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ORIGINAL ARTICLE

# Haemodynamic effects of sacubitril/valsartan in advanced heart failure

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## Abstract

**Aims** The angiotensin receptor–neprilysin inhibitor (ARNI), sacubitril/valsartan, has been shown to be effective in treatment of patients with heart failure (HF), but limited data are available in patients with advanced disease. This retrospective observational study assessed the effects of ARNI treatment in patients with advanced HF.

**Methods and results** We reviewed medical records of all advanced HF patients evaluated at our centre for unconventional therapies from September 2016 to January 2019. We studied 44 patients who started ARNI therapy and who had a haemodynamic assessment before beginning ARNI and after 6 ± 2 months. The primary endpoint was variation in pulmonary pressures and filling pressures at 6 months after starting ARNI therapy. Mean patient age was 51.6 ± 7.4 years; 84% were male. At 6 ± 2 months after starting ARNI, there was significant reduction of systolic pulmonary artery pressure [32 mmHg, interquartile range (IQR) 27–45 vs. 25 mmHg, IQR 22.3–36.5; $P < 0.0001$] and mean pulmonary artery pressure (20 mmHg, IQR 15.3–29.8 vs. 17 mmHg, IQR 13–24.8; $P = 0.046$). Five of 22 patients (23%) were deferred from the heart transplant list because of improvement, whereas four were listed *de novo*. After 23 ± 9 months, three patients were treated with a left ventricular assist device implantation, whereas six patients underwent heart transplantation (one in emergency conditions for refractory ventricular tachycardia).

**Conclusions** Sacubitril/valsartan is effective in reducing filling pressures and pulmonary pressures in patients with advanced HF. The absence of adverse events during follow-up suggests that sacubitril/valsartan is safe and well-tolerated in this cohort of patients.

**Keywords** Heart failure; Sacubitril/valsartan; Heart transplantation; Pulmonary artery pressures; Filling pressures; Real-life practice

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## Introduction

The prevalence of heart failure (HF) increases with the ageing population, and advances in medical therapy have improved HF survival overall and for the 1–10% of patients with advanced disease.[1,2] Sacubitril/valsartan is a first-in-class angiotensin-II receptor neprilysin inhibitor (ARNI) that acts on the neutral endopeptidase and renin–angiotensin–aldosterone systems and is recommended in current treatment guidelines to reduce morbidity and mortality in patients with chronic, symptomatic HF with reduced ejection fraction.[3] To date, there are limited data regarding the use of sacubitril/valsartan in patients with advanced HF who are listed for cardiac transplantation.[4] Large randomized trials have generally excluded these patients considering that (i) reverse cardiac remodelling may be difficult to obtain in advanced chronic HF; (ii) the rate of hospitalizations is expected to be high, irrespective of treatments; and (iii) donor availability, medical choices, and allocation policies may act as confounders and generate biases when evaluating survival in heart transplantation (HTx) candidates.[5,6] Furthermore, there are few published data regarding the effects of sacubitril/valsartan on filling pressures and pulmonary pressures assessed by right heart catheterization (RHC).

Therefore, the aim of the present retrospective observational study was to assess the effects of ARNI treatment on

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RHC parameters in patients with advanced HF who were candidates for heart replacement therapies.

# Methods

## Study design and population characteristics

We reviewed the medical records of all advanced HF patients evaluated at our centre for unconventional therapies from September 2016 to January 2019. From the initial 193 patients, we selected the group of 53 patients who started therapy with sacubitril/valsartan and who received RHC before the beginning of ARNI therapy and after 6 ± 2 months. Patients underwent RHC as part of the evaluation for heart replacement therapies [HTx/left ventricular assist device (LVAD)]. The other inclusion criteria were age > 18 years, a diagnosis of advanced HF according to the criteria proposed by the European Society of Cardiology position statement 2018,[1] initiation of therapy with sacubitril/valsartan after evaluation or re-evaluation for advanced HF therapies, and clinical stability in the absence of hospitalization for decompensated HF in the interval between the two haemodynamic evaluations to avoid confounding factors (use of intravenous diuretic or vasodilator therapy). We excluded patients with severe comorbidity affecting life expectancy independently of heart disease.

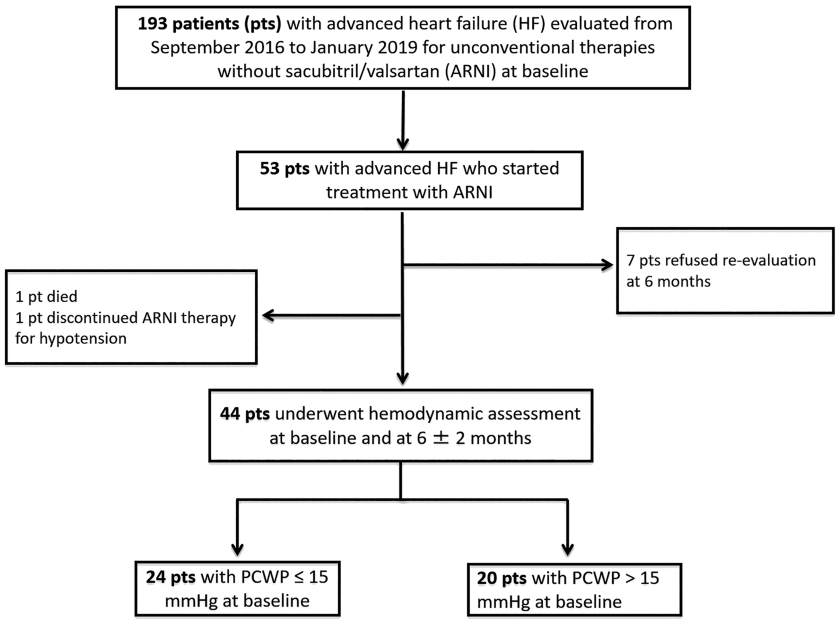
Of the 53 patients enrolled, 7 refused the second control catheterization at 6 months, 1 patient died, and 1 patient stopped ARNI therapy (due to symptomatic hypotension), leaving 44 patients. Forty-two were electively admitted at the time of the first haemodynamic assessment, one patient was admitted for HF, and one patient was admitted after a ventricular arrhythmic event. At the time of recruitment, patients were in optimized medical therapy, according to European Society of Cardiology guidelines.[3,7] Sacubitril/valsartan was administered initially at the minimum dose (24/26 mg) in nearly all patients. The safety and tolerability of ARNI were evaluated, and in some cases, the dose was titrated during the same hospitalization. Patient recruitment is presented in *Figure 1*.

At baseline and 6 months of follow-up, we evaluated clinical and laboratory parameters, echocardiographic parameters, functional tests, medical therapy, and invasive haemodynamic parameters.

## Right heart catheterization

The approach of choice for the execution of RHC was the right jugular vein on ultrasound guidance. All the procedures were performed in the catheterization lab under local anaesthesia (lidocaine 2%). In patients with post-capillary pulmonary hypertension at RHC, a pharmacological reversibility test with sodium nitroprusside (maximum 2 mcg/kg/min) was performed.

**Figure 1** Patient recruitment. ARNI, angiotensin-II receptor neprilysin inhibitor; PCWP, pulmonary capillary wedge pressure.





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## Outcomes

The primary endpoint was variation in filling pressures and pulmonary pressures from baseline to 6 months of follow-up. Secondary endpoints were the variations in echocardiographic parameters, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and dose of diuretic therapy. Moreover, we subgrouped the population according to pulmonary capil-

**Table 1** Clinical characteristics of patients with advanced heart failure treated with sacubitril/valsartan

| Parameter | Overall ($N$ = 44) | PCWP > 15 mmHg ($N$ = 20) | PCWP ≤ 15 mmHg ($N$ = 24) | $P$ |
|---|---|---|---|---|
| Age, years | 51.6 ± 7.4 | 57.2 ± 7.2 | 52.7 ± 7.8 | 0.35 |
| Female, *n* (%) | 8 (18) | 1 (2) | 7 (29) | 0.05 |
| BMI, kg/m$^2$ | 26.8 ± 3.8 | 27.4 ± 4.0 | 25 ± 7 | 0.31 |
| SBP, mmHg | 106.7 ± 11.4 | 105.4 ± 9.5 | 108 ± 12.8 | 0.31 |
| DBP, mmHg | 67.2 ± 7.3 | 68.25 ± 7.5 | 66.46 ± 7.1 | 0.67 |
| HR, b.p.m. | 65.2 ± 7.6 | 65.5 ± 6.1 | 64.6 ± 6 | 0.73 |
| Hypertension, *n* (%) | 3 (7) | 1 (5) | 2 (8) | 0.99 |
| Diabetes, *n* (%) | 3 (7) | 1 (5) | 2 (8) | 0.99 |
| AF, *n* (%) | 10 (23) | 6 (30) | 4 (16) | 0.47 |
| Ischaemic cause of HF, *n* (%) | 20 (45) | 12 (60) | 8 (33) | 0.13 |
| NYHA class, *n* (%) | | | | |
| II | 11 (25) | 4 (20) | 7 (29) | 0.49 |
| III | 33 (75) | 16 (80) | 17 (70) | 0.32 |
| MitraClip, *n* (%) | 9 (20) | 4 (20) | 5 (21) | >0.99 |
| Levosimendan, *n* (%) | 9 (20) | 7 (35) | 2 (8) | *0.01* |
| ICD, *n* (%) | 29 (65) | 12 (60) | 17 (71) | 0.53 |
| CRT-D, *n* (%) | 15 (34) | 8 (40) | 7 (29) | 0.53 |
| MAGGIC 1-year mortality (%) | 12.8 ± 5.1 | 13.5 ± 4.7 | 12.4 ± 5.4 | 0.45 |
| MAGGIC 3-year mortality (%) | 30 ± 10.2 | 28.7 (13.3) | 28.9 ± 10.6 | 0.44 |
| Ambulatory therapy | | | | |
| ACEI, *n* (%) | 25 (56) | 13 (65) | 12 (50) | 0.37 |
| ARB, *n* (%)13 | 19 (43) | 7 (35) | 12 (50) | 0.37 |
| BB, *n* (%) | 44 (100) | 20 (100) | 24 (100) | - |
| MRA, *n* (%) | 42 (95) | 19 (95) | 23 (96) | >0.99 |
| Diuretics, *n* (%) | 42 (95) | 19 (95) | 23 (96) | >0.99 |
| Right heart catheterization | | | | |
| RAP, mmHg | 4.3 ± 3.2 | 6.4 ± 3.5 | 2.5 ± 1.7 | *0.0001* |
| mPAP, mmHg | 23.3 ± 10.5 | 32.5 ± 8.9 | 15.7 ± 3.1 | *<0.0001* |
| PCWP, mmHg | 15.6 ± 8.8 | 23.3 ± 6.8 | 9.12 ± 3.12 | *<0.0001* |
| CI, L/min/m$^2$ | 1.9 ± 0.4 | 1.8 ± 0.5 | 1.9 ± 0.35 | 0.17 |
| PVRi, WU*m$^2$ | 4.3 ± 2.3 | 5.4 ± 2.8 | 3.4 ± 3.08 | 0.007 |
| CPO, W | 0.66 ± 0.17 | 0.64 ± 0.16 | 0.67 ± 0.2 | 0.8 |
| CPI, W/m$^2$ | 0.34 ± 0.08 | 0.32 ± 0.08 | 0.35 ± 0.08 | 0.36 |
| PAPI | 7.69 ± 6.2 | 6.06 ± 6.3 | 9.12 ± 5.8 | *0.03* |
| Echocardiographic parameters | | | | |
| LVEF, % | 24.7 ± 5.0 | 24.3 ± 4.2 | 25.13 ± 5.8 | 0.68 |
| LVEDD, mm | 69.2 ± 9.7 | 70.3 ± 10.2 | 68.5 ± 9.6 | 0.48 |
| LVEDV, mL | 259.3 ± 110.0 | 253 ± 83 | 260.5 ± 129 | 0.65 |
| Severe MR, *n* (%) | 20 (45) | 9 (45) | 9 (37) | 0.76 |
| TAPSE mm | 16.6 ± 2.9 | 15.6 ± 2.3 | 17.4 ± 3.11 | 0.06 |
| RV diameter medium lateral, mm | 39.6 ± 4.7 | 41.4 ± 5.7 | 37.04 ± 3.2 | 0.01 |
| Severe TR, *n* (%) | 2 (4) | 2 (10) | 0(0) | 0.20 |
| Laboratory values | | | | |
| NT-proBNP, ng/L | 1608.5 ± 1163.5 | 983 ± 1508.4 | 1311 ± 669 | 0.22 |
| Bilirubin, mg/dL | 0.9 ± 0.5 | 1.1 ± 0.7 | 0.69 ± 0.22 | *0.002* |
| Creatinine, mg/dL | 1.2 ± 0.3 | 1.1 ± 0.2 | 1.2 ± 0.34 | 0.98 |
| Urea, mg/dL | 46.0 ± 15.6 | 45.6 ± 13.5 | 46.5 ± 17.8 | 0.96 |
| Sodium, mmol/L | 141.2 ± 2.2 | 141.5 ± 2.2 | 141 ± 2.4 | 0.44 |
| Hb, g/dL | 13.6 ± 1.4 | 13.6 ± 1.6 | 13.7 ± 1.2 | 0.88 |
| Potassium, mmol/L | 4.3 ± 0.4 | 4.1 ± 0.4 | 4.4 ± 0.3 | 0.05 |

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; b.p.m., beats per minute; CI, cardiac index; CPI, cardiac power index; CPO, cardiac power output; CRT-D, cardiac resynchronization therapy defibrillator; DBP, diastolic blood pressure; Hb, haemoglobin; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure; mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; RV, right ventricular; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Unless otherwise indicated, continuous variables are expressed as mean ± standard deviation or median (interquartile range). The italic emphasis is used to evidence statistically significant values.

lary wedge pressure (PCWP) values > 15 mmHg to assess the effects of sacubitril/valsartan on PCWP and pulmonary pressures in patients with elevated filling pressures. Tolerability and safety were assessed periodically by evaluating renal function, kalaemia, and systolic blood pressure (SBP). Finally, we conducted an exploratory analysis to assess the effect of ARNI treatment on clinical outcomes, evaluating the incidence of a composite clinical endpoint (death, HTx under emergency/urgency conditions, and LVAD implantation).

### Statistical analysis

Statistical analysis was performed using GraphPad Prism software for macOS. Data are expressed as mean (standard deviation) or median [interquartile range (IQR)] depending on normality. A value of $P < 0.05$ was considered statistically significant. Paired *t*-tests and unpaired *t*-test were used to compare data for normally-distributed variables. Wilcoxon and Mann–Whitney *U* tests were used to evaluate differences for variables that are not normally distributed. Time-to-event data were evaluated with the use of Kaplan–Meier estimates. Kaplan–Meier survival curves for survival free from death, HTx, or LVAD implantation were estimated and compared between groups by means of the log-rank test.

## Results

The baseline characteristics of the study group are summarized in *Table 1*. The mean age of patients was 51.6 ± 7.4 years, with a prevalence of male patients (84%). Mean SBP at baseline was 106.7 ± 11.4 mmHg. Ischaemic heart disease was found in 45% of the cohort. Mean left ventricular ejection fraction (LVEF) was 24.7% ± 5.0%, and 34% of patients were being treated with a cardiac resynchronization therapy defibrillator. At 6 months of follow-up, 7% of the population was taking the highest dose of sacubitril/valsartan, 50% the intermediate dose, and 43% the lowest dose. Regarding RHC parameters, we found a mean cardiac index of 1.9 ± 0.4 L/min/m$^2$ and a mean pulmonary artery pressure (mPAP) of 23.3 ± 10.5 mmHg with 45% of patients (*n* = 20) with an elevated PCWP defined as PCWP > 15 mmHg. Finally, patients were stratified according to a PCWP > 15 mmHg to estimate the effects of sacubitril/valsartan in patients with elevated filling pressures (*Table 1*).

### Right heart catheterization

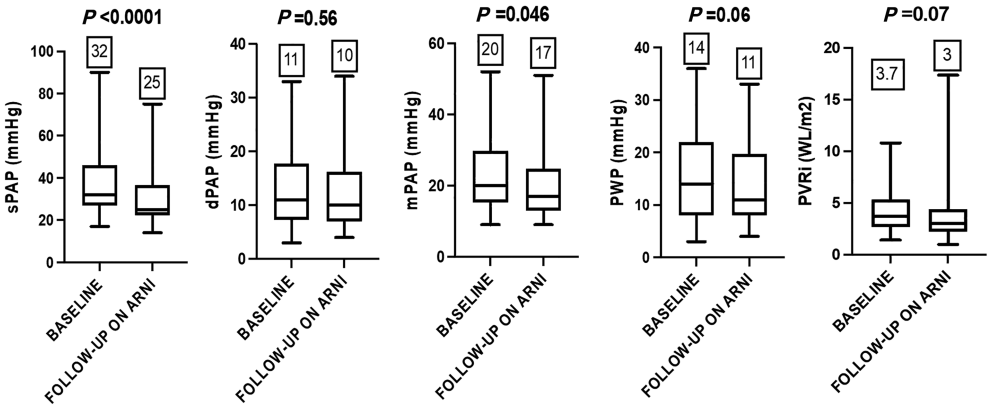
At RHC (*Table 2* and *Figure 2*), a significant reduction between baseline and 6 ± 2 months was registered in systolic pulmonary artery pressure (sPAP, 32 mmHg, IQR 27–45 vs. 25 mmHg, IQR 22.3–36.5; $P < 0.0001$) and mPAP (20 mmHg,

**Table 2** Comparison between right heart catheterization values at baseline and follow-up in patients treated with sacubitril/valsartan

| | Overall (*N* = 44) | | | | PCWP > 15 mmHg (*N* = 20) | | | | PCWP ≤ 15 mmHg (*N* = 24) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | Delta *Δ* | *P* value | Baseline | Follow-up | Delta *Δ* | *P* value | Baseline | Follow-up | Delta *Δ* | *P* value |
| RAP (mmHg) | 3 (2–12) | 4 (1.3–11) | +1 | 0.89 | 6.5 (2.8–8) | 4 (1–7.8) | −2.5 | *0.04* | 2 (1–3.7) | 3.5 (2–6) | +1.5 | 0.08 |
| sPAP (mmHg) | 32 (27–45) | 25 (22.3–36.5) | −7 | *<0.0001* | 47 (36.5–61.3) | 36 (26–48) | −11 | *0.0005* | 27.5 (23–30.7) | 24 (21–25.7) | −3.5 | 0.06 |
| dPAP (mmHg) | 11 (7.3–17.8) | 10 (7–16.3) | −1 | 0.56 | 19.5 (16–24.8) | 15 (9.5–23) | −4.5 | *0.04* | 8 (5.2–9) | 8 (6.2–10.7) | 0 | 0.37 |
| mPAP (mmHg) | 20 (15.3–29.8) | 17 (13–24.8) | −3 | *0.046* | 32 (24.3–39) | 24.5 (16.5–34.8) | −7.5 | *0.006* | 16 (13–18) | 15 (13–17.5) | −1 | 0.5 |
| PCWP (mmHg) | 14 (8–22) | 11 (8.19.8) | −3 | 0.069 | 22 (16.8–27.8) | 19.5 (11.3–22.5) | −2.5 | *0.0048* | 8.5 (7–11.75) | 9 (7–11.75) | −0.5 | 0.75 |
| CI (mL/min/m$^2$) | 1.82 (1.5–2.2) | 1.87 (1.8–2) | +0.05 | 0.7 | 1.59 (1.5–2.2) | 1.88 (1.6–2.03) | +0.29 | 0.69 | 1.9 (1.67–2.18) | 1.85 (1.8–2.1) | −0.04 | 0.9 |
| PVRi (WU/m$^2$) | 3.7 (2.7–5.3) | 3 (2.2–4.4) | −0.7 | 0.07 | 4.4 (3.3–7.6) | 3.4 (2.6–5.5) | −1 | 0.11 | 3.45 (2.5–3.9) | 2.75 (2.2–3.8) | −0.7 | 0.34 |
| CPO, W | 0.64 (0.52–0.77) | 0.63 (0.53–0.7) | −0.01 | 0.61 | 0.59 (0.52–0.79) | 0.62 (0.58–0.72) | +0.03 | 0.97 | 0.65 (0.52–0.75) | 0.64 (0.51–0.7) | −0.01 | 0.58 |
| CPI, W/m$^2$ | 0.32 (0.28–0.39) | 0.32 (0.28–0.35) | 0 | 0.64 | 0.29 (0.26–0.4) | 0.32 (0.27–0.36) | +0.03 | 0.89 | 0.34 (0.29–0.39) | 0.32 (0.22–0.35) | −0.02 | 0.38 |
| PAPI | 5.6 (3.6–10.7) | 4.9 (2.8–8.9) | −0.69 | 0.4 | 4.87 (2.9–8.86) | 5.45 (2.78–15.25) | +0.56 | 0.39 | 8.16 (5.45–12.1) | 4.5 (2.8–7.3) | −3.66 | 0.04 |

CI, cardiac index; CPO, cardiac power output; CPI, cardiac power index; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure. The italic emphasis is used to evidence statistically significant values.

**Figure 2** Graphical illustration of paired tests comparing right heart catheterization values at baseline and at follow-up after beginning therapy with sacubitril/valsartan (*N* = 44). ARNI, angiotensin-II receptor neprilysin inhibitor; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PWP, pulmonary wedge pressure; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure.




IQR 15.3–29.8 vs. 17 mmHg, IQR 13–24.8; *P* = 0.046). In the group with PCWP > 15 mmHg (*Table 2* and *Figure 3*), there were significant differences at baseline and 6 ± 2 months in pulmonary artery pressure. In particular, we found a reduction of mPAP (32 mmHg, IQR 24.3–39 vs. 24.5 mmHg, IQR 16.5–34.8; *P* = 0.006), PCWP (22 mmHg, IQR 16.3–27.8 vs. 19.5 mmHg, 11.3–22.5; *P* = 0.0048), and right atrial pressure (RAP; 6.5 mmHg, IQR 2.7–8 vs. 4, IQR 1–7.7; *P* = 0.04). Instead, these haemodynamic significant effects were not recorded in the group with PCWP ≤ 15 mmHg (*Table 2* and *Figure 4*).

Finally, we analysed the haemodynamic effects of ARNI in three subgroups: patients with high vs. low NT-proBNP values at baseline (*Table 3*), ischaemic cardiomyopathy vs. non-ischaemic myocardial disease (*Table 4*), and patients with or without a decrease of NT-proBNP at 6 months of follow-up (*Table 5*).

## Secondary endpoints

Comparing echocardiographic parameters at baseline and at follow-up (*Table 6*), after the start of sacubitril/valsartan, we found an increase in the median values of LVEF (24.5%, IQR 21.0–27.8 vs. 25.5%, IQR 21.5–29.1; *P* = 0.01) with an improvement from severe to moderate left ventricular dysfunction in five patients (11%) but without significant reverse considering the whole population. A significant reduction in right ventricular diameter (39.0 mm, IQR 37.3–42.2 vs.

**Figure 3** Graphical illustration of paired tests comparing right heart catheterization values at baseline and 6 months in patients with pulmonary capillary wedge pressure (PCWP ) > 15 mmHg at baseline. ARNI, angiotensin-II receptor neprilysin inhibitor; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PWP, pulmonary wedge pressure; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure.

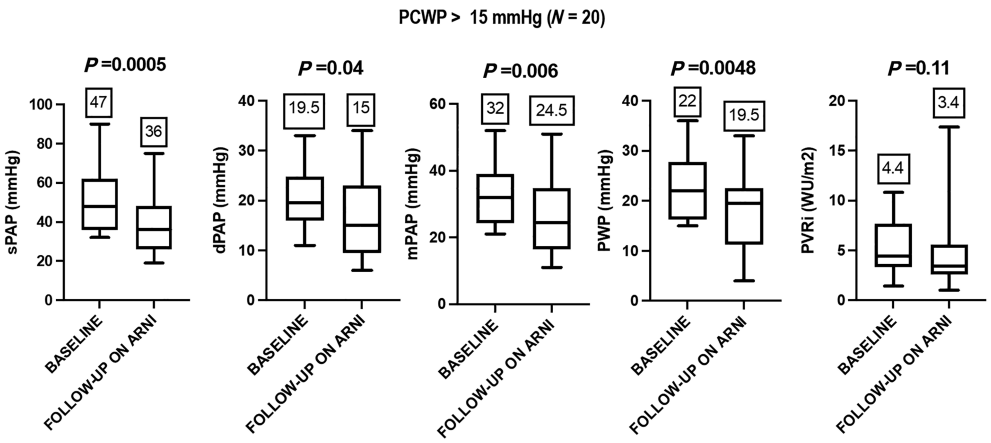
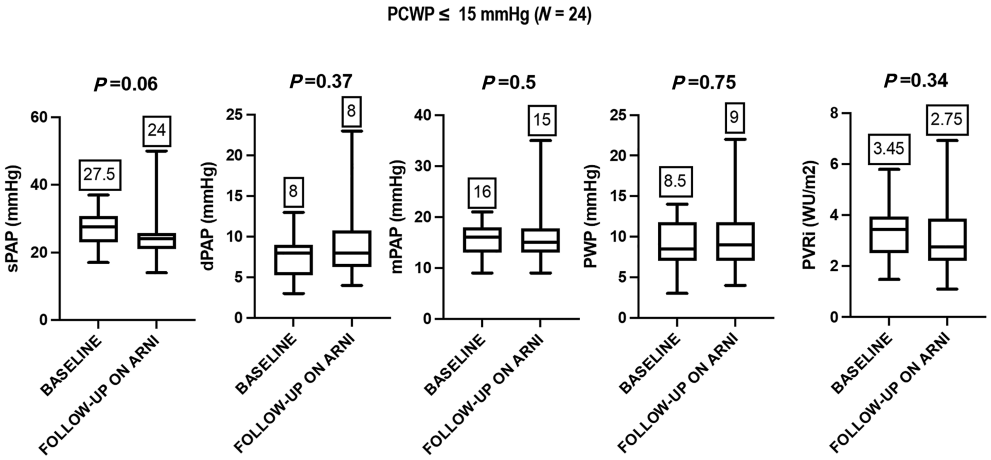


**Figure 4** Graphical illustration of paired tests comparing right heart catheterization values at baseline and 6 months in patients with pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg at baseline. ARNI, angiotensin-II receptor neprilysin inhibitor; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PWP, pulmonary wedge pressure; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure.




38.1 mm, IQR 34.1–42.0; $P$ = 0.03) was recorded after the start of sacubitril/valsartan.

Regarding laboratory tests, after the beginning of sacubitril/valsartan, we recorded a significant decrease of NT-proBNP values (1372 ng/L, IQR 807.5–1970 vs. 1035 ng/L, IQR 556.3–1624.4; $P$ = 0.01) (*Figure 5*), i.e. a 24.6% reduction in NT-proBNP from baseline. Particularly, we recorded a 50% reduction in the values of NT-proBNP in 11 patients (25%) while considering the guidelines cut-off of 125 pg/mL[3], two patients had normalized NT-proBNP values.

## Safety and tolerability

Administration of sacubitril/valsartan was safe in this cohort of patients. In particular, renal function and potassium values remained stable in both groups (*Table 7*). A slight reduction in SBP was observed at the moment of second RHC (median 100 mmHg vs. 90 mmHg; 25th–75th percentile; 105–110 mmHg vs. 90–110 mmHg; $P$ = 0.01) with a slight reduction in the mean diuretic dose (mg) (mean dose of furosemide 75.6 ± 41.2 vs. 68.4 ± 46.5; $P$ = 0.46).

## Exploratory clinical outcomes

New York Heart Association (NYHA) class was used to assess symptoms at 6 months of follow-up (*Figure 5*). We recorded an improvement in terms of NYHA class: at baseline, 75% of patients had an NYHA Class III–IV, whereas at follow-up, this percentage decreased to 39% (*Figure 5*).

Furthermore, we extended the follow-up to 23 ± 9 months to evaluate event-free survival from a composite endpoint of death, HTx in emergency/urgency conditions, and LVAD implantation. We observed an event-free survival of 79.5% (*Figure 6A*) with a major number of events in the group of patients with elevated filling pressures (25% vs. 16.7%; $P$ = 0.049; *Figure 6B*). Regarding the group of patients that was on the cardiac transplant list at baseline ($n$ = 22), five patients (23%) were suspended from this list for improvement, whereas two patients were suspended for comorbidity (*Figure 7*). Six patients underwent HTx in the follow-up, one of whom in emergency conditions for refractory ventricular tachycardia. Three patients had an LVAD implantation during follow-up. The other 11 patients continued to be on the cardiac transplant list. Finally, six of nine patients treated at the beginning with levosimendan improved sufficiently for their periodical levosimendan administration to be suspended (*Figure 7*).

# Discussion

In our real-life clinical study in patients with advanced HF, sacubitril/valsartan was well-tolerated and safe, which significantly reduced left ventricular filling pressures and pulmonary pressures and improved outcomes. Few randomized clinical trials have included this type of patient, and listing for cardiac transplantation has been considered an exclusion criterion in many studies.[5,6] To the best of our knowledge, this is one of the largest population in which the haemodynamic effects of sacubitril/valsartan are studied in advanced HF patients who are actively listed for HTx. Our experience confirms results of some smaller studies and deepens our knowledge in the particular subgroup of

**Table 3** Comparison between right heart catheterization values at baseline and follow-up in patients treated with sacubitril/valsartan. Baseline NT-proBNP ≥ 1500 vs. <1500

| | Overall (*N* = 44) | | | | NT-proBNP ≥ 1500 (*N* = 20) | | | | NT-proBNP < 1500 (*N* = 24) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | Delta Δ | *P* value | Baseline | Follow-up | Delta Δ | *P* value | Baseline | Follow-up | Delta Δ | *P* value |
| RAP (mmHg) | 3 (2–12) | 4 (1.3–11) | +1 | 0.89 | 5.5 (2–7) | 4.5 (1–7) | −1 | 0.48 | 2.5 (1.2–5) | 3 (2–5.7) | +0.5 | 0.73 |
| sPAP (mmHg) | 32 (27–45) | 25 (22.3–36.5) | −7 | <0.0001 | 41.5 (27.2–58.2) | 30.5 (21.5–49.5) | −11 | 0.01 | 31 (25–36) | 24.5 (22.25–32.7) | −6.5 | 0.0006 |
| dPAP (mmHg) | 11 (7.3–17.8) | 10 (7–16.3) | −1 | 0.56 | 16 (8.25–23.7) | 12 (7.25–23) | −4 | 0.74 | 9 (7–15.7) | 8.5 (7–12.5) | −0.5 | 0.63 |
| mPAP (mmHg) | 20 (15.3–29.8) | 17 (13–24.8) | −3 | 0.046 | 26.5 (16.25–35.7) | 19.5 (13–35) | −7 | 0.28 | 18.5 (15–23.7) | 15 (13.2–21.2) | −3.5 | 0.05 |
| PCWP (mmHg) | 14 (8–22) | 11 (8.19.8) | −3 | 0.069 | 15.5 (9.5–25) | 12.5 (9–22.7) | −3 | 0.20 | 12 (8–16.7) | 10 (7.2–16.7) | −2 | 0.168 |
| CI (mL/min/m$^2$) | 1.82 (1.5–2.2) | 1.87 (1.8–2) | +0.05 | 0.7 | 1.72 (1.5–1.9) | 1.86 (1.8–2.1) | +0.14 | 0.15 | 1.8 (1.6–2.2) | 1.9 (1.8–2.0) | +0.1 | 0.47 |
| PVRi (WU/m$^2$) | 3.7 (2.7–5.3) | 3 (2.2–4.4) | −0.7 | 0.07 | 4.1 (3.45–7.6) | 3.56 (1.9–6.7) | −0.54 | 0.34 | 3.4 (2.3–4.3) | 2.7 (2.6–3.8) | −0.7 | 0.26 |

CI, cardiac index; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure.

**Table 4** Comparison between right heart catheterization values at baseline and follow-up in patients treated with sacubitril/valsartan. Ischaemic cardiomyopathy (ICM) vs. non-ischaemic myocardial disease (non-ICM)

| | Overall (*N* = 44) | | | | ICM (*N* = 20) | | | | Non-ICM (*N* = 24) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | Delta Δ | *P* value | Baseline | Follow-up | Delta Δ | *P* value | Baseline | Follow-up | Delta Δ | *P* value |
| RAP (mmHg) | 3 (2–12) | 4 (1.3–11) | +1 | 0.89 | 4 (2–7) | 4 (1–6.7) | 0 | 0.45 | 3 (2-7) | 3.5 (2–6) | −0.5 | 0.76 |
| sPAP (mmHg) | 32 (27–45) | 25 (22.3–36.5) | −7 | <0.0001 | 36 (28–53) | 32.5 (23.5–43.2) | −3.5 | 0.0035 | 30.5 (25–37.7) | 24 (21.25–30.7) | −6.5 | 0.004 |
| dPAP (mmHg) | 11 (7.3–17.8) | 10 (7–16.3) | −1 | 0.56 | 13 (7.2–23) | 11.5 (7–20-7) | −2.5 | 0.55 | 9 (7.25–16) | 8.5 (7–13.5) | −0.5 | 0.9 |
| mPAP (mmHg) | 20 (15.3–29.8) | 17 (13–24.8) | −3 | 0.046 | 24 (17.2–24.7) | 19.5 (14.2–31.5) | −4.5 | 0.07 | 17.5 (15–24) | 15 (12.25–22) | −2.5 | 0.25 |
| PCWP (mmHg) | 14 (8–22) | 11 (8.1–9.8) | −3 | 0.069 | 17.5 (10.2–26.5) | 14 (8.2–20.7) | −3.5 | 0.06 | 11.5 (7.25–16) | 10 (7.250–12.75) | −1.5 | 0.49 |
| CI (mL/min/m$^2$) | 1.82 (1.5–2.2) | 1.87 (1.8–2) | +0.05 | 0.7 | 1.8 (1.5–2.1) | 1.87 (1.5–2.1) | 0 | 0.87 | 1.85 (1.56–2.12) | 1.87 (1.8–2) | 0 | 0.4 |
| PVRi (WU/m$^2$) | 3.7 (2.7–5.3) | 3 (2.2–4.4) | −0.7 | 0.07 | 4.0 (2.6–5.4) | 3.12 (2.5–5.5) | −0.9 | 0.54 | 3.625 (2.8–5.16) | 3 (2.2–3.8) | +0.62 | 0.17 |

CI, cardiac index; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure.


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**Table 5** Comparison between right heart catheterization values at baseline and follow-up in patients treated with sacubitril/valsartan with or without a reduction of NT-proBNP after the beginning of sacubitril/valsartan (ARNI)

| | Overall ($N$ = 44) | | | | NT-proBNP reducing after the beginning of ARNI ($N$ = 27) | | | | NT-proBNP not reducing after the beginning of ARNI ($N$ = 17) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | Delta Δ | $P$ value | Baseline | Follow-up | Delta Δ | $P$ value | Baseline | Follow-up | Delta Δ | $P$ value |
| RAP (mmHg) | 3 (2–12) | 4 (1.3–11) | +1 | 0.89 | 3 (2–6) | 4 (1–6) | +1 | *0.63* | 3 (2–6.5) | 4 (1–7) | +1 | 0.76 |
| sPAP (mmHg) | 32 (27–45) | 25 (22.3–36.5) | −7 | *<0.0001* | 31 (27–31) | 25 (21–34) | −6 | *0.0005* | 33 (27.5–47.25) | 26 (24–49) | +7 | 0.02 |
| dPAP (mmHg) | 11 (7.3–17.8) | 10 (7–16.3) | −1 | 0.56 | 11 (7–18) | 10 (7–13) | −1 | *0.28* | 13 (8.5–19) | 11 (8–23) | −2 | 0.53 |
| mPAP (mmHg) | 20 (15.3–29.8) | 17 (13–24.8) | −3 | *0.046* | 19 (15–29) | *17 (13–23)* | −2 | *0.04* | 21 (16.5–32) | 18 (15–34.5) | −3 | 0.65 |
| PCWP (mmHg) | 14 (8–22) | 11 (8.19.8) | −3 | 0.069 | 13 (8–22) | 11 (7–15) | −2 | *0.07* | 15 (9.5–23.5) | 12 (9.5–21.5) | −3 | 0.48 |
| CI (mL/min/m$^2$) | 1.82 (1.5–2.2) | 1.87 (1.8–2) | +0.05 | 0.7 | 1.8 (1.6–2) | 1.84 (1.8–2.1) | 0 | 0.23 | 1.95 (1.5–2.2) | 1.89 (1.67–2) | −0.06 | 0.35 |
| PVRi (WU/m$^2$) | 3.7 (2.7–5.3) | 3 (2.2–4.4) | −0.7 | 0.07 | 3.65 (2.5–5.46) | 3 (2.1–4.3) | −0.65 | 0.04 | 4 (2.9–4.8) | 3.4 (2.42–6.2) | −0.6 | >0.99 |

ARNI, angiotensin-II receptor neprilysin inhibitor; CI, cardiac index; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure. The italic emphasis is used to evidence statistically significant values.

**Table 6** Echocardiographic parameters at baseline and follow-up after initiation of sacubitril/valsartan ($N$ = 44)

| Parameter | Baseline | Follow-up | $P$ value |
|---|---|---|---|
| LVEDD (mm) | 68.5 (63–76.75) | 68 (62–74.75) | 0.38 |
| LVEDV (mL) | 234.5 (183–304.8) | 228 (188.3–339) | 0.48 |
| LVESV (mL) | 178.5 (134.3–242) | 172 (121.5–257.3) | 0.24 |
| LVEF (%) | 24.5 (21.0–27.8) | 25.5 (21.5–29.1) | *0.01* |
| RVD ML (mm) | 39.0 (37.3–42.2) | 38 (34.1–42.0) | *0.03* |
| TAPSE (mm) | 17 (14–18) | 17 (15–18) | 0.23 |
| Severe MR (%) | 20 (45) | 16 (36) | 0.38 |

LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; RVD ML, right ventricular diameter medium lateral; TAPSE, tricuspid annular plane systolic excursion. The italic emphasis is used to evidence statistically significant values.

patients with advanced HF and elevated filling pressures (PCWP > 15 mmHg). Cacciatore *et al*. recently reported in a smaller group of patients with advanced HF on a waiting list for HTx that treatment with sacubitril/valsartan significantly improved the haemodynamic profile without concomitant hypotension or worsening renal function. These benefits were apparent at the first visit at 1 month and were maintained over 2 years of follow-up.[8] Villani *et al*. showed in HF patients with relatively short disease duration that sacubitril/valsartan significantly improved systolic pulmonary pressure after 6 and 12 months of treatment.[9] In their echocardiographic evaluations, mean LVEF values were significantly higher, whereas left ventricular end-diastolic volume, left ventricular end-systolic volume, and sPAP values were significantly lower at 6 and 12 months compared with baseline. We concur with the authors that the reversal of an unfavourable right haemodynamic load could also explain the slight improvement in right ventricular function observed in these patients after prolonged ARNI treatment. Of note, a similar striking reduction in pulmonary pressure has recently been reported in two patients with recent-onset HF (<5 years).[10]

In our study, we observed a significant reduction in both sPAP and mPAP. Interestingly, the haemodynamic improvement and especially the reduction of left ventricular filling pressure after the start of therapy with sacubitril/valsartan was more relevant in patients with altered baseline values, suggesting a role in obtaining homoeostasis. This suggests that in patients with severe haemodynamic impairment who tolerate ARNI treatment, a neurohormonal drug effect was present with consequent measurable haemodynamic improvement. This also played a role in improving symptoms and clinical outcomes. Furthermore, some patients on planned repeated levosimendan could be weaned from this therapy after initiation of ARNI.[11]

Concerning echocardiographic data, we did not observe significant reverse remodelling in terms of reduction of left ventricular volumes. This could be explained by the short observation period and by the greater degree of left ventricular dilation than patients enrolled in randomized clinical trials

**Figure 5** Variations in N-terminal pro-B-type natriuretic peptide (NT-proBNP) values from baseline to follow-up in patients treated with angiotensin-II receptor neprilysin inhibitor (sacubitril/valsartan) (left panel). New York Heart Association (NYHA) class at baseline and at 6 months of follow-up in patients treated with angiotensin-II receptor neprilysin inhibitor (right panel).

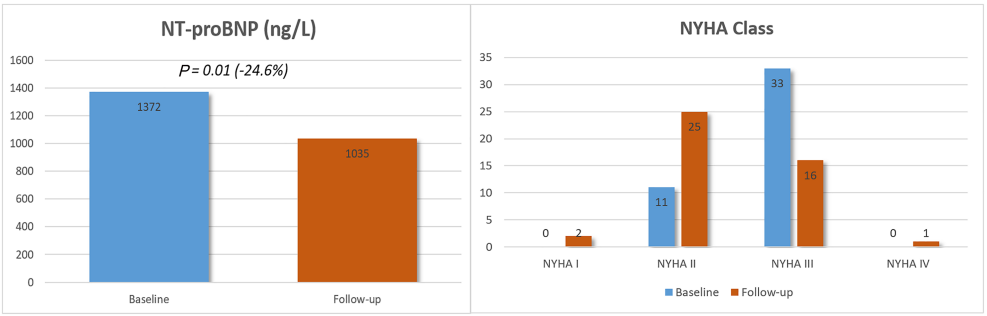



**Table 7** Safety endpoints: renal function and kalaemia at baseline and after 6 months of sacubitril/valsartan ($N = 44$)

| Laboratory value | Baseline | 6 months | *P* value |
|---|---|---|---|
| Creatinine (mg/dL) | 1.2 ± 0.3 | 1.2 ± 0.3 | NS |
| Urea (mg/dL) | 46.0 ± 15.6 | 48.5 ± 21.0 | NS |
| Potassium (mmol/L) | 4.3 ± 0.4 | 4.2 ± 0.3 | NS |

NS, not significant.
Data are mean ± standard deviation.

who have demonstrated reverse remodelling with ARNI. It is likely that patient with advanced HF could benefit from more precise techniques, such as global longitudinal strain.[12] In fact, we know that in HF patients, despite a long history of the disease, the introduction of sacubitril/valsartan provides a reverse remodelling that could be also evaluated with advanced echocardiographic parameters such as atrial and ventricular global longitudinal strain.[13]

Reduction of right ventricular diameters and improvement of the grade of mitral regurgitation represent significant targets in the framework of advanced HF when left ventricular systolic function is severely depressed.

The improvement of NYHA class and reduction of the NT-proBNP that we observed in our study are in agreement with the available data in the literature. The small sample size of our study limits the conclusions that can be drawn from this analysis, which should be considered hypothesis generating. This is a single-centre observational report on a small number of patients, without a control group.

## Limitations

The retrospective nature of the study and the small number of patients are limitations of this experience. We did not use a control group because patients without tolerance to sacubitril/valsartan in terms of hypotensive reply are generally more compromised patients. Further investigations are required to confirm our data in larger cohorts of patients.

**Figure 6** Kaplan–Meier curve of survival free from death/heart transplantation (HTx) or left ventricular assist device (LVAD) implantation in the (A) whole population and (B) according to the presence of elevated filling pressure [pulmonary capillary wedge pressure (PCWP) $>$ 15 mmHg vs. PCWP $\leq$ 15 mmHg].

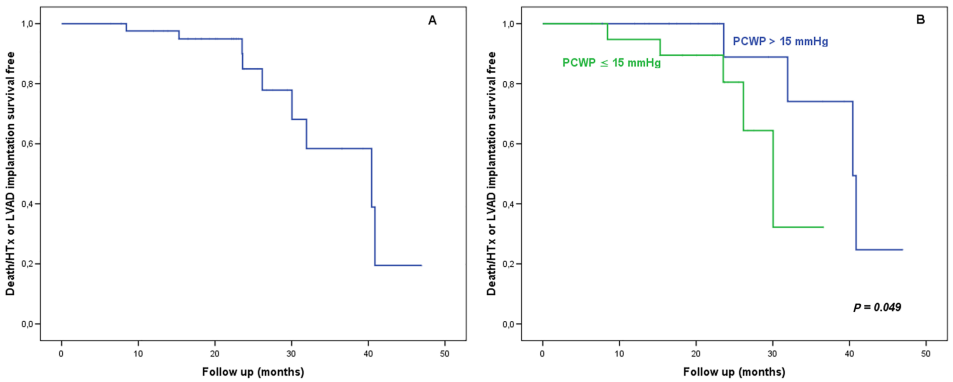
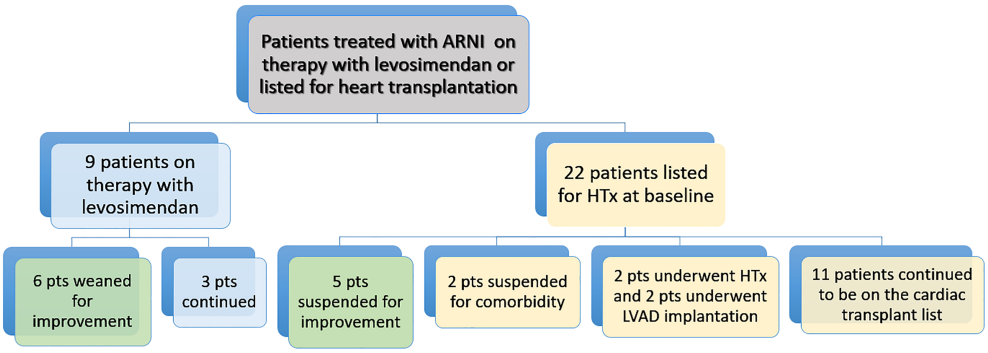


**Figure 7** Prognosis of patients on therapy with levosimendan (*N* = 9) and listed for heart transplantation (HTx; *N* = 22) at baseline. ARNI, angiotensin-II receptor neprilysin inhibitor; LVAD, left ventricular assist device.




## Conclusions

Sacubitril/valsartan was shown to be effective in reducing filling pressures and pulmonary pressures in patients with advanced HF. At 6 months of observation, there were no significant changes in the volume of the left ventricular chambers. A slight reduction in the diameter of the right ventricle and an increase in LVEF were observed. These favourable effects in surrogate endpoints such as NT-proBNP levels and mitral regurgitation may indicate a higher probability of clinical stabilization resulting in better patient outcomes.

The absence of adverse events shows that the drug can be considered safe and well-tolerated even in more fragile patients, such as those analysed in our study. These results suggest that sacubitril/valsartan can be used in this group of severely ill patients in order to treat type 2 pulmonary hypertension and right ventricle dysfunction and to preserve eligibility for HTx for patients on the waiting list.

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## Conflict of interest

The authors declare no conflict of interest.

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