Survey Report

Survey to Understand the Current Usage of Sacubitril/Valsartan in Indian Patient Population 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 condition in which the heart cannot pump enough blood and oxygen to meet the body's metabolic needs [1]. It affects approximately 64 million people globally, with its prevalence increasing due to factors such as an aging population, higher incidence of comorbidities and risk factors, and improved survival rates following myocardial infarction [2]. Despite advances in medicine, the management of HF, typically presenting as a syndrome, continues to pose challenges for healthcare providers [3].

Patients with HF are traditionally treated with oxygen, salt/water restrictions, hypertension control, and medications like nitrates, diuretics, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. Recently, angiotensin receptor/neprilysin inhibitors (ARNIs) and sodium-glucose cotransporter inhibitors are recognized as pivotal advancements in treatment [4].

Sacubitril/valsartan is the pioneering drug in the class of ARNIs [5]. It is now recognized as an evidence-based and guideline-recommended therapy that modifies the course of disease for patients with HF with reduced ejection fraction, solidifying its established role in routine clinical practice [6]. According to the results of the PARADIGM-HF trial, sacubitril/valsartan showed notable benefits compared to enalapril in lowering cardiovascular mortality, decreasing the risk of HF hospitalization, alleviating HF symptoms, and improving physical function limitations [7].

Understanding the current usage patterns, prescribing practices, and clinical experiences with sacubitril/valsartan among Indian healthcare providers is crucial for optimizing its integration into routine HF management strategies.

2 RATIONALE OF THE STUDY

The rationale for this study was to gather insights into the current usage patterns and clinical practices related to sacubitril/valsartan in the management of HF among Indian physicians. By examining prescribing behaviors, initiation practices, dosing strategies, and perceived clinical benefits and safety profiles, the study aimed to enhance the integration of sacubitril/valsartan into routine HF management strategies in India.

3 STUDY OBJECTIVE

The primary objective of this study was to assess the current usage patterns and clinical practices associated with sacubitril/valsartan in the treatment of HF among Indian physicians.

4 METHODS

This study employed a cross-sectional, questionnaire-based design involving a sample of Indian physicians who manage patients with HF. The survey comprised 15 questions focused on the physicians' clinical experience, prescribing practices, and perceptions of sacubitril/valsartan therapy.

Physicians were identified and invited to participate through professional networks and medical associations. Participants received detailed information about the study before agreeing to partake. The survey, containing 15 questions, was administered electronically, and responses were collected and securely stored. Statistical analysis was conducted to summarize the findings and identify key trends. The results were then compiled into a comprehensive report, with the intention of sharing the study findings through scientific publications and/or presentations at conferences, if deemed suitable.

The target sample size for this study was 117 Indian physicians. This number was chosen to ensure a diverse and representative sample, enabling meaningful statistical analysis of the survey data.

This study adhered to the ethical principles outlined in the Declaration of Helsinki. Ethical approval was sought from an Independent Ethics Committee. Participants were assured of their right to withdraw from the study at any time without any consequences. All responses were anonymized to ensure participant confidentiality.

5 RESULTS

A total of 117 HCPs participated in the survey. Below is the summary of the responses.

1. Which therapeutic option is usually preferred by you as a first-line in newly diagnosed patients with symptomatic heart failure?

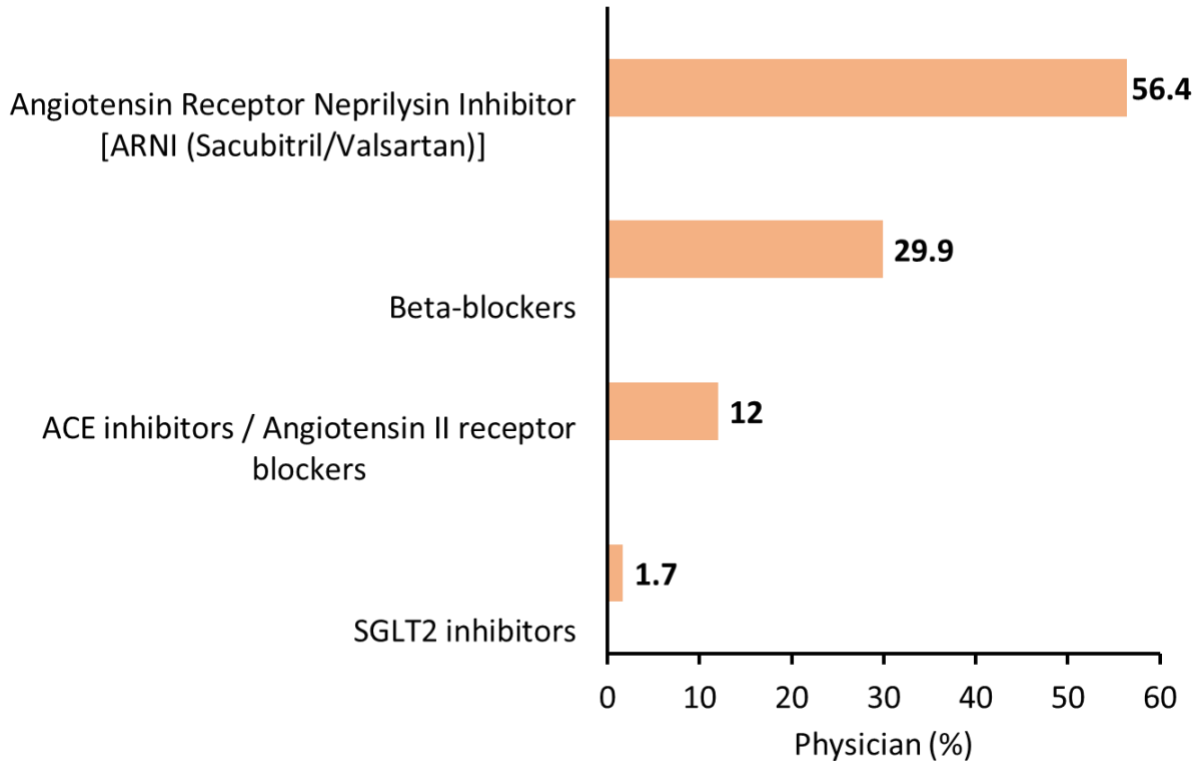
a. Angiotensin Receptor Neprilysin Inhibitor [ARNI (Sacubitril/Valsartan)]

b. Beta-blockers

c. Mineralocorticoid-receptor antagonists

d. ACE inhibitors / Angiotensin II receptor blockers

e. SGLT2 inhibitors



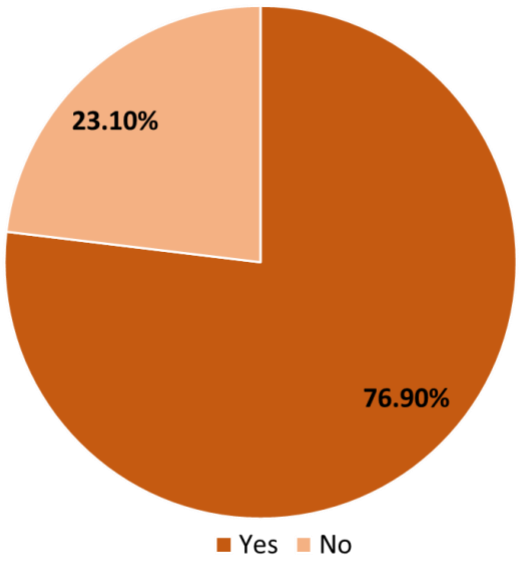
- The majority of the physicians (56.4%) preferred ARNI, specifically Sacubitril/Valsartan, as the first-line therapeutic option for newly diagnosed patients with symptomatic HFrEF.
- Approximately 29.9% of physicians preferred beta-blockers as the first-line therapeutic option for newly diagnosed patients with symptomatic HFrEF.

- Additionally, 12% of physicians preferred Acetyl Choline Esterase (ACE) inhibitors/Angiotensin II receptor blockers as the first-line therapeutic option for newly diagnosed patients with symptomatic HFrEF.
- About 1.7% of physicians preferred Sodium-glucose cotransporter-2 (SGLT2) inhibitors as the first-line therapeutic option for newly diagnosed patients with symptomatic HFrEF.
- No physician preferred mineralocorticoid receptor antagonists as the first-line therapeutic option for newly diagnosed patients with symptomatic HFrEF.

2. Do you prefer to use ARNI in patients with heart failure with preserved ejection fraction (HFpEF) in current clinical practice?

a. Yes

b. No



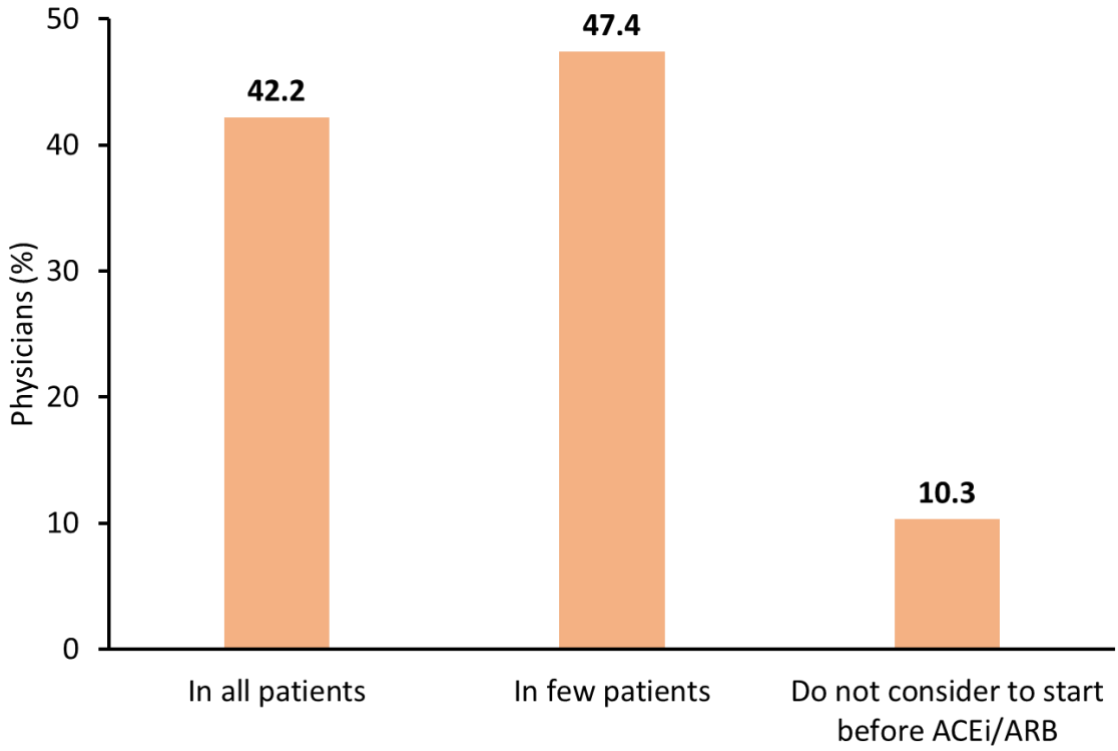
- The majority of physicians (76.9%) used ARNI in patients with HFpEF in current clinical practice, while 23.1% of physicians did not use ARNI in patients with HFpEF in current clinical practice.

3. How often do you consider to start with ARNI in heart failure 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



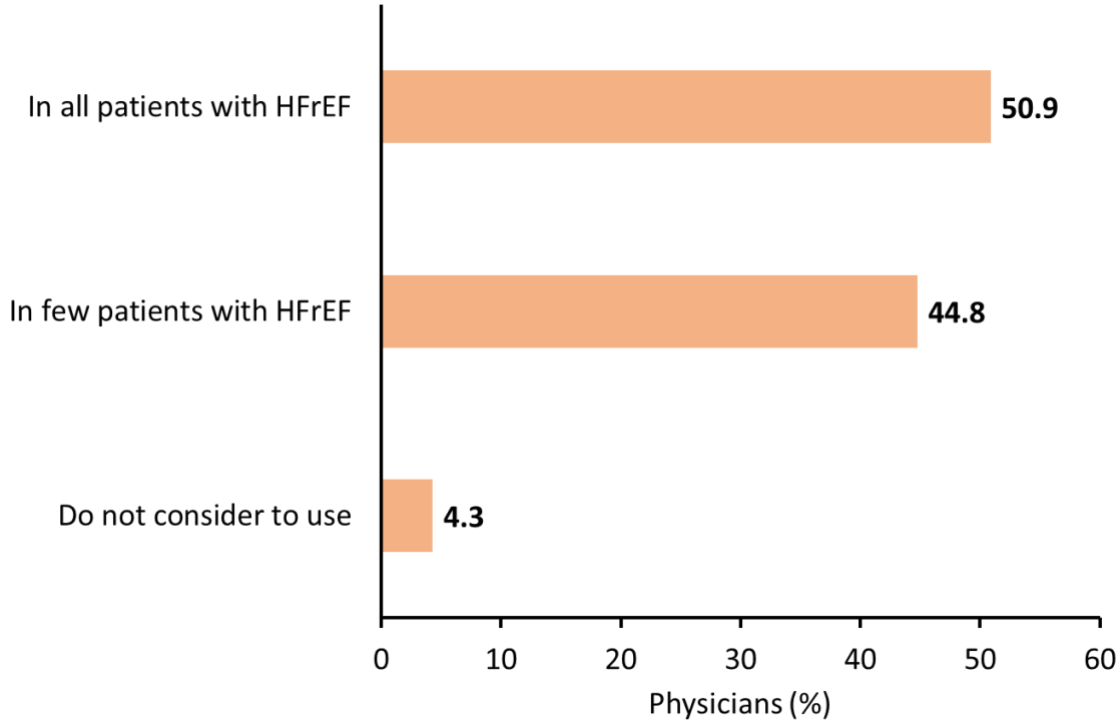
- The majority of physicians (47.4%) considered starting with ARNI in HF patients without previous use of an ACEI or angiotensin receptor blockers (ARB) in a few patients.
- While 42.2% of physicians preferred ARNI in HF patients without previous use of an ACEI or ARB in all patients.
- Additionally, 10.3% of physicians did not consider starting ARNI before ACEI/ARB in HF patients without previous use.

4. How often do you consider to use ARNI along with SGLT2 Inhibitor in current clinical practice?

a. In all patients with HFrEF

b. In few patients with HFrEF

c. Do not consider to use



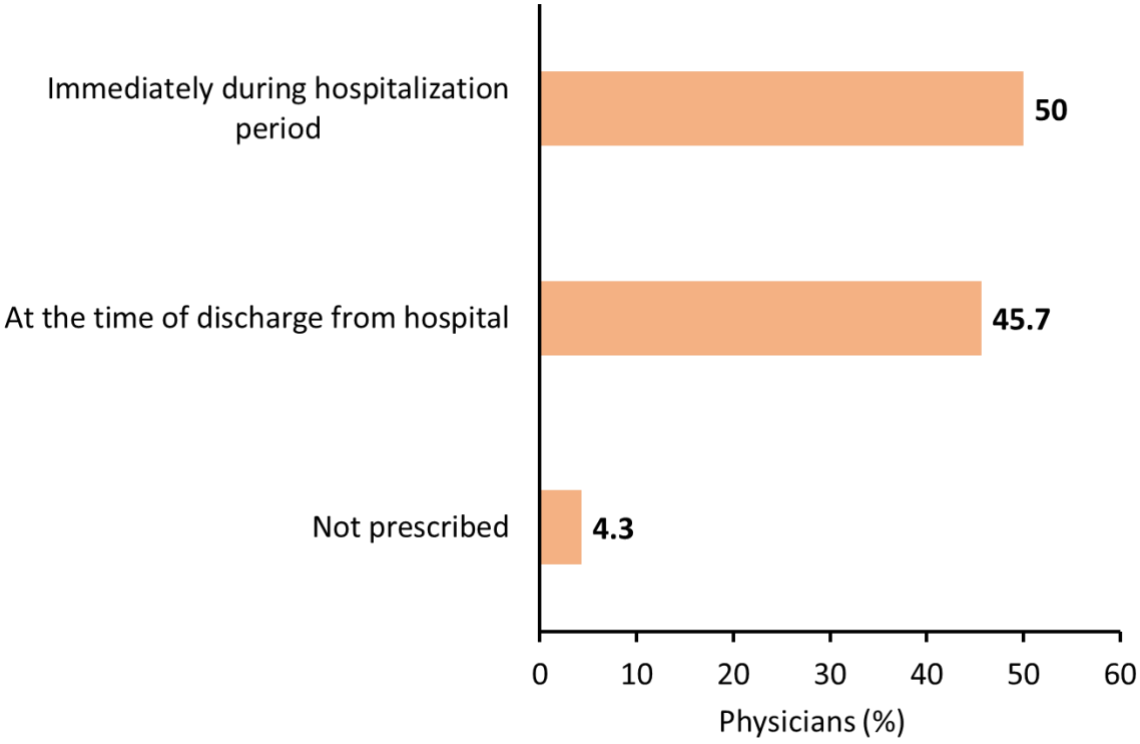
- About 50.9% of physicians concomitantly used ARNI along with SGLT2 inhibitors for all patients with HFrEF in current clinical practice.
- Additionally, 44.8% of physicians used ARNI along with SGLT2 inhibitors for all patients with HFrEF in current clinical practice.
- While 4.3% of physicians did not consider using ARNI along with SGLT2 inhibitors in current clinical practice.

5. When do you consider to prescribe ARNI in patients with HFrEF?

a. Immediately during hospitalization period

b. At the time of discharge from hospital

c. Not prescribed



- Approximately 50% of physicians prescribe ARNI in patients with HFrEF immediately during the hospitalization period.
- Additionally, 45.7% of physicians prescribe ARNI in patients with HFrEF at the time of discharge from the hospital.
- While 4.3% of physicians did not prescribe ARNI in patients with HFrEF.

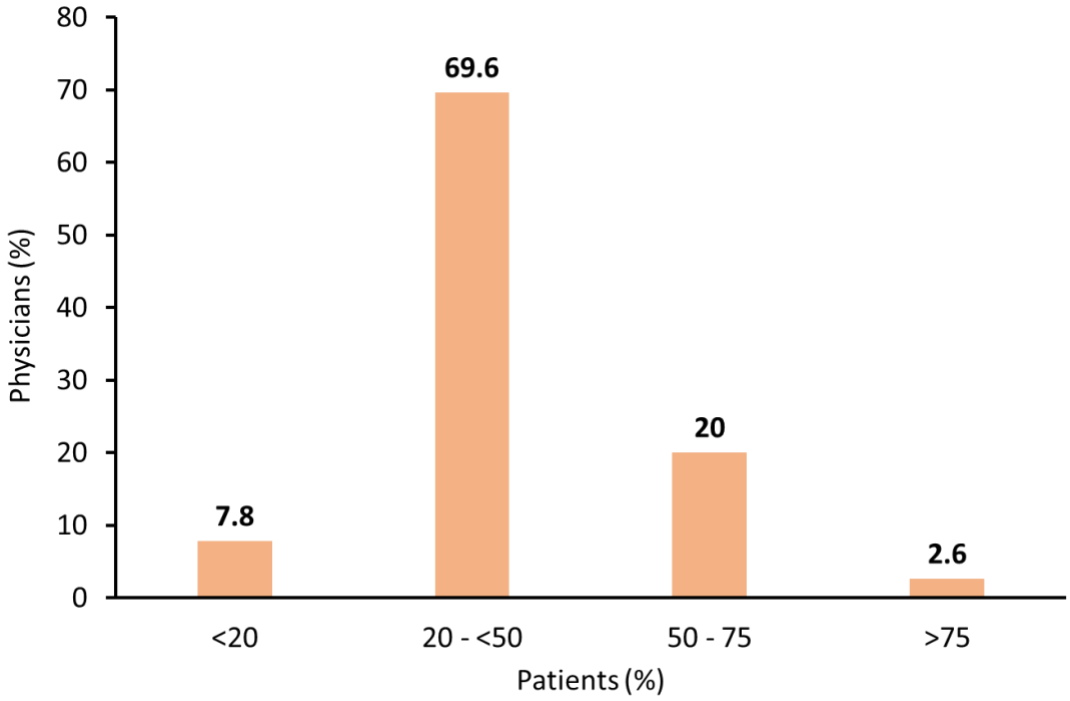
6. What is the percentage reduction in the incidence of hospitalization for heart failure (HHF) with the usage of ARNI in your clinical practice?

a. <20%

b. 20 - <50%

c. 50 - 75%

d. >75%



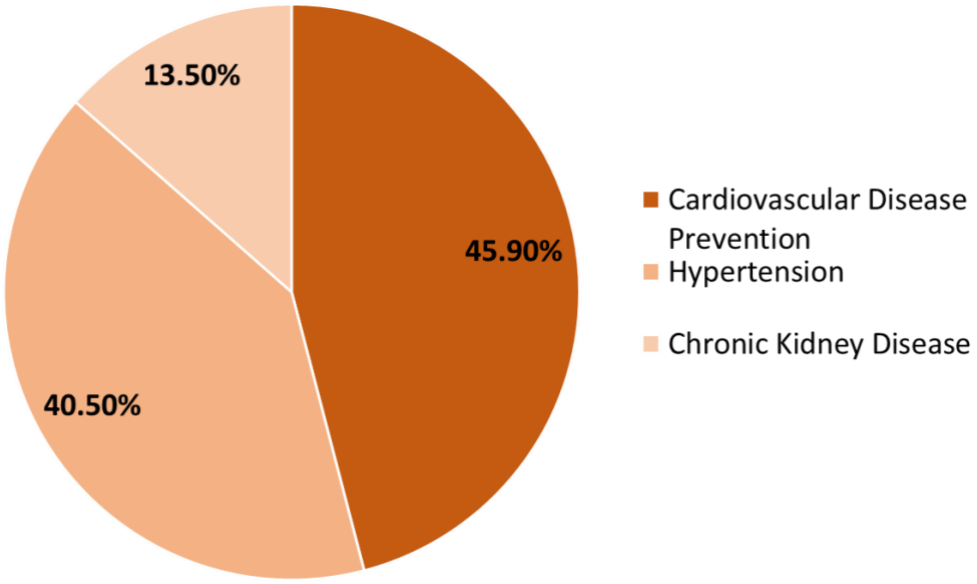
- About 69.6% of physicians reported a 20-<50% reduction in the incidence of HHF with the usage of ARNI in their clinical practice.
- Additionally, 20% of physicians noted less than a 50-75% reduction in the incidence of HHF with the usage of ARNI in their clinical practice.
- About 7.8% of physicians noted less than a 20% reduction in the incidence of HHF with the usage of ARNI in their clinical practice.
- While 2.6% of physicians noted less than a 20% reduction in the incidence of HHF with the usage of ARNI in their clinical practice.

7. In which indication other than heart failure, ARNI can be useful therapeutic option ?

a. Hypertension

b. Chronic Kidney Disease

c. Cardiovascular Disease Prevention



- About 45.90% of physicians believed that other than HF, ARNI could be useful for cardiovascular disease prevention, while 40.50% of physicians believed that other than HF, ARNI could be useful for hypertension. Only 13.50% of physicians considered ARNI could be useful for chronic kidney disease.

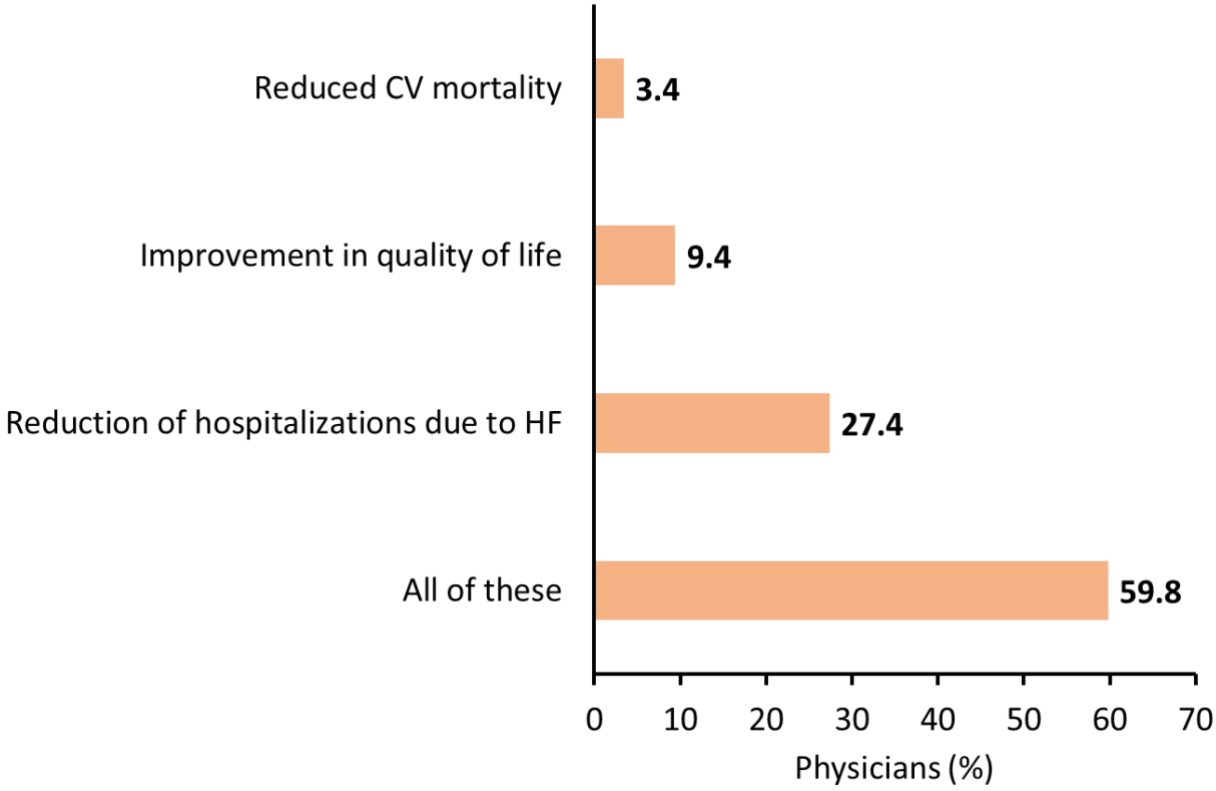
8. Which is/are the perceived key clinical benefit(s) associated with therapeutic usage of ARNI in patients with heart failure?

a. Reduced CV mortality

b. Reduction of hospitalizations due to HF

c. Improvement in quality of life

d. All of these



- According to 59.8% of physicians, reduced CV mortality, reduction of hospitalizations due to HF, and improvement in quality of life were perceived as key clinical benefits associated with the therapeutic usage of ARNI in patients with HF.
- About 27.4% of physicians considered reduction of hospitalizations due to HF as a perceived key clinical benefit associated with the therapeutic usage of ARNI in patients with HF.

- Approximately 9.4% of physicians considered improvement in quality of life as a perceived key clinical benefit associated with the therapeutic usage of ARNI in patients with HF.
- A total, 3.4% of physicians considered reduced cardiovascular mortality as a perceived key clinical benefit associated with the therapeutic usage of ARNI in patients with HF.

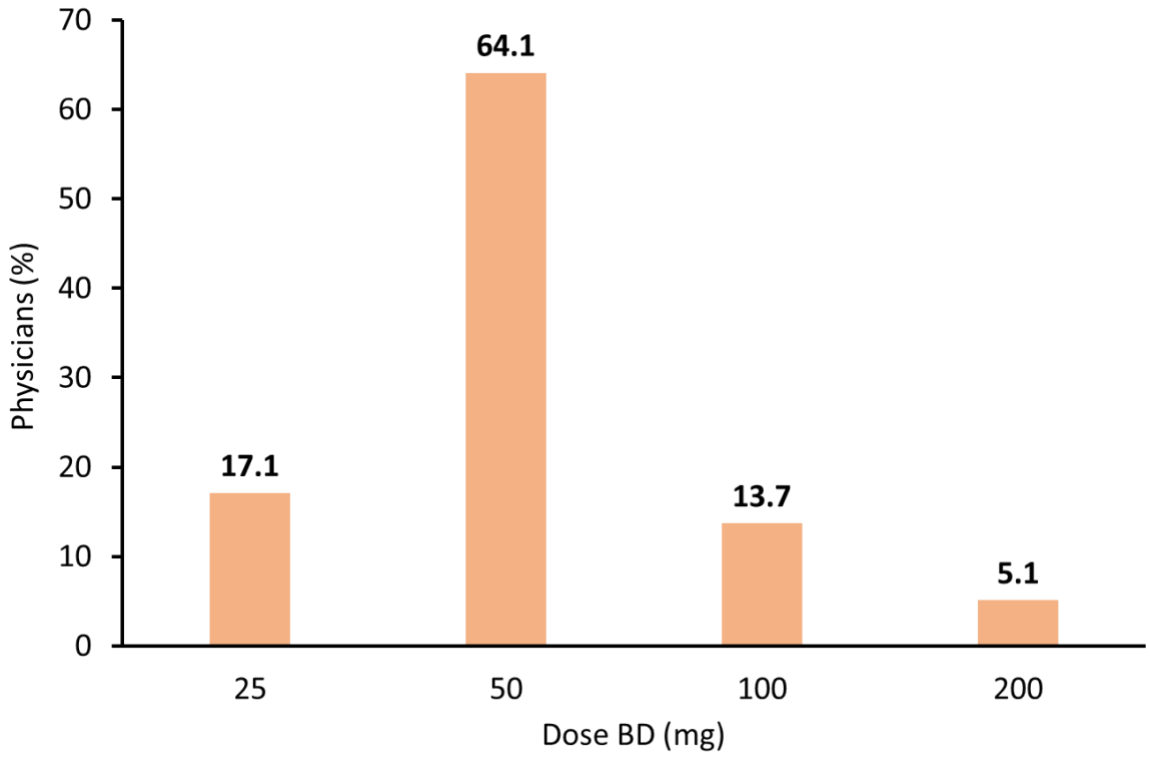
9. What is the preferred initial dose of ARNI in routine clinical practice?

a. 25 mg BD

b. 50 mg BD

c. 100 mg BD

d. 200 mg BD



- The majority of physicians (64.1%) preferred the 50 mg BD as the initial dose of ARNI in routine clinical practice.
- This was followed by 17.1% of physicians who preferred 20 mg BD as the initial dose of ARNI in routine clinical practice, and 13.7% of physicians who preferred 20 mg BD as the initial dose of ARNI in routine clinical practice.
- While 5.1% of physicians preferred 200 mg BD as the initial dose of ARNI in routine clinical practice.

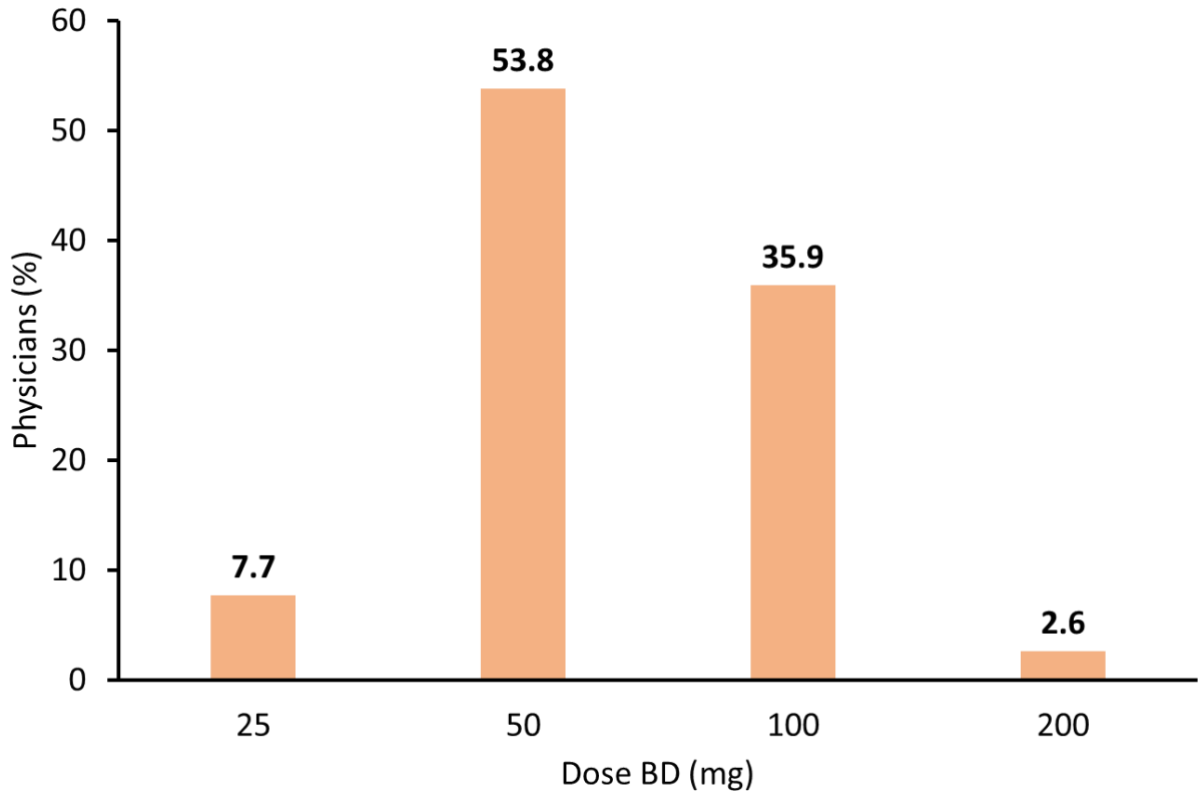
10. Which dose do you usually reach after titration and maintain for the majority of your heart failure patients?

a. 25 mg BD

b. 50 mg BD

c. 100 mg BD

d. 200 mg BD



- About 53.8% of physicians usually reached and maintained a dose of 50 mg BD after titration for the majority of HF patients.
- This was followed by 35.9% of physicians who usually reached and maintained a dose of 100 mg BD after titration for the majority of HF patients, while 7.7% of physicians reached and maintained a dose of 25 mg BD after titration for the majority of HF patients.
- Only 2.6% of physicians reached and maintained a dose of 200 mg BD after titration for the majority of HF patients.

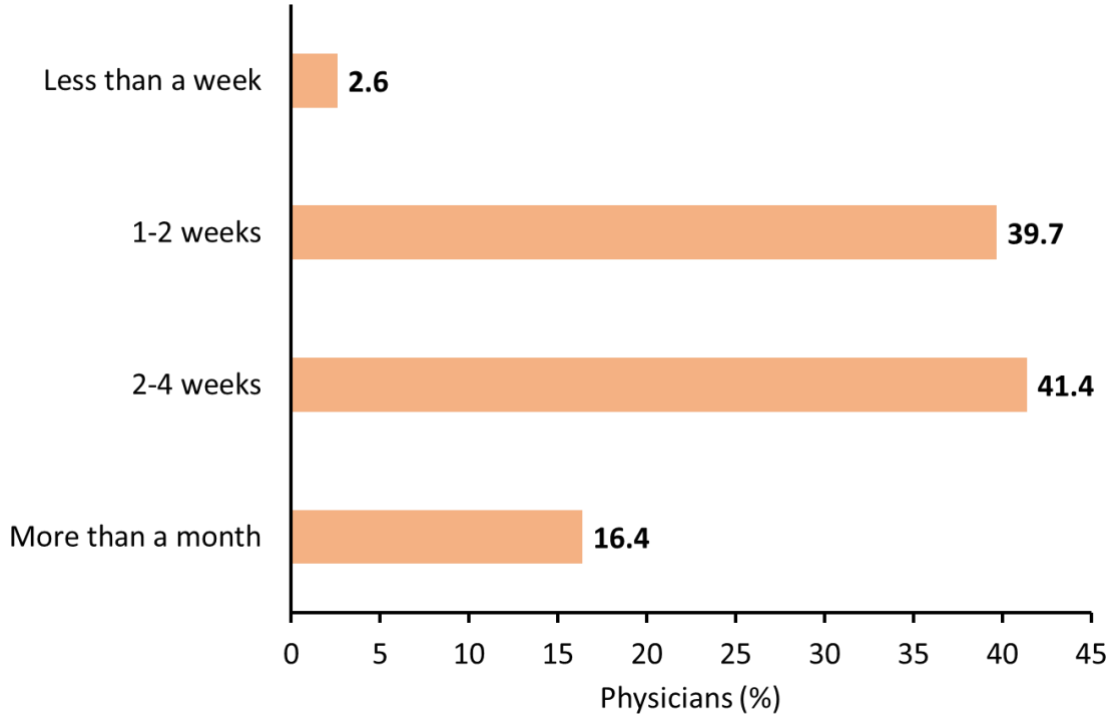
11. In your experience, how long does it typically take for patients to experience noticeable overall improvements in their condition after starting ARNI therapy?

a. Less than a week

b. 1-2 weeks

c. 2-4 weeks

d. More than a month



- According to 41.4% of physicians, it took 2-4 weeks for patients to experience noticeable overall improvements in their condition after starting ARNI therapy.
- Followed by 39.7% who believed it took 1-2 weeks, 16.4% who believed it took more than months, and 2.6% who believed it took less than week.

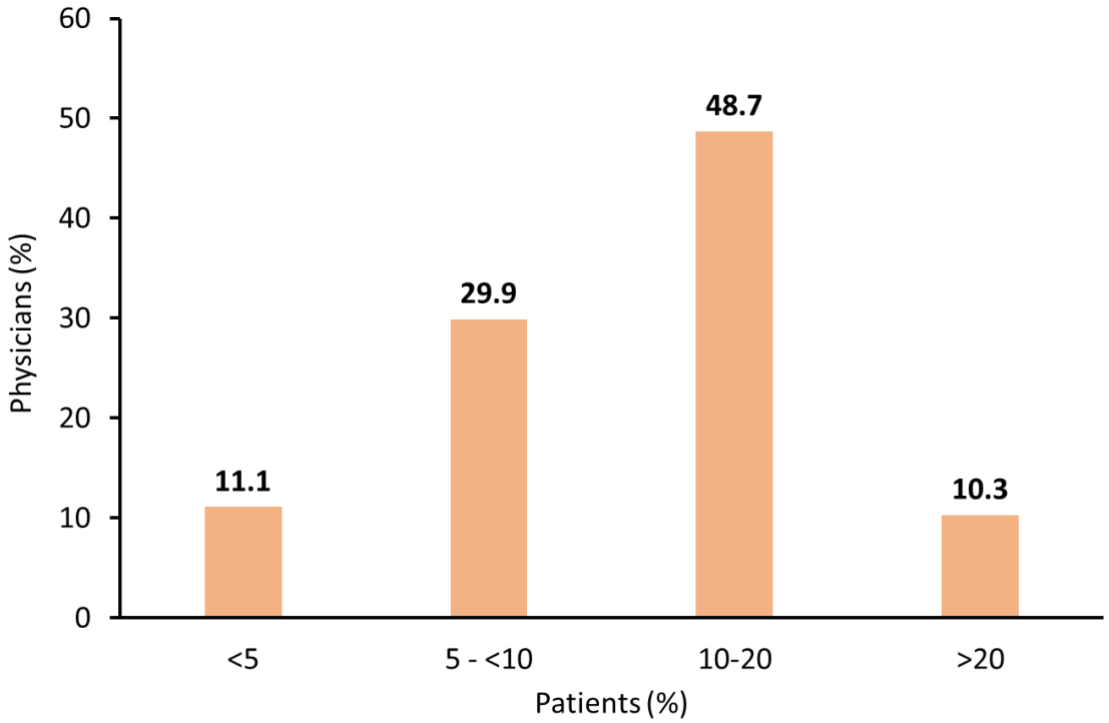
12. What is the % of Hypotension usually been observed by you with the usage of ARNI during current clinical practice?

a. <5%

b. 5 - <10%

c. 10 - 20%

d. >20



- Approximately 48.7% of physicians believed that 10-20% of hypotension was usually observed with the usage of ARNI during current clinical practice.
- About 29.9% of physicians considered 5 - <10% of hypotension to be usually observed with the usage of ARNI during current clinical practice.
- Additionally, 11.1% of physicians believed that <5% of hypotension was usually observed with the usage of ARNI during current clinical practice.
- While 10.3% of physicians believed that >20% of hypotension was usually observed with the usage of ARNI during current clinical practice.

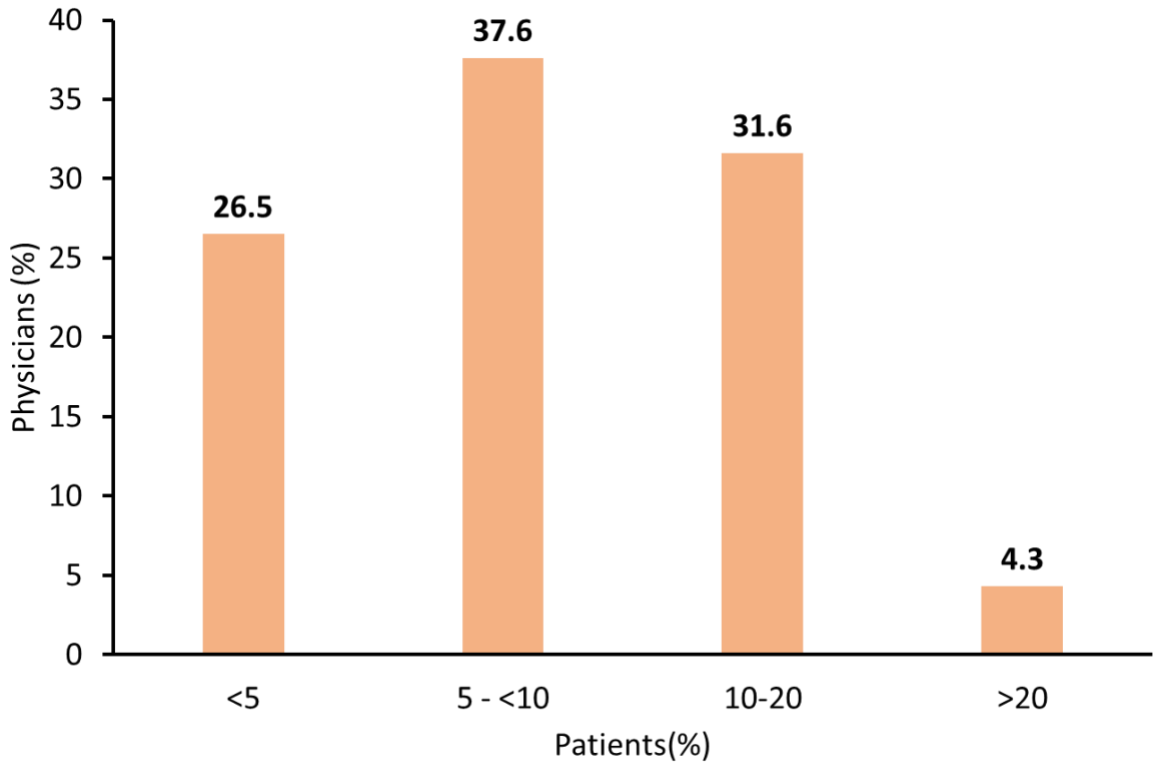
13. What is the % of Hyperkalemia usually been observed by you with the usage of ARNI during current clinical practice?

a. <5%

b. 5 - <10%

c. 10 - 20%

d. >20%



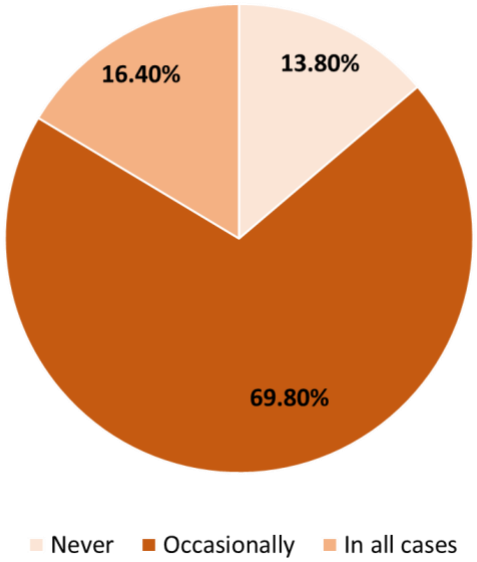
- Approximately 37.6% of physicians believed that 5 - <10% of hyperkalemia was usually observed with the usage of ARNI during current clinical practice.
- About 31.6% of physicians considered 10 - 20% of hyperkalemia to be usually observed with the usage of ARNI during current clinical practice.
- Additionally, 26.5% of physicians believed that <5% of hyperkalemia was usually observed with the usage of ARNI during current clinical practice.
- While 4.3% of physicians believed that >20% of hyperkalemia was usually observed with the usage of ARNI during current clinical practice.

14. How often have you observed the lack of patient adherence to ARNI therapy?

a. Never

b. Occasionally

c. In all cases



- About 69.8% of physicians observed that occasionally there was lack of patient adherence to ARNI therapy, followed by 16.4% who believed that in all cases there was patient adherence to ARNI therapy, and 13.8% believed there was never lack of patient adherence to ARNI therapy.

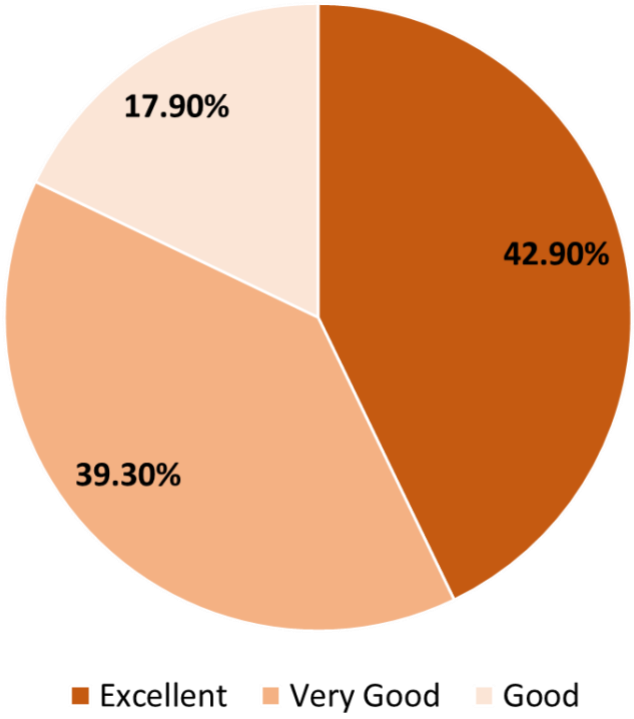
15. In your opinion, how is the long-term safety profile of ARNI therapy in heart failure patients?

A. Excellent

B. Very Good

C. Good

D. Poor



- About 42.9% of physicians believed that the long-term safety profile of ARNI therapy in HF patients was excellent, while 39.3% believed that the long-term safety profile of ARNI therapy in HF patients was very good. •
- Additionally, 17.9% of physicians believed that the long-term safety profile of ARNI therapy in HF patients was good, and no physician considered the long-term safety profile of ARNI therapy in HF patients to be poor.

6 SUMMARY

The survey of physicians on the management of HF highlighted ARNIs, particularly Sacubitril/Valsartan, as a preferred first-line therapy for newly diagnosed symptomatic HFrEF by 56.4% of respondents. Beta-blockers were favored by 29.9%, while ACE inhibitors/Angiotensin II receptor blockers were preferred by 12%, and SGLT2 inhibitors by 1.7%. Mineralocorticoid receptor antagonists were not chosen as a primary option by any physician.

In clinical practice, ARNI usage varied: 76.9% of physicians did not use ARNI for HFpEF, and 47.4% considered ARNI in HF patients without prior ACEI or ARB use, with 42.2% preferring it for all such patients. Concomitant use of ARNI with SGLT2 inhibitors was noted by 50.9% of physicians for all HFrEF patients.

Perceived benefits of ARNI therapy included reductions in cardiovascular mortality (59.8%), HF hospitalizations (27.4%), and improvement in quality of life (9.4%). Hypotension and hyperkalemia were recognized as potential side effects by 48.7% and 37.6% of physicians, respectively. Patient adherence to ARNI therapy was occasionally challenging for 69.8% of physicians. Regarding safety, opinions were positive, with 42.9% rating the long-term safety of ARNI in HF patients as excellent, 39.3% as very good, and 17.9% as good; no physicians considered it poor.

Overall, ARNI therapy in HF management is widely accepted among physicians, showing significant clinical benefits and generally favorable safety perceptions, albeit with considerations for side effects and adherence challenges.

7 DISCUSSION

The survey results indicate a strong preference among physicians for ARNI, particularly Sacubitril/Valsartan, as the leading choice for managing newly diagnosed symptomatic HFrEF. This preference aligns with clinical guidelines emphasizing ARNI's efficacy in improving patient outcomes, including reducing hospitalizations and potentially enhancing quality of life. Concurrent use of ARNI with SGLT2 inhibitors is also notable, reflecting a trend towards combination therapies aimed at optimizing therapeutic benefits in HFrEF management.

Physicians expressed varying beliefs regarding ARNI's role beyond HF, with a notable interest in its potential for cardiovascular disease prevention and hypertension management. Safety perceptions of ARNI were generally positive, with a majority rating its long-term safety profile as excellent or very good, underscoring confidence in its use despite concerns about side effects such as hypotension and hyperkalemia.

Overall, the findings highlight ARNI's growing prominence in HFrEF treatment strategies, supported by perceived clinical benefits and ongoing considerations for optimal dosing and safety management.

8 CLINICAL RECOMMENDATIONS

- Consider ARNI (Sacubitril/Valsartan) as the preferred initial therapy for newly diagnosed symptomatic HFrEF, supported by its efficacy in reducing hospitalizations and improving outcomes.
- Reserve beta-blockers and ACE inhibitors/ARBs as alternatives based on patient-specific factors and tolerability.
- Monitor for hypotension and hyperkalemia when initiating ARNI therapy.
- Encourage concomitant use of ARNI with SGLT2 inhibitors for synergistic benefits in HFrEF management.
- Initiate ARNI at 50 mg BD and titrate based on patient response, aiming to reach optimal doses gradually.
- Educate on ARNI's potential to reduce cardiovascular mortality, hospitalizations, and improve quality of life.
- Address patient adherence challenges to maximize therapeutic effectiveness.
- Acknowledge ARNI's favorable long-term safety profile in HF patients, supporting its continued use in clinical practice.

9 CONSULTANT OPINION

Based on the survey findings, ARNIs, particularly Sacubitril/Valsartan, are prominently endorsed as a first-line therapy for symptomatic HFrEF by a substantial majority of physicians. This preference underscores ARNI's perceived efficacy in reducing cardiovascular mortality, HF hospitalizations, and enhancing quality of life. However, challenges such as potential hypotension, hyperkalemia, and intermittent patient adherence are acknowledged, necessitating careful monitoring and patient education. Despite these considerations, the overwhelmingly positive perception of ARNI's long-term safety profile among a majority of respondents indicates confidence in its role in HFrEF management. The varying use patterns across HFpEF and titration strategies highlight the need for tailored treatment approaches to optimize outcomes in clinical practice.

10 MARKET OPPORTUNITIES

Based on the survey results, there are several market opportunities for ARNIs, specifically Sacubitril/Valsartan, in the management of HF. First-line Therapy Preference with 56.4% of physicians favoring ARNIs as the initial treatment for newly diagnosed symptomatic HFrEF, there is a significant market opportunity for ARNIs to expand their use in this patient population, potentially capturing a larger share of the HFrEF treatment market currently dominated by beta-blockers and ACE inhibitors/ARBs.

The concurrent use of ARNIs with SGLT2 inhibitors by 50.9% of physicians presents a strategic opportunity. This combination has shown additive benefits in reducing HF hospitalizations and improving outcomes, suggesting a potential growth area in combination therapies for HFrEF management. Addressing concerns around patient adherence (69.8% occasional lack of adherence) and safety profiles (42.9% excellent, 39.3% very good) offers opportunities for pharmaceutical companies to develop support programs and further refine safety profiles to enhance physician and patient confidence. Expanded Indications: While currently primarily used for HFrEF, exploring ARNIs' potential benefits beyond HF, such as in cardiovascular disease prevention (45.9% interest) and hypertension (40.5% interest), presents avenues for market expansion and new indications.

By leveraging these insights, pharmaceutical companies can focus on enhancing product education, supporting combination therapies, improving adherence strategies, and exploring new indications to maximize ARNI utilization and market penetration.

11 MARKET POSITIONING

Based on the survey findings, ARNIs, particularly Sacubitril/Valsartan, have established a strong market positioning in the management of HF, specifically for patients with HFrEF:

Preferred First-line Therapy

With 56.4% of physicians selecting ARNIs as the primary choice for newly diagnosed symptomatic HFrEF, ARNIs are positioned as a leading therapeutic option, ahead of beta-blockers (29.9%) and ACE inhibitors/ARBs (12%).

Combination Therapy

A significant proportion (50.9%) of physicians concurrently use ARNIs with SGLT2 inhibitors, reflecting a growing trend towards combination therapies to optimize HF management and outcomes.

Clinical Benefits

Perceived benefits of ARNI therapy include reductions in cardiovascular mortality (59.8%), HF hospitalizations (27.4%), and improvement in quality of life (9.4%), reinforcing its efficacy in clinical practice.

Dosing and Adherence

Most physicians (64.1%) initiate ARNI therapy at 50 mg BD and achieve maintenance doses suitable for HF patients, despite challenges in patient adherence reported by 69.8% of physicians.

Safety Profile

The majority (99.1%) of physicians rate the long-term safety profile of ARNI therapy in HF patients as good to excellent, underscoring confidence in its safety and tolerability.

This comprehensive positioning underscores ARNIs as pivotal in contemporary HF management strategies, offering significant clinical benefits and robust safety perceptions among healthcare providers.

12 REFERENCES

1) Emdin M, Vittorini S, Passino C, Clerico A. Old and new biomarkers of HF. Eur J Heart Fail. 2009;11(4):331-5.
2) Ohtani T, Mohammed SF, Yamamoto K, Dunlay SM, Weston SA, Sakata Y, et al. Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodelling and poor outcomes in HF with preserved ejection fraction. Eur Heart J. 2012;33(14):1742-9.
3) Inamdar AA, Inamdar AC. HF: Diagnosis, Management and Utilization. J Clin Med. 2016 Jun 29;5(7):62.
4) Niu CY, Yang SF, Ou SM, Wu CH, Huang PH, Hung CL, et al. Sacubitril/Valsartan in Patients With HF and Concomitant End-Stage Kidney Disease. J Am Heart Assoc. 2022;11(18):e026407.
5) Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, Maahs S, Ksander G, Rigel DF, Jeng AY, Lin TH, Zheng W, Dole WP. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). J Clin Pharmacol. 2010 Apr;50(4):401-14.
6) Mazza A, Townsend DM, Torin G, Schiavon L, Camerotto A, Rigatelli G, Cuppini S, Minuz P, Rubello D. The role of sacubitril/valsartan in the treatment of chronic HF with reduced ejection fraction in hypertensive patients with comorbidities: From clinical trials to real-world settings. Biomed Pharmacother. 2020 Oct;130:110596.
7) McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in HF. N Engl J Med. 2014;371(11):993-1004.