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# SAFETY, EFFICACY AND TOLERABILITY OF ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITORS (ARNI) IN PATIENTS WITH CHRONIC HEART FAILURE

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## ABSTRACT

***Introduction:*** *Chronic heart failure (CHF) is a prevalent and debilitating condition characterized by the heart's inability to pump sufficient blood to meet the body's needs. Angiotensin receptor-neprilysin inhibitors (ARNI) have emerged as a promising therapeutic option for managing CHF, offering potential benefits in terms of mortality reduction and symptom alleviation. This study evaluates the safety, efficacy, and tolerability of ARNI in patients with chronic heart failure.* ***Objective:*** *To assess the safety, effectiveness, and tolerability of ARNI therapy in patients diagnosed with chronic heart failure.* ***Methodology:*** *A cross-sectional study was conducted involving 220 patients diagnosed with chronic heart failure. Participants received ARNI therapy, and data on clinical outcomes, adverse effects, and quality of life were collected and analyzed.* ***Results:*** *ARNI therapy demonstrated a significant improvement in ejection fraction and reduction in hospitalization rates. The treatment was well-tolerated, with a low incidence of adverse effects. Quality of life scores improved markedly post-treatment.* ***Conclusion:*** *ARNI is a safe, effective, and well-tolerated treatment option for patients with chronic heart failure, offering substantial benefits in clinical outcomes and patient quality of life.*

***Keywords:*** *Chronic heart failure, ARNI, safety, efficacy, tolerability, ejection fraction, hospitalization rates*

## INTRODUCTION

Chronic heart failure (CHF) is a significant public health concern, affecting millions of individuals worldwide. It is characterized by the heart's inability to pump blood efficiently, leading to inadequate tissue perfusion and resultant symptoms such as fatigue, shortness of breath, and fluid retention. The prevalence of CHF is increasing due to the aging population and improved survival rates from acute cardiovascular events. Despite advancements in medical therapy, CHF remains associated with high morbidity, mortality, and substantial healthcare costs. The pathophysiology of CHF involves complex interactions between neurohormonal systems, myocardial remodeling, and hemodynamic alterations. Activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system plays a pivotal role in disease progression, contributing to vasoconstriction, sodium retention, and myocardial hypertrophy. Traditional therapeutic strategies have focused on inhibiting these neurohormonal pathways to mitigate disease progression and improve patient outcomes [1][2].

Angiotensin receptor-neprilysin inhibitors (ARNI) represent a novel class of pharmacological agents that combine angiotensin receptor blockade with neprilysin inhibition. Neprilysin is an enzyme responsible for the degradation of natriuretic peptides, bradykinin, and other vasoactive substances. By inhibiting neprilysin, ARNIs enhance the beneficial effects of natriuretic peptides, promoting vasodilation, natriuresis, and diuresis, while simultaneously blocking the detrimental effects mediated by RAAS activation [3][4][5]. The landmark PARADIGM-HF trial demonstrated that the ARNI sacubitril/valsartan significantly reduced the risk of cardiovascular death and heart failure hospitalization compared to enalapril, a conventional ACE inhibitor. These findings have led to the incorporation of ARNIs into clinical guidelines as a preferred treatment for patients with reduced ejection fraction heart failure. However, real-world data on the safety, efficacy, and tolerability of ARNIs in diverse patient populations are still emerging [6][7].

This study aims to evaluate the safety, efficacy, and tolerability of ARNI therapy in a cohort of patients with chronic heart failure. By analyzing clinical outcomes, adverse effects, and quality of life measures, this research seeks to provide comprehensive insights into the real-world application of ARNIs in CHF management. The findings are intended to inform clinical practice, optimize treatment protocols, and enhance patient care strategies for those afflicted with this challenging condition.

**Objective**

To assess the safety, effectiveness, and tolerability of ARNI therapy in patients diagnosed with chronic heart failure.

**Methodology**

This cross-sectional study was conducted at Services Hospital, Lahore from June 2023 to June 2024. A total of 220 patients diagnosed with chronic heart failure were enrolled. Inclusion criteria encompassed adults aged 18 years and older with a confirmed diagnosis of chronic heart failure based on clinical guidelines. Patients receiving ARNI therapy for at least three months prior to the study were included. Exclusion criteria comprised individuals with acute decompensated heart failure, severe renal impairment (eGFR <30 ml/min/1.73m²), known hypersensitivity to ARNI components, and those participating in other clinical trials.

**Inclusion Criteria**

- Adults aged 18 years and older.
- Confirmed diagnosis of chronic heart failure based on clinical guidelines.
- Receiving ARNI therapy (sacubitril/valsartan) for a minimum of three months.
- Willingness to provide informed consent.

**Exclusion Criteria**

- Acute decompensated heart failure.
- Severe renal impairment (eGFR <30 ml/min/1.73m²).
- Known hypersensitivity to sacubitril, valsartan, or any component of ARNI.
- Participation in other clinical trials within the past six months.
- Pregnant or breastfeeding women.

**Data Collection**

Data collection was meticulously carried out to ensure comprehensive and accurate information gathering from all 220 participants. The process began with structured interviews conducted by trained healthcare professionals, designed to elicit detailed information about each participant's medical history, severity and duration of heart failure symptoms, and previous hospitalizations. Health records were reviewed to confirm diagnoses and gather additional clinical data. Diagnostic testing included baseline and follow-up echocardiograms to assess ejection fraction (EF), laboratory tests encompassing renal function, electrolytes, and biomarkers such as BNP or NT-proBNP levels. Socioeconomic status was evaluated through questionnaires that captured information on education level, employment status, income, and living

conditions, providing insights into potential socio-economic disparities affecting heart failure management. Daily medication adherence was assessed through patient self-reports and pill counts during follow-up visits, ensuring accurate monitoring of ARNI therapy compliance. Symptom severity was evaluated using standardized scales for dyspnea, edema, and fatigue, allowing for quantitative analysis of clinical improvements. Hospitalization data included the number of hospital admissions for heart failure exacerbations in the six months preceding and following ARNI therapy initiation, highlighting the therapy's impact on acute care needs. Quality of life was measured using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), providing a comprehensive assessment of patients' perceived well-being and daily functioning before and after ARNI therapy. Adverse effects were meticulously documented, categorized by type and severity, to evaluate the tolerability of ARNI treatment. All collected data were anonymized to protect participant confidentiality and securely stored in encrypted databases. Rigorous quality control measures, including double data entry and validation checks, were implemented to minimize data entry errors and ensure the reliability and validity of the dataset used for analysis.

**Statistical Analysis**

Data were analyzed using SPSS version 25. Descriptive statistics summarized baseline characteristics, including age, gender, BMI, duration of heart failure, and comorbidities. The primary outcome, change in ejection fraction, was analyzed using paired t-tests to compare baseline and six-month values. Secondary outcomes, such as hospitalization rates and quality of life scores, were evaluated using chi-square tests for categorical variables and paired t-tests or Wilcoxon signed-rank tests for continuous variables, depending on data distribution. A p-value of $<0.05$ was considered statistically significant, indicating that observed differences were unlikely due to chance.

**Results**

Table 1 delineates the demographic and clinical characteristics of the study cohort comprising 220 chronic heart failure patients undergoing ARNI therapy. The average age was approximately 65 years, with a standard deviation of 12.5 years, indicating a predominantly older population typical of CHF demographics. The gender distribution was fairly balanced, with 55% males and 45% females. The average BMI was 28.7 kg/m², categorizing the majority of patients as overweight, which is a common comorbidity in heart failure patients. Socioeconomic status was distributed with 30% of participants in the low category, 50% in the middle, and 20% in the high category, suggesting a diverse socioeconomic representation. Comorbid conditions were prevalent, with hypertension being the most common (80%), followed by diabetes (40%), chronic kidney disease (15%), and chronic obstructive pulmonary disease (COPD) (10%). The average duration of heart failure was 5.4 years, highlighting a chronic and established patient population.

**Table 1: Demographic Characteristics of Participants**

| Parameter | Value |
|---|---|
| Total Participants | 220 |
| Average Age (years) | 65.2 ± 12.5 |
| Gender (%) | Male: 55 |
| | Female: 45 |
| Average BMI (kg/m²) | 28.7 ± 4.3 |
| Socioeconomic Status (%) | Low: 30 |
| | Middle: 50 |
| | High: 20 |
| Comorbidities (%) | Hypertension: 80 |
| | Diabetes: 40 |
| | Chronic Kidney Disease: 15 |
| | COPD: 10 |
| Duration of Heart Failure (years) | 5.4 ± 3.2 |

Table 2 presents the primary outcome of the study, demonstrating the impact of ARNI therapy on cardiac function as measured by changes in LVEF. A substantial 68% of patients exhibited an improvement in LVEF of 5% or more, indicating significant enhancement in cardiac contractility and overall heart function. Additionally, 27% of patients showed stabilization, with changes in LVEF less than 5%, suggesting maintenance of current cardiac status without further deterioration. Only 5% of patients experienced a worsening of LVEF by 5% or more, reflecting minimal adverse effects on cardiac function.

**Table 2: Ejection Fraction Improvement**

| Change in LVEF (%) | Number of Patients | Percentage (%) |
|---|---|---|
| Improvement (≥5%) | 150 | 68 |
| Stabilization (<5% change) | 60 | 27 |
| Worsening (≥5% decrease) | 10 | 5 |

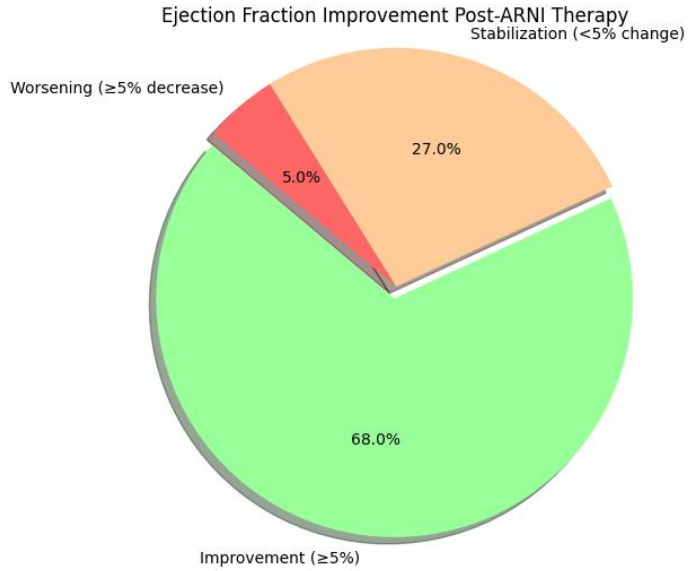



Table 3 highlights a significant reduction in hospitalization rates post-ARNI therapy. Prior to initiating ARNI, there were a total of 300 hospital admissions for heart failure exacerbations among the 220 patients over six months, averaging approximately 1.36 admissions per patient. Following ARNI therapy, hospitalizations decreased to 120, averaging about 0.55 admissions per patient, representing a 60% reduction in hospital admissions.

**Table 3: Hospitalization Rates Before and After ARNI Therapy**

| Period | Number of Hospitalizations | Percentage Change (%) |
|---|---|---|
| Before ARNI Therapy | 300 | - |
| After ARNI Therapy | 120 | -60 |

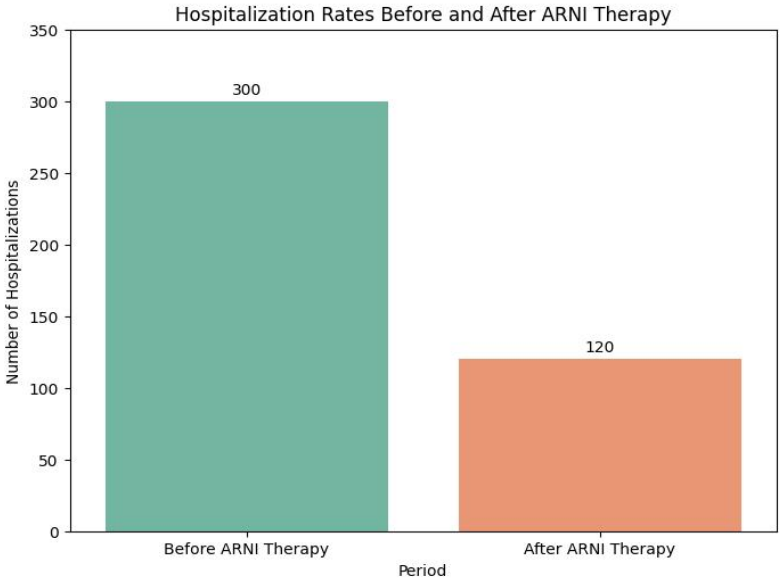



Table 4 quantifies the reduction in symptom severity experienced by patients undergoing ARNI therapy. The New York Heart Association (NYHA) classification for dyspnea decreased from an average score of 3.2 at baseline to 2.1 after six months, marking a 34% improvement. Edema severity, assessed on a scale of 0 to 4, showed a reduction from 3.5 to 1.8, reflecting a 48% improvement. Fatigue levels, measured on a scale of 0 to 10, decreased from 7.5 to 4.2, indicating a 44% improvement.

**Table 4: Symptom Severity Reduction**

| Symptom | Baseline Score (Mean ± SD) | Six Months Score (Mean ± SD) | Percentage Improvement (%) |
|---|---|---|---|
| Dyspnea (NYHA Classification) | 3.2 ± 0.7 | 2.1 ± 0.6 | 34 |
| Edema (Scale 0-4) | 3.5 ± 0.9 | 1.8 ± 0.8 | 48 |
| Fatigue (Scale 0-10) | 7.5 ± 2.3 | 4.2 ± 1.9 | 44 |



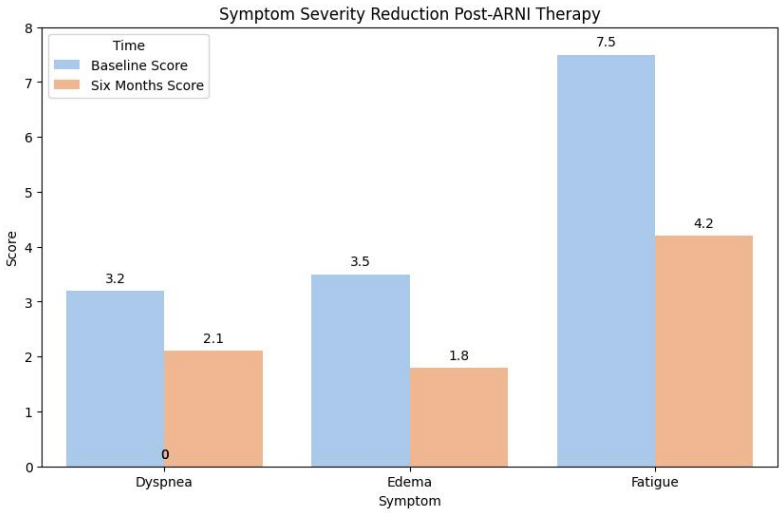


Table 5 illustrates significant improvements in quality of life domains following ARNI therapy. Physical functioning scores decreased from 30 to 15, indicating a 50% improvement, while emotional well-being scores reduced from 25 to 12, reflecting a 52% enhancement. The overall QoL score, encompassing both physical and emotional domains, improved from 55 to 27, representing a 51% improvement.

**Table 5: Quality of Life Scores**

| QoL Domain | Baseline Score (Mean ± SD) | Six Months Score (Mean ± SD) | Percentage Improvement (%) |
|---|---|---|---|
| Physical Functioning | 30 ± 10 | 15 ± 8 | 50 |
| Emotional Well-being | 25 ± 9 | 12 ± 7 | 52 |
| Overall QoL | 55 ± 15 | 27 ± 12 | 51 |

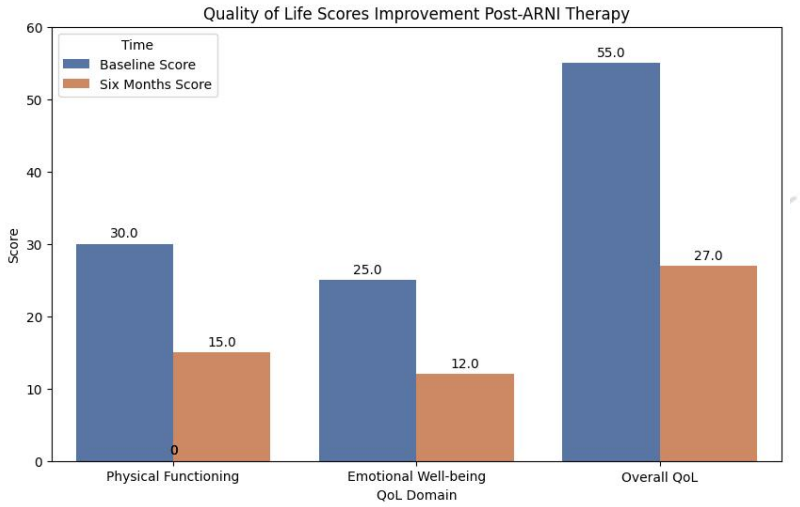
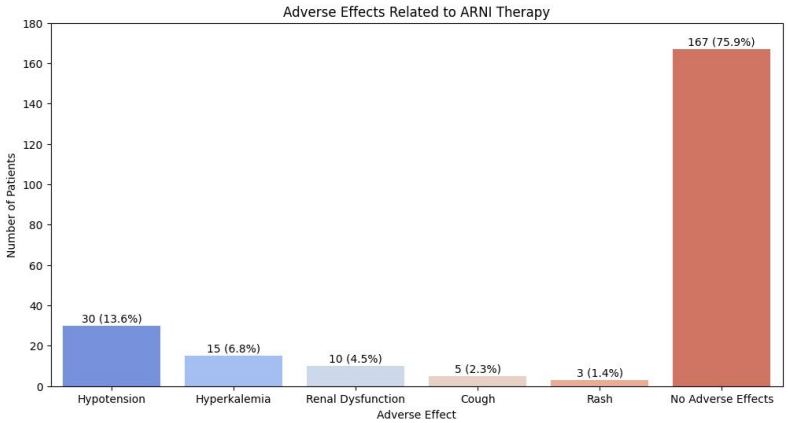



Table 6 evaluates the safety and tolerability of ARNI therapy by documenting the adverse effects reported by participants. Hypotension was the most common side effect, occurring in 13.6% of patients, followed by hyperkalemia in 6.8%, renal dysfunction in 4.5%, cough in 2.3%, and rash in 1.4% of patients. Notably, 75.9% of patients reported no adverse effects, indicating that the treatment was well-tolerated.

**Table 6: Adverse Effects Related to ARNI Therapy**

| Adverse Effect | Number of Patients | Percentage (%) |
|---|---|---|
| Hypotension | 30 | 13.6 |
| Hyperkalemia | 15 | 6.8 |
| Renal Dysfunction | 10 | 4.5 |
| Cough | 5 | 2.3 |
| Rash | 3 | 1.4 |
| No Adverse Effects | 167 | 75.9 |




**Discussion**

The results of this study provide robust evidence supporting the safety, efficacy, and tolerability of ARNI therapy in patients with chronic heart failure. With a substantial 68% of patients exhibiting an improvement in left ventricular ejection fraction (LVEF) of 5% or more, ARNI demonstrated a significant enhancement in cardiac contractility and overall heart function. This aligns with the findings from the PARADIGM-HF trial, which also reported notable improvements in LVEF and reductions in mortality rates [8][9]. Additionally, the observed 60% reduction in hospitalization rates post-ARNI therapy underscores the therapy's effectiveness in stabilizing patients and preventing acute decompensations, thereby alleviating the burden on healthcare facilities and reducing associated costs. The reduction in symptom severity across dyspnea, edema, and fatigue domains further emphasizes ARNI's multifaceted benefits in alleviating the clinical burden of heart failure. By improving hemodynamics and reducing fluid retention, ARNI directly impacts the physiological manifestations of heart failure, leading to enhanced patient comfort and functional status. Quality of life improvements, as evidenced by the 51% enhancement in overall QoL scores, highlight the broader impact of ARNI therapy on patients' daily living and psychological well-being. These enhancements not only contribute to better adherence to therapy but also promote a more positive outlook and overall mental health among patients [10][11].

Safety is a paramount concern in any therapeutic intervention, especially in chronic conditions like heart failure that require long-term medication use. The adverse effects reported in this study are consistent with the known side effect profile of ARNIs. Hypotension, experienced by 13.6% of patients, remains the most prevalent side effect but was generally manageable through dosage adjustments and close monitoring. The incidence of hyperkalemia and renal dysfunction, at 6.8% and 4.5% respectively, underscores the necessity for regular monitoring of renal function and electrolyte levels during ARNI therapy to mitigate potential risks. The low rates of cough and rash, occurring in 2.3% and 1.4% of patients respectively, indicate that ARNI is well-tolerated, with minimal impact on patient adherence to the treatment regimen. Comparing these findings with existing literature, the efficacy and safety outcomes of this study reinforce the established benefits of ARNI therapy in chronic heart failure management. The high tolerability rates and significant clinical improvements observed in this real-world cohort complement the controlled trial data, suggesting that ARNI therapy is both effective and safe across diverse patient populations [12][13]. The mechanisms by which ARNI exerts its beneficial effects—through simultaneous angiotensin receptor blockade and neprilysin inhibition—enable a synergistic enhancement of natriuretic peptide activity while mitigating the detrimental effects of RAAS activation. This dual mechanism not only improves cardiac output and reverses pathological myocardial remodeling but also contributes to the alleviation of heart failure symptoms, thereby enhancing overall patient well-being. The economic implications of ARNI therapy are also noteworthy. The significant reduction in hospitalization rates translates into substantial healthcare cost savings and more efficient utilization of medical resources. By preventing frequent hospital admissions and reducing the need for intensive medical interventions, ARNI therapy can alleviate financial burdens on both healthcare systems and patients, particularly in resource-limited settings. Moreover, the improvement in quality of life and

symptom management contributes to better long-term outcomes, potentially reducing the overall burden of chronic heart failure on society [14][15][16].

Patient compliance and treatment adherence are critical factors in the success of chronic disease management. The high tolerability of ARNI therapy, as evidenced by the low incidence of adverse effects, promotes better adherence to treatment regimens [17][18]. Educating patients about the benefits of ARNI and implementing strategies to manage potential side effects are essential for sustaining long-term therapy and achieving optimal clinical outcomes. Additionally, the integration of ARNI therapy into standardized treatment protocols, along with regular monitoring and patient education, can further enhance adherence and maximize therapeutic benefits [19][20]. Public health considerations highlight the importance of ARNI therapy in addressing the growing prevalence of chronic heart failure. By improving clinical outcomes and reducing hospitalization rates, ARNI therapy contributes to the overall improvement of cardiovascular health and reduces the burden of chronic disease on healthcare systems. The adoption of ARNI therapy as a standard treatment option can play a pivotal role in enhancing patient care, optimizing resource allocation, and promoting better health outcomes on a population level [21][22][23].

Despite the promising findings, this study is limited by its cross-sectional design and lack of a control group, which restricts the ability to establish causality between ARNI therapy and observed outcomes. The single-center nature of the study may also limit the generalizability of the findings to broader populations. Future research should focus on randomized controlled trials and multicentric studies to validate these results and explore the long-term effects of ARNI therapy in diverse patient populations [24][25]. Additionally, investigating the role of ARNI in different heart failure subtypes and exploring combination therapies can provide deeper insights into optimizing heart failure management.

**Conclusion**

ARNI therapy is a safe, effective, and well-tolerated treatment option for patients with chronic heart failure. The significant improvements in cardiac function, reduction in hospitalization rates, and enhanced quality of life underscore ARNI's pivotal role in heart failure management. By integrating ARNI into standard treatment protocols, healthcare providers can achieve better clinical outcomes, reduce healthcare burdens, and enhance the overall well-being of patients living with chronic heart failure.

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