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EXPERT OPINION ON THE CLINICAL USE OF ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITORS IN THE MANAGEMENT OF HEART FAILURE IN REAL-WORLD INDIAN SETTINGS

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ABSTRACT **Background:** Though there are several studies shown the efficacy of sacubitril/valsartan in patients with HFrEF, there is a dearth of studies among clinicians. **Objective:** To gather expert opinion on the use of angiotensin receptor-neprilysin inhibitor (ARNI) therapy in managing heart failure (HF) patients in real-world Indian settings. **Methodology:** The cross-sectional study utilized an 18-item, multiple-response questionnaire to gather expert opinion from cardiologists in managing HF. The survey encompassed questions about current prescription practices, clinical observations, preferences, and experiences related to the use of ARNI in routine settings for HF management. The data were analyzed using descriptive statistics. **Results:** More than half (66.67%) of the clinicians expressed a preference for the ARNI (sacubitril/valsartan) drug class for managing HF. Nearly 66% of the respondents noted that the dual action of ARNI on the renin-angiotensin-aldosterone system and natriuretic peptides (RAAS & NPs) pathway results in better outcomes with reduced mortality rates. Approximately 34% of clinicians highlighted cardiac remodeling as a distinct advantage of ARNI over other available drugs, while another 33% emphasized additional benefits such as biomarker improvement, reduced hospitalization, and disease progression. Majority (84.78%) of the clinicians concurred with the findings of the PIONEER-HF study, indicating that early initiation of ARNI in acute HF leads to early improvement in post-discharge outcomes. Additionally, most clinicians (89.13%) reported that sacubitril/valsartan 100 mg (49/51 mg) was commonly used for HF management. **Conclusion:** The study revealed a strong preference among clinicians for ARNI in HF management, and the widespread use of sacubitril/valsartan 100 mg (49/51 mg). It highlighted the dual action of ARNI on the RAAS and NPs pathway, leading to improved outcomes as well as the importance of early ARNI initiation in acute HF.

KEYWORDS : Heart failure, Angiotensin receptor-neprilysin inhibitor (ARNI), Renin angiotensin aldosterone system (RAAS), Natriuretic peptides (NPs)

INTRODUCTION

The burden of heart failure (HF) encompasses various aspects, including healthcare costs, hospitalizations, morbidity, mortality, and impaired quality of life for patients and their caregivers. Over the years, classification systems for HF have evolved to encompass not only symptom severity, as denoted by New York Heart Association (NYHA) classes, but also disease progression and severity, as delineated by stages outlined by the American Heart Association (AHA) and American College of Cardiology (ACC). The introduction of HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) classifications has further refined treatment approaches, focusing on addressing underlying pathophysiological mechanisms.[1]

Epidemiological data indicates that HF affects approximately 64 million individuals globally. It is estimated that by 2030, the number of HF patients will increase by 25%.[2,3] The risk of developing HF escalates with age, with estimates suggesting a 28.5% likelihood for women and a 33% likelihood for men over 55 years old.[4] While precise data on HF prevalence and incidence in India remain elusive, the country's higher prevalence of cardiovascular diseases and aging population likely contribute to a significant burden. Estimates suggest that HF affects between 1.3 million to 4.6 million individuals in India annually, with substantial mortality rates. The Trivandrum Heart Failure Registry (THFR) reported that HFpEF was 25% of the total HF burden, indicating that in Indian clinical practice, HFrEF was predominantly observed.[5] This underscores the pressing need for effective management strategies and interventions tailored to the unique challenges faced by developing countries like India.[6-9]

The first-line treatments for HFrEF typically include angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, which have demonstrated efficacy in improving outcomes. However, recent updates have introduced novel classes of medications, such as angiotensin receptor-neprilysin inhibitors (ARNIs), to further optimize HF management.[1,10] Clinical trials and guidelines endorse the utilization of ARNI in HF, considering it as one of the four recommended medications for managing HF with HFrEF. ARNIs have demonstrated efficacy in enhancing diastolic and left ventricular function, enhancing quality of life, and mitigating the risk of ventricular arrhythmias.[11]

Sacubitril/valsartan, an ARNI, has emerged as a promising therapy for patients with HFrEF, offering superior outcomes compared to traditional ACE inhibitors. The drug sacubitril/valsartan contains two active ingredients, valsartan, and sacubitril, in equal amounts by molecule count, and targets two aspects of HF treatment: the natriuretic peptides (NPs) system through sacubitril, and the renin–angiotensin–aldosterone system (RAAS) through valsartan.[12] The landmark PARADIGM-HF study and subsequent trials have demonstrated its efficacy in reducing cardiovascular death and HF hospitalization. Edgardo Kaplinsky noted that sacubitril/valsartan treatment has shown remarkable benefits, with a 20% reduction in cardiovascular death risk, a 21% decrease in HF hospitalization risk, and a 16% decrease in all-cause mortality.[11,13,14] The latest guidelines of ACC/AHA/HFSA 2022 for the management of HF state that sacubitril/valsartan is recommended as a Class IA treatment to reduce morbidity and mortality in patients with NYHA Class II-III HFrEF. The latest guidelines of ACC/AHA/HFSA 2022 for the management of HF state that sacubitril/valsartan was recommended as a Class IA treatment to reduce morbidity and mortality in patients with NYHA Class II-III HFrEF.[15] The present cross-sectional study aimed to gather expert opinion to further understand the prescription practices of ARNI for HF management in Indian routine settings.

METHODOLOGY

We carried out a cross sectional study among cardiologists in managing HF in the major Indian cities from June 2023 to December 2023. The study was conducted after receiving approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

An invitation was sent to leading cardiologists in managing HF patients in the month of March 2023 for participation in this Indian survey. About 138 physicians from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. The questionnaire booklet titled REACH (Real world Experience of ARNI across Heart Failure patients) study was sent to the physicians who were interested to participate. The REACH study questionnaire comprised 18 questions about current feedback, clinical observations, and clinical experience of specialists in managing HF with the use of ARNI (sacubitril/valsartan) in routine settings. Clinicians had the option to skip any questions they preferred not to answer. They were instructed to complete the survey independently, without consulting their colleagues. Written informed consent was obtained from all participants before the study commenced.

Statistical Analysis

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to provide a clear insight into their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. To visualize the distribution of the categorical variables, graphs were created using Microsoft Excel 2013 (version 16.0.13901.20400).

RESULTS

The study involved 138 respondents, of which 70% stated that on average, 6 to 15 individuals were diagnosed with HF monthly in routine practice. As reported by 30% of the clinicians, the most encountered HF cases in practice were ACC/AHA Stage B: pre-HF patients without current or prior symptoms with evidence of structural heart disease, abnormal cardiac function, or elevated biomarkers.

Half (50%) of the clinicians reported that most of the patients with HF belong to the New York Heart Association (NYHA) class II category of NYHA classification while 38% of them reported that the patients belong to NYHA class III. Approximately 41% of the clinicians opined that the common age group noted with HF is between 41 to 50 years. As reported by 51% of the clinicians, the incidence of HF is almost equal in both genders, while 46% of them reported it was more frequent in males. Approximately 46% of the clinicians stated hypertension as the common co-morbid condition observed in patients with HF.

About 43% of the clinicians reported that 21 to 30% of the patients with HF were at risk of re-hospitalization. Majority (73.19%) of the clinicians reported following the ACC/ AHA/ HFSA guidelines for managing HF. Approximately 51% of the clinicians reported that the renin-angiotensin-aldosterone system (RAAS) was the neurohumoral factor related to the pathology of chronic HF and the targets of conventional remedies would provide better outcomes. Nearly 46% of the clinicians opined that metoprolol was the preferred beta blocker used in a newly detected hypertensive patient.

Majority (63%) of the clinicians noted that the most commonly used RAAS-modifying therapies for managing HF were ARBs. Additionally, a significant proportion (66.67%) of clinicians opined that the most preferred drug class for HF management was ARNI (Figure 1). Nearly 66% of the respondents stated that the dual action of ARNI on the RAAS and NPs pathway provides better outcomes with a reduction in mortality rate (Table 1).

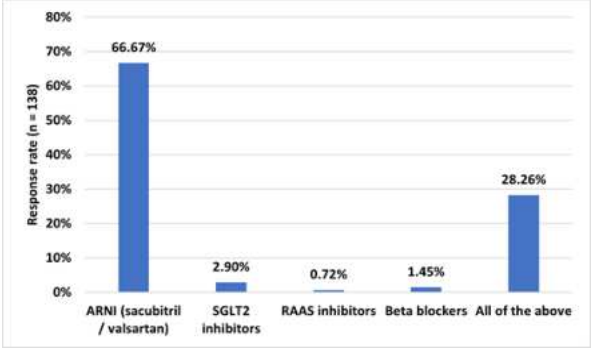

Figure 1: Distribution Of Response On The Preferred Drug For The Management Of HF

Table 1: Distribution Of Responses On The Outcomes Of ARNI Therapy On RAAS & NPS Pathway

Outcomes	Response rate (n = 138)
Decrease in mortality	65.94%
Delayed progression of disease	21.01%
Symptomatic relief	11.59%
All of the above	0.72%
Recurrent hospitalization	0.72%

About 34% of clinicians opined that cardiac remodeling was a distinct advantage of ARNI over other available drugs, while another 33% emphasized that ARNI offers additional benefits such as improved biomarkers, reduced hospitalizations, and slowed disease progression (Table 2). Furthermore, the majority (84.78%) of clinicians agreed with the findings of the PIONEER-HF study, which demonstrated that early initiation of ARNI in acute HF leads to early improvement in post-discharge outcomes (Figure 2).

Table 2: Distribution Of Responses On The Advantages Of ARNI Compared To Other Available Drugs

Advantages of ARNI	Response rate (n = 138)
Cardiac remodelling	34.06%
Biomarker improvement	2.17%
Reduction in hospitalisation	25.36%
Delayed progression of disease	5.80%
All of the above	32.61%

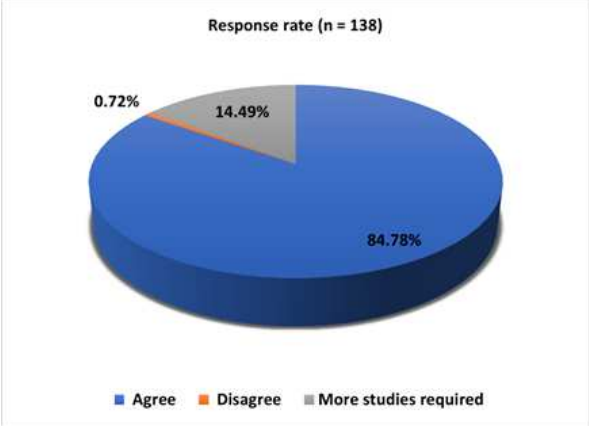

Figure 2: Distribution of response on agreement with PIONEER HF study on early initiation of ARNI and post-discharge outcomes in acute HF

Approximately 44% of the respondents reported that 10 to 30% of patients were prescribed sacubitril/valsartan in routine practice. Majority (89.13%) of the clinicians indicated that sacubitril/valsartan 100 mg (49/51 mg) was the commonly used dosage for HF management (Figure 3). Additionally, more than half (68.84%) of the clinicians preferred the use of sacubitril/valsartan to reduce the risk of cardiovascular death and hospitalization in adult patients with chronic HF.

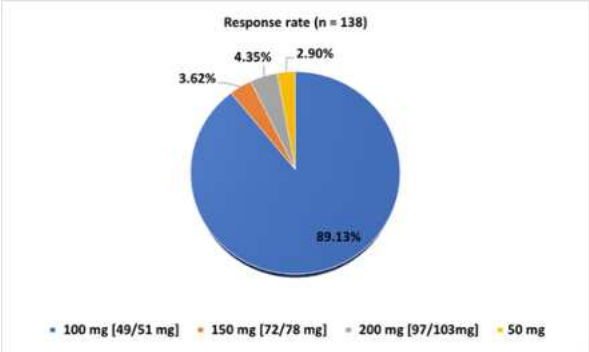

Figure 3: Distribution of responses on the commonly used strengths of sacubitril/valsartan for HF management

DISCUSSION

The survey findings underscored the preference for the ARNI in managing HF in Indian settings. The study revealed that the majority of clinicians favored ARNI as the primary drug class indicated for HF management. Consistent with these findings, Jariwala et al. noted that 97.6% of eligible patients experienced symptom improvement within an average of 6 ± 4 days of follow-up after starting ARNI treatment. Additionally, all patients treated with ARNI showed a significant reduction in HF symptoms as measured by the NYHA functional class, with a decrease from 2.6 ± 0.5 to 1.1 ± 0.3 9 ($P < 0.001$).[14] Chandra et al. also indicated that ARNI was the preferred choice of drug for the management of HF.[16]

Majority of respondents emphasized the dual action of ARNI through the RAAS and NPS pathway, and its ability to yield better outcomes with a reduced mortality rate. In line with these findings, Pascual-Figal et al. highlighted significant reductions in mortality and HF-related hospitalization rates with sacubitril/valsartan treatment.[12] Similarly, Rex C. Liu underscored the effectiveness of ARNI therapy' in targeting both the natriuretic peptide system and RAAS to lower mortality risk.[17] Ambrosy et al. also supported these findings, indicating a notable

decrease in cardiovascular mortality and improved clinical outcomes, including reduced rehospitalization rates.[18] Jhund and McMurray demonstrated a substantial reduction in the primary endpoint of cardiovascular death or HF-related hospitalization, coupled with a decrease in all-cause mortality, further validating the benefits of sacubitril/valsartan therapy.[19]

The current study revealed that ARNI has significant advantages over other drugs in terms of cardiac remodeling, biomarker enhancement, fewer hospitalizations, and slower disease progression. In the landmark PARADIGM-HF trial, Docherty et al. investigated the efficacy of sacubitril/valsartan (ARNI) compared to enalapril, an ACE inhibitor, in patients with HFrEF. Their findings revealed significant reductions in the primary endpoint of cardiovascular death or HF hospitalizations with sacubitril/valsartan as opposed to enalapril.[20,10] Velazquez et.al. showed that ARNI can lead to favorable changes in cardiac structure and function compared to ACE inhibitors or ARBs alone. This includes reductions in left ventricular dimensions and improvements in ejection fraction.[21] Januzzi et al. also reported that ARNIs have been associated with improvements in biomarkers related to HF severity and prognosis.[22] A double-blind trial by McMurray et al. showed consistent reduction in HF hospitalization following ARNI therapy compared to standard therapy with ACE inhibitors or ARBs alone.[10] Moreover, long-term follow-up studies and real-world evidence by Wachter et al. suggested that ARNIs may slow the progression of HF compared to traditional therapies.[23]

Majority of the current survey respondents supported the findings of the PIONEER-HF study, which highlighted the benefits of early initiation of ARNI in improving outcomes after discharge from acute HF. Additionally, the TRANSITION study by Velazquez et al. examined the transition of stable chronic HF patients from enalapril to sacubitril/valsartan, demonstrating favorable clinical outcomes and good tolerability with early ARNI use in stable patients.[21] DeVore emphasized the potential benefits of switching from enalapril to sacubitril/valsartan in patients with HF with reduced ejection fraction and recent hospitalization for acute decompensated HF. Switching the treatment also contributed to a significant reduction in NT-proBNP levels.[24] Jain et al. also supported the use of sacubitril/valsartan in Indian patients with chronic HF with reduced ejection fraction.[25] In a study titled PARADIGM-HF sub-analysis, conducted by McMurray et al., it was found that sacubitril/valsartan reduced the risk of HF hospitalization in patients who had recently suffered from decompensation.[26]

According to the current survey, 100 mg (49/51 mg) was the commonly used strength of sacubitril /valsartan for the management of HF in patients. In line with these findings, Loretta Fala in their study recommended that the initial dosage for treating HF was twice daily administration of sacubitril 49 mg/valsartan 51 mg, with or without food. This dosage should be increased to sacubitril 97 mg/valsartan 103 mg twice daily (the target maintenance dose) after 2 to 4 weeks, based on the patient's tolerance.[27,28] Jhund and McMurray suggested also advocated sacubitril/valsartan 49 mg/51 mg twice daily as the starting dose for HF.[19]

Majority of the current clinicians prefer to use sacubitril/valsartan to reduce the risk of cardiovascular death and hospitalization for HF in adult patients with chronic HF. In concurrence with this finding, Edgardo Kaplinsky revealed significant reductions in hospitalization among patients treated with sacubitril/valsartan, including 23% fewer hospitalizations for worsening HF ($P < 0.001$), 16% fewer hospitalizations for cardiovascular reasons ($P < 0.001$), and 29% fewer HF-related hospitalization ($P = 0.001$).[29]

The results of the present survey can help clinicians in improving treatment strategies and patient care for HF management by considering the preferences and prescription practices noted in the survey. The survey used a well-designed and validated questionnaire to collect data from clinicians, which is a major strength. However, it was important to note that the survey has certain limitations. The reliance on expert opinion may introduce bias since different perspectives and preferences among clinicians could have influenced the results. Therefore, it was essential to keep these limitations in mind when interpreting the findings. Additionally, the survey may not reflect the latest trends or emerging evidence in diabetes management. To address this limitation, prospective trials or real-world observational studies were needed to support the survey results and provide a more comprehensive understanding of the optimal treatment approaches.

CONCLUSION

The study highlighted a strong preference for the ARNI drug class for managing HF. The experts also agreed that the dual action of ARNI through RAAS and NPs pathways helps in reducing mortality rates and improving cardiac remodeling. The study also revealed that clinicians commonly prescribe a dosage of 100 mg (49/51mg) for sacubitril /valsartan and recommended its early initiation in acute HF, which was in line with the findings of PIONEER-HF study.

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Nil

Conflict Of Interest

None to declare

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