

Research Article

Efficacy and Safety of Angiotensin Receptor-neprilysin Inhibitor (ARNI) in Patients with Congestive Heart Failure

Aamir Javaid¹, Ahmad Salman², Muhammad Furrakh Maqbool³, Liaqat Ali⁴, Haroon Aziz Khan Babar⁵, Abdul Rauf Aamir⁶

¹Associate of Professor Cardiology, Sheikh Zayed Medical College and Hospital, Rahim Yar Khan, Pakistan

²Assistant Professor of Cardiology, Faisalabad Institute of Cardiology, Faisalabad, Pakistan

³Assistant Professor of Cardiology, Sheikh Zayed Medical College and Hospital, Rahim Yar Khan, Pakistan

⁴Senior Registrar, Faisalabad Institute of Cardiology, Faisalabad, Pakistan

⁵Pakistan Kidney and Liver Institute and Research Centre - PKLI, Lahore, Pakistan

⁶House Officer, Sheikh Zayed Medical College and Hospital, Rahim Yar Khan, Pakistan

Corresponding Author: Dr. Aamir Javaid, Associate of Professor Cardiology, Sheikh Zayed Medical College and Hospital, Rahim Yar Khan, Pakistan. Email: aamirkpr@gmail.com

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ABSTRACT

Background: Angiotensin Receptor-Neprilysin Inhibitors (ARNI) have changed the landscape of therapeutic options in chronic heart failure (CHF). Although efficacy is determined in trials, local practice requires real-world data in varying populations, such as Pakistan.

Objective: To determine the actual efficacy, safety, and tolerability of ARNI in CHF patients with reduced or mildly reduced ejection fraction in a Pakistani tertiary care institution.

Methods: The research was a prospective, observational study carried out at the Department of Cardiology, Nishtar Hospital, Multan, between January and December 2025. One hundred and fifty patients with symptomatic CHF (NYHA Class II-IV) and a LVEF of 45 or less were recruited. ARNI was initiated for the participants on guideline-based therapy. Baseline and 6 months were used to assess clinical, echocardiographic, biochemical, and quality of life parameters.

Results: The mean age was 61.2 ± 10.5 years, with 60.7% males. After 6 months of ARNI therapy, a significant improvement in LVEF was observed (from $31.8\% \pm 8.2\%$ to $39.5\% \pm 9.1\%$, $p < 0.001$). The rate of heart failure-related hospitalizations was reduced by 55.2% ($p < 0.001$). Symptom burden, as measured by NYHA class, dyspnea, and fatigue scores, showed marked improvement. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) score improved significantly (from 58.4 ± 16.2 to 29.3 ± 12.8 , $p < 0.001$). ARNI was well-tolerated; hypotension (12.0%) was the most common adverse event, with only 4 patients (2.7%) discontinuing therapy. Renal function remained stable.

Conclusion: ARNI therapy was found to be highly effective in enhancing cardiac function, decreasing hospitalization, eliminating symptoms, and improving the quality of life in CHF patients with a good safety and tolerability profile in a real-life cohort of Southern Punjab. These results favor its regular application in such a clinical practice.

Keywords: Chronic Heart Failure, ARNI, Sacubitril/Valsartan, Efficacy, Safety.

INTRODUCTION

Chronic Heart Failure (CHF) represents a formidable global health challenge characterized by high mortality, frequent hospitalizations, and poor quality of life. The neurohormonal model, targeting the renin-angiotensin-aldosterone and sympathetic nervous systems, has been the therapeutic cornerstone.

While the PARADIGM-HF trial established the drug's superiority over enalapril in a controlled, global setting, its performance in regions with distinct epidemiological profiles, such as a younger age at heart failure onset, a higher prevalence of diabetes and consanguinity-related

cardiomyopathies, and significant socioeconomic barriers to care, demands specific validation (1). A primary indicator of ARNI efficacy is the reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP). Unlike BNP, whose levels are artificially elevated by neprilysin inhibition, NT-proBNP provides a reliable biomarker of myocardial wall stress and is a validated predictor of outcomes (2). Real-world studies from other Asian cohorts have demonstrated significant NT-proBNP reductions following ARNI initiation, even at lower doses than those used in the PARADIGM-HF trial (3, 4). Furthermore, echocardiographic evidence of reverse remodeling, including an increase in left

ventricular ejection fraction (LVEF) and a reduction in left ventricular end-systolic volume, would provide direct structural and functional proof of the drug's benefit (5).

ARNIs can exacerbate hyperkalemia and worsen renal function, especially when combined with other renin-angiotensin system inhibitors or mineralocorticoid receptor antagonists, which are part of the foundational "quadruple therapy" for HFrEF (6). Therefore, vigilant monitoring of serum potassium and creatinine is non-negotiable. Data from the HEAAL trial on losartan dosing highlight the delicate balance between therapeutic benefit and the risk of hyperkalemia, a principle directly applicable to ARNI management (7). Another critical safety consideration is hypotension, which can lead to treatment discontinuation. Real-world European data show that older age and low baseline systolic blood pressure are strong predictors of hypotension-related intolerance (8). Given that many patients in Southern Punjab may present late in their disease course, they could be particularly susceptible. The absolute contraindication of concomitant use with ACE inhibitors due to the risk of angioedema must be strictly enforced, requiring a mandatory 36-hour washout period during the switch (9). Tolerability, often the bridge between efficacy and safety, is heavily influenced by local prescribing practices and patient support systems. Real-world studies consistently show that a significant proportion of patients fail to reach the target dose of 97/103 mg twice daily used in PARADIGM-HF (10, 11).

Despite strong trial evidence, the real-world benefits of ARNI, especially in South Asian populations with unique genetic and socio-economic profiles, need validation. This study at Nishtar Hospital, Multan, assessed ARNI's efficacy, safety, and tolerability to guide local heart failure management.

METHODOLOGY

The proposed study was planned as a prospective, single-centered, observational cohort study at the Department of Cardiology, Nishtar Hospital, Multan, between the 1st January 2025 and 31st December 2025. Ethical approval was obtained by the Institutional Review Board of Nishtar Medical University beforehand, and informed consent was taken by all the participants. The target population consisted of patients who reported to the heart failure outpatient clinic consecutively and were filtered out against certain eligibility criteria. Inclusion criteria required participants to be aged 18 years or older with a clinical diagnosis of chronic heart failure of at least three months'

duration, manifesting as New York Heart Association (NYHA) functional class II-IV symptoms, and a left ventricular ejection fraction (LVEF) of $\leq 45\%$ confirmed by transthoracic echocardiography. Moreover, participants were required to be on stable guideline-guided medical care for at least four weeks and capable and eager to give informed consent. The main exclusion criteria included a history of angioedema; a history of symptomatic hypotension (systolic blood pressure less than 100 mm Hg) or severe renal impairment (estimated glomerular filtration rate less than 30 mL/min/1.73m²) at screening; serum potassium levels greater than 5.5 mEq/L; recent history of acute decompensated heart failure or myocardial infarction in the last three months; and pregnancy or lactation.

A sample size of 150 patients was recruited, and this was calculated in accordance to feasibility and the aim of obtaining strong real-world data. The appropriate washout of any previous angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers was followed by the initiation of therapy with valsartan in eligible patients. The starting dose of the medication was 24/26 mg or 49/51 mg twice daily, followed by up-titration to the target maintenance dose of 97/103 mg twice daily, which was administered as clinically tolerated. Each patient was then followed up prospectively in 6 months. The data collection was done at two points in time: at the time of enrolment (baseline) and the six-month follow-up visit. The main outcome of efficacy was specified as the absolute change in LVEF between baseline and six-month follow-up. Outcomes of secondary efficacy included changes in NYHA functional class; NYHA-related hospitalizations, compared to the six months before enrolment; changes in specific symptoms scores on dyspnea, fatigue, and edema; change in quality of life using the Minnesota Living with Heart Failure Questionnaire (MLHFQ); and change in N-terminal pro-brain natriuretic peptide (NT-proBNP). Safety and tolerability outcomes were based on the occurrence of adverse events (hypotension, hyperkalemia, kidney dysfunction, cough, angioedema), the rate of drug discontinuation, and laboratory parameters (serum creatinine and potassium). All data were analyzed with IBM SPSS Statistics software, version 26, to conduct statistical analysis. Constant variables are described as mean + SD or median with interquartile range, depending on whether they are normally distributed, which was determined using the Shapiro-Wilk test. Frequencies and percentages are used to describe categorical variables. Paired t-tests were used to compare parameters

between baseline and the six-month follow-up of normally distributed continuous data, whereas the Wilcoxon signed-rank test was used with non-normally distributed data. The McNemar test was used to make comparisons between categorical variables. Statistically, a p-value of < 0.05 was set as a threshold to determine a statistically significant p-value.

RESULTS

150 patients attended the 6-month follow-up. The cohort had a mean age of 61.2 ± 10.5 years, with 91 (60.7%) males (Figure 1A). The mean baseline LVEF was $31.8\% \pm 8.2\%$; 112 patients (74.7%) had HFrEF (LVEF $\leq 40\%$) and 38

(25.3%) had HFmrEF (LVEF 41–45%) (Figure 1B). Ischemic heart disease (68.7%) was the most prevalent etiology (Figure 1C). Comorbidities were prevalent, with hypertension in 70.7% and diabetes mellitus in 48.0% of patients (Figure 1D). Medical treatment guided by the baseline guidelines was high (Figure 1D). ARNI therapy led to significant improvements across all measured efficacy parameters at 6 months (Table 1). Mean LVEF increased significantly by 7.7 percentage points ($p < 0.001$). 98 patients (65.3%) showed an improvement in LVEF of $\geq 5\%$, 45 patients (30.0%) had stable LVEF ($< 5\%$ change), and only 7 patients (4.7%) experienced a worsening ($\geq 5\%$ decrease).

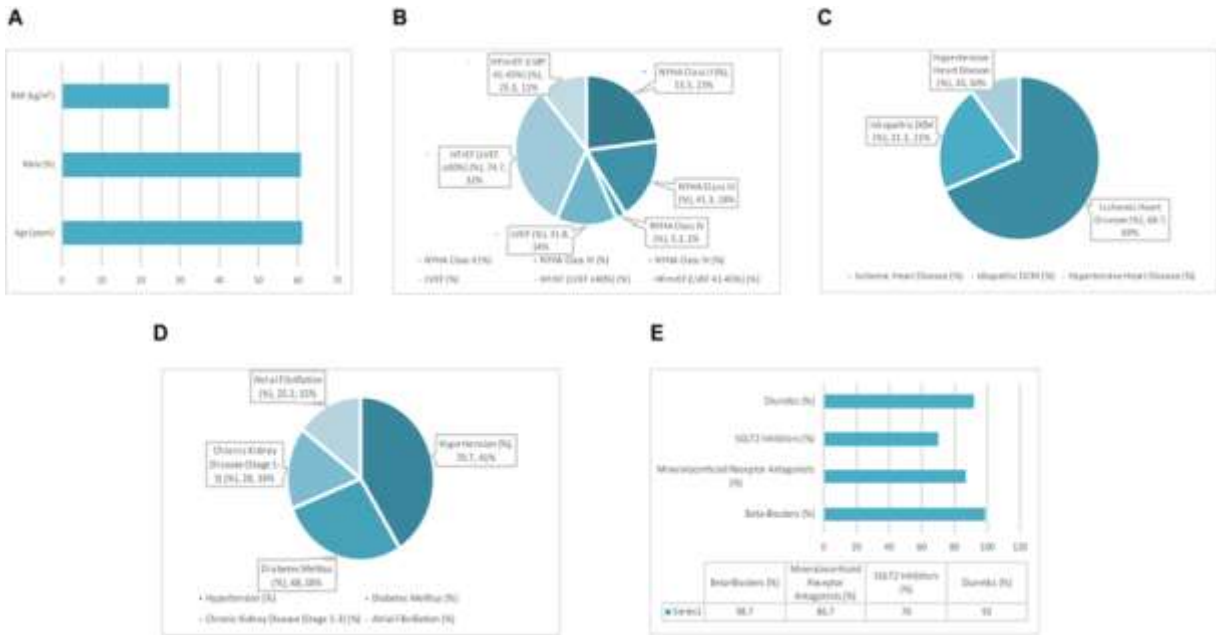


Figure 1: Baseline demographic and clinical characteristics of the study cohort (n=150). **A.** Age distribution and sex proportion **B.** NYHA functional class and LVEF subtypes **C.** Heart failure etiology: ischemic, idiopathic dilated, hypertensive **D.** Comorbidities and baseline pharmacologic therapy.

Heart failure-related hospitalizations in the 6 months after ARNI initiation (n=67) were 55.2% lower than in the 6 months before initiation (n=150) ($p < 0.001$). There was a marked shift

towards better NYHA class. The MLHFQ total score improved by 49.8%, indicating a substantial gain in health-related quality of life.

Table 1: Efficacy Outcomes at 6 Months Following ARNI Initiation

Parameter	Baseline	6 Months	Change / Outcome	p-value
LVEF (%), Mean $\pm$ SD	31.8 $\pm$ 8.2	39.5 $\pm$ 9.1	+7.7	<0.001
LVEF Response Category, n (%)				
Improvement ($\geq 5\%$ increase)	-	-	98 (65.3%)	
Stabilization ($< 5\%$ change)	-	-	45 (30.0%)	
Worsening ($\geq 5\%$ decrease)	-	-	7 (4.7%)	
HF Hospitalizations (6 months)	150*	67	Reduction: 55.2%	<0.001
NYHA Class, n (%)				<0.001

Class I	0 (0%)	25 (16.7%)		
Class II	80 (53.3%)	95 (63.3%)		
Class III	62 (41.3%)	28 (18.7%)		
Class IV	8 (5.3%)	2 (1.3%)		
MLHFQ Score, Mean $\pm$ SD	58.4 $\pm$ 16.2	29.3 $\pm$ 12.8	-29.1 $\pm$ 10.5	<0.001
NT-proBNP (pg/mL), Median (IQR)	2800 (1850-4200)	950 (550-1450)	-1850 (IQR: -2600 to -1200)	<0.001
*Hospitalizations in the 6 months <i>before</i> study enrolment.				

ARNI showed a tolerable safety profile (Table 2). The most common adverse event was hypotension, which was reported in 18 patients (12.0%), and was treated by adjusting the dose in the majority of cases. ARNI had to be

permanently discontinued in only 4 patients (2.7%) because of continuing symptomatic hypotension. No angioedema cases were reported. The cohort had stable renal function and serum potassium levels.

Table 2: Safety and Tolerability Profile of ARNI Therapy (N=150)

Parameter	Number of Patients (n)	Percentage (%)	Notes
Any Adverse Event	35	23.3%	
Specific Adverse Events			
Symptomatic Hypotension	18	12.0%	Leading cause of dose reduction
Hyperkalemia (K ⁺ >5.0 mEq/L)	11	7.3%	All medically managed
Worsening Renal Function*	8	5.3%	Serum Cr increase >0.3 mg/dL
Cough	4	2.7%	Mild, did not lead to discontinuation
Rash	2	1.3%	Resolved with antihistamines
Angioedema	0	0.0%	
Drug Discontinuation	4	2.7%	All due to refractory hypotension
Change in Lab Parameters (Mean $\pm$ SD)	Baseline	6 Months	p-value
Serum Creatinine (mg/dL)	1.12 $\pm$ 0.31	1.18 $\pm$ 0.35	0.08
eGFR (mL/min/1.73m ²)	65.8 $\pm$ 20.1	63.5 $\pm$ 19.4	0.12
Serum Potassium (mEq/L)	4.5 $\pm$ 0.5	4.6 $\pm$ 0.5	0.15
*Defined as an increase in serum creatinine >0.3 mg/dL from baseline.			

DISCUSSION

This real-world study from a major cardiac care center in Southern Punjab, Pakistan, confirms the significant therapeutic benefits and acceptable safety profile of ARNI in a typical South Asian CHF population.

The mean absolute change in LVEF of 7.7% and the 55.2% decrease in HF hospitalizations are consistent with the signals of efficacy of major trials and other real-world studies. The PARADIGM-HF trial has determined the initial advantage of valsartan versus enalapril, with a significant positive effect on cardiac structure and function(12).These results have been supported by later real-world studies, with

reports of LVEF increases of between 5 and 10 percent after the start of ARNI(13). Interestingly, 65.3% of our patients had a clinically significant ($\geq 5\%$) increase in LVEF, which is quite similar to the 68% in the mentioned article, which supports the reproducibility of ARNI in various settings(14).

The profound improvement in quality of life, as captured by a near 50% reduction in the MLHFQ score, is a critical finding supported by a study (1). The PARADIGM-HF trial reported a 21% relative risk reduction in HF hospitalizations with valsartan versus enalapril(12). It underscores that the benefits of ARNI extend beyond mere numerical metrics of cardiac function to tangibly

improve patients' daily lives, a crucial aspect of chronic disease management. The background guideline-directed therapy (beta-blockers, MRAs, SGLT2 inhibitors) is high in our cohort, which implies that the observed benefits are additive to the usual care(15, 16). This cumulative effect is vital, with modern management highlighting the speed of the sequential or near-concurrent start of all four pillars of GDMT to achieve the best results(17).

The safety data is encouraging and reflects the established profile. Hypotension was the most frequent adverse event, but it rarely resulted in permanent discontinuation (2.7%), and no new safety signals were detected. The renal stability and serum potassium levels in a six-month period directly respond to a significant issue among clinicians concerning the use of renin-angiotensin-aldosterone system (RAAS) modulators in cardiorenal comorbidity patients. Recent findings have continued to reinforce the safety and effectiveness of ARNI in more advanced CKD populations, including those under dialysis(18, 19)(20)(21). Studies have shown that sacubitril/valsartan can be safely initiated in patients with estimated glomerular filtration rates (eGFR) below 30 mL/min/1.73m², with careful monitoring, and may even provide renal protective effects through its dual mechanism of action (22, 23).

Limitations

The observational, single-center design lacks a control group, which restricts the determination of causality. The 6-month follow-up is adequate to measure change in functional and biomarkers, but inadequate to measure long-term hard outcomes such as mortality. There can be a limitation in generalizability to other tertiary care environments.

CONCLUSION

In a real-world cohort of patients with CHF from Southern Punjab, Pakistan, the initiation of ARNI therapy was associated with significant improvements in left ventricular systolic function, a substantial reduction in heart failure hospitalizations, marked alleviation of symptoms, and a greatly enhanced quality of life. The treatment showed a positive and tolerable safety profile, and a low discontinuation rate. The results offer robust supportive data on the effective and safe application of ARNI in normal clinical practice to eligible heart failure patients in Pakistan and other health care settings.

Conflicts of Interest

None declared.

Funding

Hospital resources only.

Ethical Approval

Obtained from the Institutional Review Board, Nishtar Medical University, Multan (IRB # NMU/IRB/2024/489).

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