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First signs of reverse cardiac remodeling following one-month, low dose add-on sacubitril-valsartan therapy in patients with advanced systolic heart failure

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ABSTRACT

Introduction. We investigated the early signs of reverse cardiac remodeling in symptomatic patients with heart failure (HF) with reduced left ventricular ejection fraction (LVEF) during one-month, low dose add-on sacubitril/valsartan (S/V) therapy.

Material and Methods. Thirty-seven adult patients with HF were evaluated before and after one-month treatment with a low dose (24/26 mg BID) of S/V.

Results. The patients' mean age was 64.50 ± 17.50 years and median LVEF 29.10%. The S/V treatment resulted in a significant decrease in blood levels of the N-terminal pro-B-type natriuretic peptide (-364 pg/mL; $p = 0.01$), left ventricular end-diastolic (-2 mm; $p < 0.01$) and end-systolic diameters (-2.4 mm; $p = 0.01$), end-diastolic (-9 ml; $p < 0.01$) and end-systolic volumes (-6 ml; $p < 0.01$), the indexed left atrial volume (-8 ml/m^2; $p < 0.01$), effective orifice area mitral regurgitation (-0.09 cm^2; $p = 0.03$). The left ventricular ejection fraction did not change in the course of the study.

Conclusion. One-month, low dose add-on S/V therapy in patients with HF and reduced LVEF induces reverse cardiac remodeling. The long-term effects of a low dose S/V add-on therapy in this group of patients requires further research.

Introduction

Despite the improvement in the management, heart failure (HF) remains a clinically significant problem. The 10-year survival rate is estimated in approximately 30% of patients, compared to 75% in the general population [1]. Optimal therapy is crucial in treating HF patients, as it reduces mortality and hospitalization, improves the quality of life in the symptomatic individuals [2]. Sacubitril/valsartan (S/V) therapy, as an add-on to an already existing pharmacological treatment, improves left ventricular systolic function, exercise capacity, and quality of life in HF patients [3]. During S/V therapy, the beneficial changes in the cardiac structure and function (reverse cardiac remodeling, CRR) are followed by a decrease in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponins concentration [4].

Several echocardiographic parameters, such as dimensions or volumes of the left ventricle (LV), left ventricular ejection fraction (LVEF) constitute valuable indicators of CRR [5–7].

Up to date, the studies evaluating S/V-induced CRR analyzed the effect of its full-dose treatment, i.e., 97/103 mg BID after several months of follow-up [8, 9]. However, the target doses are not often achieved in real life, and approximately two-thirds of patients remain on the lowest dose following six months of S/V treatment [10]. No data are available with regard to the early effects of a low dose of 24/26 mg of S/V on CRR of the HF patients. Therefore, we aimed to evaluate the effects of one-month therapy with a low dose of S/V (24/26 mg BID) on the echocardiographic parameters of CRR in individuals with HF with reduced LVEF <40% (HFrEF).

Material and Methods

Study population

Between November 2018 and April 2021, we prospectively enrolled 45 patients with symptomatic HFrEF. The addditional inclusion criteria included NYHA functional class II or III, at least one hospitalization due to heart failure decompensation within the last 12 months, and no previous use of S/V. All patients had to be on an optimal HF therapy recommended by the European Society of Cardiology (2016) and the American College of Cardiology/American Heart Association (2017), which included: beta-blocker and/or ivabradine, angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB), mineralocorticoid receptor antagonist (MRA), and at least one diuretic [1]. The exclusion criteria comprised: myocardial infarction or revascularization within the preceding three months; cardiac resynchronization device implantation within the preceding six months; previous intolerance to ACEI/ARB; symptomatic hypotension; history of angioedema; estimated glomerular filtration rate (eGFR) <30 mL/min/m^2; potassium concentration > 5.2 mmol/L; and poor quality of the transthoracic echocardiographic image. The summary of the study flow is shown in **Figure 1**. The study protocol and the informed consent were in accordance with the Helsinki Declaration and were approved by the Bioethics Committee of Poznan University of Medical Sciences.

Following the enrollment procedure and 36-hours of ACEI wash-out, the patients were started a low dose of S/V, i.e., 24/26 mg BID [11]. During the follow-up period, pharmacotherapy up-titration was not allowed. The NT-proBNP serum concentration and transthoracic echocardiography were performed at the baseline and after one month follow-up.

Echocardiography.

During the standard transthoracic echocardiography (Vivid-9, General Electric Medical Systems, USA), cine loops of three cardiac cycles were recorded for the offline analysis with an average frame rate of 56–92 frames/sec. Left atrial and ventricular volumes and diameters were measured according to the American Society of Echocardiography [12]. LVEF was calculated by the Simpson's method from end-systolic and end-diastolic endocardial borders using the apical 4- and 2- chamber views. If two or more contiguous LV endocardial segments were poorly visualized, LVEF was not assessed. Thus, eight patients were excluded from the study, and finally, thirty-seven patients were enrolled in the study.

Statistical analysis

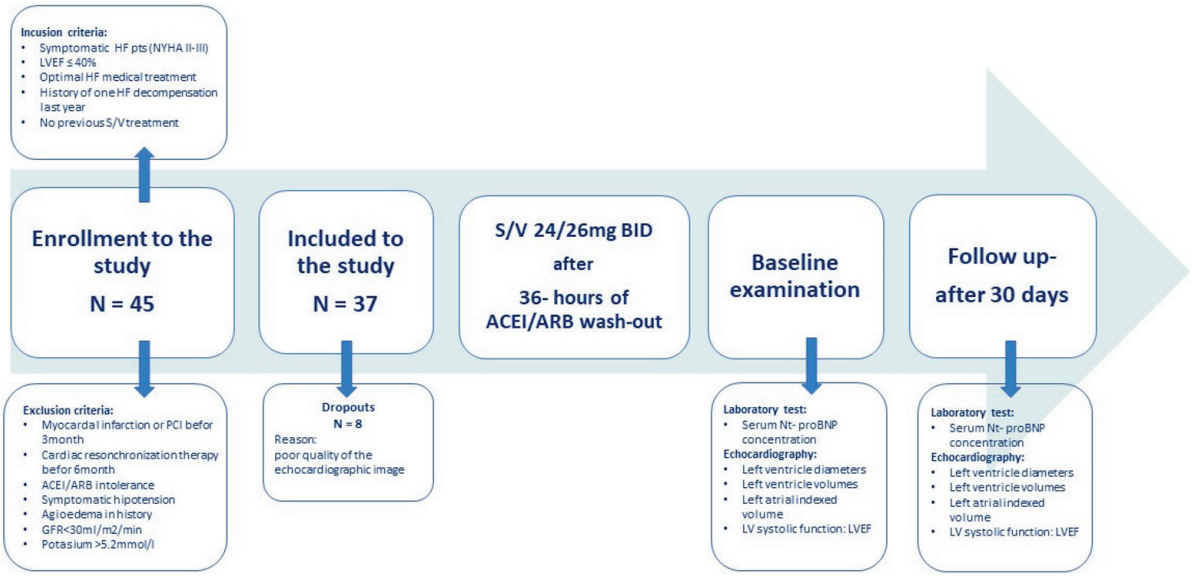
The distribution of the majority of continuous data was not normal according to the Shapiro-Wilk test, hence, the results are presented as medians. The paired nonparametric Wilcoxon

test was used to compare the data before and after one-month treatment with S/V. The p-value less than < 0.05 was considered statistically significant. Data were analyzed using Dell Statistica (data analysis software system), version 13, Dell Inc. (2016).

Results

All patients (mean age 67 years, five females) completed a one-month follow-up. The etiology of HF was ischemic in 23 patients (62%). Twenty-one patients were in NYHA class I-II, and 16 in NYHA class III-IV. The majority of the group (24 patients, 65%) presented with a very severe left ventricular systolic dysfunction (LVEF median 29.10%). The baseline characteristics of the studied group are present in **Table 1**.

After a month, NT-proBNP concentrations were significantly lower (-364 pg/mL, p = 0.01). **Table 2** presents the results of NT-proBNP in the course of the study. We observed a significant reduction of the left ventricular end-diastolic diameter (-2



Abbreviation: ACEI - angiotensin-converting enzyme inhibitor, ARB - angiotensin receptor blocker, GFR - glomerular filtration rate, HF - heart failure, LVEF - left ventricular ejection fraction, S/V - sacubitril/valsartan.

Figure 1. Study flow

Table 1. Patients characteristics at the baseline (n = 37)

	No.	(%)
Gender: – Male/female	32/5	86/14
Etiology: – Non-ischemic – Ischemic	14 23	38 62
Diabetes	16	43
Chronic renal failure (GFR≤ 90 mL per minute)	12	32
Atrial fibrillation: persistent or permanent	8	22
NYHA Class: – I-II – III-IV	16 9	64 36
CRT	8	21
Beta-blocker	36	97
Ivabradine	3	8
Loop diuretic	37	100
Mineralocorticoid-receptor antagonists	32	86
Angiotensin-converting enzyme inhibitor before S/V treatment	37	100

Abbreviations: BMI – body mass index, CRT – cardiac resynchronization therapy, GFR-glomerular filtration rate, NYHA – New York Heart Association Classification.

Table 2. Clinical, laboratory, and echocardiographic parameters at the baseline and at the follow-up (n = 37)

Parameter	Baseline [median value]	Follow-up [median value]	Paired differences	
			[median value]	p-value
SBP (mmHg)	120	120	-3	0.09
DBP (mmHg)	76	74	-1	0.36
NT-proBNP (pg/mL)	1475	1581	-364	0.01
LVEDD (mm)	69	68	-2	<0.01
LVESD (mm)	61.10	59	-2.40	<0.01
LVEDV (mL)	185	169	-9	<0.01
LVESV (mL)	123	112	-6	<0.01
LAVI (mL/m^2)	52	40	-8	<0.01
LVEF (%)	29.10	30.00	0.90	0.07
EROA (mm^2)	0.24	0.15	0.09	0.03

Abbreviations: DBP – diastolic blood pressure, EROA – effective regurgitant orifice area, LAVI – left atrial volume index, LVEF – left ventricular ejection fraction, LVEDD – left ventricular end-diastolic diameter, LVEDV – left ventricular end-diastolic volume, LVESD – left ventricular end-systolic diameter, LVESV – left ventricular end-systolic volume, NT-proBNP – N-terminal pro-b-type natriuretic, SBP – systolic blood pressure.

mm; p < 0.01), left ventricular end-systolic diameter (-2.40 mm; p < 0.01), left ventricular end-diastolic volume (-9 mL; p < 0.01) and left ventricular end-systolic volume (-6 ml; p < 0.01), indexed left atrial volume (-8 mL/m^2; p < 0.01) and the effective regurgitant orifice area of the mitral valve (-0.09 mm^2; p = 0.03). However, the left ventricular ejection fraction did not change significantly during the treatment (LVEF = 29.10 vs 30.00%, p = 0.07). **Table 2** shows the laboratory and echocardiographic parameters during the study.

Discussion

We demonstrated that one-month low dose of S/V treatment in patients with HFrEF results in a significant reverse cardiac remodeling. Furthermore, we observed a small, but significant, reduction of the left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular end-diastolic volume, and left ventricular end-systolic volume, indexed left atrial volume and mitral regurgitation severity assessed by the effective regurgitant orifice area.

Historically, reverse cardiac remodeling was defined as a 20% decrease in the left ventricular end-diastolic volume [13]. Nowadays, a ≥10% left ventricular end-systolic volume decrease is preferable, since it leads to more favorable outcomes after optimizing HF treatment [14] and strongly correlates with the patients' survival rate [13, 15]. In our study, left ventricular volume (end-diastolic and end-systolic) improved by approximately 9%. It is worth bearing in mind that this effect resulted from one-month, low-dose S/V therapy.

Significant left atrial reverse remodeling is defined as a decrease of 15% of left atrial volume [16]. Despite scarce data, left atrial reverse remodeling may result from pharmacological intervention (data for ACEI or ARB, spironolactone therapy), invasive therapy (e.g., ablation of the pulmonary veins in AF, cardiac resynchronization therapy), or the improvement of diastolic and systolic left ventricle function. Regardless of the mechanism of left atrial remodeling reverse, the left atrial volume significantly influences the prognosis of patients with HF [16–18]. Our study demonstrated that the indexed left atrial volume reduction following one month of low dose S/V therapy is one of the most efficient parameters of reverse remodeling. The severity of mitral regurgitation serves as an independent risk factor for cardiovascular morbidity and mortality [18], therefore, the improvement of left ventricular and atrial volumes reduces functional mitral regurgitation [18], which was also found in our study. All the above-mentioned improvements present completely left-sided reverse cardiac remodeling. Nevertheless, the lack of a significant improvement in LVEF in our study requires some comment. In fact, a specific, layered structure of the myocardium may account for it. The LVEF is more dependent on the function of the midwall circumferential fibers. Thus, better myocardial remodeling requires a long-term treatment in order to observe the improvement in the left ventricu-

lar systolic function, as measured by the ejection fraction [19]. In fact, this may be the reason why Mazzetti et al. observed the LVEF improvement following six months of S/V treatment, and not after three months [19]. On the other hand, the small sample size and the short observation period in our study limit the possibility of drawing definitive conclusions.

On the basis of the latest data, S/V-induced reverse heart remodeling may stem from hemodynamic changes. S/V has reduced cardiac wall stress, thus, decreasing intracardiac pressures [20], which is indirectly demonstrated by the decreasing NT pro-BNP concentration in the blood serum. In our study, the median drop of the NT-proBNP was > 364 pg/mL. This result in in line with the PROVE-HF study, which proved that NT-pro BNP reduction is related to reverse cardiac remodeling [21]. It is worth noting that in the PROVE-HF study, CRR parameters were assessed at the baseline and after 6 and 12 months. In another study, by Januzzi et al., the concentration of NT-proBNP decreased as early as 14 days after the initiation of S/V [22]. In this study, the starting dose of S/V was 24/26 mg BID, and it was titrated after 2–4 weeks to the maximum dose of 97/103 mg BID (65.0% of patients at the end of the study) or maximum tolerated dose.

Additionally, S/V possibly directly affects the concentration of natriuretic peptides through its pharmacological effect on neprilysin, in addition to the impact on intracardiac filling pressures [23]. However, further studies on larger groups are necessary to quantify this effect.

We used a low dose of S/V, i.e., 24/26 mg BID, also referred to as an initial dose in the "conservative high-dose protocol" of the TITRATION study [11]. In this study, S/V was titrated after 2 weeks to 49/53mg BID, and subsequently to a maximal dose of 97/103mg BID following 6 weeks. If a condensed regimen was chosen (a second arm of the study), patients received S/V at the dose of 97/103 mg BID after 2 weeks. The TITRATION study reported the clinical outcomes after at least three months of the S/V treatment (at this point, 85.2% of patients were on S/V 97/103mg BID). In contrast, in our study, a low S/V dose initiates a reverse cardiac remodeling after a month of therapy. According to the current ESC guidelines for diagnosing and treating acute and chronic HF, the recommended target dose of S/V is 97/103 mg BID [2, 24]. However, this dose is not often achieved in real life. In fact, up to two-thirds of patients remain on the lowest dose after six months since the onset of the therapy [25]. In the PARADIGM-HF, in 17.8% of patients a reduction of the S/V dose from 97/103 to 47/53mg BID was necessary. Moreover, in 12% of patients, S/V was withdrawn, primarily due to hyperkalemia or hypotension [3]. In our study, none of the patients required discontinuation of therapy.

Limitations

The main limitation of the study is the small number of participants. However, it was a single-center and unsponsored study including the carefully selected symptomatic patients with advanced HFrEF. Another limitation is the short-term follow-up of one month following the applied treatment. Therefore, we cannot conclusively determine the long-term effects of a low dose S/V. Nevertheless, we demonstrated that this form of treatment exerts a relevant and beneficial S/V effects on the cardiac remodeling in patients with HFrEF. Furthermore, from the economic perspective, it results in reduced costs for the health care system.

Perspectives

We have demonstrated that a low dose S/V for the period of one month reverses adverse cardiac remodeling in the patients with severe HFrEF. Nevertheless, it remains uncertain whether the beneficial effects of low doses of S/V extend beyond one month, and thus should be also investigated. Our HFrEF patients presented with a very severe systolic dysfunction with LVEF 29.10%. Therefore, further research is necessary to investigate whether a low dose S/V would provide similar benefits in patients with a less severe impairment of the systolic function.

Conclusion

One-month S/V therapy with 24/26 mg BID in patients with HFrEF induces the left-sided cardiac reverse remodeling.

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Conflict of interest statement
The authors declare that Novartis did not participate (including financial, content-related, organizational) in the scope of the presented scientific research. Wioletta Sacharczuk, Rafał Dankowski, and Andrzej Szyszka received lecture fees from Novartis.

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Data availability statement
The data supporting this study are available on a reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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