A Current Perspective of Healthcare profession in india on Angiotensin Receptor Neprilysin Inhibitor Therapy in Heart Failure patients.

Table of Content

Background and Objective of the Survey

In India, healthcare professionals are increasingly recognizing the significance of angiotensin receptor neprilysin inhibitor (ARNI) therapy in managing heart failure (HF). ARNIs combine the benefits of angiotensin receptor blockade with neprilysin inhibition, offering a novel approach to HF treatment.

Healthcare professionals in India view ARNI therapy as a valuable addition to the armamentarium against HF, particularly in patients with reduced ejection fraction (HFrEF). ARNIs have demonstrated superiority over angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) alone in reducing cardiovascular mortality and HF hospitalizations.

However, challenges exist in implementing ARNI therapy in clinical practice in India, including cost considerations, limited availability, and the need for patient education regarding potential side effects and monitoring requirements. Additionally, navigating the transition from ACEIs/ARBs to ARNIs requires careful management to minimize the risk of angioedema and hypotension.

Despite these challenges, healthcare professionals in India recognize the compelling evidence supporting ARNI therapy and strive to integrate it into HF management protocols. Collaborative efforts between clinicians, pharmacists, and policymakers are essential to overcome barriers and ensure broader access to ARNI therapy, ultimately improving outcomes for patients with HF in India.

The objective of the survey is:

To evaluate the role of angiotensin receptor neprilysin inhibitor therapy in heart failure and related healthcare professional current perspective in India

Methodology of the Survey

A survey was conducted to evaluate the role of angiotensin receptor neprilysin inhibitor therapy in heart failure and related healthcare professional current perspective in India. A total of 150 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Sacubitril/Valsartan
- Pathophysiology of cardiorenal interaction in chronic heart failure
- Dual angiotensin-neprilysin inhibition in chronic heart failure
- Cardiovascular effects of angiotensin receptor-neprilysin inhibitor
- Renal effects of angiotensin receptor-neprilysin inhibitor[3]
- Evidence for a renal protective role in chronic heart failure
- The Mechanism of Sacubitril/Valsartan in the Treatment of HF
- Pharmacological mechanism of sacubitril/valsartan in CKD
- Clinical application of sacubitril/valsartan in CKD
- Mechanism of Action of ARNIs in Mortality Reduction
- Safety and Tolerability of sacubitril/valsartan

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Sacubitril/valsartan is the first-in-class of angiotensin receptor-neprilysin inhibitors (ARNIs). Sacubitril is a prodrug that is metabolized into an active inhibitor of the endopeptidase neprilysin, the key enzyme responsible for degrading natriuretic and other vasoactive peptides. However, N-terminal pro-B-type natriuretic peptide (NT-proBNP), which is a marker of HF events in patients with HF with reduced ejection fraction (HFrEF), is not a substrate for sacubitril.

The PARADIGM-HF trial showed that sacubitril/valsartan reduced the risk of CV mortality compared to standard therapy with an ACE-I in patients with HFrEF [hazard ratio, 0.80; 95% confidence interval (CI), 0.71–0.89; $P < 0.001$]. The relative risk reduction in CV events with sacubitril/valsartan was similar in patients with and without CKD at baseline [stratified by ≥estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m^2 or <eGFR 60 mL/min/1.73 m^2, and excluding those with eGFR <30 mL/min/1.73 m^2], and the renal safety profile and rate of decline of GFR with sacubitril/valsartan were more favourable than that of enalapril.

More recently, the PIONEER-HF trial, the TRANSITION study, and the TITRATION study have shown that sacubitril/valsartan is safe and effective in a broad range of HFrEF patients, extending to patients with mid-range, borderline, or mildly reduced ejection fraction. However, patients with an eGFR <30 mL/min/1.73 m^2 were excluded from these trials, and thus data on the efficacy and tolerability of sacubitril/valsartan in patients with advanced CKD are limited.

Sacubitril/valsartan has subsequently become regarded as an evidence-based and guideline-recommended disease-modifying therapy for patients with HFrEF with an established role in routine clinical practice.

Furthermore, evidence from large randomized controlled trials (RCTs) has shown that sacubitril/valsartan is superior to renin–angiotensin system inhibitors in preserving renal function in patients with HFrEF and has a beneficial role on eGFR, compared with standard optimal medical therapy, in the ‘real-world’ setting.

Several meta-analyses have shown that combined neprilysin-RAAS inhibition with sacubitril/valsartan or omapatrilat may have beneficial effects on renal function in HF compared with RAAS inhibition alone. However, data on the role of sacubitril/valsartan in the preservation of renal function in patients with HFrEF are limited.

Sacubitril/Valsartan[2,3]

Sacubitril/valsartan is the first agent to be approved in a new class of drugs called angiotensin receptor neprilysin inhibitor (ARNI). The medication is FDA-approved to treat patients with chronic heart failure with reduced ejection fraction (HFrEF) with NYHA class II, III, or IV. Sacubitril/valsartan is to be used in place of an ACEI or angiotensin II receptor blocker (ARB) and conjunction with other standard heart-failure treatments (beta-blocker, aldosterone antagonist).

According to the 2016 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America (ACC/AHA/HFSA) Focused Update on New Pharmacological Therapy for Heart Failure, ACEI, ARB, or ARNI are now recommended in patients with chronic symptomatic HFrEF to reduce morbidity and mortality (class I recommendation). Patients must be able to tolerate ACEI or ARB before being started on sacubitril/valsartan.

New AHA/ACC/HFSA guidelines (2022) recommend using sacubitril-valsartan to manage patients with heart failure with preserved ejection fraction (HFpEF).

In a recent case series, four patients with chemotherapy-related acute cardiac failure with severely reduced ejection fraction were successfully treated with sacubitril/valsartan. In addition, sacubitril/valsartan was also demonstrated to be valuable in anthracycline-related cardiac toxicity. Cancer therapy-related cardiac dysfunction (CTRCD) is a critical problem impacting oncological and cardiovascular health prognosis, especially when it prevents patients from receiving cancer treatment. In a recent clinical trial, sacubitril/valsartan emerged as a promising treatment option in patients with refractory CTRCD. The data is limited but demonstrates the promising results of prior clinical studies for using sacubitril/valsartan in cardio-oncology patients. However, more clinical studies are needed to confirm the efficacy and safety of sacubitril/valsartan in cancer therapy-related cardiac dysfunction (CTRCD).

Mechanism of Action

The pathophysiology of heart failure involves a maladaptive response during which the renin-angiotensin-aldosterone system (RAAS) is activated. RAAS activation leads to vasoconstriction, hypertension, increased aldosterone levels, increased sympathetic tone, and eventually, cardiac remodeling, all of which are detrimental to the progression of the disease. ACEIs or ARBs play a major role in reducing morbidity and mortality due to heart failure by blocking these maladaptive elements.

Simultaneously, the natriuretic peptide system is also activated, hence the elevated BNP and NT-pro BNP seen in heart failure exacerbations. This compensatory mechanism leads to vasodilation, natriuresis, and diuresis. Consequently, the natriuretic peptide system decreases blood pressure (BP), lowers the sympathetic tone, and reduces aldosterone levels. The natriuretic peptide system functions antagonistically to the RAAS and has favorable effects on the pathogenesis of heart failure. Natriuretic peptides are broken down by an enzyme called neprilysin.

Sacubitril/valsartan is a combination product. Sacubitril is a pro-drug that, upon activation, acts as a neprilysin inhibitor. It works by blocking the action of neprilysin, thus preventing the breakdown of natriuretic peptides, which leads to a prolonged duration of the favorable effects of these peptides.

Valsartan is an angiotensin receptor blocker, and it works on blocking the RAAS system. However, because neprilysin breaks down angiotensin II, inhibiting neprilysin will accumulate angiotensin II. For this reason, a neprilysin inhibitor cannot be used alone; it must always be combined with an ARB to block the effect of the excess angiotensin II.

Another important substance broken down by neprilysin is bradykinin; neprilysin inhibition will also cause a build-up of bradykinin. Therefore, sacubitril cannot be used with an ACEI due to an increased risk of angioedema if ACEI and ARNI are used together or dosed in a short timeframe. When switching between ACEI and sacubitril/valsartan, the patient must undergo a 36-hour washout period to lower the risk of angioedema.

Pharmacokinetics

- Absorption: Following oral administration, sacubitril/valsartan is broken down into sacubitril and valsartan. Sacubitril is metabolized to LBQ657. The absolute oral bioavailability of sacubitril is estimated to be ≥ 60%. The peak plasma concentrations(Cmax) of sacubitril, LBQ657, and valsartan are obtained at 0.5 hours, 2 hours, and 1.5 hours, respectively. Sacubitril and valsartan do not accumulate significantly at a steady-state (achieved in 3 days), but LBQ657 is accumulated by 1.6-fold. Food has no clinically significant effect on the absorption parameters of sacubitril or valsartan. Consequently, it can be administered with or without food.
- Distribution: The mean apparent volumes of distribution of valsartan and sacubitril are 75 and 103 L, respectively. Sacubitril, LBQ657, and valsartan have high plasma protein binding (94% to 97%). LBQ657 crosses the blood-brain barrier to a small extent (0.28%).
- Metabolism: Sacubitril is converted to LBQ657 by esterases. Valsartan is minimally metabolized (20%), and a hydroxyl metabolite is present in plasma at low concentrations (< 10%).
- Elimination: After oral administration, 52% to 68% of sacubitril (as LBQ657) and approximately 13% of valsartan are excreted in the urine. 37% to 48% of sacubitril (as LBQ657) and 86% of valsartan are excreted in feces. Sacubitril, LBQ657, and valsartan have a mean elimination half-life (t1/2) of about 1.4 hours, 11.5 hours, and 9.9 hours.

Administration

Sacubitril/valsartan is available as an oral tablet in three dosage strengths containing: sacubitril (24 mg, 49 mg, or 97 mg) and valsartan (26 mg, 51 mg, or 103 mg). The valsartan component in this combination has a higher bioavailability than regular valsartan tablets; therefore, valsartan 26 mg, 51 mg, and 103 mg in the brand-name combination are equivalent to valsartan 40 mg, 80 mg, and 160 mg in other formulations, respectively.

- When prescribing this drug, the dose of both ingredients should be included, although dosing in clinical trials was based on the total amount of both components (50 mg, 100 mg, and 200 mg).

- Sacubitril/valsartan is to be taken twice a day and maybe administered without regard to meals.
- Allow at least a 36-hour washout period when switching from an ACEI before starting sacubitril/valsartan.
- Patients must be able to tolerate an ACEI or an ARB before being started on sacubitril/valsartan.
- Clinicians can replace sacubitril/valsartan oral suspension at the recommended tablet dosage in patients unable to swallow tablets. The suspension can be stored for up to 15 days. Do not refrigerate or store above 25°C (77°F). Shake the suspension before each use.

Recommended Dosing

- Patients on low-dose ACEI or ARB or not previously on ACEI or ARB start with sacubitril 24 mg/valsartan 26 mg twice per day. Double the dose every 2 to 4 weeks as tolerated, up to sacubitril 97 mg/valsartan 103 mg orally twice per day.
- Patients on moderate to a high dose of ACEI or ARB start with sacubitril 49 mg/valsartan 51 mg twice per day. Double the dose every 2 to 4 weeks as tolerated, up to sacubitril 97 mg/valsartan 103 mg orally twice per day.

Specific Patient Population

- Patients with Renal Impairment: Patients with eGFR less than 30 should be started with sacubitril 24 mg/valsartan 26 mg twice per day.
- Patients with Hepatic Impairment: Patients with moderate hepatic impairment (Child-Pugh class B) should be started with sacubitril 24 mg/valsartan 26 mg twice per day. Sacubitril/valsartan is not recommended for patients with severe hepatic impairment (Child-Pugh class C).
- Pregnancy Considerations: Refer to the Boxed Warning in the contraindication section.

- Breastfeeding Considerations: There is a lack of sufficient data regarding the concentration of sacubitril/valsartan in human milk and its effects on the breastfed infant. However, in preclinical studies, sacubitril/valsartan has been detected in rat milk. Consequently, there is a potential for serious adverse drug reactions in breastfed infants from sacubitril/valsartan. Hence, clinicians should advise nursing women that breastfeeding is not recommended during treatment and suggest alternate therapy.

Adverse Effects

Adverse effects include hypotension, hyperkalemia, renal failure, cough, and angioedema.

In the PARADIGM-HF trial comparing sacubitril/valsartan to enalapril 10 mg twice per day, sacubitril/valsartan was associated with a higher incidence of hypotension and symptomatic hypotension. Sacubitril/valsartan was associated with a lower risk of elevation in serum potassium or serum creatinine and a lower risk of cough than enalapril. More patients experienced angioedema in the sacubitril/valsartan arm than in the enalapril; however, this outcome was not statistically significant.

Contraindications

Sacubitril/valsartan is contraindicated in patients with:

- Hypersensitivity to any component of the product
- A prior history of angioedema due to an ACEI or ARB
- In diabetic patients receiving the renin inhibitor, aliskiren, specifically, the valsartan (any ARB), is contraindicated with aliskiren due to an increased risk of hypotension, hyperkalemia, and renal impairment.
- Patients who have received an ACE-inhibitors within 36 hours due to increased risk of angioedema.

Box Warning

- Drugs that work directly on the renin-angiotensin system, such as sacubitril/valsartan, can cause injury and/or death to the developing fetus. When pregnancy is confirmed, discontinue sacubitril/valsartan as soon as possible.

Monitoring

Monitor for improvement in the clinical signs and symptoms of heart failure. The PARADIGM-HF trial showed an improvement in subjective symptoms reported by patients as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) and a reduction in hospitalizations and mortality.

Monitor volume status, weight, chemotherapy drugs, sodium intake, and the ability to perform activities of daily living.

Transthoracic echocardiogram to assess ejection fraction (EF) and potentially identify the etiology of heart failure (systolic/diastolic dysfunction or valvular dysfunction).

Because sacubitril/valsartan therapy affects several biomarkers and specifically inhibits the breakdown of brain natriuretic peptide (BNP), BNP will be elevated in patients taking this drug. Therefore, BNP will not be a reliable marker of heart failure exacerbations in these patients. In addition, NT-pro-BNP is not a substrate for neprilysin and is therefore not affected by sacubitril. Therefore, NT-pro-BNP should be utilized in patients on sacubitril/valsartan when a heart failure exacerbation is suspected.

Regarding safety, renal function and serum potassium should be monitored, especially at the initiation of therapy and in patients with risk factors that would predispose them to renal impairment and hyperkalemia.

Toxicity

Limited literature is available concerning toxicity in human subjects. However, a single dose of 583 mg sacubitril/617 mg valsartan in healthy volunteers and multiple doses of 437 mg sacubitril and 463 mg valsartan for 14 days were studied. Hypotension resulting from overdose requires prompt treatment. As mentioned in pharmacokinetics, sacubitril is converted to

LBQ657. All three compounds (sacubitril, LBQ657, and valsartan) are highly bound (94% to 97%) to plasma protein. Hence, it is unlikely to be removed by hemodialysis. Nicolas D

Pathophysiology of cardiorenal interaction in chronic heart failure[1]

CHF and CKD share several etiologic risk factors, including 'traditional' CV risk factors such as age, gender, hypertension, dyslipidaemia, and diabetes. As well as aetiological risk factors, there is an interaction of respective pathophysiologies. In CHF, structural or functional abnormalities that affect the cardiac cycle impair the ability of the heart to maintain tissue perfusion adequate to meet metabolic requirements and to accommodate venous return. The deterioration of renal function in CHF is further accelerated by the presence of type 2 diabetes mellitus.

In CHF, impaired cardiac function, together with reduced cardiac output, decreases renal blood flow and the perfusion gradient, exacerbating renal haemodynamic changes.[17] Several compensatory mechanisms follow as the failing heart attempts to maintain adequate function, including increased cardiac output, ventricular remodelling, and activation of neurohormonal systems to augment mean arterial pressure. While the pathophysiology of HF with preserved ejection fraction (HFpEF) is more heterogeneous compared to HFrEF, the increases in serum creatinine are largely similar in both HFpEF and HFrEF, and thus the mechanisms leading to renal impairment may be similar.

The neurohormonal adaptive mechanisms that regulate renal perfusion in CHF are illustrated in Figure 1. In patients with stable HF (Figure 1A), the decrease in renal perfusion leads to adaptive mechanisms through activation of the RAAS, which induces a predominant angiotensin II-mediated vasoconstriction of the efferent arteriole with a secondary increase in post-glomerular resistance and, consequently, increased intra-glomerular pressure. The increase in post-glomerular resistance increases the intracapillary hydraulic pressure even though kidney perfusion is decreased secondary to a decrease in systemic blood pressure (BP). Accordingly, the proportion of renal plasma flow that is ultra-filtered through the glomerular barrier increases, enabling the maintenance of GFR despite decreased kidney perfusion.

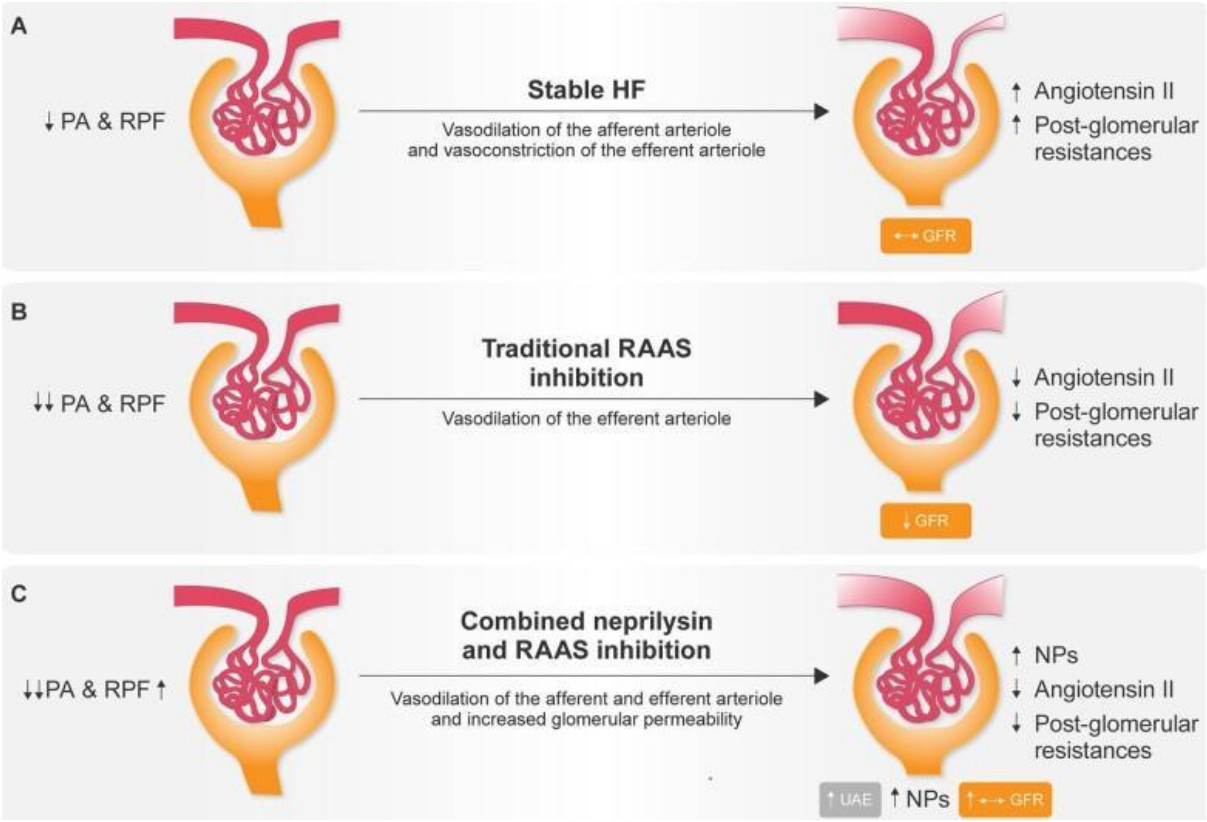


Figure 1: Renal adaptive mechanisms to renal hypoperfusion in chronic heart failure. (*A*) Adaptive mechanisms in stable heart failure. (*B*) Effects of renin–angiotensin system inhibition on adaptive mechanisms to renal hypoperfusion. (*C*) Effects of combined neprilysin and renin–angiotensin system inhibition on adaptive mechanisms to renal hypoperfusion. GFR, glomerular filtration rate; NPs, natriuretic peptides; PA, arterial pressure; RPF, renal plasma flow; UAE, urinary albumin excretion.

RAAS inhibition by ACE-I or ARBs in the presence of the greatly reduced renal blood flow counteracts renal auto-regulation, decreasing intra-glomerular pressure by preventing angiotensin II-induced predominant vasoconstriction of the efferent arteriole (Figure 1B), contributing to a decrease in intracapillary hydraulic pressure and, consequently, filtration fraction and GFR, which therefore becomes BP dependent.

Inhibition of neprilysin enhances the bioavailability of natriuretic peptides; concomitant inhibition of the angiotensin II type-1 receptor and neprilysin inhibition further reduces systemic BP and kidney perfusion pressure, inducing preferential vasorelaxation of the pre-glomerular arteriole and relative vasoconstriction of the post-glomerular arteriole (Figure 1C). The consequent decrease in pre-glomerular resistance and increase in post-glomerular

resistance contributes to increasing intracapillary hydraulic pressure, despite a decrease in the renal perfusion pressure, increasing the filtration fraction and GFR. The increased intracapillary hydraulic pressure possibly combined with a direct effect of ARNIs on the glomerular barrier may contribute to increased albumin ultrafiltration which, in combination with possible attenuation of tubular protein reabsorption, may lead to the clinically modest albuminuria which may be observed after starting ARNI treatment.

Over the last two decades, several large RCTs have shown that targeting neurohumoral imbalances of the RAAS, the natriuretic peptide system, and the sympathetic nervous system provides incremental benefit and is cost-effective in terms of survival and quality of life. Specifically, ACE-I (which target the angiotensin-converting enzyme), ARBs (which target the angiotensin receptor), beta-blockers (BB; beta-adrenergic receptor antagonists), MRA (which target the mineralocorticoid receptor), and more recently ARNIs, inhibitors of both the angiotensin-II receptor and the endopeptidase neprilysin, have all been shown to be effective in HFrEF and are recommended unless contraindicated or not tolerated. Furthermore, current treatment guidelines for the treatment of HF recommend that ARNI should replace ACE-I or ARB in patients with New York Heart Association class II or III HFrEF who tolerate an ACE-I or ARB in order to further reduce morbidity and mortality.

In PARADIGM-HF, sacubitril/valsartan provided greater renal protection as compared to enalapril despite slightly lower BP values. Furthermore, analysis of the relationship between renal effects and CV and renal outcomes in PARADIGM-HF showed that the modest increase in urine albumin excretion associated with ARNI treatment was not associated with a higher risk of renal endpoints,[3] suggesting that the rise in the urinary albumin/creatinine ratio over time is likely mediated by an increase in glomerular permeability, a mechanism that does not lead to a progressive reduction of renal function. This was further demonstrated by the beneficial effect of sacubitril/valsartan therapy on the risk for HF hospitalization of CV mortality compared with enalapril. Therefore, the J-curve phenomenon has been somewhat challenged by the distinctive dual-acting mechanism of action of sacubitril/valsartan (Figure 2) in inhibiting both neprilysin and angiotensin II. This is deemed to be due to specific pathophysiological changes taking place under sacubitril/valsartan treatment at the glomerular level, which, taken together, may lead to preservation of renal function despite a substantial reduction in systemic BP.

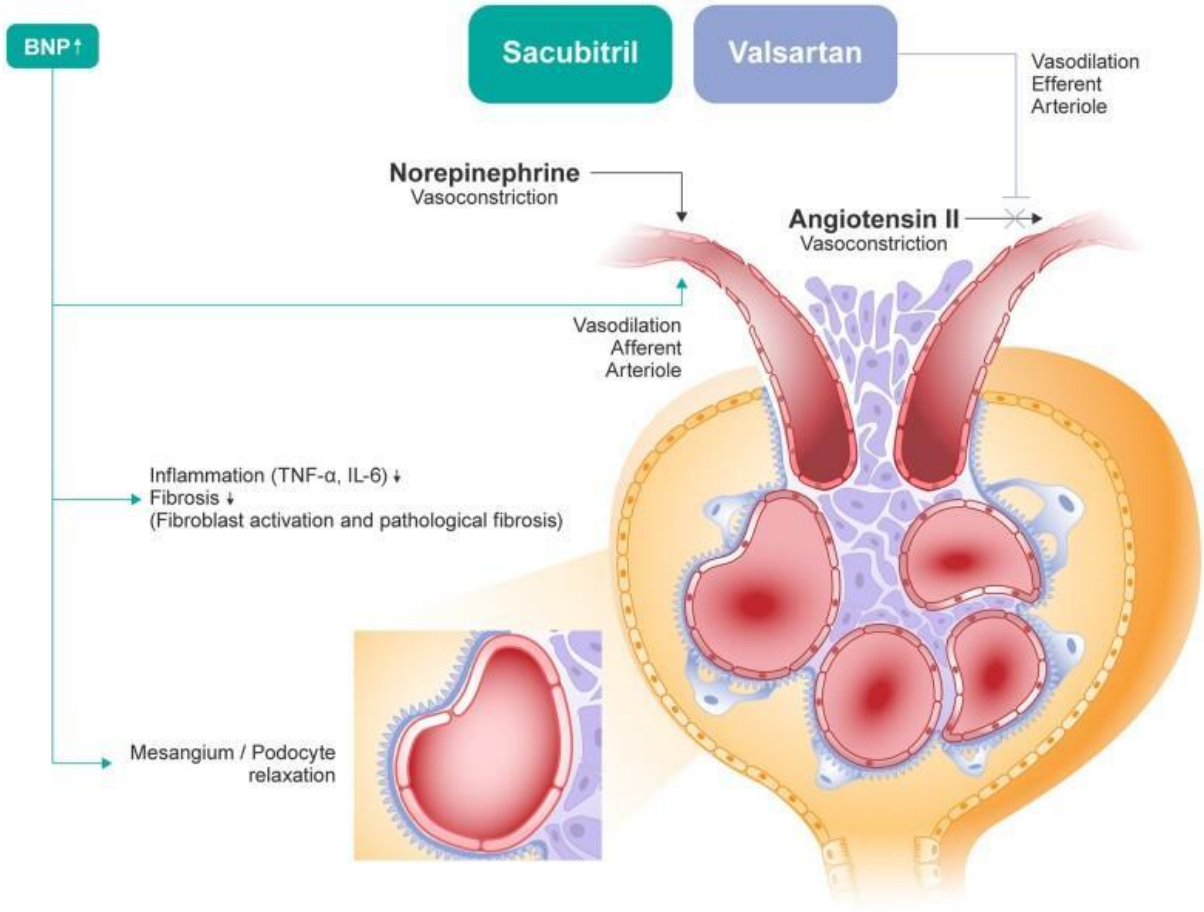


Figure 2: Renal mechanisms of sacubitril/valsartan. ANP, atrial natriuretic peptide.

Dual angiotensin-neprilysin inhibition in chronic heart failure[1]

Dual angiotensin-neprilysin inhibition by the ARNI sacubitril/valsartan inhibits degradation of endogenous natriuretic peptides, in addition to other vasoactive peptides, including atrial natriuretic peptide (ANP), angiotensin II, bradykinin, adrenomedullin, endothelin, brain (B-type) natriuretic peptide (BNP), and C-type natriuretic peptide, increasing the levels of these substances. Activation of neprilysin increases intracellular cGMP, leading in turn to vasodilatation, natriuresis and diuresis, inhibition of cardiac fibrosis and hypertrophy, and inhibition of the RAAS. These effects are mediated by the natriuretic peptide receptors (NPRs), NPR-A, and NPR-B, whereas the primary role of NPR-C is to bind and internalize natriuretic peptides, clearing them from circulation, although they may also mediate anti-fibrotic effects.

The simultaneous blockade of the angiotensin II type 1 receptor by sacubitril/valsartan also counteracts the potential long-term harmful effects of RAAS over-activation (i.e. increased BP and sodium and water retention) that may result from neprilysin inhibition. There is also

evidence that increased activity of natriuretic peptides exerts direct antioxidant, anti-inflammatory, and anti-fibrotic effects in experimental models, and that sacubitril/valsartan may prevent fibrosis and reduce the oxidative stress, apoptosis, and mitochondrial damage observed in the kidney and heart tissues of animal models of cardio-renal syndrome.

Increased renal perfusion because of sacubitril/valsartan-related improvement of cardiac function may partly explain the effects of sacubitril/valsartan on kidney function in an HF population. As NPRs and neprilysin are expressed in the kidney as well as the myocardium, neprilysin inhibition is postulated to increase the bioavailability of renal natriuretic peptides and contribute to the preservation of renal function. It has also been shown that drugs that provide natriuretic peptide system augmentation assist in the preservation of renal function and improve GFR. There is further evidence that sacubitril mainly acts by enhancing ANP instead of BNP, suggesting that the benefit of neprilysin inhibition may be mediated, at least in part, by increased ANP concentrations.

Cardiovascular effects of angiotensin receptor-neprilysin inhibitor[3]

The long-term benefits of sacubitril/valsartan on cardiovascular morbidity and mortality over other RAAS inhibitors in patients with chronic HFrEF was first described in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, which showed that sacubitril/valsartan was superior to enalapril in reducing the risk of HF hospitalization and cardiovascular death by 20%. According to the result of PARADIGM-HF, guidelines have recommended sacubitril/valsartan as a replacement for ACEIs or ARBs. Claggett et al. suggested that the life expectancy of patients receiving ARNI might increase by 1 to 2 years compared with patients receiving ACEI, supporting a strong recommendation to use sacubitril/valsartan for patients with HFrEF. Furthermore, the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Entresto Therapy for Heart Failure (PROVE-HF) trial, Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial, and the Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event (TRANSITION) study have shown that sacubitril/valsartan was effective and safe in a wide range of HFrEF, including those with acute decompensated HF, newly diagnosed HF,

and HF without prior ACEI or ARB use, all of which supports the expansion of ARNI application in a broad range of patients with HFrEF.

In contrast to the promising results from patients with HFrEF, the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial in patients with HFpEF showed that sacubitril/valsartan did not result in a significantly lower rate of total HF hospitalizations and cardiovascular deaths among patients with HFpEF (LVEF > 45%), even though there was a suggestion of possible benefit with sacubitril/valsartan and in women and in patients with lower LVEF (ejection fraction < 57%). The Angiotensin Receptor Neprilysin Inhibition Versus Individualized RAAS blockade (PARALLAX) trial which randomized 2,572 patients with an HFpEF (LVEF > 40%) showed mixed results, in which only one of two co-primary endpoints showed significant improvement in the sacubitril/valsartan group compared to the comparator (enalapril, valsartan, or placebo), and the reduction in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was 16% greater in the sacubitril/valsartan group (adjusted geometric mean ratio, 0.84; 95% confidence interval [CI], 0.80–0.88), while there was no significant difference between groups in the 6-minute walk distance. However, severe adverse events were lower in the sacubitril/valsartan group than in the individualized medical therapy group; first hospitalization due to HF (hazard ratio [HR], 0.49; 95% CI, 0.30–0.81; p = 0.005) and composite of death due to HF or HF hospitalization (HR, 0.64; 95% CI, 0.42–0.97; p = 0.034) were lower, although they were not the primary endpoints of the PARALLAX trial. The U.S. Food and Drug Administration has recently approved the indication of sacubitril/valsartan in patients with HFpEF with LVEF below normal to reduce worsening HF (total HF hospitalizations and urgent HF visits), although further clarification is still needed for HFpEF subgroups who can benefit mostly.

Renal effects of angiotensin receptor-neprilysin inhibitor[3]

Inhibition of RAAS reduces urinary albumin excretion and delays the progression of CKD to ESRD. However, treatment with RAAS inhibitors is limited in patients with CKD, as the risk of serum creatinine increase or hyperkalemia is greater in CKD patients than in those without this medical condition. RAAS inhibition by ACEIs or ARBs decreases intra-glomerular pressure by preventing angiotensin II-induced predominant vasoconstriction of the efferent arteriole, contributing to a decrease in albuminuria and eGFR.

Three natriuretic peptides are present in humans; atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide. ANP and BNP are synthesized in cardiac myocytes, whereas C-type natriuretic peptide is mainly expressed in endothelial cells. ANP increases renal perfusion through systemic vasodilation, and there is evidence that sacubitril mainly acts by enhancing ANP instead of BNP. Concomitant inhibition of angiotensin II and neprilysin induces selective vasorelaxation of preglomerular afferent arterioles and relative vasoconstriction of the postglomerular efferent arteriole, contributing to increased intracapillary hydraulic pressure and eGFR. Sacubitril/valsartan may also affect renal tubular reabsorption. By increasing ANP, it inhibits sodium reabsorption in the renal proximal tubule, which may account for the benefits of ARNI therapy in patients with HF. Sacubitril/valsartan has been shown to prevent fibrosis, mitochondrial damage, oxidative stress, and apoptosis in kidney and heart tissues of cardiorenal syndrome rat models. The urine albumin creatinine ratio (ACR) modestly increases after ARNI initiation, increasing concerns regarding deterioration of kidney function after ARNI use. However, in contrast to worse renal outcome related to the increase in albuminuria with enalapril therapy, an increase in the ACR was not related to worse renal outcome with ARNI therapy, suggesting the increase in the ACR is mediated by a mechanism that does not result in low renal filtration. Despite a similar increase in ACR, the Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction (PARAMOUNT) trial reported a slower deterioration of eGFR in patients with HFpEF after scubitril/valsartan use. A plausible explanation for this specific dissociation phenomenon between albuminuria and renal function deterioration is the selective vasorelaxation of preglomerular afferent arterioles with ARNI use, leading to an increase in intracapillary hydraulic pressure, which may contribute to increased albumin ultrafiltration and a modest increase in albuminuria without renal function deterioration.

The renal safety of sacubitril/valsartan has been reported consistently in patients with HFrEF and HFpEF, which included a significant number of patients with stage 2 and 3 CKD (eGFR, 30–59 mL/min/1.73 m^2). PARADIGM-HF *post-hoc* analysis and PARAGON-HF showed that sacubitril/valsartan led to a slower rate of decrease in eGFR and improved renal outcomes in patients with HFrEF and HFpEF. In a study of patients with acute decompensated HF, sacubitril/valsartan showed similar renal event rates to those of enalapril. In a meta-analysis, Kang et al. reported that compared to other RAAS inhibitors, sacubitril/valsartan significantly increased the eGFR and decreased blood pressure, suggesting that it may have renal and cardiovascular benefits in patients with HF and CKD. The efficacy and safety of

sacubitril/valsartan have also been studied in patients with other cardiovascular or renal diseases, although many recent studies have investigated patients with HF. Sacubitril/valsartan demonstrated a low prevalence of renal side effects including hyperkalemia, hypokalemia, and creatinine elevation in patients with hypertension despite its superior blood pressure-lowering effect compared to olmesartan. The United Kingdom Heart and Renal Protection-III (UK HARP-III) trial investigating 414 patients with CKD (eGFR, 20–60 mL/min/1.73 m^2) without HF showed that sacubitril/valsartan had similar effects on kidney function and albuminuria to irbesartan, but it has the additional effect of lowering blood pressure and cardiac biomarkers.

Hyperkalemia is a potentially serious complication in CKD patients receiving RAAS inhibitors, which can impact clinical outcomes directly and can limit the use of GDMT. The benefits of MRA in patients with HFrEF are well established. However, physicians are reluctant to initiate MRA in patients with CKD due to concerns of hyperkalemia, even though it is recommended to initiate MRA in conjunction with ACEIs, ARBs, or an ARNI to reduce morbidity and mortality in patients with New York Heart Association classes II–IV symptoms. In the PARADIGM-HF trial, potassium levels of >6.0 mmol/L occurred in 4% of the patients treated with sacubitril/valsartan and in 6% of the patients with enalapril, and the difference was statistically significant. Moreover, sacubitril/valsartan has been reported to attenuate the risk of hyperkalemia when MRAs are combined with other inhibitors of the RAAS system, suggesting the safer use of MRAs when combined with ARNI.

Evidence for a renal protective role in chronic heart failure[1]

The two largest studies of sacubitril/valsartan in patients with HF, the PARADIGM-HF and PARAGON-HF trials, demonstrated positive renal outcomes with sacubitril/valsartan, compared with ACE-I (enalapril) or ARB (valsartan). In PARADIGM-HF in patients with HFrEF, 33% of patients had CKD at baseline. In addition to improving CV outcomes, sacubitril/valsartan was associated with a slower rate of decrease in eGFR, compared with enalapril. During follow-up, the decrease in eGFR was −1.61 mL/min/1.73 m^2/year with sacubitril/valsartan (95% CI, −1.77 to −1.44 mL/min/1.73 m^2/year) vs. −2.04 mL/min/1.73 m^2/year with enalapril (95% CI, −2.21 to −1.88 mL/min/1.73 m^2/year; $P < 0.001$), despite a greater increase in urinary albumin/creatinine ratio with sacubitril/valsartan (1.20 mg/mmol vs. 0.90 mg/mmol, $P < 0.001$).

Neprilysin inhibition had an incremental benefit on renal function in diabetic patients with HFrEF in PARADIGM-HF. Patients treated with sacubitril/valsartan had a slower rate of decline of eGFR compared with enalapril recipients (a difference of 0.6 vs. 0.3 mL/min/1.73 m^2 per year in patients with vs. without diabetes; $P = 0.038$ for the interaction). The effect was independent of treatment effect on the course of HF or changes in glycated haemoglobin. Furthermore, in PARADIGM-HF, sacubitril/valsartan caused less hyperkalaemia than enalapril and reduced the use of loop diuretics, with which there is a dose-dependent association with impaired survival outcomes in patients with advanced HF.

In PARAGON-HF in patients with HFpEF, in which approximately 45–50% of patients had CKD or diabetes at baseline, worsening renal function occurred in 1.4% of patients in the sacubitril/valsartan group, compared with 2.7% in the valsartan group (hazard ratio, 0.50; 95% CI, 0.33–0.77). During follow-up, the decrease in eGFR was −2.0 mL/min/1.73 m^2/year with sacubitril/valsartan (95% CI, −2.2 to −1.9 mL/min/1.73 m^2/year) vs. −2.7 mL/min/1.73 m^2/year with valsartan (95% CI, −2.8 to −2.5 mL/min/1.73 m^2/year; $P < 0.001$). PARAGON-HF also showed that sacubitril/valsartan was effective in reducing the primary outcome (hospitalizations for HF and death from CV causes) in patients with renal impairment or diabetes. In the PIONEER-HF trial,[7] which investigated sacubitril/valsartan vs. enalapril in hospitalized patients with acute decompensated HFrEF, in which renal perfusion is further compromised, sacubitril/valsartan also showed a good safety profile in terms of worsening renal function and decrease in eGFR.

A recent systematic review and meta-analysis of 10 RCTs underscores the protective role of sacubitril/valsartan on the kidney in terms of a lower risk of worsening renal function in HF and other conditions. The meta-analysis included a total of 16 456 patients across the indications of HFrEF, HFpEF, hypertension, and CKD, although most data were available for patients with HF. The analysis showed a 30% lower risk of renal events and progressive decline of eGFR compared to patients treated with RAAS inhibitors (ACE-I and ARBs) alone (pooled odds ratio 0.70, 95% CI 0.57–0.85; $P < 0.001$). Risk reduction was greater in older patients and patients with HFpEF.

Another meta-analysis investigated the effects of sacubitril/valsartan in 3460 patients with HF and CKD enrolled in three RCTs; PARADIGM-HF (vs. enalapril in patients with HFrEF), PARAMOUNT (vs. valsartan in patients with HFpEF), and the United Kingdom Heart and Renal Protection-III (HARP-III) trial (vs. irbesartan in patients with HF and

CKD). Sacubitril/valsartan significantly increased eGFR compared with RAAS inhibitors (mean difference, 1.90; $P = 0.02$) and was more effective in reducing BP and NT-proBNP, suggesting CV and renal benefits over RAAS inhibition alone in patients with HF and CKD. There was no between-group difference in urinary albumin/creatinine ratio.

Insights into the favourable renal effects of sacubitril/valsartan in the real-world HFrEF population are available from three recent studies. In a study in 54 consecutive outpatients followed for 12 months, over half of the patients were aged ≥65 years, and 53.7% had CKD at baseline. Compared with historical controls who received optimal medical therapy, renal function improved during the 12 months of follow-up ($P < 0.001$ for improvement in eGFR vs. controls). There was no interaction between eGFR trend and systolic BP or baseline left ventricular ejection fraction (LVEF). Meanwhile, systolic BP decreased ($P = 0.014$) and LVEF slightly increased ($P < 0.001$). There was a greater benefit in subjects aged <65 years and in patients with CKD ($P = 0.009$). A statistically ($P = 0.009$), but not clinically, significant increase in serum potassium was also found, regardless of age and CKD.

In a real-world study in 108 patients with HFrEF, eGFR values increased significantly (73.8 vs. 61.2 mL/min/1.73 m^2, $P < 0.05$) in sacubitril/valsartan recipients, compared to the control arm. There were also greater improvements in LVEF with sacubitril/valsartan (42.4% vs. 34.2%, $P < 0.05$), while values of NT-proBNP, systolic and diastolic BP, and uricaemia also decreased to a greater extent in the sacubitril/valsartan arm ($P < 0.05$).

Additionally, 932 patients with HFrEF were treated at an HF referral centre (466 with sacubitril/valsartan and 466 with standard HF treatment without ARNI). Sacubitril/valsartan was more effective than standard HF treatment in reducing CV deaths or hospitalizations for HF in patients with significant renal insufficiency at baseline, reducing these endpoints by 28% in patients with severe renal impairment (GFR <30 mL/min/1.73 m^2).

Finally, renal outcomes with the SGLT2 inhibitors dapagliflozin and empagliflozin have been assessed in large CV outcomes trials in which a proportion of patients were being treated with sacubitril/valsartan. In the DAPA-HF trial, the dapagliflozin vs. placebo hazard ratio was 0.74 (95% CI: 0.65–0.85; $P < 0.0001$) for the primary composite endpoint (CV death or a worsening HF event) and had a consistent effect if background therapy included either an MRA or sacubitril/valsartan. In the EMPEROR trial which studied cardiac and renal outcomes with empagliflozin, the hazard ratio for the primary outcome (death from CV causes or hospitalization for HF) was 0.64 (95% CI 0.45–0.89) vs. 0.77 (95% CI 0.66 to 0.90) among

patients who were not on therapy with sacubitril/valsartan. A small study in 108 patients with type 2 diabetes and HFrEF treated with sacubitril/valsartan and empagliflozin further reported that the combination appeared to be safe considering renal function. Thus, for both SGLT2 inhibitors, benefits were seen in patients treated with sacubitril–valsartan for HF.

The Mechanism of Sacubitril/Valsartan in the Treatment of HF[4]

Sacubitril/valsartan contains valsartan and sacubitril in a 1:1 mixture by molecule count and has 2 therapeutic targets in the treatment of HF: the natriuretic peptide system for sacubitril and the RAS for valsartan (Figure 3). The natriuretic peptide system mainly comprises of atrial-derived natriuretic peptides (ANP), B-type (brain) natriuretic peptides (BNP), and C-type natriuretic peptides (CNP). BNP is secreted mainly from the left ventricle and is markedly increased in HF patients, compared with ANP and CNP. BNP is a biomarker for predicting the severity of HF and guiding therapy for HF; moreover, it has the marked benefit of increasing sodium excretion in the treatment of HF, compared with ANP and CNP. Pro-BNP degrades into BNP and N-terminal pro-BNP (NT-pro-BNP) (Figure 3). BNP binds to natriuretic peptide receptor B on the cell membrane, which induces cleavage of guanosine triphosphate to cyclic guanosine monophosphate (cGMP) by cytoplasmic G proteins and initiates an intracellular cGMP signaling cascade involving protein kinase G, ultimately regulating downstream expression of genes involved in smooth muscle cell relaxation, diuresis, and natriuresis (Figure 3). Sacubitril, as a neprilysin inhibitor, is converted to sacubitrilat by esterase and regulates the natriuretic peptide system by inhibiting the degradation of BNP (Figure 3). Therefore, sacubitril increases the level of BNP resulting in vasodilation, sodium excretion and improvement of cardiac remodeling. In addition, sacubitril inhibits the degradation of angiotensin, endothelin 1, adrenomedullin, opioids and amyloid-β peptide, which might also participate in the beneficial effect in HF patients. However, considering that sacubitril increases the plasma angiotensin II (Ang II) concentration, sacubitril alone does not have an obvious superiority and should be combined with ARBs such as valsartan in the treatment of HF. The reason why sacubitril combines with ARBs rather than ACEIs is because both sacubitril and ACEIs inhibit the degradation of bradykinin which induces angioneurotic edema. The RAS is activated in HF, enhancing sympathetic nerve activity and inducing cardiac remodeling, which aggravates the progression of HF. In the RAS, Ang II is synthesized from angiotensinogen by renin and angiotensin-converting enzyme (Figure 3). Ang II binds to the

Ang II type 1 receptor on the cell membrane, which regulates arterial vasoconstriction, renal tubular reabsorption of sodium and water, vascular smooth muscle contraction and aldosterone release. Valsartan inhibits the effects of Ang II by selectively blocking the type-1 receptor, which improves cardiac remodeling and dysfunction in HF patients.

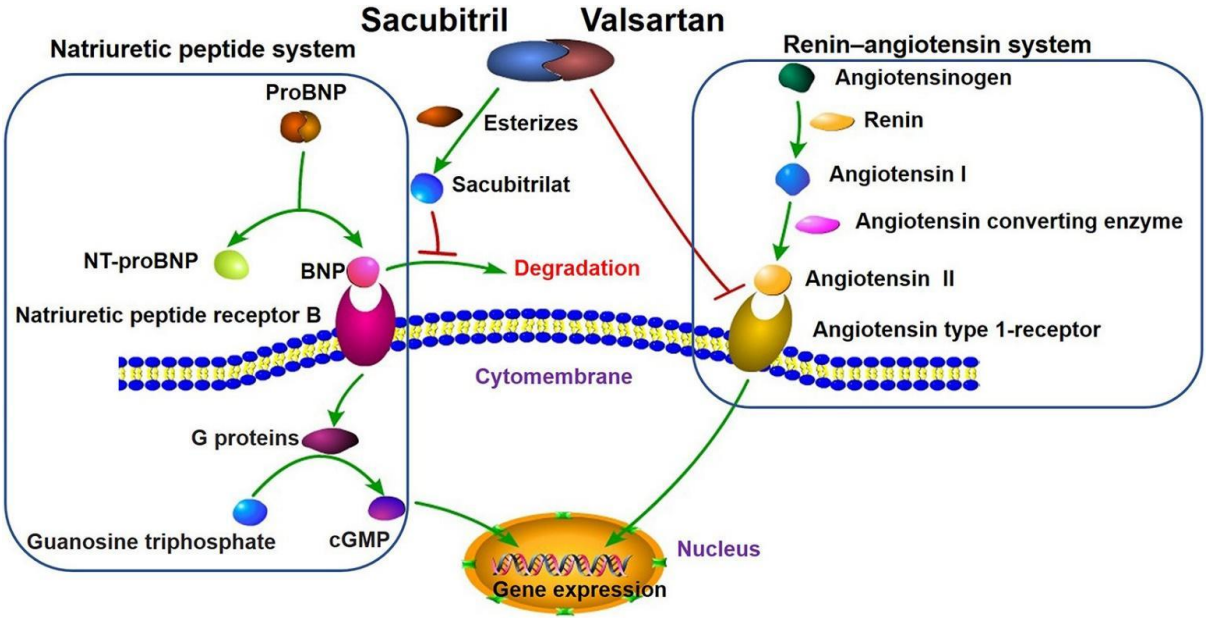


Figure 3: The mechanism of sacubitril/valsartan in the treatment for HF patients through regulating natriuretic peptide system and renin-angiotensin system. BNP indicates B-type (brain) natriuretic peptides; NT-pro-BNP, N-terminal pro-BNP; cGMP, cyclic guanosine monophosphate.

Pharmacological mechanism of sacubitril/valsartan in CKD[5]

Inhibition of neprilysin through sacubitril

Neprilysin, also known as neutral endopeptidase (Enkephalinase, NEP), is a membrane-bound metalloproteinase that is mostly expressed in the brush border membrane of the proximal renal tubular cells and responsible for degrading natriuretic peptides (NPs). NPs are composed of a class of peptides with similar structures, which exert an important effect on regulating the water-sodium and maintaining homeostasis of the cardiovascular system, mainly including atrial-type NP (ANP), brain-type NP (BNP), and C-type NP (CNP). Among the NPs, ANP and BNP are cardiac hormones mainly synthesized and secreted by cardiac atrial myocytes and

ventricular myocytes, respectively, but CNP is a neuropeptide synthesized by the brain or vascular endothelial cell. To be specific, NPs have a variety of important physiological functions: inhibiting RAAS, suppressing the expression of endothelin, and promoting vasodilation et al. Inhibition of NEP activity increases levels of NPs, which in turn stimulates the synthesis of cyclic guanosine monophosphate (cGMP) via guanylyl cyclase− linked receptors. Increased cGMP levels exert effects on glomerular hemodynamics such as increased glomerular filtration rate and renal blood flow by reducing the reabsorption of renal sodium and promoting vasodilation of the afferent arteriole, as well as a relaxation of the heart muscles (Fig. 1). Sacubitril is a prodrug that is quickly metabolized into an active NEPi, LBQ657, thereby reducing the degradation of NPs and increasing the concentration of NPs, which in turn dilates blood vessels, lowers blood pressure, and improves ventricular remodeling. The advent of NEPi has brought promising benefits to patients with chronic heart failure, and became a significant option for the treatment of chronic heart failure.

Blockade of angiotensin II type 1 receptor through valsartan

However, NEPi not only increases the level of NPs, but also increases the concentration of Ang II in the circulation, which counteracts the positive effects of NPs. To tackle this problem, NEPi must be combined with RAAS blockers to play a more effective role, otherwise, the activated RAAS will worsen the progression of CKD. At the outset, omapatrilat, a dual NEP/ACE inhibitor that was the most widely studied, exerted effects of renal protection in patients with CHF and delayed the progression of CKD. However, subsequent studies found that omapatrilat caused a high incidence of angioedema, making its application discontinued. The adverse event of omapatrilat led to the emergence of another dual NEP/RAAS blocker, ARNI. Valsartan is an angiotensin receptor blocker (ARB. The application of valsartan can greatly reduce the level of Ang II in the body. LCZ696 antagonizes the binding of Ang II to its receptor by combining NEPi and ARB. Eventually, sacubitril and valsartan coordinate with each other to exert a cardiorenal protective effect, which can effectively reduce the risk of hypotension and angioedema.

Others

It is well acknowledged that progressive deterioration of renal function in CKD is allied to oxidative stress, inflammation, and renal fibrosis. Studies have shown that compared with valsartan in CKD animal models, LCZ696 more significantly inhibit inflammation (through inhibition of NF-κB pathway), oxidative stress (through activation of Nrf2/HO-1 pathway), and renal fibrosis (through decreased levels of PAI-1, TGF-β, and α-SM actin). It was also found that LCZ696 was more effective in delaying the decline of renal function in patients with CKD, compared to RAAS blocker. Besides, the concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the decline of renal function were significantly improved in CKD animal models after administration of LCZ696. Additionally, LCZ696 relieved cardiac hypertrophy and fibrosis as well as aortic fibrosis, decreased markers of cardiac inflammation and oxidative stress, and ameliorated indicators of mitochondrial function. These results suggest that LCZ696 can significantly improve renal function and decrease the risk of cardiovascular events in CKD, compared with valsartan alone.

Clinical application of sacubitril/valsartan in CKD[5]

Reduction of cardiovascular risk in CKD

Progressive deterioration of renal function is associated with increased risks of cardiovascular events in patients with CKD, which often manifests as heart failure, hypertension, and sudden cardiac death. UK HARP-III was a randomized double-blind trial including 414 participants with moderate-to-severe CKD who were randomly assigned to LCZ696 versus irbesartan. Compared with irbesartan, LCZ696 reduced average systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 5.4 and 2.1 mmHg ($P < 0.001$), and levels of troponin I and NT-proBNP by 16% and 18% ($P < 0.001$), respectively. Similarly, the results of PARAMOUNT trial which included 301 patients with CKD and heart failure showed that, mean BP was reduced by 7.5 ± 15.1/5.1 ± 10.8 mmHg ($P = 0.004$) in the LCZ696 group and by 1.2 ± 16.1/0.2 ± 11.6 ($P = 0.001$) mmHg in the valsartan group, and NT-proBNP was also associated with a greater reduction (22.73% vs 3.13%, $P = 0.005$) than was valsartan. It is still controversial whether lowering blood pressure can reduce the progression of CKD, but there is sufficient evidence to suggest it reduces the risks of cardiovascular events. Of note, according to the KDIGO 2021 clinical practice guideline for the management of blood pressure in patients with CKD, a systolic blood pressure target of less than 120 mm Hg was proposed. The revised

guideline indicates that hypotensive targets of less than 120 mmHg in patients with CKD have benefits in terms of cardiovascular protection, improved survival, and prevention of cognitive decline, regardless of renal protection. In addition to lowering blood pressure and NT-proBNP, PARADIGM-HF trial showed that LCZ696 also reduced the risks of hospitalization for heart failure and cardiovascular death by 27% ($P < 0.001$) and decreased the symptoms and physical limitations of heart failure in patients with CKD, compared with enalapril (Table 1). A meta-analysis of randomized controlled trials (RCTs) including a total of 3460 individuals with heart failure and CKD also indicated that compared with the RAAS blocker, LCZ696 significantly decreased levels of blood pressure and NT-proBNP ($P < 0.0001$), indicating again that it might have cardiovascular benefits in patients with heart failure and CKD.

In addition to the above three RCTs, some observational studies were conducted to explore the effects of LCZ696 on cardiovascular risk in patients with CKD, and results were basically consistent with those obtained by RCTs. One study including 66 CKD outpatients with systolic dysfunction followed up in outpatient care found that, the level of NTpro-BNP was significantly decreased ($P < 0.05$) and left ventricular ejection fraction (LVEF) improved from $31 \pm 9\%$ to $39 \pm 15\%$ ($P < 0.001$) with improved renal function, at the end of follow up. Similarly, results from another observational study which included 54 outpatients with CKD and heart failure showed that both SBP (from 119.0 ± 14.3 to 114.8 ± 15.8 mmHg, $P = 0.014$) and DBP (72.2 ± 10.1 to 67.5 ± 10.0 mmHg, $P = 0.002$) were significantly decreased during follow-up, and a statistically significant improvement in LVEF ($29.7 \pm 5.0\%$ to $32.2 \pm 7.2\%$, $P < 0.001$) was found. These results represent an important confirmation outside the peculiar world of RCTs.

Improvement of renal outcomes in CKD

Recently, an 8-week multicenter, randomized, double-blind, activecontrolled trial (PIONEER-HF) evaluated the safety and efficacy of LCZ696 in comparison with enalapril in patients stabilized during hospitalization for acute decompensated heart failure. Results showed that the initiation of LCZ696 therapy led to a greater reduction in the NT-proBNP concentration than enalapril therapy. Meanwhile, the rate of worsening renal function (defined as an increase in serum creatinine >0.5 mg/dL and worsening of eGFR >25%) did not differ significantly between the two groups. Therapeutic benefits of LCZ696 concerning renal outcomes are also reported among patients with heart failure and CKD. The eGFR is usually reduced in the

progression of CKD. Clinical studies have shown that LCZ696 can delay the decline of eGFR. UK HARP-III, PARAMOUNT, and PARADIGM-HF trials all evaluated the effects of LCZ696 on eGFR in patients with CKD. Results suggested that allocation to LCZ696 gave rise to a slower rate of decrease in the eGFR to some extent, compared with RAAS blockers. While ARB inhibits the RAAS and reduces eGFR, NPs can inhibit the reabsorption of sodium in the proximal and distal nephron, increase urinary sodium excretion and urine flow, and regulate tubuloglomerular feedback, which may be one of the mechanisms by which LCZ696 retards eGFR reduction. Diabetes is the main cause of CKD. Studies have found that increased neprilysin levels in diabetic patients lead to a decrease in NPs levels, causing an increase in cGMP levels in the renal tubule, which in turn activates the RAAS, promotes renal fibrosis, worsens glomerular hemodynamics, and results in CKD finally. Therefore, LCZ696 may exert benefits in the treatment of patients with diabetes and CKD. Current clinical evidence such as PARADIGM-HF trial showed that compared with diabetic patients treated with enalapril, those treated with LCZ696 had a slower rate of decline in eGFR versus those without diabetes. Although this study did not analyze the effect of LCZ696 on renal function in patients with diabetes and CKD, it provided evidence that LCZ696 can prevent the occurrence of CKD by delaying the decline of eGFR in diabetic patients, and future research should focus on the impact of LCZ696 on patients with diabetes and CKD.

Although LCZ696 reduces the decline of eGFR and delays the deterioration of renal function, current clinical studies have been controversial regarding the effect of LCZ696 on urinary albumin in patients with CKD, regardless of urinary albumin are reported to be reduced by LCZ696 in animal studies. On the one hand, an open-label study assessed the efficacy and safety of LCZ696 in Japanese patients with hypertension and CKD, and results showed that the administration of LCZ696 led to a reduction of 15.1% in urinary albumin ratio to creatinine ratio (UACR) from baseline to endpoints. UK HARP-III trail also found that allocation to LCZ696 group led to a non-significant reduction of 9% ($P = 0.08$) in UACR than that of irbesartan group compared with baseline. On the other hand, secondary analyses of data from PARAMOUNT and PARADIGM-HF trials showed that LCZ696 delayed the decline of renal function compared with RAAS blockers, but an increase in UACR ($P < 0.001$). Based on the results of the above RCTs, a meta-analysis evaluated the effect of LCZ696 on UACR in patients with CKD, that is, compared with RAAS blockers, LCZ696 had no additional effect on albuminuria and caused no difference ($P = 0.59$) in UACR. Given these results, the reasons for the difference in UACR caused by LCZ696 in patients with CKD may be an intrinsic effect of

the drug or well within the variability of the measurement and the day-to-day variability of urinary albumin excretion. More researches are needed to clarify the effect of LCZ696 on urinary albumin in the future.

Benefits of sacubitril/valsartan in the treatment of patients with Heart Failure With Reduced Ejection Fraction (HFrEF) [6]

Reduced Mortality in HF Patients

The PARADIGM-HF study demonstrated a clear and early benefit of sacubitril/valsartan compared to enalapril, with a 20% relative risk reduction in the combined primary endpoint of CV death and HF hospitalization (HR 0.80 95% CI 0.73–0.87 $p < 0.001$), as well as in the individual components of the primary endpoint. These results contrast with those of many pivotal studies of ACEI/angiotensin II receptor antagonists (ARA II) (SOLVD-T, CHARM-Alternative, EMPHASIS-HF, ATLAS, HEAAL) where the reduction is more pronounced in HF hospitalizations than in CV death. In addition, ARNI reduced the risk of death from any cause by 16% [Hazard ratio (HR) 0.84 95% CI 0.76–0.93 $p < 0.009$] and improved quality of life. The benefits were consistent across all pre-specified subgroups analyzed, including age groups.

Reduction of CV Mortality Due to Sudden Death

Following the initial publication of PARADIGM-HF, a specific and very detailed analysis of the mode of death was conducted and adjudicated by a blinded independent committee. Causes of death were initially classified as CV, non-CV and unknown. CV deaths were subclassified into sudden death, death due to myocardial infarction, worsening HF, stroke or other cause of death. Sudden death was defined as unexpected death in a stable patient and was subclassified according to whether patients were seen alive 1 h or between 1 and 24 h before death. Sudden deaths in patients who were last seen alive >24 h before death were categorized separately as "apparent sudden deaths."

Of the total 1,546 patients who died in the study, there were 1,251 deaths that were considered CV (80.9%), with a 20% risk reduction observed in the ARNI vs. enalapril group (13.30 vs. 16.5%, respectively; HR 0.80 CI 9% 0.72–0.89 $p < 0.001$). Most CV deaths were sudden death

(44.8%) (also in patients considered “stable” in NYHA class I and II) or HF-related (26.5%). In both cases, a reduction in the risk of death of 20 and 21%, respectively, was observed in the ARNI group vs. enalapril (HR 0.80 95% CI 0.68–0.94 $p = 0.008$ and HR 0.79 95% CI 0.64–0.98 $p = 0.034$).

For sudden deaths (both resuscitated and non-resuscitated), a 22% risk reduction was observed in patients in the ARNI treatment arm compared to enalapril. The magnitude of this effect did not differ in patients with or without an implantable defibrillator (ICD). Notably, this incremental benefit in reducing sudden death with ARNI over the active comparator enalapril was also observed in patients receiving optimal treatment with beta-blockers (93%) and MRA (55%). Both drugs are known to reduce all-cause mortality and sudden death, and interestingly, in patients with an ICD, in whom the reduction of sudden death with ARNI reached 50%. Additionally, this protective effect on sudden death had not been observed with ACEIs or ARA II. Thus, the SOLVD study showed a reduction in mortality from HF progression with enalapril vs. placebo, but not of sudden death.

Effect on Ventricular Arrhythmias

The effect of ARNIs on ventricular arrhythmias was evaluated in a prospective, observational study in a cohort of 120 patients with HFrEF and an ICD with remote monitoring capability. Patients in the study were treated with an ARNI for 9 months after having previously been on ramipril or valsartan for 9 months. All arrhythmic events during the 9 months before and 9 months after the switch to ARNI were analyzed: appropriate shocks, non-sustained ventricular tachycardia (NSVT) and supraventricular tachycardia (SVT), ventricular extrasystolic load and percentage of biventricular pacing, where indicated. The patients, most of whom were in NYHA class II, experienced clinical improvement, reduced NT-proBNP levels, improved left ventricular remodeling (increase in ejection fraction of ~5 points), and a significant reduction in arrhythmic load after switching to ARNI. Specifically, patients had fewer episodes of SVT (≥ 30 beats or treated with the ICD) or NSVT (≥ 4 beats and <30 s) and an 80% reduction in appropriate ICD shocks (0.8 vs. 6.6% $p < 0.002$). Additionally, patients had fewer ventricular premature beats, leading to an increase in the percentage of biventricular pacing (from 95% ± 6% to 99% ±1%, $p < 0.02$) in patients on cardiac resynchronization therapy.

Conversely, patients with ventricular arrhythmias had higher NT-proBNP levels ($p < 0.0001$), and the reduction of arrhythmic load correlated with the grade of NT-proBNP improvement. Previous studies have shown that elevated NP levels are independent predictors of sustained ventricular arrhythmias and ICD shocks. Likewise, appropriate ICD shocks have been associated with increased mortality, so ARNI would be beneficial in both cases.

Mechanism of Action of ARNIs in Mortality Reduction[6]

There are two main mechanisms that can lead to sudden death. The first is sustained ventricular tachycardia, that is typically presented in patients with mild HF symptoms and underlying ischemic etiology, which can be treated by ICD implantation. The second mechanism is an acute mechanical failure of the left ventricle (LV), which manifests on the electrocardiogram as bradyarrhythmia, asystole or electromechanical dissociation. Regardless of the mechanism, a common underlying pathogenesis involves adverse left ventricular remodeling with interstitial fibrosis and myocardial distension, which promotes a pro-arrhythmic substrate and may trigger cascade failure, ending in electrical storm or mechanical collapse.

It has been reported that treatment with an ARNI can reduce mortality beyond treatment with beta-blockers, ACEI and MRAs, mainly due to the beneficial effects of neprilysin inhibition in reducing myocardial fibrosis and improving cardiac remodeling (wall stress, inflammation, hypertrophy and cell death), as well as its anti-arrhythmic effect through sympathetic inhibition and the increase of enkephalins, endorphins and bradykinin (Figure 4).

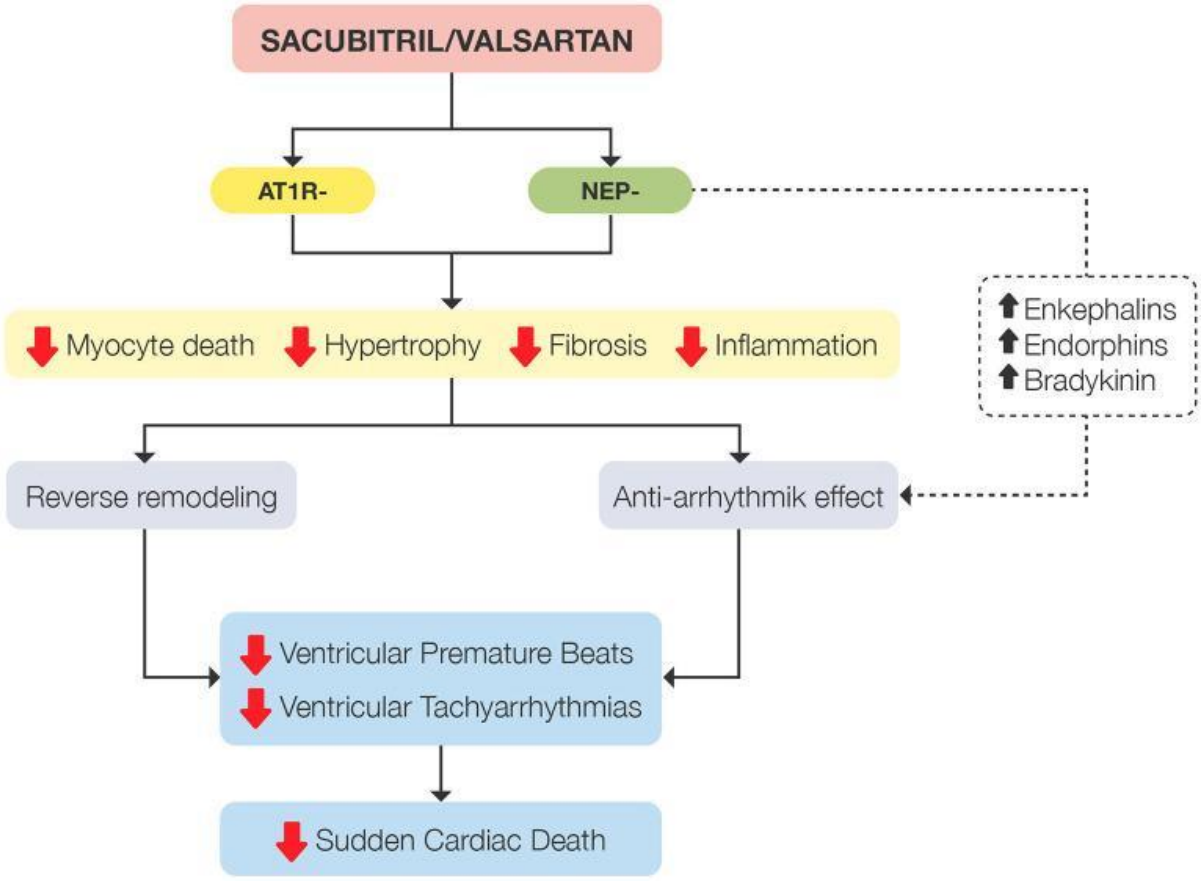


Figure 4: Summary of mechanisms involved in reducing the sudden death rate demonstrated by sacubitril/valsartan. AT1R-, angiotensin type 1 receptor inhibition; NEP-, neprilysin inhibition.

Thus, in patients with HFrEF, sacubitril/valsartan has shown vs. enalapril a further reduction in all-cause mortality, CV mortality (including sudden death) and HF hospitalization, as well as improving patient quality of life, irrespective of age. In addition, switching from treatment with ramipril or valsartan to treatment with an ARNI has been shown to reduce episodes of both SVT and NSVT, as well as ventricular premature beats. The beneficial effects observed with ARNIs on cardiac remodeling, as well as their anti-arrhythmic effect, would stem from their primary mechanism of action by inhibiting neprilysin

Safety and Tolerability of sacubitril/valsartan[4]

There are differences in safety and tolerability between sacubitril/valsartan and ACEIs/ARBs in the treatment of HF. This is usually assessed by the adverse events of sacubitril/valsartan, which include hypotension, hyperkalemia, dizziness, cough, liver related adverse events, headaches, angioedema and renal impairment (Figure 5). In this review, we mainly discussed the safety and tolerability of sacubitril/valsartan in HFrEF or HFpEF patients.

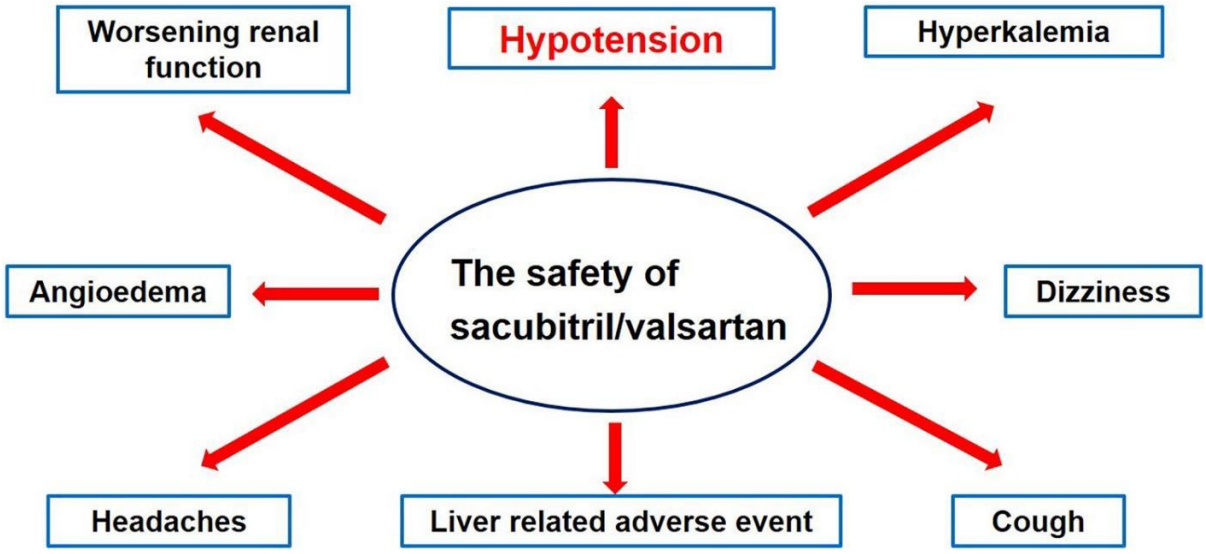


Figure 5. The safety of sacubitril/valsartan in the treatment for HF patients.

Three RCTs, 2 observational studies and 2 meta-analyses evaluated the safety and tolerability of sacubitril/valsartan in HFrEF patients. In the PARADIGM-HF trial, 12.3% of subjects in the enalapril group and 10.7% of subjects in the sacubitril/valsartan group withdrew due to an adverse event during the run-in phase ($P = 0.03$) The incidences rates of hypotension, hyperkalemia (>6.0 mmol/L), renal impairment (serum creatinine ≥ 2.5 mg/dL), and cough were 14%, 4.3%, 3.3% and 11.3% respectively in the sacubitril/valsartan group, while they were 9.2%, 5.6%, 4.5% and 14.3% respectively in the enalapril group ($P < 0.05$, respectively). Another RCT, the PIONEER-HF trial, showed that the rates of worsening renal function (13.6% vs. 14.7%, RR, 0.93; 95% CI, 0.67 to 1.28), hyperkalemia (11.6% vs. 9.3%, RR, 1.25; 95% CI, 0.84 to 1.84), and symptomatic hypotension (13.3% vs. 14.0%, RR, 0.95; 95% CI, 0.83 to 1.09) did not differ significantly between the sacubitril/valsartan group and the enalapril group. One observational study evaluated the difference in adverse effects between HFrEF inpatients and HFrEF outpatients treated with sacubitril/valsartan. The incidence rates of

discontinuation (17.0% vs. 11.5%, $P = 0.13$), hypotension (16.0% vs. 16.7%, $P = 0.88$), renal dysfunction (7.0% vs. 6.8%, $P = 0.94$), and hyperkalemia (1.0% vs. 4.9%, $P = 0.09$) were similar between the 2 groups. Additionally, the rate of discontinuation due to hypotension-related adverse events was similar (0.9% vs. 0.7%; $P = 0.38$). A meta-analysis, including 3 studies, compared the safety in HFrEF patients treated with sacubitril/valsartan or ACEIs. Sacubitril/valsartan was associated with an increased risk of hypotension, but reduced risks of renal dysfunction and hyperkalemia in all 3 trials, compared with ACEIs. Another meta-analysis showed that sacubitril/valsartan had a beneficial effect on serious adverse events compared with ACEIs/ARBs in HFrEF patients (37.4% vs. 41.8%, RR, 0.89; 95% CI, 0.86 to 0.94; $P \leq 0.00001$), including the risk of hyperkalemia (RR, 0.44; 95% CI, 0.26 to 0.76; $P = 0.003$), fatigue (RR, 0.10; 95% CI, 0.10 to 0.79; $P = 0.03$) and syncope (RR, 0.62; 95% CI, 0.43 to 0.91; $P \leq 0.01$). The evidence from RCTs, meta-analyses and observational studies indicated that sacubitril/valsartan had a good tolerability in HFrEF patients compared with ACEIs/ARBs.

Two RCTs and one meta-analysis investigated the safety and tolerability of sacubitril/valsartan in HFpEF patients. In the PARAGON-HF trial, the incidences rates of hypotension, angioedema and hyperkalemia (>6.0 mmol/L) were 15.8%, 0.6%, and 3.1% respectively in HFpEF patients treated with sacubitril/valsartan, while they were 10.8%, 0.2%, and 4.3% respectively in the valsartan group ($P < 0.001$, $P = 0.02$, and $P = 0.04$, respectively). However, liver-related adverse events (6.3% vs. 7.5%, $P = 0.11$) were similar between the 2 groups. In the PARAMOUNT-HF trial, the incidences rates of any adverse events (64% vs. 73%, $P = 0.14$), hypotension (19% vs. 18%, $P = 0.88$), renal dysfunction (2% vs. 5%, $P = 0.34$), and hyperkalemia (8% vs. 6%, $P = 0.50$) were similar between HFpEF patients treated with sacubitril/valsartan or valsartan. A meta-analysis showed no evidence of a difference in serious adverse events between the sacubitril/valsartan group and the ACEIs/ARBs group (55.5% vs. 56.1%; RR, 0.99; 95% CI, 0.94 to 1.04; $P = 0.63$) in HFpEF patients. Although few studies have explored the safety and tolerability of sacubitril/valsartan in HFpEF patients, these clinical studies supported the fact that the safety and tolerability might be similar between sacubitril/valsartan and valsartan in HFpEF patients.

Although some studies did not distinguish the type of HF, they still provided valuable evidence for comparing the safety between sacubitril/valsartan and ACEIs/ARBs or placebo in the treatment of HF patients. A meta-analysis showed that sacubitril/valsartan significantly decreased the risk of discontinuation of treatment for any adverse events (RR, 0.97; 95% CI,

0.80 to 1.17, *P* = 0.75), compared with ACEIs/ARBs or placebo. Sacubitril/valsartan increased the risk of angioedema (RR, 1.93; 95% CI, 1.02 to 3.68, *P* = 0.04) and dizziness (RR, 1.28; 95% CI, 1.08 to 1.52, *P* = 0.004) and decreased the risk of renal dysfunction (RR, 0.73; 95% CI, 0.59 to 0.91, *P* = 0.004) and bronchitis (RR, 0.82; 95% CI, 0.68 to 0.98, *P* = 0.03) in HF or hypertension patients. No significant difference was found in the incidence rates of hypotension, hyperkalemia, cough, upper respiratory tract inflammation, diarrhea, back pain, nasopharyngitis, headache or influenza between the sacubitril/valsartan group and the ACEIs/ARBs group. The meta-analysis concluded that sacubitril/valsartan was associated with lower drug-risks than ACEIs/ARBs or a placebo. These studies implied that compared with ACEIs/ARBs, sacubitril/valsartan was safe and well-tolerated in the treatment of HFrEF or HFpEF. However, the incidence of hypotension or dizziness might be high.

References:

1. Pontremoli R, Borghi C, Perrone Filardi P. Renal protection in chronic heart failure: focus on sacubitril/valsartan. *Eur Heart J Cardiovasc Pharmacother*. 2021;7(5):445-452.

2. Nicolas D, Kerndt CC, Reed M. Sacubitril/Valsartan. [Updated 2022 May 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507904/

3. Cho IJ, Kang SM. Angiotensin receptor-neprilysin inhibitor in patients with heart failure and chronic kidney disease. *Kidney Res Clin Pract*. 2021;40(4):555-565.

4. Zhang R, Sun X, Li Y, et al. The Efficacy and Safety of Sacubitril/Valsartan in Heart Failure Patients: A Review. *Journal of Cardiovascular Pharmacology and Therapeutics*. 2022;27.

5. Kuang, H., Huang, X., Zhou, Z., Cheng, X., & Xu, G. (2021). Sacubitril/valsartan in chronic kidney disease: From pharmacological mechanism to clinical application. *European Journal of Pharmacology*, 907, 174288.

6. Pascual-Figal D, Bayés-Genis A, Beltrán-Troncoso P, et al. Sacubitril-Valsartan, Clinical Benefits and Related Mechanisms of Action in Heart Failure With Reduced Ejection Fraction. A Review. *Front Cardiovasc Med*. 2021;8:754499.

Survey Form

1) What is the approximate prevalence of heart failure (HF) been observed by you in current clinical practice?

A. <25%
B. 26-50%
C. 51-75%
D. >75%

2) As per your opinion, which are the unmet needs in the management of HF in current clinical scenario?

A. Early detection and diagnosis
B. Personalized treatment approaches
C. Strategies to reduce hospital readmissions
D. Affordability and access to medications

3) In your clinical practice, how frequently do you prescribe Angiotensin Receptor Neprilysin Inhibitor (ARNI) for patients with heart failure with reduced ejection fraction (HFrEF)?

A. Always
B. In most cases
C. Only in specific cases
D. Never

4) As per your opinion does the early initiation of ARNI in heart failure is the good therapeutic strategy?

A. Yes, specifically in patients with HFrEF.
B. Yes, specifically in patients with HFrEF.
C. Yes, in patients with all types of HF.
D. No early initiation

5) As per your clinical experience, which are the clinical benefits associated with the early initiation of ARNI in heart failure management?

A. Early initiation of ARNI in patients with HFrEF may lead to better outcomes.
B. Starting treatment early in the course of the disease may help in preventing disease progression.
C. Starting treatment early in the course of the disease may help to improving overall prognosis.

6) What is the usual duration of ARNI therapy being prescribed by you in patients with HF during current clinical practice?

A. <4 Weeks
B. 4 to <12 Weeks
C. 12 to <24 Weeks
D. >24 Weeks

7) In your experience, how long does it typically take for patients to experience noticeable 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

8) What clinical criteria do you usually consider while initiating ARNI therapy in a patient with HF?

A. Patient overall symptoms
B. Functional status of patient
C. Tolerance to other heart failure medications
D. Renal function
E. Liver function

9) What is your usual approach to initiate with the ARNI therapy in HF?

A. Initiates ARNI in hospital once the patient stabilizes.

B. Initiates ARNI in out-patient setting.

C. Initiates ARNI de-novo as the drug of choice.

D. First initiates an ACEI or ARB and then switches to ARNI.

10) How often you initiate ARNI in therapy naive patients with heart failure?

A. Much often

B. Rarely

C. Never

11) In your experience, have you observed any notable improvements in patient outcomes (e.g., reduced hospitalizations) with the use of ARNI?

A. Yes

B. No

C. Not sure

12) How do you monitor and assess the effectiveness of ARNI in your patients with HFrEF?

A. Symptom Assessment/Improvement in symptom

B. HF-related hospitalizations

C. Left Ventricular Ejection Fraction (LVEF)

D. NT-proBNP (N-terminal pro B-type natriuretic peptide) levels

E. Serum Creatinine level

13) How often do you experience the reduction in blood pressure on initiating with ARNI in patient with HF?

A. Always

B. In most cases

C. Only in specific cases

D. Never

14) How often you observed hyperkalemia on initiating with ARNI therapy in patient with HF?

A. Always
B. In most cases
C. Only in specific cases
D. Never

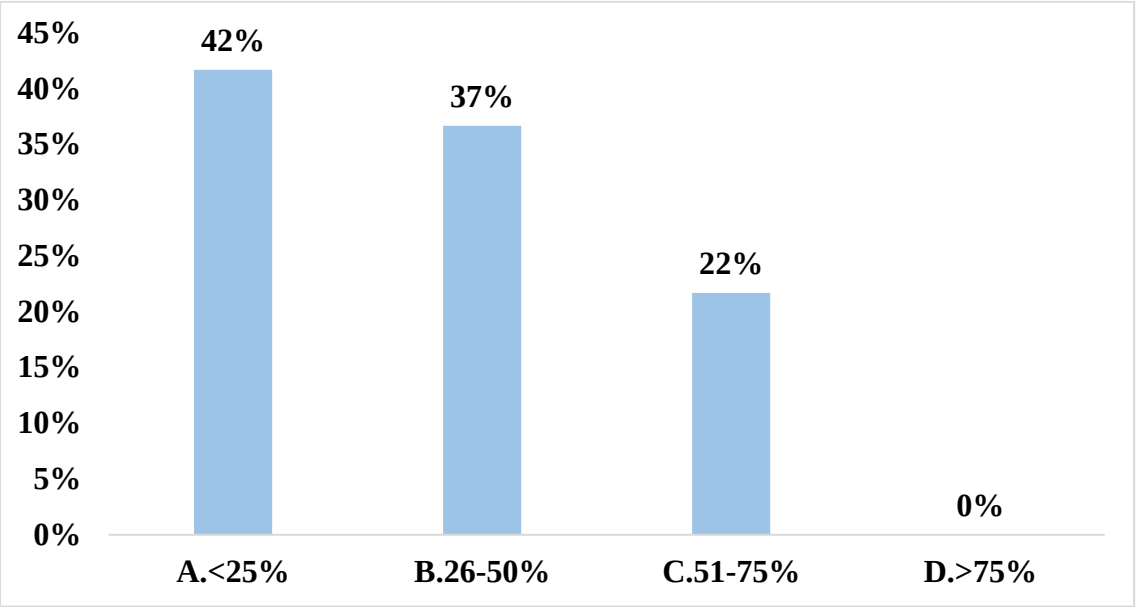
15) How often you observed with elevation in serum creatinine levels on initiating with ARNI therapy in patient with HF?

A. Always
B. In most cases
C. Only in specific cases
D. Never

Survey Findings

1) What is the approximate prevalence of heart failure (HF) been observed by you in current clinical practice?

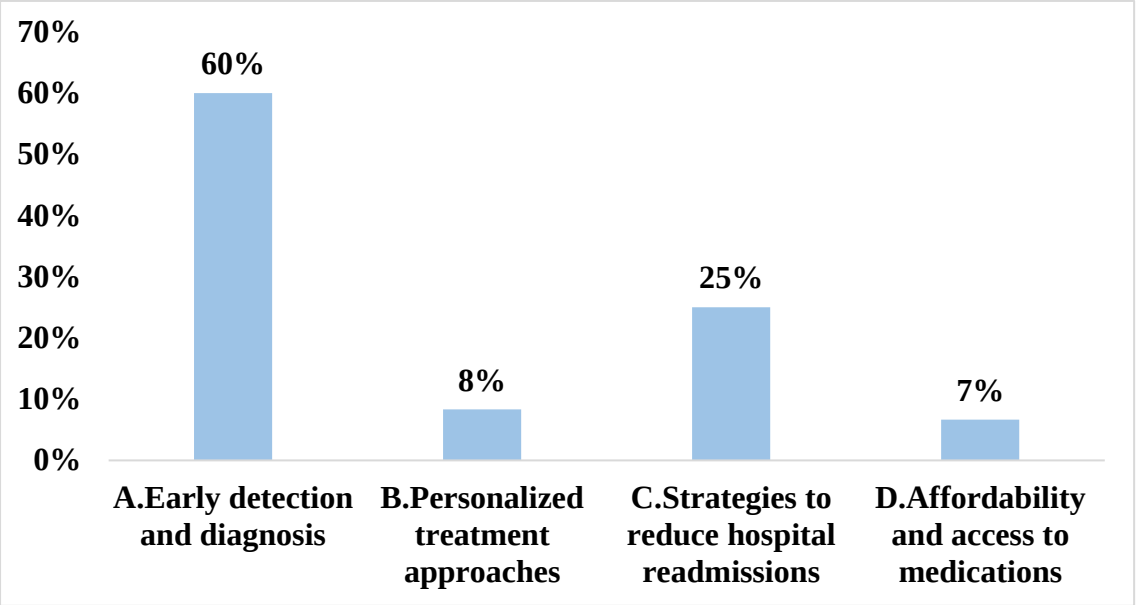
A. <25%
B. 26-50%
C. 51-75%
D. >75%



As per 42% of doctors, <25% is the approximate prevalence of heart failure (HF) been observed in current clinical practice.

2) As per your opinion, which are the unmet needs in the management of HF in current clinical scenario?

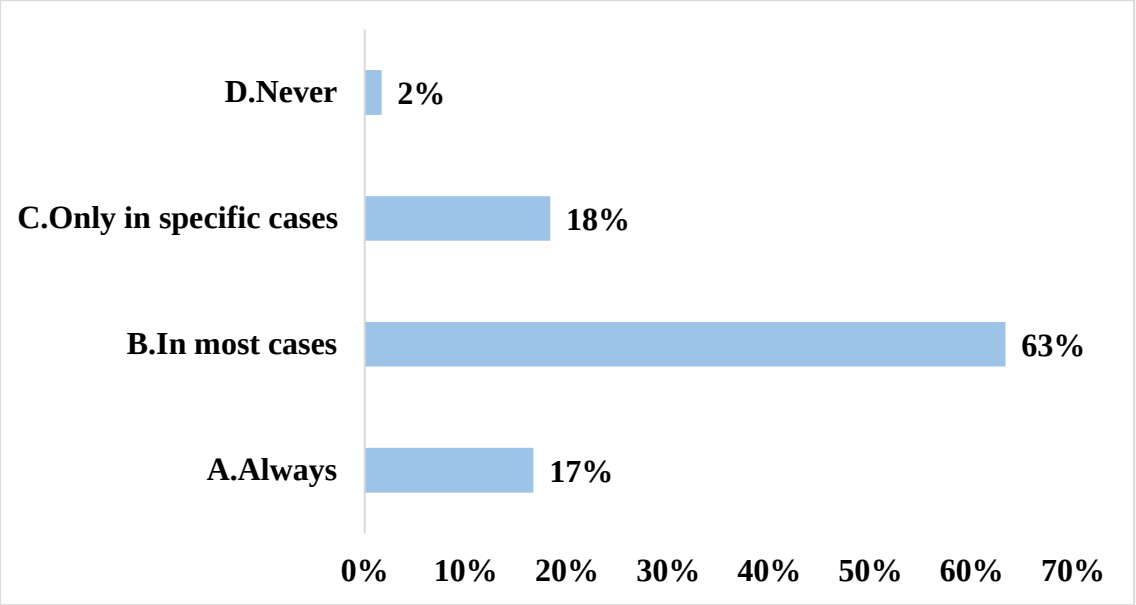
A. Early detection and diagnosis
B. Personalized treatment approaches
C. Strategies to reduce hospital readmissions
D. Affordability and access to medications



According to 60% of doctors, early detection and diagnosis are the unmet needs in the management of HF in current clinical scenario.

3) In your clinical practice, how frequently do you prescribe Angiotensin Receptor Neprilysin Inhibitor (ARNI) for patients with heart failure with reduced ejection fraction (HFrEF)?

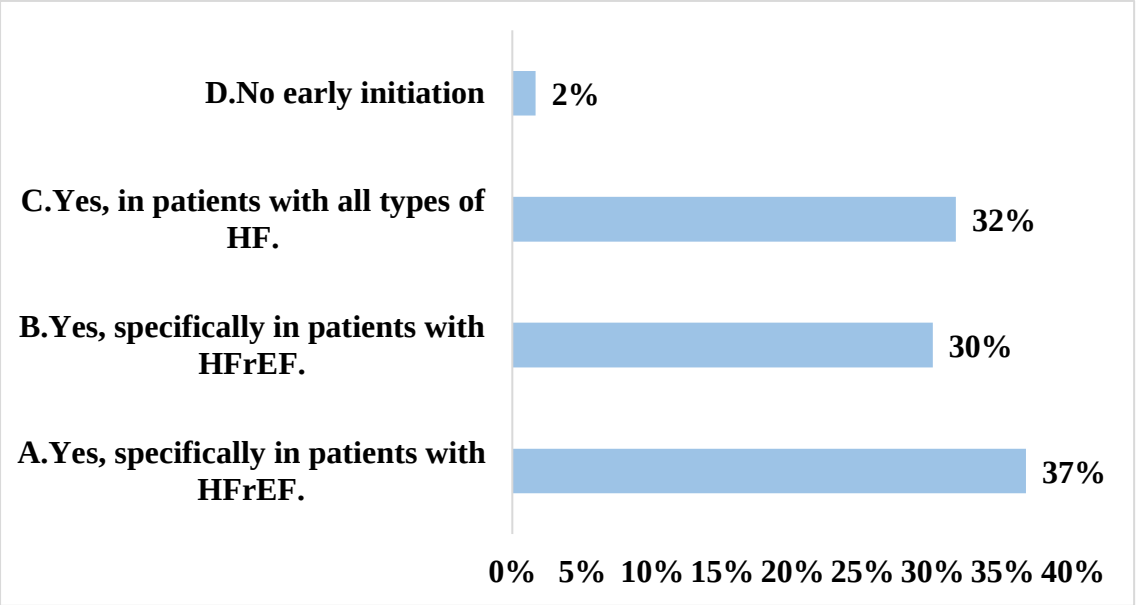
A. Always
B. In most cases
C. Only in specific cases
D. Never



According to 63% of doctors, in most cases they prescribe Angiotensin Receptor Neprilysin Inhibitor (ARNI) for patients with heart failure with reduced ejection fraction (HFrEF).

4) As per your opinion does the early initiation of ARNI in heart failure is the good therapeutic strategy?

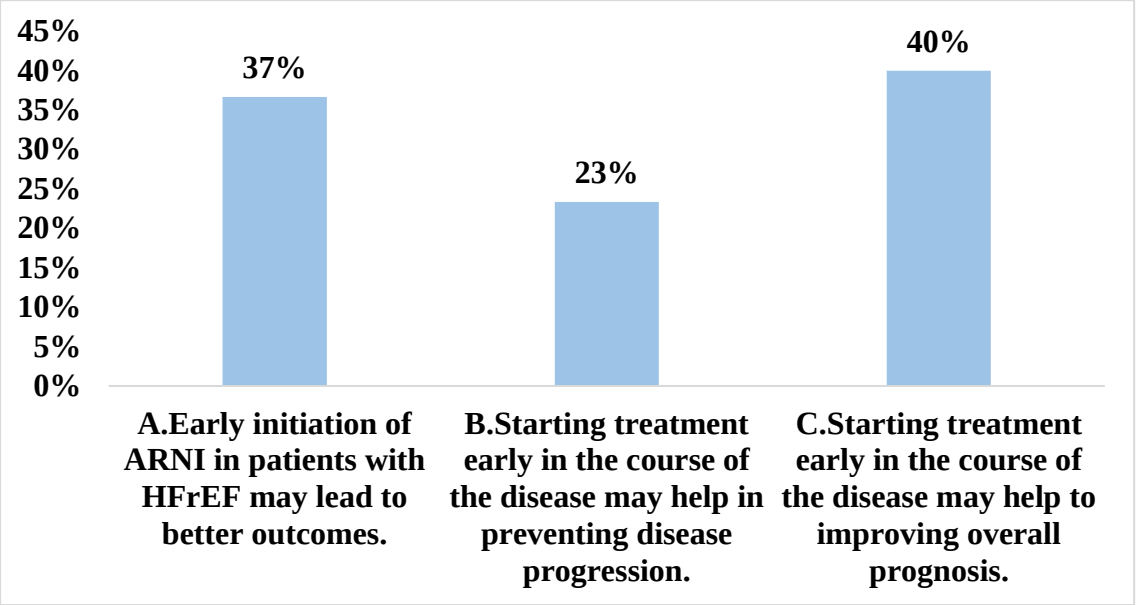
A. Yes, specifically in patients with HFrEF.
B. Yes, specifically in patients with HFrEF.
C. Yes, in patients with all types of HF.
D. No early initiation



According to 37% of doctors, the early initiation of ARNI in heart failure is the good therapeutic strategy specifically in patients with HFrEF.

5) As per your clinical experience, which are the clinical benefits associated with the early initiation of ARNI in heart failure management?

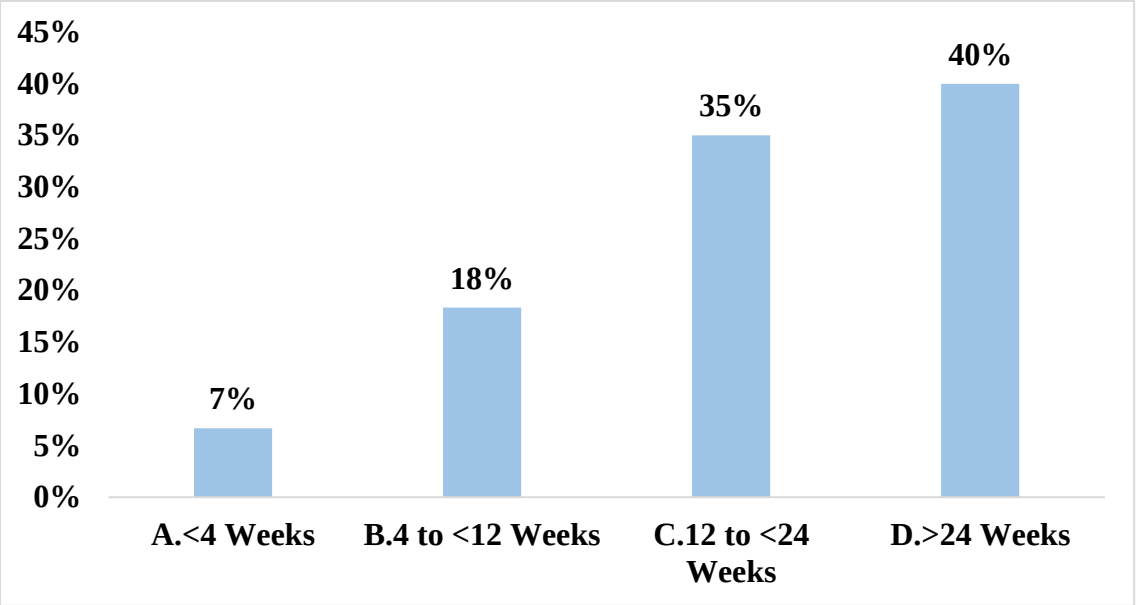
A. Early initiation of ARNI in patients with HFrEF may lead to better outcomes.
B. Starting treatment early in the course of the disease may help in preventing disease progression.
C. Starting treatment early in the course of the disease may help to improving overall prognosis.



According to 40% of doctors, the clinical benefits associated with the early initiation of ARNI in heart failure management is that starting treatment early in the course of the disease may help in improving overall prognosis.

6) What is the usual duration of ARNI therapy being prescribed by you in patients with HF during current clinical practice?

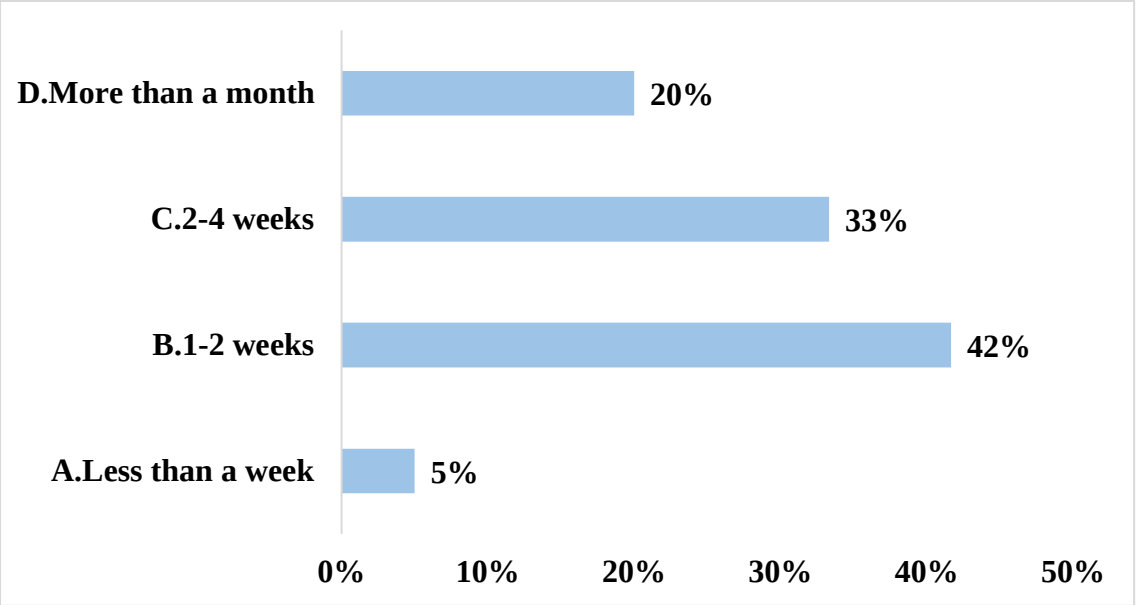
A. <4 Weeks
B. 4 to <12 Weeks
C. 12 to <24 Weeks
D. >24 Weeks



According to 40% of doctors, >24 weeks is the usual duration of ARNI therapy being prescribed by them in patients with HF during current clinical practice.

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

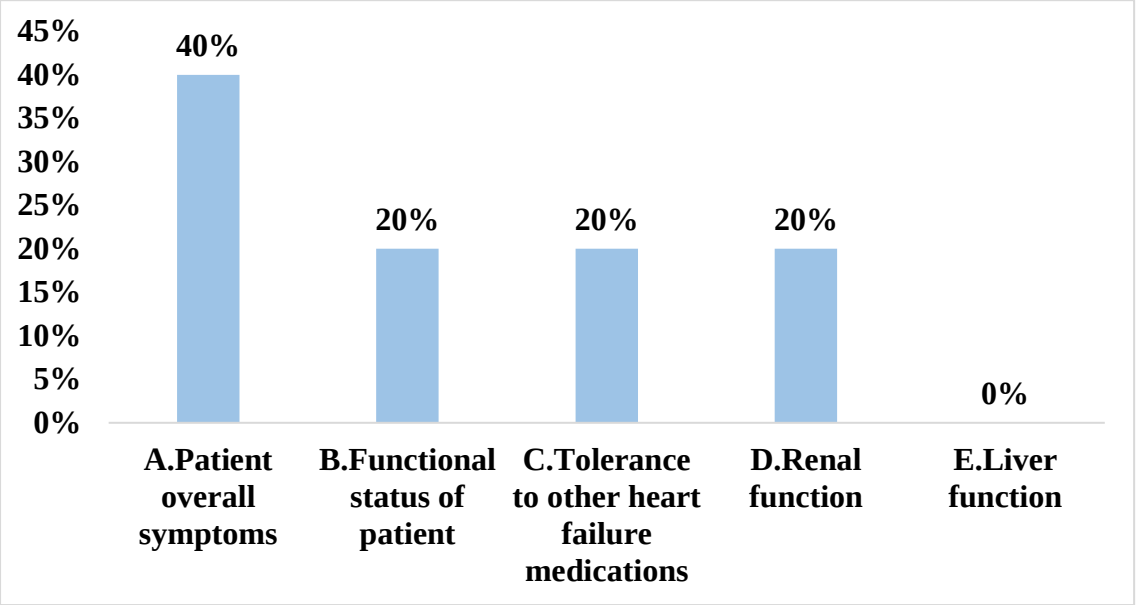
A. Less than a week
B. 1-2 weeks
C. 2-4 weeks
D. More than a month



According to 42% of doctors, 1-2 weeks is the duration typically taken for patients to experience noticeable improvements in their condition after starting ARNI therapy.

8) What clinical criteria do you usually consider while initiating ARNI therapy in a patient with HF?

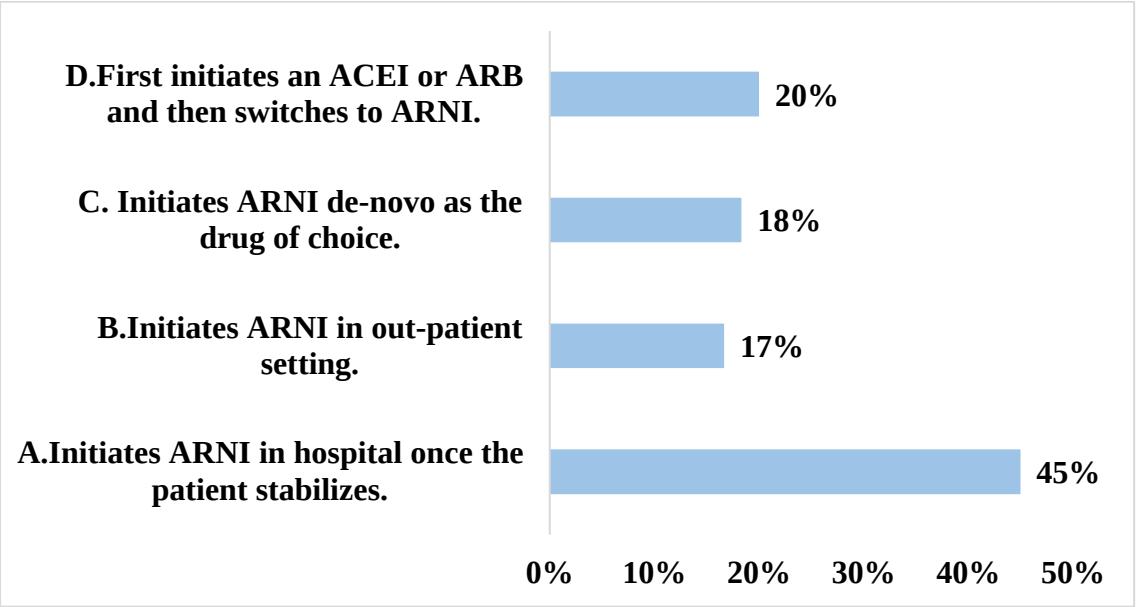
A. Patient overall symptoms
B. Functional status of patient
C. Tolerance to other heart failure medications
D. Renal function
E. Liver function



According to 40% of doctors, patient overall symptoms is the clinical criteria usually considered while initiating ARNI therapy in a patient with HF.

9) What is your usual approach to initiate with the ARNI therapy in HF?

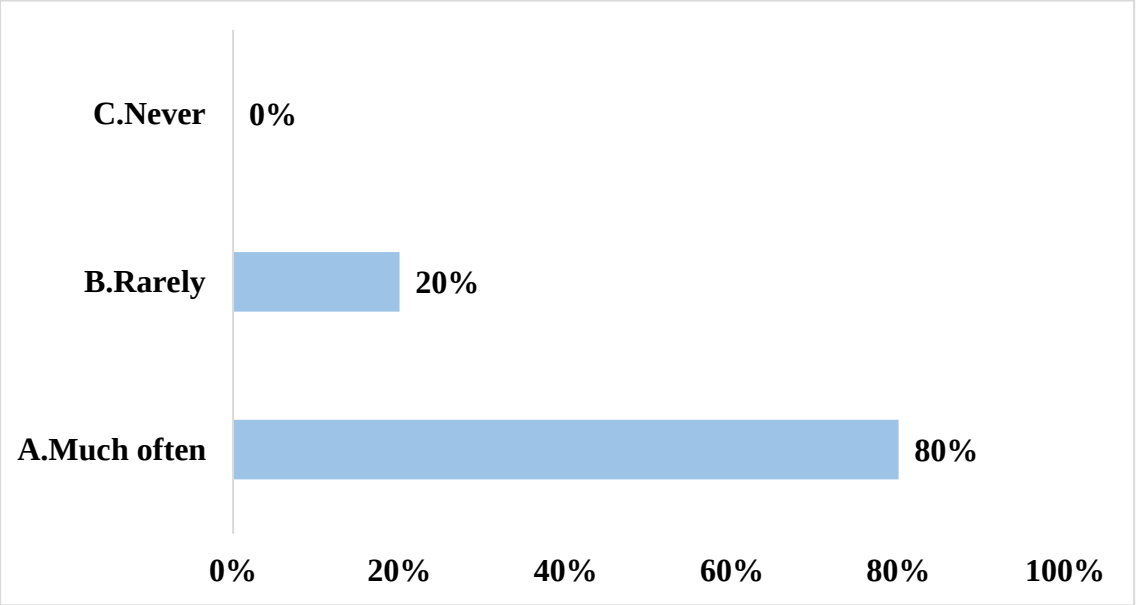
A. Initiates ARNI in hospital once the patient stabilizes.
B. Initiates ARNI in out-patient setting.
C. Initiates ARNI de-novo as the drug of choice.
D. First initiates an ACEI or ARB and then switches to ARNI.



According to 45% of doctors, the usual approach to initiate with the ARNI therapy in HF is initiating ARNI in hospital once the patient stabilizes.

10) How often you initiate ARNI in therapy naive patients with heart failure?

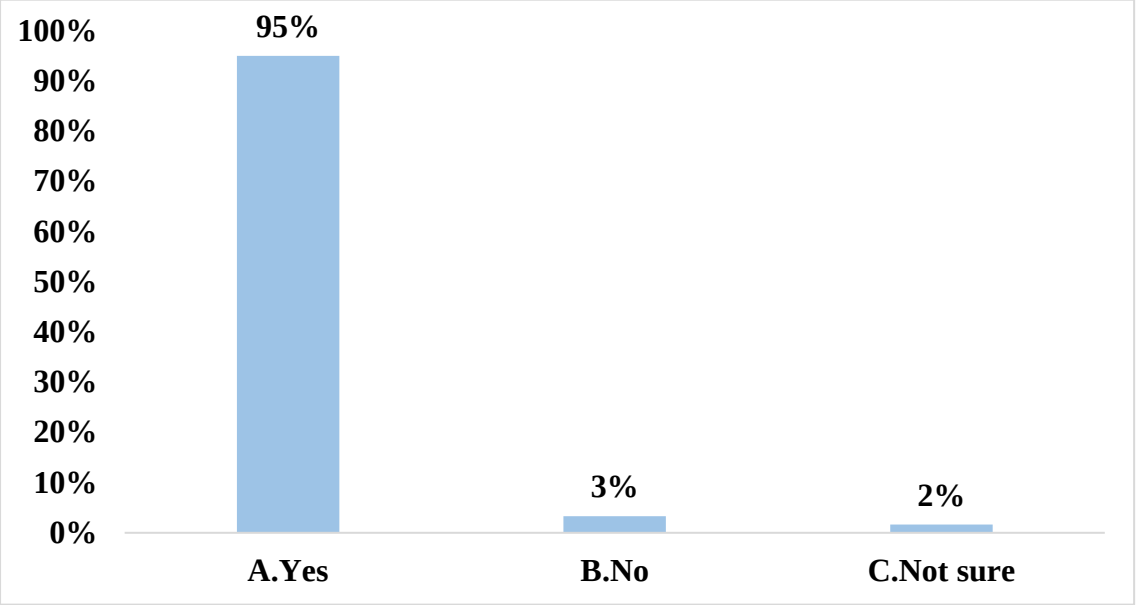
A. Much often
B. Rarely
C. Never



As per majority (80%) of doctors, they have much often initiated ARNI in therapy naive patients with heart failure.

11) In your experience, have you observed any notable improvements in patient outcomes (e.g., reduced hospitalizations) with the use of ARNI?

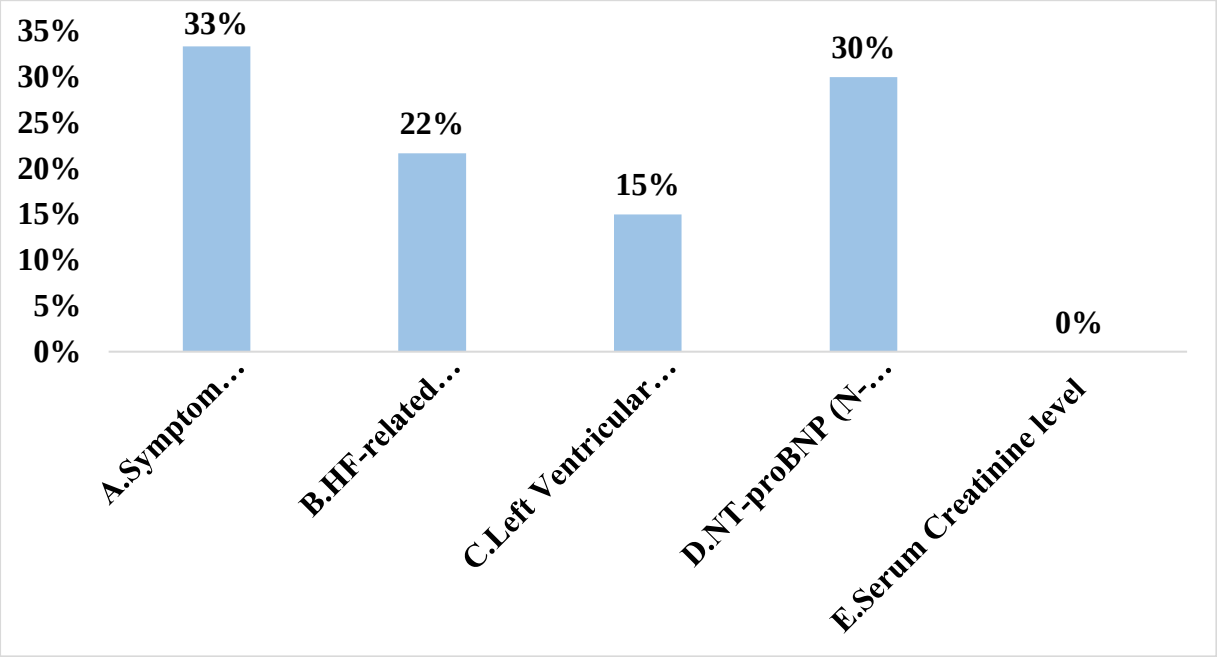
A. Yes
B. No
C. Not sure



According to majority (95%) of doctors, they have observed notable improvements in patient outcomes (e.g., reduced hospitalizations) with the use of ARNI.

12) How do you monitor and assess the effectiveness of ARNI in your patients with HFrEF?

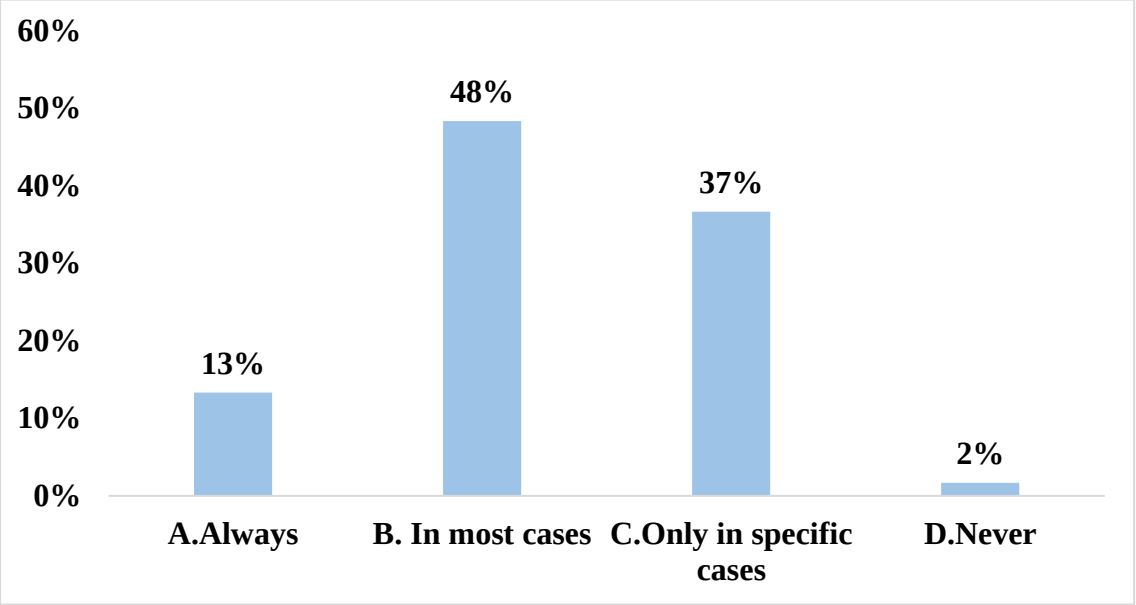
A. Symptom Assessment/Improvement in symptom
B. HF-related hospitalizations
C. Left Ventricular Ejection Fraction (LVEF)
D. NT-proBNP (N-terminal pro B-type natriuretic peptide) levels
E. Serum Creatinine level



According to 33% of doctors, symptom assessment/improvement in symptom helps to monitor and assess the effectiveness of ARNI in their patients with HFrEF.

13) How often do you experience the reduction in blood pressure on initiating with ARNI in patient with HF?

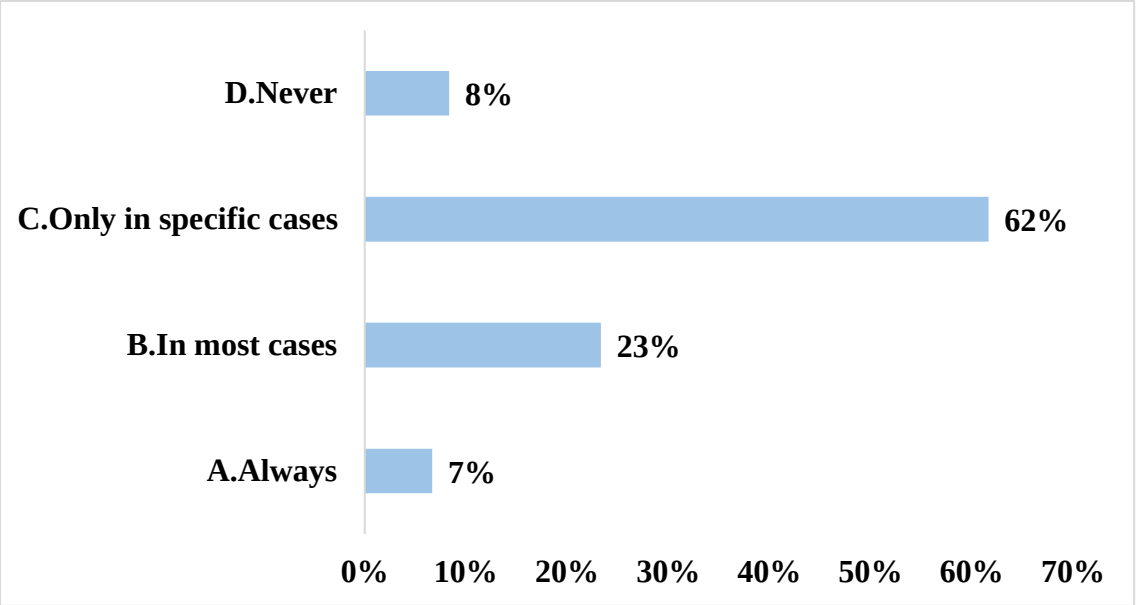
A. Always
B. In most cases
C. Only in specific cases
D. Never



According to 48% of doctors, in most cases they have experienced the reduction in blood pressure on initiating with ARNI in patient with HF.

14) How often you observed hyperkalemia on initiating with ARNI therapy in patient with HF?

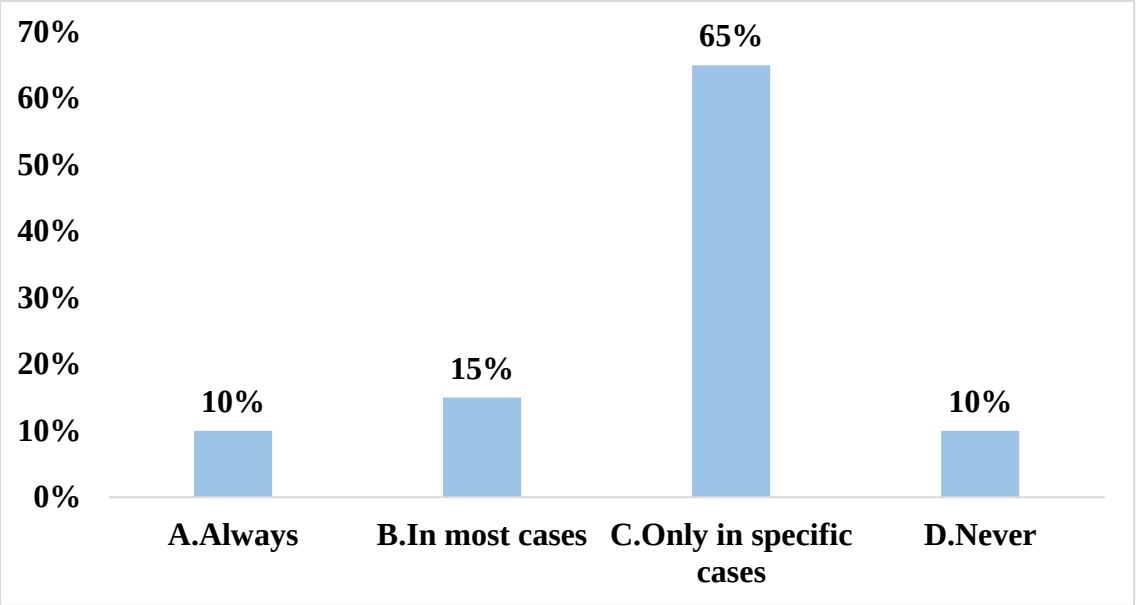
A. Always
B. In most cases
C. Only in specific cases
D. Never



As per majority (62%) of doctors, only in specific cases they have observed hyperkalemia on initiating with ARNI therapy in patient with HF.

15) How often you observed with elevation in serum creatinine levels on initiating with ARNI therapy in patient with HF?

A. Always
B. In most cases
C. Only in specific cases
D. Never



According to majority (65%) of doctors, only in specific cases they have observed with elevation in serum creatinine levels on initiating with ARNI therapy in patient with HF.

Summary

- As per 42% of doctors, <25% is the approximate prevalence of heart failure (HF) been observed in current clinical practice.
- According to 60% of doctors, early detection and diagnosis are the unmet needs in the management of HF in current clinical scenario.
- According to 63% of doctors, in most cases they prescribe Angiotensin Receptor Neprilysin Inhibitor (ARNI) for patients with heart failure with reduced ejection fraction (HFrEF).
- According to 37% of doctors, the early initiation of ARNI in heart failure is the good therapeutic strategy specifically in patients with HFrEF.
- According to 40% of doctors, the clinical benefits associated with the early initiation of ARNI in heart failure management is that starting treatment early in the course of the disease may help in improving overall prognosis.
- According to 40% of doctors, >24 weeks is the usual duration of ARNI therapy being prescribed by them in patients with HF during current clinical practice.
- According to 42% of doctors, 1-2 weeks is the duration typically taken for patients to experience noticeable improvements in their condition after starting ARNI therapy.
- According to 40% of doctors, patient overall symptoms is the clinical criteria usually considered while initiating ARNI therapy in a patient with HF.
- According to 45% of doctors, the usual approach to initiates with the ARNI therapy in HF is initiating ARNI in hospital once the patient stabilizes.
- As per majority (80%) of doctors, they have much often initiated ARNI in therapy naive patients with heart failure.
- According to majority (95%) of doctors, they have observed notable improvements in patient outcomes (e.g., reduced hospitalizations) with the use of ARNI.
- According to 33% of doctors, symptom assessment/improvement in symptom helps to monitor and assess the effectiveness of ARNI in their patients with HFrEF.
- According to 48% of doctors, in most cases they have experienced the reduction in blood pressure on initiating with ARNI in patient with HF.
- As per majority (62%) of doctors, only in specific cases they have observed hyperkalemia on initiating with ARNI therapy in patient with HF

Consultant Opinion

Based on the analysis of the survey regarding the management of heart failure (HF), here are some recommendations and potential opportunities for improvement in patient care and strategies for pharmaceutical companies:

Market Opportunities:

- Develop innovative strategies and educational campaigns to raise awareness about the prevalence of HF and the importance of early detection and diagnosis.

Value for Healthcare Professionals:

- Provide continued medical education and training programs to healthcare professionals to enhance their skills in early detection and management of HF.

Adverse Effect Management:

- Invest in research and development to address concerns related to adverse effects such as hyperkalemia and elevation in serum creatinine levels associated with ARNI therapy.

Withdrawal Management:

- Develop protocols and guidelines for the appropriate initiation and withdrawal of ARNI therapy in HF patients to ensure optimal management and minimize risks.

Market Positioning:

- Position ARNI therapy as a first-line treatment option for patients with HF with reduced ejection fraction (HFrEF), emphasizing its clinical benefits and potential to improve patient outcomes.

Personalized Treatment Decisions:

- Explore personalized approaches to HF management, considering factors such as patient symptoms, disease severity, comorbidities, and individual response to therapy.

Improving Patient Outcomes:

- Collaborate with healthcare providers to implement comprehensive care plans for HF patients, including regular monitoring of symptoms, medication adherence, lifestyle modifications, and timely adjustments in treatment.

Innovation and Research:

- Continue investing in research and development to identify novel therapeutic targets and innovative treatment modalities for HF management, addressing the unmet needs identified in the survey.

By addressing these aspects, both healthcare professionals and pharmaceutical companies can work together to optimize patient care, improve treatment outcomes, and enhance the overall management of heart failure.

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

Weston Medical Education Foundation of India

CTS-77, Shop No.11, Swapna Siddhi CHS LTD, Akurli Road Near Malad Sahakari Bank
Kandivali (E), Mumbai - 400101. M: 9322615653 I W: www.wmefi.co.in