

Sacubitril/valsartan in patients listed for heart transplantation: effect on physical frailty[†]

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Abstract

Aims The aim of this study was to investigate prospectively the effect of sacubitril/valsartan in advanced heart failure (HF) patients in waiting list for heart transplantation (HT) and the effect on physical frailty (PF).

Methods and results We treated 37 consecutive patients with advanced HF with sacubitril/valsartan. Patients were followed up until HT, device implant, or last follow-up visit after 2 years of follow-up. At baseline, mean New York Heart Association (NYHA) class was 3.1 ± 0.4 , with 64.9% in NYHA III and 35.1% NYHA IIIB. Left ventricular ejection fraction was $23.5 \pm 5.8\%$, VO_2 max was 10.3 ± 2.3 mL/kg/min, cardiac index was 2.3 ± 0.5 L/min/m², and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) was 4943.0 ± 5326.8 pg/mL. After a mean follow-up of 17.1 ± 4.4 months, no deaths were observed, but NYHA class improved significantly with 56.8% in NYHA II, 40.5% in NYHA III, and 2.7% in NYHA IIIB ($P < 0.001$). VO_2 max and 6 min walk test (6MWT) increased, whereas pulmonary systolic blood pressure, E/E' , VE/VCO_2 slope, and NT-pro-BNP decreased. At right heart catheterization performed after 1 year of follow-up, cardiac index and pulmonary vascular resistance remained stable, while a decrease in systolic pulmonary artery pressure and pulmonary capillary wedge pressure is observed. Furosemide dosage decrease from 102.7 ± 69.4 to 78.7 ± 66.3 mg ($P = 0.040$). PF decreased from 3.35 ± 1.0 at baseline to 1.57 ± 1.3 at the end of follow-up ($P < 0.001$), with a reduction in all PF domains.

Conclusions Our study showed a rapid improvement in PF in HT waiting list patients treated with sacubitril/valsartan. The improvement in all PF domains was paralleled by VO_2 and 6MWT increase and together with an NT-pro-BNP reduction constant over the follow-up.

Keywords Heart Failure; Sacubitril/Valsartan; Frailty

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Background

Heart failure (HF) strongly affects quality of life and physical performance.^{1,2} Treatment with sacubitril/valsartan is associated with reduction in mortality and HF admission paralleled by improved quality of life and tolerance to exercise.^{3,4} Frailty is a common condition in HF patients

with unfavourable effects on the course of disease,^{5–7} especially for those patients where physical frailty (PF) is predominant.^{8,9} Moreover, frailty provides a risk stratification in patients undergoing cardiac surgical interventions or heart transplantation (HT)¹⁰ and in patients with advanced HF undergoing surgical intervention with bridge to ventricular assist device.¹¹

Aim

The aim of this study was to evaluate the midterm effects (2 years' follow-up) on functional parameters, including PF, of sacubitril/valsartan in advanced HF patients listed for HT.

Methods

Between November 2016 and November 2018, we enrolled 45 consecutive patients with advanced HF in non-urgent waiting list for HT. Patients were required to have ejection fraction (EF) of $\leq 35\%$ and to be taking a stable dose of a beta-blocker and an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARBs) for at least 4 weeks before enrolment. Angiotensin-receptor neprilysin inhibitor was started 36 h after discontinuation of ACEI/ARB therapy. Two patients with systolic blood pressure (BP) < 90 mmHg and one patient with EF > 35 did not initiate treatment. Thus, 42 patients attended the first follow-up evaluation after 2 weeks of treatment, and then a monthly appointment was scheduled. The dosage of sacubitril/valsartan was increased if tolerance was good. All patients initiated with the dosage of 24/26 bis in die (b.i.d.).

Frailty

Frailty was considered as primary endpoint of the study and was assessed using an adapted version of Fried's frailty phenotype⁹ in a modified version previously used in advanced HF patients in waiting list for HT.¹⁰ The five functional domains assessed were exhaustion, slowness, weakness, physical inactivity, and loss of appetite. Appetite was assessed by asking: 'Have you, in the last three months, been eating more/less than usual?' A response of 'less' was classified as poor appetite.¹⁰

Cardiovascular evaluation

All patients were evaluated by means of echocardiogram, right heart catheterization, cardiopulmonary exercise test, 6 min walk test (6MWT), and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) (considered as secondary endpoints). Drug consumption, creatinine, blood urea nitrogen, sodium, and potassium were assessed at the beginning of the treatment and monthly during the treatment.

Statistical analysis

Variables are reported as means with standard deviations. Categorical variables are expressed as number (percentages).

The only variable not normally distributed was pro-BNP presented as median and inter-quartile range. We analysed before-treatment and after-treatment differences using paired Student's *t*-test for continuous variables and Fisher's exact test to compare categorical values. One-way repeated-measures ANOVA was used for normally distributed data to evaluate differences in 6MWT, systolic pulmonary artery pressure (PAPs), and PF at baseline, 1 month, 6 months, 12 months, and end of follow-up; and post-hoc Bonferroni analysis was used to evaluate differences between measures among different time points. Kruskal–Wallis test was performed for non-parametric data as NT-pro-BNP.

Results

Of the 42 patients in waiting list for HT enrolled, five patients (12.5%) discontinued therapy owing to intolerable side effects, leading the final sample to 37 patients. All patients had an implantable cardioverter defibrillator, 45.9% of patients had a cardiac resynchronization therapy, and 18.9% of patients have been previously treated with MitraClip for severe mitral regurgitation. All patients were on treatment with beta-blockers, ACEIs, or ARBs and furosemide; 62.2% with mineralocorticoid antagonist; 5.7% with metolazone; 18.9% with digitalis; and 21.6% with ivabradine (*Table S1*). After 3 months of treatment with sacubitril/valsartan, 40.5% of patients received the target dose of 97/103 mg b.i.d., 43.2% the half dose (49/51 mg b.i.d.), and 16.2% the low dose (24/26 mg b.i.d.). Dosage of beta-blockers, ivabradine and digoxin remained stable during the follow-up, furosemide decreased, and mineralocorticoid agonist was used by 73.0% instead of 62.2% at baseline. After a mean follow-up of 17.1 ± 4.4 months (minimum 10 and maximum 24 months), there were no deaths, and two patients were suspended from waiting list because of age (70 and 67 years old) in stable clinical condition. Seven patients were underwent transplantation, and treatment was discontinued. Two patients were treated with mechanical support, one total artificial heart and one left ventricular assist device (LVAD), because of worsening of clinical status. At baseline, 64.9% were in New York Heart Association (NYHA) III and 35.1% NYHA IIIB. At the end of follow-up, NYHA class improved significantly (3.1 ± 0.4 at baseline vs. 2.4 ± 0.6 at the end of follow-up; $P = 0.002$), specifically 56.8% in NYHA II, 40.5% in NYHA III, and 2.7% in NYHA III B ($P < 0.001$). PF decreased from 3.35 ± 1.0 at baseline to 1.57 ± 1.3 at the end of follow-up ($P < 0.001$) with a significant reduction in all domain of PF (*Table 1*). At the end of follow-up, 32.4% had a frailty score ≥ 3 with respect to 78.4% at baseline ($P < 0.001$). VO_2 max consumption and 6MWT increased, while pulmonary systolic BP, E/E' , VE/VCO_2 slope, and NT-pro-BNP decreased. Both diastolic and systolic BP

Table 1 Comparison of physical frailty domain before and after the start of sacubitril/valsartan

Physical frailty	Pre	Post	P value
All	3.95 ± 0.8	1.59 ± 1.3	0.000
Exhaustion	94.3	37.1	0.000
Slowness	85.7	22.9	0.000
Weakness	88.6	31.4	0.000
Physical inactivity	91.4	62.9	0.003
Loss of appetite	28.6	0	0.001

decreased, but only diastolic BP was statistically significant. No differences were observed during follow-up for left ventricular EF, tricuspid annular plane systolic excursion, and inferior vena cava, while a significant reduction in mitral regurgitation was found in 28 patients free of MitraClip (*Table 2*). Moreover, a significant decrease in furosemide dosage was observed (102.7 ± 69.4 mg to 78.7 ± 66.3 mg; $P = 0.040$), while no differences were observed in mineralocorticoid antagonist and metolazone (*Table 2*). A significant

reduction in pulmonary artery systolic and mean pressure was observed; pulmonary capillary wedge pressure measured by right heart catheterization at baseline and after 1 year of follow-up was observed. No statistically significant differences were found in right atrial pressure, diastolic pressure, cardiac index, cardiac output, and pulmonary vascular resistance (*Table 3*). These improvements occurred starting at the first month of treatment and were persistent during follow-up. The mean scores for NT-pro-BNP (*Figure 1A*), PAPs (*Figure 1B*), 6MWT (*Figure 1C*), and PF (*Figure 1D*) statistically significantly different between each time point. Post-hoc tests revealed that sacubitril/valsartan elicited a considerable reduction in NT-pro-BNP concentration from pretreatment progressively to the end of follow-up (2557.9 ± 3413.0 pg/mL) ($P = 0.008$) (*Figure 1A*). A reduction statistically significant was also observed for PAPs after 1 month of treatment and remained stable during the follow-up (*Figure 1B*). Similarly, 6MWT increased from pretreatment to the end of follow-up (*Figure 1C*), while PF reduced from pretreatment

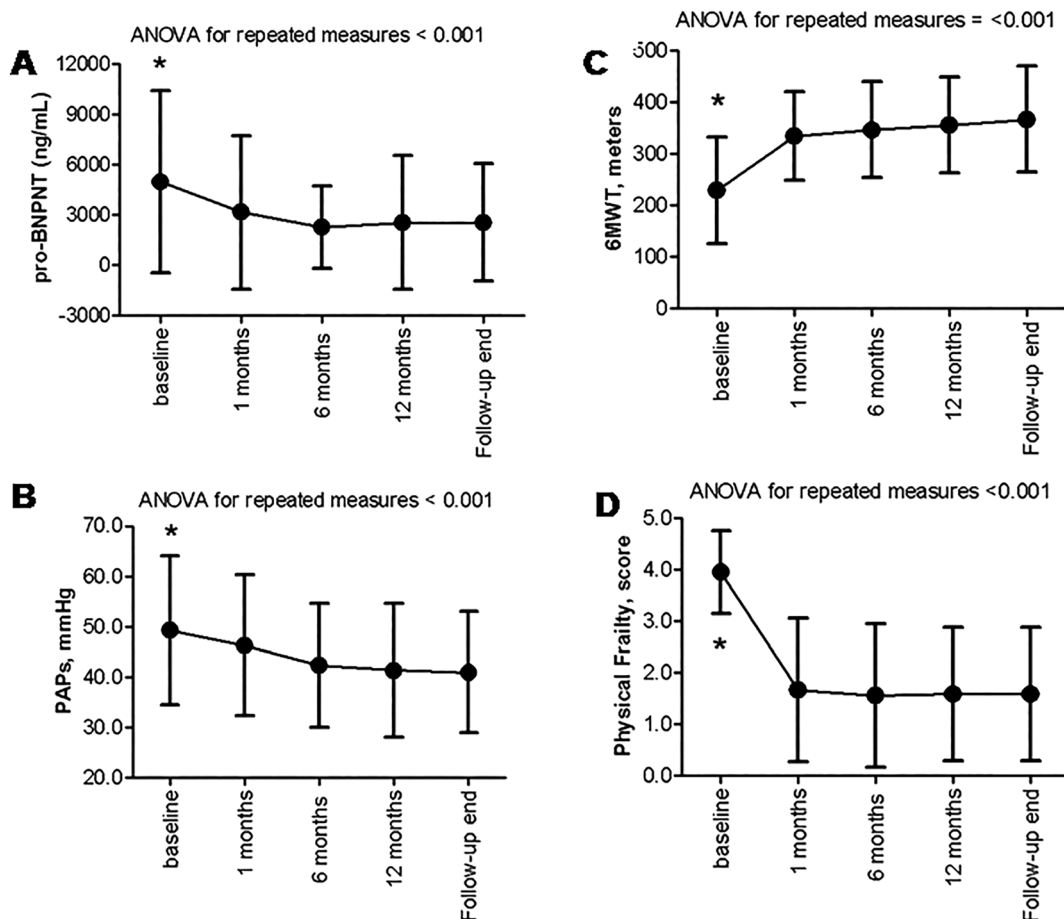
Table 2 Comparison of the analytical and clinical characteristics before and after the start of sacubitril/valsartan

Clinical features of heart failure	Pre #37	Post #37	P value
NYHA class	3.1 ± 0.4	2.4 ± 0.6	0.000
NYHA class II (%)	0	56.8	0.000
NYHA class III (%)	64.9	40.5	—
NYHA class III B (%)	35.1	2.7	—
Left ventricular ejection fraction (%)	23.5 ± 5.8	24.4 ± 6.3	0.299
E/E'	15.4 ± 5.2	13.6 ± 5.1	0.044
TAPSE	16.5 ± 4.6	16.3 ± 3.7	0.862
Pulmonary systolic blood pressure (mmHg)	49.4 ± 14.8	42.3 ± 12.3	0.013
IVC (mm)	19.3 ± 4.2	18.1 ± 4.0	0.167
Mitral regurgitation—absent (%)	25.0	32.1	0.003
Mitral regurgitation—mild (%)	46.4	42.9	—
Mitral regurgitation—moderate (%)	21.4	17.9	—
Mitral regurgitation—severe (%)	7.1	7.1	—
6 min walk test (m)	229.2 ± 103.2	367.5 ± 102.5	0.000
VO ₂ max (mL/kg/min)	10.3 ± 2.3	11.9 ± 2.6	0.000
VE/VCO ₂ (slope)	38.0 ± 10.8	34.5 ± 6.8	0.003
Systolic blood pressure (mmHg)	110.0 ± 11.5	104.3 ± 17.1	0.056
Diastolic blood pressure (mmHg)	73.1 ± 8.1	66.4 ± 10.8	0.002
Heart rate (b.p.m.)	71.3 ± 15.5	69.8 ± 11.4	0.426
Creatinine (mg/dL)	1.3 ± 0.4	1.3 ± 0.4	0.428
BUN (mg/dL)	70.4 ± 50.4	61.7 ± 30.1	0.177
Na (mEq/L)	139.0 ± 2.4	139.9 ± 2.4	0.083
K (mEq/L)	4.5 ± 0.5	4.6 ± 0.5	0.410
NT-pro-BNP (pg/mL)	4943.0 ± 5326.8	2257.9 ± 3413.1	0.000
HbA1c (%)	6.3 ± 1.0	6.2 ± 0.8	0.083
Treatment			
Furosemide (mg b.i.d.)	102.7 ± 69.4	78.7 ± 66.3	0.040
Mineralocorticoid agonist (mg b.i.d.)	36.8 ± 38.7	46.0 ± 37.0	0.136

BUN, blood urea nitrogen; HbA1c, glycated haemoglobin; IVC, inferior vena cava; NT-pro-BNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion; VE/VCO₂, ventilation/carbon dioxide production; VO₂ max, peak oxygen consumption.

Table 3 Comparison of right heart catheterization parameters before and after the start of sacubitril/valsartan

Right heart catheterization	Pre	Post	P value
Right atrial pressure (mmHg)	11.2 ± 3.4	9.5 ± 2.4	0.062
Pulmonary artery pressure systolic (mmHg)	45.3 ± 12.3	40.6 ± 11.1	0.002
Pulmonary artery pressure diastolic (mmHg)	24.4 ± 7.1	22.2 ± 7.6	0.071
Pulmonary artery pressure mean (mmHg)	32.9 ± 9.9	29.7 ± 9.5	0.000
Pulmonary capillary wedge pressure (mmHg)	24.9 ± 9.5	23.4 ± 8.3	0.039
Pulmonary vascular resistance (Wood units/m ²)	3.6 ± 2.0	3.5 ± 1.4	0.702
Cardiac output	4.7 ± 0.8	4.6 ± 0.9	0.556
Cardiac index	2.4 ± 0.5	2.3 ± 0.6	0.305

Figure 1 Mean scores for N-terminal pro-brain natriuretic peptide (NT-pro-BNP) (A), pulmonary blood pressure (mmHg) [systolic pulmonary artery pressure (PAPs)] (B), 6 min walk test (6MWT) (C), and physical frailty (PF) (D), in each time point (baseline, 1 month, 6 months, 12 months, and end of follow-up). Post-hoc tests revealed that sacubitril/valsartan elicited a considerable reduction in NT-pro-BNP concentration, PAPs, 6MWT, and PF from pretreatment to the end of follow-up (**P* < 0.01).

to 1 month (*P* < 0.000) and remained stable during the follow-up (Figure 1D). Moreover, when we analysed differences between the 15 patients who reached target dose of 400 mg vs. the 22 patients who reached 200 mg, we do not find any statistical differences in 6MWT, VO₂ max, NYHA, NT-pro-BNP, and PAPs measured at entry and after 1 year of follow-up.

Discussion

Our study demonstrates an improvement of PF in patients with advanced HF on waiting list for HT treated with sacubitril/valsartan. PF improvement was similar to that observed for 6MWT and for haemodynamic parameters, that is, NT-pro-BNP and PAPs. These changes appeared early

already in the first visit at 1 month and maintained over 2 years of follow-up.

In the present study, the main effect of sacubitril/valsartan is the improvement of functional performance including PF together with 6MWT and VO_2 max and a reduction in PAPs, E/E' , VE/VCO_2 slope, and NT-pro-BNP. At the same time, right heart catheterization demonstrated a decrease in pulmonary artery mean and systolic pressure and pulmonary capillary wedge pressure. In addition, mitral regurgitation decreased in the patients free of MitraClip.¹² Previous studies have demonstrated a strong impact of frailty on outcomes such as institutionalization and mortality.^{5–11} Even frailty is considered a typical geriatric syndrome^{5,6}; in the last decade, it is used to identify the advanced phase of chronic disease such as HF.¹³ PF is one of the domains frequently used to assess the severity of disease in order to decide the possible medical treatment (transcatheter aortic valve implantation, LVAD, and HT).^{10,11} In advanced stages of HF, a loss of skeletal muscle mass (sarcopenia) is commonly observed, and this contributes to reduced exercise capacity and frailty.^{14,15}

Limitation of the study

We acknowledge that this is a small single-centre study lacking of control group. However, the overwhelming benefit demonstrated by sacubitril/valsartan in Paradigm-HF trial³ rendered non-ethical the decision to limit this important treatment in a second arm of the study not receiving the drug.

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Conclusions

Our data established that sacubitril/valsartan could improve PF in patients with advanced HF in waiting list for HT. The relevance of this treatment is due to the rapid and persistent effect of the treatment in the midterm.

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Conflict of Interest

None of the authors have a conflict of interest in the connection with the present study (which includes honorary fee, consultancy, or other profits from the industries producing the drug).

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This study was not funded.

Supporting information

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

Table S1. Baseline characteristics of patients prior to the start of co-treatment with sacubitril/valsartan.

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