ORIGINAL ARTICLE

Sacubitril/valsartan affects pulmonary arterial pressure in heart failure with preserved ejection fraction and pulmonary hypertension

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Abstract

Aims   Prior studies have not fully characterized the haemodynamic effects of the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan in heart failure with preserved ejection fraction and pulmonary hypertension (HFpEF–PH). The aim of the Treatment of PH With Angiotensin II Receptor Blocker and Neprilysin Inhibitor in HFpEF Patients With CardioMEMS Device (ARNIMEMS-HFpEF) study is to assess pulmonary artery pressure (PAP) dynamics by means of implanted PAP monitors in patients with HFpEF–PH treated with sacubitril/valsartan.

Methods and results   This single-arm, investigator-initiated, interventional study included 14 consecutive ambulatory symptomatic HFpEF–PH patients who underwent CardioMEMS implantation prior to enrolment [mean ejection fraction 60.4 ± 7.2%, baseline mean PAP (mPAP) 33.9 ± 7.6 mmHg]. Daily PAP values were examined during three periods: a 6 week period after CardioMEMS implantation and before sacubitril/valsartan treatment (pre-ARNI), a 6 week period with sacubitril/valsartan treatment (ARNI ON), and a 6 week period of sacubitril/valsartan withdrawal (ARNI OFF). The primary endpoint was change in mPAP with and without sacubitril/valsartan. Secondary endpoints included changes in 6 min walking distance, B-line sum in lung ultrasound, and quality of life (QoL). During the study period, 1717 mPAP measurements were recorded. Between pre-ARNI vs. ARNI ON, mPAP significantly declined by −4.99 mmHg [95% confidence interval (CI) −5.55 to −4.43]. Between ARNI ON vs. ARNI OFF, mPAP significantly increased by +2.84 mmHg [95% CI +2.26 to +3.42]. Between pre-ARNI vs. ARNI ON, we found an improvement in 6 min walking distance, B-lines, and QoL. Mean loop diuretic management did not differ between periods.

Conclusions   Sacubitril/valsartan significantly reduced mPAP in patients with HFpEF–PH, independent of loop diuretic management, together with improvement in functional capacity, lung congestion, and QoL. Sacubitril/valsartan may be a therapeutic alternative in HFpEF–PH.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a highly prevalent syndrome affecting approximately one-half of patients with heart failure (HF). The estimation of the prevalence of pulmonary hypertension (PH) in HF is difficult because a reliable diagnosis of PH by echocardiography is not possible in cross-section studies, and all invasive studies suffer from a very substantial referral bias because the indication for right heart catheterization in these patients most likely was based on evidence of PH in the echocardiogram.[1] Using a non-invasive PH definition, up to 80% of patients with HFpEF develop PH. Patients with HFpEF and PH (HFpEF–PH) have worse quality of life (QoL) and increased mortality than HFpEF patients without PH.[2]

Attempts to treat PH in HFpEF–PH have resulted in a succession of failures, despite approaching this problem from different pathobiological angles. The endothelin receptor antagonist bosentan, which is effective in pulmonary arterial hypertension, has failed in HFpEF–PH.[3] The potent phosphodiesterase type 5 inhibitor sildenafil increases cyclic guanosine monophosphate (cGMP) levels, causing endogenous nitric oxide-mediated vasodilatation in both systemic and pulmonary vasculature. Despite the initial positive trial in the field reported by Guazzi et al.,[4] other attempts have failed to show a reduction in pulmonary artery pressure (PAP) or improvement in other haemodynamic parameters in HFpEF–PH.[5,6] Increased cGMP levels by oral soluble guanylate cyclase stimulators also increase cGMP levels but do not affect PAP, pulmonary vascular resistance, or transpulmonary pressure gradient.[7] Lastly, direct NO donors were examined in the INDIE-HFpEF (Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trial but resulted in no benefit in terms of exercise capacity, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, New York Heart Association (NYHA) functional class, diastolic function, or N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.[8]

The angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan (Sac/Val) is a particulate guanylyl cyclase activator that increases natriuretic peptides, which signal through cGMP and exert potent antimitogenic and vasodilatory effects. Evidence regarding the effects of Sac/Val on PH is mainly limited to experimental research. In a well-characterized rat model of PH, 6 weeks of Sac/Val treatment led to PH reduction associated with decreased pulmonary vascular remodelling.[9]

Clinical evidence regarding Sac/Val in HFpEF has been derived from the PARAGON-HF trial, which included patients with HF and an ejection fraction (EF) $\geq$ 45%. The primary endpoint fell just short of showing a statistically significant reduction in HF-related hospitalizations and deaths ($P = 0.06$).[10] No PH subanalyses were performed, yet the results suggested heterogeneity, with a possible benefit of Sac/Val in patients with EF below the median ($<57\%$) and among women. The FDA has recently approved the use of Sac/Val for patients with HFpEF and a below-normal left ventricular ejection fraction (LVEF).[11]

There is paucity of data regarding the haemodynamic effects of Sac/Val on PH in patients with HFpEF–PH. Recently, Burgdorf et al. described a significant reduction of PAP after transition to Sac/Val in a retrospective case series of 18 patients with HFpEF and PH assessed during right heart catheterization.[12] In contrast, we conducted the ARNIMEMS-HFpEF prospective study (Treatment of PH With Angiotensin II Receptor Blocker and Neprilysin Inhibitor in HFpEF Patients With CardioMEMS Device; NCT04753112) to assess the effects of maximum tolerated doses of Sac/Val on PAP dynamics measured using an implanted PAP monitoring device.

Methods

Study design

The ARNIMEMS-HFpEF study is a non-randomized, single-arm, investigator-initiated, interventional trial that enrolled consecutive ambulatory patients with symptomatic HFpEF and an implanted haemodynamic monitor (CardioMEMS device) for longitudinal PAP monitoring. Patients were instructed to upload their PAP data daily, and their adherence to daily PAP uploads and PAP data was visible to site staff. Investigators evaluated PAP twice weekly and guided case management based on the average diastolic PAP over the previous 3–4 days.

In the present study, we examined daily PAP values during three periods: a 6 week period after CardioMEMS implantation and before Sac/Val treatment (pre-ARNI), a 6 week period following initiation of Sac/Val treatment (ARNI ON), and a 6 week period following Sac/Val withdrawal (ARNI OFF). During the pre-ARNI period (Weeks −6 to 0), baseline treatment was maintained and adjusted according to mean PAP (mPAP). Diuretics, beta-blockers, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blockers (ARB), and/or mineralocorticoid-receptor antagonists were used based on systemic blood pressure (BP), heart rate, and right heart catheterization data. During the ARNI ON period (Weeks 1–6), Sac/Val was initiated, replacing ACEI/ARB when necessary, and was then up-titrated every 2 weeks to the maximum tolerated dose. During the ARNI OFF period (Weeks 7–12), Sac/Val was withdrawn, and baseline therapy was restarted and maintained until the end-of-study visit.

Pre-specified scheduled visits occurred at baseline (Week −6) and at Weeks 0, 2, 4, 6, and 12. All visits included clinical assessment. The visits at baseline and at 0, 6, and 12 weeks included the 6 min walking test (6MWT), KCCQ-12, European

Quality of Life-Visual Analog Scale (EQ-VAS), echocardiography, and a lung ultrasound (LUS) exam.

Patient selection

From October 2020 to May 2021, we enrolled patients with HFpEF–PH. The inclusion criteria were as follows: (i) male or female patients ≥18 years of age, and exhibiting NYHA Class II–III HFpEF with LVEF > 45% (measured within the past year, excluding patients with improved EF); (ii) NT-proBNP of >200 pg/mL in cases with HF-related hospitalization in the previous 9 months, or >300 pg/mL in cases without previous HF hospitalization, or three times these values in patients with atrial fibrillation; (iii) implantation of the CardioMEMS HF System, with the patient regularly transmitting information and system functioning appropriately; (iv) average mPAP > 20 mmHg during the 7 days prior to enrolment, including at least five daily measurements[13]; (v) systolic BP (SBP) > 100 mmHg at most recent clinical assessment; and (vi) stable ambulatory patients not requiring a change in diuretics or other HF drugs during the last week.

The exclusion criteria were as follows: (i) estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, as measured by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI); (ii) Sac/Val treatment within the past 30 days; (iii) history of hypersensitivity, intolerance, or angioedema upon previous treatment with renin-angiotensin system (RAS) blocker, ACEI, ARB, or Sac/Val; (iv) serum potassium > 5.4 mmol/L; (v) acute coronary syndrome, stroke, transient ischaemic attack, cardiovascular surgery, PCI, or carotid angioplasty within the preceding 3 months; (vi) coronary or carotid artery disease likely to require surgical or percutaneous intervention within 3 months after trial entry; (vii) dyspnoea primarily caused by a non-cardiac condition(s); (viii) documented untreated ventricular arrhythmia with syncopal episodes within the prior 3 months; (ix) symptomatic bradycardia or second-degree or third-degree heart block without a pacemaker; (x) hepatic dysfunction, evidenced by total bilirubin > 3 mg/dL; or (xi) pregnancy or breastfeeding.

Study endpoints

The primary endpoint was the change of mPAP with Sac/Val (ARNI ON) compared with the pre-ARNI and ARNI OFF periods. For analysis of this primary endpoint, we calculated that a sample size of 14 participants was required, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided contrast, to detect an mPAP difference of ≥4 mmHg, assuming a standard deviation (SD) of 5 mmHg and 10% loss to follow-up.

Secondary endpoints included changes in systolic and diastolic PAP, mPAP change at Day 7 after Sac/Val initiation, change in daily diuretic dose, and changes in 6MWT, B-line sum in LUS, QoL (measured using the KCCQ-12 and EQ-VAS questionnaires), biomarkers [NT-proBNP, cancer antigen 125 (CA-125), ST2, and high-sensitivity troponin T (hs-TnT)], and echocardiographic parameters (E/eʹ and left atrium diameter index).

The investigators reported all adverse events (AEs). Pre-specified AEs of interest included decline in renal function (≥50% decrease in the eGFR, development of end-stage renal disease, or death due to renal failure), hypotension (SBP < 100 mmHg), hyperkalaemia (>5.5 mmol/L), and angioedema.

The study was approved by the Spanish Agency of Medicines and Medical Devices (AEMPS) and the local institutional review board (AC-20-066-HGT-CEIM). All patients provided signed informed consent. The study was monitored by an independent committee and performed in accordance with the Declaration of Helsinki and local and national regulations.

Lung ultrasound exams

Lung ultrasound examination was performed by an experienced investigator, blinded to clinical status and visit data. Patients were in a semi-supine position during the exam, and 28 areas were examined, as established by a previous expert panel.[14] LUS was performed using a phased-array transducer, perpendicular to the ribs, with an imaging depth of 14 cm. Clip videos of 6 s were recorded. The same investigator analysed the LUS images offline and recorded the number of B-lines in the sagittal scan of every thoracic area. A B-line was defined as a discrete laser-like vertical hyperechoic reverberation artefact that arises from the pleural line, extends to the bottom of the screen without fading, and moves synchronously with lung sliding. The presence of 10 B-lines was considered to indicate pleural effusion. The main analyses were performed using the sum of B-lines across the 28 lung zones. One patient was excluded due to a previous diagnosis of pulmonary fibrosis.

Blood tests

N-terminal pro-brain natriuretic peptide and hs-TnT levels were determined by electrochemiluminescence immunoassays using a Cobas E601 platform (Roche Diagnostics, Switzerland). Interleukin 1 receptor-like 1 (ST2) was measured based on immunoturbidimetry using the SEQUENT-IA reagent kit (Critical Diagnostics, Ireland), on an AU-5800 platform (Bekman Coulter, Ireland). CA-125 was measured using the ARCHITECT CA-125 II chemiluminescent microparticle

immunoassay (CMIA), on the ARCHITECT *i* System (Abbott Laboratories).

Statistical analysis

Categorical variables were expressed as absolute numbers and percentages. Continuous variables were expressed as the mean ± SD or median (quartile Q1 to Q3), depending on the assumption of the normality distribution criteria, assessed by means of normality Q–Q plots. For the primary endpoint, data were plotted using the ggplot2 package,[15] and a local polynomial regression (loess) was fitted.

Table 1 Baseline characteristics

Age in years, median [IQR]	79 [72–84]
Female sex, *n* (%)	11 (78.6)
Medical history, *n* (%)	
Hypertension	12 (85.7)
Hyperlipidaemia	11 (78.6)
Diabetes	4 (28.6)
Smoking	2 (14.3)
Atrial fibrillation or flutter	10 (71.4)
Stroke	2 (14.3)
CKD	5 (35.7)
COPD	1 (7.1)
Hospitalization for heart failure	9 (64.3)
Myocardial infarction	1 (7.1)
Body mass index, kg/m^2	30.7 ± 4.2
Clinical features of heart failure	
Aetiology, *n* (%)	
Hypertensive cardiomyopathy	8 (57.1)
Valvular heart disease	4 (28.6)
Ischaemic	1 (7.1)
Amyloidosis	1 (7.1)
Left ventricular ejection fraction, %	60.4 ± 7.2
Systolic blood pressure, mmHg	143 ± 14
Diastolic blood pressure, mmHg	77 ± 9
Heart rate, beats/min	73 ± 16
NT-proBNP, ng/L	1506 ± 680
NYHA functional class, *n* (%)	
II	1 (7.1)
III	13 (92.9)
Baseline treatment, *n* (%)	
Loop diuretic	14 (100)
Other diuretic	1 (7.1)
ACE inhibitor or ARB	11 (78.6)
Mineralocorticoid-receptor antagonist	9 (64.3)
Beta-blocker	7 (50)
Hydralazine	4 (28.6)
Cardiac catheterization data	
Right atrial pressure, mmHg	6.9 ± 3.8
Mean pulmonary artery pressure, mmHg	33.9 ± 7.6
Mean wedge pulmonary pressure, mmHg	16.1 ± 7.0
Cardiac index, L/min/m^2	2.6 ± 0.3
Mean transpulmonary pressure gradient, mmHg	17.8 ± 7.1
Diastolic transpulmonary pressure gradient, mmHg	5.8 ± 7.4
Pulmonary vascular resistance, Wood units	4.0 ± 1.6

Note: Values are shown as mean ± standard deviation, *n* (%), or median [interquartile range].
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NYHA, New York Heart Association.

Comparison was performed using linear mixed-effects models, with the *lmer* function of the lme4 package.[16] Multiple comparisons were corrected using the *glht* function of the multcomp package.[17] Comparisons for secondary endpoints were performed using Student's *t*-test for paired data or the Wilcoxon test depending on whether the data distribution was assumed normal or non-normal. Categorical variables were compared using χ^2, Fisher's exact tests, or the McNemar test, as appropriate.

Quality of life assessments were compared using the obtained data as continuous variables and also based on the proportion of patients showing an improvement of ≥5 points on the KCCQ-12 score (clinically meaningful change) with Sac/Val treatment. We recorded the average loop diuretic dose (in daily furosemide equivalents) at each follow-up visit at which concomitant medications were collected (Weeks −6, 0, 2, 4, 6, and 12) and recorded the average Sac/Val dose at Weeks 0, 2, 4, and 6. Because there were a very small number of HF hospitalizations or urgent HF visits, we described these using only descriptive statistics. Safety outcomes were assessed with descriptive statistics only.

Statistical analyses were performed using SPSS 24 (SPSS Inc., Chicago, Illinois) and R (A language and environment for statistical computing. Version 4.1.0.; R Foundation for Statistical Computing, Vienna, Austria). When available, a two-sided *P*-value of <0.05 was considered significant. When a *P*-value was not available, 95% upper and lower confidence interval (CI) limits were considered to indicate statistical significance if they did not cross zero.

Results

From October 25, 2020, through May 5, 2021, 15 patients received an implanted PAP haemodynamic monitor (CardioMEMS device) and were considered for inclusion in this study. One patient died due to COVID-19 before starting Sac/Val treatment, and thus, 14 patients were finally included in the study. *Table 1* presents the demographic and clinical characteristics and treatment before Sac/Val initiation. During the study period, 1717 PAP measurements were recorded (per patient: mean 122.6 ± 7.8, minimum 96, maximum 128).

Primary endpoint

We observed statistically significant differences between study periods in mPAP longitudinal dynamics. Between the pre-ARNI vs. ARNI ON periods, mPAP significantly declined by −4.99 mmHg [95% CI −5.55 to −4.43]. Between the ARNI ON vs. ARNI OFF periods, mPAP significantly increased by +2.84 mmHg [95% CI +2.26 to +3.42]. *Figure 1* depicts the Loess curve of longitudinal mPAP measurements, showing a smooth U-shaped morphology of the mPAP changes through-

Figure 1 Loess curve of mean PAP measurements through the study. Smooth blue line displays mean PAP. Shaded regions around the blue line represent the 95% confidence interval. Weeks −6 to 0: pre-ARNI treatment after CardioMEMS implantation. Weeks 0 to 6: ARNI ON period. Weeks 6 to 12: ARNI OFF period. ARNI, angiotensin receptor-neprilysin inhibitor; PAP, pulmonary artery pressure.
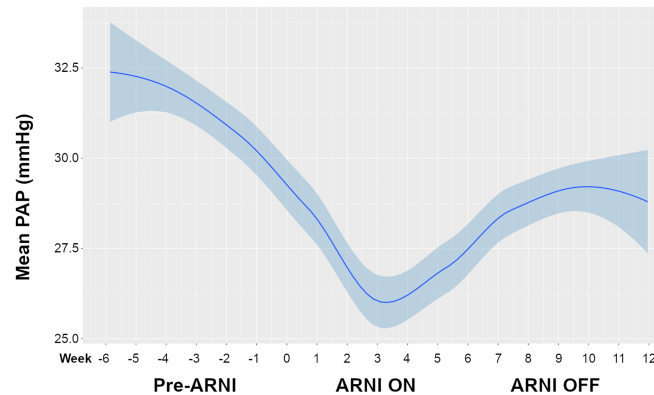

out the study. Supporting Information, *Figure S1* shows a similar morphology when assessing pulmonary artery pulse pressure. As a single measurement, the change in mPAP from the day before starting Sac/Val to Day 7 of treatment showed a decline of −4.14 ± 5.7 mmHg ($P = 0.019$) (*Figure 2*). In a binomial logistic regression, we did not find any relationship between ARNI responders and age, sex, NT-proBNP, pulmonary artery pulse pressure, and LVEF, although LVEF was significantly lower in responders (56 ± 5.5% vs. 65 ± 5.9%, $P = 0.013$).

Table 2 shows the weekly mPAP dynamics relative to the pre-ARNI, ARNI ON, and ARNI OFF periods. During pre-ARNI,

we observed a non-significant mPAP reduction following CardioMEMS implantation. During ARNI ON, we detected a significant mPAP decline during all weeks of the treatment period. After Sac/Val withdrawal (ARNI OFF), we observed an increase of mPAP, which was statistically significant during the first weeks after withdrawal.

Daily mPAP analyses revealed a slight downward trend during the pre-ARNI period, observed from CardioMEMS implantation to Sac/Val initiation, with an estimated daily mPAP change of −0.018 mmHg [95% CI −0.052 to +0.015]. During ARNI ON, we observed a sharp and significant mPAP decline, with an estimated daily mPAP change of −0.153 mmHg [95%

Figure 2 Changes in mPAP at the seventh day of treatment. Black lines represent changes in individual patient measurements (solid for patients with a drop ≥4 mmHg in mPAP). Red squared boxes represent mean values, and red upright lines standard deviation. Solid red line represents mean changes. ARNI, angiotensin receptor-neprilysin inhibitor; mPAP, mean pulmonary artery pressure.
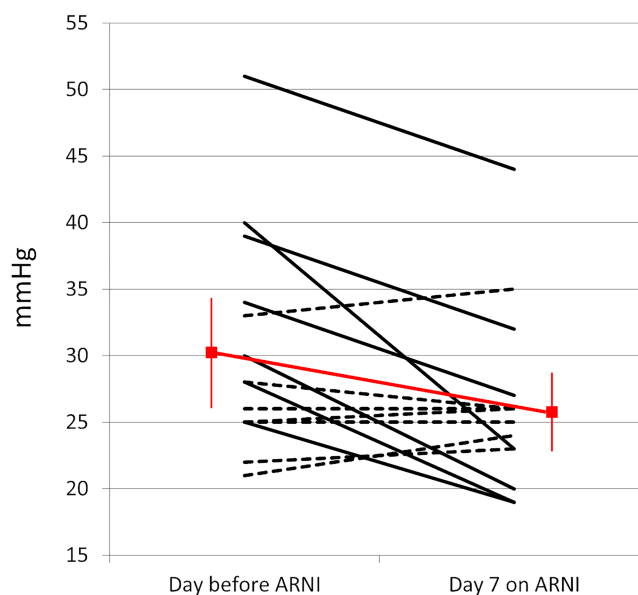
Table 2 Mean pulmonary artery pressure weekly changes before, during, and after treatment with sacubitril/valsartan

Phase	Weeks	Estimate	95% CI	
Pre-ARNI	−6 vs. −1	−0.941	−2.66 to 0.78	
ARNI ON	−1 vs. 0	−3.93	−5.60 to −2.26	*
	−1 vs. 1	−5.15	−6.79 to −3.51	*
	−1 vs. 2	−5.56	−7.21 to −3.90	*
	−1 vs. 3	−5.62	−7.26 to −3.97	*
	−1 vs. 4	−6.55	−8.21 to −4.90	*
	−1 vs. 5	−5.72	−7.37 to −4.07	*
	−1 vs. 6	−3.86	−5.51 to −2.21	*
ARNI OFF	6 vs. 7	+2.16	+0.53 to +3.79	*
	6 vs. 8	+2.62	+0.99 to +4.25	*
	6 vs. 9	+1.56	−0.06 to +3.20	
	6 vs. 10	+1.00	−0.64 to +2.63	
	6 vs. 11	+0.06	−1.59 to +1.71	

Abbreviations: ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval.
*Statistically significant.

CI −0.181 to −0.125] during the first 4 weeks of treatment. During ARNI OFF, mPAP tended to progressively increase, with an estimated mPAP change of +0.022 mmHg [95% CI −0.013 to +0.058] during the first 4 weeks after Sac/Val withdrawal.

Secondary endpoints

Six-minute walking test
We observed a significant increase in the walked distance between the first pre-ARNI visit (6 weeks before starting Sac/Val) and the visit at the end of ARNI ON: 270.6 ± 101.3 m vs. 298.3 ± 88.4 m ($P < 0.001$) (*Figure 3*). At the final ARNI OFF visit (6 weeks after Sac/Val withdrawal), we observed a significant reduction to 268.5 ± 109 m ($P < 0.001$) (*Figure 3*). The highest improvement was observed in the patients with the lowest initial functional capacity.
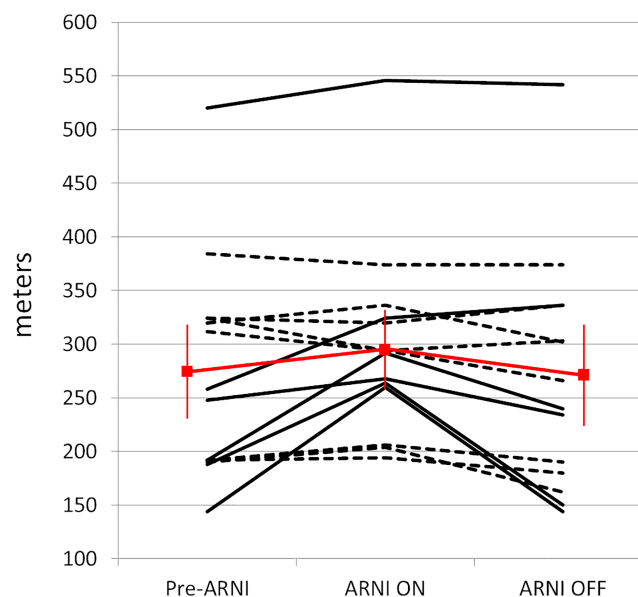
Lung ultrasound exams
Figure 4 depicts changes of the B-lines sum from LUS exams. We observed a significant B-line reduction between the first pre-ARNI visit and the visit at the end of ARNI ON (9.3 ± 6.2 vs. 4.9 ± 4.0, $P = 0.04$). At the final ARNI OFF visit, we observed a non-significant increase to 6.9 ± 8.4 B-lines ($P = 0.32$).

Quality-of-life questionnaires
Figure 5 and Supporting Information, *Figure S2* show the results obtained from KCCQ-12 and EQ-VAS between the first pre-ARNI visit, the visit at the end of ARNI ON, and the final ARNI OFF visit. We found that QoL was significantly improved with Sac/Val treatment during ARNI ON, according to both the HF-specific QoL questionnaire KCCQ-12 ($P = 0.02$) and the non-specific questionnaire EQ-VAS ($P = 0.04$). On KCCQ-12, we observed a >5 point increase in 7 of the 14 patients, and an additional 3 patients had improved scores but did not reach the 5-point threshold for a clinically significant change. In the ARNI OFF period, we observed a reduced perception of QoL, which reached statistical significance on the KCCQ-12 questionnaire ($P = 0.04$).

Figure 3 Changes in 6 min walk test distance. Black lines represent changes in the distance walked by individual patients. Solid lines indicate improvement ≥20 m (considered clinically meaningful). Red squared boxes represent mean values, red upright lines represent standard deviation, and solid red line represents mean changes. ARNI, angiotensin receptor-neprilysin inhibitor.

Figure 4 B-lines sum on the lung ultrasound exam in the three study periods. Black lines represent changes in individual patient measurements (solid for patients with a drop ≥3 B-lines). Red squared boxes represent mean values, and red upright lines standard deviation. Solid red line represents mean changes. ARNI, angiotensin receptor-neprilysin inhibitor.
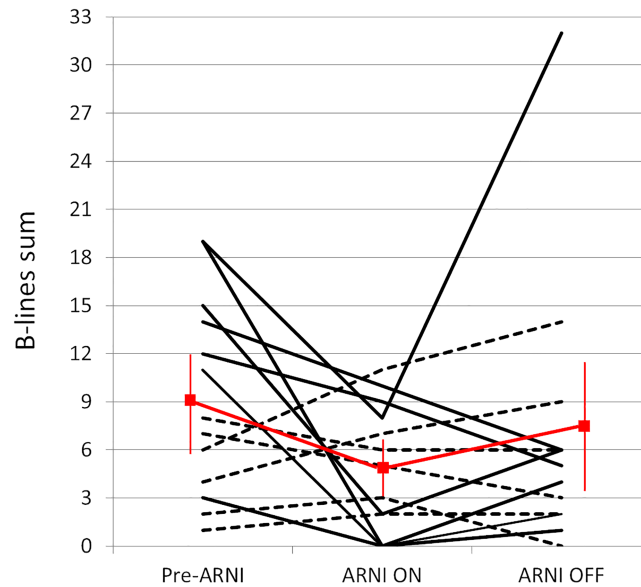

Biomarkers

Supporting Information, *Table S1* presents the serum concentrations of biomarkers for each study period. During ARNI ON, we observed no significant change in any studied biomarker. During ARNI OFF, we observed a significant rise in hs-TnT ($P = 0.03$) and a trend of increase in CA-125 ($P = 0.08$).

Figure 5 Changes in the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) items score. Black lines represent changes in measurements for individual patients. Solid line indicates improvement ≥5 points (considered clinically meaningful). Red squared boxes represent mean values, red upright lines represent standard deviation, and solid red line represents mean changes. ARNI, angiotensin receptor-neprilysin inhibitor.
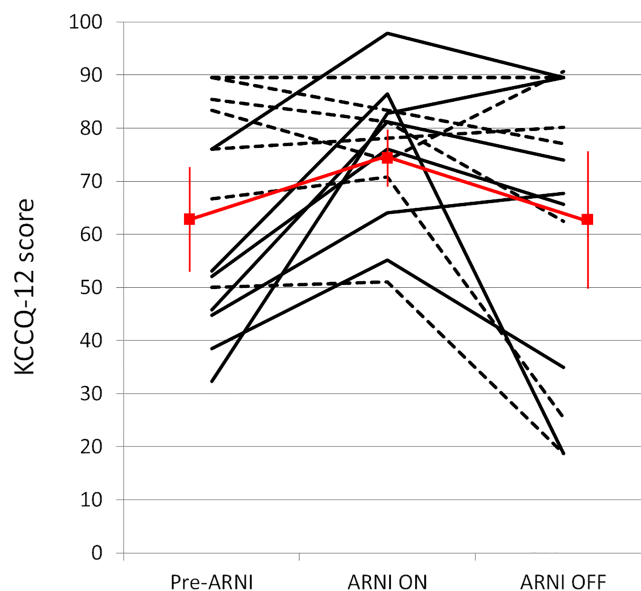
Table 3 Echocardiography data during the study periods

	Pre-treatment$_a$	With treatment$_b$	After treatment withdrawal$_c$	P-value*	P-value#
SPAP, mmHg	46.7 ± 14[a]	35.4 ± 8.4	41.1 ± 10.8	0.012[a]	0.042
LVEF, %	58.3 ± 5.6	60.9 ± 5.7	55.9 ± 5.6	0.15	0.043
iESLVD, mm/m^2	18.9 ± 3.6	18.9 ± 2.9	19.6 ± 3.2	1.00	0.33
iEDLVD, mm/m^2	25.2 ± 4.2	25.6 ± 3.4	26.7 ± 2.2	0.75	0.21
iLAD, mm/m^2	27.7 ± 3.4	26.1 ± 3.8	27.4 ± 4.4	0.029	0.044
E/e′ ratio	12.5 ± 5.6[a]	9.9 ± 3.0[b]	11.6 ± 5.2	0.13[c]	0.27[b]
TAPSE, mm	17.5 ± 2.2[b]	18.1 ± 2.3[b]	17.8 ± 4.1[b]	0.20[a]	0.96[a]

Abbreviations: iEDLVD, indexed end-diastolic left ventricular diameter; iESLVD, indexed end-systolic left ventricular diameter; iLAD, indexed left atrium diameter; LVEF, left ventricular ejection fraction; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.
[a]Available in 12 patients.
[b]Available in 13 patients.
[c]Available in 11 patients.
*P-value between subscripts a and b.
#P-value between subscripts b and c.

Echocardiography studies

Table 3 shows the echocardiography data obtained in every study period. The left atrial diameter index decreased during ARNI ON (P = 0.029) and increased during ARNI OFF (P = 0.044). We observed no changes in left ventricular (LV) diameters, E/e′, or tricuspid annular plane systolic excursion (TAPSE).

CardioMEMS measurements

Pulmonary artery pressure and cardiac output were obtained from CardioMEMS recordings. Sac/Val treatment led to alterations in systolic and diastolic PAP, similar to mPAP, with no changes in cardiac output.

Medication

The mean daily diuretic dose was 78 ± 47 mg during the pre-ARNI period, 67 ± 42 mg during ARNI ON, and 70 ± 40 mg during ARNI-OFF (P > 0.05 for all comparisons). ARNI was initiated at a low dose in all patients and up-titrated every 2 weeks. The mean daily ARNI dose achieved was 282 ± 127 mg. No changes in other baseline medications were performed during the study.

Adverse events

During the study, we recorded no deaths or hospitalizations, nor any AEs leading to treatment discontinuation. The eGFR remained relatively stable during the three study periods: 54 ± 16 mL/min in the pre-ARNI period, 49 ± 15 mL/min during ARNI-ON, and 44 ± 16 mL/min during ARNI-OFF (all P > 0.05). No patient presented a significant decline in renal function—defined as a ≥50% decrease in the eGFR, development of end-stage renal disease, or death due to renal failure. Baseline SBP was 143 ± 14 mmHg, decreased to 133 ± 15 mmHg during ARNI ON period (P = 0.031), and remained without significant changes during ARNI OFF period (135 ± 22 mmHg, P > 0.05). No cases of symptomatic hypotension were reported. There were no cases of hyperkalaemia (>5.5 mmol/L) or angioedema related to the use of ARNI.

Discussion

The main finding of this mechanistic study was that treatment with Sac/Val for 6 weeks led to a significant reduction of mPAP by ~5 mmHg in patients with HFpEF–PH who were longitudinally monitored with CardioMEMS. These results were consistent for systolic and diastolic PAP and were accompanied by significant improvement in the distance walked in the 6MWT, a significant reduction of B-lines determined by LUS, and a significant and meaningful improvement in QoL. The effect appeared early and was already significant at 1 week after treatment initiation, with an average mPAP decrease of −4.99 mmHg. Remarkably, after ARNI withdrawal, we observed a significant +2.84 mmHg mPAP rebound, along with the deterioration of the 6MWT, LUS congestion signs, and QoL parameters. The vasodilatory effects of Sac/Val in the pulmonary vascular system through increases in the levels of biologically active peptides may have contributed to the improvement in QoL and decongestion.

The available clinical evidence regarding Sac/Val in HFpEF is mainly derived from the PARAGON-HF trial,[10] in which Sac/Val was examined in HFpEF patients without phenotype granularity. Notably, the PARAGON-HF trial did not examine the presence of concomitant PH in the enrolled patients (it was not an entry criteria) and did not provide longitudinal functional or haemodynamic data. A recent retrospective study suggested that Sac/Val was associated with and improvement of PH in HFpEF.[12]

To our knowledge, ARNIMEMS-HFpEF (Treatment of PH With Angiotensin II Receptor Blocker and Neprilysin Inhibitor in HFpEF Patients With CardioMEMS Device) is the first trial to evaluate the effect of Sac/Val in the subset of patients with HFpEF–PH monitored with CardioMEMS. Overall, our

results highlight the role of Sac/Val in HFpEF–PH and thereby open a new therapeutic avenue in this patient phenotype.

Pulmonary hypertension is a common comorbidity in patients with cardiopulmonary diseases, and there is not yet any targeted therapy approved for PH associated with HFpEF. In the experimental model of PH, Sac/Val treatment leads to reductions of pulmonary vascular remodelling and PAPs, which are associated with increased natriuretic peptide/cGMP signalling in the pulmonary vasculature. Both ANP and BNP result in pulmonary vasodilation, and Sac/Val treatment yielded increased lung levels of ANP and BNP, which are likely to mitigate vasoconstriction and medial thickening. In contrast, experimental data indicate that treatment with valsartan alone has no effect in mitigating PH.[9]

Longitudinal assessment of PAP is likely the best direct surrogate of LV filling haemodynamics and is highly predictive of clinical events. Frequent measurement of PAP had been difficult until recently, due to the requirement for invasive right-sided heart catheterization procedures. The advent of remote PAP sensors has made this process substantially easier. The CHAMPION trial utilized home transmission of PAP with an implanted PAP sensor, and the post hoc evidence revealed that diuretic adjustment led to reduced HF hospitalizations in patients with HFpEF, with and without PH.[18,19]

A clinical strategy of combining a pulmonary artery sensor with a powerful vasodilatory agent like Sac/Val may improve the therapeutic accuracy of not only using this particulate guanylate cyclase donor in patients with HFpEF but also improve the target dose that will effectively achieve a treatment effect without causing the potential harm of dropping both pulmonary venous and systemic BPs. Therefore, the implantation of a CardioMEMS device, as performed upon enrolment in our study, may be considered a reasonable first management approach. Notwithstanding, in our study, the effect of Sac/Val treatment appeared to be independent of loop diuretic management.

The CardioMEMS sensor has been successfully used to assess the pulmonary haemodynamic impact of other novel HF therapies, such as sodium glucose co-transporter 2 inhibitors.[20] The results of the EMBRACE-HF trial indicated that empagliflozin also reduces PAP in patients with HF. That study was conducted mainly in patients with reduced or mildly reduced EF, and the authors observed a modest −1.7 mmHg decrease in PAPs following empagliflozin treatment, without significant benefits in terms of KCCQ scores or 6 min walking distance. In contrast, our present results showed a −4.99 mmHg reduction following Sac/Val treatment in patients with HFpEF–PH. Moreover, this remarkable improvement in haemodynamic parameters was associated with significantly improved functional capacity and QoL. Notably, in the setting of PH, with regard to PAPs, every single mmHg counts and is associated with an increased risk of adverse outcomes.[21]

Limitations

The results of our trial should be interpreted in the context of several potential limitations. First, this was a mechanistic trial with limited sample size. We have tried to mitigate these limitations by including over 1700 daily PAP values and designing a treatment protocol with three periods: pre-ARNI (6 weeks of standard therapy after monitor implantation), ARNI ON (6 weeks of ARNI treatment), and ARNI OFF (6 weeks following Sac/Val withdrawal and resumption of standard therapy). Importantly, our frequent assessments of PAPs provided adequate power for the evaluation of the primary endpoint. Second, the study was not designed to evaluate the mid-term to long-term functional and clinical effects of ARNI on HFpEF–PH. Third, although the correct definition of PH in this context would be mPAP > 20 mmHg + mean pulmonary artery wedge pressure (mPAWP) > 15 mmHg, some of the included patients presented an mPAWP < 15 mmHg at implantation time, as they were clinically stable and well compensated and had a mixed precapillary and postcapillary PH due to pulmonary vascular remodelling. Lastly, despite the limited sample size, the exquisite phenotyping of the included population revealed that the main endpoint was associated with positive changes in the LUS, echocardiography, and functional capacity parameters, together with meaningful improvement on the QoL scales. All these secondary endpoints were evaluated by study personnel blinded to patient treatment.

Conclusions

In patients with HFpEF–PH and an implanted CardioMEMS PAP sensor, Sac/Val treatment yielded rapid reductions in PAPs, which were accompanied by significant improvement in the distance walked in the 6MWT, a significant reduction of B-lines according to LUS, and a significant and meaningful improvement in QoL. These effects appeared to be independent of loop diuretic management. Sac/Val may be a treatment of choice in the HFpEF phenotype associated with PH.

Conflict of interest

Supporting information

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

Table S1. Biomarkers' levels during the study periods.
Table S2. Mean values obtained by CardioMEMS during the three study periods.

Figure S1. Loess Curve of Pulmonary Artery Pulse Pressure Measurements Through the Study.
Figure S2. Quality of life assessments (EQ-VAS) in the three study periods.

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