JOURNAL OF RARE CARDIOVASCULAR DISEASES

The clinical outcomes from administration of angiotensin receptor-neprilysin inhibitor in heart failure patients and reduced ejection fraction: A sample from Iraqi cardiac centers

Zainab Abbass Hassan Manshad[1,*] and Nagham Yahya Ghafil[2]
[1]Al-Hussein Teaching Hospital, Thi-Qar Health Directorate, Iraq
[2]Faculty of Pharmacy, Kufa University, Iraq
Correspondance: (e-mail: zainaba.alzirjawi@student.uokufa.edu.iq).

Received 09 June 2024 Revised 10 August 2024 Accepted 30 December 2024 Published 24 February 2025

ABSTRACT **Background:** Treatment choices for heart failure vary depending on the type of heart failure and are related to the unique characteristics of each patient. The three main goals are to limit or prevent hospitalization, improve symptoms and functional capacity, and reduce mortality. Despite the latest advancements in treatment techniques for patients with heart failure with reduced ejection fraction, the prognosis remains poor and leads to harmful short- and long-term outcomes, even when symptoms improve with standard medications. Sacubitril/valsartan is a novel pharmacological therapy for heart failure with reduced ejection fraction. It is an effective medication that improves cardiac structure and function, reduces hospitalizations, and enhances the overall quality of life in patients with heart failure with reduced ejection fraction. When administered early in the course of the disease at appropriate doses, it lowers the incidence of adverse cardiovascular events and, consequently, readmission rates. **Aim of Study:** To evaluate the clinical outcomes following the administration of the sacubitril/valsartan combination in a sample of patients previously diagnosed with heart failure and reduced ejection fraction. **Patients and Methods:** This interventional trial was conducted over a seven-month period on patients with heart failure and reduced ejection fraction who were treated at one of the Cardiac Centers in Iraq. Each patient received two months of follow-up. **Results:** There was a significant decrease in the key biomarkers related to heart failure, accompanied by an improvement in the overall clinical state. **Conclusions:** The use of the sacubitril/valsartan combination in Iraqi heart failure patients yielded satisfactory clinical results.

KEYWORDS sacubitril/valsartan combination, heart failure with reduced ejection fraction

1. INTRODUCTION

Heart failure (HF) is typically the result of myocyte damage induced by coronary artery disease (CAD), hypertension (HT), and diabetes mellitus (DM) with associated complications such as diabetic nephropathy. After an acute coronary syndrome (ACS), there remains a significant risk of developing HF. HF may also be caused by, coexist with, or be worsened by atrial fibrillation (AF). Additionally, comorbidities such as previous myocardial infarction (MI) or stroke are closely linked to HF [1], [2]. Sacubitril/Valsartan (S/V), a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI), has garnered significant attention in the treatment of HF due to its dual effects on the renin-angiotensin system (RAS) and natriuretic peptides (NP) [3], [4].

According to the 2022 AHA/ACC/HFSA guidelines for the management of heart failure with reduced ejection fraction (HFrEF), increased prescription of S/V in clinical practice is recommended to maximize benefits. The guidelines emphasize demonstrating the effectiveness of the S/V combination by closely monitoring patients' clinical states throughout the study.

2. METHODOLOGY

This interventional trial was conducted over a seven-month period, from November 2023 to May 2024, on 146 patients with HFrEF, who had previously been diagnosed and were receiving treatment at the Nasiriyah Heart Center in ThiQar Province, Iraq. Patients were enrolled during their routine visits to the center's cardiac outpatient clinic and were followed up accordingly.

3. RESULTS

There were no significant differences in demographic features (gender, age, weight, BMI, and smoking history) between the two groups, as shown in Table 1. However, the control group

TABLE 1. Socio-demographic characteristics of patients

Characteristic	Group	Number	Mean ± SD	Range	P-value
Age	Intervention	73	63.89 ± 10.65	36–80	0.469
	Control	73	64.95 ± 6.35	35–72	
BMI (Kg/m^2)	Intervention	73	29.57 ± 4.48	20.7–42	0.056
	Control	73	30.97 ± 4.31	24–43	
Gender (Number (%))	Intervention	73	48 (65.8%) Male, 25 (34.2%) Female		0.307
	Control	73	42 (57.5%) Male, 31 (42.5%) Female		
Smoking (Number (%))	Intervention	–	37 (50.7%) No, 36 (49.3%) Yes		0.740
	Control	–	39 (53.4%) No, 34 (46.6%) Yes		
Education (Number (%))	Intervention	73	20 (27.4%) Illiterate, 36 (49.3%) Primary, 17 (23.3%) Secondary or higher		0.009*
	Control	73	35 (47.9%) Illiterate, 19 (26.0%) Primary, 19 (26.0%) Secondary or higher		

had a significantly higher percentage of illiterate patients (47.9%) compared to the intervention group (27.4%).

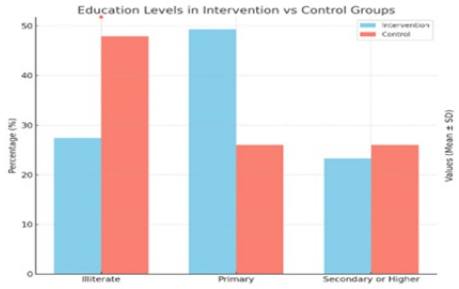

FIGURE 1. Education levels in the intervention versus control groups.

The intervention group exhibited higher educational attainment, which may positively influence health outcomes through improved understanding and management of health conditions.

3.1 Comparison of Heart Failure Etiologies between the Control Group and the Intervention Group Receiving Sacubitril/Valsartan for Two Months

No significant differences (P > 0.05) were observed in the distribution of heart failure etiologies between the control and intervention groups, as shown in Table 2. The table presents the numbers and percentages of patients with various etiologies—including CAD, HT, and DCM; CAD, HT, and DM; and CAD with AF—in each group. Furthermore, the accompanying figure (Figure 2) illustrates cardiac function parameters in both groups. Overall, the intervention group demonstrated improvements in cardiac function (with higher ejection fraction and oxygen saturation, and lower NT-proBNP levels), suggesting the effectiveness of S/V therapy in managing heart failure.

3.2 Assessment of Cardiac Function Parameters

Significant improvements were observed in key cardiac function parameters following two months of S/V therapy. Specifically, the intervention group exhibited a significant increase in ejection fraction and oxygen saturation, along with a significant decrease in NT-proBNP levels, compared with the control group. In contrast, no significant differences were found in systolic or diastolic blood pressure between the two groups, as demonstrated in Table 3.

TABLE 2. Distribution of Heart Failure Etiologies in the Control and Intervention Groups Receiving Sacubitril/Valsartan for Two Months

Etiologies of Heart Failure		Group		P-value
		Intervention	Control	
CAD, HT and DCM	Number	22	15	0.278
	%	30.2%	20.5%	
CAD, HT and DM	Number	46	49	
	%	63.0%	67.2%	
CAD and AF	Number	5	9	
	%	6.8%	12.3%	
	Total	73	73	

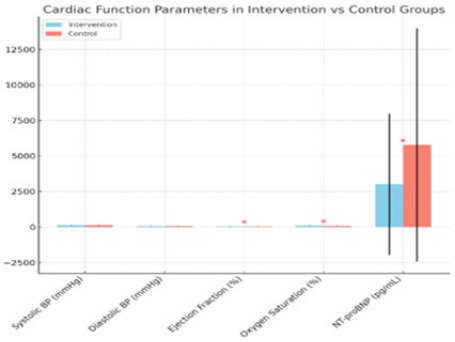

FIGURE 2. Cardiac function parameters in the intervention versus control groups.

TABLE 3. Differences in Cardiac Function Parameters between the Control and Intervention Groups Receiving Sacubitril/Valsartan after Two Months in HF Patients

Cardiac Parameter	Group	Number	Mean ± SD	P-value
Systolic BP (mmHg)	Intervention	73	125.76 ± 23.56	0.501
	Control	73	128.15 ± 19.12	
Diastolic BP (mmHg)	Intervention	73	76.60 ± 13.19	0.173
	Control	73	73.85 ± 10.99	
Ejection Fraction (%)	Intervention	73	43.59 ± 6.97	0.0001**
	Control	73	37.51 ± 6.81	
Oxygen Saturation (%)	Intervention	73	95.26 ± 3.70	0.0001**
	Control	73	90.42 ± 4.23	
NT-proBNP (pg/mL)	Intervention	73	3003.36 ± 4963.81	0.015*
	Control	73	5781.69 ± 8212.92	

4. DISCUSSION

The current study found that the intervention group had a mean age of 63.89 ± 10.65 years. A comprehensive eval-

uation comparing baseline characteristics from real-world studies and a prospective HF trial reported that patients on S/V had an average age of 63.8 ± 11.5 years [5]–[8]. In our study, the age ranges were 36–80 years for the intervention group and 35–72 years for the control group. Notably, these findings differ from another study performed on Chinese HF patients, which reported an age range of 51–72 years [9]–[13].

As shown in Table 1, the intervention group consisted of 48 male patients (65.8%) and 25 female patients (34.2%), whereas the control group included 42 male patients (57.5%) and 31 female patients (42.5%). The male-to-female ratios were 1.92:1 in the intervention group and 1.35:1 in the control group, indicating a higher incidence of HF in male Iraqi patients compared to females. This result aligns with previous findings [14]–[17]. With regard to BMI, the intervention group had a mean ± SD of 29.57 ± 4.48 kg/m^2, which is comparable to results reported in other studies [18]–[22].

The present study also showed that 49.3% of patients in the intervention group and 46.6% in the control group were active smokers during the study period. In addition, the intervention group demonstrated significantly better educational attainment than the control group (P = 0.009). The mean systolic blood pressure in the intervention group after two months of S/V therapy was 125.76 ± 23.56 mmHg, which is somewhat consistent with the PARADIGM-HF trial that reported a mean systolic BP of 122.0 ± 15.0 mmHg [23]–[29]. Furthermore, patients treated with S/V exhibited a significant improvement in ejection fraction compared to those treated with ACE inhibitors or ARBs in the control group (P = 0.0001, Table 3). Similarly, oxygen saturation significantly improved in the intervention group (P = 0.0001), which supports the role of S/V in increasing maximal oxygen uptake. Finally, there was a significant reduction in NT-proBNP levels (P = 0.037) in the intervention group from baseline to two months post-treatment, relative to the control group. These findings are consistent with results from previous trials [30]–[32].

REFERENCES

[1] Buda, Valentina, et al. "An up-to-date article regarding particularities of drug treatment in patients with chronic heart failure." *Journal of Clinical Medicine* 11.7 (2022): 2020.

[2] Cabral, Joana, et al. "Sacubitril/valsartan in everyday clinical practice: an observational study based on the experience of a heart failure clinic." *Cardiovascular Diagnosis and Therapy* 11.6 (2021): 1217-1227.

[3] Damman, Kevin, et al. "Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure." *JACC: Heart Failure* 6.6 (2018): 489-498.

[4] El-Battrawy, Ibrahim, et al. "The impact of sacubitril/valsartan on outcome in patients suffering from heart failure with a concomitant diabetes mellitus." *ESC Heart Failure* 10.2 (2023): 943-954.

[5] Hu, Tianyang, Yiting Liu, and Yake Lou. "Sacubitril–valsartan versus enalapril for the treatment of acute decompensated heart failure in Chinese settings: A cost-effectiveness analysis." *Frontiers in Pharmacology* 14 (2023): 925375.

[6] Proudfoot, Clare, et al. "Real-world effectiveness and safety of sacubitril/valsartan in heart failure: a systematic review." *International Journal of Cardiology* 331 (2021): 164-171.

[7] Sasmita, Bryan Richard, et al. "Edema index predicts mortality in patients with chronic heart failure: a prospective, observational study." *Global Heart* 19.1 (2024): 5.

[8] Zhang, Mingsong, et al. "The history and mystery of sacubitril/valsartan: From clinical trial to the real world." *Frontiers in Cardiovascular Medicine* 10 (2023): 1102521.

[9] Zhang, Rui, et al. "The efficacy and safety of sacubitril/valsartan in heart failure patients: a review." *Journal of Cardiovascular Pharmacology and Therapeutics* 27 (2022): 10742484211058681.

[10] Margiana, Ria, et al. "Functions and therapeutic interventions of non-coding RNAs associated with TLR signaling pathway in atherosclerosis." *Cellular Signalling* 100 (2022): 110471.

[11] Arif, Anam, et al. "The functions and molecular mechanisms of Tribbles homolog 3 (TRIB3) implicated in the pathophysiology of cancer." *International Immunopharmacology* 114 (2023): 109581.

[12] Lei, Zimeng, et al. "Detection of abemaciclib, an anti-breast cancer agent, using a new electrochemical DNA biosensor." *Frontiers in Chemistry* 10 (2022): 980162.

[13] Lafta, Holya A., et al. "Tumor-associated macrophages (TAMs) in cancer resistance; modulation by natural products." *Current Topics in Medicinal Chemistry* 23.12 (2023): 1104-1122.

[14] Hjazi, Ahmed, et al. "The pathological role of CXC chemokine receptor type 4 (CXCR4) in colorectal cancer (CRC) progression; special focus on molecular mechanisms and possible therapeutics." *Pathology-Research and Practice* 248 (2023): 154616.

[15] Hjazi, Ahmed, et al. "Unraveling the impact of 27-hydroxycholesterol in autoimmune diseases: Exploring promising therapeutic approaches." *Pathology-Research and Practice* 248 (2023): 154737.

[16] Gupta, Jitendra, et al. "Double-edged sword role of miRNA-633 and miRNA-181 in human cancers." *Pathology-Research and Practice* 248 (2023): 154701.

[17] Sane, Shahryar, et al. "Investigating the effect of pregabalin on postoperative pain in non-emergency craniotomy." *Clinical Neurology and Neurosurgery* 226 (2023): 107599.

[18] Farhan, Shireen Hamid, et al. "Exosomal non-coding RNA derived from mesenchymal stem cells (MSCs) in autoimmune diseases progression and therapy; an updated review." *Cell Biochemistry and Biophysics* 82.4 (2024): 3091-3108.

[19] Qasim, Maytham T., and Zainab I. Mohammed. "The Association of Helicobacter pylori Infection and Virulence Factors in Gastric Cancer in Thi-Qar, Iraq." *Asian Pacific Journal of Cancer Biology* 9.4 (2024): 541-545.

[20] Zamanian, Mohammad Yasin, et al. "Effects of resveratrol on non-melanoma skin cancer (nmsc): a comprehensive review." *Food Science & Nutrition* 12.11 (2024): 8825-8845.

[21] Hsu, Chou-Yi, et al. "MicroRNA-enriched exosome as dazzling dancer between cancer and immune cells." *Journal of Physiology and Biochemistry* 80.4 (2024): 811-829.

[22] Lv, Jing, et al. "A comprehensive immunobiology review of IBD: With a specific glance to Th22 lymphocytes development, biology, function, and role in IBD." *International Immunopharmacology* 137 (2024): 112486.

[23] Ul Hassan Shah, Zameer, et al. "Development of antihyperlipidemic drug loaded β-CD-based microparticulate carrier systems: tuning and optimization." *Polymer-Plastics Technology and Materials* 63.11 (2024): 1438-1463.

[24] Hsu, Chou-Yi, et al. "A comprehensive insight into the contribution of epigenetics in male infertility; focusing on immunological modifications." *Journal of Reproductive Immunology* (2024): 104274.

[25] Qasim, M. T., M. N. Fenjan, and H. A. Thijail. "Molecular identification of cystoisospora belli in patients infected with the virus human immunodeficiency." *International Journal of Drug Delivery Technology* 12.2 (2022): 701-704.

[26] Qasim, M. T., et al. "Ovine pasteurellosis vaccine: assessment of the protective antibody titer and recognition of the prevailing serotypes." *Archives of Razi Institute* 77.3 (2022): 1207.

[27] Qasim, Maytham T., and Zainab I. Mohammed. "Investigating treatment response and viral immunity in early rheumatoid arthritis via immune response profiling." *Journal of Rare Cardiovascular Diseases* 4.8 (2024): 166-173.

[28] Patel, Ayyub Ali, et al. "Application of mesenchymal stem cells derived from the umbilical cord or Wharton's jelly and their extracellular vesicles in the treatment of various diseases." *Tissue and Cell* (2024): 102415.

[29] Zamanian, Mohammad Yasin, et al. "Chemopreventive and Anticancer Role of Resveratrol against non-melanoma skin cancer (NMSC): Focusing on cellular and molecular mechanisms and biochemistry." *ESS Open Archive Eprints* 979 (2024): 97976792.

[30] Fakhrioliaei, Azadeh, et al. "Potential Role of Nrf2, HER2, and ALDH in Cancer Stem Cells: A Narrative Review." *The Journal of Membrane Biology* 257.1 (2024): 3-16.
[31] Ramaiah, Pushpamala, et al. "Dietary polyphenols and the risk of metabolic syndrome: a systematic review and meta-analysis." *BMC Endocrine Disorders* 24.1 (2024): 26-39.
[32] Al-Hawary, Sulieman Ibraheem Shelash, et al. "Tumor-derived lncRNAs: Behind-the-scenes mediators that modulate the immune system and play a role in cancer pathogenesis." *Pathology-Research and Practice* 254 (2024): 155123.