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Is Sacubitril/Valsartan Able to Change the Timing for Implantation of Cardiac Devices in Heart Failure with Reduced Ejection Fraction?

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Abstract: Aims: The aim of this study was to evaluate the impact of sacubitril/valsartan on left ventricular (LV) reverse remodeling, potentially modifying the timing for cardiac device implantation in heart failure with reduced ejection fraction (HFrEF), which has not been specifically addressed. Methods and results: A secondary data analysis of a prospective cohort of HFrEF patients was conducted. Inclusion criteria: patients who started sacubitril/valsartan between November 2017 and August 2019 after previous optimal medical therapy. Primary endpoint: time to achieve LV Ejection Fraction (EF) > 35%. Kaplan–Meier was used to estimate median time and Cox regression model to investigate the patients' characteristics associated with event incidence rate. In total, 48 patients were included, with a mean age of 72.5 years, predominantly male (70.8%). From the initial 48 patients with LVEF $\leq$ 35%, 27 (56%) reached LVEF > 35%, in a median time of 11.3 months (95% confidence interval [95%CI]: 9.4–19.6). In multivariate analysis, baseline LVEF between 30% and 35% was associated with increased cumulative incidence of attaining LVEF > 35% (Incidence rate ratio = 3.9; 95%CI: 1.6–9.9; *p*-value = 0.004). Conclusion: We observed an improvement in LVEF to >35% in the majority of patients who switched to sacubitril/valsartan, illustrating its role in cardiac remodeling. We speculate that this improvement may allow delaying implantation of Cardioverter-Defibrillator/Cardiac Resynchronization Therapy.

Keywords: heart failure; left ventricular ejection fraction; sacubitril/valsartan; angiotensin receptor neprilysin inhibitor; cardiac devices; real-world evidence

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1. Introduction

The main goals of available pharmacological treatment for heart failure with reduced ejection fraction (HFrEF) are the prevention of hospitalizations and the reduction of mortality while improving patients' clinical status, functional capacity and quality of life [1]. Current treatment options specifically indicated to treat HFrEF, and that can also lead to cardiac reverse remodeling include beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA), which should be up-titrated to the maximum evidence-based dose, as long as tolerated by the patient. Neurohormonal antagonists (ACEi, MRA and beta-blockers) have been shown to improve survival and are recommended in all patients with HFrEF [1] ARB have not consistently proven to reduce mortality and should only be considered in patients intolerant to ACEi or who take ACEi but are unable to tolerate an MRA [1,2].

If patients, despite optimal medical treatment (OMT), remain symptomatic, the use of cardiac devices can be considered. Implantable cardioverter-defibrillators (ICD) are recommended for primary prevention of sudden cardiac death in patients with a New

York Heart Association (NYHA) class II or III and with a left ventricular ejection fraction (LVEF) $\leq$ 35%, despite more than 3 months of OMT, whereas cardiac resynchronization therapy (CRT) is recommended in symptomatic patients with LVEF $\leq$ 35% and a QRS duration $\geq$ 150 msec [1]. Cardiac devices, however, carry a non-negligible risk of complications, including inappropriate shocks, displacement, pneumothorax, hematoma and infection [3]. Therefore, one of the objectives of pharmacological therapy should be to improve LVEF to a level where cardiac devices would no longer be needed or at least their implantation would be postponed [4].

Sacubitril/valsartan, a first-in-class angiotensin receptor neprilysin inhibitor, demonstrated superiority compared to the ACEi enalapril in patients with HF and LVEF < 40% [5]. The clinical trial PARADIGM-HF demonstrated that patients treated with sacubitril/valsartan had a significantly lower rate of total mortality, mortality due to cardiovascular causes and hospitalizations for heart failure decompensation [6]. The most recent American and European guidelines recommend sacubitril/valsartan to replace ACEi in ambulatory patients who fit the trial criteria [1,2].

PROVE-HF trial as well as case reports and observational studies have further shown that sacubitril/valsartan is able to induce reverse cardiac remodeling, which has the potential to avoid Implantable Cardioverter-Defibrillator (ICD) or Cardiac Resynchronization Therapy (CRT) implantation [7–12].

This study aimed to assess the impact of the initiation of sacubitril/valsartan treatment on left ventricular reverse remodeling, in a cohort of patients with HFrEF, in terms of time-to-event outcomes and identify predictors for earlier reverse remodeling.

2. Methods

This study was a secondary analysis of data from a prospective cohort of patients followed at the Heart Failure Clinic (HFC) of Cascais Hospital in Portugal.

The HFC currently follows 171 heart failure patients. Patients are usually referred to the HFC by the attending physician within the Hospital or following an emergency room visit or hospitalization due to acute heart failure. Other referral criteria include the following: LVEF < 40%, specific diagnosis of hypertrophic or restrictive cardiomyopathy and having an ICD or CRT implanted.

The following eligibility criteria for this study were applied consecutively to the HFC patients:

LVEF $\leq$ 35% without any ICD/CRT implanted.

New York Heart Association (NYHA) functional class II or III before the initiation of sacubitril/valsartan.

Beginning of sac/val between November 2017 and August 2019, after previous OMT for over a year, and had at least 6 months of follow-up at the HFC.

At each appointment, all patients were evaluated by a heart failure trained nurse who registered vital parameters, therapeutic compliance and quality of life data, as well as by a cardiologist dedicated to heart failure. Whenever needed, patients were also consulted by other medical specialists in close cooperation with the HFC's team. Follow-up appointments were scheduled after a maximum of six weeks, with a minimum of at least three appointments during a one-year period.

Regarding complementary exams, 12-lead electrocardiograms were usually performed on the same day as the transthoracic echocardiograms.

Moreover, every echocardiogram was performed in the Hospital's echocardiography laboratory and executed by the same echocardiographers that perform, on a regular basis, all the HFC patients' exams.

The clinical and prognostic impact of the multidisciplinary approach in our HFC has been previously published [13].

The primary endpoint of the present study was the time from sacubitril/valsartan initiation to the achievement of an LVEF > 35%, which, in a model of decision still largely based on LVEF, implied that patients would have lost indication to implant a cardiac device [1].

Analysis was performed comparing baseline values to the last follow-up data, where the baseline was defined as the initiation of sacubitril/valsartan.

All continuous variables were expressed as mean ± standard deviation (SD) or median ± interquartile range (IQR). Categorical data were summarized by absolute and relative frequencies.

A time-to-event analysis was performed to estimate the median time to achieve an LVEF > 35% through Kaplan–Meier method. Patients who did not achieve an LVEF > 35% were censored at the last follow-up date. Cox regression models were used to estimate the crude and adjusted incidence rate ratio (IRR) for the event according to the following baseline patient characteristics: sex, age, NYHA functional class, etiology of heart failure, chronic kidney disease (CKD), diabetes *mellitus* and LVEF (further divided in two subgroups: moderately reduced LVEF [30–35%] versus severely reduced LVEF [15–30%]). CKD was defined as an estimated glomerular filtration rate (eGFR) value $\leq$ 60 mL/min/1.73 m^2 (using the CKD-EPI formula), meaning at least moderate dysfunction. The adjusted analyses included all characteristics mentioned above. To present a more parsimonious multivariate Cox regression model, a stepwise procedure was adopted to select, by the Akaike Information criteria, the most relevant variables, with age and sex fixed as adjusted characteristics. Residual analysis of the final model was conducted to check Cox regression assumption of proportionality.

Statistical significance was set at a level of 0.05, and all analyses were conducted in R software (version 3.6, Lucent Technologies, NJ, USA) [14].

This study was approved by the Hospital's Ethics Committee, and all patients freely signed written informed consent before inclusion in the HFC.

3. Results

A total of 48 patients met the inclusion criteria for this analysis.

At baseline, patients had a mean age of 72.5 ± 9.8 years, and the majority were male (70.8%). More than half of the patients (58.3%) had an ischemic etiology, and the vast majority (87.5%) had some degree of renal function impairment, mainly mild to moderate dysfunction (stages 2 and 3 of CKD). All patients were either in NYHA class II (60.4%) or III (39.6%). The most frequent comorbidities were hypertension (70.8%), dyslipidemia (50.0%), atrial fibrillation (47.9%) and diabetes *mellitus* (33.3%). Regarding treatment at baseline, the majority of patients were on beta-blockers (95.8%), ACEi (81.3%), loop diuretics (81.3%) and MRA (54.2%). Further details regarding baseline characteristics are depicted in Table 1.

Table 1. Baseline characteristics of overall study population.

Characteristics	Patients (*n* = 48)
Age (years), mean (SD [#])	72.5 (9.8)
Male sex, *n* (%)	34 (70.8)
Weight (Kg), mean (SD [#])	76.2 (15.0)
BMI *, mean (SD [#])	26.8 (4.8)
Systolic blood pressure (mm Hg), mean (SD [#])	128.4 (20.6)
Heart rate (bpm), mean (SD [#])	71.9 (15.8)
Ischemic etiology, *n* (%)	28 (58.3)
LVEF [$] (%), mean (SD [#])	27.9 (5.6)
NT-proBNP [+] (pg/mL), median (IQR)	3714 (3637)
NYHA [§] functional class, *n* (%)	
II	29 (60.4)
III	19 (39.6)

Table 1. *Cont.*

Characteristics	Patients (n = 48)
Valvular prosthesis	5 (10.4)
Stages of CKD [†] according to eGFR [†], *n* (%)	
Stage 1 (≥90 mL/min/1.73 m^2)	5 (10.4)
Stage 2 (≥60 and <90 mL/min/1.73 m^2)	16 (33.3)
Stage 3 (≥30 and <60 mL/min/1.73 m^2)	18 (37.5)
Stage 4 (≥15 and <30 mL/min/1.73 m^2)	3 (6.3)
Other comorbidities, *n* (%)	
Atrial fibrillation	23 (47.9)
Anemia	10 (20.8)
COPD [‡]	5 (10.4)
Diabetes *mellitus*	16 (33.3)
Dyslipidemia	24 (50.0)
Hypertension	34 (70.8)
Treatment at baseline, *n* (%)	
ACEi [¶]	39 (81.3)
ARB [¶]	5 (10.4)
Beta-blockers	46 (95.8)
Digitalis glycosides	1 (2.1)
Ivabradine	8 (16.7)
Loop diuretics	39 (81.3)
MRA [¶]	26 (54.2)
Thiazides	1 (2.1)

* BMI: body mass index (weight in kilograms divided by the square of the height in meters); [$] LVEF: left ventricular ejection fraction; [+] NT-proBNP: N-terminal pro-B-type natriuretic peptide expressed as pg/mL (equivalent to ng/L, SI units); IQR: interquartile range; [†] CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate using the formula CKD-EPI; [§] NYHA: New York Heart Association class reflects the functional status of the patients; [‡] COPD: chronic obstructive pulmonary disease; [¶] ACEi: angiotensin converting enzyme inhibitors/ARB: angiotensin receptor blockers/MRA: mineralocorticoid receptor antagonists; [#] SD: standard deviation.

The median follow-up time from the start of sacubitril/valsartan until the last follow-up date was 13.4 months (95%CI: 10.1–18.4).

Figure 1 depicts the cumulative probability of achieving an LVEF > 35%. Of the 48 patients, a total of 27 (56%) reached an LVEF > 35% at the end of follow-up, within an estimated median time of 11.3 months (95%CI: 9.4–19.6).

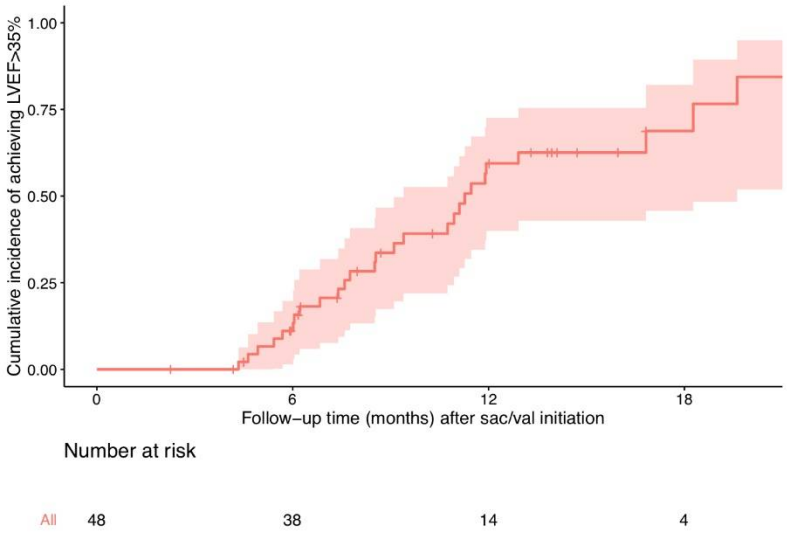

Figure 1. Cumulative incidence of reaching left ventricular ejection fraction (LVEF) above 35%. Sac/val = sacubitril/valsartan.

The crude and adjusted IRR for an LVEF > 35%, regarding all baseline patient characteristics, are presented in Table 2. Some characteristics, such as age, NYHA class, ischemic etiology, CKD and diabetes *mellitus*, did not present a statistically significant effect on the incidence rate. Moreover, females that have shown an improvement in the incidence rate in the crude analysis lost statistical significance when the effect was adjusted for other patient characteristics.

Additionally, Figure 2 presents the result of a more comprehensive multivariate model accomplished by the stepwise procedure, for which baseline LVEF between 30% and 35% was the main driver to achieving an LVEF above 35%. The incidence rate for these patients, after adjustment for sex, age and CKD, was 3.9-fold higher when compared with patients starting with LVEF between 15% and 30% (IRR = 3.9; 95%CI: 1.6–9.9; *p*-value = 0.004).

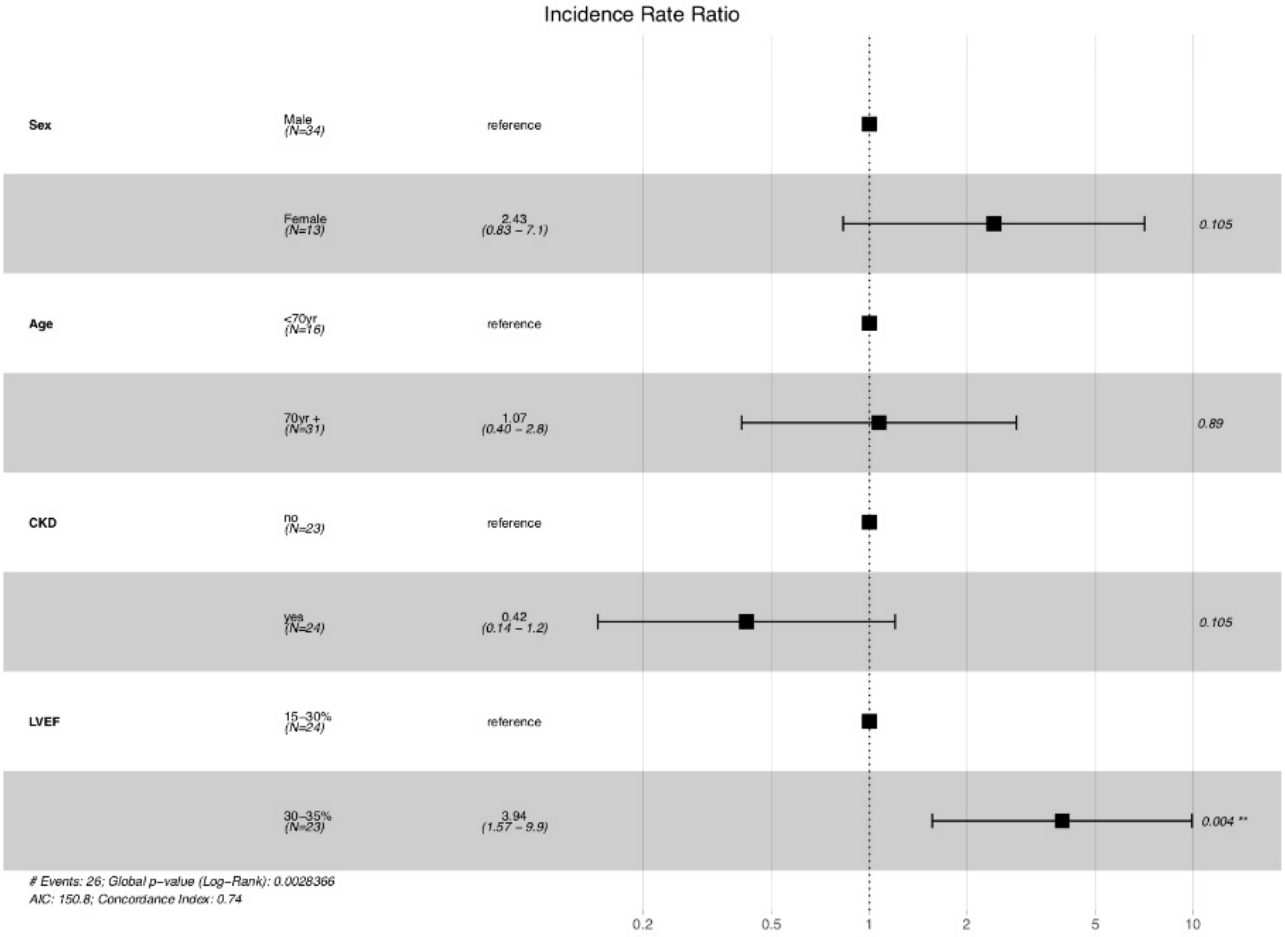

Figure 2. Multivariate stepwise model for the cumulative probability of achieving LVEF above 35%. CKD: Chronic kidney disease; LVEF: Left ventricular ejection fraction. ** Statistically significant.

During the entire follow-up, there was no evidence of malignant ventricular arrhythmias (symptomatic ventricular tachycardia or ventricular fibrillation) or sudden cardiac death, considering clinical and electrocardiographic data.

Finally, no patient discontinued sacubitril/valsartan due to an adverse event.

Table 2. Crude and adjusted results of the Incidence Rate Ratio of achieving an LVEF above 35% estimated by Cox regression model.

Characteristics	Crude Analysis		Adjusted Analysis	
	IRR *	95%CI	IRR *	95%CI
Sex: female vs. male	2.4	1.1–5.5	2.4	0.8–8.4
Age: ≥70 years vs. <70 years	1.0	0.4–2.1	1.1	0.4–3.1
NYHA [#] class: III vs. II	0.8	0.4–1.7	0.8	0.3–2.2
Ischemic etiology: yes vs. no	0.2	0.4–1.8	0.8	0.3–2.2
CKD [†]: yes vs. no	0.7	0.3–1.6	0.5	0.2–1.4
Diabetes *mellitus*: yes vs. no	0.8	0.3–1.8	0.9	0.3–2.7
LVEF [§]: 30–35% vs. 15–30%	4.5	1.8–11.1	3.7	1.4–10.1

* IRR: incidence rate ratio; [#] NYHA: New York Heart Association class reflects the functional status of the patients; [†] CKD: chronic kidney disease, in this case, with an estimated glomerular filtration rate (using the formula CKD-EPI) value equal or below 60 mL/min/1.73 m^2; [§] LVEF: Left ventricular ejection fraction.

4. Discussion

This study demonstrates that reverse cardiac remodeling, using the improvement of LVEF > 35% as a surrogate marker, occurred after a median of 11.3 months of sacubitril/valsartan initiation. Patients with a baseline LVEF between 30% and 35% (moderately reduced ejection fraction) showed a 3.9-fold higher incidence rate of LVEF > 35% at the last follow-up after adjusting for age, sex and CKD. These data suggest that, mainly in this subgroup of patients under treatment with sacubitril/valsartan, the need for cardiac device implantation should be reassessed probably in a time frame longer than the usual 3 months, illustrating the sacubitril/valsartan effect on reverse remodeling in a real-world setting. In terms of safety, this delay in the decision for ICD/CRT implantation did not translate into an increase in sudden arrhythmic death.

To our knowledge, this study was the first to assess the time to attain an LVEF > 35% after sacubitril/valsartan initiation. The real-world population treated with sacubitril/valsartan in this study is comparable to those in previous research conducted in clinical practice, such as a higher proportion of male patients, mean age of around 70 years and a high percentage of patients treated with beta-blockers at baseline [10–12]. All these studies were conducted in populations at more severe stages of HF than patients in the PARADIGM-HF trial (that included patients with lower mean age and with lower levels of NT-proBNP at baseline) [6]. This fact actually emphasized the need for studies outside the controlled clinical trial environment.

Previous case report studies have demonstrated similar results to the present study, showing a substantial benefit from the initiation of sacubitril/valsartan, particularly in reverse cardiac remodeling, even in the elderly population. In these case reports, it has been demonstrated that sacubitril/valsartan was able to improve patients' condition to the point that they actually lost the indication to implant cardiac devices [8,9].

Other observational studies have also shown the beneficial effect of sacubitril/valsartan in left ventricular reverse remodeling [10–12].

The present study demonstrated that higher LVEF at baseline was the only independent predictor of surpassing the cut-off level of 35%, differing from other studies [15–17].

Despite the innovative results presented, there are some limitations that should be addressed, mainly the small sample size and its single-center origin. Due to the observational nature of this study, patients were evaluated according to their usual schedules or by physician recommendation and not at a predefined time interval, which might have extended the time to attain the target LVEF. Still, the scheduled echocardiographic parameters were performed according to usual clinical practice, reflecting real-world evidence, and all echocardiograms were performed by the same echocardiography laboratory team in order to reduce interobserver variability. In addition, despite being a non-randomized study and not having a comparative alternative treatment, we believe observational studies are still valuable for understanding the actual treatment effects under real-world conditions. In fact, this study design only included patients who switched to sacubitril/valsartan after

at least one year of OMT; therefore, clinical benefits documented are likely attributable to sacubitril/valsartan.

Moreover, as Cascais Hospital has a Joint Commission International accreditation and a stage 7 certificate of the Electronic Medical Record Adoption Model by the Healthcare Information and Management Systems Society Analytics, it means that data are readily available and reliable to further support observational studies.

Finally, this study presented an interesting perspective that could potentially provide physicians with valuable information for clinical practice. Instead of simply providing characteristics associated with left ventricular reverse remodeling, it has estimated a median time for improvement, which may guide clinical pathways in terms of added therapy or timing for the decision to implant cardiac devices.

By the time of data collection, the guidelines did not recommend sodium-glucose co-transporter-2 (SGLT-2) inhibitors. Current European guidelines recommend the use of an SGLT-2 inhibitor to additionally reduce heart failure hospitalizations and cardiovascular mortality; nevertheless, to date, there is no robust evidence regarding cardiac reverse remodeling using this class of drugs [1].

In conclusion, switching from ACEi or ARB to sacubitril/valsartan in heart failure patients with LVEF $\leq$ 35% led to the achievement of LVEF > 35% in less than a year in a significant proportion of patients, effectively reversing or at least postponing the indication for cardiac device implantation, without an increase in sudden arrhythmic death. A baseline LVEF between 30 and 35% was the only patient characteristic associated with an improved incidence rate of surpassing the cut-off level of 35% due to left ventricular reverse modeling when adjusted for sex, age and CKD. Based on these findings, we suggest an earlier introduction of sacubitril–valsartan in HFrEF patients and propose a longer time frame than 3 months before deciding on the implantation of ICD/CRT, especially in the subgroup with moderately reduced LVEF.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee, on 24 April 2019 with approval number 14/EC.

Informed Consent Statement: Written Informed Consent was obtained from all subjects involved in the study to published this paper.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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