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Improvement in quality of life with sacubitril/ /valsartan in cardiac resynchronization non-responders: The RESINA (RESynchronization plus an Inhibitor of Neprilysin/Angiotensin) registry

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Abstract

Background: *Clinical management of cardiac resynchronization therapy (CRT) non-responders is difficult, and their prognosis is poor. The aim of the present study was to evaluate whether treatment with sacubitril/valsartan can improve quality of life (QoL) parameters in these patients.*

Methods: *Thirty five non-responders to CRT were included (75 ± 7 years, 28% females, mean left ventricular ejection fraction 28 ± 8%, 54% non-ischemic cardiomyopathy) with maximally optimized drug therapy and New York Heart Association class II–III. They were all on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and were switched to sacubitril/valsartan. One week before and 6 months after initiation of the therapy they completed both the Minnesota Living with Heart Failure (MLWHF) and the 12-item Kansas City Cardiomyopathy Questionnaires (KCCQ-12). The primary outcome was the effect of sacubitril/valsartan on the physical, clinical, social and emotional QoL parameters and number of hospitalizations.*

Results: *The mean total scores of both questionnaires improved from baseline to the follow-up visit at 6-months (KCCQ-12 40 ± 10 to 47 ± 10; $p < 0.001$; MLWHF 40 ± 15 to 29 ± 15; $p < 0.001$). The best results were seen in the KCCQ-12 total symptom domains (77% improvement), the MLWHF physical domain (81% improvement), and the MLWHF emotional domain (71% improvement). Two patients died during follow-up. The mean number of hospitalizations reduced significantly (1 ± 0.6 vs. 0.5 ± 0.8; $p = 0.003$)*

Conclusions: *In CRT non-responders, sacubitril/valsartan significantly improved overall QoL, physical limitations and emotional domains and reduced the number of hospitalizations.* (Cardiol J 2021; 28, 3: 402–410)

Key words: resynchronization, sacubitril/valsartan, quality of life

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Introduction

Cardiac resynchronization therapy (CRT) is the therapeutic option of choice for patients with heart failure (HF) and conduction disorders [1, 2], but 30% to 40% of them are considered non-responders and have a poor quality of life (QoL). The reasons are diverse: type of cardiomyopathy, previous non-left bundle branch block morphology, comorbidity factors, suboptimal left ventricular (LV) lead position or inadequate pacing optimization [3, 4]. Management of these patients is difficult, and they are a particularly high-risk HF group with < 50% survival at 5 years [5]. The presence of significantly limited QoL is becoming increasingly relevant for health care stakeholders, as HF is one of the main causes of poor QoL.

Sacubitril/valsartan is a new angiotensin receptor neprilysin inhibitor (ARNI), and are a class I recommendation for patients with chronic HF, reduced LV ejection fraction (LVEF) and New York Heart Association (NYHA) class II–IV instead of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) in conjunction with other standard HF treatments [2]. Data on the clinical benefit of sacubitril/valsartan in patients with CRT are scarce, because very few patients with these devices have been included in trials (usually less than 20%) [6, 7], although some sub-group analyses have demonstrated that they experience similar clinical beneficial effects to those of patients without CRT. The aim of the current study was to determine whether administering sacubitril/valsartan instead or an ACEI/ARB in non-responders to CRT could result in a beneficial effect on morbidity and QoL.

Methods

Patients with CRT were included (CRT-D defibrillator or CRT-P pacing only) who were referred to the cardiology HF/arrhythmia outpatient clinics from the Fundación Jiménez Díaz (FJD; Madrid, Spain) and the Hospital Central de la Defensa (HCD; Madrid, Spain). They needed to fulfill the following criteria before enrollment: 1) age > 18 years; 2) recipient of a CRT device for > 6 and < 36 months for standard indications; 3) optimized medical therapy since implantation, including ACEI/ARB; 4) naïve to sacubitril-valsartan; 5) presence of sinus rhythm, or atrial fibrillation (AF) with spontaneous or induced complete atrioventricular block; 6) at least > 95% LV stimulation; 7) unchanged or worsened clinical status by CRT, according to the HF composite end point described by Packer [8], in the absence of a reversible cause. Exclusion criteria were: 1) systolic blood pressure (SBP) < 100 mmHg; 2) estimated glomerular filtration rate (eGFR) < 30 mL/m/1.73 m^2 or chronic renal dialysis; 3) serum potassium levels > 5.2 mmol/L; 4) severe anemia (hemoglobin < 9 mg/dL) or thyroid disease; 5) life-expectancy < 1 year because of concomitant, non-cardiovascular disorders; 6) history of stroke, myocardial infarction, or unstable angina pectoris within the prior 3 months; 7) presence of correctible valvular disease; 8) subject unable to attend follow-up at the study site or unable, for physical or mental reasons, to comply with the trial procedures, or to sign the informed consent; 9) subject participates in another research project.

As in the PARADIGM-HF trial, all patients taking ACEI/ARB were considered for participation, but they were required to take a stable dose of a beta-blocker (BB) and an ACEI/ARB dose equivalent to at least 10 mg of enalapril daily for a minimum of 4 weeks prior to screening [6]. After inclusion, ACEI/ARB was suspended and sacubitril/valsartan was initiated after 36 hours, at an initial dose of 24/26 mg. All the patients continued with the same BB, mineralocorticoid receptor antagonist (MRA) or diuretic dose unless they experienced symptoms due to sustained SBP < 90 mmHg. After 1 month, the sacubitril/valsartan dose was titrated according to the initial response of the patient, tolerability of the drug and patient characteristics, always trying to achieve the highest doses.

One week prior to inclusion in the study, all patients filled in two QoL questionnaires: Minnesota Living with Heart failure (MLWHF) [9] and 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12) [10], to establish their clinical status before enrollment. The MLWHF is a self-administered disease-specific questionnaire comprising 21 items answered on a 6-point Likert scale, representing different degrees of impact of HF on QoL, from 0 (none) to 5 (very much) [11]. It provides a total score (range 0–105, from best to worse), as well as scores for two dimensions, physical (range 0–40) and emotional (range 0–25). The other 8 items are only considered for the calculation of the total score. The KCCQ-12 quantifies 8 domains of patients' HF-related health status: Physical Limitation (3 items); Swelling frequency (1 item); Fatigue frequency (1 item); Dyspnea frequency (1 item); Dyspnea — sleeping upright (1 item); Enjoyment of life (1 item); Rest of life as is now (1 item); Social limitation (3 items). Item

responses are coded sequentially (1, 2, 3, etc.) from worst to best status. For analysis, five domains are calculated: Physical limitation, Symptoms, Life status, Social limitation, and an Overall summary score. Both questionnaires have been translated into Spanish and have been validated [12, 13].

Clinical and demographic data were obtained for every patient: sex; age; presence of cardiovascular risk factors (diabetes mellitus, hypertension, and smoking) and chronic obstructive pulmonary disease; time from CRT implantation to study inclusion; type of cardiomyopathy (ischemic, non-ischemic); type of CRT device; and drugs used. The following data were also collected before inclusion and after 6 months: eGFR; potassium levels; hemoglobin levels; and NYHA class. A baseline echocardiographic study was performed in all patients, including end-diastolic LV diameter (mm), end-diastolic right ventricular diameter (mm), LVEF, and left atrium (LA) size (mm) measurements. Patients were divided according the type of CRT device.

The primary outcome was any change from baseline to the 6-month follow-up visit in all the items and total domains analyzed from both the KCCQ-12 and the MLWHF questionnaires. The secondary end point was to compare the number of hospitalizations (> 24-h before discharge)/ /Emergency Department consultations (< 24-h before discharge) because of HF 6 months before the inclusion and at 6-month follow-up. All patients provided written informed consent. The study protocol was approved by the hospital's Institutional Review Board. The study complied with the tenets of the Declaration of Helsinki.

Statistical analysis

Continuous values were expressed as mean ± standard deviation and nominal variables as counts and percentages. Median values with the corresponding interquartile range (IQR) were computed for non-normally distributed variables. A two-tailed t-test was used for comparison of normally-distributed variables, and the non-parametric Kruskal-Wallis test for values that were not normally distributed. For comparisons of categorical data, two-tailed χ^2 statistics with the Yates correction or the Fisherexact test were used, as applicable. Mean values were calculated from patient scores of both questionnaires for all domains. Values were obtained at baseline and after a 6-month follow-up period. The principal efficacy analysis was the change in mean total scores and individual domains between baseline and the follow-up visit at 6 months. In the MLWHF total score, patients were divided into cohorts on the basis of change as follows: worse ($\Delta \geq +6$ points), similar, ($\Delta < +6$ and < -6 points), better ($\Delta \geq -6$ points). Similar cohorts were made for the specific domains (Physical, Emotional, Rest) but with a difference of 2 points in each of them. Similarly, in the 12-KCCQ overall summary score, patients were divided into cohorts on the basis of change as follows: worse ($\Delta \geq -4$ points), similar ($\Delta < -4$ and < 4 points), better ($\Delta \geq +4$ points). Similar cohorts were made for the four specific domains but with a difference of 1 point in each of them. Missing values were not accounted for in the primary analysis. A value of $p < 0.05$ was considered to indicate a statistically significant difference. All analyses were done using IBM® SPSS® Statistics version 20.0.0 (Armonk, NY, USA).

Results

Tables 1 and 2 show the clinical characteristics of the patients by CRT type. 35 patients were included (mean age 75 ± 7 years, 28% females). Patients with CRT-P were significantly older compared with those with CRT-D (78 ± 6 vs. 73 ± 8 years; $p = 0.029$), and with a higher mean LVEF (32 ± 5 vs. 25 ± 9, respectively; $p = 0.005$). Mean time from CRT device implantation to inclusion in the study was 23 ± 17 months.

After initiation of sacubitril/valsartan, 6 (20%) patients experienced persistent SBP < 90 mmHg, but only one of them did not definitively tolerate the drug. In the remaining 5 patients the BB and/or diuretic dose was adjusted, and the drug was maintained at the 24/26 mg dose. Although the highest doses of sacubitril/valsartan were intended, after 6 months 46% of patients remained on the same dose and 50% used the 49/51 mg dose. There was only a slight but significant deterioration in eGFR (58 ± 16 to 54 ± 17 mL/min/1.73 m^2; $p < 0.001$) after administration of the drug. Two patients died because of refractory HF before completing the 6-month follow-up. Two patients needed outpatient treatment with levosimendan, also maintaining the lower dose of sacubitril/valsartan.

The mean number of hospitalizations/Emergency Department consultations reduced significantly after the 6-month follow-up (1 ± 0.6 to 0.5 ± 0.8 ($p < 0.001$). Although there was a slight increase in LVEF after the 6-month follow-up, it was not statistically significant (27 ± 8 vs. 28 ± 8; $p = 0.09$).

Table 1. Clinical characteristics of patients included.

	All	CRT-P	CRT-D	P
Number	35	15	20	
Age	75 ± 7	78 ± 6	73 ± 8	0.029
Female sex	10 (28%)	9 (60%)	1 (5%)	< 0.001
Diabetes	14 (40%)	7 (47%)	7 (35%)	0.363
Hypertension	30 (86%)	11 (73%)	19 (95%)	0.093
Dyslipidemia	24 (69%)	7 (47%)	17 (85%)	0.020
Former smoker	9 (23%)	1 (7%)	8 (35%)	0.055
BMI [kg/m^2]	26 ± 4	25 ± 4	27 ± 3	0.154
Ischemic disease	16 (46%)	1 (7%)	15 (75%)	< 0.001
Non-ischemic	19 (54%)	14 (93%)	5 (25%)	< 0.001
Beta-blockers	34 (97%)	14 (93%)	20 (100%)	0.429
Diuretics	35 (100%)	15 (100%)	20 (100%)	–
MRA	12 (34%)	1 (7%)	11 (55%)	0.003
Amiodarone	11 (31%)	3 (20%)	8 (40%)	0.187
Digoxin	2 (6%)	1 (7%)	1 (5%)	0.681
SGTL2	10 (28%)	5 (33%)	5 (25%)	0.433
Atrial fibrillation	12 (34%)	6 (40%)	6 (30%)	0.397
NYHA class II	29 (83%)	14 (93%)	15 (75%)	0.167
NYHA class III	6 (17%)	1 (7%)	5 (25%)	0.167
eGFR	57 ± 16	53 ± 15	60 ± 17	0.224
Potassium [mmol/mL]	4.4 ± 0.3	4.4 ± 0.3	4.5 ± 0.3	0.564
Hemoglobin [mg/dL]	13 ± 1.4	13 ± 1.3	13 ± 1.4	0.843
SBP [mm Hg]	120 ± 12	120 ± 14	120 ± 11	0.939

CRT-P — cardiac resynchronization therapy pacing only; CRT-D — cardiac resynchronization therapy with defibrillator; BMI — body mass index; eGFR — estimated glomerular filtration rate; MRA — mineralocorticoid receptor antagonist; SGTL2 — inhibitors of sodium-glucose contansporter-2; NYHA — New York Heart Association; SBP — systolic blood pressure

Table 2. Echocardiographic parameters and QRS width of patients included.

	All	CRT-P	CRT-D	P
Number	35	15	20	
LA [mm]	45 ± 9	45 ± 6	46 ± 10	0.628
LVEDD [mm]	57 ± 7	55 ± 5	58 ± 7	0.116
RVEDD [mm]	41 ± 5	40 ± 6	41 ± 4	0.383
LVEF [mm]	28 ± 8	32 ± 5	25 ± 9	0.005
QRS width pre-CRT [ms]	150 ± 30	144 ± 30	155 ± 30	0.310
QRS width with CRT [ms]	136 ± 12	132 ± 13	140 ± 11	0.090

CRT-P — cardiac resynchronization therapy pacing only; CRT-D — cardiac resynchronization therapy with defibrillator; LA — left atrium; LVEDD — left ventricular end-diastolic diameter; RVEDD — right ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction

Changes in QoL questionnaires

The KCCQ-12 baseline total physical limitation domain was worse in the CRT-P group, without any significant differences in the baseline of the remaining scores (Table 3). After the 6-month follow-up visit, 31 patients filled in both questionnaires (2 patients died because of refractory HF and 2 patients were lost to follow-up).

Table 4 show the status after the 6-month follow-up visit for the different scores analyzed. The best results were obtained in the KCCQ-12 total physical limitation and total symptom domains

Table 3. Baseline quality of life domains of patients included

Baseline QoL domains	CRT-P	CRT-D	P
KCCQ-12 Total physical limitation	8 ± 2	10 ± 3	0.04
KCCQ-12 Total symptoms	16 ± 4	17 ± 4	0.531
KCCQ-12 Life status	5 ± 2	6 ± 2	0.089
KCCQ-12 Social limitations	9 ± 3	10 ± 4	0.310
KCCQ-12 Overall summary	37 ± 9	42 ± 11	0.185
MLWHF Physical	21 ± 6	18 ± 7	0.222
MLWHF Emotional	12 ± 5	10 ± 5	0.248
MLWHF Total	41 ± 14	40 ± 17	0.825

CRT-P — cardiac resynchronization therapy pacing only; CRT-D — cardiac resynchronization therapy with defibrillator; QoL — quality of life; KCCQ-12 — Kansas City Cardiomyopathy Questionnaire; MLWHF — Minnesota Living with Heart Failure

Table 4. Clinical situation after 6-month treatment with sacubitril/valsartan.

Domains at follow-up	Result					
	CRT-P (n = 14)			CRT-D (n = 17)		
	Better	Similar	Worse	Better	Similar	Worse
KCCQ-12 Total physical limitation	10 (72%)	3 (21%)	1 (7%)	12 (71%)	5 (29%)	0 (0%)
KCCQ-12 Total symptoms	10 (72%)	4 (28%)	0 (0%)	14 (82%)	2 (12%)	1 (6%)
KCCQ-12 Life status	7 (50%)	6 (43%)	1 (7%)	8 (47%)	7 (41%)	2 (12%)
KCCQ-12 Social limitations	6 (44%)	5 (35%)	3 (21%)	6 (35%)	7 (41%)	4 (24%)
KCCQ-12 Overall summary	10 (72%)	1 (7%)	3 (21%)	10 (59%)	5 (29%)	2 (12%)
MLWHF Physical	12 (86%)	1 (7%)	1 (7%)	13 (77%)	3 (17%)	1 (6%)
MLWHF Emotional	10 (72%)	3 (21%)	1 (7%)	12 (71%)	5 (29%)5	0 (0%)
MLWHF Total	12 (86%)	2 (14%)	0 (0%)	14 (83%)	3 (17%)	0 (0%)

CRT-P — cardiac resynchronization therapy pacing only; CRT-D — cardiac resynchronization therapy with defibrillator; KCCQ-12 — Kansas City Cardiomyopathy Questionnaire; MLWHF — Minnesota Living with Heart Failure; Better, Similar, Worse, Improvement, similar status, worse in each of the specific quality of life domains

(72% were better in both) and also in the MLWHF physical and emotional domains (81% and 71% were better, respectively). In the KCCQ-12 overall summary score, 65% of patients were better, 19% similar and 16% worse. When the emotional and social domains were analyzed, in the KCCQ-12 life status domain, 48% of the patients were better, 42% similar and 10% worse. In the KCCQ-12 social limitation domain, 39% were better, 39% similar and 22% worse. In the MLWHF emotional domain, 71% were better, 26% similar and only 3% worse. No significant differences between CRT-D and CRT-P patients in all the domains analyzed were demonstrated. Table 5, Figures 1 and 2 show the mean value of all the scores at baseline and at 6-month follow-up, demonstrating a significant improvement in all domains except for the KCCQ-12 Social limitations.

Discussion

Quality of life has been defined by the World Health Organization (WHO) as a broad-ranging concept affecting physical health, psychological state and social relationships [14]. Moreover, achieving a better QoL in patients with HF is important regardless of the device or drug used, because a decrease in mortality or morbidity is not always accompanied by better QoL. BBs do not significantly improve QoL [15], and ACEI/ARBs have demonstrated mixed results [16], although many trials were conducted without using actual HF-specific QoL questionnaires like the ones used in the present study. On the other hand, sacubitril/valsartan is one of the few HF therapies that have demonstrated a significant improvement in morbidity and mortality as well as in physical and social activity limitations [17, 18].

Table 5. Mean ± standard deviation values of different quality of life domains pre and after 6-month treatment with sacubitril/valsartan (S/V).

Quality of life domains	Pre S/V	Post S/V	P
KCCQ-12 Total physical limitation	9 ± 2	11 ± 3	< 0.001
KCCQ-12 Total symptoms	16 ± 4	19 ± 5	0.001
KCCQ-12 Life status	6 ± 2	7 ± 2	0.009
KCCQ-12 Social limitations	9 ± 3	10 ± 3	0.228
KCCQ-12 Overall summary	40 ± 10	47 ± 10	0.001
MLWHF Physical	19 ± 7	13 ± 6	< 0.001
MLWHF Emotional	11 ± 5	8 ± 6	< 0.001
MLWHF Total	40 ± 15	29 ± 15	< 0.001

KCCQ-12 — Kansas City Cardiomyopathy Questionnaire; MLWHF — Minnesota Living with Heart Failure

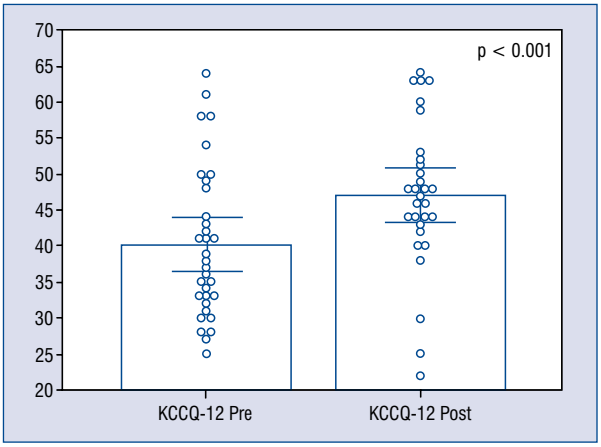

Figure 1. Kansas City Cardiomyopathy Questionnaire (KCCQ-12) overall summary scores at baseline and after 6-months of treatment with sacubitril/valsartan.

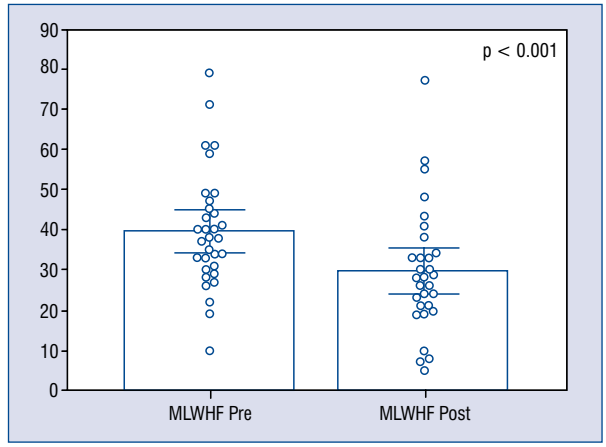

Figure 2. Minnesota Living with Heart Failure (MLWHF) total scores at baseline and after 6-months of treatment with sacubitril/valsartan.

This is the first study to provide evidence that adding sacubitril/valsartan to CRT non-responders is associated with an improvement in most HF--specific QoL domains. More specifically, there was a significant improvement in physical activities and symptoms, which were the maximum limitations of patients at baseline. Also, the improvement in the social and emotional domains was very relevant. This is important for all patients, but particularly for those with chronic HF, as most of them feel that they have a chronic disease with a poor prognosis and generally have a poor QoL. The general answer when adding sacubitril/valsartan is that patients say they "feel better now", and this resulted in a better status in emotional QoL domains.

For the analysis, we decided to differentiate between CRT-D and CRT-P devices because CRT-P patients were older, more frequently female and with non-ischemic cardiomyopathy, but the results in QoL improvement were similar in both groups, demonstrating a good effect of the drug regardless of the CRT type and patient characteristics [19].

One important fact in the present study is that the mean age was 75 ± 7 years, much higher than in other large, randomized trials with sacubitril/valsartan (64 ± 11 and 63 ± 11 years in the PARADIGM-HF [6] and PRIME [20] trials, respectively). This is important because before this study, it was assumed that some baseline physical limitations of the patients could be related more to age or muscular or neurological disorders rather than to HF symptoms, but surprisingly, most of them experienced a better physical situation, something that could be related to the better perception in

their QoL emotional domains. Depression and anxiety are not systematically studied in patients with HF, but they are very important components of QoL [21, 22]. Dereli et al. [23] have demonstrated a significant positive effect of sacubitril/valsartan on different depression and anxiety parameters in patients with HF and a reduced LVEF. In this study, 43% of the patients had clinically significant depressive symptoms at baseline, and 38% of them also had moderate to severe anxiety, and these was related to poor QoL scores regardless of functional status. Carels [24] have also reported a stronger relationship between QoL and functional capacity rather than cardiac function in HF patients and an improvement in functional capacity leading to better QoL.

Results herein are similar to other studies with sacubitril/valsartan. Chandra et al. [17] reported a significant improvement in nearly all KCCQ-12 physical and social activities compared with enalapril, with the largest responses in household chores and sexual relations, but also with a significantly 5-point or greater improvement in the combined physical and social activity mean scores. Also, at baseline, patients with the greatest limitations attributable to HF in physical and social activities were older, more likely to be women, and more likely to have a worse NYHA class. In addition, the authors reported a reduced likelihood of cardiovascular death, all-cause mortality, and HF hospitalizations. One important limitation as pointed out by the authors of this study is that the patients did not complete their baseline KCCQ-12 until randomization, and so we decided to conduct the baseline study 1 week prior to inclusion, to know the real situation of the patients before using the drug. In a study by Lewis et al. [18], the authors also reported a significant improvement in the different KCCQ-12 scores and KCCQ-12 overall summary scores in patients treated with sacubitril/valsartan compared with those treated with enalapril, with consistency in most domains, and this persisted during the follow-up that lasted over 8 months.

It was decided to set the follow-up visit at 6 months, to be sure that the initial effect of the drug was maintained in the long-term, although in most of the studies with sacubitril/valsartan the different positive effects can be seen in the first 2 months. In the PIONEER-HF [7], the authors reported an early separation of the event curves for clinically relevant end points. Examining the end points of cardiovascular death or hospitalization for HF, they observed an early effect of sacubitril/valsartan with the initiation of in-hospital treatment for 8 weeks, something consistent with the efficacy of the drug in chronic HF patients in other studies.

Limitations of the study

The present study has some limitations. Firstly, although the results are the first to point out the benefit of sacubitril/valsartan in CRT non-responder patients, the population was relatively small, so the findings should be further corroborated in a larger study. Another important limitation of the current study is that although the highest doses of sacubitril/valsartan were intended, 46% of the patients remained on the same initial dose, 51% had the 49/52 mg dose, and no patients received the highest dose. Mean baseline SBP of the patients was 120 ± 12 mmHg, similar to other studies, but as pointed out before, our patients were significantly older and had a longer HF history, perhaps reflecting a real-life situation. Taking in account these characteristics, we decided to be cautious when achieving the highest doses to avoid renal failure or significant hypotension. The incidence of hypotension was 20%, similar to other studies, and only 1 patient decided to discontinue the drug definitively. Several studies with sacubitril/valsartan have demonstrated that achieving the highest dose is difficult, and usually only half of the patients are on the highest drug dose [25]. In the PARADIGM-HF trial [6], 42% had a reduced dose, and in the PIONEER trial [26] only 55% of the patients had the highest dose. In a real-life study by Du et al. [27], at the 6-month follow-up visit 27% of patients had the highest dose, 41% the mean dose and 32% the lowest dose. In elderly patients, dose reduction or discontinuation of the drug has been associated with hypotension and/or onset of renal failure. In spite of this, Vardeny et al. [28] have demonstrated that although drug reduction identified patients at higher risk of a major cardiovascular event, the benefit for patients on lower doses of sacubitril/valsartan compared with those on lower doses of enalapril was similar to that of patients who remained on target doses for both drugs. All these data suggest that patients taking doses lower than the target doses of the drug would still derive greater benefit from sacubitril/valsartan when compared with enalapril [29].

Conclusions

In non-responder patients to CRT despite optimal medical treatment, sacubitril/valsartan significantly improved overall QoL, physical limitation and emotional scores and reduced the number of

hospitalizations. New controlled studies are needed to validate these results and to extend this benefit to more patients.

Conflict of interest: None declared

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