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The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction

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Summary

Background: Major classes of medical therapy for heart failure with reduced ejection fraction (HFrEF) induce reverse remodeling. The revere remodeling response to sacubitril/valsartan remains unstudied.

Methods: We performed a single-center, prospective assessor-blinded study to determine the reverse remodeling response of sacubitril/valsartan therapy in HFrEF patients with a class I indication (New York heart Association [NYHA]-class II-IV, Left ventricular ejection fraction [LVEF] < 35%, optimal dose with Renin-Angiotensin-System-Blocker [RAS-blocker]). Doses of sacubitril/valsartan were optimized to individual tolerance. Echocardiographic images were assessed offline by 2 investigators blinded to both the clinical data and timing of echocardiograms.

Results: One-hundred-twenty-five HFrEF patients (66 ± 10 years) were prospectively included. The amount of RAS-blocker before and after switch to sacubitril/valsartan was similar(P = .290), indicating individual optimal dosing of sacubitril/valsartan. Over a median(IQR) follow-up of 118(77-160) days after initiation of sacubitril/valsartan, LVEF improved (29.6 ± 6% vs 34.8 ± 6%; P < .001) and Left ventricular end-systolic (LVESV) and end-diastolic volume (LVEDV) decreased (LVESV; 147 ± 57 mL vs 129 ± 55 mL; P < .001 and LVEDV; 206 ± 71 mL vs197 ± 72 mL; P = .027). Volumetric remodeling was associated with a reduction in the degree of mitral regurgitation (1.59 ± 1.0 vs 1.11 ± 0.8; P < .001; [scale from 0-4]). Metrics of diastolic function improved; including a drop in the E/A-wave ratio (1.75 ± 1.13 vs 1.38 ± 0.88; P = .002) and diastolic filling time (% of cycle length) prolonged (48 ± 9% vs 52 ± 1%; P = .005). The percent of patients with a restrictive mitral filling pattern dropped from 47% to 23% (P = .004). A dose-dependent effect was noted for changes in LVEF (P < .001) and LVESV (P = .031), with higher doses of sacubitril/valsartan leading to more reverse remodeling.

Conclusion: Switching therapy in eligible HFrEF patients from a RAS-blocker to sacubitril/valsartan induces beneficial reverse remodeling of both metrics of systolic as diastolic function.

KEYWORDS

echocardiography, heart failure, left ventricular ejection fraction, reverse remodeling, sacubitril/valsartan

1 | INTRODUCTION

Despite optimal medical therapy with Angiotensin Converting Enzyme Inhibitors (ACE-I) or Angiotensin Receptor Blockers (ARB), Beta-blockers and Mineralocorticoid Receptor Antagonists (MRA), many heart failure patients with reduced ejection fraction (HFrEF) exhibit a residually depressed cardiac function, paralleled by an increased risk for heart failure hospitalization and cardiovascular mortality.[1-4] Therapy with an ACE-I, ARB, beta-blocker, and MRA all induce beneficial reverse remodeling in HFrEF patients paralleled by a reduction in heart failure hospitalization and cardiovascular mortality.[5-12] In the Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, sacubitril/valsartan significantly reduced both heart failure hospitalization and cardiovascular mortality in comparison to guideline recommended doses of enalapril.[13] However, the effect of therapy with sacubitril/valsartan on cardiac function remains unknown. Indeed, it has not been studied if switching therapy from an ACE-I or ARB to sacubitril/valsartan induces incremental reverse remodeling. The current study sought out to determine the effect of sacubitril/valsartan therapy on cardiac function in patients with a current class-I indication for therapy with sacubitril/valsartan.[14]

2 | METHODS

2.1 | Study population

The study was a prospective longitudinal assessor blinded study to test the reverse remodeling response to therapy with sacubitril/valsartan. Patients were eligible for the study in accordance to the Belgian reimbursement criteria for sacubitril/valsartan, which consists of (1) symptomatic heart failure defined as New York Heart Association (NYHA) class II-IV, (2) Left ventricular ejection fraction (LVEF) below 35% measured by echocardiography, (3) pretreatment with an individual optimal dose of ACE-I or ARB for at least 4 weeks. For the latter inclusion criteria, no minimal dose (eg, at least 10 mg of enalapril equivalents) of ACE-I or ARB is defined. Exclusion criteria for the current study included; (1) concomitant initiation of a therapy known to induce reverse remodeling (eg, Cardiac Resynchronization therapy [CRT]) during study follow-up or in the previous 6 months, (2) Participation in another prospective interventional study, (3) Insufficient echocardiographic image quality to allow reliable offline assessment. Patients were initiated on a sacubitril/valsartan dose of 49/51 mg if on a dose of ACE-I or ARB of at least 50% of target dose. Elderly patients, patients on a doses of ACE-I or ARB of less than 50% of target dose, or with a history of liver or kidney insufficiency were initiated on the 24/26 mg dose. Uptitration was performed every 2 weeks if tolerated by the patient. Changes in doses of other neurohormonal blockers, such as beta-blockers and mineralocorticoid receptor antagonists, was not allowed during the study follow-up. All patients provided informed consent to participate in the study. The study was approved by the local ethical committee and is in accordance to the declaration of Helsinki.

2.2 | Data collection and follow-up

Physical examination with registration of NYHA class and echocardiographic evaluation was performed at baseline and follow-up. Comprehensive 2-dimensional echocardiography exams were performed with a commercially available system (Philips Medical Systems, iE33). Images were acquired in the left lateral decubitus position, triggered to QRS complex and digitally stored in cine loops in digital imaging and communications in medicine (DICOM) format. Analysis were performed offline by a 2 investigators (H.B. and P.M.) who were both blinded to the clinical data and timing of the echocardiographic images (not aware which images were baseline vs follow-up). All offline analyses were performed on a dedicated station using TomTec 2D measurements, image arena (TomTec Imaging Systems GMBH, Unterschleissheim, Germany). All reported echocardiography measurements were averaged from 3 consecutive cycles (or 5 if atrial fibrillation was present) and assessed as recommended by the American Society of Echocardiography.[15] Left ventricular end-diastolic (LVEDV) and end-systolic volume (LVESV) were measured from an apical 4-chamber image. Left ventricular ejection fraction was calculated using the Simpson biplane formula. Stroke volume (SV) was defined as the difference between LVEDV and LVESV. Mitral flow velocities were recorded using an apical 4-chamber image, placing a pulsed wave Doppler sample volume between the tips of mitral leaflets. E and A-wave velocities and their ratio (E/A) were recorded. Deceleration time (Dt) of the E-wave was recorded as the time interval from peak early mitral filling to an extrapolation of the deceleration to 0 m/s. A restrictive mitral filling pattern was defined as an E/A ratio above 2 or an E/A ratio above 1 with an Dt < 140 ms.[5,16] Diastolic filling time (DFT) was timed between the onset of the E-wave and termination of the A-wave. As DFT is heart rate-dependent, it was indexed (adjusted DFT) by the cycle length (time interval between the onset of 2 consecutive E-waves). Severity of mitral and tricuspid valve regurgitation was assessed in a 4-chamber image using color Doppler imaging, with a visual severity grading from 0 (absent) to 4 (severe). Right ventricular systolic pressure (RVSP) was measured from a continuous wave Doppler regurgitate tricuspid jet signal if present. To allow for maximal patient inclusion the timing of the follow-up visit was not prefixed, but coincided with the scheduled follow-up appointment, which was left at the discretion of the treating physicians. However, follow-up had to be between 6 weeks to 6 months after the dose optimization of sacubitril/valsartan, with doses being uptitrated every 2 weeks after initiation. Baseline echocardiography measurement coincided with the initiation of the starting dose of sacubitril/valsartan. All echocardiographic variables measured by the 2 independent blinded investigators were averaged and the inter-observer variability was calculated using the intraclass correlation coefficients.

2.3 | Statistical analysis

Formal power calculation predicted, in order to detect a 3% rise in LVEF with a standard deviation of 6% on the measurement and an $\alpha = .05$ with a power of 90%, that 44 patients should be enrolled. Power calculation was performed for LVEF, as this is the most studied metric of reverse remodeling in the literature of medical therapies in HFrEF. Continuous variables are expressed as mean ± standard deviation if normally distributed or median (interquartile range) if not normally distributed. Normality was checked by the Shapiro-Wilk statistic. Categorical data were expressed as numbers and percentages and compared with the Pearson χ^2-test or Fisher's exact when appropriate. Continuous variables were compared with the Student's *t* test, paired t test, ANOVA-test, Mann-Whitney U-test or Kruskal-Wallis test when appropriate. Post hoc testing for ANOVA was performed using the Bonferroni test. To assess the impact of duration of treatment exposure in relation to reverse remodeling response, changes in echocardiographic parameters were assessed using repeated measures with in between subject assessment for drug dosing and defining time of therapy as a fixed covariate. Pearson correlation was used to assess the relationship between 2 continuous (explanatory and dependent) variables. To adjust for differences in baseline characteristics between dosing intensity groups of sacubitril/valsartan and reverse remodeling, a linear regression model was built for change in LVEF and LVESV with both univariate analysis and multivariate adjustment. Statistical significance was always set at a 2-tailed probability level of < .05. Statistics were performed using SPSS version 22 (IBM, Chicago, IL).

3 | RESULTS

3.1 | Baseline population

A total of 141 patients were prospectively included between November 2016 and December 2017. However, 5 patients died and 4 patients discontinued the intake of sacubitril/valsartan before echocardiographic follow-up. Additionally 5 patients were excluded due to insufficient imaging quality and 2 patients were excluded because they underwent CRT placement during follow-up. Therefore, the final study population constituted of 125 patients. Baseline characteristics are reflected in Table 1. At the moment of the follow-up echocardiogram, 44 (35%) patients were treated with the 24/26 mg dose, 46 (37%) with the 49/51 mg dose and 35 (28%) were treated with the 97/103 mg dose of sacubitril/valsartan. Table 2 reflects changes in pivotal clinical and biochemical data from baseline to follow-up. Ninety-three (74%) patients were switched from an ACE-I after 24 hours washout period and the remaining 32 (26%) patients were directly switched from an ARB. Expressing the amount of ACE-I or ARB before initiation of sacubitril/valsartan as percent of target dose, patients were treated with 57 ± 31% of target dose.[17] The median (25^{th}-75^{th} percentile) duration of heart failure before initiation of sacubitril was 3.3 years (1.2-8.4 years) indicating sufficient time for neurohormonal blocker uptitration before initiation of sacubitril/valsartan. Calculating the dose of valsartan in sacubitril/valsartan in a similar way, patients were treated with 53 ± 30% of target dose at the time of echocardiographic follow-up. Thus the dose of Renin-Angiotensin-Blocking

TABLE 1 Baseline characteristics

Variable	Total population (n = 125)
Demographics	
Age, y	66 ± 10
Male	101 (81%)
Active smoker	33 (26%)
Duration of heart failure, y	3.3 (1.2-8.2)
Heart failure etiology	
Ischemic	69 (55%)
Nonischemic	56 (45%)
Physical features	
Systolic blood pressure, mm Hg	121 ± 20
Diastolic blood pressure, mm Hg	69 ± 12
Weight, Kg	81 ± 14
BMI, kg/m²	27 (25-30)
Heart rate, beats/min	70 ± 15
Comorbidities	
Atrial fibrillation	49 (40%)
COPD	16 (13%)
Hypertension	76 (61%)
Dyslipidemia	68 (54%)
Diabetes	32 (26%)
History valve surgery	26 (21%)
Laboratory analysis	
Sodium, mmol/L	139 ± 3
Potassium, mmol/L	4.4 ± 0.5
Hemoglobine, g/dL	13.9 ± 1.7
Serum Creatinine, mg/dL	1.3 ± 0.4
NYHA class	
Class II	74 (60%)
Class III	49 (39%)
Class IV	1 (1%)
Electrocardiogram feature	
QRS duration, ms	130 ± 33
PR-duration, ms	171 ± 43
Guideline directed heart failure therapy	
ACE-I or ARB	125 (100%)
Beta-blocker	119 (95%)
Aldosterone antagonist	102 (82%)
Loop diuretic	74 (59%)
CRT	70 (56%)
ICD	70 (56%)

TABLE 2 Changes in pivotal clinical and biochemical parameters from baseline to follow-up

Parameter	(N) patients	Baseline value	Follow-up value	Mean difference	*P*-value
Systolic BP, mm Hg	125	121 ± 19	116 ± 17	−5	**.014**
Diastolic BP, mm Hg	125	69 ± 11	67 ± 11	−2	.058
Heart rate, bpm	125	71 ± 11	67 ± 11	−3	**.011**
Weight, kg	125	82 ± 17	82 ± 17	0	.437
Potassium, meq/L	71	4.4 ± 0.5	4.5 ± 0.5	+0.1	.288
Sodium, meq/L	71	139 ± 3	139 ± 3	0	.619
Creatinine, mg/dL	71	1.34 ± 0.45	1.43 ± 0.55	+0.11	.051

Bold indicates significant *P*-values.

agent was similar before and after initiation of sacubitril/valsartan (*P* = .290), indicating optimal uptitration of sacubitril/valsartan to an individual tolerable dose. At follow-up 39 (32.5%) patients reported an improvement of NYHA-class, 75 (62.5%) patients reported no change and 6 (5.0%) patients reported worsening of their functional status NYHA-class. Systolic blood pressure dropped on average 7.4 mm Hg at follow-up.

3.2 | Reverse remodeling response

All 125 patients had baseline and follow-up echocardiographic evaluation available for paired analysis. The median (IQR) time to follow-up at which echocardiographic reverse remodeling was measured was 118 (77-160) days. The baseline and follow-up echocardiographic analysis are reflected in Table 3. Some patients had a baseline LVEF just above 35%, during offline analysis (LVEF 29.6 ± 5.9%), however this is common given the inter-observer variability when calculating a LVEF using Simpson method. Following the initiation of sacubitril/valsartan, patients exhibited a significant drop in LVESV and LVEDV, resulting in an augmented LVEF and SV. This improvement in systolic function and volumetric remodeling was associated with a reduction in visually graded mitral valve regurgitation.

In addition, metrics of diastolic function improved. As illustrated by the reduction in E and A-wave velocity and the reduction in the E/A-wave ratio. The A-wave could not be assessed in 29 patients as they were in atrial fibrillation. Furthermore, the cycle length adjusted diastolic filling time improved significantly, indicative of a reduction of the isovolumetric relaxation and isovolumetric contraction time. Figure 1 illustrates the proportion of patients with a restrictive mitral valve filling pattern before and after initiation of sacubitril/valsartan indicating significant improvement in diastolic function/cardiac filling pressures. A trend toward reduction in RVSP was noted. RVSP could be measured in 43 patients as they did not have tricuspid regurgitation.

Figure 2 depicts the dose-dependent impact of sacubitril/valsartan therapy on left ventricular reverse remodeling (change in LVEF and LVESV). Higher dosages were significantly associated with higher degrees of left ventricular reverse remodeling. Patients treated with a higher dose (97/103 mg) tended to be more often female and more often had a nonischemic etiology of heart failure. As these factors are associated with more reverse remodeling in both CRT literature as in literature regarding heart failure with recovered ejection fraction, multivariate adjustment was performed for these covariates.[18] After adjustment a higher drug-dose independently predicted more improvement in LVEF (*P* = .001) and more reduction

TABLE 3 Echocardiographic changes following initiation of sacubitril/valsartan

Echocardiographic parameter	(N) patients	Baseline value	Follow-up value	Mean difference	*P*-value
LVEDV (mL)	125	206 ± 71	197 ± 72	−10.2	**.027**
LVESV (mL)	125	147 ± 57	129 ± 55	−18.4	**<.001**
LVEF (%)	125	29.6 ± 5.9	34.8 ± 6.2	5.2	**<.001**
SV(mL)	125	59.5 ± 24	67.7 ± 29	8.2	**.004**
E (ms)	125	84.4 ± 36	79.0 ± 29	−5.4	**.033**
A (ms)	96	60.1 ± 27.7	66.6 ± 27	6.5	**.026**
E/A	96	1.75 ± 1.13	1.38 ± 0.88	−0.374	**.002**
Dt (ms)	125	202.5	198.4	−4.1	.879
aDFT (% cycle length)	125	48 ± 9	52 ± 1	4.0	**.005**
RVSP (mm Hg)	82	38.7 ± 14	34.0 ± 16	−4.79	.054
MI (grade 1-4)	125	1.59 ± 1.0	1.11 ± 0.8	−0.48	**<.001**
TI (grade 1-4)	125	1.22 ± 0.9	1.00 ± 0.74	−0.22	**.015**

Bold indicates significant *P*-values.

in LVESV (P = .001). In a repeated measure analysis of change in LVEF with treatment dose and treatment duration as fixed covariates, there was also a trend toward more improvement in LVEF in patients treated for a longer duration (P = .053).

Finally, the table S1 illustrates the relationship between changes in NYHA class and echocardiographic parameters, indicating that both improvement in metrics of systolic as well as diastolic function and pulmonary pressures were associated with functional status improvement after the initiation of sacubitril/valsartan. The average inter-observer variability using interclass coefficients was 0.9.

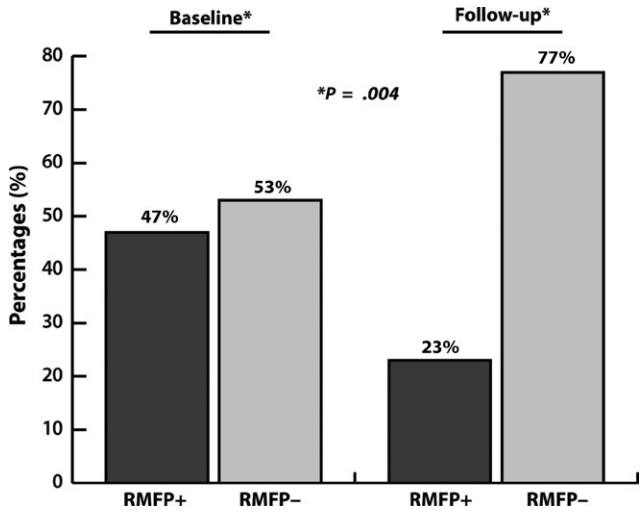

FIGURE 1 Changes in prevalence of restrictive mitral filling pattern. RFMP denotes restrictive mitral filling pattern

4 | DISCUSSION

The current analysis determines the effect of sacubitril/valsartan therapy on cardiac structure in HFrEF patients previously treated with a maximum tolerated dose of ACE-I or ARB. Our main findings indicate that switching to sacubitril/valsartan induces incremental reverse remodeling, affecting both metrics of systolic as diastolic function. Additionally, this reverse remodeling effect was dose-dependent. Both improvements in metrics of systolic and diastolic function were associated with functional improvement.

Pharmacotherapy remains the cornerstone of therapy for patients with HFrEF. Major drug classes including ACE-I, ARB, beta-blockers, and MRAs have significantly reduced morbidity and mortality in these patients.[1-4] Strikingly, these medical therapies all have the potential to induce beneficial reverse remodeling.[18] Indeed, ACE-I and ARBs improve LVEF between 1%-4%,[8,9,12] beta-blockers improve LVEF between 4%-12%[6,7,10,11] and MRAs generally improve LVEF by another 4%.[5,19] Our study now reports on the reverse remodeling response to therapy with sacubitril/valsartan. Importantly, an incremental improvement of 5% in LVEF was noticed after switching therapy from 1 Class I therapy (ACE-I or ARB) to another Class I therapy (sacubitril/valsartan).

By initiating sacubitril/valsartan not only the Renin-Angiotensin-Aldosteron system (RAAS) is suppressed, but also the natriuretic peptide system is being modulated. Sacubitril is the prodrug of the active metabolite sacubitrilat, which inhibits neprilysin.[20] Neprilysin degrades several small bio-active peptides including A-type natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). The resulting increase in natriuretic peptides counter-regulates the detrimental effects of RAAS activation (such as water and sodium retention and vasoconstriction).[21]

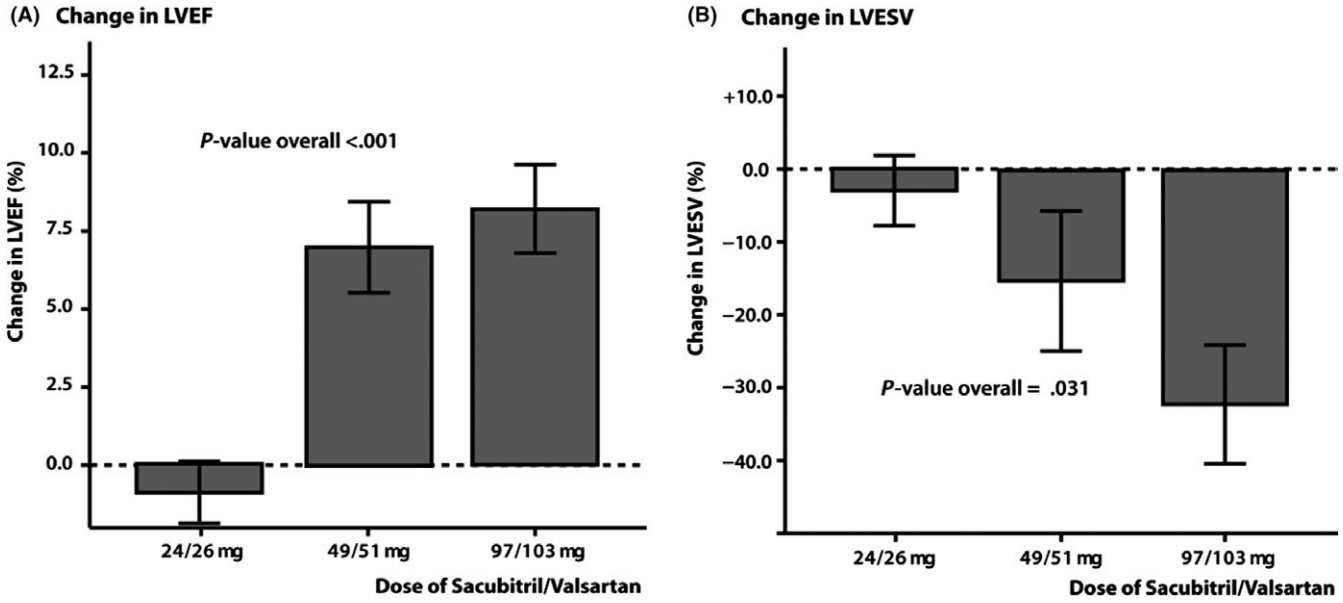

FIGURE 2 Reverse remodeling according to dosing strata. Bars and error bars indicate mean changes ± standard error mean. LVEF denotes left ventricular ejection fraction and LVESV denotes Left ventricular end systolic volume. P-values in figure indicate general P-value of ANOVA-test

In sheep with induced heart failure neprilysin inhibition improves vasodilatory response and natriuresis and diuresis.[22] Furthermore, in mice with myocardial infarction induced heart failure, neprilysin inhibition combined with valsartan resulted in less fibrosis and hypertrophy in comparison to valsartan alone.[23] This resulted in less dilation of LVESV, a more preserved LVEF and a reduction in the A-wave velocity.[23] Mechanistically, sacubitril is implicated in attenuating cardiomyocyte cell death, hypertrophy and impaired myocyte contractility.[24] Based on these preclinical and mechanistic evaluations of sacubitril, the incremental beneficial effect on systolic and diastolic function might seem more straightforward.

As with other heart failure therapies, the impact of sacubitril/valsartan on systolic function is most noted on the change in LVESV.[5,8,10,11] After initiation of an ACE-I, ARB, beta-blocker, or MRA the LVESV often drops more than the LVEDV, resulting in an improved LVEF and SV. We found a similar occurrence for sacubitril/valsartan. It is unclear if this is a result of the cellular effects of neprilysin inhibition or is a mere reflection of hemodynamic changes. It is well known that the failing heart is afterload sensitive, although this might be more clinically relevant during episodes of acute heart failure. As in PARADIGM-HF, our patients exhibited a lower systolic blood pressure following initiation of sacubitril/valsartan.[13] This allows the heart to operate at an improved more steeper Frank-Starling relationship. Furthermore, as other changes in HF therapy were not allowed in our study, the natriuretic and diuretic effects of sacubitril/valsartan could reduce cardiac preload. A reduction in preload allows the failing heart to move away from the flat part of the Frank-Starling curve, hereby beneficially influencing stroke volume. Similarly to MRAs (which also strongly act on the kidney and cardiac fibrosis), sacubitril/valsartan therapy resulted in less patients with a restrictive mitral filling pattern.[5] Additionally, the diastolic filling time improved. Although we did not directly measure the duration of isovolumetric relaxation or isovolumetric contraction, it is conceivable that a reduction in these time intervals (as a reflection of improved systolic and diastolic function) contributes to the longer diastolic filling time. Additionally, we corrected the diastolic filling time for heart rate, excluding a longer diastolic filling time secondary to a slower heart rate. Interestingly, both metrics of systolic and diastolic improvement associated with functional improvement. This might underscore the potential of sacubitril/valsartan therapy in heart failure with preserved ejection fraction (as being studied in the ongoing PARAGON-HF study).

To add further biologic credence to the reverse remodeling effect of sacubitril/valsartan we noted a dose-dependent effect. A similar dose response effect has been noted for other heart failure therapies.[5] It is important to note that patients before initiation were not treated with lower doses of RAS-blockers and given the long duration of heart failure before initiation of sacubitril/valsartan, therapies should be deemed as optimized. Indeed, the dose valsartan after initiation of sacubitril/valsartan was equipotential to the preinitiation dose of ACE-I or ARB. Altogether, our study reliably documents the incremental reverse remodeling potential of sacubitril/valsartan therapy. Additionally, longer treatment with sacubitril/valsartan was associated with a trend toward more reverse remodeling ($P = .053$). This might suggest that our analysis under-estimates the true reverse remodeling response, which could be even higher with longer follow-up.

Just as in the PARADIGM-HF trial, the proportion of women in our cohort was low. This might be due to several reasons, for instance initiation of sacubitril/valsartan requires a reduced LVEF and toleration of a substantial dose of ACE-I or ARB, which might be more likely to occur in men.[25] Additionally, it is well known that women tend to exhibit a more pronounced reverse remodeling response following initiation of heart failure therapies including pharmacotherapy or CRT.[18]

Although cardiologists should be convinced about the compelling benefit of sacubitril/valsartan based on the results of the PARADIGM-HF trial, prescription of sacubitril/valsartan remains rather low.[26,27] The underappreciation of the residual risk for morbidity and mortality in the ostensibly stable heart failure patient, the practical hurdles to prescribe and uptitrate of the drug, and perceived incremental costs might all explain the low prescription rate.[26,27] However, the recognition of an incremental reverse remodeling response to such an effective class-I lifesaving therapy might help to convince more cardiologists about the drug potential.

4.1 | Limitations

Several limitations should be addressed. First, this study was not randomized. Double blind randomized controlled trials remain the gold standard to determine the incremental effect of 1 therapy vs another. However, prospective longitudinal studies with multiple blinded assessors are a well-accepted design to evaluate echocardiographic changes. Second, for some analysis such as changes in RVSP or study might have been underpowered, as the power calculation was performed for changes in LVEF predominantly. Nevertheless, we demonstrated a clear impact on changes in LVEF (and LVESV), which have been used as the preference metric in previous studies assessing the impact of pharmacotherapy on reverse remodeling. Third, by design we chose not to evaluate reverse remodeling at a predefined time interval, to allow for easy recruitment during scheduled follow-ups. Finally, we parameters of systolic and diastolic function, which have been previously validated in studies with ACE-I, ARB, beta-blockers, and MRAs. However, many more informative echocardiographic assessments can be performed such as atrial volumes, strain analysis, and tissue Doppler imaging. In addition, for volumetric analysis the diagnostic acuity of 3D-echocardiography or magnetic resonance imaging might trump classic 2D-echocardiographic assessment. Nevertheless, by selection of symptomatic HFrEF patients with a LVEF < 35%, many patients will have implantable cardiac devices hampering optimal imaging acquisition for magnetic resonance imaging.

5 | CONCLUSION

In heart failure patients with reduced ejection fraction on optimal medical therapy who remain symptomatic, switching from an ACE-I or

ARB to sacubitril/valsartan induces beneficial cardiac reverse remodeling. Both metrics of systolic and diastolic function improve in a dose-dependent relationship following initiation of sacubitril/valsartan.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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

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