ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION TAKING LOW-DOSE SACUBITRIL-VALSARTAN

Department of Cardiology, Liaquat National Hospital and Medical College

Address for correspondence:
Abeer Sarfaraz
Department of Cardiology, Liaquat National Hospital and Medical College

E-mail:
abeer_sana@hotmail.com

Date Received:
6th February, 2023
Date Revised:
12th June, 2023
Date Accepted:
11th July, 2023

Kaleem Ullah Sheikh, Abeer Sarfaraz✉, Amna Farooq, Sanjana Devi, Sana Shoaib

ABSTRACT

Objective: To examine the impact of administering low-dose sacubitril-valsartan on the quality of health in individuals suffering from heart failure and reduced ejection fraction.

Methodology: It is a prospective, cohort study comprising n=77 heart failure patients from a Tertiary Care Hospital with low ejection fraction. An FDA-approved KCCQ questionnaire was used for data collection at admission and after a 6-week follow-up. Descriptive statistics were reported in terms of percentage and mean± Std. dev. For mean comparison paired t-test was used. P value <0.05 was considered statistically significant.

Results: Out of 77 patients, 28 (36.4%) were women and 49 (63.6%) were men. The study included participants with an average age of 60.05±11.80 years. Among the participants, 68.8% had hypertension and 51.9% had diabetes. 29.9% of the patients included had an EF of 30%, 49.3% had it between 31-39%, and 20.8% had an EF of 40%. Regarding classification by New York Heart Association (NYHA), before initiating Sacubitril/Valsartan, around 84.4% of patients were categorized as class 3, while 15.6% as class 4. Six weeks after therapy 79.2% of patients improved to functional class 2 and 20.8% to class 3. Statistical analysis revealed a significant difference in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores of heart failure patients when comparing scores prior to and after receiving treatment of sacubitril/valsartan, 24/26mg BID.

Conclusion: The study showed that patients with heart failure having a low ejection fraction experienced an improvement in quality of life as judged by KCCQ scores even while using sacubitril-valsartan at a low dose.

Keywords: Heart Failure; Reduced Ejection Fraction; Health-Related Quality of Life

INTRODUCTION

As a global epidemic, HF alone accounts for around 1 million admissions in the USA.[1] In the subcontinent, where about two-thirds of the nations are classified as having a poor income[2], the occurrence of HF is on the surge due to increased dominance of risk factors such as increased blood pressure and glucose levels. Asians have a higher mortality rate than other ethnic groups and are likely to develop HF at young age[2]. The potency, effectiveness, safety, and tolerability of cardiovascular medications have also been shown to vary.[2]

As a result of evolving innovations in medical therapies in patients with HF and low ejection fraction, the prognosis for heart failure has progressively improved.[3] According to the most current recommendations, a new medication has been added to the list of medications used to treat heart failure patients. The medication has proven ground-breaking results in extending survival and enhancing life quality in heart failure patients.[4] First agent approved in the new family of medications, angiotensin receptor neprilysin inhibitors (ARNI) is sacubitril/valsartan. Natriuretic peptide's cardiorenal actions and of other neprilysin substrates counterbalance effects of the sympathetic nervous system and renin-angiotensin-aldosterone system.[5] Number of CV and renal effects of NPs, including BP reduction, vasodilation, natriuresis, and diuresis, increase in glomerular filtration and renal blood flow, and inhibition of renin are mediated by second messenger cyclic guanosine monophosphate (cGMP), activated by the natriuretic peptide receptors (NPR)-A and [NPR]-B.[6] Combined approach of neprilysin and AT1 blockade demonstrated superior efficacy in reducing the hypertrophic and fibrotic effects on cardiac and renal cells induced by Angiotensin II (Ang-II). In comparison to individual neprilysin inhibition or AT1 blockade, the combined therapy more effectively attenuated these effects.[6,7]

This article may be cited as

Sheikh UK, Sarfaraz A, Farooq A, Devi S, Shoaib S. Assessment of health-related quality of life in patients with heart failure and reduced ejection fraction taking low-dose sacubitril-valsartan. J Postgrad Med Inst 2023;37(3):166-70. http://doi.org/10.54079/jpmi.37.3.3220

According to FDA approval, CHF patients with reduced ejection fraction (HFrEF) and NYHA class II, III, or IV can use it. [8] Sacubitril/valsartan is also used as an alternative to ACEIs or angiotensin II receptor blockers (ARBs) in conjunction with beta-blockers, aldosterone antagonists, SGLT-2 inhibitors, which are the standard treatments for heart failure. According to studies, this combination also reduces the number of hospitalizations for HF or CV fatalities. [8,9]

It is of utmost importance in treating HF to improve quality of life along with improving cardiovascular morbidity and mortality.[10] Hospitalizations decreased as a result of adding disease-modifying medicines which have shown benefit.[11] The patients affected by HF not only suffer from physical symptoms but their quality of life is affected due to psychosocial impact.[12] The parameters that encompass information about the efficacy of therapy from the patient's point of view described in terms of improved functional class or ability to exercise to a greater extent are now given their due recognition and acknowledgment in managing heart failure.[12]

Based on convincing evidence supporting its efficacy, recent recommendations now advocate for the utilization of sacubitril/valsartan in heart failure patients with reduced ejection fraction. [13] Though, there aren't enough statistics available for its beneficial effects in short and long-term use at a low dosage of 50mg BID. Our study mainly focuses on its short-term advantages for patients at a low dose.

METHODOLOGY

After obtaining clearance from the Institutional Review Board and Ethical Review Committee, we undertook a prospective cohort study at a Tertiary Care Hospital spanning from June 2022 to August 2022, covering a duration of six weeks. This study was centered around patients who had been diagnosed with heart failure (HF) and exhibited reduced ejection fraction. These patients received medical treatment during their stay at the hospital and were subsequently released. Subsequently, we conducted follow-up assessments with these patients at the cardiac outpatient department six weeks post-discharge. Inclusion in the study was based on the criterion that patients who had undergone KCCQ evaluations within the stipulated time frame were considered.

We included patients of any gender who fell within the adult age group (18 years and older). However, we excluded patients with incomplete medical records, those previously diagnosed with heart failure and treated with medications other than sacubitril-valsartan, individuals with HF and preserved ejection fraction, patients who exhibited hypotension during the screening phase (systolic blood pressure less than 100 mmHg), those with an estimated glomerular filtration rate (eGFR) of ≤30 ml/min/1.73 m², and individuals who were intubated or had impaired consciousness.

In our study, the definition of heart failure aligns with the ESC guidelines, which define it as the presence of typical symptoms and signs of heart failure resulting from structural or functional cardiac abnormalities. Specifically, patients with heart failure and reduced ejection fraction (HFrEF) typically exhibited a left ventricular ejection fraction (LVEF) of 40% or lower, along with symptoms categorized as New York Heart Association (NYHA) classes II, III, or IV.[14]

Essential patient information was collected using an FDA-approved questionnaire[15] designed to assess changes in quality of life before and after treatment for heart failure with reduced ejection fraction (EF). The questionnaire gathered basic personal details such as age and gender. Baseline data were collected by the Cardiology team, comprising a cardiology consultant, a third-year cardiology resident, and a senior registrar, at the time of discharge. Follow-up data was obtained six weeks after discharge at the outpatient department, in accordance with the hospital's protocol.

In our study, low-dose sacubitril-valsartan was defined as 50mg taken twice daily. The patients included in the study were already receiving guideline-directed medical therapy at tolerated doses, along with diuretics, and were classified as NYHA class III-IV.[16] To streamline the assessment process, we modified the original Kansas City Cardiomyopathy Questionnaire (KCCQ-23), which evaluates symptom frequency, social-physical limitations, and overall quality of life, into a shorter version consisting of 12 items (KCCQ-12). It is worth noting that the KCCQ-12 has demonstrated excellent clinical and overall summary scores, exhibiting a strong correlation with scores obtained from the full questionnaire. Since our study was conducted in the context of routine clinical care, using the KCCQ-12 provided a feasible option for patients.

The scores on the KCCQ range from 0 to 100 and are typically expressed in a 25-point range, reflecting a person's health status. Scores between 0 and 24 indicate very poor to poor health, scores between 25 and 49 indicate poor to fair health, scores between 50 and 74 indicate good to excellent health, and scores between 75 and 100 indicate excellent health.[17]

Based on previously published data and utilizing the online open-source tool OpenEpi, the anticipated sample size for comparing two means was determined to be 77 (for paired data) with a study power of 80% and a 95% confidence interval.[18] A non-probability sampling technique was employed. The collected data were analyzed using IBM SPSS Statistics v26.0. Descriptive statistics, frequencies, and proportions were computed based on the demographic characteristics of

Table 1: Descriptive statistics of the study population

Variables		N (%)
Age (18 years and above)	Age (in years); mean± std. dev	60.05± 11.80
Gender	Male	49 (63.6)
	Female	28 (36.4)
Co-morbidities	Hypertensive	53 (68.8)
	Diabetic	40 (51.9)
Ejection Fraction	<30%	23 (29.9)
	31-39%	38 (49.3)
	40%	16 (20.8)
NYHA Class (Beginning of Treatment)	Class I	0 (0)
	Class II	0 (0)
	Class III	65 (84.4)
	Class IV	12 (15.6)
NYHA Class (After 6 weeks of treatment)	Class I	0 (0)
	Class II	61 (79.2)
	Class III	16 (20.8)
	Class IV	0 (0)

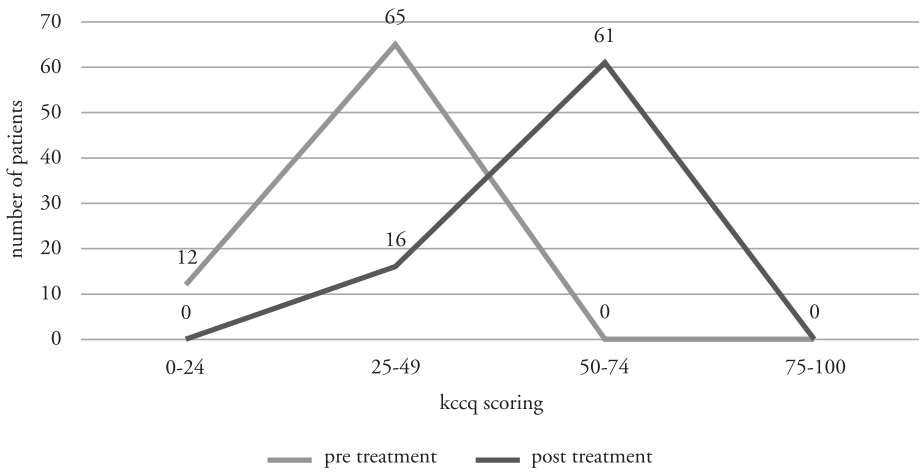

Figure 1: KCCQ score before and after treatment.

the participants and the questionnaires they completed. The summary statistics included means with standard deviations, medians with interquartile ranges, and frequencies with percentages. Mean comparisons were performed using a paired t-test. A significance level of less than 0.05 was considered statistically significant.

RESULTS

The study had 77 patients in total, of whom 28 (36.4%) were women and 49 (63.6%) were males. It included participants with average age of 60.05±11.80 years. 51.9% had diabetes and 68.8% had hypertension. All patients included in the study had reduced EF. Specifically, 29.9% had an EF of 30%, 49.3% had an EF of 31% to 39%, and 20.8% had an EF of 40%. Prior to the initiation of Sacubitril/Valsartan, 84.4% of patients were in NYHA class 3, while 15.6% were in class 4. Functional class improved 6 weeks after therapy, with 79.2% of patients in functional class 2 and 20.8% in functional class 3.

There was a significant mean difference between KCCQ before and after treatment (before 34.80±8.87, after= 55.96±11.67, p=0.000). Graph-1 compares KCCQ scores of patients with HF before and after therapy with sacubitril/valsartan 24/26mg BID. In the pretreatment group, approximately 12 patients were categorized as having very poor scores and 65 having poor to fair while post-treatment the KCCQ score of the same patients improved to 16 patients having poor to fair and 61 patients having good KCCQ scores.

DISCUSSION

Patients who have low ejection fraction and heart failure have severe physical and social impairments at baseline. Our findings relate to those of Lewis et al, who discovered that sacubitril/valsartan enhanced the patients' overall quality of life when compared to enalapril. [19] Knowing each KCCQ activity outcome allows us to communicate treatment expectations to patients and physicians much more effectively.[19] Former studies have proven the degree of impairment caused by HF is comparable to depression in social activities while it is also comparable to individuals receiving hemodialysis.[20] Angiotensin-converting enzyme inhibitors and beta blockers possess uncertain effects in improving health-related quality of life. [21] Additionally, medicines pose effects on different facets resulting in a change in score that is neutral overall.[22]

The combination of sacubitril and valsartan represents one of the few heart failure drugs which significantly and permanently decrease morbidity and mortality and the limitations on physical and social activities.[23] Many of these unbiased health-related research on the quality of life were carried out prior to KCCQ and Minnesota Living with Heart Failure Questionnaire.[24] Despite statistical significance seen in patients randomized to sacubitril/valsartan, the amount of change remained below five points on the KCCQ, which some investigators claim equates to major alterations in a patient.[25] Additionally,

sacubitril/valsartan was substantially linked to patients rising up the point scale for a variety of personal activities, including running, gardening, 100-yard walks, hobbies, housework, and romantic relationships. These findings may help understand the potential advantages of a particular treatment.[26] The limitation was a short number of patients, short duration, and single centre.

CONCLUSION

The study provides detailed information regarding the potential benefits of sacubitril-valsartan in enhancing the quality of life for patients diagnosed with heart failure with reduced ejection fraction. Notably, the study demonstrates positive outcomes even with low doses of 50mg taken twice daily. To further expand our understanding, future research could specifically focus on the influence of patient age and the etiology of heart failure in individuals receiving lower doses of sacubitril and valsartan. This investigation would provide valuable insights into the effects of the medication in different patient populations, thereby contributing to a more comprehensive understanding of its therapeutic potential.

REFERENCES

1. Velazquez EJ, Morrow DA, DeVore AD, Ambrosy AP, Duffy CI, McCague K, et al Rationale, and design of the comparison of sacubitril/valsartan versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an acute Heart Failure episode (PIONEER-HF) trial. Am Heart J. 2018; 198:145-151. DOI.10.1016/j.ahj.2018.01.004.
2. Dewan P, Docherty KF, McMurray JJ. Sacubitril/valsartan in Asian patients with heart failure with reduced ejection fraction. Korean Circ J. 2019;49(6):469-84. DOI:10.4070/kcj.2019.0136.
3. Kobalava Z, Kotovskaya Y, Averkov O, Pavlikova E, Moiseev V, Albrecht D, et al. Pharmacodynamic and pharmacokinetic profiles of sacubitril/valsartan (LCZ 696) in patients with heart failure and reduced ejection fraction. Cardiovasc Ther. 2016;34(4):191-8. DOI .10.1111/12183.
4. erreira JP, Girerd N, Rossignol P, Zannad F. Geographic differences in heart failure trials. Eur J Heart Fail. 2015;17(9):893-905. DOI.10.1002/ejhf.326.
5. Khariton Y, Fonarow GC, Arnold SV, Hellkamp A, Nassif ME, Sharma PP, et al. Association between sacubitril/valsartan initiation and health status outcomes in heart failure with reduced ejection fraction. J Am Coll Cardiol H Fail. 2019;7(11):933-41.
6. Jalal Z, Cabdi S, Khan N, Dorsch M, Gill N, Stalker F, et al. Sacubitril/valsartan in patients with symptomatic chronic heart failure with reduced ejection fraction. J Pharm Pract. 2019;1(4):182-92. DOI.10.12968/jprp.2019.1.4.182
7. Liang L, Bin-Chia Wu D, Aziz MI, Wong R, Sim D, Leong KT, et al. Cost-effectiveness of sacubitril/valsartan versus enalapril in patients with heart failure and reduced ejection fraction. J Med Econ. 2018 ;21(2):174-81. DOI.10.1080/2017.1387119.
8. Spertus JA, Jones PG. Development and validation of a short version of the Kansas City Cardiomyopathy Questionnaire. Circ Cardiovasc Qua Outcomes. 2015;8(5):469-76. DOI: 10.1161/CIRCOUTCOMES.115.001958
9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891-975.
10. Giallauria F, Vitale G, Pacileo M, Di Lorenzo A, Oliviero A, Passaro F, et al. Sacubitril/valsartan improves autonomic function and cardiopulmonary parameters in patients with heart failure with reduced ejection fraction. J Clin Med. 2020;9(6):1897. DOI: 10.3390/jcm9061897
11. Ferreira JP, Duarte K, Graves TL, Zile MR, Abraham WT, Weaver FA, et al. Natriuretic peptides, 6-min walk test, and quality-of-life questionnaires as clinically meaningful endpoints in HF trials. J Am Coll Cardiol. 2016;68(24):2690-707.
12. Alosco ML, Spitznagel MB, Cohen R, Sweet LH, Hayes SM, Josephson R, et al. Decreases in daily physical activity predict acute decline in attention and executive function in heart failure. J Card Fail 2015;21(4):339-46. DOI.10.1016/j.cardfail.2014.12.010.
13. Chang HY, Feng AN, Fong MC, Hsueh CW, Lai WT, Huang KC, et al. Sacubitril/valsartan in heart failure with reduced ejection fraction patients: real world experience on advanced chronic kidney disease, hypotension, and dose escalation. J Cardiol. 2019;74(4):372-80. DOI.10.1016/j.jjcc.2019.03.010.
14. Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in clinical trials and clinical care: JACC state-of-the-art review. J Am Coll Cardiol. 2020;76(20):2379-90. DOI: 10.1016/j.jacc.2020.09.542
15. Campal JM, Del-Castillo H, Rivera BA, de Juan Bitria C, Urquia MT, Borque PS, et al. Improvement in quality of life with sacubitril//valsartan in cardiac resynchronization non-responders: The RESINA (RESynchronization plus an Inhibitor of Neprilysin/Angiotensin) registry. Cardiol J. 2021;28(3):402-10.
16. Proudfoot C, Studer R, Rajput T, Jindal R, Agrawal R, Corda S, et al. Real-world effectiveness and safety of sacubitril/valsartan in heart failure: a systematic

review. Int J Cardiol. 2021;331:164-71. DOI: 10.1016/j.ijcard.2021.01.061
17. van den Berge JC, van Vark LC, Postmus D, Utens EM, Hillege HL, Boersma E, et al. Determinants of quality of life in acute heart failure patients with and without comorbidities: a prospective, observational study. Eur J Cardiovasc Nurs. 2022;21(3):205-12. DOI:10.1093/eurjcn/zvab061.
18. Lewis EF, Claggett BL, McMurray JJ, Packer M, Lefkowitz MP, Rouleau JL, et al. Health-related quality of life outcomes in PARADIGM-HF. Circ Heart Fail. 2017;10(8).e003430. DOI: 10.1161/CIRCHEARTFAILURE.116.003430
19. Wachterman MW, Pilver C, Smith D, Ersek M, Lipsitz SR, Keating NL. Quality of end-of-life care provided to patients with different serious illnesses. JAMA Intern Med.2016;176(8):1095-02.DOI:10.1001/jamainternmed.2016.1200.
20. Turgeon RD, Barry AR, Hawkins NM, Ellis UM. Pharmacotherapy for heart failure with reduced ejection fraction and health-related quality of life: a systematic review and meta-analysis Eur J Heart Fail. 2021;23(4):578-89.
21. Riaz M, Smith SM, Dietrich EA, Pepine CJ, Park H. Effectiveness of sacubitril/valsartan versus aldosterone antagonists in heart failure with reduced ejection fraction: A retrospective cohort study. Pharmacotherapy: J Human Pharmacol Drug Therap.2021;41(9):710-21. DOI:10.1002/phar.2610
22. Martens P, Belien H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. Cardiovasc Ther. 2018;36(4). e12435. DOI: 10.1111/1755-5922.12435
23. Tsutsui H, Momomura SI, Saito Y, Ito H, Yamamoto K, Sakata Y, Desai AS, Ohishi T, Iimori T, Kitamura T, Guo W. Efficacy and Safety of Sacubitril/Valsartan in Japanese Patients with Chronic Heart Failure and Reduced Ejection Fraction-Results From the PARALLEL-HF Study. Circ J. 2021;85(5):584-94. DOI:10.1253/circj.CJ-20-0854
24. Karim MA, Siddiqui HU, Ullah S, Khan NA. Sacubitril/Valsartan: Practice Changing Guideline in the Management of Congestive Heart Failure. J Coll Physicians Surg Pak. 2017;27(11):733-40.
25. Wu Y, Tian S, Rong P, Zhang F, Chen Y, Guo X, et al. Sacubitril-valsartan compared with enalapril for the treatment of heart failure: A decision-analytic markov model simulation in China. Front Pharmacol. 2020;11:1101. DOI:10.3389/fphar.2020.01101
26. Piepoli MF, Hussain RI, Comin-Colet J, Dosantos R, Ferber P, Jaarsma T, Edelmann F. OUTSTEP-HF: randomised controlled trial comparing short-term effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction. Eur J Heart Fail. 2021;23(1):127-35. DOI: 10.1002/ejhf.2076.

Author's Contribution

KUS conceived the idea and drafted the manuscript and performed data analysis. AS drafted the manuscript and checked for technical issues manuscript. AF and SS helped in designing and data collection for the study and drafting of the manuscript. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

Grant Support and Financial Disclosure

None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.