Cardiol Ther
https://doi.org/10.1007/s40119-023-00346-1

ORIGINAL RESEARCH

Add-on Sacubitril/Valsartan Therapy Induces Left Ventricular Remodeling in Non-responders to Cardiac Resynchronization Therapy to a Similar Extent as in Heart Failure Patients Without Resynchronization

Krisztina Mária Szabó · Anna Tóth · László Nagy · Vivien Rácz · Zsófia Pólik · Katalin Hodosi · Attila C. Nagy · Judit Barta · Attila Borbély · Zoltán Csanádi

Received: October 8, 2023 / Accepted: December 13, 2023

ABSTRACT

Introduction: Non-responders to cardiac resynchronization therapy (CRT-NR) have poor prognosis. Sacubitril/valsartan (SV) treatment improved the outcome of patients with heart failure with reduced left ventricular (LV) ejection fraction (HFrEF) in randomized trials with no data on the specific cohort of CRT-NRs. The aim of this study was to compare the echocardiographic and biomarker changes in CRT-NR patients treated with versus without SV, and in patients with HFrEF on SV therapy.

Methods: CRT-NR patients initiated on SV (group I), CRT-NR patients on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) (group II), and patients with HFrEF (without CRT) initiated on SV (group III) were identified in our heart failure (HF) registry. CRT-NR was defined as < 10% improvement in left ventricular ejection fraction (LV EF) 6 months after the implantation. Echocardiographic parameters and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at baseline and at the end of follow-up were compared.

Results: A total of 275 patients (group I, 70; group II, 70; and group III, 135) were included. After a follow-up of 7.54 ± 1.8 months (mean ± standard deviation [SD]), LV EF (%) increased in group I (25.2 ± 5.7 versus $29.4\% \pm 6.7$; $p < 0.001$) and in group III (26.6 ± 6.4 versus 29.9 ± 6.7; $p < 0.001$). LV end-systolic diameters (mm) decreased in group I (56.6 ± 9.0 versus 54.3 ± 8.7; $p = 0.004$) and in group III (55.9 ± 9.9 versus 54.3 ± 11.2; $p = 0.021$). The levels of NT-proBNP (pg/mL) decreased in group I (2058.86 [1041.07–4502.51] versus 1121.55 [545–2541]; $p < 0.001$) and in group III (2223.35 [1233.03–4795.96] versus 1123.09 [500.38–2651.27]; $p < 0.001$). The extent of improvement was similar in groups I and III ($p > 0.05$). No significant changes were detected in group II.

Prior Presentations: These data were presented in part at two international congresses, as detailed below: ESC Congress (European Society of Cardiology), August 26–29, 2022, Barcelona, moderated poster: "The effectiveness of ARNI medication in patients non-responder to cardiac resynchronization therapy". ACC Congress (American College of Cardiology), March 4–6, 2023, New Orleans, poster: "Short-term effect of add on ARNI medication on echocardiographic parameters and NT-pro-BNP levels in patients nonresponder to cardiac resynchronization therapy".

K. M. Szabó (✉) · A. Tóth · L. Nagy · V. Rácz · Z. Pólik · K. Hodosi · J. Barta · A. Borbély · Z. Csanádi
Department of Cardiology, Faculty of Medicine, University of Debrecen, Móricz Zsigmond Krt. 22., Debrecen 4032, Hungary
e-mail: dr.szabo.krisztina.maria@med.unideb.hu

A. C. Nagy
Department of Health Informatics, Faculty of Health Sciences, University of Debrecen, Debrecen, Hungary

Published online: 12 January 2024

Conclusion: SV therapy induced similar improvements in echocardiographic parameters and in NT-proBNP levels in CRT-NR patients and in patients with HFrEF without resynchronization.

Keywords: Heart failure with reduced ejection fraction; Cardiac resynchronization therapy; Sacubitril/valsartan; NT-pro-B-type natriuretic peptide

Key Summary Points

Why carry out this study?

Cardiac resynchronization therapy (CRT) fails to improve echocardiographic parameters and clinical outcome in up to 40% of patients.

Sacubitril/valsartan (SV) applied as a replacement for angiotensin-converting enzyme 2 inhibitor (ACE2i) or angiotensin receptor blocker (ARB) resulted in left ventricular (LV) reverse remodeling and improved clinical outcomes in patients with heart failure with reduced ejection fraction (HFrEF).

Herein, we investigated whether SV would also result in cardiac remodeling in the specific subgroup of CRT non-responders (CRT-NRs), similarly to what was demonstrated in general patients with HFrEF.

What was learned from the study?

This study demonstrated that a minimum 6-month treatment with SV induced LV reverse remodeling in CRT-NRs, evidenced by a significant increase in left ventricular ejection fraction (LV EF), a reduction in LV end-systolic diameter, and a decrease in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration.

The extent of improvement in CRT non-responders was similar to what was observed in general patients with HFrEF with no CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure (HF) with reduced ejection fraction (HFrEF), intraventricular delay, and mild to moderate HF symptoms despite guideline-dictated medical treatment [1–3]. CRT has been demonstrated to induce reverse remodeling, improve quality of life, exercise capacity, HF-related mortality, and hospitalization rates [4, 5]. However, in up to 40% of patients, CRT fails to improve echocardiographic parameters and clinical outcome [6–8]. These patients are referred to as CRT non-responders (CRT-NR) based on various criteria used in different studies to describe this clinical entity in the absence of a widely accepted definition. Functional improvement (NYHA (New York Heart Association) functional class, 6-min walk test, and quality of life assessments), the rate of HF hospitalizations, changes in echocardiographic parameters—including a reduction in left ventricular end-systolic volume (LVESV), an improvement in left ventricular ejection fraction (LV EF), or the combination of these measures—have been proposed to assess the response to CRT at different time points, usually at the 6-month or at the 1-year follow-up after device implantation [9]. The rate of non-response is related to the criteria used: a definition of response based on echocardiographic parameters usually results in higher rates of non-responders as compared to a definition based on functional or quality of life assessment. Despite extensive clinical research focusing on patient selection, left ventricular lead placement, and device programming, the phenomenon of CRT non-response is still not fully understood, and the prognosis of CRT-NR patients remains poor [6–10]. In addition, data from the ADVANCE CRT registry indicated that many CRT-NR patients are managed passively in clinical practice with no effort to maximize available therapeutic options—including medical treatment—to improve life expectancy and quality of life [7].

The introduction of sacubitril/valsartan (SV), a new therapeutic class of agents acting on the renin–angiotensin system (RAS) and the neutral

endopeptidase system (ARNI, angiotensin receptor neprilysin inhibitor) is considered a highly significant development in HF therapy. SV is recommended as part of the baseline therapy with class I indication according to recent guidelines [1, 3]. These recommendations were based on the significant improvement in both cardiovascular mortality and HF hospitalization with SV applied as a replacement for angiotensin-converting enzyme 2 inhibitor (ACE2i) or angiotensin receptor blocker (ARB) demonstrated in the PARADIGM study [11]. Available data suggest that the outcome benefit with SV is related to left ventricular (LV) remodeling. The improvement in LV contractility and the decrease in LV diameters are accompanied by a significant reduction in the plasma level of NT-pro-B-type natriuretic peptide (NT-proBNP) which can be detected within 6–12 months after the initiation of SV therapy in patients with HFrEF [12, 13].

However, the efficacy of SV in the specific subgroup of patients with HFrEF and previous CRT implantation—and specifically in those who did not respond to CRT—remains ill defined. In a few observational studies which enrolled a limited number of CRT-NR patients and had relatively short follow-up durations, the echocardiographic signs of cardiac remodeling, along with the improvement in functional status, quality of life, as well as reduced rates of hospitalization and mortality have been demonstrated after the initiation of SV [14–16].

Herein, we compared the short-term changes in echocardiographic parameters and in NT-proBNP levels in three groups of patients: 1. CRT-NR patients treated with SV; 2. CRT-NR patients treated with ACEi or ARB; 3. patients with HFrEF with no indication for CRT (general HFrEF cohort) treated with SV. The rationale behind this study design was to evaluate the potential benefit of switching ACEi/ARB medication to SV in CRT-NR patients and to compare the extent of improvement with SV treatment in a CRT-NR versus in a general HFrEF cohort.

METHODS

The clinical database for patients with heart failure in our department was searched to identify patients with HFrEF with LV EF < 40% treated as an inpatient or outpatient between January 2018 and June 2021 as well as consecutive patients who had CRT implantation based on standard indications (pacemaker or implantable cardioverter-defibrillator (ICD) at the discretion of the treating physician) during the same period. Management of patients including medical treatment was guided by their treating physician. Only patients receiving guideline-dictated medical therapy including ACEi/ARB or SV were considered for this analysis. The responder status of CRT patients was determined by comparing the LV EF obtained before and at least 6 months after the implantation. CRT non-responder status was defined as a less than 10% increase in LV EF measured on two-dimensional (2D) echocardiography using Simpson's biplane method. CRT patients with biventricular capture rate below 95% were excluded from this study. The database was searched for further information on the medical treatment of these patients collected at routine follow-up visits every 3–6 months during the study period. The study was approved by the Medical Research Council (Ministry of Interior, P.O. Box 314, Budapest, 1903, Hungary) File no. BMEÜ/4388-1/2022/EKU. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Use of the clinical database was approved by the head of department.

Patients were enrolled and assigned to one of three treatment groups based on the following criteria (Fig. 1):

Group I CRT-NR patients initiated on SV. SV was started during the study period as a replacement for ACEi/ARB therapy and the results of 2D echocardiography and plasma NT-proBNP concentration obtained before the initiation of SV and after at least 6 months on SV were available.

Group II CRT-NR on ACEi/ARB. Patients were receiving evidence-based medical treatment including ACEi/ARB during the whole study period, and the results of 2D echocardiography and plasma NT-proBNP concentration from two time points (minimally 6 months apart) were available.

Group III Patients with HFrEF initiated on SV. These patients represented a general HFrEF cohort with no indication for CRT implantation based on LV EF or QRS (representing ventricular depolarization) duration criteria. SV was started during the study period as a replacement for ACEi/ARB therapy and the results of 2D echocardiography and plasma NT-proBNP concentration obtained before the initiation of SV and after at least 6 months on SV were available.

In addition to the treatment with ACEi/ARB or SV, patients received beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and diuretics as baseline therapy. SV was always initiated after the discontinuation of ACEi/ARB with a daily starting dose of 100 mg (24/26 BID = two times a day) or 200 mg (49/51 BID) and titrated to the maximum tolerated dose up to 400 mg daily (97/103 mg BID).

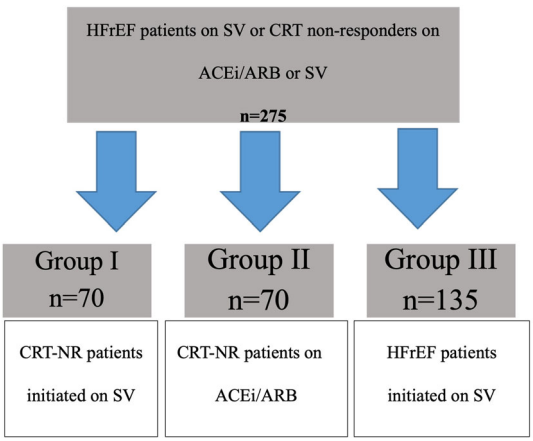

Fig. 1 Group assignments of patients. *HFrEF* heart failure with reduced ejection fraction, *SV* sacubitril/valsartan, *CRT* cardiac resynchronization therapy, *CRT-NR* non-responder to cardiac resynchronization therapy, *ACEi/ARB* angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Endpoints

The primary endpoints of the study were the changes in LV EF and in NT-proBNP levels between baseline and the final measurements at the end of follow-up in each group. In groups I and III, baseline measurements were performed before the initiation of SV and the final measurements at the end of follow-up on S/V treatment for at least 6 months. In group II, patients had been on continuous ACEi/ARB therapy even before device implantation and therefore measurements used for comparison were not related to a change in therapy. The first and second measurements used for comparison were performed at least 6 months apart on steady ACEi/ARB therapy. The extent of changes obtained for these primary endpoints in groups I and III was also compared. Changes in other echocardiographic parameters including end-diastolic and end-systolic diameters (LVEDD, LVESD), left ventricular outflow tract velocity time integral (LVOT VTI), stroke volume and dP/dt (representing the ratio of pressure change in the ventricular cavity during the isovolumetric contraction period) were considered as secondary endpoints. Systolic and diastolic blood pressure, estimated glomerular filtration rate (eGFR), and potassium levels were evaluated as safety endpoints.

Statistical Analysis

Statistical calculations were performed using IBM SPSS 26 and STATA V17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Continuous data were described as means ± standard deviation (SD) or as median [IQR], and discrete variables were reported as case counts and percentages. Missing data were replaced using the last observation carried forward (LOCF) method. The distribution of continuous variables was characterized by the Kolmogorov–Smirnov test.

Table 1 Baseline patient characteristics

	Group I (*n* = 70)	**Group II (*n* = 70)**	**Group III (*n* = 135)**	***p* (Gr. I vs II vs III)**	***p* (Gr. I vs II)**	***p* (Gr. I vs III)**	***p* (Gr. II vs III)**
Age (years)	66.1 ± 9.1	65.5 ± 11.3	62.4 ± 11.3	0.018	0.879	0.011	0.036
Female sex (%)	9 (12.9%)	9 (12.9%)	31 (22.9%)	0.128	0.831	0.134	0.087
Body weight (kg)	90.9 ± 18.8	89.1 ± 20.9	92.3 ± 23.6	0.669	0.433	0.901	0.411
NYHA class I	1 (1.4%)	0 (0.0%)	0 (0.0%)	0.231	0.315	0.163	ø
NYHA class II	19 (27.2%)	28 (40%)	43 (31.9%)	0.256	0.107	0.486	0.244
NYHA class III	47 (67.2%)	37 (52.8%)	86 (63.7%)	0.181	0.084	0.624	0.132
NYHA class IV	3 (4.3%)	5 (7.1%)	6 (4.5%)	0.663	0.466	0.301	0.753
LV EF (%)	25.2 ± 5.7	28.3 ± 5.9	26.6 ± 6.5	0.005	0.001	0.121	0.027
NT-proBNP (pg/mL)	2058 [1041–4502]	1474 [655–5274]	2223 [1233–4795]	< 0.001	0.037	0.850	0.014
Ischemic etiology	33 (47.2%)	26 (37.1%)	66 (48.9%)	0.264	0.259	0.737	0.106
Non-ischemic etiology	37 (52.9%)	44 (62.8%)	69 (51.2%)	0.744	0.304	0.769	0.104
Systolic BP (mmHg)	122.9 ± 20.3	122.1 ± 16.4	117.7 ± 14.5	0.181	0.910	0.148	0.111
Diastolic BP (mmHg)	77.1 ± 10.6	76.4 ± 12.5	77.3 ± 13.1	0.907	0.687	0.763	0.701
eGFR (mL/min/1.73 m^2)	65.7 ± 17.8	66.9 ± 18.3	68.3 ± 18.1	0.591	0.636	0.306	0.649
Potassium (mmol/mL)	4.6 ± 0.5	4.5 ± 0.7	4.5 ± 0.5	0.679	0.639	0.379	0.734
Hypertension *n* (%)	67 (97.7%)	49 (70%)	89 (65.9%)	< 0.001	< 0.001	< 0.001	0.553
Diabetes *n* (%)	42 (60%)	35 (50%)	48 (35.6%)	0.003	0.271	0.061	0.045
Atrial fibrillation *n* (%)	39 (55.7%)	23 (32.8%)	46 (34.1%)	0.006	0.008	0.003	0.887
Dyslipidemia *n* (%)	64 (91.4%)	36 (51.4%)	74 (54.9%)	0.001	< 0.001	< 0.001	0.639
Smoking *n* (%)	18 (25.7%)	19 (27.1%)	36 (26.7%)	0.968	0.868	0.836	0.943
Hyperuricemia *n* (%)	25 (35.7%)	20 (28.5%)	37 (27.4%)	0.492	0.379	0.246	0.861
Chronic renal failure *n* (%)	26 (37.2%)	31 (44.2%)	36 (26.7%)	0.033	0.351	0.139	0.011
ACEi/ARB	70 (100%)	68 (97.1%)	135 (100%)	0.052	0.496	0.999	0.115

Table 1 continued

	Group I (n = 70)	Group II (n = 70)	Group III (n = 135)	p (Gr. I vs II vs III)	p (Gr. I vs II)	p (Gr. I vs III)	p (Gr. II vs III)
Beta-blockers	67 (95.7%)	68 (97.1%)	127 (94.1%)	0.661	0.376	0.888	0.450
MRA	65 (92.8%)	67 (95.7%)	124 (91.8%)	0.355	0.170	0.731	0.240

All data are presented as mean ± standard deviation (SD)

NYHA New York Heart Association, *LV EF* left ventricular ejection fraction, *CMP* cardiomyopathy, *BP* blood pressure, *ACEi/ARB* angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. *MRA* mineralocorticoid receptor antagonist, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *Gr* group, *eGFR* estimated glomerular filtration rate, Ø not calculable

Most of the data series showed a non-normal distribution, and the tests were selected accordingly. To compare treatment groups, we used the Kruskal–Wallis test, the Mann–Whitney test, and Student's t test. The Wilcoxon test was used to compare data obtained at different time points. For discrete variables, we used the Pearson's chi-squared test and the Fisher's exact test. Multiple linear regression or multiple robust regression models were created to adjust for potential confounders. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Baseline Patient Data

A total of 275 patients were enrolled, including 70 patients in group I, 70 patients in group II, and 135 patients in group III. Baseline patient data are listed in Table 1. Patients in both CRT groups (groups I and II) were older and had more comorbidities as compared with the general HFrEF cohort (group III), with no difference in the etiology of HF. The majority of patients were in NYHA functional class III in all three groups. LV EF was significantly higher in group II as compared to the other two groups. Mean levels of NT-proBNP were similar in the three groups (Table 1).

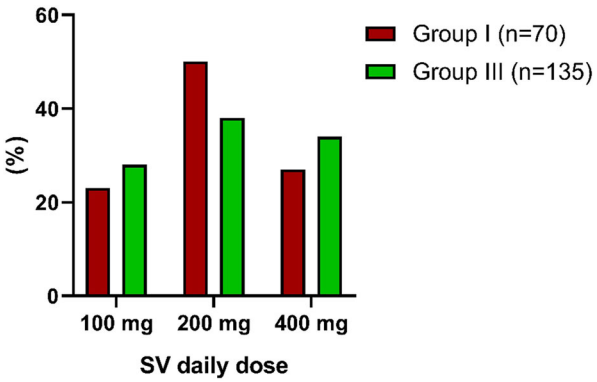

Fig. 2 Maximum doses of sacubitril/valsartan (SV) after titration in groups I and III

Medical Therapy

Maximum tolerated doses of SV are displayed in Fig. 2. Maximum tolerated daily doses were 100 mg (16 patients, 22.8%), 200 mg (35 patients, 50%), and 400 mg (19 patients, 27.1%) in group I and 100 mg (39 patients, 28.8%), 200 mg (50 patients, 37.1%), and 400 mg (46 patients, 34.1%) in group III. No statistical difference was found between the highest tolerated SV doses between groups I and III (p = 0.587).

The basic principle of uptitrating all HF medications to the maximum tolerated dose was also applied to MRAs and beta-blockers in all three groups throughout the study. MRA doses were increased in 21 (30%), 12 (17%), and 28 (40%) while beta-blocker doses were increased in 25 (35.7%), 28 (40%), and 49 (36.2%) patients during the whole follow-up period in groups I, II and III, respectively. ACEi dose was increased in 13 patients (18.5%) in group II.

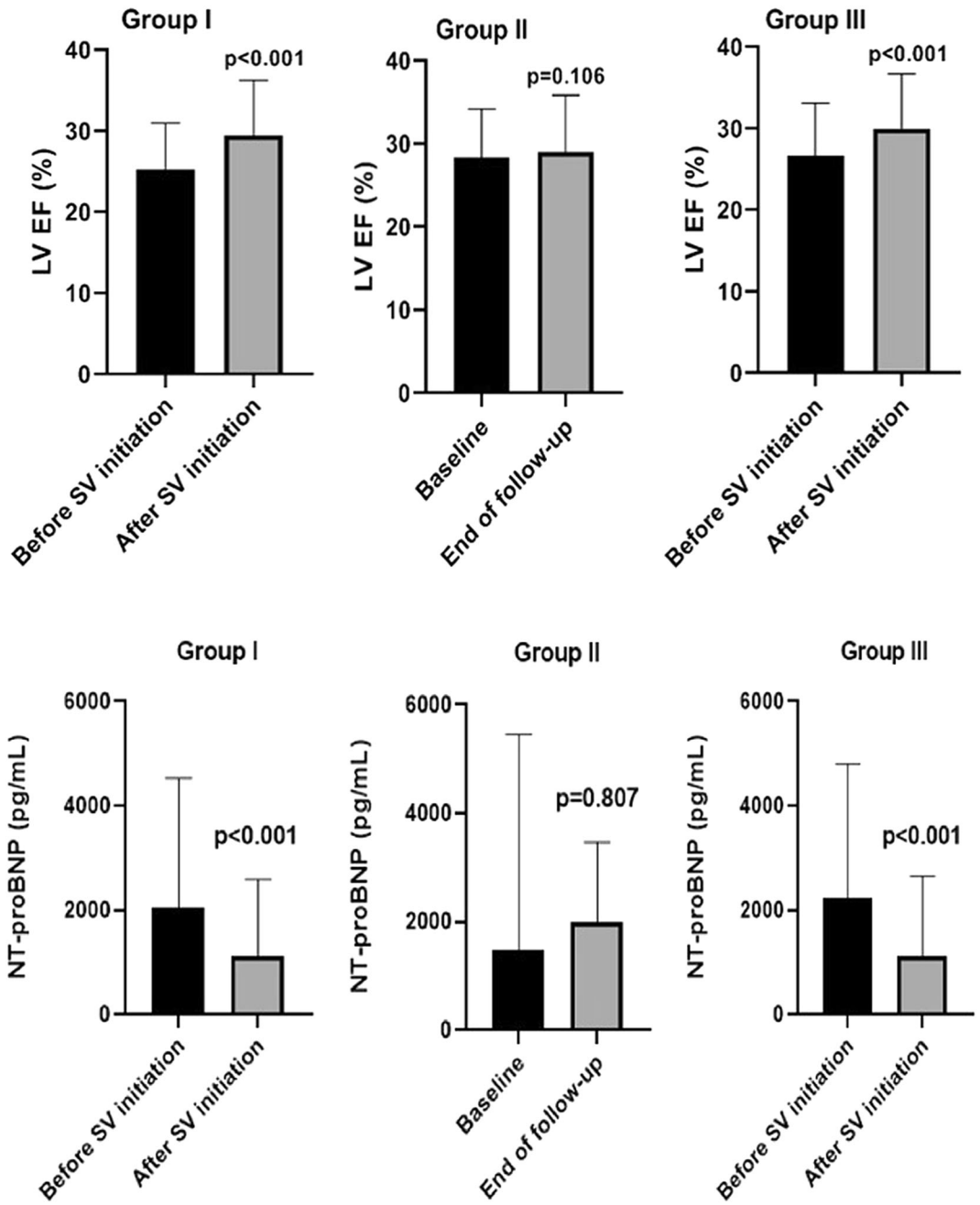

Fig. 3 Primary endpoints. Left ventricular ejection fraction (LV EF; upper panel) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level (lower panel) changes during follow-up. SV (sacubitril/valsartan)

Primary Endpoints

The time duration between the baseline and the final measurements was 6–9 months (mean ± SD 7.54 ± 1.8 months for the whole patient cohort; 7.45 ± 1.6 for group I; 7.75 ± 2.2 for group II; 7.51 ± 1.5 for group III). LV EF increased between the baseline (prior to SV initiation) and the final (on SV for > 6 months) measurements in groups I and III (from 25.2 ± 5.7% to 29.4% ± 6.7%, $p < 0.001$; and from 26.6 ± 6.4% to 29.9 ± 6.7%, $p < 0.001$,

Table 2 Echocardiographic parameters

	LVEDD (mm)	LVESD (mm)	LVOT VTI (m)	Stroke volume (mL)	d*P*/d*t* (mmHg/s)
Before SV initiation	68.4 ± 8.1	56.6 ± 9.0	0.13 ± 0.4	45.4 ± 12.3	617.7 ± 201.2
Group I					
After SV initiation	67.2 ± 7.4	54.3 ± 8.7	0.14 ± 0.5	48.2 ± 12.8	645.7 ± 221.1
p value	0.085	0.004	0.006	0.144	0.084
Baseline	65.1 ± 11.1	52.2 ± 10.7	0.13 ± 0.4	48.7 ± 10.2	595.0 ± 156.8
Group II					
End of follow-up	64.4 ± 11.1	51.0 ± 11.6	0.14 ± 0.5	48.5 ± 11.9	662.7 ± 165.7
p value	0.108	0.131	0.651	0.950	0.239
Before SV initiation	68.6 ± 9.5	55.9 ± 9.9	0.12 ± 0.5	45.8 ± 16.3	652.3 ± 168.3
Group III					
After SV initiation	67.8 ± 10.7	54.3 ± 11.2	0.14 ± 0.6	48.1 ± 17.2	642.4 ± 163.6
p value	0.262	0.021	0.067	0.108	0.292

Data are presented in mean ± standard deviation (SD)
LVEDD left ventricular end-diastolic diameter, *LVESD* left ventricular end-systolic diameter, *LVOT VTI* left ventricular outflow tract velocity time integral, d*P*/d*t* contractility of the left ventricle using echocardiography, *SV* sacubitril/valsartan

respectively). With a multiple regression model adjusted for age, sex, LV EF before the initiation of SV, etiology, comorbidities (hypertension, diabetes, AF (atrial fibrillation), hyperlipidemia, chronic kidney disease) SV remained an independent predictor of the increase in LV EF both in group I (Coeff = 2.57; $p = 0.010$) and in group III (Coeff = 2.19; $p = 0.014$). No significant change in LV EF was demonstrated between the baseline and the final measurements in group II (28.3 ± 5.9% versus 29 ± 6.8%, $p = 0.106$; Fig. 3). A significant decrease in the serum levels of NT-proBNP (pg/mL) was demonstrated in groups I and III (from 2058.86 [1041.07–4502.51] to 1121.55 [545–2541], $p < 0.001$ and from 2223.35 [1233.03–4795.96] to 1123.09 [500.38–2651.27], $p < 0.001$, respectively). With a robust multiple regression model adjusted for age, sex, EF before the initiation of SV, etiology, comorbidities (hypertension, diabetes, AF, hyperlipidemia, chronic kidney disease) SV remained an independent predictor of the decrease in NT-proBNP both in group I (Coeff = − 763.66; $p = 0.004$) and in group III (Coeff = − 812.38; $p = 0.001$). No significant change in NT-proBNP was detected in group II (1474.57 [655.8–5273] versus 1986.3 [1025.3–3359.1], $p = 0.807$; Fig. 3). The extent of improvement between groups I and III was similar with no significant differences either for LV EF ($p = 0.161$) or for NT-proBNP ($p = 0.850$).

Echocardiographic parameters considered as secondary endpoints are displayed in Table 2. A significant decrease in the left ventricular end-systolic diameter (LVESD) was demonstrated on SV therapy from 56.6 ± 8.9 mm to 54.3 ± 8.7 mm; $p = 0.004$ and from 55.9 ± 9.9 mm to 54.3 ± 11.2 mm; $p = 0.021$ in groups I and III, respectively. No significant changes were detected in any other parameters. Systolic and diastolic blood pressure values decreased on SV therapy in both groups, while eGFR (estimated glomerular filtration rate) decreased in group I and potassium levels were elevated in group III (Table 3). The

Table 3 Safety parameters

	SBP (mmHg)	DBP (mmHg)	eGFR (mL/min/1.73 m^2)	Potassium (mmol/mL)
Before SV initiation	122.8 ± 20.2	77.1 ± 10.5	65.7 ± 17.8	4.5 ± 0.5
Group I				
After SV initiation	116.1 ± 18.1	73.2 ± 10.6	63.1 ± 20.3	4.6 ± 0.5
p value	0.018	0.015	0.026	0.442
Baseline	122.1 ± 16.4	76.4 ± 12.5	69.9 ± 18.3	4.5 ± 0.7
Group II				
End of follow-up	119.7 ± 18.2	76.1 ± 9.8	65.8 ± 18.3	4.6 ± 0.5
p value	0.209	0.753	0.285	0.152
Before SV initiation	117.7 ± 17.7	77.3 ± 13.1	68.3 ± 18.1	4.5 ± 0.4
Group III				
After SV initiation	111.8 ± 7.9	72.1 ± 11.9	68.5 ± 18.7	4.6 ± 0.5
p value	< 0.001	< 0.001	0.896	0.037

Data are presented in mean ± standard deviation (SD)
SBP systolic blood pressure, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *SV* sacubitril/valsartan

discontinuation of SV was not required in any patient. The potential clinical implications of the data in Tables 2 and 3 are discussed.

DISCUSSION

Main Findings

In this observational study a significant LV reverse remodeling evidenced by an increase in LV EF and a decrease in LVESD and in the level of NT-proBNP were detected in CRT-NR patients after 6–9 months of SV therapy. The extent of improvement was similar to what was found in general patients with HFrEF on SV therapy, while no improvement was demonstrated in CRT non-responders who remained on evidence-based HF therapy including ACEi/ARB. Importantly, improvements in the CRT-NR cohort were observed despite these patients being older and having lower LV EF, higher NT-proBNP values, and more comorbidities (hypertension, diabetes, atrial fibrillation, and dyslipidemia) as compared with the other groups.

SV therapy was associated with a significant decrease in systolic and diastolic blood pressures in both patient groups. eGFR decreased in CRT-NR patients, while potassium levels increased in patients with HFrEF with no need to stop the therapy in any of them. Although statistically significant, these changes related to SV treatment had no clinical relevance, as no therapy discontinuation was required in any patient.

Clinical Implications

More than two decades after the introduction of CRT into clinical practice, non-response to resynchronization remains a problem [17]. CRT-NR patients show high hospitalization and less than 50% survival rates free of assist device or cardiac transplantation at 5 years after the implantation [10]. Unlike patients with other chronic diseases (e.g., malignancies), many of these patients with HF are less willing to seek

medical support despite the substantial evidence on poor prognosis [8]. Moreover, data from the ADVANCE CRT registry indicate that in the absence of a widely accepted consensus on the definition of this condition, patients may not be categorized properly as non-responders to CRT [7]. Furthermore, tighter follow-up and therapy intensification are not offered by many physicians even to those identified as non-responders. Consequences of this inertia include deteriorating functional status, quality of life and reduced life expectancy in these patients despite recent developments in the medical therapy of HF.

To our knowledge, this is the first study which evaluated shorter-term changes both in the echocardiographic parameters and plasma levels of NT-proBNP in CRT-NRs in response to SV by comparing the results not only to those who were kept on ACE/ARB therapy but as well as to a general HFrEF cohort treated with SV. This double comparison design including two control groups allowed us to prove that the improvement in CRT-NR patients was truly due to SV therapy and did not simply reflect a natural fluctuation in echocardiographic parameters and biomarker levels. It was also confirmed that the extent of improvement induced by SV therapy was similar in CRT-NR and in general patients with HFrEF. The statistically significant improvements in echocardiographic and NT-proBNP measurements observed on SV therapy in groups I and III are also of clinical relevance as they suggest LV reverse remodeling, a known predictor of favorable outcome. Whether hospitalization and mortality endpoints in CRT-NRs on SV treatment will also be similar to what was demonstrated by the large-scale randomized PARADIGM trial in patients with HFrEF [11] should be answered by further investigations. The results of a few observational studies on the effects of SV therapy in CRT-NRs also support these expectations [14–16]. In a retrospective analysis, lower cardiac mortality was proven after 6-month follow-up in 22 CRT-NR patients who were started on SV treatment as compared to those 28 who remained on ACEi/ARB medication [14]. Improvement in quality-of-life indicators and a reduction in hospitalization rates were demonstrated after 6-month treatment with SV in the RESINA (Resynchronization plus an Inhibitor of Neprilysin/Angiotensin) registry [15]. These observations need to be confirmed by multicenter randomized clinical trials involving a sufficient number of CRT non-responders and a longer follow-up period.

Of note, CRT patients in our study were non-responders and therefore our results may not apply to all CRT patients. Indeed, the absence of CRT was a predictor of reverse LV remodeling after the initiation of SV in a registry study on patients with HFrEF including 43% with an implanted CRT device [18]. The authors' proposed explanation for this finding was that the potential myocardial reserve was already realized by cardiac resynchronization, thereby leaving no room for further improvement with SV. However, the information on whether these patients included CRT responders or non-responders was not disclosed and therefore these observations may not apply to CRT-NR patients.

Although 2D echocardiography represents the gold standard to assess patients with HF, significant interobserver variations pose a well-known shortcoming of this diagnostic modality. The correlation between the echocardiographic features of LV remodeling and the reduction of plasma NT-proBNP concentrations has been substantiated in many studies [13, 19–22]. Moreover, the level of this biomarker is a known predictor of long-term outcome [19, 21, 22]. Importantly, improvements in the echocardiographic parameters observed in our study were validated by a significant decrease in plasma NT-proBNP concentrations also to a similar extent as in the CRT-NR and in the general (group III) HFrEF cohort.

Limitations and Strengths

This is a single-center observational study with a relatively short observation period including a limited number of patients and a low female representation; nevertheless, the population size was still larger in our analysis than in the few reports published so far on the efficacy of SV in CRT-NR patients. Significant differences were found in the baseline parameters of the three groups. However, improvements on SV therapy

were observed in the CRT-NR cohort despite these patients being older and having lower LV EF, higher NT-proBNP values, and more comorbidities as compared with the other groups. In the absence of widely accepted standard criteria, the definitions of CRT non-responders were arbitrary in our study. We decided to use LV EF as a readily available parameter measured routinely in daily practice. To our knowledge, our work is the only one so far to include NT-proBNP measurements to validate the echocardiographic assessment of reverse LV remodeling in CRT non-responders treated with SV. Although this was a registry study, the brief period of data collection and the uniform principles applied for HF management at our institute ensured that the baseline characteristics of the patients assigned to the different groups were comparable and showed only minor differences. Our CRT-NR patients demonstrated a significant improvement on SV despite more comorbidities and lower baseline LV EF values as compared with the other two groups. With the inclusion of two control cohorts, we were able to demonstrate that the favorable changes detected in CRT-NR patients on SV were indeed the result of the therapy, and the extent of improvements was similar to what was detected in general patients with HFrEF treated with SV. In the future, most patients will likely undergo CRT implantation while on treatment with SV and an SGLT2 inhibitor (sodium-glucose co-transporter 2 inhibitor). However, as of today, our findings are still relevant to many patients who demonstrate no significant improvement after CRT implantation.

CONCLUSION

Cardiac remodeling as evidenced by improvements in echocardiographic parameters and in NT-proBNP levels were demonstrated to a similar extent in CRT non-responders who were started on SV therapy as well as in a general HFrEF cohort. Our results support the early replacement of ACEi/ARB with SV at the largest tolerated dose in CRT-NRs in the absence of contraindication or intolerance to the medication.

Author Contributions. Conceptualization: Krisztina Mária Szabó, Zoltán Csanádi; Methodology: Anna Tóth, László Nagy, Vivien Rácz, Zsófia Pólik; Formal analysis and investigation: Judit Barta, Attila Borbély, Katalin Hodosi, Attila C Nagy; Writing—original draft preparation: Krisztina Mária Szabó, Zoltán Csanadi; Writing—review and editing: Krisztina Mária Szabó, Zoltán Csanádi, Anna Tóth, László Nagy, Vivien Rácz, Zsófia Pólik, Judit Barta, Attila Borbély, Katalin Hodosi, Attila C Nagy.

Funding. Sponsorship for this study and the journal's Rapid Service Fee were funded with support provided by the Ministry of Culture and Innovation of Hungary from the National Research, Development and Innovation Fund, financed under the TKP2021-EGA funding scheme.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Krisztina Mária Szabó, Anna Tóth, László Nagy, Vivien Rácz, Zsófia Pólik, Katalin Hodosi, Attila C Nagy, Judit Barta, Attila Borbély and Zoltán Csanádi have nothing to disclose.

Ethical Approval. The study was approved by the Medical Research Council (Ministry of Interior, P.O. Box 314, Budapest, 1903, Hungary) File no. BMEÜ/4388-1/2022/EKU. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Use of the clinical database was approved by the head of department.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–726.

2. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) with the special contribution of the European Heart Rhythm Association (EHRA). Eur Heart J. 2021;2:3427–520.

3. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Am Coll Cardiol. 2022;79:263–421.

4. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140–50.

5. Moss AJ, Hall WJ, Cannom D, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361:14.

6. Mullens W, Auricchio A, Martens P, et al. Optimized implementation of cardiac resynchronization therapy: a call for action for referral and optimization of care. Eur J Heart Fail. 2020;22:2349–69.

7. Varma N, Boehmer J, Bhargava K, et al. Evaluation management and outcomes of patients poorly responsive to cardiac resynchronization device therapy. J Am Coll Cardiol. 2019;74:21.

8. Ruschitzka F. The challenge of nonresponders to cardiac resynchronization therapy: lessons learned from oncology. Heart Rhythm. 2012;9:S14–7.

9. Naqvi SY, Jawaid A, Goldenberg I, Kutyifa V. Non-response to cardiac resynchronization. Curr Heart Fail Rep. 2018;15:315–21.

10. Rickard J, Cheng A, Spragg D, et al. Durability of the survival effect of cardiac resynchronization therapy by level of left ventricular functional improvement: fate of "nonresponders." Heart Rhythm. 2014;11:412–6.

11. McMurray JV, Packer M, Desai A, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:11.

12. Chang HY, Chen KC, Fong MC, et al. Recovery of left ventricular dysfunction after sacubitril/valsartan: predictors and management. J Cardiol. 2020;75:233–41.

13. Januzzi JL, Prescott MF, Butler J, et al. Association of change in N-terminal Pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. JAMA. 2019;322:1085–95.

14. Russo V, Ammendola E, Gasperetti A, et al. Add-on therapy with sacubitril/valsartan and clinical outcomes in CRT-D nonresponder patients. J Cardiovasc Pharmacol. 2022;79:472–8.

15. Chun KH, Oh J, Yu HT, Lee CJ, et al. The role of sacubitril/valsartan in the management of cardiac resynchronization therapy non-responders: a retrospective analysis. ESC Heart Fail. 2020;7:4404–7.

16. Campal JMR, Castillo H, Rivera BA, et al. Improvement in quality of life with sacubitril/ /valsartan in cardiac resynchronization non-responders: the RESINA (RESynchronization plus an Inhibitor of Neprilysin/Angiotensin) registry. Cardiol J. 2021;3:402–10.

17. Cazeau S, Ritter P, Lazarus A, et al. Multisite pacing for end-stage heart failure: early experience. Pacing Clin Electrophysiol. 1996;19:1748–57.

18. Maizels L, Wasserstrum Y, Fishman B, et al. Characterization of heart failure patients with reverse left ventricular remodeling post-angiotensin receptor blockers/neprilysin inhibitors therapy. ESC Heart Fail. 2022;10:1002.

19. Januzzi JL, Ahmad T, Mulder H, et al. Natriuretic peptide response and outcomes in chronic heart

failure with reduced ejection fraction. J Am Coll Cardiol. 2019;74:1205–17.

20. Myhre PL, Vaduganathan M, Claggett B, et al. B-type natriuretic peptide during treatment with sacubitril/valsartan: the PARADIGM-HF Trial. J Am Coll Cardiol. 2019;73:1264–72.

21. Zile M, Claggett BL, Prescott MF, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. J Am Coll Cardiol. 2016;68:22.

22. Murphy S, Prescott MF, Maisel AS, et al. Association between angiotensin receptor-neprilysin inhibition, cardiovascular biomarkers and cardiac remodeling in heart failure with reduced ejection fraction. Circulation Heart Fail. 2021;14:e008410.