Title

The first symptoms of cardiac reverse remodeling and clinical improvement after one-month, low-dose of Sacubitril-Valsartan therapy

Shortened title:

Cardiac remodeling with Sacubitril-Valsartan

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Abstract

Introduction: Little is known about reverse cardiac remodeling (CRR) under the low-dose S/V therapy. Methods: In 37 patients (mean age 64.5±17.5 years, five females) 24/26mg S/V BID was started. After one month of observation, the following CRR parameters improved: LVEDD (-Δ2,9±2.6mm, p<0.01), LVESD (-Δ 2,4±2.5mm, p<0.01), LVEDV(-Δ14.6±33.1ml, p=0.04), LVESV (-Δ13.4±30.6ml, p=0.04), LAVI (-Δ8.7±37.7ml/m2, p<0.01), and EROA (-Δ 0.09 ± 0,01cm2; p=0.03). In opposite to LVEF global longitudinal strain (GLS) changed from -6.6% to -7.9% (absolute improvement of 16%, p <0.001). Walked distance in 6-MWT (+Δ65.4 ± 75.8 m, p <0.001), and the quality of life (MLHFQ 22 vs 16 scores, p<0.01) improved. Decreasing NT-proBNP (-Δ 1,203,1±3,121,4pg/ml, p=0.03) and troponin T (-Δ 4.7±9.4pg/ml, p=0.004) were observed. Correlation between GLS and LVESV (r = -0,43, p = 0.027) was found. ROC curve analysis showed that GLS cut-off value -8% is a good predictor of clinical improvement (6MWT: AUC 0.69 p=0.04) and CRR (MRvol: AUC:0.74 p=0.01; LAVI: AUC 0.71 p=0.04). Conclusion: One-month, low-dose (24/26 mg BID) S/V therapy initiates CRR. GLS's ability to evaluate LV function is better than LVEF's. S/V should be started early as patients with symptomatic HFrEF and less impaired LV systolic function (GLS <-8%) are more likely to develop CRR and clinical improvement.

Introduction

In patients (pts) with heart failure with reduced ejection fraction (HFrEF), Sacubitril/ Valsartan (S/V), has a positive effect on the neurohormonal status, exercise capacity, mitral regurgitation, and quality of life. [1] Moreover, during S/V therapy, a decrease of NT-proBNP level is followed by beneficial changes in the cardiac structure and function – cardiac reverse remodeling (CRR).[2] Several parameters, like left ventricular (LV) dimensions or volumes, left ventricular ejection fraction (LVEF), are useful indicators of cardiac remodeling.[3] The assessment of cardiac deformation derived from global longitudinal strain (GLS), is currently a well-established technique to assess cardiac systolic function. GLS has the potential to improve risk stratification, redefine criteria for HFrEF classification (very severe >-8, severe -8 to- 12%, reduced <-16%), and thus might determine treatment. It has been also demonstrated that GLS is an independent predictor for CRR. [4] So far, the studies evaluating S/V-induced CRR have usually analyzed the effect of the recommended full-dose treatment, i.e. 97/103 mg BID after at least several months of follow-up.[5] [6] Nonetheless, there is no data on CRR during low-dose S/V therapy after a short follow-up. So that, our study aimed to evaluate the early effects of treatment with low doses of S/V (24/26 mg BID) during one month of therapy on the echocardiographic parameters of CRR, and its relation to biomarker levels, exercise performance, and the quality of life in patients with HFrEF (LVEF<40%), severe and very severe LV systolic dysfunction (GLS cut-off -8%).

Methods

Study population.

In our study, patients (pts) were prospectively enrolled from November 2018 to August 2020. The main inclusion criteria were: symptomatic heart failure with NYHA class II and III, and a history of at least one hospitalization due to decompensation of HF within the last year, optimal heart failure therapy. The exclusion criteria were: myocardial infarction or revascularization within the preceding three months, CRT implantation within the preceding six months, previous intolerance to ACEI/ARB, symptomatic hypotension, history of angioedema, estimated glomerular filtration rate (eGFR) lower than 30 ml/min/m^2, and potassium level higher than 5.2 mmol/l. All pts gave informed consent, and the Bioethical Committee of Poznan University of Medical Sciences approved the study protocol.

Follow−up management

After the enrollment and 36-hours of ACEI wash-out, treatment with a low dose of S/V, i.e. 24/26 mg BID, according to the results from –the TITRATION study[7], was started. The evaluation was performed at the baseline and after 30 days. The dose of S/V was unchanged during the study period. The following parameters were assessed at the baseline and follow-up: laboratory test results (creatinine, potassium, NT-proBNP, troponin T), 6MWT and MLHFQ, and echocardiographic assessment with an advanced approach such as speckle tracking echocardiography (STE).

Clinical assessment

The 6MWT test was performed according to the standard protocol.[8] The pts were asked by the physician to walk the length of a hallway, as many times as possible.

The total distance walked by the patient was measured. Patients were also asked to rate their effort and exertion using 10 point- calibrated Modified BORG scale (0- Nothing at all; 10- Maximal).

The Minnesota Living with Heart Failure (MLHFQ) is a self-administered questionnaire designed for the assessment of the quality of life in pts with HF.[9] The questionnaire provides a total score (range 0–105 point) from best to worst quality of life.

Echocardiographic measurements

All individuals underwent a standard echocardiographic examination with Vivid 9 Digital Ultrasound System Echocardiograph (GE Medical Systems). Three cardiac cycles in the cine loops format were recorded for offline analysis with an averaged frame rate of 56–92 frames/sec. Left atrial and ventricular volumes and diameters were measured according to the recommendations of the American Society of Echocardiography. LV ejection fraction was calculated by Simpson's method from end-systolic and end-diastolic endocardial borders using apical 4- and 2-chamber views. The tricuspid annular plane systolic excursion (TAPSE) was used to estimates RV systolic function. The noninvasive evaluation of native valvular regurgitation was performed according to the American Society of Echocardiography.

LV strain values

Longitudinal left ventricular strain values were assessed in the 4−chamber, 2−chamber, and 3−chamber apical views. Radial and circumferential strain and rotation of the left ventricle were evaluated in 3 levels at short views (basal, papillary muscle, and apical). The endocardial borders were traced semi-automatically by using the

Automated Function Imaging (AFI) software. If the tracings were considered suboptimal, there were adjusted manually. All the strain parameters were acquired from 3 beats, and the cine loops were recorded for further off-line analysis using dedicated software – EchoPac Clinical Workstation Software (revision 201).

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) values were used. Categorical variables are shown as frequency and percentage. Data comparisons were done by the use of Wilcoxon test or Student's t-test for paired data, when appropriate. The significance of the results was checked at the level of alpha = 0.05. The correlations were calculated by the use of Pearson's correlation coefficient. The ROC (Receiver Operating Characteristic) and AUC (area under the curve) curves were used to evaluate the validity of a single variable (GLS) in order to predict clinical improvement and complete left-sided cardiac reverse remodeling. Data were analyzed using Dell Statistica (data analysis software system), version 13, Dell Inc. (2016).

Results

Thirty-seven pts were enrolled in the study (mean age 64.5 years, five females). The etiology of HF was ischemic in 23 pts (62%), non-ischemic in 14 pts (38%). Twenty-one pts presented NYHA class II,16 pts NYHA class III. The majority of the group (26pts, 65%) were patients with very severe LV systolic function assessed by GLS (GLS> -8.0%). The baseline characteristics of the studied group are presented in Table 1. All patients included in the study completed a follow-up of one month. We did not observe any significant increase in creatinine or potassium levels after the one-month treatment. The Nt pro-BNP and Troponin T level were significantly lower

(-Δ 1,203,1±3,121,4pg/ml, p=0.03; -Δ 4.7±9.4pg/ml,p=0.004; respectively). None of the patients experienced significant hypotension. The mean value of the walked distance increased significantly by an average of 65.4±75.8m, p<0.001. We also observed an improvement in the quality of life according to the MLHFQ results (22 vs 16 scores, p<0.01). All clinical and laboratory results are presented in Table 2. Echocardiographic parameters confirmed CRR. There was a significant reduction in LV: end-diastolic diameters (LVEDD -Δ 2,9±2.6mm, p<0.01), end-systolic diameters (LVESD -Δ 2,4±2.5mm, p<0.01), end-diastolic volumes (LVEDV -Δ14.6±33.1 ml, p=0.04) and end-systolic volumes (LVESV-Δ13.4±30.6 ml, p=0.04). Reduction of indexed left atrial volume (LAVI:-Δ 8.7±37.7ml/m2, p<0.01) and the degree of mitral regurgitation (EROA: 0.24 vs 0.15, p=0.03) were observed. Global longitudinal strain changed from -6.6% to -7.9% (p <0.001), which was a 16% absolute improvement. The GLS changes in three patients during the study are presented in Bull Eye in Figure1. There was no significant change in the left ventricular ejection fraction (LVEF 29.0 vs 31.0%, p=0.42). All echocardiographic parameters are presented in Table 2. A weak linear correlation was found between GLS at baseline and LV end-systolic volumes at follow-up (r = -0,43, p = 0.027, Figure 2). Similar strength of correlation was found for changes in GLS and troponin during the study (r=0.42, p=0.023). ROC curve analysis showed that GLS cut-off value -8% is a good predictor of clinical improvement (6MWT: AUC 0.69 p=0.04, Figure 3) and CRR (MRvol: AUC:0.74 p=0.01, Figure 4; LAVI: AUC 0.71 p=0.04) under low-dose S/V therapy.

Discussion

According to our best knowledge, this is the first report on the very early effects of treatment with S/V in HFrEF patients. Previous studies reported the outcomes

achieved after at least three months or a longer follow-up period [2,5-10,] and analyses were carried out after up-titration to a maximally tolerated dose. In contrast to these studies, we evaluated the effects of the lowest dose of S/V, i.e. 24/26 mg BID, which was the initial dose in the "conservative high-dose protocol" in the TITRATION study.[7] Despite these, we observed left ventricular and left atrial reverse remodeling, a significant decrease in NT-pro BNP levels, troponin, an improvement in the clinical status of pts measured by 6MWT, and an improvement in the quality of life (QoL).

According to the PARADIGM-HF study, published in 2014, the recommended dose of S/V is 97/103 mg BID.[1] However, in real-life settings, the target dose is often not achieved, and as many as two-thirds of pts remain on the lowest dose after six months from the initiation of therapy.[11] Moreover, in the PARADIGM-HF trial, in 47% of patients, the dose of the S/V was reduced mostly because of hyperkalemia or hypotension. Thus, in our opinion, was reasonable to analyze the effects of low-dose treatment with S/V.

We observed a significant decrease in NT-pro BNP levels, the average drop was $-\Delta$ 853.3±2,732.0 pg/ml, the same trend of improvement in troponin was observed: $-\Delta$ 4.7±9.4pg/ml,p=0.004. In the PROVE-HF study, it was shown that a reduction of NT-pro BNP concentration is related to reverse cardiac remodeling.[12] S/V seems to affect the concentration of natriuretic peptides also by its direct pharmacologic effect on neprilysin and either by its effect on intracardiac filling pressures.[13] It was also observed that the level of NT-pro BNP decreases as early as 14 days after the initiation of S/V therapy. [14]. High-sensitivity troponin allows accurate quantification of CRR process. In a study of patients with ICM or NICM heart failure with LVEF ≤40%, those with high-sensitivity troponin T <11 ng/l had the highest frequency of reverse remodeling during follow-up.[15] In conclusion, circulating biomarkers such as NT

proBNP and troponin, combined with improved clinical status and echocardiographic features, can help assess the CRR process.

Heart failure deteriorates the quality of life, and its improvement is becoming an increasingly important treatment goal. Our study revealed an improvement in the Minnesota Living with Heart Failure Questionnaire scores. These results are in line with data from the PARADIGM-HF study, which showed significantly higher improvement in the quality of life in the S/V group, compared to enalapril.[16]

The 6MWT has also been proved as a good prognostic tool in pts with HF.[17] Täger et al.[18] have shown that the "minimal important difference" for pts with HF is at least 35 meters. In our study, we observed an increase in the walked distance (table 2). The mean delta was 65.4±75.8m,which is a clinically and statistically significant improvement. We can hypothesize that the improvement in the quality of life is mostly due to improved exercise capacity. Our findings are similar to previously reported results. Beltran et al.[19] reported that treatment with S/V in HF pts was associated with a 13.9% improvement in the walked distance (+Δ =41.8 m). It remains unclear what mechanism of S/V therapy improves exercise capacity in the early phase of treatment. We can hypothesize that the inhibition of neprilysin by sacubitril would augment the hemodynamic effects of natriuretic peptides resulting in a reduction of filling pressures and thus improving exercise tolerance.[20] In our study, we observed a significant decrease of LAVI and mitral regurgitation levels, which are reliable markers of improved hemodynamics. Furthermore, beyond the influence on B-type natriuretic peptide, the inhibition of neprilysin could also affect the activity of other endogenous peptides such as atrial natriuretic peptide, c-type natriuretic peptide angiotensins, endothelin-1, -2, and -3. An increased activity of these substrates promotes peripheral vasodilation, and thus improves exercise capacity. Cardiac

remodeling is defined as adverse changes in cardiac size, shape, and function after cardiac injury. More recently, GLS has been shown as a useful index of cardiac reverse remodeling.[21,22] In a retrospective analysis of 44 pts, De Vecchis et al.[10] reported a significant improvement of GLS after one-year treatment with S/V (-10.142±3.080% vs -18.238±7.284%, p< 0.001). Castrichini et al.[23] reported amelioration of GLS from -8.3 ± 4% to -12 ± 4.7% (*p*<0.001) after 9 months S/V therapy. In our study after only one month of follow-up, GLS changed from -6.6% to -7.9% (p <0.001), which is a 16% absolute improvement. GLS changes parallels with other parameters of CRR: reduction in left ventricle diameters (LVEDd:-Δ 2,9±2.6mm; LVESd:-Δ 2,4±2.5mm, p<0.01) and volumes (LVEDV:-Δ14.6±33.1 ml, LVESV:-Δ13.4±30.6 ml), indexed left atrial volume (LAVI :-Δ 8.7±37.7ml/m2) degree of mitral regurgitation (EROA: 0.24 vs 0.15). The lack of improvement of LVEF (29.0 vs 31.0%, p=0.42) could be explained by a specific, layered structure of the myocardium. As the LVEF is more dependent on the function of the midwall circumferential fibers,[24] a one-month therapy is not sufficient to improve their function. Accordingly, Mazzetti et al. observed the LVEF improvement after six months of S/V treatment, but not at three months.[25] Among echocardiographic parameters assessing left ventricular systolic function (GLS, LVEF, LVs), positive correlations only for GLS and changes in troponin T and LV end-systolic volumes during the study, were found. ROC curve analysis showed that GLS cut-off value -8% is a good predictor of clinical improvement under low-dose S/V therapy. The likelihood of an increase in walked distance (6MWT: AUC 0.69 p = 0.04 Fig. 8) is higher in patients with GLS values <-8% (severe but not very-severe LV systolic dysfunction). Left-sided CRR is also more likely to occur in this group (MRvol: AUC:0.74 p=0.01, Fig. 9; LAVI: AUC 0.71 p=0.04, Fig. 10). These results emphasize that mitral

regurgitation and left atrial volume can be considered not only as functional bystanders but also independent predictors of CRR. Decreasing mitral regurgitation and left atrial dilatation has been already proved to be independent predictors of better outcomes.[26] All these changes are in line with complete left-sided cardiac reverse remodeling. This early favorable GLS change, observed in our study could be attributed to hemodynamic changes related to S/V therapy. S/V causes a reduction in intracardiac pressures and, thus, reduces cardiac wall stress.[27] In conclusion, our study shows that GLS is a more valuable method for the evaluation of LV function than LVEF, which is consistent with recently published studies.[28, 29] The therapy of low-dose (24/26 mg BID) S/V after one month initiates a left-sided CRR. S/V therapy should be initiated early because in the group of pts with symptomatic HFrEF and less impaired LV systolic function (GLS <-8%, severe or reduced LV systolic function), the likelihood of CRR and symptoms of clinical improvement is greater.

Limitations

The main limitation of our prospective study is a small group of participants. Due to these facts, more sophisticated statistical analyses such as regression or interquartile comparison, which might offer better insights into the analyzed problems, could not be performed either.

Conclusion

Following one-month, 24/26 mg BID of S/V therapy, often called the starting dose, an improvement in exercise capacity, better attitude to HF symptoms, hemodynamic changes manifested by decreasing biomarkers level (Nt pro -BNP, Troponin T) and first symptoms of CRR are observed. These changes correlate with GLS, which

ability to evaluate LV function is better than LVEF's. Patients with less impaired LV systolic function, defined as GLS <-8% (HFrEF with severe or reduced systolic function) are more likely to develop CRR and clinical improvement. Thus GLS can be used as a valuable tool for guided- HF therapy.

"Take-home" message

Sacubitril / Valsartan should be given to HFrEF patients with less impairment of LV systolic function (GLS <-8%) who are more likely to develop myocardial reverse remodeling. GLS should be used to evaluate this process.

Figure 1. Global longitudinal strain (GLS) values as a bull's eye presentation at baseline – upper row, below images after a follow-up period, for each patient respectively.
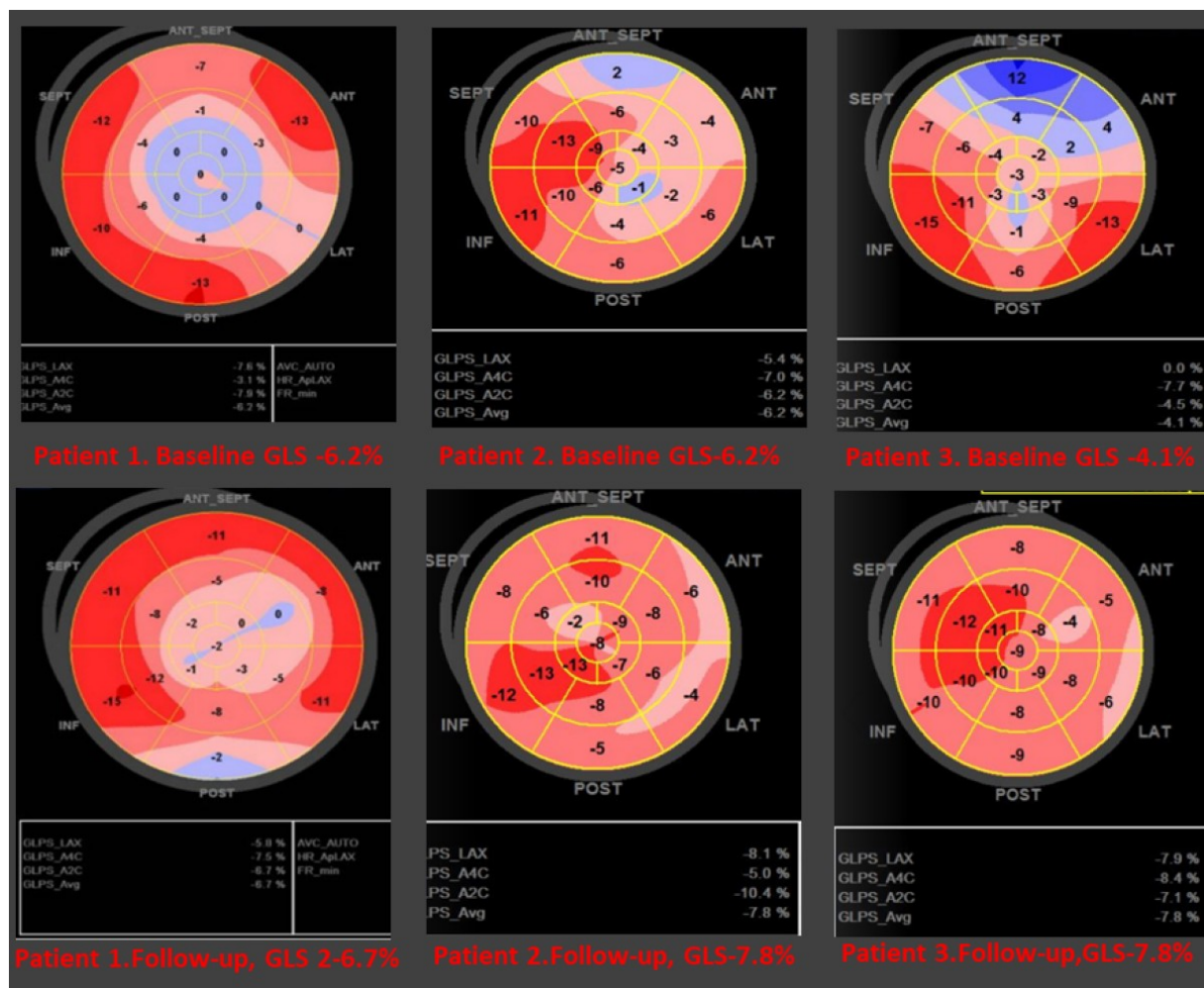
Figure 2. Correlation between global longitudinal strain at baseline (GLS AVG 1) and changes of left ventricle end-systolic volumes at follow up (LVESV2) during the study; Correlation r = 0.43, p = 0.027
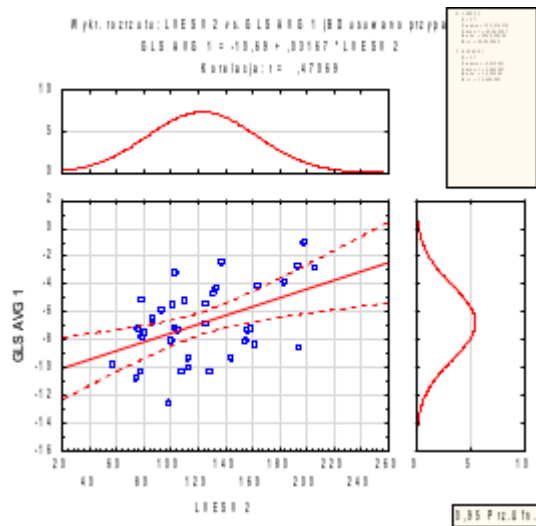
Figure 3. ROC curve analysis presenting capability of GLS to distinguish the improvement in walked distance measured in 6-MWT between two HFrEF groups with severe and very severe (GLS cut-off value -8%) LV dysfunction. In the group with sever impaired LV function, improvement in the walked distance (> 69.4 m) is more likely to occur. (AUC = 0.69; p = 0.04)
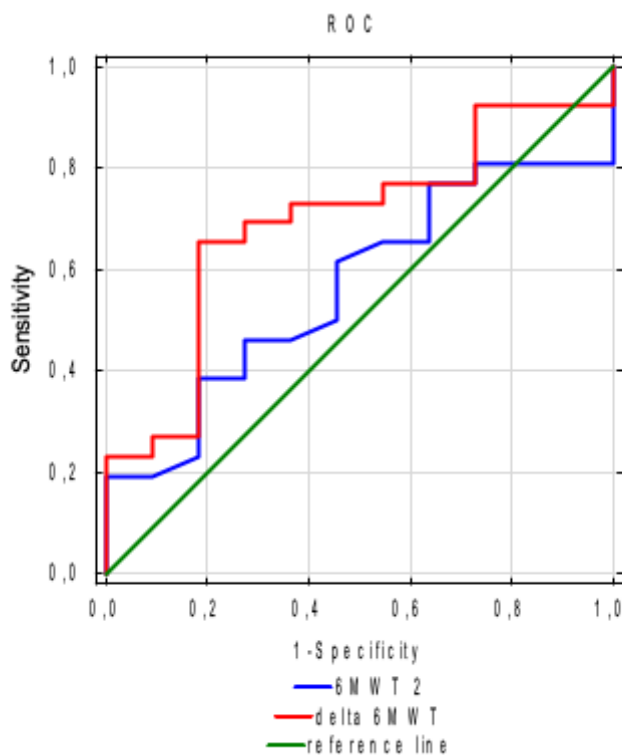
Figure 4. ROC curve analysis presenting capability of GLS to distinguish changes in mitral regurgitations volumes between two HFrEF groups with severe and very severe (GLS cut-off value -8%) LV dysfunction. In the group with sever impaired LV function, decreasing mitral regurgitations volumes (values 15 mL or less) are more likely to occur. (AUC = 0,74; p = 0.006)
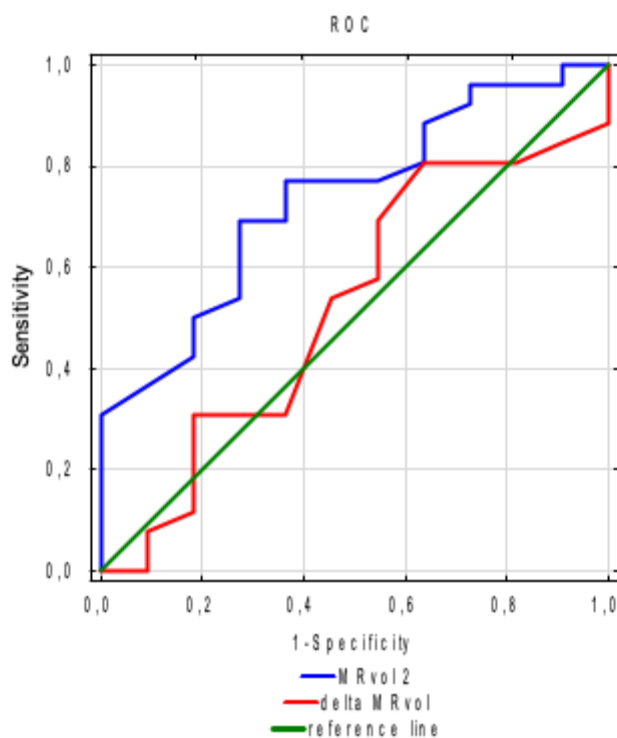
Figure 5.Graphical abstract
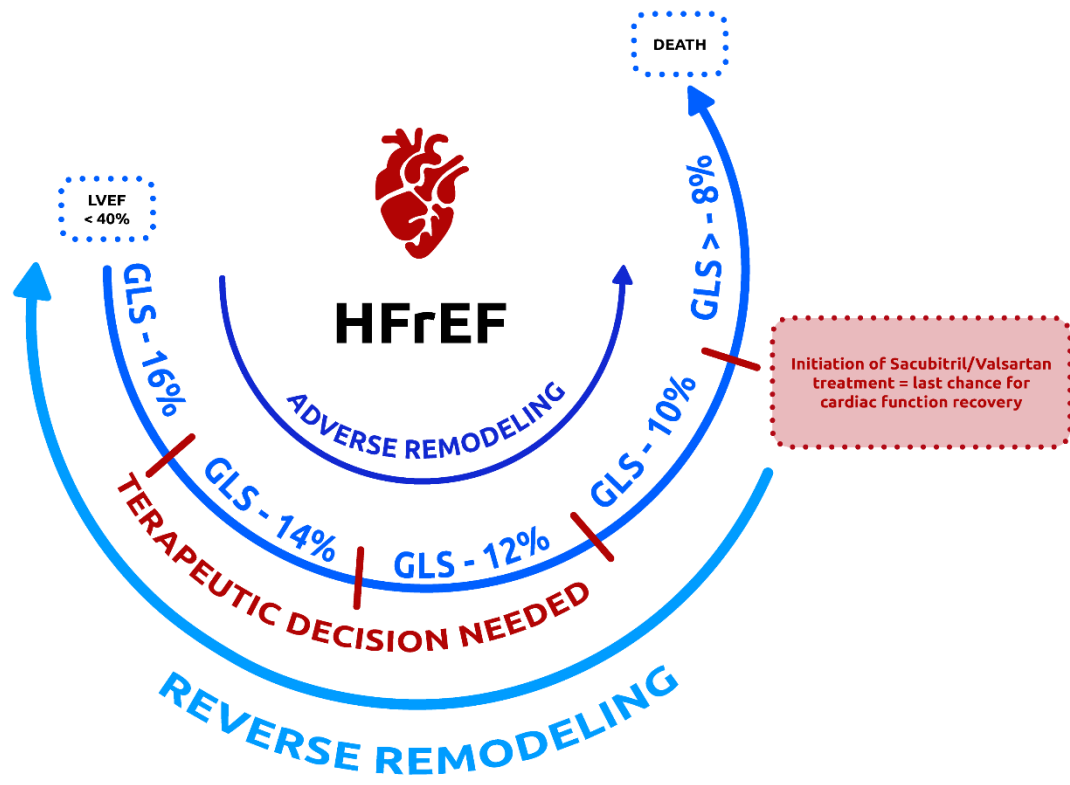
Table 1. Patients characteristics at baseline (n = 37)

Age, year, mean ± SD	64.5±17.5
Gender: male, no.(%)/ female, no.(%)	32(86)/5(14)
BMI mean±SD;	30.1±8.6
Etiology, no. (%) Non-ischemic Ischemic	 14 (38) 23 (62)
Diabetes mellitus, no. (%)	16 (43)
Chronic renal failure, no. (%)	12 (32)
Atrial fibrillation, no. (%)	8 (22)
Left ventricle systolic dysfunction by GLS Reduced or Severe: -8% to -16% Very severe: less than -8%	 13 (35%) 24 (65%)
NYHA Class, no. (%) I II III IV	 0 (0) 21 (57) 16 (43) 0 (0)
CRTD no.(%)	8 (21)

Abbreviations: BMI – body mass index; GLS – Global Longitudinal Strain; NYHA – New York Heart Association Classification; CRTD – cardiac resynchronization therapy defibrillator

Table 2. Changes in observed parameters at baseline and follow-up (n = 37)

Parameter	Baseline	Follow-up	P-Value
Heart rate (beats/min) mean±SD	75±13	71±10	0.02
SBP (mmHg) mean±SD	126±14	122.0±12	0.09
DBP (mmHg) mean±SD	79±12	77±11	0.36
Troponin T (pg/mL) median (IQR)	24 (5.0–75.0)	16 (3.0–16.0)	< 0.001
Creatinine (mg/dL) mean±SD	1.3±0.4	1.2±0.3	0.07
GFR (mg/mL/m^2) mean±SD	65.2±22.8	69.3±19.8	0.29
Potassium (mmol/L) mean±SD	4.4±0.4	4.4±0.5	0.97
NT-proBNP (pg/mL) mean±SD	3617±4767	2414±2740.3	0.03
MHFLQ (scores) mean±SD	22.0±9.8	16.0±9.5	< 0.001
6MWT (m) median (IQR)	323.7 (92.4–516.0)	389.0 (192.0–552.0)	< 0.001
Borg scale (point) median (IQR)	2.0 (0.0–9.0)	1.0 (0.0–5.0)	< 0.001
LVEDD (mm) mean±SD	67.8±8.1	65.2±7.7	< 0.001
LVESD (mm) mean±SD	61.1±9.1	58.8±9.2	< 0.001
LVEDV (mL) median (IQR)	185.0 (112.0–308.0)	169.0 (99–265.0)	0.005
LVESV (mL) median (min–max)	123.0 (74.0–217.0)	112.0 (56–206.0)	0.005
LAVI (mL/m^2) median (IQR)	51.6 (22.2–167.4)	43.1 (13.1–175.0)	< 0.001
LVEF (%)median (IQR)	29.0 (10.0–40.0)	31.0 (8.0–42.0)	0.42
ERO (mm^2) mean±SD	0.24±0.5	0.15±0.1	0.03
TAPSE (MM) mean±SD	16.3±3.6	17.5±3.3	0.003
TRV max (m/s) mean±SD	2.7±0.7	2.5±0.7	< 0.001
GLS (%) mean±SD	-6.6±2.7	-7.9±2.9	< 0.001
CS (%) mean±SD	-10.6±2.6	-10.3±3.2	0.64

RA (%) median (IQR)	8.3 (2.5–36)	9.7 (2.5–40.5)	0.25
RO MV (%) mean±SD	-2.5±2.7	-3.0±3.1	0.99
RO AP (%) mean±SD	2.3±4.9	2.0±5.2	0.76
TORSION (°/cm) median (IQR)	2.1 (0.2–15.4)	2.75 (0.2–16.6)	0.72

Abbreviations: SBP – systolic blood pressure; DBP – diastolic blood pressure; GFR – Glomerular Filtration Rate; NT-proBNP – N-terminal pro b-type natriuretic peptide; MLHFQ – Minnesota Living with Heart Failure Questionnaire; LVEDD – left ventricle end-diastole diameter; LVESD – left ventricle end-systole diameter; LVEDV – left ventricle end-diastole volume; LVESV – left ventricle end-systole volume; LAVI – left atrial volume index; LVEF – left ventricle ejection fraction; ERO – effective regurgitant orifice; GLS – global longitudinal strain; CS – global circumferential strain; RA – global radial strain; RO MV – rotation at the mitral valve level; RO AP – rotation at the apical level.

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