ORIGINAL ARTICLE

EVALUATION OF ANGIOTENSIN RECEPTOR AND NEPRLYSIN INHIBITION (ARNI) IN PATIENTS OF HEART FAILURE WITH REDUCED EJECTION FRACTION (HFREF) - A REAL-WORLD STUDY

Mohammad Hafizullah[1], Wahaj Aman[2], Hisar Afridi[3]

[1]Lady Reading Hospital, Peshawar, Pakistan, [2]Memorial Hermann Hospital, Katy, Texas, [3]Shamshatu BHU, Peshawar, Karachi, Pakistan

Objectives: This is a real world prospective study to evaluate the effects of Neprlysin Inhibition (ARNI) using sacubitril/valsartan in patients with heart failure with reduced ejection fraction (HFrEF).

Methodology: This was an outpatient study on patients of HFrEF (EF<40%) and stable blood pressure after obtaining informed consent. Consecutive patients were enrolled and followed at 6 and 12 weeks. Detailed clinical and echocardiographic examinations were performed on all visits. Biochemistry evaluating ProBNP, renal profile, HbA1C and electrolytes were performed in 24 patients at baseline and follow-up.

Results: We enrolled 80 patients, but 63 patients could be followed. Mean age was 53.54±13.32 years and 55% were males. After 12 weeks treatment improvement in NYHA functional class was seen in 66% and improvement by more than one grade in 31% (p<0.01). Pro-BNP reduced from 3552.71±1804.74 at the baseline to 723±930 on the second FU visit (p<0.002). Structural improvement was seen in 33% of patients. Left ventricular (LV) end-diastolic diameter (EDD) reduced by 3.49 mm and LV end systolic diameter (ESD) by 3.97 mm (p<0.014). Fractional shortening (FS) increased by 2.07% and EF by 3.52 (p<0.01). Patients tolerated the drug well, but most could not tolerate the higher recommended dosage. Renal status, electrolytes, and HbA1C did not alter significantly.

Conclusion: Treatment with sacubitril/valsartan in addition to the guideline directed medical therapy (GDMT) resulted in marked reduction in ProBNP, significant improvement in functional class and enhancement of cardiac pumping activity with reduction in LVEDD and LVESD and improvement in FS and EF.

Keywords: Sacubitril/Valsartan, Heart failure, Reduced EF

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INTRODUCTION

Heart failure (HF) results from all cardiac insults sustained over time and is the most increasing cardiovascular ailment in the current scenario. It is estimated that 20% of people aged 40 years and above will develop heart failure in their lifetime. The prevalence of HF is speculated to rise in developed and developing countries as age increases and facilities for treatment improve. In the US, it is supposed to increase from 2012 to 2030 by 46%.[1]

Inhibition of renin-angiotensin-aldosterone system (RAAS) employing Angiotensin converting Enzyme Inhibitors (ACEI) was shown convincingly to reduce mortality and morbidity in patients with heart failure in the setting of reduced EF, and hence ACEI ruled the world of heart failure like an undisputed king for more than three decades.[2,3] Later, Angiotensin Receptor Blockers (ARBs) were shown to have similar but inconsistent effects – showing no clear superiority on ACEI hence reserved for patients who could not tolerate ACEI.[4]

PARADIGM-HF introduced a new rival to the hegemony of ACEI in the form of sacubitril/valsartan combination in patients with HF with reduced EF (HFrEF).[5-7] Sacubitril/valsartan was superior to ACE inhibition alone in reducing death risks and hospitalization for heart failure, and it reduced heart failure's symptoms and physical limitations (p=0.001) compared to enalapril. Instructively the extent of the beneficial effect on CV mortality was more than that of the long-term treatment with enalapril, as compared

with a placebo in patients with heart failure.[3] This finding credences that combined inhibition of the sacubitril/valsartan is superior to inhibition of RAAS alone in patients with chronic heart failure.

Neprilysin is an endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin.[8] When neprilysin is inhibited, it resultantly increases the levels of these substances. This counteracts the neurohormonal stimulation leading to vasoconstriction, sodium retention, and maladaptive remodeling.[9] Inhibition of RAAS and neprilysin together demonstrated superior effects to those of either approach alone in experimental studies.[10] Neprilysin's role in the treatment of heart failure was appreciated and more studies were conducted in HF patients.[11]

Our local experience dictates that we have a different patient population, and they have varied responses to drugs. No prospective study has been done employing sacubitril/valsartan in this patient cohort locally. This project was undertaken as a real-world prospective open-label single-center study to monitor patients' hemodynamics, functional status, echocardiographic and biochemical response to sacubitril/valsartan in the short term in patients with heart failure with low EF who were either switched from ACEI/ARB or started de novo on sacubitril/valsartan.

METHODOLOGY

This was a real-world prospective single-center study open-label study conducted in an outpatient setting in a cardiology speciality clinic on all comers with an established diagnosis of heart failure of any age and sex from January 2021 to June 2021. Consecutive patients with HFrEF were enrolled in the study. Informed written consent was obtained from all patients. Patients were enrolled in NHYA II to IV with either decompensated or compensated status with systolic blood pressure (SBP) of more than 110 mm Hg. Patients were examined in detail, and their demographics were recorded. All patients underwent detailed echocardiographic examination - documenting EF of less than 40%. Detailed demographics were recorded, and clinical and echocardiographic examinations were repeated at the baseline.

Biochemistry entailing Pro BNP, renal profile, electrolytes and HbA1C was performed on 24 patients at the baseline and repeated at 6- and 12-weeks intervals. Patient data were recorded at the baseline and two follow-up visits at 6 and 12 weeks.

All patients served as their control and paired. T-test was applied for all continuous parameters. Data from the patients completing the study was analyzed. Data were stored and analyzed using IBM-SPSS version 23.0, and counts with percentages were given for qualitative variables. Whereas mean with standard deviation was given for quantitative parameters from baseline to the third visit. Wilcoxon signed Ranks test was used to measure the difference from baseline to first and final visit for qualitative variables. A paired sample t-test was done to compare the mean differences from baseline to second and third visit for quantitative parameters. P-values less than 0.05 were considered statistically significant. Bar diagrams were used to give a graphical presentation of the data.

RESULTS

Demographics: In total, 80 patients were enrolled in the study, but 63 patients could be followed up, hence their analysis is being presented here. The average age was 53.54 ± 13.32 years. Of them, 55% were males; all patients had LV EF less than 40%, and 75% had ischemic cardiomyopathy. The average duration of heart failure was 1.75 ± 3.2 years. Of them, 75% had documented coronary artery disease, 30% had hypertension, and 23% had diabetes mellitus. Most patients were already on evidence-based treatment. All patients were on diuretics and ACEI or ARBs, 82.5% on aldosterone, 88% on beta-blockers, 44.4% on nitrates, 9.5% on Digoxin, and 19% on Ivabradine. At the baseline, 44.4% of patients were in decompensated status. Most patients were in sinus rhythm except for 9.5% in AF Table 1.

Table 1: Baseline characteristics of study participants

Characteristics	Summary
Age (years)	53.54 ±13.32
Heart Failure Duration (years)	1.75±0.72
Sex	
Male	28 (71.8)
Female	11 (28.2)
Co-morbid conditions	
Isch CM	29 (74.4)
COCM	9 (23.1)
Others	2 (5.1)
Coronary artery disease	28 (71.8)
Hypertension	7 (17.9)
Diabetes mellitus	8 (20.5)

Hemodynamics: All patients were reviewed after 6 and 12 weeks. Seven patients did not report for follow-up, and ten for the second follow-up. A complete

follow-up on 63 patients is being presented. Average heart rate was 82.05 ± 15.37 at baseline, on the first FU visit, 79.54 ± 13.69, and on the second follow-up, 76.67 ± 15.41 (p<0.04). Systolic blood pressures were 114 ± 14.67 at baseline, on first visit 110.4 ± 16.17 and second visit 109.5 ± 16.94 (p=0.16) and diastolic BP 71.62 ± 11.52, on first visit 71.15 ± 11.09 and second visit 70.14 ± 10.60 (p=0.81). Weight was recorded as 74.82 ± 14.66 kg at baseline and reduced to 73.53 ± 11.76 kg at the first FU visit and 72.49 ± 14.71 at the second FU visit (p<0.01) Table 2.

Table 2: Quantitative outcomes

	Baseline	2nd Visit	3rd Visit	P-value
Pulse Rate	82.05 ± 15.37	79.54 ± 13.69	76.67 ± 15.41	0.04
Systolic BP	114.36 ± 14.67	110.4 ± 16.17	109.5 ± 16.94	0.16
Diastolic BP	71.62 ± 11.52	71.15 ± 11.09	70.14 ± 10.6	0.81
Weight	74.82 ± 14.66	73.53 ± 11.76	72.49 ± 14.71	0.01
LVEDD	65.02 ± 5.21	63.4 ± 5,5	61.53 ± 5.6	0.014
LVESD	54.84 ± 5.59	53.2 ± 5.9	50.87 ± 7.58	0.014
LV FS	15.65 ± 2.23	16.08 ± 2.42	17.72 ± 3.29	0.01
LV FF	330.94 ± 4.43	32.5 ± 4.73	34.46 ± 5.12	0.01

Echocardiographic parameters: All patients underwent detailed echocardiographic examination at the baseline and on first and second follow-up visits. Left ventricular end-diastolic diameter (LVEDD) was 65.02 ± 5.21 cm at the baseline and significantly reduced to 63.40 ± 5.5 cm on the first visit and 61.53 ± 5.6 cm (p<0.014) on the final visit after 12 weeks of treatment. Left ventricular end-systolic diameter (LVESD) was 54.84 ± 5.59 at the baseline and decreased significantly to 53.2 ± 5.9 at the first follow-up and 50.87 ± 7.58 at the second follow-up visit (p<0.014). Left ventricular function improved as determined by echocardiography. Fractional shortening increased from 15.65 ± 2.23% at the baseline to 16.08 ± 2.42% on the first FU visit and 17.72 ± 3.29% on the final visit (p<0.01). Calculated ejection fraction increased from 30.94 ± 4.43% at the start to 32.50 ± 4.73% on first FU visit to 34.46 ± 5.12% on the final visit. Not all patients showed evidence of positive remodeling; only 33.3% of patients showed a reduction in LV end-systolic and diastolic dimensions and an improvement in LV pumping capacity Table 2.

Functional evaluation: At baseline, 44.4%; on the first visit, 22.2% and on the second visit, 0 patients were in decompensated status (p<0.01). NYHA status was documented on all visits – at the baseline, there was none in NHYA I, 38.1% in NYHA II, 52.4% in NYHA III and 9.5% in NYHA IV. On the first visit, most patients exhibited improvement in exercise capacity and functional class: on the first FU visit, patients in NYHA I were 31.7%, NYHA II 66.66%, and NYHA III 1.6%. On the second FU visit, after 12 weeks of treatment, patients in NYHA I were 41.7%, NYHA 66.66% and NYHA III 1.6%, and none in NYHA IV (p<0.024). Patients presenting in NYHA IV at the baseline, 50% improved to NYHA I and 33.3% to NYHA II on the first visit. On the second visit, 66 % improved to NYHA I and 33.3% to NYHA II (p<0.02). More than 66% showed improvement in a functional class by one grade and 31% by more than one grade Table 3.

Table 3: Functional evaluation for NYHA after visits 1 and 2

	NYHA Baseline		
	II	**III**	**IV**
	6 (25)	14 (58.3)	4 (16.7)
NYHA After visit 1			
I	12 (70.6%)	2 (11.8%)	3 (17.6%)
II	2 (33.3%)	4 (66.7%)	0 (0.0%)
III	0 (0.0%)	0 (0.0%)	1 (100.0%)
IV	0	0	0
P-value	0.014		
NYHA after visit 2			
I	14 (60.9%)	6 (26.1%)	3 (13.0%)
II	0 (0.0%)	0 (0.0%)	1 (100.0%)
III	0	0	0
IV	0	0	0
P-value	0.01		

Biochemical profile: Pro BNP, renal profile, electrolytes, and HbA1C were performed on 24 patients and repeated at 6- and 12-weeks intervals. A significant reduction in Pro BNP was seen from baseline to two subsequent follow-up visits. It reduced from 3552.71 ± 1804.74 at the baseline to 1756 ± 1098 on the first FU visit to 723 ± 930 on the second FU visit (p<0.002). HbA1C did not change significantly. It was 6.06 ± 0.89 at the baseline, 6.20 ± 0.89 on the first FU visit, and 6.16 ± 0.76 on the final visit (p=0.13). Urea and creatinine did not change appreciably (p = NS). Sodium and Potassium remained the same over 12 weeks of the treatment period (p=0.13) Table 4.

Dosage, Safety, and tolerance: Fifty-seven percent of patients could tolerate 24/26 BD dosage, only 18.8% could tolerate high dosage 49/51 BD, whereas 23.8%

required a reduction of dosage to once a day at night. In 50.7% of patients' diuretic and mineralocorticoid, doses could be reduced, and Ivabradine could be stopped in five patients. Most patients tolerated it very well except 23.8% of patients, for which dosage had to be adjusted due to a reduction in blood pressure.

Table 4: Biochemical profile of the patient

	Baseline	2nd Visit	3rd Visit	p-value
Pro BNP	3552.71 ± 1804.74	1756.32 ± 1098.71	723.26 ± 930.09	0.002
HbA1c	6.06 ± 0.89	6.2 ± 0.89	6.16 ± 0.76	0.13
Urea	43.67 ± 11.7	52.21 ± 41.81	42.63 ± 16.14	0.13
Creatinine	1.11 ± 0.29	1.27 ± 0.71	1.08 ± 0.27	0.19
Sodium	138.17 ± 3.86	136.57 ± 4.6	138.09 ± 3.74	0.34
Potassium	4.21 ± 0.54	4.25 ± 0.57	4.27 ± 0.53	0.89

DISCUSSION

This is a real-world single-center prospective study that offers a wealth of information on hemodynamic effects, functional evaluation, and evaluation of cardiac structure and function assessed non-invasively in HFrEF patients in various NYHA classes treated with sacubitril/valsartan. It is unique as there is a paucity of international and national real-world studies. It evaluates the effects of sacubitril/valsartan in patients with HFrEF who were already on ACEI or ARBs or de novo initiation in an outpatient setting.

It shows convincing improvement in functional evaluation in two-thirds of patients, with more than 66% showing improvement in a functional class by one grade and 31% by more than one grade. Weight was reduced significantly with a little reduction of SBP and DBP. Patients presenting with decompensated status improved over 12 weeks. Diuretics and MRA could be reduced in nearly half of patients. Structural improvements were observed with a significant increase in fractional shortening and ejection fraction with a reduction of LV end-diastolic and systolic dimensions in nearly one-third of the population. Left ventricular end-diastolic diameter was reduced by 3.49 cm and end-systolic diameter by 3.97 cm ($p<0.014$). Left ventricular function improved as determined by echocardiography, fractional shortening increased by 2.07% and ejection fraction (EF) by 3.52% ($p<0.01$). Some patients showed more dramatic improvement. However, when data was averaged for the whole group, it remained highly significant.

In a study on 80 patients with HFrEF, guideline-directed therapy starting sacubitril/valsartan was possible in 89% of patients. Clinically significant improvement was seen with treatment with sacubitril/valsartan as NYHA functional classification score (2.3 vs. 1.9, $p<0.001$), Minnesota Living with Heart Failure Questionnaire score (46 vs. 38, $p=0.016$), left ventricular ejection fraction (26% vs. 33%, $p<0.001$) and left ventricular end-systolic diameter (5.2 vs. 4.9 cm, $p=0.013$) compared with baseline. There were no significant changes in renal function or serum potassium.[11] In a retrospective single-center study employing 48 patients of HFrEF, treatment with sacubitril/valsartan for a median duration of 3 months resulted in enhancement of EF and multiple measures of reverse remodeling, including reduced LVESD, LVEDD, and left ventricular mass.[12] A study on 200 patients with HFrEF for 4 months reported symptom improvements (fatigue and shortness of breath) and a reduction in hospitalizations with sacubitril/valsartan treatment.[13]

Our study, in a way, supports earlier findings and provides mechanistic insights, and elaborates the impressive findings of the study showing improved survival and decreased hospitalization.[14,15] This study agrees with observations made in the secondary analysis showing significant improvements in the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical and overall summary scores.[15] These effects are similar to those seen in health-related QoL levels with cardiac resynchronization therapy observed in HFrEF. [16]

A study on a large population showed a time-averaged reduction in the NT-ProBNP concentration, significantly more in the sacubitril–valsartan group than in the enalapril group (percent ratio of change was −46.7% vs. −25.3%). The augmented reduction in the NT-ProBNP concentration was apparent early after a week's treatment and persisted till the final visit. The rate of deterioration of renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups.[17]

It is interesting to point out that sacubitril/valsartan showed a marked reduction in ProBNP in most patients in our study. However, it seemed to work better in certain patient cohorts as improvement in functional class was observed in two-thirds.

Demonstrable effects in the enhancement of LV pumping capacity with a reduction in LV end-diastolic and end-systolic dimensions were seen in nearly one-third patients in this short follow up study. Could it be a temporal phenomenon and three months was a short period to realize the full benefits of the drug? But similar trends were seen in the real-world study, and certain groups of patients may respond more favorably to this drug combination.[11] If this is so, this requires a larger study for a longer duration to identify patients who benefit more from this unique therapy.

Sacubitril/valsartan was tolerated well, and studies have shown that de novo initiation or earlier transfer to it after acute heart failure exacerbation is tolerable in most patients. A randomized trial that compared two titration regimens showed a similar tolerability profile to other HF treatments such as ACEI/ARBs.[18] Another study provided good corresponding to support the earlier findings.[19] These studies suggest that it is safe to start the therapy early at or after discharge and up-titrate the dosage taking usual care in stabilized after acute decompensation or starting in ACEI/ARBs naïve patients. In our study, only 18.8 % could tolerate a dosage of 49/51 BD; 57% of patients remained on 24/26 BD despite various attempts to increase the dosage. Due to intolerability, 23.8% required a dosage reduction to once a day at night. In real world study, 15% of patients received a lower dosage as they could not tolerate optimal dosage due to low BP.[11] In the PARADIGM study, the most common side effect was hypotension - 16.7% seen in the sacubitril/valsartan group as against 10.6% in the enalapril group.[5-7] The inability to obtain the desired functional or cardiac structural improvement may be due to this.

CONCLUSION

It is concluded that in an outpatient setting, patients with HFrEF in any NYHA class and systolic blood pressure more than 110 mmHg treatment with sacubitril/valsartan in addition to the guideline-directed treatment resulted in a marked reduction in ProBNP, significant improvement in functional class and enhancement of cardiac pumping activity with a reduction in LVEDD and LVESD. Patients tolerated the drug well, but most could not tolerate the higher recommended dosage, renal status and electrolytes remained stable.

AUTHORS' CONTRIBUTION

MH and WA: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. HA: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

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REFERENCES

1. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nature Rev Cardiol. 2016;13(6):368-78.
2. Swedberg K, Kjekshus J, CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). Am J Cardiol. 1988;62(2):60A-6A.
3. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N England J Med. 1991;325(5):293-302.
4. Young JB, Dunlap ME, Pfeffer MA, Probstfield JL, Cohen-Solal A, Dietz R, et al. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation. 2004;110(17):2618-26.
5. Lillyblad MP. Dual angiotensin receptor and neprilysin inhibition with sacubitril/valsartan in chronic systolic heart failure: understanding the new PARADIGM. Ann Pharmacoth. 2015;49(11):1237-51.
6. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin?converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM?HF). Eur J Heart Fail. 2013;15(9):1062-73.
7. Desai AS, Vardeny O, Claggett B, McMurray JJ, Packer M, Swedberg K, et al. Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: a secondary analysis of the PARADIGM-HF trial. JAMA Cardiol. 2017;2(1):79-85.
8. Cruden NL, Fox KA, Ludlam CA, Johnston NR, Newby DE. Neutral endopeptidase inhibition augments vascular actions of bradykinin in patients treated with angiotensin-converting enzyme inhibition. Hypertension. 2004;44(6):913-8.
9. Maric C, Zheng W, Walther T. Interactions between angiotensin ll and atrial natriuretic peptide in renomedullary interstitial cells: the role of neutral endopeptidase. Nephron Physio. 2006;103(3):p149-56.
10. Kuhn M. Molecular physiology of natriuretic peptide signalling. Basic Res Cardio. 2004;99(2):76-82.
11. Ganesananthan S, Shah N, Shah P, Elsayed H, Phillips J, Parkes A, et al. Real-world treatment switching to sacubitril/valsartan in patients with heart failure with reduced ejection fraction: A cohort study. Open Heart. 2020;7(2):e001305.
12. Gu J, Noe A, Chandra P, Al?Fayoumi S, Ligueros?Saylan M, Sarangapani R, et al. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual?acting angiotensin receptor-neprilysin inhibitor (ARNi). J Clin Pharma. 2010;50(4):401-14.
13. Almufleh A, Marbach J, Chih S, Stadnick E, Davies R, Liu P, et al. Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients. Am J Cardiovas Dis. 2017;7(6):108.

14. Antol DD, Casebeer AW, DeClue RW, Stemkowski S, Russo PA. An early view of real-world patient response to sacubitril/valsartan: a retrospective study of patients with heart failure with reduced ejection fraction. Adv Therapy. 2018;35(6):785-95.
15. Lewis EF, Claggett BL, McMurray JJ, Packer M, Lefkowitz MP, Rouleau JL, et al. Health-related quality of life outcomes in PARADIGM-HF. Circul: Heart Fail. 2017;10(8):e003430.
16. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. J Am College Cardio. 2010;56(5):392-406.
17. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. N England J Med. 2019;380(6):539-48.
18. Senni M, McMurray JJ, Wachter R, McIntyre HF, Reyes A, Majercak I, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double?blind, randomized comparison of two uptitration regimens. Euro J Heart Fail. 2016;18(9):1193-202.
19. Wachter R, Senni M, Belohlavek J, Straburzynska?Migaj E, Witte KK, Kobalava Z, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. Euro J Heart Fail. 2019;21(8):998-1007.

Address for Correspondence:

Dr. Mohammad Hafizullah, Lady Reading Hospital, Peshawar, Pakistan.
Email: hafizullah.mohammad@gmail.com