addition to the aforementioned data, the recent results of the PIONEER-HF study [25] favor early initiation, even in naive patients treated with ACEI or ARB.

Study Limitations

Several limitations of this study have to be stated. First, this was a retrospective observational single-center study. Secondly, the time to the control visits, blood tests, and echocardiography were not homogenous, and this could have induced biases. Thirdly, the cardiologist attitude when clinical or laboratory alteration was found was not protocolled and this could have led to differences in the up-titration or sacubitril/valsartan withdrawal decision.

Conclusions

Sacubitril/valsartan in real-life is prescribed to a more advanced HF population, which could be responsible for the difficulties in reaching high doses of the drug. However, after a 6-month follow-up, sacubitril/valsartan significantly reduces HF hospitalization and seems to induce cardiac reverse remodeling, without remarkable adverse events.

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Compliance with Ethical Standards

Conflict of Interest JAG, SM, ER have received speaker honorariums from Novartis. JAG, SM, have received speaker honorariums from Rovi. MRL, PF have received an educational grant from Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Ethical Approval All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed Consent Due to the retrospective nature of the study, it was considered by the ethical research committee that informed consent was not required.

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