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ORIGINAL ARTICLE

# Deformation Imaging by Strain in Chronic Heart Failure Over Sacubitril-Valsartan: A Multicenter Echocardiographic Registry

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## Abstract

**Aims** Sacubitril/valsartan has changed the treatment of heart failure with reduced ejection fraction (HFrEF), due to the positive effects on morbidity and mortality, partly mediated by left ventricular (LV) reverse remodelling (LVRR). The aim of this multicenter study was to identify echocardiographic predictors of LVRR after sacubitril/valsartan administration.

**Methods and results** Patients with HFrEF requiring therapy with sacubitril/valsartan from 13 Italian centres were included. Echocardiographic parameters including LV global longitudinal strain (GLS) and global peak atrial longitudinal strain by speckle tracking echocardiography were measured to find the predictors of LVRR [= LV end-systolic volume reduction ≥10% and ejection fraction (LVEF) improvement ≥10% at follow-up] at 6 month follow-up as the primary endpoint. Changes in symptoms [New York Heart Association (NYHA) class] and neurohormonal activations [N-terminal pro-brain natriuretic peptide (NT-proBNP)] were also evaluated as secondary endpoints; 341 patients (excluding patients with poor acoustic windows and missing data) were analysed (mean age: 65 ± 10 years; 18% female, median LVEF 30% [inter-quartile range: 25−34]). At 6 month follow-up, 82 (24%) patients showed early complete response (LVRR and LVEF ≥ 35%), 55 (16%) early incomplete response (LVRR and LVEF < 35%), and 204 (60%) no response (no LVRR and LVEF < 35%). Non-ischaemic aetiology, a lower left atrial volume index, and a higher GLS were all independent predictors of LVRR at multivariable logistic analysis (all $P < 0.01$). A baseline GLS < −9.3% was significantly associated with early response (area under the curve 0.75, $P < 0.0001$). Left atrial strain was the best predictor of positive changes in NYHA class and NT-proBNP (all $P < 0.05$).

**Conclusions** Speckle tracking echocardiography parameters at baseline could be useful to predict LVRR and clinical response to sacubitril–valsartan and could be used as a guide for treatment in patients with HFrEF.

**Keywords** Heart failure; Sacubitril/valsartan; Speckle tracking; Echocardiography; Remodelling; Imaging; Biomarkers; Cardiovascular disease; Ultrasound

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# Background

Sacubitril/valsartan (LCZ696) is the first agent of the new class of angiotensin receptor–neprilysin inhibitor (ARNI) drugs, which marked a revolutionary point in the treatment of heart failure (HF). It was integrated into the 2021 European Society of Cardiology (ESC) HF guidelines with Level 1b recommendation for the treatment of patients with left ventricular (LV) ejection fraction (LVEF) less than or equal to 40% still symptomatic despite optimal medical therapy.[1] Comprising a neprilysin inhibitor and an angiotensin receptor blocker (ARB), sacubitril/valsartan operates on multiple targets, with a natriuretic, sympatholytic, and vasodilating effect and preventing myocardial remodelling. In fact, it has a double effect on haemodynamics, consisting in a reduction of preload and also of afterload. It was shown to be superior to enalapril in the main prospective trial PARADIGM-HF[2] in patients with HF with reduced ejection fraction (HFrEF) for the reduction of clinical endpoints of all-cause and cardiovascular mortality, hospitalization for HF, and quality of life, whereas it failed to provide significant benefits over valsartan for similar endpoints in patients with HF with preserved ejection fraction (EF) in the PARAGON-HF trial.[3] Of note, sacubitril/valsartan has shown to favour LV reverse remodelling (LVRR) and improvement of LVEF in patients with HFrEF.[4–7] Studies conducted in small cohorts have also shown a positive effect of sacubitril/valsartan on LV and left atrial (LA) deformation properties detected by advanced echocardiography [i.e. speckle tracking echocardiography (STE)].[8–11] However, whether there is a correlation between STE indices and LVRR in these patients is not known. The aim of this multicentre observational study was to describe the changes in LV and LA deformation parameters assessed by STE and to investigate their possible relationship with response to treatment with sacubitril/valsartan in terms of LVRR and improvement of congestive state.

# Methods

## Study population

In this Italian multicentre study involving 13 centres (see Supporting Information, *Table S1* for the complete list of the centres), patients with HFrEF in optimal medical therapy (according 201 ESC HF guidelines) and without therapeutic changes in the last 6 months, requiring treatment with sacubitril/valsartan according to the ESC guidelines[1] between the years 2017 and 2019, were included. All patients underwent a baseline ambulatory visit with echocardiographic evaluation and, after the appropriate washout (36 h) from angiotensin-converting enzyme (ACE) inhibitors, started treatment with sacubitril/valsartan. Clinical, biochemical, anamnestic data and echocardiographic measures were collected from the first visit report. STE was performed offline by a single independent echocardiographer for each centre who analysed all the echocardiographic images previously acquired by a second experienced operator in the same centre. Speckle tracking analysis was performed from one single operator for each centre. Patients with missing data and a poor acoustic window were excluded. Data from follow-up visits were collected after 6 months of treatment with sacubitril/valsartan, including clinical parameters, dose adjustments, basic echocardiography, and STE measurement. New York Heart Association (NYHA) class and N-terminal pro-brain natriuretic peptide (NT-proBNP) were used to assess the burden of symptoms and peripheral congestion as well as neurohormonal activation, according to the latest HF guidelines.[1,12] As the primary endpoint, we investigated clinical, biohumoral, and echocardiographic predictors of LVRR associated with the administration of sacubitril–valsartan. As a secondary endpoint, the association with symptoms and congestive state was evaluated. Each centre obtained approval from the local ethics committee. All procedures were conducted in accordance with the Declaration of Helsinki.

## Standard echocardiography

Echocardiographic images were acquired by an expert imager using a commercially available system (GE Medical Systems, Horthern, Norway) equipped with a 1.5–3.6 MHz transducer. All subjects were studied in the left lateral recumbent position. Standard LV diameters were measured in long-axis parasternal view. LV and right ventricular (RV) dimensions were calculated using standard views. LV end-diastolic and end-systolic volumes (LVEDV and LVESV) and EF, LA volume, and area were assessed from the apical four- and two-cham-


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ber views (for LVEF, the biplane Simpson method was used). LVRR was defined as a relative reduction of LVESV of at least 10% and an increase of LVEF of at least 10% at follow-up compared with baseline, according to previous studies conducted in similar cohorts.[13–15] The study cohort was then divided into three groups based on the presence, at 6 month follow-up, of LVRR and LVEF over/under 35%: early complete response (LVRR and LVEF $\geq$ 35%; *Group 1*), early incomplete response (LVRR and LVEF $<$ 35%; *Group 2*), and no early response (no LVRR and LVEF $<$ 35%; *Group 3*). LV dimensions and LA volumes were indexed to body surface area obtaining LV mass index and maximum and minimum LA volume index (LAVi), according to the European Association of Cardiovascular Imaging/American Society of Echocardiography (EACVI/ASE) recommendations.[16] LV diastolic function grade was assessed according to current recommendations.[17] Measurements of RV diameters and longitudinal function were made according to the EACVI/ASE recommendations.[18] Valvular heart diseases were evaluated and graded according to ESC guidelines.[19]

### Speckle tracking echocardiography

Speckle tracking analysis was performed offline using two-dimensional (2D) grey-scale apical four-, two-, and three-chamber views acquired during three consecutive cardiac cycles, with a frame rate of 40–80 frames per second and with a stable electrocardiographic recording, using a commercially available semi-automated 2D strain software (EchoPAC, GE, Milwaukee, WI, USA). The endocardial border was manually traced in apical views, delineating a region of interest (ROI), with the lowest width, composed of six segments for each view. Then, necessary manual adjustments of the ROI were performed, and the longitudinal strain curves for each segment were generated by the software. The average LV global longitudinal strain (GLS) was calculated as the average value of four-chamber, two-chamber, and three-chamber GLS curves, which was in turn measured as the negative peak of the dashed average curve of all segments. For the calculation of LA strain, QRS was used as the reference point for the strain curves, according to recent evidence on its slightly higher feasibility over the *P*-wave method.[20] Global peak atrial longitudinal strain (PALS) and peak atrial contraction strain were calculated at the end of the reservoir phase and of the systolic phase, respectively, by averaging the values observed in all LA segments in the four- and two-chamber views.

### Statistical analysis

Statistical analyses were performed using the SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) software Release 20. Variables were tested for normality via the Shapiro–Wilk test. Continuous variables were expressed as means ± SD or median and inter-quartile range (IQR) according to the variable distribution; binary variables were expressed as counts and percentages. A $P$ value $<0.05$ was considered to be statistically significant.

Changes from baseline after sacubitril–valsartan administration were evaluated by using the paired *t*-test or Wilcoxon signed-rank test for continuous variables and the $\chi^2$ test for categorical variables. Comparison among groups was done by using one-way ANOVA or Kruskal–Wallis test, as appropriate with Bonferroni *post hoc* correction. Univariate and multivariate logistic regression analyses, including the emerged predictors and other well-known potential confounders, were performed to assess independent association with LVRR. Variables to include into multivariate analysis were chosen based on biological plausibility and included as a block. Then, a stepwise model was used as a confirmatory analysis. Spline curves were computed to estimate the optimal cut-off points for continuous variables selected as predictors of LVRR. The goodness of fit of the logistic regression model employed was finally evaluated through receiver operating characteristic (ROC) curves.

## Results

### Baseline

The DISCOVER–ARNI registry was originally composed of 457 patients. However, 50 patients were excluded for missing follow-up data, 56 patients for missing STE data, and 10 patients for poor acoustic windows. The final population included in the analysis was thus composed of 341 patients. The characteristics of the study population are reported in *Table 1*.

Mean age was 65 ± 10 years, and 18% were female (64 patients). As regards HF aetiology, 46% (158) patients had ischaemic heart disease, 25% had dilated cardiomyopathy, 18% had severe chronic valvular heart disease, 7% had hypertrophic cardiomyopathy, and 4% had infiltrative cardiomyopathy (amyloidosis, Fabry disease, and sarcoidosis). The majority of our patients (66%, 212 patients) had NYHA Class II disease at baseline. Median values of brain natriuretic peptide and NT-proBNP were 257 [IQR: 144–657] (available for 100 patients) and 1000 [IQR: 533–2095] pg/mL, respectively (available for 241 patients), at baseline.

As for echocardiographic parameters at baseline, our cohort showed enlarged LV and LA, moderate to severe LV dysfunction as evidenced by a mean LVEF of 29 ± 6%, and different degrees of diastolic dysfunction severity. RV longitudinal function was at lower values of normality. Moreover, 40% of patients had more than moderate mitral regurgitation. STE showed a considerably reduced LV GLS

**Table 1** Clinical and echocardiographic characteristics of the overall study population at baseline and after 6 months of treatment with sacubitril/valsartan; mean differences obtained with matched-pairs analysis

| Overall population ($n$ = 341) | Baseline ($n$ = 341) | 6 months | Mean difference | $P$ |
|---|---|---|---|---|
| Age (years) | 65 ± 10 | | | |
| Female (%, $n$) | 18% (64) | | | |
| Systolic arterial pressure (mmHg) | 120 ± 16 | 116 ± 16 | −3.7 [CI −5.6; −1.8] | <0.0001 |
| Heart rate (b.p.m.) | 68 ± 11 | 67 ± 11 | −0.7 [−2.1; −0.6] | 0.266 |
| NYHA class (%, $n$) | | | | |
| I | — | 10% (33) | — | <0.0001 |
| II | 66% (212) | 55% (187) | — | |
| III | 31.3% (124) | 9% (31) | — | |
| IV | 0.09% (3) | 0.6% (2) | — | |
| Creatinine (mg/dL) | 1.27 [1; 1.3] | 1.08 [0.9; 1.29] | −0.02 [−0.05; −0.001] | 0.06 |
| eGFR (mL/min) | 72 [70.1–74] | 71.9 [70–74] | −0.1 [−0.3; −0.09] | 0.2 |
| N-terminal pro-BNP (pg/mL) | 1000 [533–2095] | 578 [246–1150] | −443 [65; −952] | 0.087 |
| LVEDV (mL) | 191 ± 63 | 181 ± 63 | −10 [CI −13; −6] | <0.0001 |
| LVESV (mL) | 135 ± 50 | 120 ± 51 | −15 [CI −18; −12] | <0.0001 |
| LVEF (%) | 29 ± 6 | 34 ± 7 | −5 [CI −6; −4] | <0.0001 |
| LV mass index | 156 ± 78 | 137 ± 49 | −18 [CI −28; −8] | <0.0001 |
| Maximum LAVi (mL/m$^2$) | 63 ± 28 | 45 ± 18 | −22 [CI −27; −17] | <0.0001 |
| E/E′ avg ratio | 14 ± 6 | 12 ± 6 | −1.9 [CI −2.5; −1.3] | <0.0001 |
| sPAP (mmHg) | 35 ± 12 | 32 ± 10 | −2.5 [CI −3.6; −1.4] | <0.0001 |
| TAPSE (mm) | 18 ± 4 | 19 ± 4 | 0.6 [CI 0.2; 1] | 0.004 |
| GLS (%) | −9.2 ± 3 | −10.7 ± 3 | −1.5 [CI −1.2; −1.7] | <0.0001 |
| Four-chamber LS (%) | −9.1 ± 3 | −10.6 ± 3.7 | −1.5 [−1.8; −1.2] | <0.0001 |
| Two-chamber LS (%) | −8.8 ± 3 | −10.4 ± 3.5 | −1.6 [−2; −1.2] | <0.0001 |
| Three-chamber LS (%) | −8.8 ± 3 | −10 ± 3.3 | −1.2 [−1.5; −0.8] | <0.0001 |
| Global PALS (%) | 16 ± 8.7 | 19 ± 9 | −2.9 [CI −4; −2] | <0.0001 |
| Global PACS (%) | 8.2 ± 6 | 9.7 ± 7 | −1.5 [−2.3; −0.7] | <0.0001 |

CI, confidence interval; eGFR, estimated glomerular filtration rate; E/E′, early diastolic wave by pulsed-wave Doppler/average early diastolic wave by tissue Doppler imaging in the three points of mitral annulus descent; GLS, global longitudinal strain; LAVi, left atrial volume index; LS, longitudinal strain; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; PACS, peak atrial contraction strain; PALS, peak atrial longitudinal strain; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

and LA strain. Regarding medications, 81% ($n$ = 277) of patients were treated with ACE inhibitors/ARBs at baseline before being switched to sacubitril/valsartan, 96% ($n$ = 325) were on beta-blockers, 70% ($n$ = 239) were on mineralocorticoid receptor antagonists, and 86% ($n$ = 291) were on loop diuretics. The majority of patients (66%, $n$ = 228) had implantable devices [41% implantable cardioverter defibrillator (ICD), 23% cardiac resynchronization therapy (CRT) device, and 0.2% pacemaker]. Notably, 72% (246) of patients started treatment with the lowest dose (24/26 mg) of sacubitril/valsartan, 27% (93 patients) started with the intermediate (49/51 mg), and only 1% (2 patients) started with the higher dose (97/103 mg). At 6 months, the sacubitril/valsartan dose was up-titrated in 120 patients (74% from 24/26 mg b.i.d. to 49/51 mg b.i.d., 26% from 24/26 mg b.i.d. to 97/103 mg b.i.d., and 30% from 49/51 mg b.i.d. to 97/103 mg b.i.d.); 219 patients continued with the starting dose (169 patients with 24/26 mg b.i.d., 48 patients with 49/51 mg b.i.d., and 2 patients with 97/103 mg b.i.d.). Two patients were down-titrated from 49/51 to 24/25 mg due to persistent hypotension.

## Follow-up

In the whole population after 6 months of therapy, 3.3% and 2.8% reduction in systolic and diastolic blood pressure were observed (both $P < 0.0001$). The clinical benefit associated with sacubitril/valsartan was also corroborated by a significant reduction in NT-proBNP plasma levels, which were reduced by 42% ($P < 0.0001$).

Clinical and echocardiographic parameters of the study population at follow-up and their mean changes after 6 months of sacubitril/valsartan are shown in *Table 1*. Notably, all STE parameters significantly improved at 6 months after sacubitril/valsartan (*Figure 1* and Supporting Information, *Figure S1*).

## Predictors of left ventricular reverse remodelling

Of interest, 137 (40%) patients showed LVRR at 6 month follow-up. Among patients showing LVRR, 82 (24%) patients also showed LVEF values ≥35%, identified as *Group 1*: early complete response, and 55 (16%) still had LVEF < 35% and were identified as *Group 2*: early incomplete response. The remaining 204 (60%) patients did not show any LVRR and were defined as *Group 3*: no early response (*Figure 2*). Patients' baseline clinical and echocardiographic characteristics according to the division of the cohort into the three groups are shown in *Table 2*. Notably, the initial and the final dose of sacubitril/valsartan did not significantly vary between the three groups ($P$ = 0.21 and $P$ = 0.39, respectively). NYHA

**Figure 1** Box plots showing the changes of E/E' ratio (A), left ventricular ejection fraction (LVEF) (B), peak atrial longitudinal strain (PALS) (C), and left ventricular global longitudinal strain (GLS) (D) from baseline to 6 month follow-up in the study cohort.

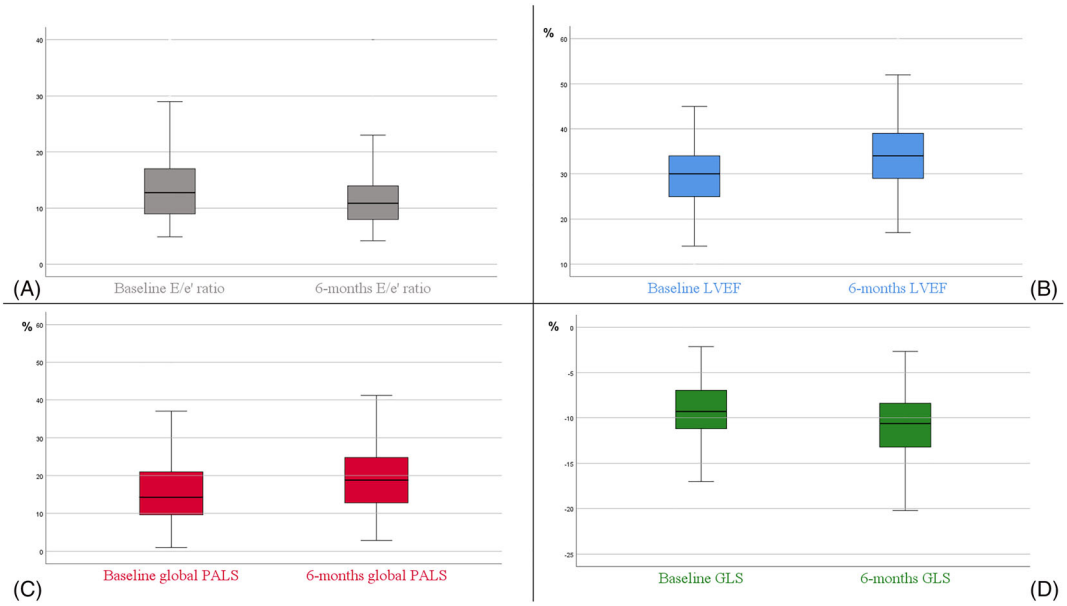
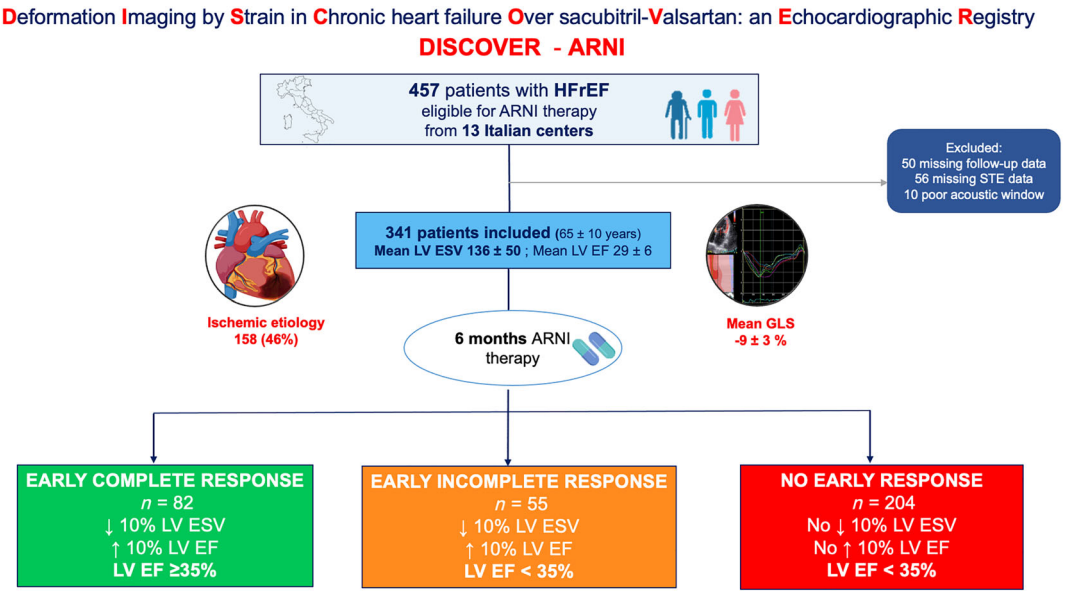



**Figure 2** Design of the study and division of the study cohort in three groups. ARNI, angiotensin receptor–neprilysin inhibitor; EF, ejection fraction; ESV, end-systolic volume; HFrEF, heart failure with reduced ejection fraction; GLS, global longitudinal strain; LV, left ventricular; STE, speckle tracking echocardiography.




class and NT-proBNP at baseline did not significantly differ between the groups. Non-responders were more likely to have an ischaemic aetiology as compared with responders.

As regards standard echocardiographic parameters, the three groups showed gradually lower LV dimensions and higher LVEF ($P < 0.0001$). STE parameters were considerably better in Group 1 compared with Groups 2 and 3, at both baseline and follow-up: the median GLS at baseline was −10.4% [IQR: −12.4%; −8.3%] in Group 1 vs. −7.6% [IQR: −7.7%; −5.7%] in Group 2 vs. −8.9% [−11%; −6.9%] in

**Table 2** Baseline clinical characteristics and biomarkers of the study population divided into three groups based on the presence of early LVRR and LVEF over or under 35% after 6 months of treatment with sacubitril/valsartan

| Variables | LVRR ($n$ = 137) | | No LVRR ($n$ = 204) | |
|---|---|---|---|---|
| | Group 1 ($n$ = 82): early complete response | Group 2 ($n$ = 55): early incomplete response | Group 3 ($n$ = 204): no early response | $P$ |
| Age (years) | 64 [58; 71.25] | 67 [60; 75] | 65 [57; 72] | 0.19 |
| Female (%, $n$) | 6% (21) | 4% (13) | 9% (30) | 0.06 |
| Body mass index | 27.25 [24.5; 31] | 27 [25; 31] | 27 [24; 30.5] | 0.67 |
| Systolic arterial pressure (mmHg) | 120 [110; 136.25] | 115 [110; 130] | 120 [110; 130] | 0.008 |
| NYHA class | | | | |
| II | 17% (57) | 10% (32) | 38% (123) | 0.4 |
| III | 7% (22) | 6% (21) | 19% (63) | |
| IV | 0 | 0.31% (1) | 0.62% (2) | |
| Heart rate (b.p.m.) | 68 [60; 75] | 70 [60.25; 76] | 66 [60; 75] | 0.46 |
| Hypertension (%, $n$) | 13% (44) | 11% (36) | 37% (125) | 0.38 |
| Diabetes mellitus (%, $n$) | 6% (22) | 5% (18) | 19% (64) | 0.69 |
| Dyslipidaemia (%, $n$) | 10% (35) | 7% (23) | 30% (102) | 0.37 |
| Ischaemic aetiology (%, $n$) | 8% (27) | 7% (23) | 31% (108) | 0.006 |
| Atrial fibrillation (AF) | | | | |
| Current AF (%, $n$) | 1% (4) | 3% (11) | 8% (26) | 0.35 |
| History of AF (%, $n$) | 3% (11) | 3% (11) | 8% (27) | |
| Creatinine (mg/dL) | 0.98 [0.79; 1.21] | 1 [0.86; 1.36] | 1.03 [0.89; 1.3] | 0.13 |
| N-terminal pro-BNP (pg/mL) | 998 [505; 1768] | 1373 [570.5; 3429] | 945 [535.5; 2110] | 0.18 |
| Sacubitril/valsartan starting dose (%, $n$) | | | | |
| 24/26 mg b.i.d. | 11% (21) | 10% (19) | 31% (62) | 0.21 |
| 49/51 mg b.i.d. | 15% (29) | 6% (11) | 27% (53) | |
| 97/103 mg b.i.d. | 0 | 0.51% (1) | 0.51% (1) | |

AF, atrial fibrillation; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodelling; NYHA, New York Heart Association.

**Table 3** Univariable and multivariable logistic regression analyses for the association with LV reverse remodelling at 6 months

| Parameter | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | $\chi^2$ | $P$ | $\chi^2$ | $P$ |
| Age | | 0.9 | 1.08 | 0.29 |
| Sex | | | 1.92 | 0.16 |
| Systolic blood pressure | 7.99 | 0.004 | | 0.2 |
| Ischaemic aetiology | 9.78 | 0.001 | 7.71 | 0.005 |
| LVEF | | 0.94 | 0.99 | 0.31 |
| Maximum LAVi | 6.05 | 0.01 | 7.12 | 0.0076 |
| GLS | 4.93 | 0.02 | 6.78 | 0.0092 |

GLS, global longitudinal strain; LAVi, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction.

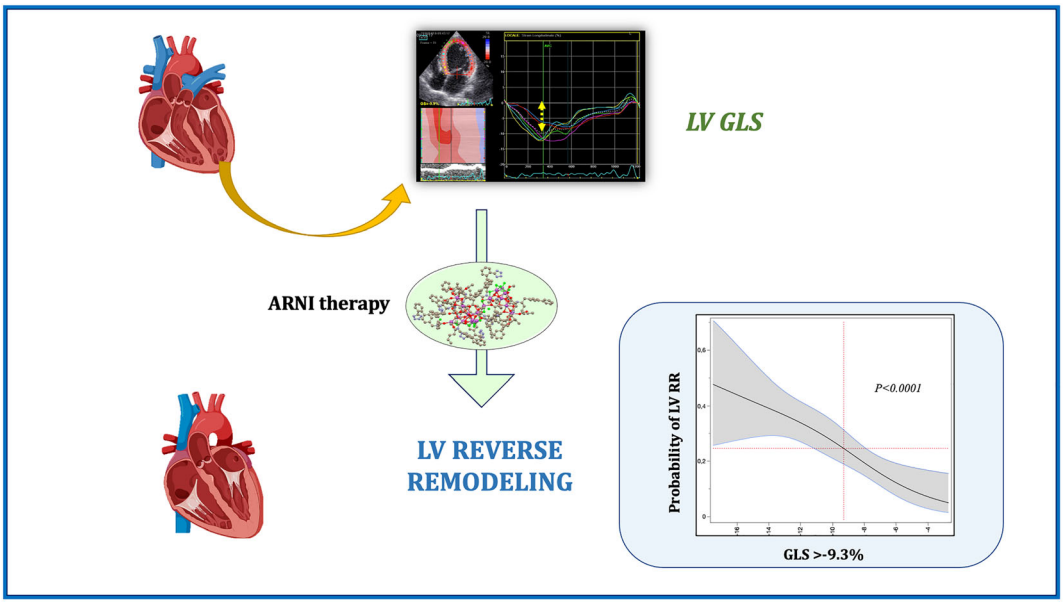
Group 3, $P < 0.0001$; median global PALS at baseline was 13.75% [9%; 21%] vs. 10.4% [6%; 15%] vs. 8.2% [4.8%; 12%]. Ischaemic aetiology, maximum LAVi, and GLS were all predictors of LVRR at both univariable and at multivariable logistic regression analyses (*Table 3*).

Spline curve showed a considerable probability of LVRR for baseline GLS values −9.3%, which gradually worsens and becomes very low for GLS values >−9.3% (*Figure 3*). With ROC curves (Supporting Information, *Figure S2*), GLS at baseline showed fair accuracy for the detection of early response with a cut-off value of −9.3% [area under the curve (AUC) 0.75, 95% confidence interval (CI) 0.67–0.83, $P < 0.0001$; Akaike information criterion (AIC) = 340 and Bayesian information criterion (BIC) = 367 by logistic regression], an acceptable discrimination between Group 1 and Group 3 (AUC 0.66, 95% CI 0.57–0.72, $P = 0.02$; AIC = 628 and BIC = 658 by logistic regression), and a poorer discrimination between Group 2 and Group 3 (AUC = 0.53, 95% CI 0.44–0.61, $P = 0.02$; AIC = 645 and BIC = 656 by logistic regression). The inclusion of GLS into a multiparametric model composed by age, ischaemic aetiology, sex, LVEF, and LAVi max enhanced its accuracy for the discrimination between Group 2 and Group 3 (AUC 0.66, 95% CI 0.57–0.74, $P = 0.0002$; AIC = 628 and BIC = 658 by logistic regression).

## Correlation of strain parameters with congestive state

Considering the STE role as a predictor of congestion markers, global PALS was associated with NYHA class at baseline and 6 month follow-up, contrary to GLS (baseline: $\chi^2$ = 7.11 for global PALS, $P = 0.007$ vs. $\chi^2$ = 4 for GLS, $P = 0.07$; 6 months: $\chi^2$ = 4 for global PALS, $P = 0.001$ with AIC = 132 and BIC = 138 vs. $\chi^2$ = 0.83 for GLS, $P = 0.07$). Similar results were obtained for NT-proBNP at baseline and 6 month follow-up (all $P < 0.0001$). Moreover, with

**Figure 3** Representation of the predictive value of left ventricular (LV) global longitudinal strain (GLS) >−9.3% for LV reverse remodelling (RR) after 6 months of therapy with sacubitril/valsartan, showed by a spline curve. ARNI, angiotensin receptor–neprilysin inhibitor.




univariate and multivariate analyses that included LVEF and LV GLS, global PALS remained the only independent predictor of NT-proBNP improvement at 6 months ($P$ = 0.003).

## Discussion

Given that sacubitril/valsartan has already been shown to induce improvement of LV function and LVRR at long-term follow-up in patients with HFrEF, including those in more advanced stages of the disease,[4,21] our study provided new data from multiple Italian centres confirming previous findings on the positive effects of sacubitril/valsartan on myocardial deformation assessed by STE. This represents an early marker of myocardial structural and functional properties and has shown clear superiority over conventional echocardiographic parameters for the study of all chambers, particularly for the evaluation of patients with HF.[22–24] Moreover, to our knowledge, this is the first research to show the existence of an association between baseline GLS and early response to treatment with sacubitril/valsartan in terms of LVRR at 6 months, proving the great value of LV GLS as an independent predictor of LVRR and also providing the optimal cut-off value of GLS = −9.3% for this purpose.

Our study also highlighted the tendency of clinicians, probably due to uncertainties about renal function or blood pressure, to prescribe sacubitril/valsartan starting with the lowest initial dose, which did not influence the subsequent beneficial effects of this drug in terms of LVRR.

### Effects of angiotensin receptor–neprilysin inhibitor on myocardial deformation

In our cohort, the measures of myocardial deformation regarding all cardiac chambers were significantly reduced at baseline, compared with the normality values available in the literature,[25–27] increasing at 6 months of follow-up. As sacubitril/valsartan considerably improves haemodynamic conditions and functional parameters in HFrEF, some authors have already hypothesized its potential effects on myocardial deformation parameters assessed by STE, finding a considerable improvement of LV strain in patients treated with ARNI.[11,28] In particular, Mazzetti *et al*. described an early improvement of LV GLS at 3 and 6 months in a small cohort of patients with HFrEF and a significant progressive LVRR at 6 months; however, they did not analyse the correlation between these two findings, only focusing on the potential value of LV GLS as early marker of LVRR, because it varied after 3 months of therapy, unlike LV volumes and EF.[9] This improvement may be the result of a double mechanism: (i) sacubitril/valsartan has an important natriuretic effect, which reflects on the reduction of preload and consequently on an improvement of LV GLS, which highlights this unloading effect, and (ii) the effect of sacubitril/valsartan on LVRR, which provides an actual improvement in contractility, showed by LV GLS improvement as an early marker of LV function.

Also, an improvement of PALS was described in a recent small retrospective study of patients treated with sacubitril/valsartan and at least one episode of atrial fibrillation at

1 year follow-up.[13] Our study not only showed a considerable improvement of PALS after 6 months of therapy with sacubitril/valsartan but also demonstrated the unique value of PALS as a predictor of NYHA class and NT-proBNP improvement.

## Predictors of left ventricular reverse remodelling

A meta-analysis involving 10 175 patients showed that ARNI outperformed ACE inhibitors/ARBs in terms of LVRR indices, with great changes in LVEF, LV diameters, and LV volumes in patients with HFrEF.[29] Because multiple studies have shown the beneficial effect of sacubitril/valsartan on LVRR, which was suggested to be related to its proved inhibition of cardiac fibroblasts proliferation,[30] it would be important for clinicians to find the baseline indices able to identify those patients who are more likely to benefit from ARNI developing LVRR, in order to provide early initiation of this therapy.

The PROVE-HF trial was a big multicentre study investigating the correlation of NT-proBNP changes with echocardiographic modification after 12 months of treatment with sacubitril/valsartan: it showed a weak but significant correlation of NT-proBNP reduction at 12 months with LVEF improvement and LVEDV, LVESV, LAVi, and E/E' reduction.[5] This was also associated with favourable outcomes (lower HF hospitalizations and mortality) in a further analysis.[31]

To date, no one has developed a baseline clinical or echocardiographic index able to predict response to sacubitril/valsartan.

Left ventricular GLS emerged as the best predictor of early LVRR probably due to its capability to detect intrinsic myocardial structural anomalies, with high sensitivity; in fact, it also previously proved to accurately detect myocardial fibrosis.[32] Therefore, patients with worse baseline GLS would have higher degrees of intrinsic myocardial damage, which results in being irreversible with pharmacological therapy; on the contrary, patients with less impaired LV strain would have lower grades of damage resulting in more chances of recovery. In fact, GLS has already been shown to be a predictor of LVRR at long-term follow-up in different cohorts of patients, for example, with dilated cardiomyopathy or acute myocardial infarction.[33–35]

## Predictors of symptoms and congestion

As opposed to GLS, baseline LA strain did not distinguish between patients who develop LVRR or not, probably because it is a dynamic measure deeply influenced by loading conditions. In fact, it has shown a strong correlation with LV filling pressures in cohorts with HFrEF.[36] Thus, its utility in patients with HFrEF could be more as a marker of congestive state and diastolic function, as already shown in a patient treated with sacubitril/valsartan,[37] whereas it is not the ideal parameter to predict LV structural remodelling. In fact, in our cohort, baseline global PALS but not GLS was related to symptomatic status at baseline as well as at 6 months of follow-up. This supports the idea that symptomatic status and (for the first time) its improvement depend on LA function. Furthermore, relatively preserved LA function implies less LA fibrosis and may act as a buffer between LV (filling pressure) and pulmonary circulation (symptoms).[38]

## Clinical impact

The latest ESC guidelines for the treatment of HF[1] have led to reconsidering the therapeutic approach to HF, which should be tailored on the single patient in light of the international recommendations. Patient profiling is starting to be one of the main objectives after HF diagnosis, because the possible underlying conditions may strongly influence the therapeutic efficacy, tolerability, and titration. Some clinical parameters have already been proposed for improving patient profiling, such as age, heart rate, blood pressure, hyperkalaemia, renal function, and atrial fibrillation.[39] LV GLS may be integrated in a multiparametric evaluation of patients with HF in order to evaluate ultrastructural myocardial modifications, which may guide in the identification of the patients most prone to positively respond to reverse-remodelling therapy, particularly to sacubitril/valsartan, leading to an improved patient profiling, which may serve as a guide for not only therapeutic decisions but also follow-up schedules.

Of interest, 33% of our patients were not ICD or CRT carriers and only 23% were CRT carriers, whereas 60% of patients without ICD or CRT despite having the guideline-directed criteria at baseline improved either LVEF reaching >35% or NYHA class reaching values = I after 6 months of sacubitril/valsartan, as we showed in a recent DISCOVER–ARNI sub-analysis.[40] This suggests that a satisfying LVRR could also be achieved with pharmacological therapy. Accordingly, the initiation of sacubitril/valsartan reduced the incidence of ventricular arrhythmias in the PARADIGM trial, which was confirmed in a smaller study by Martens *et al.*, who observed that HFrEF ICD carriers receiving sacubitril/valsartan had lower degrees of ventricular tachycardia (VT) or fibrillation after 1 year, resulting in fewer ICD interventions, and that the degree of LVRR was related to non-sustained VT; therefore, they hypothesized that the beneficial effect on ventricular arrhythmias might be related to cardiac RR.[4]

Moreover, we observed that even a low dose of sacubitril/valsartan produced a satisfying degree of LVRR and improvement of LV function in most of the patients. However, it is known that some patients have large areas of fibrosis, which predispose them to life-threatening arrhythmias. These results suggest considering the use of this drug in the management algorithms to obtain LV volumes and EF

improvement and to individualize the indications to ICD or CRT implantation based on the single case and on international recommendation. This approach may sometimes lead to spare ICD indications, thus saving healthcare services from additive costs and patients from unnecessary infective risks.

All this given, there is a higher need of reliable baseline indices to assess patients' probability to develop LVRR with sacubitril/valsartan, with possible consequent improvement of LV function associated with better clinical outcome and reduction of ventricular arrhythmias. This will help clinicians in the decision-making processes on early referral of patients for ICD/CRT implantation or to opt for optimizing medical therapy and re-evaluate patients after a short period of follow-up to observe if LVRR and recover of LV function occurred.

Moreover, our results suggest the inclusion of advanced echocardiography, in particular STE, to provide an additive value on the evaluation of patients with HFrEF before starting therapy with sacubitril/valsartan, in order to provide a tailored follow-up planning and therapeutic strategy regarding dosage, up-titration, and concomitant therapies.

In fact, our division into groups and the excellent results for STE to differentiate them suggest that performing STE with LV GLS in patients with HFrEF referred for sacubitril/valsartan could be useful to discriminate patients who would particularly benefit from the medical treatment with an early and complete response and those with an early structural response who would probably require more time until functional recovery (incomplete response), from patients who are less likely to recover with sacubitril/valsartan and need more aggressive therapies in addition to it. The evaluation of global PALS could be highly informative, to evaluate not only the possible structural remodelling but also the improvement in symptoms (as a consequence of overall congestive state), which is the most important element from the patients' point of view and also represents one of the main criteria for changes in patient management.

### Limitations

This study has two main limitations: the observational nature of the study and the dependence on image quality and correct acquisition for STE. In fact, these led to the exclusion of many patients (70) due to missing data or absence of the technical requirements for strain analysis (dedicated RV views and absence of electrocardiographic recording). Moreover, the short follow-up made the investigation of prognostic implications more challenging due to the low number of clinical events. However, new prospective data collection is ongoing to address this gap. Also, RV function by STE was not included in our analysis due to the high number of missing data; however, future research is already planned in a similar cohort focused on RV strain.

## Conclusions

This multicenter study demonstrated a progressive improvement of myocardial deformation parameters assessed by STE in patients with HFrEF after 6 months of treatment with sacubitril/valsartan, particularly LV and LA longitudinal strain, which are known as early predictors of structural and functional changes of cardiac chambers. LV GLS before ARNI initiation proved to be an independent predictor of LVRR after 6 months of therapy. Moreover, global PALS emerged as a predictor of symptoms and congestion parameters (NYHA class and NT-proBNP at baseline). Therefore, STE could represent an additional tool to help guide clinical management of HFrEF patients, particularly in the selection of those patients to refer to pharmacological or more aggressive therapy.

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## Conflict of interest

None declared.

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None.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Scatter plots showing variation of left ventricular (LV) ejection fraction (EF) (Panel A), LV end-systolic volume (ESV) (Panel B), LV global longitudinal strain (GLS) (Panel C) and peak atrial longitudinal strain (PALS) (Panel D) from baseline to 6-months follow up in the study cohort.

**Figure S2.** Receiver Operating Characteristc (ROC) curves for the discriminative power of left ventricular (LV) global longitudinal strain (GLS) for LV reverse remodeling after 6 months of therapy with sacubitril/valsartan (panel A), for group 1 vs. group 3 (panel B) of our cohort and group 2 vs. group 3 of our cohort as lone parameter or after inclusion in a

multiparametric model including age, sex, ischemic etiology, maximum left atrial volume index, left ventricular ejection fraction and LV GLS (panel C).

**Table S1.** List of the Italian centers contributing to the **D**eformation **I**maging by **S**train in **C**hronic heart failure **O**ver sacubitril-**V**alsartan: a multicenter **E**chocardiographic **R**egistry (**DISCOVER**)–**ARNI.**

**Table S2.** Baseline echocardiographic characteristics of the overall study population and of the study population divided into two groups based on the presence of left ventricular reverse remodeling after 6-months of treatment with Sacubitril/Valsartan.

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