ROLE OF NEPRILYSIN INHIBITORS IN HEART FAILURE

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ABSTRACT

Despite the availability of many rationally designed drugs, Heart failure (HF) continues to be a major cause of morbidity and mortality. Invention of Angiotensin Converting Enzyme inhibitor (ACEI) is one the cornerstone of heart failure management. ACEI’s are able to prevent the worsening of cardiac failure by preventing myocyte apoptosis and myocardial remodelling. There is still an unmet need and search of potentiating endogenous compounds to facilitate cardiac function throws light on Neprilysin. Combined angiotensin and Neprilysin inhibitor is expected to create a greater impact in the treatment of heart failure.

Keywords
ACE inhibitors, Heart failure, Neprilysin inhibitors

Heart Failure:

More than 20 million people suffering from heart failure worldwide. Incidence of heart failure in developed countries is 2% and approaches 6-10% in people aged more than 65 years. Heart failure and its management needs considerable attention because of its prevalence and increased survival of patients undergoing heart surgery or with previous history of infarction or arrhythmias than the past. Rheumatic fever still a major cause of heart failure in Asian and African countries. In the developed and developing nations, Hypertension remains the most significant contributor for heart failure along with dyslipidaemia, diabetes and ischemic heart disease [7]. From symptomatic management by diuretics and oral inotropic agent digoxin, the advent of ACEI causes transition in treatment aspect of heart failure. The two distinct advantages of ACEI are good safety margin and ability to reverse the myocardial remodelling is the main reason for selecting them as first line management of heart failure even in asymptomatic high cardiovascular risk patients. Following ACEI, angiotensin receptor blockers (ARB’s), cardio selective beta blockers and aldosterone antagonist plays additive role in preventing myocyte damage.

Meeting the unmet need:

Even these days, prognosis of symptomatic heart failure is not promising, 30-40% of patients die within a year and more than 60% of patients die within five years of diagnosis. To meet the unmet, researchers have started addressing the cause myocardial injury due to oxidative stress, up regulation of vasoconstrictors molecules in endothelium has been done in recent years. Statins role in improving endothelial function is underway and endothelin antagonist also appears to be promising in heart failure. One of the successful approach was isolating and formulating the endogenous compound natriuretic peptide.

Role of natriuretic peptie and neprilysin pathophysiology of heart failure:

Natriuretic peptides are produced from atrium, brain and named as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) respectively, in addition to c-type natriuretic peptide (CNP). These peptides exert their action by binding natriuretic peptides receptors and activate guanyl cyclase and produces vasodilation. Brain Natriuretic peptide is produced by any factors that stretches atria and its plasma concentration is used as diagnostic tool in assessment of heart failure. Recently, the recombinant form brain

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natriuretic peptide, Nesiritide is indicated for acute severe heart failure and given as intravenous bolus infusion at the rate of 0.01-0.03μg/kg/minute.

Apart from vasodilation, pleiotropic effects of natriuretic peptide’s includes diuresis, decreased sympathetic activation and inhibition rennin angiotensin system, decreases mesangial cell proliferation, attenuation of endothelins, control of and smooth muscle cells and fibroblast proliferation in the vessels [8,9].

Neprilysin is a metalloproteinase enzyme. It degrades many vasoactive and other peptides like natriuretic peptides, bradykinin, angiotensin etc. This was targeted and found to be rational that inhibition of Neprilysin will result in accumulation of endogenous peptides and results in pronounced diuresis, more vasodilation, attenuation of rennin angiotensin activation and fall in blood pressure [10, 11, 12, 13, 14].

The combined Neprilysin and angiotensin converting enzyme inhibitors are known as vasopeptidase inhibitors. Two molecules, namely samapatrilat and omapratilat came into existence of which omapratilat undergone many clinical trials for its efficacy and safety. Large trial involving nearly 25000 patients was done with omapatrilat known as Omapratilat cardiovascular treatment versus enalapril (OCTAVE), 24 weeks, randomized, active controlled study. Omapatrilat was started with 10 mg and increased to 80 mg OD, similarly enalapril was 5 mg d and titrated to 40 mg d. Blood pressure reduction with omapatrilat was non inferior to enalapril. Angioedema was the most the striking adverse effect seen with omapatrilat, from the OCTAVE it was concluded 274 patients develop
angioedema in omapatrilat group and 86 patients in enalapril group in 2000, sponsors Bristol Meyer Squibb withdrew their new drug application (NDA) from Food and drug administration (FDA), United States. In another study namely (CV 137037), 10 week active controlled study of omapatrilat 40 mg d and lisinopril 10 mg d, the efficacy of omapatrilat was proved without antecedent angioedema [5].

These combined angiotensin converting enzyme inhibitor, also known as vasopeptidase inhibitors or super ACE inhibitors due to synergistic inhibitors of endogenous peptides. Reason for angioedema is sought to be increased level of bradykinin and angiotensin by omapatrilat. Bradykinin levels were increased more than 10 fold on patients developed angioedema following treatment with omapatrilat. This adverse event was found to be more dose dependent. Incidence of angioedema is a recognised complication of ACEI is very less, but escalates when it is combined with Neprilysin inhibitors [5].

The expected other beneficial actions are Omapatrilat are decreasing the proteinuria in chronic kidney disease, anti anginal effects and reducing left ventricular hypertrophy. Though omapatrilat was considered as magic bullet in the cardiac failure treatment, the adverse effects were unsolved and FDA announced to stop further clinical trials with omapatrilat. Nevertheless, it was just hibernation not the end of Neprilysin inhibitors.

**Reborn of neprilysin inhibitors:**

Angiotensin converting enzyme inhibitors producing angioedema due to inhibiton of bradykinin metabolism is superceded by angiotensin receptor blockers (ARB’s). The same approach has been utilised to re introduce neprilysin inhibitors with angiotensin receptors blockers . The combination is known as Angiotensin receptor neprilysin inhibitors (ANRI’s). LCZ696 is the first angiotensin neprilysin inhibitor , this molecule comprises of angiotensin receptor blocker valsartan and neprilysin inhibitor AHU377. This molecule successive passed pre clinical studies , very effective in various animal model of hypertension like stroke prone rats , spontaneous hypertensive rats model etc. Pharmacokinetic analysis of angiotensin receptor neprilysin inhibitors in humans showed their maximum plasma concentration achieved in 1.6-4h[2].

**Clinical trails with ARNI’s**

A significant trial was done in heart failure patients with preserved ejection fraction known as PARAMOUNT in which 371 patients were enrolled and randomized to receive either valsartan alone or LCZ696 . Study concludes LCZ696 showed greater reduction in blood pressure than valsartan group. The drug was well tolerated with single case of angioedema . LCZ696 is undergoing extensive clinical trial by Novartis namely Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) in which LCZ696 is compared with angiotensin converting enzyme inhibitor , enalapril . Incidence of heart failure , frequency of hospitalisation , incidence of atrial fibrillation are being analyzed . This phase III multi centric trials now comprises of more than ten thousand patients evaluated for endpoints mentioned above . Another studied is also planned to compare LCZ696 with an angiotension receptor blocker in heart failure patients namely PARAGON-HF [1]. The anticipated action of antiprotenuirc effects from animal models is also examined in UK-HARPIII trial in which LCZ696 and irbesartan is compared in 360 chronic kidney disease patients. Results are yet to be known to find its efficacy in those patients.

**Conclusion:**

Angiotensin Neprilysin inhibitors are showing their efficacy in reducing worsening of heart failure, number of hospitalisation due to heart failure .Overall long term efficacy and safety is yet to be studied in detail. Success of this group of drugs may be more beneficial for heart failure management.
REFERENCES:


