

Study Report

Long-term Effect of Angiotensin Receptor/Neprilysin Inhibitor over Angiotensin Converting Enzyme Inhibitors on Cardiovascular Mortality or Morbidity in Indian Patients with Heart Failure

Version No.: 1.1

The study was conducted according to the approved protocol and in compliance with the protocol, Good Clinical Practice (GCP), and other applicable local regulatory requirements.

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1 INTRODUCTION

Heart failure (HF) is a widespread condition worldwide, increasingly prevalent due to an aging population and advancements in treating cardiovascular diseases. Effective management of HF, particularly heart failure with reduced ejection fraction (HFrEF), is critical to improving patient outcomes. Medications such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists are essential in the pharmacological management of HF [1].

Current HF guidelines recommend angiotensin receptor neprilysin inhibitors (ARNIs) as the first line treatment for patients with HFrEF [1]. ARNIs, a novel class of medication, combine the effects of angiotensin receptor blockade with neprilysin inhibition, leading to enhanced natriuretic peptide activity and more comprehensive cardiovascular benefits [2]. ARNIs have proven to reduce morbidity and mortality more effectively than ACEIs in patients with HFrEF [3]. ARNIs can enhance diastolic and left ventricular function, improve quality of life, and lower the risk of ventricular arrhythmias [4]. The Paradigm-HF trial evaluated the effect of ARNI, indicating a 20% relative reduction in the primary endpoint of cardiovascular death or HF hospitalization [5].

These findings strongly support the preferential use of ARNIs in the treatment of chronic HF [3]. While ACEI have long been a cornerstone in the management of HFrEF, emerging evidence suggests that ARNIs may offer superior benefits in terms of reducing cardiovascular mortality and morbidity. Recent evidence suggests that in the coming years, the application of ARNIs will expand to encompass other cardiovascular diseases, including heart failure with preserved ejection fraction and hypertension [2]. However, there is limited real-world evidence regarding the efficacy of ARNIs in elderly hypertensive patients with HFrEF and additional comorbidities. Understanding the long-term impact of ARNIs in the Indian context is crucial for guiding clinical decision-making and optimizing HF management.

This study seeks to fill the gap in existing literature by providing valuable data on the effectiveness of ARNIs in improving the prognosis for Indian patients with HFrEF, thereby contributing to better healthcare outcomes and quality of life for this growing patient population.

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2 RATIONALE OF THE STUDY

The rationale for this study was to evaluate whether ARNI offered superior clinical outcomes compared to traditional ACEi therapies in Indian patients with HFrEF. Understanding the impact on cardiovascular mortality, hospitalizations for HF, and quality of life parameters specific to this population provided valuable insights for clinical practice. The purpose of this study was to evaluate and compare the impact of ARNI versus ACEi on cardiovascular mortality and morbidity in Indian patients with HF, providing valuable insights into optimizing treatment strategies and improving patient outcomes.

3 STUDY OBJECTIVE

The primary objective of this study was to assess the long-term efficacy of ARNI compared to ACEi on cardiovascular mortality or morbidity in Indian patients with HFrEF.

4 METHODS

The study was designed as a cross-sectional, questionnaire-based investigation involving a sample of Indian physicians responsible for managing patients with HF. Identification and invitation of participants were conducted through professional networks and medical associations. Detailed information was provided to potential participants prior to their enrollment in the study. The survey comprised 14 questions designed to capture insights into physicians' clinical experiences, prescribing practices, and perceptions regarding ARNI and ACEi therapies specifically in patients with HFrEF.

Utilizing electronic administration, responses from participants were collected and securely stored for subsequent analysis. Ethical considerations were integral to the study, aligning with the ethical principles set forth in the Declaration of Helsinki. Approval was obtained from an Independent Ethics Committee to ensure adherence to ethical standards. Participants were informed of their right to withdraw from the study at any point without repercussions. Anonymization of all responses was rigorously implemented to safeguard participant confidentiality throughout the data collection process.

A sample size of 121 Indian physicians was targeted to ensure the study's findings were based on a diverse and representative cohort, enabling robust

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statistical analysis of the survey data. Data analysis employed both descriptive and inferential statistical methods. Descriptive statistics summarized demographic details and response frequencies, while inferential statistics, such as chi-square tests or logistic regression, were used to explore potential associations between physician characteristics and their perceptions and prescribing behaviors.

The primary focus of the study was to gather perspectives and experiences related to the use of ARNI and ACEi therapies in managing HFrEF patients, rather than administering treatments.

5 RESULTS

A total of 121 HCPs participated in the survey. Below is the summary of the responses.

1. Which of the Renin-Angiotensin-Aldosterone System (RAAS) inhibitor option is preferred by you as the first-line therapeutic option in patients with Heart failure with reduced ejection fraction (HFrEF)?

- a. Angiotensin-converting enzyme inhibitors (ACEi)
- b. Angiotensin II receptor blockers (ARB)
- c. Angiotensin receptor/neprilysin inhibitor (ARNI)



- Majority of physicians (57.9%) preferred ARNI as the RAAS inhibitor of choice as the first-line therapeutic option in patients with HFrEF in their clinical practice.
- About 29.8% of physicians preferred ARB as the RAAS inhibitor of choice as the first-line therapeutic option in patients with HFrEF.
- Approximately 12.4% of physicians preferred ACEi as the RAAS inhibitor of choice as the first-line therapeutic option in patients with HFrEF.

2. How often do you consider to start with ARNI in HF Patients without previous use of an ACEI or ARB?

- a. In all patients
- b. In few patients
- c. Do not consider to start before ACEi/ARB



- Majority of physicians (58.7%) considered starting ARNI in all heart failure patients without previous use of an ACEI or ARB in their clinical practice.
 While 28.1% considered it in a few patients.
- About 13.2% did not preferred starting ARNI before using an ACEI or ARB.

3. What is the percentage reduction in the incidence of hospitalization for heart failure (HHF) with the usage of ARNI in your practice?

a. <20%

- b. 20-<50%
- c. 50-75%
- d. >75%



- Majority of physicians (50.4%) observed a 50-75% reduction in the incidence of HHF with the use of ARNI.
- Approximately, 38.8% of physicians observed a 20-<50% reduction in the incidence of HHF with the use of ARNI.
- This was followed by 6.6% saw a reduction of over 75%, and 4.1% observed less than a 20% reduction in the incidence of HHF with the use of ARNI.

4. What is the percentage reduction in the incidence of hospitalization for heart failure (HHF) with the usage of ACEi in your practice?

a. <20%

- b. 20-<50%
- c. 50-75%
- d. >75%



- About, 45.5% of physicians observed a 20-<50% reduction in the incidence of HHF with the use of ACEi.
- Approximately, 32.2% of physicians observed a 50-75% reduction in the incidence of HHF with the use of ACEi.
- This was followed by 19.8% saw a reduction of less than 20%, and 2.5% observed a reduction of over 75% in the incidence of HHF with the use of ACEi.

5. Which parameter is notably found to be improved more with ARNI Vs. ACEi on long-term usage in HFrEF patients? (Can mark more than 1 options, if required)

a. New York Heart Association (NYHA) Functional Class

- b. Left ventricular ejection fraction (LVEF)
- c. N-terminal pro b-type natriuretic peptide (NT-proBNP)



- About, 47.9% of physicians noted significant improvement in LVEF with ARNI compared to ACEi in long-term usage among HFrEF patients during their clinical practice.
- Approximately, 39.7% observed a notable improvement in NYHA with ARNI compared to ACEi in long-term usage among HFrEF patients.
- However, only 12.4% reported significant improvement in NT-proBNP with ARNI compared to ACEi.
- This highlights LVEF as the parameter most notably improved by ARNI compared to ACEi in managing HFrEF patients over the long term.

6. Do patients receiving ARNI had significantly lower rates of cardiovascular (CV) death than ACEI users in your practice?

- a. Yes
- b. No



- Majority of physicians (95%) observed that patients receiving ARNI had significantly lower rates of CV death compared to ACEI users in their practice.
- In contrast, 8% indicated no significant difference in CV death rates compared to ACEI users.
- This indicates a strong perception among physicians of ARNI's efficacy in reducing CV mortality relative to ACEIs.

7. As per your opinion, is ARNI is superior to ACEi in patients with HF in terms of impact on cardiac reverse remodeling?

a. Yes

b. No



- Majority of physicians (92.6%) believed that ARNI was superior to ACEi in patients with HF regarding its impact on cardiac reverse remodeling.
- In contrast, 7.4% expressed the opinion that ARNI was not superior in this regard.
- This reflected a strong consensus among most physicians regarding ARNI's perceived efficacy in promoting cardiac reverse remodeling compared to ACEi.

8. In which HFrEF patient profile does ARNI therapy appears to improve echocardiographic parameters of left ventricular function over and above ACEi/ARB? (Can mark more than 1 options, if required)

- a. Patients with nonischemic HF
- b. Patients with LVEF < 30%
- c. Patients with lower degree of neurohumoral activation



- Majority of physicians (86.8%) observed ARNI therapy notably improved echocardiographic parameters of left ventricular function over ACEi/ARB in patients with LVEF < 30% during their practice.
- About 7.4% of physicians observed ARNI therapy notably improved echocardiographic parameters of left ventricular function over ACEi/ARB in patients with nonischemic HF.
- However, only 5.8% of physicians observed ARNI therapy notably improved echocardiographic parameters of left ventricular function over ACEi/ARB in patients with a lower degree of neurohumoral activation.

9. Do you agree that, ARNI should replace an ACEi/ARB as the foundation of treatment of symptomatic patients (NYHA II–IV) with HF and a reduced ejection fraction?

- a. Yes
- b. No



- The majority of patients (95%) respondents agreed that ARNI should replace ACEi/ARB as the foundational treatment for symptomatic patients (NYHA II– IV) with heart failure and reduced ejection fraction.
- In contrast, 4.1% respondents disagreed with this regard.

10. As per your opinion which of the clinical benefit(s) is/are associated more with ARNI Vs. ACEi in patients with HF? (Can mark more than 1 options, if required)

- a. Reduction in incidence of CV death
- b. Reduction in incidence of hospitalisation for HF
- c. Reduction in incidence of all-cause mortality



- Majority of physicians (53.7%) believed that ARNI was associated more with a reduction in the incidence of hospitalization for HF compared to ACEi.
- Additionally, 25.6% of physicians observed that ARNI was associated more with a reduction in the incidence of cardiovascular (CV) death compared to ACEi in patients with HF.
- Approximately 6% identified a reduction in the incidence of all-cause mortality as being more associated with ARNI.

11. For which of the parameter the highest benefits are observed with ARNI therapy compared to ACEi? (Can mark more than 1 options, if required)

- a. Incidence of CV death
- b. Incidence of hospitalisation for HF
- c. Incidence of all-cause mortality



- Majority of physicians (60.3%) noted that the highest benefits were observed with ARNI therapy compared to ACEi in reducing the incidence of hospitalization for HF during their clinical practice.
- Meanwhile, 20.7% identified a benefit of ARNI in reducing the incidence of CV death compared to ACEi.
- Only 19% mentioned a benefit of ARNI over ACEi in reducing the incidence of all-cause mortality.

12. Which component(s) of quality of life considered to assess the long-term effect of HF drug therapy? (Can mark more than 1 options, if required)?

- a. Respiratory efficiency
- b. Domestic activities
- c. 6-minute walk test
- d. Sexual activity



- About 42.1% of physicians considered domestic activities as a component of quality of life when assessing the long-term effects of HF drug therapy.
- Similarly, 41.3% mentioned the 6-minute walk test as another crucial measure for evaluating quality of life outcomes.
- 15.7% of physicians observed respiratory efficiency as a component relevant to assessing the impact of HF drug therapy on quality of life.
- However, only 0.8% emphasized sexual activity as a component relevant to assessing the impact of HF drug therapy on quality of life.

13. Which of the component of quality of life is improved the highest with longterm usage of ARNI Vs. ACEi? (Can mark more than 1 options, if required) ?

- a. Respiratory efficiency
- b. Domestic activities
- c. 6-minute walk test
- d. Sexual activity



- Approximately, 39.7% of physicians observed the highest improvement in the 6-minute walk test with long-term usage of ARNI compared to ACEi i.
- Similarly, 39.7% noted significant improvement in domestic activities as a component of quality of life with ARNI therapy.
- Only 18.2% reported respiratory efficiency showing the highest improvement with ARNI compared to ACEi. However, just 2% identified sexual activity as significantly improved with ARNI therapy compared to ACEi, reflecting varying impacts on different aspects of quality of life in heart failure patients.

14. In your opinion, how is the long-term safety profile of ARNI therapy in HF patients?

- A. Excellent
- B. Very Good
- C. Good
- D. Poor



- The long-term safety profile of ARNI therapy in HF patients was considered excellent by the majority of physicians (53.7%). Meanwhile, 34.7% considered it very good, and 10.7% rated it as good.
- However, only 0.8% perceived the safety profile as poor. This reflects a strong consensus among physicians on the favorable long-term safety profile of ARNI in managing HF.

6 SUMMARY

The surveys provide a comprehensive view of how physicians perceive and utilize ARNI compared to ACEi in managing HFrEF. Initially, a clear preference for ARNI emerged, with 57.9% of physicians opting for ARNI as their first-line RAAS inhibitor, highlighting a significant shift in clinical practice away from ACEi (12.4%) and towards ARNI. When initiating treatment, 58.7% of physicians favored starting ARNI in all HFrEF patients without prior ACEi or ARB, reflecting varied initiation practices.

In terms of efficacy, ARNI demonstrated notable benefits in reducing HHF: 50.4% of physicians reported a 50-75% reduction, with additional reductions noted by 38.8% (20-<50% reduction), 6.6% (over 75% reduction), and 4.1% (less than 20% reduction). ACEi showed varied effectiveness in comparison, with reductions reported by 45.5%, 32.2%, 19.8%, and 2.5% respectively. Physicians also observed specific improvements with ARNI over ACEi: 47.9% noted significant improvements in LVEF, 39.7% in NYHA functional class, and 12.4% in NT-proBNP levels, emphasizing ARNI's efficacy in enhancing cardiac function, particularly LVEF, in HFrEF patients.

Regarding mortality outcomes, 95% of physicians perceived lower CV death rates with ARNI compared to ACEi, underscoring a strong belief in ARNI's effectiveness in reducing CV mortality. Similarly, 92.6% of physicians believed ARNI to be superior in promoting cardiac reverse remodeling compared to ACEi, reflecting a consensus on its structural benefits. Echocardiographic improvements were notably observed in patients with LVEF < 30%, where 86.8% reported significant enhancements with ARNI compared to ACEi/ARB, highlighting specific patient profiles that benefit more from ARNI therapy.

Physicians identified various perceived benefits of ARNI, with 60.3% emphasizing its role in reducing HHF, 20.7% in lowering CV death rates, and 19% in reducing all-cause mortality, illustrating diverse impacts on clinical endpoints. Quality of life assessments focused on domestic activities (42.1%) and the 6-minute walk test (41.3%) as crucial measures, with respiratory efficiency (15.7%) also noted, though sexual activity (0.8%) received less attention in evaluating HF therapy impact. The long-term safety profile of ARNI was highly regarded, with 53.7% rating it as excellent, 34.7% as very good, and

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10.7% as good, indicating a consensus on its favorable safety profile in managing HF over extended periods.

Overall, these findings illustrate a strong trend among physicians towards adopting ARNI as the preferred RAAS inhibitor for managing HFrEF, driven by its perceived efficacy in reducing hospitalizations, improving cardiac function, and maintaining quality of life, supported by favorable long-term safety assessments. These insights underscore the evolving clinical practices and confidence in ARNI's role in optimizing outcomes for patients with heart failure.

7 DISCUSSION

The data from surveys underscore a significant shift towards ARNI as the preferred treatment choice among physicians for managing HFrEF over ACEi. The clear preference for ARNI (57.9%) reflects its perceived superior efficacy in clinical outcomes such as reducing HHF rates and improving LVEF, NYHA functional class, and NT-proBNP levels compared to ACEi. Physicians also strongly believed in ARNI's ability to lower CV mortality rates and promote cardiac reverse remodeling, particularly in patients with LVEF < 30%. Quality of life assessments highlighted domestic activities and the 6-minute walk test as critical indicators, underscoring ARNI's comprehensive benefits beyond traditional endpoints. Moreover, the favorable long-term safety profile further supports ARNI's adoption, with a majority rating it as excellent. These findings suggest a growing confidence among healthcare providers in ARNI's role in optimizing therapeutic outcomes and enhancing the management of heart failure with reduced ejection fraction.

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8 CLINICAL RECOMMENDATIONS

- First-line Therapy Preference: Consider ARNI as the preferred RAAS inhibitor due to its superior efficacy demonstrated in reducing HHF and improving cardiac function parameters such as LVEF and NT-proBNP levels.
- Initiation Practices: Initiate ARNI early in treatment for all suitable HFrEF patients, especially those without prior ACEi or ARB use, to maximize therapeutic benefits and potentially reduce disease progression.
- Patient Profiling: Tailor therapy based on patient characteristics such as LVEF < 30%, where ARNI has shown significant echocardiographic improvements. Consider ARNI particularly in patients with nonischemic HF who may benefit from its specific clinical advantages.
- Mortality Benefits: Acknowledge ARNI's perceived advantages in lowering CV mortality rates compared to ACEi. Monitor and assess outcomes closely to leverage these benefits effectively in clinical practice.
- Quality of Life Considerations: Integrate assessments of domestic activities and the 6-minute walk test routinely in patient evaluations. While respiratory efficiency improvements with ARNI are notable, sexual activity impacts, although less emphasized, should also be considered in holistic quality of life assessments.
- Safety Profile: Emphasize the favorable long-term safety profile of ARNI, as rated by a majority of physicians, in discussions with patients. Monitor for adverse effects and educate patients on potential benefits to ensure adherence and improved treatment outcomes.

9 CONSULTANT OPINION

Based on the survey findings, comparing ARNI and ACEi in managing HFrEF, it is evident that ARNI presents a compelling option for clinicians seeking to optimize outcomes in heart failure management. The preference for ARNI as the first-line RAAS inhibitor, coupled with its observed benefits in reducing hospitalizations and improving cardiac function parameters such as LVEF and NT-proBNP levels, underscores its efficacy in clinical practice. The substantial perception of lower CV mortality rates and superior cardiac remodeling with ARNI further solidifies its role in enhancing patient outcomes. While acknowledging varying initiation practices and patient-specific responses, ARNI's favorable long-term safety profile reinforces its suitability for extended use in managing HFrEF. Quality of life assessments, although focused predominantly on functional measures like domestic activities and the 6-minute walk test, suggest broader impacts that align with patient-centered care. Overall, these insights support a consultant's view that integrating ARNI early and systematically into treatment protocols can lead to significant improvements in both clinical outcomes and patient well-being in heart failure management.

10 MARKET OPPORTUNITIES

Based on the survey finding comparing ARNI comparing with ACEi in managing HFrEF, several marketing opportunities emerge that can enhance ARNI adoption among physicians and healthcare providers. Highlighting ARNI's preference among 57.9% of physicians as a first-line RAAS inhibitor underscores its growing acceptance in clinical practice, positioning it as a modern therapeutic choice. Emphasizing its efficacy in reducing HHF, with 50.4% reporting substantial reductions and superior outcomes compared to ACEi, can resonate strongly in marketing campaigns. Specific benefits such as significant improvements in LVEF (47.9%), NYHA functional class (39.7%), and perceived lower CV mortality rates (95%) highlight key advantages that can be effectively communicated to healthcare professionals. Moreover, targeting quality of life enhancements through metrics like domestic activities and the 6-minute walk test (42.1% and 41.3%, respectively) aligns with patient-centered care approaches. Lastly, reinforcing ARNI's excellent long-term safety profile, as rated by 53.7% of physicians, can build trust and confidence in its sustained use. By strategically focusing on these strengths in marketing efforts, pharmaceutical companies and healthcare providers can effectively promote ARNI as a preferred treatment option, driving increased adoption and improved patient outcomes in heart failure management.

11 MARKET POSITIONING

Preferred First-Line Therapy

ARNI was chosen by 57.9% of physicians as the primary RAAS inhibitor for managing HFrEF, signaling a significant shift in clinical practice away from ACEi and ARB.

Efficacy in Reducing Hospitalizations

A substantial proportion of physicians noted ARNI's effectiveness, with 50.4% reporting a 50-75% reduction in HHF hospitalizations compared to ACEi's varied effectiveness.

Improvements in Clinical Parameters

ARNI demonstrated significant enhancements in LVEF (47.9%), NYHA functional class (39.7%), and NT-proBNP levels (12.4%), underscoring its efficacy in improving cardiac function.

Mortality Outcomes

A strong consensus (95%) among physicians perceived lower CV death rates with ARNI compared to ACEi, highlighting its effectiveness in reducing mortality in HFrEF patients.

Patient Profile Benefits: Echocardiographic improvements were notably observed in patients with LVEF < 30%, reflecting specific patient profiles benefiting more from ARNI therapy.

Quality of Life Impact

Physicians emphasized improvements in domestic activities (42.1%) and the 6minute walk test (41.3%) as crucial measures, aligning with patient-centered care approaches.

Long-Term Safety Profile

ARNI's favorable long-term safety profile, rated as excellent by 53.7% of physicians, supports its sustained use in managing HF over extended periods.

Market Perception

These insights position ARNI as a preferred choice in HFrEF management, emphasizing its efficacy, mortality benefits, and positive impact on quality of life, thereby aligning with evolving clinical preferences and enhancing confidence among healthcare providers.

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