

Add-on Therapy With Sacubitril/Valsartan and Clinical Outcomes in CRT-D Nonresponder Patients

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Abstract: No data on the add-on sacubitril/valsartan (S/V) therapy among cardiac resynchronization therapy with a defibrillator (CRT-D) nonresponder patients are currently available in literature. We conducted a prospective observational study including 190 CRT-D nonresponder patients with symptomatic heart failure with reduced ejection fraction despite the optimal medical therapy from at least 1 year. The primary endpoint was the rate of additional responders (left ventricular end-systolic volume reduction >15%) at 12 months from the introduction of S/V therapy. At the end of the 12 months follow-up, 37 patients (19.5%) were deemed as “additional responders” to the combination use of CRT + S/V therapy. The only clinical predictor of additional response was a lower left ventricular ejection fraction [OR 0.881 (0.815–0.953), $P = 0.002$] at baseline. At 12 months follow-up, there were significant improvements in heart failure (HF) symptoms and functional status [New York Heart Association 2 (2–3) vs. 1 (1–2), $P < 0.001$; physical activity duration/day: 10 (8–12) vs. 13 (10–18) hours, $P < 0.001$]. Compared with the 12 months preceding S/V introduction, there were significant reductions in the rate of HF rehospitalization (35.5% vs. 19.5%, $P < 0.001$), in atrial tachycardia/atrial fibrillation burden [6.0 (5.0–8.0) % vs. 0 (0–2.0) %, $P < 0.001$] and in the proportions of patients experiencing ventricular arrhythmias (21.6% vs. 6.3%; $P < 0.001$). Our results indicate that S/V add-on therapy in CRT-D nonresponder patients is associated with 19.5% of additional responders, a

reduction in HF symptoms and rehospitalizations, AF burden, and ventricular arrhythmias.

Key Words: sacubitril/valsartan, cardiac resynchronization therapy, heart failure, ventricular remodeling, arrhythmias

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INTRODUCTION

Cardiac resynchronization therapy (CRT) is recommended for patients with medically refractory heart failure with reduced ejection fraction (HFrEF) and wide QRS complex to improve symptoms and reduce morbidity and mortality.¹ About 30% of CRT recipients do not experience significant benefits from this treatment and are classified as “nonresponders,”² although a more flexible approach to the concept of “nonresponse” to CRT has been recently proposed.³ Despite the current the European Society of Cardiology guidelines for the diagnosis and treatment of chronic and acute HF suggesting the combination of upfront medications for heart failure (HF) with CRT as the optimal strategy to further control symptoms and compensation,¹ CRT nonresponders are often passively managed without clear protocols on treatment options, with poor outcomes.⁴

Sacubitril/Valsartan (S/V) is a new medical option for HFrEF treatment, showing a 20% relative risk reduction in both sudden cardiac death (SCD) and death because of HF worsening compared with full-dose enalapril in a selected cohort of patient with HFrEF (<40%) and elevated levels of natriuretic peptides.⁵ S/V also has a remarkable impact on the left ventricular (LV) reverse remodeling, an improvement on mitral regurgitation (MR) and a decrease of ventricular arrhythmia (VA) events.⁶ Given these benefits, it seems plausible that S/V as “add on” on top of CRT may provide additional benefits in patients with HFrEF; however, few studies have tested this approach^{7–9} and none have investigated patients with CRT-D implanted because of associated VA. The aim of this analysis was to evaluate the clinical impact of the add-on S/V therapy among CRT-D nonresponder patients, in a prospective single-center observational cohort study.

MATERIALS AND METHODS

Study Design

The study was a prospective cohort, single-arm, observational study conducted at Monaldi Hospital, Naples, Italy.

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Recruitment started in January 2016 and ended in December 2019. The study design is shown in Figure 1. The study protocol was approved by the local ethics committee. The study was conducted according to the declaration of Helsinki. All enrolled patients provided written informed consent.

Patient Selection

CRT-D nonresponder patients with symptomatic HFrEF despite the optimal medical therapy were eligible for inclusion. Only patients who were not taking S/V at the time of assessment were included. Nonresponders were defined as patients with a left ventricular end-systolic volume (LVESV) reduction <15% after at least 12 months of CRT therapy.¹⁰

Exclusion criteria: Patients on optimal medical therapy for less than 1 year; those with contraindication to S/V therapy according to the summary of product characteristics¹¹; patients with an achievable biventricular pacing <95%; those with less than 1 year of life expectancy because of advanced cancer; and those who did not give informed consent. The flow chart of the study population is shown in Figure 2.

S/V Administration

The standard S/V starting dose was 49/51 mg twice daily and was up titrated during follow-up. Patients with severe renal impairment or taking low doses of angiotensin converting enzyme inhibitors or angiotensin receptor blockers received an S/V starting dose of 24/26 mg S/V twice daily. The target of S/V dosing was 97/103 mg twice daily.

Endpoints

The primary endpoint was the rate of additional responders at 12 months from the introduction of S/V therapy. Additional responders were defined as patients fulfilling the a priori echocardiographic criteria of CRT responder (LVESV reduction >15%) after introduction of S/V therapy. Secondary endpoints included the following: clinical status; HF hospitalizations and overall mortality; changes in echocardiographic parameters; the total atrial tachycardia/atrial

fibrillation (AT/AF) burden (defined as the percentage of time in AT/AF per day, as detected by the device); the mean number of ventricular tachycardia/ventricular fibrillation (VT/VF) episodes; and the number of appropriate or inappropriate implantable cardiac defibrillator (ICD) therapies. All endpoints were centrally adjudicated with the review of clinical and device-stored details by 2 independent investigators (V.R. and R.P.).

Data Collection and Patients' Follow-up

Patient demography, pharmacological therapy, NHYA class, hours of physical activity/day, number of hospitalizations in the 12 months preceding the S/V introduction, echocardiographic data, atrial and ventricular CRT-estimated parameters, and device-detected arrhythmia burden at S/V introduction were collected into a centralized de-identified database. After being started on S/V, all patients were followed-up for 12 months in a dedicated outpatient HF clinic. Multiple clinical appointments were scheduled after S/V introduction to re-assess and up-titrate the therapy, the first being scheduled after 3 weeks from S/V start. All patients received a full device interrogation and a complete echocardiography assessment at 12 months.

During follow-up, HF rehospitalizations and overall mortality were collected. All CRT-D data collected remotely were evaluated to identify AT/AF burden, ventricular arrhythmic events (VT/VF), and appropriate/inappropriate ICD therapies.

Echocardiographic Assessment

Echocardiographic examination was performed using Vivid E9 machine (GE Medical Systems, Milwaukee, WI) with a 3.5–4-MHz phased-array probe (M3S). Echocardiographic images were digitally stored and analyzed off-line by 2 blinded independent observers (V.R., R.B.). Chamber quantification was obtained following current guidelines.¹² LV ejection fraction (LVEF) was measured using Simpson's biplane method. LV diastolic function was determined following Nagueh criteria.¹³ Mitral and tricuspid

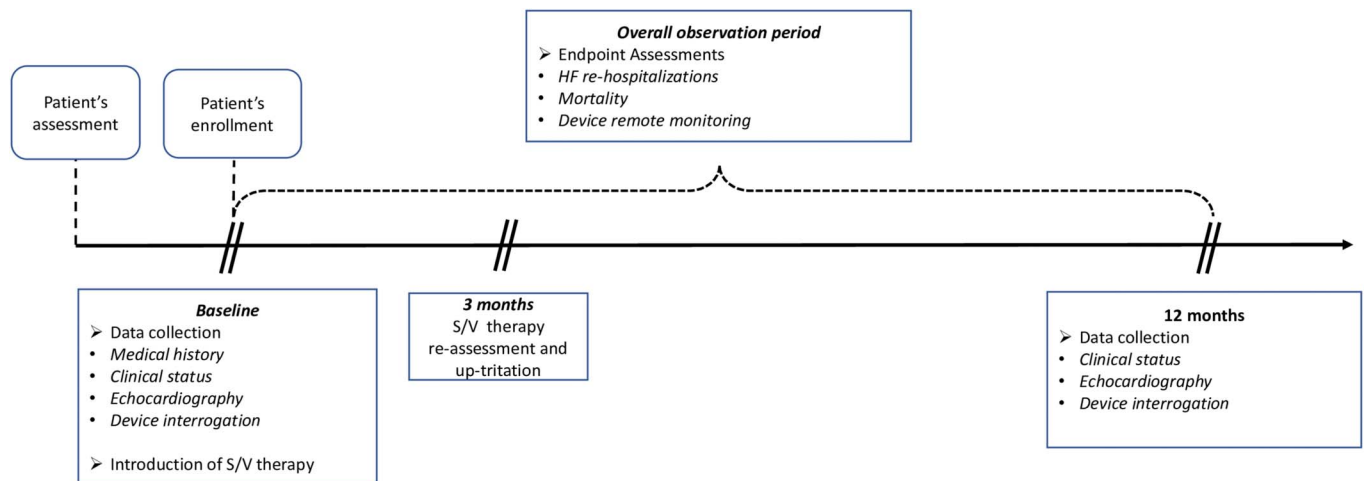


FIGURE 1. Study protocol.

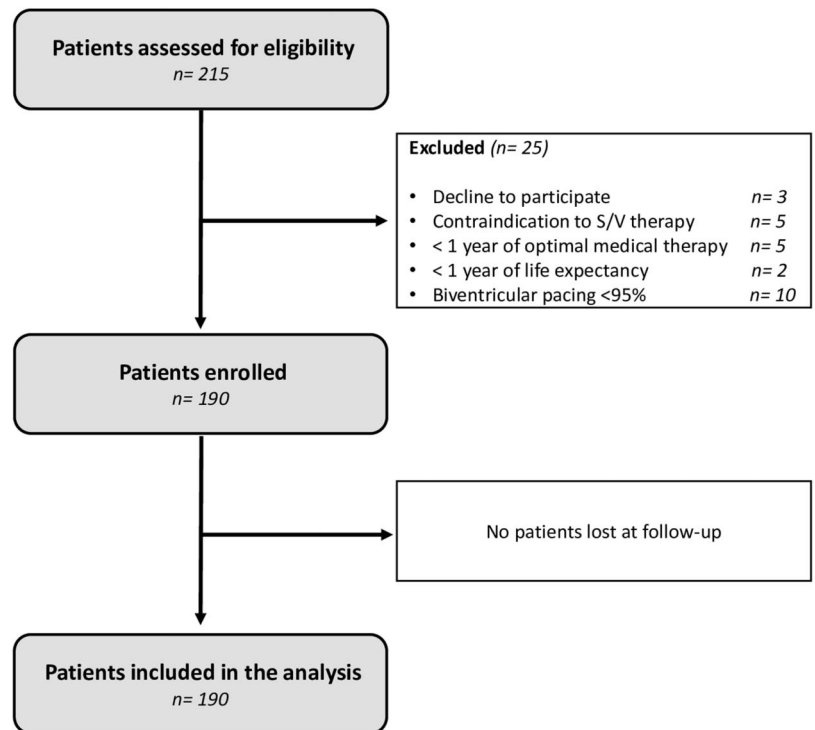


FIGURE 2. Flow chart of study population.

valve regurgitations were quantified following the American Society of Echocardiography recommendations for noninvasive evaluation of native valvular regurgitation.¹⁴ The investigators who analyzed the echocardiographic images were blinded to the timing for acquisition of the images (pre or post S/V therapy starting).

Device Programming and Analysis of Device Interrogations

The following programming for VT/VF zones was adopted: VT1 at 150–169 bpm was only monitor zone; VT2 at 170–200 included up to 3 ATPs and 8 shocks; VF >200 bpm included only shocks. AT/AF detection algorithm was enabled at 171 bpm. From the device interrogation, episodes of VT, VF, sustained AT/AF (AT defined as high atrial rate ≥ 30 seconds), and the appearance of appropriate (ie, shocks and anti-tachycardia pacing due to VT/VF) or inappropriate (ie, shocks and anti-tachycardia pacing due to AT/AF) therapies have been evaluated. The type of tachycardia as defined by the device was confirmed by 2 independent electrophysiologists blinded to the patients' clinical status.

Statistical Analysis

All statistical analysis were performed using STATA v. 14.0 (STATA Corp, LakeDrive Way, TX). Numerical variables were reported as mean \pm SD if normally distributed or as median [inter-quartile range (IQR)] if not normally distributed. Categorical data were reported as count (percentage). Per-patient paired comparisons of variables were performed using paired *t* test or sign test, if numerical, or using McNemar-Bowker test, if categorical, as appropriate. Predictors of responder status were assessed using univariate

logistic regression analysis; multivariate analysis was not performed because just one variable reached a *P* value < 0.10 at univariate analysis. A two-tailed *P*-value of 0.05 or lower was considered statistically significant.

RESULTS

A total of 190 CRT-D nonresponder patients [median age 64.0 (IQR 56.0–72.0) years; 72.6% male] who met the inclusion criteria were enrolled. The median time of CRT-D devices implantation was 20 (IQR: 13–26) months before baseline assessment. The distribution of starting times for S/V relative to the initiation of CRT therapy is shown in Figure 3. All enrolled patients showed no change or worsening of their EF after CRT implantation. The most common comorbidity was hypertension (69.0%), followed by AF (47.4%), chronic obstructive pulmonary disease (34.7%), and diabetes mellitus (33.7%). Ischemic dilated cardiomyopathy was the underlying HF substrate in 79 patients (41.6%), whereas the remaining had a nonischemic dilated cardiomyopathy. All patients showed pre-implantation left bundle branch block. Baseline study population characteristics were summarized in Table 1.

S/V Administration

The S/V starting dose was 49/51 mg twice daily in 112 patients (59%); 78 (41%) patients received a S/V starting dose of 24/26 mg S/V twice daily because of severe renal impairment or low doses of angiotensin converting enzyme inhibitor or angiotensin receptor blocker intake. S/V was well tolerated in our cohort, with 91.1% of patients up-titrating the dosage and 54.7% of the cohort reaching the maximal

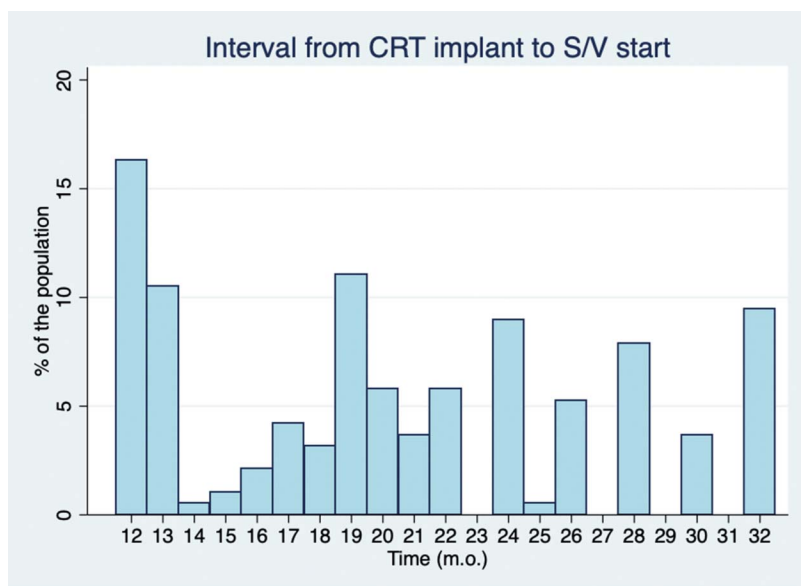


FIGURE 3. Time interval distribution from CRT implant to initiation of S/V therapy.

commercially available dosage. No drop-outs or S/V discontinuation were observed. The cohort was on maximal tolerated S/V for a median of 6 months (IQR 4–8).

Primary Endpoint

All patients completed the 1-year follow-up. At the end of follow-up, 37 patients (19.5%) were classified as “additional responders” to the combination of CRT + S/V therapy (Fig. 4). The only predictor of additional response after introduction of S/V therapy was a lower left ventricular ejection fraction (LVEF) [OR 0.881 (0.815–0.953), *P* = 0.002] at baseline (Table 2).

Secondary Endpoints

HF symptom functional status improved significantly, both subjectively [New York Heart Association 2 (2–3) vs. 1 (1–2), *P* < 0.001] and objectively [hours of physical activity/day: 10 (8–12) vs. 13 (10–18), *P* < 0.001]. The rate of HF rehospitalization was decreased significantly compared with the 12 months before the start of S/V therapy (35.5% vs. 19.5%, *P* < 0.001). Survival curves showing the combined outcome of HF rehospitalization and overall mortality are shown in Figure 5.

At 12 months after S/V introduction, we found a statistically significant improvement in LVEF (*P* < 0.001); left ventricular end-diastolic volume (LVEDV; *P* < 0.001); (LVESV; *P* < 0.001); and left atrial volume index (LAVi; *P* = 0.001) (Table 2). There was significant reduction of patients with restrictive diastolic function (32.2% vs. 13.7%, *P* < 0.0001). The severity of both MR and tricuspid regurgitation was reduced (severe MR 35.8% vs. 5.7%, *P* < 0.001; severe tricuspid regurgitation 8.9% vs. 0%, *P* < 0.001) at the end of follow-up (Table 3).

In patients with a history of AT/AF, the AT/AF burden was decreased significantly [6.0 (5.0–8.0) % vs. 0 (0–2.0) %, *P* < 0.001] without any significant modification in anti-

arrhythmic therapy. The rate of patients experiencing at least one VAs episode (21.6% vs. 6.3%; *P* < 0.001), and the overall number of patients experiencing both appropriate and inappropriate ICD therapies (21.6% vs. 6.3%, *P* < 0.001% and 7.4% vs. 2.6%, *P* = 0.034, respectively) were reduced, when compared with the 12 months preceding S/V

TABLE 1. Baseline Characteristics of Study Population (n = 190)

Age (years), median [IQR]	64.0 [56.0–72.0]
Male, n (%)	138 (72.6)
BMI, median [IQR]	26.0 [23.2–30.0]
Hypertension, n (%)	131 (69.0)
Diabetes, n (%)	64 (33.7)
CKD, n (%)	50 (26.3)
Atrial fibrillation, n (%)	90 (47.4)
COPD, n (%)	66 (34.7)
Ischemic cardiomyopathy, n (%)	79 (41.6)
HF hospitalization in the previous 12 months, n (%)	67 (35.3)
Pre-implant left bundle branch block, n (%)	190 (100%)
Time from CRT implantation (months), median IQR	20 (13.0–26.0)
Pharmacological Therapy	
Ace inhibitors, n (%)	109 (57.4)
ARBs, n (%)	81 (42.56)
Beta blockers, n (%)	182 (95.8)
Loop diuretics, n (%)	129 (67.9)
ARA, n (%)	121 (63.7)
Digoxin, n (%)	12 (6.3)
Amiodarone, n (%)	33 (17.4)
Sotalol, n (%)	4 (2.1)

ARA, aldosterone receptor antagonists; ARBs, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure.

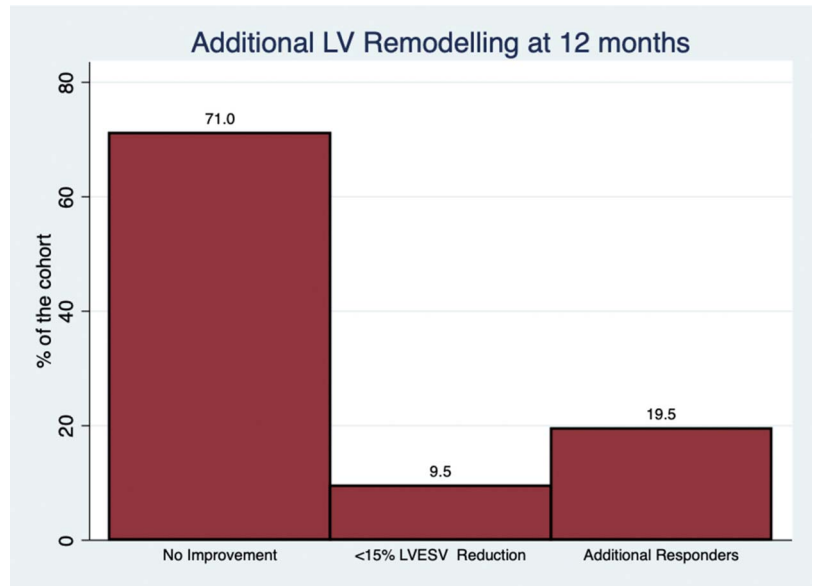


FIGURE 4. Cohort stratification on the base of left ventricular end-systolic volume (LVESV) modification after 12 months from sacubitril–valsartan introduction.

introduction. CRT-D electrical parameters remained stable over the time (Table 3).

DISCUSSION

To date, little is still known about the clinical impact of add-on S/V therapy among HFrEF patients with CRT who are nonresponders, based on the traditional criterion of LVESV reduction <15%.^{10,15} The principal findings of the study are as follows: (1) Among nonresponding patients undergoing optimized CRT for at least 12 months, S/V introduction resulted in approximately 20% of additional responders, with an overall increase in LVEF and an improvement in LV and atrial dimensions; (2) HF hospitalizations, VAs, and AT/AF burden after S/V introduction were significantly reduced by S/V + CRT use; and (3) Patients with lower LVEF at baseline were more likely to be additional responders to S/V + CRT.

Our observations suggest the need for a prospective randomized trial of S/V in CRT nonresponders, given the lack of evidence-based strategies in CRT nonresponders. The concept of “response to CRT,” based on a rigid assessment of the reduction in end-systolic volumes has been object of criticisms, with the proposal of abandoning the term “non-response” and adopting the concept of “disease modification.”³ The findings of our study can also be interpreted, in line with the new concept of “disease modification,” associated with implementation of S/V that leads to improvement of LV function, reverse structural remodeling, and positive effects on arrhythmias, at the atrial and ventricular level.

Very limited data have been published thus far on an add-on strategy with S/V administrated in CRT patients.⁷⁻⁹ A post hoc analysis showed that 38% of CRT nonresponder patients at 6 months were still eligible for add-on therapy with S/V therapy.⁷ In the setting of nonresponders to CRT, the retrospective study by Chun et al⁸ showed a better clinical outcome for patients who were treated with S/V; however,

they did not report data on increased CRT responsiveness after initiation of S/V therapy, nor the echocardiographic changes after institution of S/V therapy.

Previous observational studies have shown a positive effect of S/V in reverse structural remodeling, arrhythmias, and clinical outcome among HFrEF patients during follow-up; however, their study cohort was more heterogeneous and their results were not focused on patients treated with CRT.^{6,16} In

TABLE 2. Predictors of “Additional Responder” Status in the Study Cohort

Predictors	OR [95% C.I.]	P
Age	0.993 [0.962–1.024]	0.657
Male sex	1.216 [0.531–2.788]	0.644
BMI	1.002 [0.927–1.084]	0.948
CKD	0.479 [0.187–1.229]	0.126
COPD	1.363 [0.652–2.850]	0.410
AF	0.709 [0.342–1.470]	0.355
Ischemic cardiomyopathy	0.554 [0.259–1.183]	0.127
LVEF at baseline	0.881 [0.815–0.953]	0.002
LVEDD at baseline	1.013 [0.945–1.086]	0.707
LVEDD at baseline	1.017 [0.963–1.073]	0.555
LVESV at baseline	1.001 [0.994–1.007]	0.843
LVEDV at baseline	1.002 [0.992–1.012]	0.678
TAPSE	0.967 [0.839–1.116]	0.645
Atrial sensing	1.036 [0.822–1.306]	0.762
RV sensing	1.003 [0.973–1.035]	0.943
LV sensing	1.027 [0.986–1.069]	0.191
Maximal dosage reached	0.737 [0.364–1.495]	0.398

AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LV, left ventricle; LVEF, left ventricular ejection; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

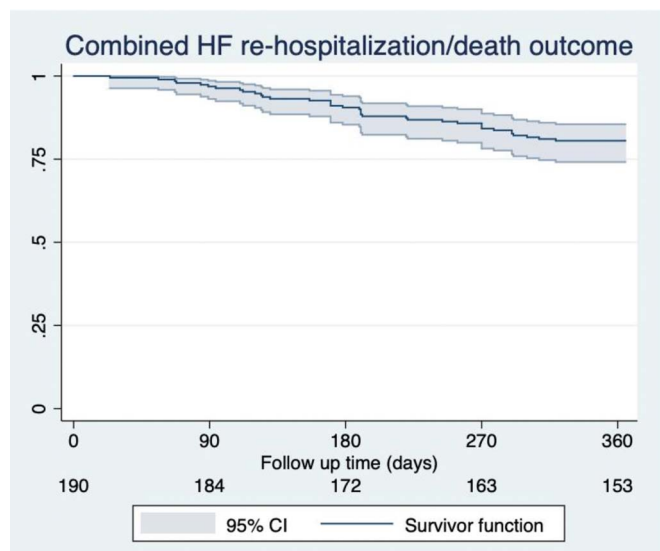


FIGURE 5. Overall cohort combined outcomes during the 12-month follow-up. Event rate was 1.8 [1.3–2.4] %/month.

our study, the add-on therapy with S/V in a defined cohort of CRT-D non-responders was associated with clinical benefits, suggesting promising alternative strategy for improving the prognosis of nonresponders to CRT. In our study cohort, S/V therapy was well tolerated, with no drop-outs or S/V discontinuation and approx. 55% of the cohort reaching the maximal commercially available dosage. In the PARADIGM-HF trial, the maximum dose of S/V was not tolerated in almost half of the patients randomized because of side effects, mainly hypotension, which required a reduced deescalating dose.⁵

The European Society of Cardiology Guidelines on HF¹ state that CRT and ARNI could be considered to improve LVEF when is still $\leq 35\%$ with optimal medical therapy, although data of an upfront or late combination of S/V and CRT are currently lacking.¹⁷ Although our data are mainly focused on a late introduction of SV in nonresponder CRT-D patients, our results also advocate for early combined therapy with S/V and CRT.¹⁷ In patients who have left bundle branch block, medical therapy has a limited effect on LVEF, indicating that electrical (ie, CRT) therapy and medical therapy have different targets, with the potential for additive and even synergistic effects.¹⁷

Impact of S/V on Ventricular and Supraventricular Arrhythmias

The PARADIGM-HF trial showed a significant reduction of SCD with S/V when compared with enalapril⁵; however, data on the underlying mechanism(s) of SCD were lacking. Two previous studies^{6,18} reported a reduction in VAs and appropriate ICD shocks in HFrEF patients with ICD/CRT on S/V therapy, and the role of the cardiac reverse remodeling was hypothesized, because of an observed concomitant improvement in LVEF. Our study, prospectively evaluating a homogeneous cohort of nonresponder CRT-D patients, supports these data, showing a significant reduction of VA yearly rate (from 21.6% to 6.3%) after introduction of S/V therapy. We believe that cardiac reverse remodeling through a net

TABLE 3. Baseline and Follow-up Clinical, Echocardiographic and CRT-D Data

Echocardiography Specifics			
	At Baseline	At Follow-up	P
LVEF (%), mean \pm SD	28.7 \pm 4.6	31.2 \pm 4.2	<0.001
LVEDD (mm), mean \pm SD	63.7 \pm 5.2	62.7 \pm 5.4	0.001
LVESD (mm), median [IQR]	44 [41–48]	43 [40–48]	<0.001
LVEDV (mL), median [IQR]	231 [147–255]	208 [145–249]	<0.001
LVESV (mL), median [IQR]	109 [88–140]	103 [74–140]	<0.001
LAVI (ml/mq), median [IQR]	33 [28–33]	30 [28–30]	0.001
Restrictive diastolic function, n (%)	65 (32.2)	26 (13, 7)	<0.0001
Mitral regurgitation			<0.001
Mild, n (%)	29 (15.2)	58 (30.5)	
Moderate, n (%)	93 (49.0)	121 (63.7)	
Severe, n (%)	68 (35.8)	11 (5.7)	
Tricuspid regurgitation			<0.001
Mild, n (%)	112 (59.0)	162 (85.3)	
Moderate, n (%)	61 (32.1)	28 (14.7)	
Severe, n (%)	17 (8.9)	0	
TAPSE (mm), median [IQR]	19.0 \pm 2.5	20.1 \pm 2.3	<0.001
CRT Specifics			
P wave sensing (mV), median [IQR]	3.0 [2.0–4.2]	3.1 [2.5–4.5]	<0.001
RV R wave sensing (mV), median [IQR]	11.9 [7.7–14.0]	12.0 [9.0–14.0]	<0.001
LV R wave sensing (mV), median [IQR]	8.0 [6.1–12.0]	9.0 [6.6–13.1]	0.014
Physical activity (h/d),	10 [8–12]	13 [10–18]	<0.001
AF burden (%), median [IQR]	6.0 [5.0–8.0]	0 [0–2.0]	<0.001
Clinical Specifics			
NYHA class	2 [2–3]	2 [1–2]	<0.001
Additional responders, n (%)	—	37 (19.5)	—
Patients being hospitalized for HF, n (%)	67 (35.5)	37 (19.5)	<0.001
Patients with VAs, n (%)	41 (21.6)	12 (6.3)	<0.001
Patients with appropriate ICD therapies, n (%)	31 (16.3)	7 (3.7)	<0.001
Patients with inappropriate ICD therapies, n (%)	14 (7.4)	5 (2.6)	0.034
Death, n (%)	—	5 (2.6)	—

AF, atrial fibrillation; HF, heart failure; ICD, implantable cardioverter-defibrillator; LAVI, left atrial volume index; LV, left ventricle; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; VAs, ventricular arrhythmias.

improvement of the LVEF plays a key role in reducing VAs events and possibly SCD events, perhaps with reduction in the extent of fibrosis (especially in nonischemic cardiomyopathies) and modulation of sympathetic tone.¹⁹

Among HF_{rEF} patients, AF is a well-known harbinger of adverse events. Previously, both trial⁵ and real-world data⁶ did not show any effect of S/V therapy on AF burden; however, no atrial echocardiographic data were reported. Our study described a reduction of AF burden (>50%) in more than 80% CRT nonresponder patients with AF after S/V introduction in parallel with a reduction in LAVi and in MR severity. Our results confirm the hypothesis of a complete atrial electromechanical remodeling in HF patients with cardiac implantable electronic devices treated with S/V.²⁰

Clinical Endpoints and Hospitalizations With Combined Strategy

In our population the rate of HF hospitalizations after S/V introduction was significantly reduced during the entire follow-up, also evident in the survival analysis combining death and hospitalization rate. Of note, S/V therapy on top of CRT improved clinical status, as assessed as New York Heart Association class and physical activity, reflecting the improvement of LVEF. When compared with nonresponders, responders to CRT have lower rates of postimplant HF hospitalization rate, which can have a positive impact on health care costs.

Limitations

Our study shares all the limitations of nonrandomized cohort studies. The absence of control-group including CRT patients not in S/V therapy determines the inability to assess if the results of the present study reflect a continuation of a natural timeline post-CRT, the effect of S/V therapy or a combination of these 2 factors. However, the lack of improvement after a median time of 20 months before enrollment reduces the possibility of a late-onset response to the CRT; because it has previously shown that post-CRT improvements are constant over time and greater in the first-year postimplantation.²¹

No universal definition of response to CRT exists³; however, the reduction of LV end-systolic volumes (LVESV) seems to be the most useful measure to define the response to CRT in prognostic terms,^{10,15} becoming so far the most widely accepted definition.¹⁰ We did not routinely measure pro-BNP levels, that may represent a surrogate of the previously described reverse cardiac remodeling.

CONCLUSIONS

The use of S/V add-on therapy was associated with nearly 20% of additional responders among CRT nonresponder patients. The introduction of S/V was also associated with a significant ventricular and atrial positive remodeling, resulting in a reduction in HF symptoms and rehospitalizations, AF burden and VAs.

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