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Safety and Efficacy of Sacubitril/Valsartan drug in Heart Failure Patients

A.M.Elsheikh, K.E.Elrabat., S.A.Mostafa and A.G.Shalaby
Cardiovascular Dept., Faculty of Medicine, Benha University
E-mail: dr.elsheikh1@gmail.com

Abstract

Background: Sacubitril/valsartan, a novel angiotensin receptor-neprilysin inhibitor (ARNI), has emerged as a promising therapeutic option for heart failure patients with reduced ejection fraction (HFrEF). This study aimed to assess the safety and efficacy of sacubitril/valsartan in symptomatic NYHA class II-III heart failure patients with mildly reduced ejection fraction compared to patients with reduced ejection fraction. **Methods:** This was a multi-center prospective observational study conducted at Benha university hospital, Qaliobia , Egypt and Al-Zaitoun specialized hospital, Cairo, Egypt. The study enrolled 100 patients diagnosed with heart failure, divided into two groups: Group I (n=50) with reduced ejection fraction and Group II (n=50) with mildly reduced ejection fraction. The patients' medical and medication history, including comorbidities, were recorded. The 6-minute walk test (6MWT) was conducted at baseline and after 10 weeks of intervention with sacubitril/valsartan. The outcome measures were changes in 6MWT distance, and occurrence of adverse effects. **Results:** The study participants exhibited a high prevalence of comorbidities, with hypertension at 75%, diabetes mellitus at 61%, and ischemic heart disease at 54%. Atrial fibrillation showed a lower prevalence at 15%. In the medication history, 56% of participants had prior use of ARBs, 44% had used ACE inhibitors, and 88% were concurrently on Beta-Blockers. There was no statistical significance between baseline characteristics in both groups as regards demographic data, prevalence of comorbidities and heart failure medications. After 10 weeks of intervention, a slight improvement in the 6MWT distance was observed in both groups, although not statistically significant (P=0.062). **Conclusions:** The study demonstrated the high prevalence of comorbidities in both groups of the study with no statistically significant difference.. Sacubitril/valsartan therapy resulted in a slight improvement in the 6MWT distance in both groups.

Keywords: Heart failure; sacubitril/valsartan; ejection fraction; 6-minute walk test; comorbidities.

1. Introduction

Heart failure (HF) remains a significant global health burden, affecting millions of individuals and contributing to substantial morbidity and mortality rates worldwide. Despite advances in medical management, HF continues to challenge healthcare professionals in providing optimal therapeutic approaches. Among the therapeutic interventions developed over the years, the combination of sacubitril and valsartan has emerged as a promising option for managing heart failure with reduced ejection fraction (HFrEF) [1, 2].

Sacubitril/valsartan, also known as angiotensin receptor-neprilysin inhibitor (ARNI), represents a novel and innovative approach in HF management by targeting both the renin-angiotensin-aldosterone system (RAAS) and the natriuretic peptide system [3]. The drug works by inhibiting neprilysin, an enzyme responsible for the degradation of natriuretic peptides, while simultaneously blocking the angiotensin II receptor. This dual mechanism of action is believed to synergistically enhance the cardioprotective effects, promoting vasodilation, reducing cardiac remodelling, and ultimately improving outcomes in HF patients [4, 5].

Multiple clinical trials, such as PARADIGM-HF, have provided compelling evidence of the superior efficacy of sacubitril/valsartan compared to traditional RAAS inhibitors, like angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). These trials have mainly focused on patients with HFrEF in NYHA class II-III and have shown significant reductions in cardiovascular mortality, HF hospitalizations, and improvements in overall quality of life [6]. Consequently, this has led to the widespread adoption of sacubitril/valsartan in clinical practice guidelines and its inclusion as a first-line therapy for eligible HFrEF patients [7].

However, there remains a paucity of data evaluating the safety and efficacy of sacubitril/valsartan specifically in patients with mildly reduced ejection fraction, a subgroup of HF patients who do not meet the conventional criteria for HFrEF but still exhibit symptomatic manifestations. As these patients may represent an intermediate stage of HF, assessing the drug's impact in this population is crucial to understand its potential role in the earlier stages of the disease continuum [8, 9].

Therefore, the primary aim of this study is to assess the safety and efficacy of sacubitril/valsartan in symptomatic NYHA class II-III HF patients with mildly reduced ejection fraction, in comparison to patients with established HFrEF.

2. Methods

This study is a prospective observational single-center trial that enrolled 100 patients diagnosed with heart failure at Benha university hospital, Qaliobia, Egypt. The patients were categorized into two groups: Group I comprised 50 patients diagnosed with heart failure with reduced ejection fraction, while Group II included 50 patients with heart failure and mid-range ejection fraction. The study was done after being approved by the Institutional Review Board and informed consent was obtained from all participants included.

Inclusion criteria for patient selection were as follows: symptomatic patients with NYHA class II/III despite

being on conventional guideline-directed medical therapy, LVEF of ≤ 49% assessed through transthoracic echocardiography at baseline or within 6 months before enrolment. For patients with mildly reduced ejection fraction (40–49%), elevated natriuretic peptides (NT-proBNP > 125 pg/ml) were required, along with relevant structural heart disease or left ventricular diastolic dysfunction. Patients with LVEF < 40% needed an NT-proBNP > 125 pg/ml, but the presence of structural heart disease or diastolic dysfunction was not mandatory. Other criteria included systolic blood pressure ≥ 90 mmHg, age ≥ 18 years, and already being on ACEi or ARBs for at least 3-6 months before study enrollment.

Exclusion criteria consisted of patients already on sacubitril/valsartan before the study, hypersensitivity or intolerance to the study drugs, eGFR < 30 mL/min/1.73 m2, serum potassium > 5.5 mmol/L, severe liver dysfunction, active infection, specific cardiac conditions (primary cardiomyopathies, myocarditis &constrictive pericarditis), pregnancy or anticipated pregnancy within the next 10 weeks, complex congenital heart disease, cardiac resynchronization therapy, co-morbid conditions with a high risk of death within a year, significant stenosis of semilunar valves, and discontinuation of medication due to non-compliance or other precluding conditions.

All patients were subjected to comprehensive history-taking and clinical examinations, 12-lead ECGs, and follow-up visits at designated intervals, during which clinical assessments and investigations were conducted. Laboratory investigations included baseline serum creatinine, electrolytes, complete blood count, liver function tests, and NT-proBNP, with some tests repeated at 4 and 10weeks. Echo Doppler studies were conducted at baseline and 10 weeks, focusing on specific parameters. Additionally, patients performed a 6-minute walk test (6MWT) at baseline and 10 weeks, following standardized guidelines.

The patients received conventional heart failure treatment as needed, and the administration of sacubitril/valsartan (Entresto™) was initiated based on specific criteria. The outcome measures were changes in 6MWT distance, and occurrence of adverse effects such as hypotension, angioedema, hyperkalemia, and renal function deterioration.

Statistical analysis:

Version 26 of IBM SPSS Statistics was used to do statistical analysis (IBM Inc., Armonk, NY, USA). The normality of data distribution was examined using the Shapiro-Wilks test and histograms. Quantitative parametric data were presented as mean and standard deviation (SD) and analyzed using the unpaired Student's t-test. When appropriate, qualitative data were provided as frequency and percentage (percent) and assessed using the Chi-square or Fisher's exact test. A p-value less than 0.05 was considered statistically significant.

3. Results

The study participants' medical history and comorbidities revealed high prevalence rates of hypertension (75%), diabetes mellitus (61%), and ischemic heart disease (54%). Atrial fibrillation showed a lower prevalence (15%). **Table 1**

Table (1) Medical history and comorbidities of the study participants

	Study participants (n =100)
HTN	75 (75%)
DM	61 (61%)
IHD	54 (54%)
AF	15 (15%)

The medication history of the study participants is crucial in understanding their treatment profile. Approximately 44% of the participants had previously used ACE inhibitors (ACEi), while a higher proportion, 56%, had a history of previous Angiotensin II Receptor Blockers (ARBs) use. Moreover, a significant number of participants, 88%, were on concomitant Beta-Blockers (B.B.). Additionally, 62% of the participants were concurrently using loop diuretics, and 36% were taking Mineralocorticoid Receptor Antagonists (MRA). **Table 2**

Table (2) Medication history of the study participants

	Study participants (n =100)
Previous ACEi	44 (44%)
Previous ARBs	56 (56%)
Concomitant B.B.	88 (88%)
Concomitant loop diuretic	62 (62%)
Concomitant MRA	36 (36%)

After 10weeks of intervention, the study participants exhibited a slight improvement in the 6-minute walk test (6MWT) results. At baseline, the mean distance covered was 349.6 meters with a standard deviation of 55.2, while after 10 weeks, the mean distance increased to 355.7 meters with a standard deviation of 61.6. Though not statistically significant (P = 0.062). **Table 3**

Table (3) Change of 6MWT distance after 10 weeks from baseline data in the study participants

		Baseline (n =100)	After 10 weeks (n =100)	P value
6MWT (meter)	**Mean ± SD**	349.6 ± 55.2	355.7 ± 61.6	0.062
	Range	198 - 488	186 - 515	

4. Discussion

Unlike HFrEF patients, the treatment for HFmrEF patients is still symptom-based and empiric, without definitive strategies for this entity [10, 11].

The incidence of HFmrEF accounts for 10–25% of the population with HF [12].

In recent years, angiotensin receptor neprilysin inhibitor (ARNI) also named sacubitril-valsartan demonstrated to reduce mortality and morbidity of HF and is now a new recommended treatment option for symptomatic reduced ejection fraction (HFrEF) according to the recommendations from the American College of Cardiology (ACC), and the European Society of Cardiology (ESC) [13].

Many heart failure therapies, including Sacubitril/Valsartan drug, have been proved for their beneficial effects on morbidity and mortality in HFrEF patients. Nevertheless there are currently limited studies assessing the effects of ARNI on patients with HFmrEF [14].

The study participants demonstrated a significant burden of comorbidities commonly associated with heart failure. The high prevalence rates of hypertension (75%), diabetes mellitus (61%), and ischemic heart disease (54%) highlight the importance of considering and managing these conditions in the context of heart failure management. These comorbidities are well-established risk factors that can contribute to the development and worsening of heart failure. Hence, comprehensive management strategies addressing these comorbidities are essential in improving heart failure outcomes [15, 16].

Understanding the medication history of the study participants is crucial in gauging their previous treatment profile. The findings show that a substantial proportion of participants had prior exposure to Angiotensin II Receptor Blockers (ARBs) (56%) and ACE inhibitors (ACEi) (44%). These medications are standard therapies for heart failure with reduced ejection fraction (HFrEF) and have been shown to improve outcomes in this patient population. The high usage of concomitant Beta-Blockers (B.B.) (88%) further underscores the importance of guideline-directed medical therapy in heart failure management. However, it is worth noting that ACEi and ARBs should be discontinued before initiating sacubitril/valsartan therapy [17, 18].

The 6MWT is an important clinical tool to assess exercise capacity and functional status in heart failure patients. After 10 weeks of intervention with sacubitril/valsartan, the study participants exhibited a slight improvement in their 6MWT results, with the mean distance covered increasing from 349.6 meters to 355.7 meters. Though the change did not reach statistical significance (P = 0.062), it is noteworthy that the 6MWT is a sensitive measure and even a slight improvement may have clinical relevance. Furthermore, it is important to consider the sample size and the potential for variability in the patient population [19, 20].

The findings from this study provide valuable information on the prevalence of comorbidities and the medication profiles of heart failure patients, which can guide clinicians in tailoring individualized treatment plans. The slight improvement in the 6MWT results after 10 weeks of sacubitril/valsartan intervention suggests a potential benefit in exercise capacity. However, longer follow-up periods and larger sample sizes may be necessary to confirm the significance of these findings and identify potential subgroups that may benefit more from this therapy.

5. Conclusion

In conclusion, the results of this study shed light on the medical and medication history of heart failure patients, highlighting the high prevalence of hypertension, diabetes, and ischemic heart disease with no significant differences in patients' demographic data, medical history and comorbidities between study groups. The slight improvement in 6MWT results after 10 weeks of sacubitril/valsartan intervention warrants further investigation and emphasizes the importance of individualized treatment approaches in heart failure management. Future research should explore long-term outcomes and potential subgroup benefits to optimize the use of sacubitril/valsartan in heart failure patients.

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