Brief Report

The Effect of Sacubitril/Valsartan on Left Ventricular Myocardial Deformation in Heart Failure with Preserved Ejection Fraction (PARAMOUNT trial)

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ABSTRACT

Background: Global longitudinal strain (GLS) and global circumferential strain (GCS) have been shown to be impaired in heart failure with preserved ejection fraction. We sought to assess whether treating patients with heart failure with preserved ejection fraction with sacubitril/valsartan would significantly improve GLS and GCS compared with valsartan alone.

Methods and Results: PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction Trial) was a phase II, randomized, parallel-group, double-blind multicenter trial in 301 patients with New York Heart Association functional class II−III heart failure, a left ventricular ejection fraction of 45%, and an N-terminal pro-B-type natriuretic peptide of ≥400 pg/mL. Participants were randomly assigned (1:1) to sacubitril/valsartan titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily for 36 weeks. We assessed changes in the GLS and the GCS from baseline to 36 weeks, adjusting for baseline value, in patients with sufficient imaging quality for 2-dimensitonal speckle tracking analysis at both timepoints ($n = 60$ sacubitril/valsartan, $n = 75$ valsartan only). GCS was significantly improved at 36 weeks in the sacubitril/valsartan group when compared with the valsartan group (Δ4.42%, 95% confidence interval [CI] 0.67−8.17, $P = .021$), with no significant difference observed in GLS (Δ0.25%, 95% CI, −1.19 to 1.70, $P = .73$). Patients with a history of hospitalization for heart failure had a differentially greater improvement in GCS when treated with sacubitril/valsartan.

Conclusions: In patients with heart failure with preserved ejection fraction, sacubitril/valsartan improved GCS but not GLS when compared with valsartan during a 36-week period. This trial is registered at ClinicalTrials.gov, NCT00887588. (*J Cardiac Fail 2023;29:968−973*)

Key Words: HFpEF, randomizel clinical trial, sacubitril, strain, echocardiography.

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Brief lay summary

Both circumferential and longitudinal function have been shown to be impaired in patients with heart failure with preserved ejection fraction. In the present study we assessed whether treating these patients with sacubitril/valsartan would improve left ventricular contraction compared with valsartan alone. In this trial of 301 patients with heart failure with preserved ejection fraction, participants were randomly assigned to sacubitril/valsartan or valsartan. The left circumferential function of the left ventricle improved after 36 weeks of treatment in the sacubitril/valsartan group when compared with the valsartan group. There was no significant difference in longitudinal function.

Heart failure with preserved ejection fraction (HFpEF) is common, increasing in prevalence, and accounts for approximately one-half of all HF cases in the community and causes substantial morbidity and mortality.[1] In a phase II trial, sacubitril/valsartan decreased N-terminal pro-B-type natriuretic peptide (NT-proBNP), left atrial size and improved New York Heart Association (NYHA) functional class.[2] Two-dimensional speckle tracking echocardiography is a noninvasive technique that can be used to quantify left ventricular deformation with the measures global longitudinal strain (GLS) and global circumferential strain (GCS).[3] These measures have been shown to be impaired in HFpEF.[4] The aim of the present study was to assess whether treatment with sacubitril/valsartan would significantly improve myocardial deformation as assessed by GLS and GCS as compared with valsartan alone.

Methods

Study population

The PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction Trial) study was a randomized, double-blind, parallel group, active controlled trial.[2] Patients with HF were enrolled if aged >40 years, had at least NYHA functional class II symptoms, a left ventricular ejection fraction (LVEF) of ≥45%, and an NT-proBNP level of >400 pg/mL. Additional details regarding the inclusion and exclusion criteria, study design, and primary findings have been reported elsewhere.[2] All patients who satisfied enrolment criteria were randomly assigned (1:1) to treatment with either sacubitril/valsartan or valsartan. The study continued for 36 weeks. The study protocol was approved by individual sites' institutional review boards or ethics committees and all enrolled patients provided written informed consent. This trial is registered at ClinicalTrials.gov, NCT00887588.

Echocardiography

Digital echocardiographic images were acquired according to guidelines set forth by the American Association of Echocardiography. All echocardiographies were analyzed in a blinded fashion. Conventional echocardiographic measurements including LV chamber quantification, left atrial measurements, and transmitral inflow velocities were performed as previously described.[4] GLS and GCS were obtained by two-dimensional speckle tracking analyses using the TomTec system (2D Cardiac Performance Analysis v1.1, TomTec Imaging Systems, Unterschleißheim, Germany) as previously described.[4] Before speckle tracking measurement of each image in each view, quality was assessed by the reader and defined as inadequate for analysis if any of the following features were present: lack of a full cardiac cycle, >1 segment dropout, missing view, or significant foreshortening of the LV. Peak longitudinal strain was measured from 6 segments in each apical view (the 4- and the 2-chamber views) and GLS was automatically generated by the software. GCS was also generated automatically by the software which assessed peak circumferential strain from 6 segments from the parasternal short axis view at the level of the papillary muscles.

Statistics

The effect of treatment on myocardial deformation was assessed using an analysis of covariance model with treatment assignment as the fixed factor and the baseline value of GLS and GCS as covariates, respectively. All 36-week analyses were based on completers only. Analysis of changes in GLS and GCS were tested in prespecified subgroups. Furthermore, we assessed whether changes in GLS and GCS were associated with the previously described changes in systolic blood pressure, NT-proBNP, left atrial size, and NYHA functional class, adjusting for baseline values at treatment assignment. Statistical analysis was performed using Stata software v13.1 (Stata Corp LP, College Station, TX). A 2-sided *P* value of .05 was used to define statistical significance.

Results

Of the 301 patients randomized in the PARAMOUNT trial, 241 completed the 36 weeks of assessment. Of these, 135 had echocardiographies of sufficient quality at baseline and follow-up for the assessment of GLS and 81 for GCS, respectively.

All baseline characteristics were similar between the treatment groups (Table 1). Overall, patients were elderly with a mean age of 71 years, most were female (59%), overweight (mean body mass index of 30 kg/m^2), and had dyspnea symptoms

Table 1. Baseline Demographics and Clinical and Echocardiographic Characteristics

	Valsartan ($n = 75$)	Sacubitril/Valsartan ($n = 60$)	*P* value
Demographics			
Age (years)	69.9 ± 8.6	71.7 ± 9.3	.26
Women, *n* (%)	44 (59%)	35 (58%)	.97
Clinical			
NYHA functional class, *n* (%)			.56
- Class I	1 (1%)	0 (0%)	
- Class II	61 (81%)	47 (78%)	
- Class III	13 (17%)	13 (22%)	
Heart rate (bpm)	70.1 ± 13.8	68.2 ± 12.4	.40
BMI	30.5 ± 5.8	30.0 ± 5.2	.61
Systolic blood pressure (mm Hg)	134.6 ± 15.5	136.1 ± 12.7	.55
Diastolic blood pressure (mm Hg)	77.2 ± 9.8	77.7 ± 9.2	.72
Previous admission to hospital for heart failure, *n* (%)	38 (51%)	29 (48%)	.79
History of atrial fibrillation, *n* (%)	36 (48%)	29 (48%)	.97
Atrial fibrillation at screening, n (%)	21 (28%)	17 (28%)	.97
History of hypertension, *n* (%)	65 (87%)	56 (93%)	.21
History of diabetes, *n* (%)	24 (32.0%)	14 (23.3%)	.27
History of myocardial infarction, *n* (%)	15 (20.0%)	13 (21.7%)	.81
Baseline treatments			
ACE inhibitors, *n* (%)	39 (52%)	27 (45%)	.42
ARBs, *n* (%)	31 (41%)	27 (45%)	.67
ACE inhibitors or ARBs, *n* (%)	70 (93%)	53 (88%)	.31
Diuretics, *n* (%)	75 (100%)	60 (100%)	1.00
β-Blockers, *n* (%)	59 (79%)	43 (72%)	.35
Aldosterone antagonists, *n* (%)	20 (27%)	13 (22%)	.50
Laboratory work			
Mean eGFR (mL/min per 1.73 m^2)	62.6 ± 20.5	66.7 ± 20.0	.24
eGFR <60 mL/min per 1.73 m^2, *n* (%)	37 (50%)	23 (38%)	.18
NT-proBNP (pg/mL), median [IQR]	917.5 [498.0, 1420.0]	946.5 [565.0, 1672.0]	.56
Baseline echocardiographic measures			
Left ventricular ejection fraction (%)	58.9 ± 8.3	58.4 ± 8.1	.70
E′ (cm/s)	7.3 ± 2.9	7.5 ± 2.5	.58
E/A	1.2 ± 0.8	1.3 ± 0.7	.84
E/E′	13.0 ± 6.1	12.5 ± 5.3	.67
Left atrial dimension (cm)	3.7 ± 0.5	3.7 ± 0.4	.31
Left atrial volume (mL)	69.6 ± 26.9	65.7 ± 22.7	.40
Left atrial volume index (mL/m^2)	36.8 ± 13.5	35.1 ± 11.7	.46
Left ventricular end-diastolic volume (mL)	115.3 ± 32.4	109.7 ± 25.5	.29
Left ventricular end-systolic volume (mL)	48.5 ± 22.2	46.1 ± 15.8	.52
Left ventricular mass (g)	148.5 ± 38.1	143.0 ± 34.2	.41
Left ventricular mass index (g/m^2)	78.0 ± 20.3	76.9 ± 20.5	.77
Relative wall thickness	0.4 ± 0.1	0.4 ± 0.1	.75
Tricuspid regurgitant velocity (m/s)	2.5 ± 0.3	2.4 ± 0.3	.64
Baseline strain measures			
GCS (%)	−27.6 ± 9.2	−30.5 ± 9.7	.17
GLS (%)	−15.3 ± 4.8	−15.4 ± 4.9	.91

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; GLS = global longitudinal strain; GCS = global circumferential strain; eGFR = estimated glomerular filtration rate; IQR = interquartile range; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

corresponding with NYHA functional class II (80%). Patients included had reduced GLS (−15.5%) and relatively preserved GCS (−28.8%). A higher absolute GLS was associated with lower history of previous HF hospitalization, lower NT-proBNP, higher LVEF, and higher GCS, and higher GCS was associated with lower history of prior HF hospitalization, lower history of previous myocardial infarction, higher LVEF, and higher GLS (data not shown).

Over 36 weeks, sacubitril/valsartan was associated with greater relative improvement in GCS (Δ4.42%, 95% confidence interval [CI] 0.67−8.17, $P = .0215$), whereas GLS was not affected by sacubitril/valsartan treatment (Δ0.25%, 95% CI −1.19 to 1.70, $P = .73$), when compared with valsartan (Fig. 1). Baseline characteristics did not seem to influence the effect of treatment (Fig. 2). None of the subgroups experienced a differential effect in GLS when treated with sacubitril/valsartan when compared with valsartan (Fig. 2). However, for GCS, patients with a history of HF hospitalization had a differentially greater improvement in GCS when treated with sacubitril/valsartan (interaction $P = .002$) (Fig. 2).

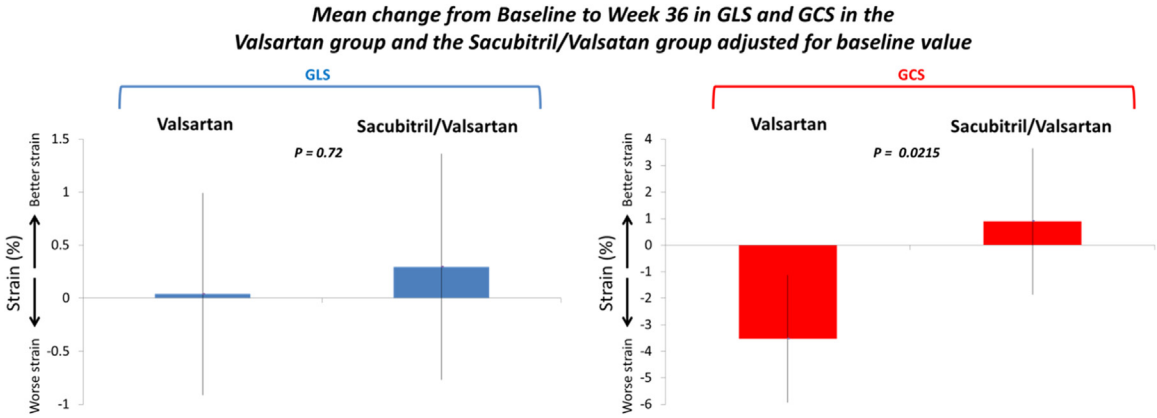

Fig. 1. Change in myocardial deformation after 36 weeks of treatment. Displaying the mean change from baseline to week 36 in GLS and GCS in the Valsartan group and the Sacubitril/Valsartan group adjusted for baseline value. Hence, a positive value indicates an increase in absolute strain from baseline to week 36, whereas a negative value indicates a decrease in absolute strain from baseline to week 36. GLS = global longitudinal strain; GCS = global circumferential strain; S/V = sacubitril/valsartan.

In patients with more impaired GCS at baseline (GCS > median of −28.1%), sacubitril/valsartan was associated with greater relative improvement than valsartan (Δ7.44%, 95% CI 12.8−2.03, $P = .008$), whereas this was not the case in patients with more preserved GCS at baseline (GCS < median) (Δ1.56%, 95% CI 7.06 to −3.95, $P = .57$). This pattern was not observed for GLS ($P > .05$ in both groups).

Sacubitril/valsartan was associated with a greater improvement in GCS when compared with valsartan, even after adjustment for the change at 36 weeks in NT-proBNP ($P = .022$), blood pressure ($P = .012$), NYHA functional class ($P = .034$), and left atrial volume index ($P = .011$). In addition, the change found in GCS was not significantly associated with neither the change in NT-proBNP ($P = .52$), blood pressure

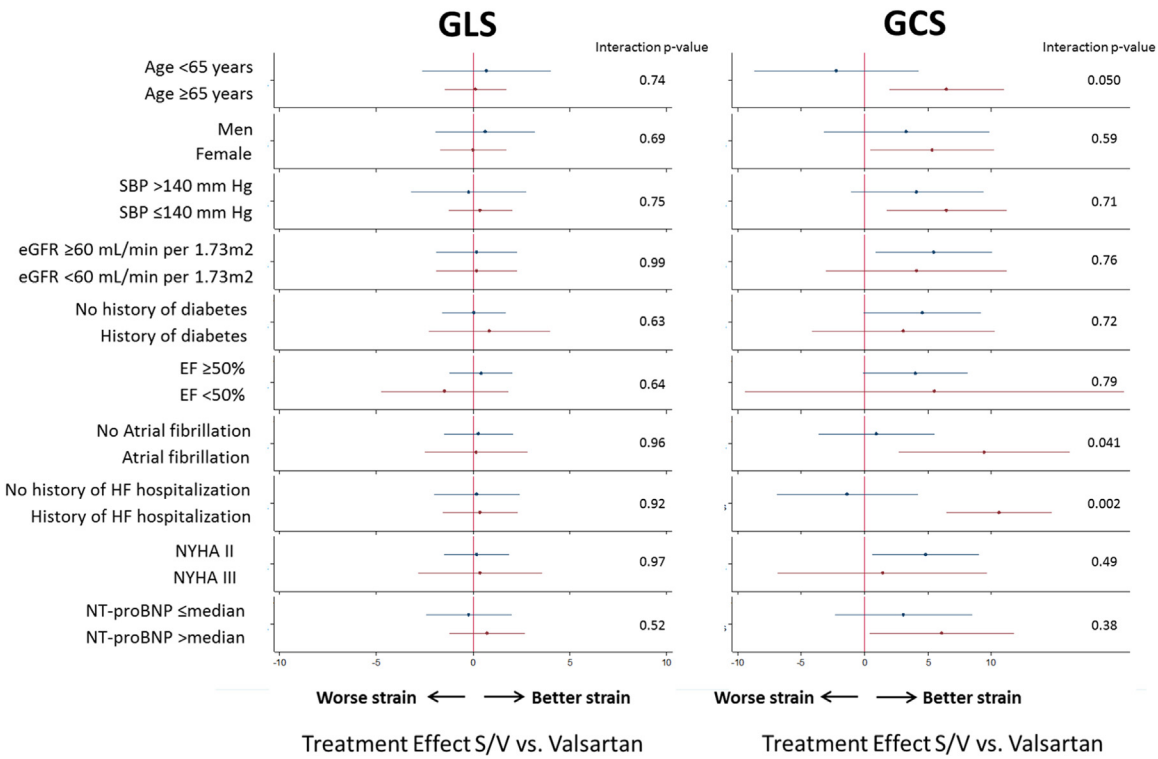

Fig. 2. Change in myocardial deformation in prespecified subgroups. Displaying the treatment effect of sacubitril/valsartan vs. Valsartan on GLS and GCS in prespecified subgroups. Hence, a positive value indicates an increase in absolute strain from baseline to week 36, whereas a negative value indicates a decrease in absolute strain from baseline to week 36. EF = ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; NYHA = New York Heart Association; SBP = systolic blood pressure. Other abbreviations as in Fig. 1.

($P = .16$), NYHA functional class ($P = .65$), or left atrial volume index ($P = .68$). There were no significant changes in LV size or LVEF, diastolic function, LV mass index, or tricuspid regurgitant velocity from baseline to 36 weeks between the treatment groups in the study population.

Discussion

In this study, we found that, in patients with HFpEF, sacubitril/valsartan improved GCS to a greater extent than did valsartan after 36 weeks of treatment. These results seemed to be independent of improvement in NT-proBNP, left atrial size, blood pressure, and NYHA functional class. In contrast, GLS was not improved by sacubitril/valsartan.

LV deformation is altered despite preserved LVEF in conditions predisposing to HF, including diabetes, hypertension, stable angina, obesity, and renal dysfunction. In participants from the general population, impaired LV deformation is associated with later development of HF.[3] These early signs of impaired LV are characterized by decreased GLS and relatively preserved GCS.[5,6]

We found a similar pattern in the present study; participants had reduced baseline GLS and less reduced GCS. The pattern of decreased longitudinal deformation and relative preserved circumferential deformation in HFpEF has been suggested as the main explanation for the observed preserved LVEF despite a failing heart.[7] This myocardial deformation pattern may be a natural cause of the anatomical distribution of myocardial fiber direction throughout the LV with longitudinal fibers formed in a left-handed helix in the subepicardium and a right-handed helix in the subendocardium and the cardiac mid-wall consisting of circumferential fibers.[6] Hence, under conditions leading to mainly subendocardial impairment, GLS will be impaired, GCS relatively preserved or augmented, and LVEF preserved.

In the present study, sacubitril/valsartan resulted in a greater absolute improvement in GCS compared with valsartan. This finding may be due to an irreversible early impairment in the vulnerable subendocardial fibers of the LV. When the subendocardial fibers are impaired, longitudinal deformation is maintained mainly by the angulated subepicardial fibers which especially contribute to circumferential deformation and a preserved LVEF.[8] Hence, decreasing the afterload and wall stress with sacubitril/valsartan may preferentially improve subepicardial fiber performance, which might explain the more pronounced effect of sacubitril/valsartan on GCS rather than GLS found in this study.

Sacubitril/valsartan has previously been demonstrated to decrease NT-proBNP, blood pressure, NYHA functional class, and left atrial volume index.[2] In the present study, we show that sacubitril/valsartan remained associated with a greater improvement in GCS than in the valsartan group even after adjustment for the changes in these previously described parameters. This finding indicates that sacubitril/valsartan might improve intrinsic myocardial performance. Interestingly, we found a trend toward a differentially greater improvement in GCS when treated with sacubitril/valsartan when compared with valsartan in patients with a history of HF hospitalization. This finding may indicate that in patients with more advanced HFpEF, sacubitril/valsartan improves GCS more than in patients with less advanced disease. This finding is in line with our observation that patients with worse GCS at baseline had the greatest effect of sacubitril/valsartan treatment. However, we cannot rule out that this finding represented the play of chance.

Several limitations of the study warrant consideration. Echocardiograms were performed at several different sites and on echocardiography machines from a variety of vendors, owing to the multicenter design of the trial. However, all analyses were performed centrally at the core laboratory using vendor-independent software. In addition, strain analysis was feasible at both baseline and week 36 in only 45% of the PARAMOUNT population because of non-DICOM imaging format, missing views, and poor image quality. The sample size is therefore small, which limited the power to assess treatment effect related to sacubitril/valsartan. The extent to which our findings are generalizable to unselected populations with a wider representation of age, race/ethnicity, and clinical characteristics is not known.

Conclusions

Sacubitril/valsartan improved global circumferential but not longitudinal strain when compared with valsartan over a 36-week period in HFpEF patients. These findings suggest that sacubitril/valsartan may improve or prevent decline in myocardial circumferential deformation in HFpEF.

Bullet points

1. Sacubitril/valsartan may improve or prevent decline in myocardial circumferential deformation in heart failure with preserved ejection fraction.
2. Our findings may indicate that sacubitril/valsartan improved the circumferential cardiac function more in patients with more advanced disease than in patients with less advanced disease.
3 Sacubitril/valsartan improved global circumferential strain but not global longitudinal strain after 36 weeks of treatment.

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Declaration of Competing Interest

T.B.S. has received speaker honorarium from Novartis; M.H.L., A.S., B.C., and E.K.-K. declare that they have no conflicts of interest. M.Z., B.P., A.V., A. S., M.P., J.J.V.M., and S.D.S. have received research support and have consulted for Novartis. M.P. has not consulted for Novartis recently. V.S. and M.L. are employees of Novartis.

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