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Review Article

A REVIEW ON GLOBAL TRENDS IN HEART FAILURE AND EVOLUTION OF ANGIOTENSIN–NEPRILYSIN INHIBITOR

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ABSTRACT

Heart failure (HF) is a major global public health problem irrespective of its causes. It generates an enormous clinical, societal, and economic, health loss burden with an increase in its prevalence reaching an epidemic proportion. The morbidity and mortality associated with heart failure are increasing the health-related burdens worldwide, especially in low- and middle-income countries. This review highlights the trends in HF burden, the clinical spectrum of HF, and the importance of neurohormonal pathways and the evolution of angiotensin receptor neprilysin inhibition in HF with updated clinical practice guidelines.

Keywords: Heart failure, Sacubitril/valsartan, Neprilysin, Angiotensin receptor blockers.

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INTRODUCTION

Irrespective of the underlying cause, heart failure (HF) being a major global public health problem generates an enormous clinical, societal and economic, health loss burden with an increase in its prevalence reaching an epidemic proportion. There is not only an increase in the number of patients with recurrent HF or its complications but also mortality is also seen to be increasing, especially in the elderly and in people living in low socio-demographic index (SDI) regions [1-5]. Worldwide, the prevalence of HF is 26 million with 6.5 million in the United States and 15 million in the European Union [6,7]. The prevalence in Asia varies with different countries. It is estimated to be 4.5 million in 2014 in China [8]. India with its 1.3 billion population having limited resources and out-of-pocket expenditures poses a great challenge. And because of the lack of a surveillance system and poor documentation of patient's clinical records, there is a dearth of epidemiological data which hampers the nationwide estimates. Based on existing evidence on underlying HF risk factors, the incidence of HF is in the range of 0.4–1.8 million and the prevalence of HF is in the range of 1.3–4.6 million in the Indian population [9-14]. Therefore, in this article, we aimed to review the global trends in HF associated burden, the clinical spectrum of HF and neurohormonal importance in HF, and the evolution of angiotensin neprilysin inhibitors with updated clinical practice guidelines.

TRENDS IN HF

Due to the aging population, increase in the prevalence of cardiovascular risk factors and associated cardiovascular diseases, the increasing prevalence of HF imposes a high burden on the entire world, particularly to the low- and middle-income countries. It often fails to attract the awareness and emphasis it deserves, though many cardiovascular diseases are ending in HF [2,15-20]. With more than 60% of the global population and more than two-thirds of low- and middle-income countries in Asia, the residing population is at high risk for HF and associated morbidities. This increasing burden of cardiovascular disease is attributed to the increasing prevalent risk factors such as diabetes, obesity, and hypertension, coronary artery disease, and rheumatic heart disease [21-29]. Recently published national, international studies had shown that an increased epidemiologic impact of HF, contrary to past decades' evidence, which had shown almost the opposite trend [2-5,30].

The current socio-demographic distribution of HF and the past 28-year trend around the world deserve special focus as the recent trend shows that changes in worldwide HF case distribution, though the burden of HF is still largely prevalent in middle to high SDI regions and which would increase the further burden in low to middle SDI regions by reversing the current scenario [1-5]. This will impose additional challenges to low-income countries toward attaining anticipated outcomes with their poor health-care infrastructure availability, access, and quality [22], and severe economic burden on virtually every country around the world by staggering costs related to HF, which are mainly due to repeated hospitalizations and the loss of productivity in patients with HF [31,32]. This requires the implementation of well-tailored health-care services to facilitate the unsustainable burden in local health-care systems particularly in low-income countries. With the better utilization of recent advancements in HF treatment options and improved awareness, this burden could be possibly minimized.

CLINICAL SPECTRUM OF HF

The clinical spectrum of HF can be divided into four interrelated stages, as shown in Table 1. HF can further be divided based on the left ventricular ejection fraction (LVEF) into the following categories [33,34].

- HF with reduced ejection fraction (HFrEF): LVEF <40%
- HF with mid-range ejection fraction: LVEF = 40–49%
- HF with preserved ejection fraction: >50%.

NEUROHORMONAL MODEL OF HF

Development and progression of HF involve activation of neurohormonal pathways, which include the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS). Activation of these two systems increases blood pressure (BP), heart rate, and blood volume. This, in normal cardiac physiology, leads to further activation of compensatory mechanisms such as natriuretic peptide system (NPS) including atrial NP (ANP) and B-type NP (BNP) causing natriuresis, vasodilatation, and diuresis, whereas in patients with HF, the effects of NPS were dampened due to decreased ANP and BNP, or due to their increased degradation by neprilysin and maybe because of reduced expression of NP receptors. In due course, the inability of NPS to compensate for the overactivation of RAAS and SNS leads to fluid overload, thereby continuous hemodynamic stress leads

to cardiac remodeling [35-42]. Therefore, neurohormonal activation has been pharmacological targets for the treatment of HF patients with reduced ejection fraction with disease-modifying drugs such as beta-blockers acting on SNS, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor inhibitors (ARBs) acting on RAAS, and mineralocorticoid receptor antagonists (MRAs). Despite the use of disease-modifying drugs, the HF associated mortality and morbidity is significantly high.

EVOLUTION OF ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITION (ARNI)

The potential ameliorative benefits of NPS such as natriuresis, vasodilatation, and diuresis on the effects of RAAS overactivity and significantly high morbidity and mortality associated with HF, despite the use of disease-modifying drugs, led to several lines of research in finding therapeutic use of these peptides. During initial research, exogenous NP were administered at supra-physiological doses to mimic the endogenous NP to the patients with decompensated HF. Carperitide, a synthetic analog of ANP, and nesiritide, a human recombinant form of BNP, both have been associated with vasodilatation, diuresis with symptomatic improvement in HF patients [43]. Both drugs need continuous infusion rather than bolus administration due to their short duration of action failed to show sustained clinical benefits, which limited the clinical application of these two agents in treating acute decompensated HF [44-54]. The alternative approach was to augment the level of endogenous NP, thereby its activity by reducing elimination through an NP clearance receptor (NPRC or NPRC3), and the other is through degradation by the enzyme neprilysin, a membrane-bound endopeptidase found in many tissues, most prominently in the kidney. Neprilysin also plays a role in the degradation of several other peptides, which may contribute to the benefits of neprilysin inhibition [55-58]. Candoxatril, a selective neprilysin inhibitor, has been reported to exert vasodilator and diuretic activity in patients with HF and improved exercise duration when combined with ACEI [59-62]. But this too did not show significant clinical benefit in treating patients with chronic HF, due to sustained hypotensive effect. Hence, candoxatril drug development was consequently halted [63].

Disinhibiting the effect of neprilysin inhibitor on the potent vasoconstrictor peptides such as angiotensin I and II potentiate the RAAS and neutralizing the effects of NP. These findings demonstrated the need to combine neprilysin inhibition along with inhibition of RAAS [58-65]. Omapatrilat, a vasopeptidase inhibitor, comparison with enalapril showed a modest reduction in all-cause mortality and HF-related hospitalization in chronic HF patients. However, significant high-frequency angioedema compared to enalapril halted the development of omapatrilat. The reason behind the high-frequency angioedema is the inhibition of multiple enzymes responsible for bradykinin degradation such as an ACE, neprilysin, and aminopeptidase leading to its high level [66-70]. An attempt was made with a combination of ARB and neprilysin inhibitor, despite the failure of exogenous NP, lone neprilysin inhibitor, and its combination with ACEIs. ARNI, a combination of ARB with neprilysin inhibitor, has the benefit of not affecting ACE mediated bradykinin degradation and associated risk of angioedema (Fig. 1).

Table 1: Stages of heart failure

Stage	Description
Stage A	Patients at risk of HF but without structural heart disease or symptoms, for example, patients with diabetes or hypertension
Stage B	Patients with structural heart disease but without symptoms, for example, asymptomatic LV dysfunction or patients with the previous myocardial infarction, patients with LV hypertrophy, or valvular heart disease. All of these patients are considered to be in NYHA Class I.
Stage C	Patients with structural heart disease with current or previous symptoms of HF, for example, patients with previous myocardial infarction and dyspnea. Their symptoms may be classified as NYHA I, II, III.
Stage D	Patients with refractory HF symptoms at rest despite maximal medical therapy or are hospitalized and require special interventions. For example, HF patients waiting for cardiac transplantation. All such patients are considered to be in NYHA IV class of symptoms

HF: Heart failure, LV: Left ventricular, NYHA: New York Heart Association

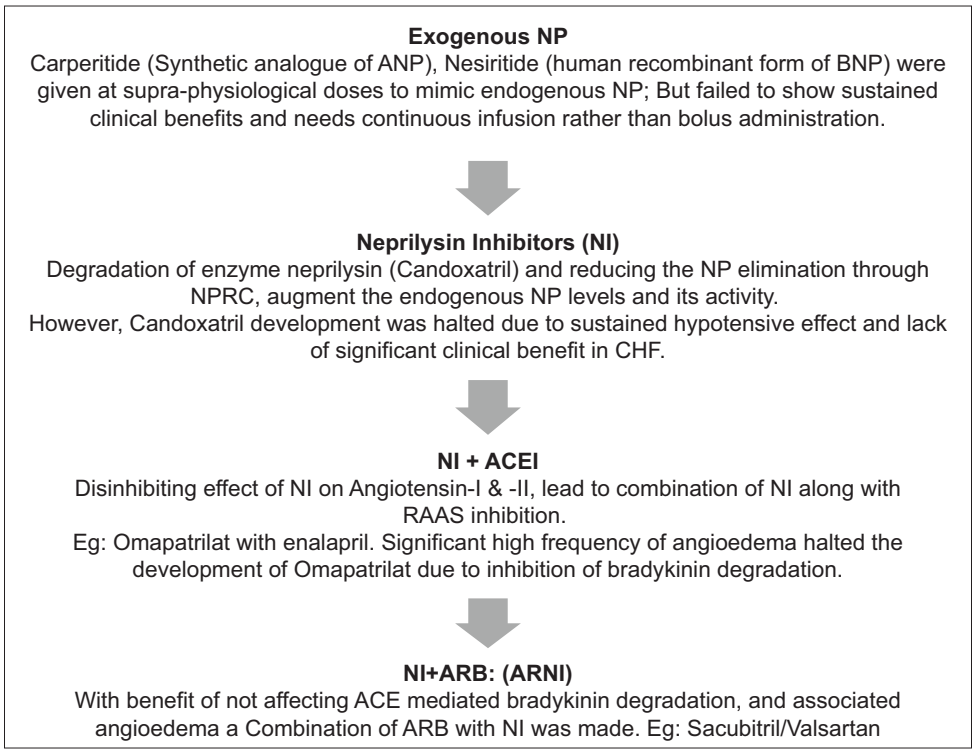

Fig. 1: Evolution of angiotensin receptor neprilysin inhibitors

ARNI

Sacubitril/Valsartan (LCZ696) is the first-in-class ARNI approved for the treatment of HF. It consists of the 1:1 combination of the valsartan, an ARB, and sacubitril, the neprilysin inhibitor [71-76]. On oral administration, through dissociation of combination, the prodrug sacubitril is converted to its active metabolite called sacubitrilat. Based on the half-lives of sacubitrilat and valsartan (approximately 12 and 9.9 h, respectively), this combination can be given twice daily to ensure neprilysin inhibition and RAAS inhibition around the clock [77-81]. Valsartan from valsartan formulation of sacubitril/valsartan combination has more bioavailability than conventional valsartan, due to 40% more systemic exposure per mg of drug [82]. Accordingly, the target dose of sacubitril/valsartan (97/103 mg twice daily) gives plasma concentrations of valsartan equivalent to 160 mg twice daily of the conventional compound with a sustained increase in cyclic guanosine monophosphate, reflecting the second-messenger response to the increase in NPs resulting from neprilysin inhibition by sacubitrilat [77,82].

Based on the findings of the landmark Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF (PARADIGM-HF) trial, the U.S. Food and Drug Administration approved sacubitril/valsartan combination in July 2015 for the treatment of patients with New York Heart Association (NYHA) Class II through IV HF symptoms and a reduced ejection fraction with elevated BNP, NT-proBNP levels. At present, the sacubitril/valsartan combination has been approved in more than 57 countries including India [83-86].

The existing cost-effective studies by the University of Utah and the Institute for Clinical and Economic Review made the drug to get good value by the American College of Cardiology (ACC), American Heart Association, and World Health Organization based on the accepted cost-effectiveness in the United States [87-89]. Similar findings from a cost-effectiveness study from the perspective of the Swiss health-care system supports ARNI treatment in HFrEF individuals [90]. However, the Singapore based cost-effective analyses for the patients with HFrEF revealed that the drug ARNI may not signify good value based on their current health expenditures [91]. In the meantime, in the absence of such cost-effective analyses, the generalization of findings to Indian patients may not be justifiable. Therefore, it would necessitate individualizing ARNI treatment to each patient after discussion of costs and benefits of therapy.

CLINICAL PRACTICE GUIDELINES RECOMMENDATIONS

Promising results obtained from the PARADIGM-HF trial made the guidelines to be updated. The 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF emphasizes the sequence of using the standard therapies, and its optimization such as ACEIs or ARBs, beta-blockers, and MRA before initiating ARNI [34] (Table 2). The 2017 ACC/AHA/HF Society of America (HFSA) focused update on new pharmacological therapy for HF has given Class 1 recommendation for ARNI or ACEIs or ARBs along with beta-blockers and MRA to reduce the mortality in HFrEF, and also recommended substitution of ACEI or ARB with ARNI in chronic HF patients who have a place in NYHA Class II or III to reduce the morbidity and mortality. In the view of angioedema, Class III recommendation is given to administer ARNI with or within 36 h of ACEI, or to patients with prior history of angioedema (Table 3) [92].

Table 2: The ESC guidelines recommendation of ARNI

Class of recommendation	Level of evidence	ESC guidelines recommendations
I	B	Sacubitril/valsartan is recommended as a replacement for ACE-I to further reduce the risk of hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker, and an MRA
I	A	Treatment with beta-blockers, MRA, and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias (as for other patients)

ACE-I: Angiotensin-converting enzyme inhibitors, ARNI: Angiotensin receptor neprilysin inhibitor, ESC: European Society of Cardiology, HF: Heart failure, HFrEF: Heart failure with reduced ejection fraction, MRA: Mineralocorticoid receptor antagonist

Table 3: The ACC/AHA/HFSA guidelines recommendation of ARNI

Class of recommendation	Level of evidence	ACC/AHA/HFSA guidelines recommendations
I	B-R	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (level of evidence: A), OR ARBs (level of evidence: A), OR ARNI (level of evidence: B-R) in conjunction with evidence-based beta-blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality
I	B-R	In patients with chronic symptomatic HFrEF NYHA Class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce mortality and morbidity
III	B-R	ARNI should not be administered concomitantly with ACE inhibitors or within 36 h of the last dose of an ACE inhibitor
III	C-EO	ARNI should not be administered to a patient with a history of angioedema

ACC: American College of Cardiology, ACE: Angiotensin-converting enzyme, AHA: American Heart Association, ARB: Angiotensin receptor blocker, ARNI: Angiotensin receptor neprilysin inhibitor, HFrEF: Heart failure with reduced ejection fraction, HFSA: Heart Failure Society of America, NYHA: New York Heart Association

CLINICAL USES [33]

- In patients with symptomatic HFrEF, preference should be given to ARNI as compared to ACEI/ARB, if the cost of drug therapy is not an issue
- Although initiating dose of ARNI is 49/51 or 100 mg BD, it should be started at a low dose of 24/26 or 50 mg BD in elderly patients, in patients with the lower systolic BP, patients who are inexperienced with ACEI/ARB, chronic kidney disease (CKD) patients with severe reduction of eGFR, < 30mL/min/1.73m^2 (CKD stage G4, G5), and patients with moderate hepatic impairment
- Increase the dose after 2–4 weeks. To avoid the risk of angioedema a gap of at least 36 h should be kept between discontinuation of ACEI and initiation of ARNI
- In case of the development of hypotension in the patient, decrease the loop diuretic dose before decreasing the dose of ARNI.

ADVERSE EFFECTS [33]

- Hypotension, a dose-limiting side effect, with a fall of 4–6 mm Hg systolic BP seen in patients on ARNI independent of baseline BP. Symptomatic hypotension can be seen in patients with systolic BP <110 mm Hg

- Hyperkalemia, relatively less risk was observed as compared to enalapril even with MRA in the PARADIGM-HF trial.

CONCLUSION

Despite the global epidemic prevalence of HF, and its paradigmatic shift toward low- and middle-income countries, the better utilization of evidence-based clinical recommendations with a clear emphasis on individual patients' needs can minimize the futuristic burden in terms of morbidity and mortality.

AUTHORS' CONTRIBUTION

All the authors have contributed to the preparation and editing of this review article.

CONFLICTS OF INTREST

The authors declare that they have no conflicts of interest.

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