Research paper

Effect of Sacubitril-Valsartan in reducing depression in patients with advanced heart failure

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A B S T R A C T

Background: Depression is highly prevalent in Heart Failure (HF). Treatment with sacubitril/valsartan improved quality of life and survival in HF patients. Aim of the study was to investigate prospectively the effect of sacubitril/valsartan on depression in advanced HF patients in waiting list for heart transplant (HT).
Methods: 37 consecutive patients with advanced HF in waiting list for HT were treated with sacubitril/valsartan. We analyzed data derived from the assessment performed the year before the beginning of sacubitril/valsartan, at study entry, and at one year of follow-up. Depression was assessed with Beck Depression Inventory II (BDI) scale. Cognitive function were assessed with Mini-Mental State Examination (MMSE). Functioning was evaluated measuring meters at 6 Minute Walking Test (6MWT) and maximum rate of oxygen consumption (VO$_2$ max).
Results: At baseline, 64.9% of HF patients were in NYHA III and 35.1% NYHA IIIB, BDI was 15.2 $\pm$ 5.2 with 59.5% of patients with a score > 13. MMSE was 27.8 $\pm$ 2.6. After one year of follow-up NYHA class improved significantly, with 56.8% in NYHA II, 40.5% in NYHA III and 2.7% NYHA in IIIB (p < 0.001). VO$_2$ max and 6MWT increased. Notably, BDI was 9.5 $\pm$ 3.9 with 21.6% of patients with a score > 13. MMSE remain stable (28.2 $\pm$ 2.1) (p = 0.104). No statistical differences are observed between data collected in the evaluation 1-year before and soon before treatment with sacubitril/valsartan. Multivariate regression analysis demonstrate a relationship between reduction in BDI-II score and improvement in six-minute walking test independently by the effect of sex, age, selective serotonin reuptake inhibitors, VO$_2$ max, NT-proBNP, PAPs, NYHA class differences evaluated at follow-up versus baseline.
Conclusions: Our study showed a reduction in depressive symptomatology in heart transplant waiting list patients treated with sacubitril/valsartan. The improvement in depressive symptomatology was paralleled by 6MWT increase in the follow-up.

1. Introduction

Heart failure (HF) significantly affects quality of life and physical performance (Hoekstra et al., 2011; Warraich et al., 2018). Depressive disorders have a high prevalence ($\approx 20.0\%$) and incidence in patients with heart failure. Patients with heart failure in New York Heart Association (NYHA) functional class IV have nearly 4-fold higher rates of depression compared with NYHA functional class I (Abete et al., 2013, Rutledge et al., 2006). Several studies have shown that depression tends

to exacerbate coexisting heart failure and its clinical outcomes and vice versa (Vaccarino et al., 2001), especially in advanced form where prevalence is higher (38% NYHA III and 42% in NYHA IV) and the effect on mortality is 2-fold greater (Rutledge et al., 2006; Yost et al., 2017). We have previously demonstrated the effect of depressive symptoms on mortality in elderly subjects with heart failure (Testa et al., 2011). Low depressive symptomatology at time of wait-listing is related to increased survival after heart transplant (Spaderna et al., 2017). Up to now, the negative synergism between

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List of abbreviation

HF	heart failure
HT	heart transplantation
BDI	beck depression inventory
LVEF	left ventricular ejection fraction
ACE inhibitor	angiotensin converting enzyme inhibitor
ARB	angiotensin receptor blocker
ARNI	sacubitril/valsartan
NYHA	New York heart association
VO_2 max	maximum rate of oxygen consumption
NT-proBNP	N-terminal pro brain natriuretic peptide

VE/VCO2 slope	ventilation/carbon dioxide production
E/E'	the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity
TAPSE	tricuspid annular plane systolic excursion
IVC	inferior vena cava diameter
TAH	total artificial heart
LVAD	left ventricular assist device
ICD	implantable cardioverter defibrillator
CRT	cardiac resynchronization therapy
SSRI	selective serotonin reuptake inhibitors
6MWT	six minute walking test

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heart failure and depression may be approached only taking into account the complex pathophysiological characteristics underlying both these conditions, such as behavioral factors, neurohormonal activation, inflammatory mediators, hypercoagulability and vascular damage (Liguori et al., 2018). Nevertheless, the pathophysiological link between these two conditions is not well established. Pharmacological therapy with selective serotonin reuptake inhibitors, despite conflicting results, improves quality of life but does not guarantee better outcomes (Jha et al., 2019). Recently, a new class of drugs (ARNI), with two active components: sacubitril, a neprilysin inhibitor and valsartan, an angiotensin receptor blocker was indicated to treat chronic heart failure with reduced ejection fraction. The drug increases the levels of peptides that are degraded by neprilysin. Valsartan inhibits the effects of angiotensin II by blocking the AT1 receptor and by inhibiting the release of angiotensin II-dependent aldosterone, inhibiting deleterious effects mediated by angiotensin-II such as vasoconstriction, hypertrophy, and fibrosis. Sacubitril prevents breakdown of endogenous natriuretic peptides. The overall effects of ARNI are vasodilatation, natriuresis, and diuresis, as well as inhibition of fibrosis and hypertrophy. Another effect of sacubitril is the increase of endogenous enkephalins due to the inhibition of their catabolism. PARADIGM-HF study demonstrate the effect of sacubitril/valsartan in reducing risk for heart failure admission and improvement in Heart Related Quality of Life Kansas symptom score compared with treatment with enalapril (McMurray et al., 2014). All-cause mortality is less in the sacubitril/valsartan versus the enalapril group adding an average of 1 year of increased life expectancy and survival. In addition, a recent study shows that sacubitril/valsartan improves the tolerance to exercise (Vitale et al., 2019). Thus, since patients with severe heart failure on waiting list for heart transplant are difficult to treat, the aim of this study was to evaluate the effect on depression and functional parameters of sacubitril/valsartan in advanced heart failure patients.

2. Methods

In Heart Transplant Centre at Monaldi Hospital in Naples, between November 2015 and November 2018, we enrolled 37 consecutive patients with advanced heart failure in non urgent waiting list for heart transplant. Patients tolerant to Angiotensin Converting Enzyme-inhibitor (ACEi) and or Angiotensin Receptor Blocker (ARBs) were treated with sacubitril/valsartan (ARNI) after 36 hours of suspension. Patients were required to have ejection fraction of ≤35% and to be taking a stable dose of a β-blocker and an ACE inhibitor or an ARBs for at least 4 weeks before enrollment. Thus, 37 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. All patients in waiting list were previously evaluated with echocardiogram, cardiopulmonary exercise test (CPET), six minute walking test (6MWT), NT-proBNP, creatinine, blood urea nitrogen, sodium and potassium were assessed at entry in waiting list and

monthly during treatment. Cognitive function was evaluated by means of Mini-mental state examination (MMSE) (Cacciatore et al., 1998) and depression with Beck Depression Inventory II (BDI-II) (Beck et al., 1996) in the year before the beginning of sacubitril/valsartan, at study entry, and at one year of follow-up. The study was conducted in accordance with the Helsinki Declaration as revised 1989.

3. Cardiopulmonary exercise test protocol

The cardiopulmonary exercise test was performed every year during waiting list permanence and before starting administration of sacubitril/valsartan and after 12 months. All CPETs were performed using the Medgraphics Cardiorespiratory Diagnostic Systems. The relationship between minute ventilation and carbon dioxide production (VE/VCO$_2$ slope) was used as a measure of ventilatory efficiency and was calculated from 1 min after the beginning of loaded exercise up to the end of the isocapnic buffering period. Reported values of VO_2, ventilation, and tidal volume at peak exercise are the averages over the 30 s in which the examined event occurred. Percent predicted VO_2 represents the achieved peak VO_2 adjusted for age, weight, and height and expressed as a percentage. CPET was limited by symptoms (fatigue in 32/37 or dyspnea in 5/37). The CPET protocol was completed on a stationary bicycle ergometer.

3.1. Six-minute walking test

The six-minute walking test (6MWT) was performed every month during waiting list permanence, at baseline and 1 month, 6 months and 12 months over a 30 meters long straight corridor, by a nurse team dedicated to the evaluation of patients in waiting list for heart transplant. Subjects were told to "walk as quickly as you can for six minutes so that you cover as much ground as possible". They were informed that they could slow down or rest if necessary. At the end of each minute subjects were given feedback on the elapsed time and standardized encouragement in the form of statements such as "you're doing well, keep it up" and "do your best. Heart rate and oximetry were monitored continuously (Cacciatore et al., 2012).

3.2. Echocardiographic evaluation

The echocardiography evaluation was performed every month during waiting list permanence, at baseline, 1 month, 6 months, 12 months and end of follow-up. Expert cardiologists (GS and VM) who were dedicated to advanced heart failure program, performed a standard 2-dimensional and Doppler echocardiographic examination on all patients using a Philips CX50 Portable Ultrasound. The Left Ventricular Ejection Fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), pulmonary blood pressure (mmHg) (PAPs), ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e'), inferior vena cava (IVC), and mitral regurgitation (mild/moderate/severe) were evaluated.

3.3. Beck depression inventory-II

Beck Depression Inventory II (BDI-II) is widely recognized as a valid and reliable screening test for depression. The BDI-II is a 21-item self-report instrument to assess severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association 1994). Each of the 21 items of the BDI-II corresponding to a symptom of depression is summed to give a single score. Total score of 0–13 is considered minimal, 14–19 mild, 20–28 moderate, and 29–63 severe depression.

3.4. Mini mental state examination

The Mini-Mental State Examination (MMSE) was used to measure cognitive mental status.

Cognitive impairment was defined as a score of less than 24 on the MMSE (Cacciatore et al., 1998).

3.5. Drug consumption

Drugs used at baseline and follow-up were registered every monthly visit. In particular, dosage of diuretics (furosemide, metolazone and mineralocorticoid receptor antagonist) was carefully monitored during treatment. Selective serotonin reuptake inhibitors (SSRI) and other antidepressant drugs were evaluated.

3.6. Follow-up

Patients were followed monthly during the listing permanence. In this analysis we presented data collected in the year before the beginning of sacubitril/valsartan, at study entry, and at one year of follow-up.

4. Statistical Analysis

Variables are reported as means with standard deviations. Categorical variables are summarized as frequencies and percentages and were compared using $\chi2$. Kolmogorov-Smirnov test demonstrated NT-proBNP as not normally distributed and was presented as median and interquartile (IQ) range. We analyzed data collected the year before the beginning of sacubitril/valsartan, at study entry, and after one year of treatment differences using paired Student's t test for continuous variables and Fisher's exact test to compare categorical values. Kruskal-Wallis test were performed for non- parametric data as NT-proBNP. Multiple linear regression analysis was used to evaluate the relationship between delta BDI-II (score at follow-up – score at baseline) and delta 6 minute walking test (meter at follow-up – meter at baseline). Delta – VO_2 (score at follow-up – score at baseline), Delta - NT-proBNP (value at follow-up – value at baseline), Delta PAPs (value at follow-up – value at baseline), Delta – NYHA (value at follow-up – value at baseline), SSRI treatment, sex and age. We considered a p value < 0.05 to be statistically significant. We performed all analyses with SPSS, Version 12.0.

5. Results

Thirty-seven patients in waiting list for heart transplant were enrolled with a mean age of 57.7 $\pm$ 7.6 years, 89.2% male, LVEF was 23.5 $\pm$ 5.8, VO_2 max (ml/Kg/min) was 10.3 $\pm$ 2.3, cardiac index (L/min/m^2) was 2.4 $\pm$ 0.6, and NT-proBNP (pg/ml) was 3087 [IQR 1244-6812]. All patients had an Implantable Cardioverter Defibrillator (ICD), 45.9% of patients had a Cardiac Resynchronization Therapy and 18.9%

Table 1

Comparison of the analytical and clinical characteristics before and after the start of sacubitril–valsartan.

Characteristics	1-year before#37	Pre #37	Post #37	P value
NYHA class	3.1 $\pm$ 0.4	3.1 $\pm$ 0.4	2.4 $\pm$ 0.6	<0.001
BDI - II	14.9 $\pm$ 5.2	15.2 $\pm$ 5.2	9.5 $\pm$ 3.9	<0.001
MMSE	28.0 $\pm$ 1.6	27.8 $\pm$ 2.6	28.2 $\pm$ 2.1	0.104
Clinical features of heart failure				
Left ventricular ejection fraction (%)	23.6 $\pm$ 5.9	23.5 $\pm$ 5.8	24.4 $\pm$ 6.3	0.299
TAPSE	17.9 $\pm$ 4.5	16.5 $\pm$ 4.6	16.3 $\pm$ 3.7	0.862
Pulmonary systolic blood pressure (mmHg)	48.5 $\pm$ 14.3	49.4 $\pm$ 14.8	42.3 $\pm$ 12.3	0.013
E/E'	15.4 $\pm$ 5.2	15.4 $\pm$ 5.2	13.6 $\pm$ 5.1	0.044
iVC (mm)	19.8 $\pm$ 4.1	19.3 $\pm$ 4.2	18.1 $\pm$ 4.0	0.167
Mitral Regurgitation – Absent (%)	28.0	25.0	32.1	0.003
Mitral Regurgitation – Mild (%)	42.0	46.4	42.9	–
Mitral Regurgitation – Moderate (%)	24.5	21.4	17.9	–
Mitral Regurgitation – Severe (%)	5.5	7.1	7.1	–
Six Minute Walking Test (meters)	269.7 $\pm$ 187.9	229.2 $\pm$ 103.2	367.5 $\pm$ 102.5	<0.001
VO2 max (ml/Kg/min)	10.7 $\pm$ 2.2	10.3 $\pm$ 2.3	11.9 $\pm$ 2.6	<0.001
VE/VCO2 (slope)	40.0 $\pm$ 11.8	38.0 $\pm$ 10.8	34.5 $\pm$ 6.8	0.003
Systolic Blood pressure **(mmHg)**	112.3 $\pm$ 11.6	110.0 $\pm$ 11.5	104.3 $\pm$ 17.1	0.056
Diastolic Blood pressure **(mmHg)**	73.2 $\pm$ 8.3	73.1 $\pm$ 8.1	66.4 $\pm$ 10.8	0.002
Heart Rate (bpm)	72.1 $\pm$ 14.0	71.3 $\pm$ 15.5	69.8 $\pm$ 11.4	0.426
Creatinine (mg/dl)	1.3 $\pm$ 0.3	1.3 $\pm$ 0.4	1.3 $\pm$ 0.4	0.428
BUN (mg/dl)	68.4 $\pm$ 50.2	70.4 $\pm$ 50.4	61.7 $\pm$ 30.1	0.177
Na (mEq/L)	139.4 $\pm$ 2.3	139.0 $\pm$ 2.4	139.9 $\pm$ 2.4	0.083
K (mEq/L)	4.4 $\pm$ 0.6	4.5 $\pm$ 0.5	4.6 $\pm$ 0.5	0.410
NT-proBNP (pg/ml)	4604.5 $\pm$ 4124.8	4943.0 $\pm$ 5326.8	2257.9 $\pm$ 3413.1	<0.001
HbA1c (%)	6.2 $\pm$ 1.2	6.3 $\pm$ 1.0	6.2 $\pm$ 0.8	0.083
Treatment				
Furosemide – dosage (mg/die)	98.6 $\pm$ 70.4	102.7 $\pm$ 69.4	78.7 $\pm$ 66.3	0.040
Mineralocorticoid agonist (mg/die)	37.2 $\pm$ 38.5	36.8 $\pm$ 38.7	46.0 $\pm$ 37.0	0.136
Selective serotonin reuptake inhibitors (SSRI)	5 (13.5)	5 (13.5)	5 (13.5)	0.999

NYHA = New York Heart Association; DDI – II = Beck Depression Inventory; MMSE = Mini Mental State Examination; TAPSE = Tricuspid Annular Plane Systolic Excursion; IVC = inferior vena cava; VO2 max = peak oxygen consumption; VE/VCO2 = ventilation/carbon dioxide production; BUN = Blood Urea Nitrogen; NT-proBNP = N-terminal pro B-type natriuretic peptide; HbA1C = Glicated Emoglobin

P value is referred to the differences between evaluation pre and post sacubitril/valsartan treatment. No statistical differences are observed between data 1-year before and soon before treatment

of patients have been previously treated with mitraclip for severe mitral regurgitation. All patients were on treatment with beta-blockers, ACE-inhibitors or ARBs and furosemide, 62.2% were treated with miner-alocorticoid antagonist (mean dose 36.8 ± 38.7 mg/die), 5.7% with metolazone, 18.9% with digitalis and 21.6% with ivabradine. 13.5% were on SSRI treatment (**Suppl - Table 1**). After 3 months of treatment, 40.5% of patients received the target dose of 97/103 mg - bis in die, 43.2% the half dose (49/51 mg - bis in die) and 16.2% the low dose (24/26 mg - bis in die).

No statistical differences are observed between data collected 1-year before and soon before treatment with sacubitril/valsartan. After one year of sacubitril/valsartan treatment there were no deaths, 2 patients were suspended from waiting list because of age (70 and 67 years old) in stable clinical condition. Seven patients were transplanted and treatment was discontinued. Two patients were treated with mechanical support, 1 total artificial heart and 1 left ventricular assisting device because of worsening of clinical status. At baseline, mean NYHA class was 3.1 ± 0.4, with 64.9% 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). More importantly, BDI-II score decreased from 15.2 ± 5.2 with 59.5% of patients with a score > 13 to 9.5 ± 3.9 with 21.6% of patients with a score > 13 (p < 0.001). The main improvement was observed in somatic symptoms in particular in reduction in fatigue or loss of energy, changes in sleep patterns and changes in appetite. These symptoms were also the most pronounced at baseline. None of these patients have an actual diagnosis of depression. (Table 1) VO$_2$ max consumption, six Minute Walking Test increased while pulmonary systolic blood pressure, E/e', VE/VCO$_2$ slope, and NT-proBNP, decreased. Both Diastolic and Systolic blood pressure decrease, but only DBP was statistically significant. No differences were observed during follow-up for LVEF, TAPSE, IVC. No statistical significant modifications were observed for creatinine, BUN, Na and K. Similarly, no differences were observed for MMSE score (baseline 27.8 ± 2.4 vs 28.2 ± 2.1; p = 0.104) A significant reduction 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 mineral corticoids antagonist and metolazone (Table 2). Delta BDI (score at follow-up – score at baseline) was negatively correlated to delta walking test (beta = −0.554; p < 0.007) independently by the role exerted by age, sex, delta VO$_2$ max, delta NT-proBNP, delta PAPs, delta NYHA (Fig. 1), meaning that an improvement in 6MWT is accompanied by a decrease in BDI-II score. Moreover, BDI-II improvement was of 5.3 ± 2.4 in patients not treated with SSRI vs 8.0 ± 4.7 in patients treated with SSRI. In multivariate analysis SSRI treatment. (beta - 0.453 and p value = 0.040) is an independent predictor of delta-BDI-II.
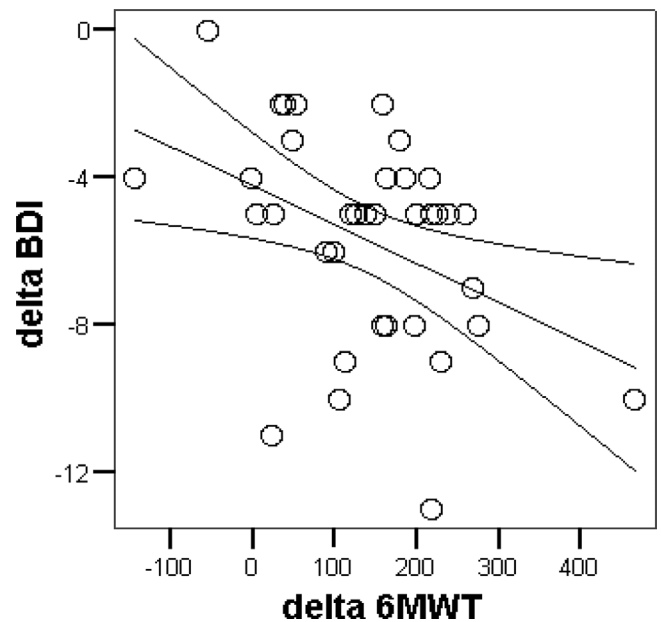

Fig. 1. Delta BDI (score at follow-up score at baseline) correlation to delta walking test independently by the role exerted by age, sex, delta VO$_2$ max, delta NT-proBNP, delta PAPs, and delta NYHA.

6. Discussion

Our study demonstrates a reduction in depressive symptomatology in patients with advanced heart failure in waiting list for heart transplant after 1 year of sacubitril/valsartan treatment. This is associated with the improvement in physical functioning as demonstrated by the positive relationship with 6MWT increase, independently by improvement in NYHA class, VO$_2$ max, NT-pro-BNP, PAPs and SSRI treatment.

6.1. Depression and heart failure

Depression is a frequent condition in patients with heart failure affecting quality of life and mortality (Rutledge et al., 2006, Testa et al., 2011). These conditions are frequently dependent one from the other, interacting at several different pathophysiological levels. Depression is a frequent condition in chronic diseases (Jokela et al., 2019) especially those in which quality of life and survival are reduced. Cardiovascular disease and heart failure affect depression through common pathways related to the induction of a pro-inflammatory and hyper-coagulability state (Khandaker et al., 2019).

In advanced heart failure the neurohormonal dysfunction is particularly involved conditioning both the progression of heart failure and the depression. In fact, acting through both hypercortisolism and

Table 2
Multiple regression analysis on delta BDI-II (score at follow-up – score at baseline).

Variable	Mean (± SD)	Beta	t	P
Delta – BDI - II	***−5.7 ± 2.9***	–	–	–
Delta – 6MWT (meters)	**138.9 ± 110.7**	**−0.464** −0.554	**−2631** −3.017	**0.014** 0.007
Delta – VO2 (ml/Kg/min)	1.6 ± 2.0	0.294 0.340	1.807 1.943	0.082 0.066
Delta - NT-proBNP	−2637.1 ± 2708.8	0.018 −0.052	0.108 −0.176	0.915 0.862
Delta PAPs	−7.0 ± 13.8	−0.168 -0.226	−1.028 −1.307	0.313 0.205
Delta - NYHA	−0.7 ± 0.6	0.150 0.136	0.828 0.727	0.415 0.476
Sex (M/F)	33/4	−0.135 0.251	0.791 1.427	0.436 0.165
Age, years	57.7 ± 7.6	0.205 0.177	1.289 1.067	0.208 0.298
SSRI	5/37	−0.453	−2.195	0.040

Delta = (score at follow-up – score at baseline); BDI – II = Beck Depression Inventory; 6MWT = Six Minute Walking Test; VO2 max = peak oxygen consumption; NT-proBNP = N-terminal pro B-type natriuretic peptide; PAPs = Pulmonary systolic blood pressure; NYHA = New York Heart Association; SSRI = Selective serotonin reuptake inhibitors

autonomic nervous system imbalance, neurohormonal dysfunction not only worsen heart failure but also depression. The proinflammatory and hypercoagulability state and the neurohormonal dysfunction lead to the next level of interaction between depression and heart failure, represented by the vascular involvement (Khandaker et al., 2019). This condition is responsible for the development and worsening of depressive state through ischemic brain lesions and for the progression of cerebrovascular disease associated with heart failure (Abete et al., 2014). Finally, the behavioral component of the interaction between depression and heart failure acts when one or both conditions are present contributing either to the rise of the other one or to their mutual worsening through social issues related to heart failure and poor compliance associated to depression (Goldstein et al., 2017). Moreover, patients who attended a cardiac rehabilitation program had significantly lower anxiety and depression scores and better medication adherence (Kotseva et al., 2018).

6.2. Sacubitril/valsartan, heart failure, cognition and depression

Treatment with sacubitril/valsartan was associated with reduction in risk for heart failure admission and improved Heart Related Quality of Life Kansas symptom score compared with treatment with enalapril (Jha et al., 2019). Up to date there are no data on the effect on depressive symptoms in advanced heart failure patients. One of possible mechanism involved in the positive effect on depression is the increase of endogenous enkephalins due to the inhibition of enkephalins catabolism, by means of neprilysin inhibition as effect of sacubitril, inducing a clinically antidepressant-like effects (Roques, 2018, Andersen et al., 2016) More attention was posed to the possible effect on dementia because neprilysin is also one of many enzymes clearing amyloid-β peptides from the brain, and consequently there is a theoretical concern about the long-term effects of sacubitril/valsartan on cognition. In PARADIGM-HF, the rates of dementia in both treatment groups were similar (Cannon et al., 2017). and this data is similar to those observed in three other recent trials conducted in patients with heart failure with reduced ejection fraction. Similar results were carried out from the Analysis of the Food and Drug Administration Adverse Event Report System Database (Perlman et al., 2018)

Other possible mechanism involved in depressive symptoms relief is the improved physical functioning demonstrated in preclinical studies, it was proposed the increase of beta-endorphin concentrations as a potential mechanism of action leading to improvement in exercise tolerance seen after treatment with sacubitril/valsartan (Maslov et al., 2018). and this is in line with our observation of an increase in physical functioning with the reduction of depressive symptoms over the time.

In conclusion, our study demonstrates a reduction in depressive symptomatology in patients with advanced heart failure in waiting list for heart transplant after 1 year of sacubitril/valsartan treatment. This is associated with the improvement in physical functioning as demonstrated by the positive relationship with 6MWT increase.

Role of the funding source

We have not financial interest and we have not received direct o indirect funding, and there is not conflict of interest.

CRediT authorship contribution statement

Francesco Cacciatore: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Cristiano Amarelli:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Ciro Maiello:** Funding acquisition, Project administration, Investigation. **Mariella Pratillo:** Investigation, Methodology, Data curation. **Piera Tosini:** Investigation, Methodology, Data curation.

Irene Mattucci: Investigation, Methodology, Data curation. **Gemma Salerno:** Investigation, Methodology, Data curation. **Francesco Curcio:** Investigation, Methodology, Data curation. **Francesco Elia:** Investigation, Methodology, Data curation. **Valentina Mercurio:** Investigation, Methodology, Data curation. **Paolo Golino:** Resources, Supervision, Validation. **Domenico Bonaduce:** Resources, Supervision, Validation. **Pasquale Abete:** Resources, Supervision, Validation.

Declaration of Competing Interest

The authors have no conflict of interest

Acknowledgment

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.03.158.

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