







Outcome of angiotensin receptor-neprilysin inhibitor on anxiety and depression in heart failure with reduced ejection fraction vs. heart failure with preserved ejection fraction

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ABSTRACT

Objective: In patients with heart failure (HF), anxiety and depression are commonly observed and confer an adverse outcome. The first-in-class member of angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril/valsartan has been demonstrated to improve functional class and decrease mortality in patients with heart failure with reduced ejection fraction (HFrEF) and reduce the readmission of heart failure with preserved ejection fraction (HFpEF). However, its effects on anxiety and depression levels remain unknown.

Methods: Sacubitril/valsartan was started on 764 symptomatic patients with HFrEF and HFpEF who were receiving guideline-directed medical therapy (GDMT) with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). Patients were evaluated using Hamilton's depression rating scale (HDRS) and the hospital anxiety and depression scale (HADS) for their levels of depression and anxiety before and after treatment at a six-month follow-up.

Results: A significant reduction in HADS and HDRS scores was observed in patients with HFrEF (9.7 ± 1.3 to 6.4 ± 0.7 , $p = 0.032$ and 19.2 ± 2.2 to 8.9 ± 1.6 , $p < 0.001$, respectively) compared with HFpEF ($p = 0.161$ and 0.273 , respectively). The six-minute walk test (6-MWT) significantly increased HFrEF from 195 ± 68 to 321 ± 97 ($p < 0.001$). There was an overall improvement in the functional class of all patients.

Conclusion: Patients with HFrEF have the additional advantage of using sacubitril/valsartan in the form of decreased anxiety and depression symptoms in addition to an improvement in functional class. However, patients with HFpEF did not exhibit significant improvement in their psychological scores.

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1. Introduction

Over the past decade, the comprehension of the complex pathophysiological mechanism involved in HF has evolved significantly, resulting in established modern treatments to reduce morbidity and increase the survival in patients with heart failure with reduced ejection fraction (HFrEF) [1]. There is, nonetheless, a lofty residual burden of morbidity and mortality, especially in patients with heart failure with preserved ejection fraction (HFpEF) [2].

Among other clinical effects, HF imparts a psychological impact on the patient. The prevalence of depression and anxiety ranges from 10–60% and 10–40%, respectively, in patients with HF [3,4]. In HF, depression can lead to decreased self-care and medical non-adherence, which is strongly associated with the worsening of symptoms, low functional class, and overall impaired health [5]. Anxiety typically co-exists with depression and can contribute to

an exacerbation of symptoms, resulting in repeated hospitalizations and poor clinical outcomes [6].

The first-in-class member of the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan has shown to reduce morbidity and confer a mortality benefit in patients with HFrEF in the PARADIGM-HF trial [7]. Hence, it has been identified as a Class I recommendation in the American Heart Association and European Society of Cardiology guidelines [8]. Although PARAGON-HF reported no mortality benefit in HFpEF, it leads to a modest improvement in the New York Heart Association (NYHA) class [9]. In addition, many studies have reported a better cardiovascular outcome with sacubitril/valsartan, but its effect on depression and anxiety levels is not yet known [10,11].

This study aimed to investigate the effect of sacubitril/valsartan on depression and anxiety symptoms via Hamilton's depression rating scale (HDRS) and the hospital anxiety and depression scale (HADS) in

HFrEF and HFpEF patients before and after six months of treatment.

2. Methods

This was an observational study and included patients on follow-up at the cardiology outpatient clinic who had a diagnosis of HFrEF and HFpEF. All patients provided written informed consent, and the study was approved by the ethical review board of our institute following the Declaration of Helsinki. All patients with an ejection fraction (EF) of less than or equal to 40% for HFrEF and more than or equal to 40% for HFpEF, with NYHA class II–IV symptoms, and receiving guideline-directed medical therapy (GDMT) with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) were included in the study from February 2020 through September 2020. Patients with decompensated left ventricular failure (LVF) at the initial visit, prior cardiac resynchronization therapy (CRT) within the previous one-year or during follow-up, a detection of malignancy, acute coronary syndrome (ACS), surgery, or history of trauma within the previous six months, known unacceptable side effects or hypersensitivity of sacubitril/valsartan, non-compliance to treatment, and any use of antidepressants or anxiolytics were excluded.

According to GDMT, sacubitril/valsartan was switched from ACEI after a 36-hour washout period, while others were directly shifted from ARB. Patients were started on an initial dose of 24/26 mg twice daily for frail patients, those with renal and liver impairment, or those taking less than a 50% ACEI/ARB dose of the target dose. A dose of 49/51 mg twice daily was started for those receiving equal to or more than 50% of the target dose. Every four weeks, the drug was up-titrated to 97/103 mg if tolerated by the patient. If side effects occurred throughout the study, the drug dose was reduced, and if the side effects were unacceptable to the patient, it was discontinued; those who discontinued the drug were excluded from the study. Beta-blockers and mineralocorticoid receptor blockers were not titrated if no adverse clinical effects were noted in patients, and a stable dose was maintained throughout the study.

Upon the initiation of sacubitril/valsartan and at the six-month follow-up, the clinical characteristics, physical examination findings, GDMT, and NYHA class of all patients were recorded. Blood was drawn to obtain a complete blood count and biochemistry. The patients' weight and height were measured, and the body mass index (BMI) was calculated. Depression and anxiety screening was performed using Hamilton's depression rating scale (HDRS) and the hospital anxiety and depression scale (HADS) by a clinical psychologist upon the initiation

of sacubitril/valsartan and at the six-month follow-up. Both questionnaires were completed during the initial visit and six-month follow-up in English in person by the psychologist. Caregivers were allowed to offer assistance if the patients were unable to answer appropriately. Functional class was assessed via a six-minute walk test (6-MWT) at those two different periods. An increase in walking distance of > 50 meters was considered clinically significant.

The HDRS is recognized as a valid screening test for depression, with a test-retest reliability quotient of 0.65 to 0.98 [12]. It is a 17-item structured interview questionnaire used to assess the severity of depression and its symptoms. Each of the 17 items of the HDRS corresponds to a symptom of depression, and it is then summed to give a single score. Scores of 0–7 are considered normal, 8–16 indicate mild depression, 17–23 indicate moderate depression, and scores above 24 are suggestive of severe depression; the maximum score is 52. Patients who scored above 17 were considered to have significant depressive symptoms. Meanwhile, the HADS is a simple seven-question self-report assessment tool for anxiety [13]. The following ranges are used in interpreting the level of anxiety: 0–7 is normal, 8–10 represents mild to moderate anxiety, and 11–21 represents severe anxiety. Patients who scored above eight indicated clinically significant anxiety.

3. Statistical analysis

The continuous variables were tested for normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Normally distributed data were expressed as the mean \pm standard deviation (SD), while non-normally distributed data were expressed as the median and a quartile range. The categorical variables were extracted as frequencies and percentages and compared with the Chi-square test. Moreover, the continuous variables were compared with the Mann-Whitney U test and Student's t-test. For HDRS and HADS, a paired sample t-test was applied. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26 (IBM, Armonk, NY). A p-value of less than 0.05 was considered significant.

4. Results

In total, 842 registered HF patients at our institute were prospectively included in the study. Thirteen patients were excluded because they were initiated on anxiolytic drugs, and nine patients were excluded because of CRT implantation. During follow-up, 36 patients died of various cardiovascular etiologies, and 11 patients were excluded due to intolerance of sacubitril/valsartan. Furthermore, nine patients were either lost by follow-up or non-compliant with the

GDMT. Therefore, a total of 764 patients with HFrEF and HFpEF were included in the study. They were followed up with for a mean duration of 176 ± 31 days.

The baseline characteristics of the patients are presented in (Table 1), and the clinical, psychological, and lab parameters are expressed in (Table 2). The mean age for HFrEF and HFpEF was 67 ± 11 and 63 ± 16 , respectively. Approximately 71.8% of the study population was male. Regarding the etiology of HF, ischemia was prevalent in 75.1%. According to the NYHA classification, a total of 208 (27.2%) patients belonged to class II, 339 (44.3%) belonged to class III, and 217 (28.4%) belonged to class IV. The patients had poor mobility and walked an average of 236 ± 47 meters during the 6-MWT. Moreover, 237 patients stopped before six minutes, and 536 (70.1%) patients walked less than 300 meters (Table 2)

The mean HDRS was 19.2 ± 2.2 for HFrEF and 16.8 ± 1.7 for HFpEF, and 339 (64.8%) patients in the HFrEF group and 126 (52.5%) in the HFpEF group had clinically significant depression. The mean HADS in the HFrEF and HFpEF groups was 9.7 ± 1.3 and 9.3 ± 0.9 , respectively, while 367 (70.1%) patients with HFrEF and 109 (45.2%) with HFpEF scored above 11, stipulating a significant anxiety state.

At follow-up, 321 (42%) patients were treated with a dose of 24/26 mg, 206 (27%) received 49/51 mg, and 237 (31%) received 97/10 mg twice daily. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and C-reactive protein (CRP) were significantly decreased in HFrEF ($p = 0.015$ and $p = 0.002$, respectively), but HFpEF did not demonstrate a statistically significant decrease ($p = 0.057$ and $p = 0.451$, respectively). However, the patients in

Table 1. Baseline characteristics

Variable	HFrEF (n=523)	HFpEF (n=241)	P-value
Age, years	67 ± 11	63 ± 16	0.531
Male, n(%)	397 (76%)	152 (63%)	0.005
Duration of heart failure, years	3.7 ± 2.6	5.4 ± 2.9	0.001
Etiology			
Ischemic n(%)	413 (79%)	161 (67%)	0.784
Non-ischemic n(%)	110 (21%)	80 (33%)	0.611
Systolic blood pressure, mmHg	116.2 ± 24	124.2 ± 19	0.157
Diastolic blood pressure, mmHg	61.1 ± 11	78.3 ± 16	0.463
Weight, kg	68.4 ± 15	73.8 ± 17	0.043
BMI, kg/m	27.5 ± 5.3	28.6 ± 4.7	0.003
HR, beats/min	81.4 ± 16	76.3 ± 14	0.934
DM	293 (56%)	103 (43%)	0.043
HTN	329 (62%)	155 (64.8%)	0.543
Dyslipidemia	221 (42.4%)	91 (38.1%)	0.165
Smoking	146 (27.9%)	87 (36%)	0.032
Atrial fibrillation	125 (24%)	64 (26.5%)	0.732
Revascularization			
CABG	98 (18.7%)	36 (14.9%)	0.176
PCI	127 (24.2%)	102 (42.3%)	0.001
Valve surgery	52 (9%)	34 (14.1%)	0.038
EF, (%)	32.6 ± 5.7	41.1 ± 9.3	0.001
Sodium, mmol/L	135 ± 4	137 ± 6	0.072
Potassium, mmol/L	4.7 ± 0.5	4.3 ± 0.6	0.523
Hgb, g/dL	11.3 ± 1.2	12.5 ± 0.9	0.171
Creatinine, mg/dL	1.2 ± 0.4	0.8 ± 0.3	0.016
NT-proBNP, ng/L	683 (342-825)	341 (211-512)	0.006
LDL-C, mg/dL	109 ± 23	117 ± 12	0.179
CRP, mg/dL	1.7 (0.2-5.3)	1.1 (0.3-4.1)	0.162
Albumin, g/dL	4.5 ± 1.2	3.6 ± 1.7	0.004
NYHA class			
Class II n(%)	81 (15.4%)	127 (53%)	0.003
Class III n(%)	256 (49%)	83 (34.4%)	0.044
Class IV n(%)	186 (35.5%)	31 (12.8%)	0.012
Beta-blocker n(%)	460 (88%)	178 (74%)	0.254
Aldosterone antagonist n(%)	423 (81%)	166 (69%)	0.003
Loop diuretic n(%)	381 (72.8%)	98 (40.6)	0.001
Ivabradine n(%)	135 (26%)	26 (11%)	0.031

Values are mean ± standard deviation or number (%), non-normal distributed variables expressed as median (minimum-maximum).

BMI: body mass index; HR: heart rate; DM: diabetes mellitus; HTN: hypertension; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; EF: ejection fraction; Hb: hemoglobin; NT-proBNP: N-terminal pro-b-type natriuretic peptide; LDL: low density lipoprotein; CRP: C-reactive protein; NYHA: New York Heart Association

Table 2. Clinical features, lab parameters, functional class, and psychological indexes at initiation and follow-up of treatment

Variable	HFrEF (n=523)			HFpEF (n=241)		
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
HADS score	9.7 ± 1.3	6.4 ± 0.7	0.032	9.3 ± 0.9	8.4 ± 1.1	0.161
HDRS score	19.2 ± 2.2	8.9 ± 1.6	<0.001	16.8 ± 1.7	15.2 ± 1.2	0.273
6-MWT, m	195 ± 68	321 ± 97	<0.001	225 ± 94	268 ± 109	0.251
NYHA class			0.024			0.116
Class I n(%)	0	188 (35.9%)	n/a	0	28 (11.6%)	n/a
Class II n(%)	81 (15.4%)	172 (32.9%)	0.041	127 (52.7%)	131 (54.4%)	0.681
Class III n(%)	256 (49%)	108 (20.7%)	0.012	83 (34.4%)	63 (26.1%)	0.152
Class IV n(%)	186 (35.5%)	55 (10.5%)	0.038	31 (12.9%)	19 (7.9%)	0.123
Sodium, mmol/l	135 ± 4	138 ± 5	0.782	137 ± 5	132 ± 3	0.822
Potassium, mmol/l	4.7 ± 0.5	4.5 ± 1.0	0.347	4.3 ± 0.6	4.7 ± 1.0	0.786
Hb, g/dL	11.3 ± 1.2	12.1 ± 1.6	0.068	12.5 ± 0.9	12.7 ± 1.2	0.172
Creatinine, mg/dL	1.2 ± 0.4	1.3 ± 0.6	0.237	0.8 ± 0.3	1.2 ± 0.6	0.115
NT-proBNP, ng/L	683 (342-825)	272 (164-523)	0.015	341 (211-512)	216 (185-418)	0.057
LDL-C, mg/dL	109 ± 23	118 ± 14	0.317	117 ± 12	109 ± 11	0.529
CRP, mg/dL	1.7 (0.2-5.3)	1.4 (0.1-4.9)	0.002	1.1 (0.3-4.1)	1.0 (0.1-3.3)	0.451
Albumin, g/dL	4.5 ± 1.2	4.3 ± 1.0	0.174	3.6 ± 1.7	3.1 ± 1.2	0.835

Values are mean ± standard deviation or number (%), non-normal distributed variables expressed as median (minimum-maximum).

HADS: hospital anxiety and depression score; HDRS: Hamilton depression rating scale; 6-MWT: six-minute walk test; NYHA: New York Heart Association; Hb: hemoglobin; NT-proBNP: N-terminal pro-b-type natriuretic peptide; LDL: low-density lipoprotein; CRP: c-reactive protein

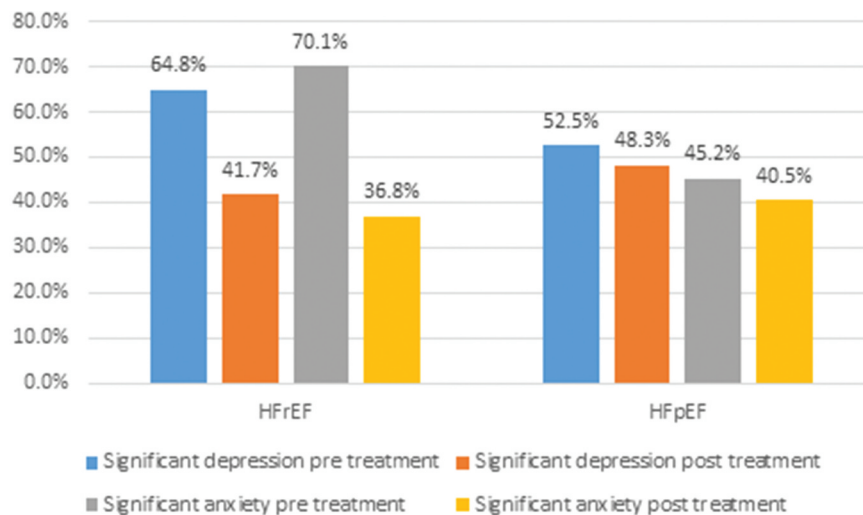


Figure 1. HDRS and HADS for a significant depression/anxiety cohort in HFrEF and HFpEF.

Significant depression was defined as HDRS of more than 17 and significant anxiety was defined as HADS of more than 8. HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction. * $p < 0.05$.

both categories (HFrEF, HFpEF) exhibited marked improvement in functional class, though it was not statistically significant in HFpEF. Symptomatic improvement was predominantly seen in patients with a higher NYHA class (III and IV) upon the initiation of sacubitril/valsartan. Moreover, the 6-MWT significantly increased in HFrEF ($p < 0.001$), and 57% of patients walked more than 300 meters after therapy.

The mean HDRS scores improved from 19.2 ± 2.2 to 8.9 ± 1.6 in HFrEF after treatment ($p < 0.001$), but no significant increase was observed in HFpEF patients ($p = 0.273$). The mean HADS score improved from 9.7 ± 1.3 to 6.4 ± 0.7 in HFrEF after treatment ($p = 0.032$). At the six-month follow-up, 23.1% of patients improved to clinically non-significant depression in HFrEF, while 4.2% did so in HFpEF ($p = 0.004$ and $p = 0.287$, respectively) (Figure 1).

5. Discussion

This study demonstrates a marked improvement in anxiety and depression indices after treatment of HFrEF patients with sacubitril/valsartan. When HFrEF and HFpEF patients were screened for anxiety and depression using HADS and HDRS upon the initiation of ARNI therapy, they revealed a myriad of depressive symptoms, even with GDMT. However, after a follow-up with the treatment, sacubitril/valsartan was shown to significantly improve anxiety and depression. The mechanism of this drug in alleviating depressive symptoms is unclear, but a hypothesis can be drawn in the ensuing literature review and discussion.

Depression is associated with the occurrence and progression of HF [14]. In various prospective studies conducted on patients with no overt heart disease, a diagnosis of depression was related to an increased risk of HF development by 20% [15]. Furthermore, depression is considered a poor prognostic marker in patients with established HF. It is associated with increased mortality, concurrent cardiac events, repeated hospital admission, and frequent use of healthcare services. Two meta-analyses and systematic reviews of 32 and 18 articles, respectively, suggested that depression is an important and independent predictor of mortality among HF patients [16,17]. In addition to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, various other criteria and scores are available for the diagnosis of depression, such as Health Questionnaire-2, Beck's Depression Index, the Geriatric Depression Scale, and the Epidemiologic Studies Depression Scale [18,19]. In this study, we adopted the HDRS to assess the severity of depression, as it does not impart an effect of somatic symptoms on the overall score; hence, it is an adequate screening tool for depression in patients with heart disease [20].

In this study, the mean HDRS was 19.2 ± 2.2 for HFrEF and 16.8 ± 1.7 for HFpEF, and 44.3% of patients had clinically significant depression upon the initiation of therapy with sacubitril/valsartan. At follow-up, the mean HDRS was reduced to 8.9 ± 1.6 , demonstrating a significant improvement of depression indices. The HADS is a common score system used to assess the general symptoms of anxiety [13].

Patients are considered to have significant anxiety if they have a score of 11 or greater in the HADS. In this study, the mean HADS decreased significantly after treatment with sacubitril/valsartan.

Most patients in our study felt somatic symptoms such as anhedonia, reduced energy, poor quality of sleep, and decreased libido. However, the exact pathophysiology of anxiety and depression in HF remains unclear. Some studies explain a hypothesis regarding the mechanism behind these symptoms and the mental state [21]. Remarkably, many somatic symptoms in depression are related to the functional status, and an improvement of the functional status in our study might serve as a key factor for improved psychological scores. It is the symptom burden that affects the overall decreased quality of life, and one study reported a relationship between functional capacity and quality of life. As such, an improvement of functional capacity can lead to a better quality of life, even with a low EF [22].

One other hypothesis can help us to understand the improvement in depression after treatment with sacubitril/valsartan. Due to various mechanisms, a systemic inflammatory response is triggered in HF [23]. One such mechanism is the stimulation of the renin-angiotensin-aldosterone system (RAAS), which can exacerbate congestive cardiac failure. Additionally, there are increased circulating inflammatory cytokines in HF that can contribute to psychological symptoms, as major depression is associated with a perpetual inflammatory state in the human body [24]. Through various computed models, sacubitril/valsartan has been shown to reduce systemic inflammation and inhibit the RAAS and neprilysin pathway, which can potentially explain the alleviation of depressive symptoms [25,26]. In our study, CRP levels were within the normal range in HF patients; however, we observed a statistically significant decrease in CRP after treatment with sacubitril/valsartan in patients with HF_{rEF}. This can support our idea of sacubitril/valsartan causing a suppressed inflammatory response and improving the psychological symptoms [27].

Symptoms of anxiety and depression are difficult to treat in patients with HF, as antidepressants are sometimes inadequate in ameliorating these manifestations [28]. Therefore, it is important to improve the functional capacity of HF patients. The results of our study demonstrated effective control of anxiety and depression symptoms in addition to an improvement in the functional class in terms of the 6-MWT. We believe that sacubitril/valsartan should be used in daily practice to reduce repeated hospitalizations and HF-associated mortality due to poor mood.

This study had several limitations. In a literature search, it was observed that different diagnostic criteria and scales were used to assess anxiety and depression.

We employed the HADS and HDRS in our study, which were convenient for the patients and our psychologist to follow. Moreover, the study was not randomized or blinded, as randomized controlled trials can determine the measure of effect in a more controlled fashion.

6. Conclusion

In symptomatic HF_{rEF} patients, despite GDMT, the switching of ACEI/ARB to sacubitril/valsartan improves anxiety and depression symptoms along with the functional class; however, no difference is observed in patients with HF_{pEF}. Different, randomized, and controlled criteria should be applied in further studies to validate our results.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

JM; concept, first and final draft, analysis, methodology, approval

AWS; first and final draft

MS; methodology, analysis, first draft

GR; data collection, methodology, final draft, analysis, supervision, approval

AK; first and final draft, approval

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