

# Angiotensin-neprilysin inhibition vs. enalapril in heart failure

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## Abstract:

**Background:** This is a small trial where we compared the angiotensin receptor–neprilysin inhibitor ARNI with enalapril in patients with heart failure and reduced ejection fraction.

**Methods:** In this single centre trial, we randomly assigned 512 patients with class II, III Heart failure and an ejection fraction of 35% or less to receive either ARNI or enalapril. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

**Results:** Death from cardiovascular causes or hospitalization for heart failure (the primary endpoint) occurred in 42 patients in ARNI group compared to 63 in enalapril group (hazard ratio, 0.67; 95% CI, 0.47 to 0.94;  $p=0.022$ ). 23 people died in ARNI and 31 in enalapril group due to cardiovascular causes (hazard ratio, 0.74; 95% CI, 0.44 to 1.21;  $p=0.251$ ). 26 patients were hospitalized for heart failure in ARNI group, as compared with 36 patients receiving enalapril (hazard ratio, 0.72; 95% CI, 0.45 to 1.16;  $p=0.177$ ). 33 patients in the ARNI group and 45 patients in the enalapril group died (hazard ratio for death from any cause, 0.74; 95% CI, 0.49 to 1.11;  $p=0.141$ ).

**Conclusion:** ARNI was superior to enalapril in reducing the risks of death and of hospitalization for heart failure.

**Keywords:** Angiotensin • Neprilysin • Heart attack • Enalapril • Cardiovascular disorders

## Introduction

Heart Failure (HF) is defined as a complex clinical syndrome, and can result from any structural or functional cardiac disorders which impair the ability of ventricles to fill with or eject blood [1-3]. The incidence of HF in India is rising as a result of an ageing population and increasing numbers of patients living longer with chronic cardiovascular disease; HF is one of the leading causes of hospitalization in adults in India [3,4]. There have been considerable advances in the pharmacological management of HF over the past 20 years. Anti-heart failure medications, including beta-blockers, ACEIs (angiotensin-converting enzyme inhibitors), ARBs (angiotensin receptor blockers), and aldosterone antagonists, improve the chances of survival in HF patients [5-9]. However, even with optimal anti-failure medical treatment, the mortality and morbidity of patients with advanced HF remain high, with almost 50% mortality at 5 years [1,2].

Inhibition of neurohumoral pathways such as the renin angiotensin aldosterone and sympathetic nervous systems is central to the understanding and treatment of Heart Failure (HF). Conversely, until recently, potentially beneficial augmentation of neuro humoral systems such as the natriuretic peptides has had limited therapeutic success [10,11]. Administration of synthetic natriuretic peptides has not improved outcomes in acute HF but modulation of the natriuretic system through inhibition of the enzyme that degrades natriuretic (and other vasoactive) peptides, neprilysin, has proven to be successful. After initial failures with neprilysin inhibition alone or dual neprilysin-Angiotensin Converting Enzyme (ACE) inhibition, the Prospective comparison of angiotensin receptor neprilysin inhibitor (ARNI) with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) trial demonstrated that morbidity and mortality can be improved with the angiotensin receptor blocker neprilysin inhibitor sacubitril/valsartan (formerly LCZ696).

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In comparison to the ACE inhibitor enalapril, sacubitril/valsartan reduced the occurrence of the primary end point (cardiovascular death or hospitalization for HF) by 20% with a 16% reduction in all-cause mortality [3]. These findings suggest that sacubitril/valsartan should replace an ACE inhibitor or angiotensin receptor blocker as the foundation of treatment of symptomatic patients (NYHA II–IV) with HF and a reduced ejection fraction. We designed this small trial to evaluate prospectively sacubitril/valsartan with enalapril in HFrEF patients coming to our hospital Coronary Care Unit.

## Material and Methods

### Study design

Patients of Heart failure admitted to ICCU of RMLIMS from May 2016 to June 2018 with Ejection fraction 35% or less and NYHA Class II or III were enrolled in this study after stabilization. All were receiving optimal medical therapy. They were randomized into two groups one received ARNI (starting at 100 mg twice daily and uptitrated to 200 mg twice daily) over and above the OMT and the other was given Enalapril at a dose of 10 mg twice daily.

Patients were evaluated at 15 days and 30 days for any features of heart failure, adverse events, renal dysfunction. Additional visits were planned at 3, 6 and 12 months after randomization.

### Study patients

This is a prospective randomised single centre trial on HFrEF patients admitted in Ram Manohar Lohia Institute of Medical Sciences. We enrolled patients with ejection fraction of 35% or less and New York Heart Association (NYHA) class II, III symptoms.

Patients were on optimal medical therapy including an angiotensin-converting-enzyme inhibitor, or angiotensin-receptor blocker, plus a beta-blocker, and MRA and a diuretic where required [6-9]. Exclusion criteria include symptomatic hypotension, a systolic blood pressure of less than 100 mmHg, eGFR <30 ml/min/1.73 m<sup>2</sup>, history of angioedema, any adverse side effects of ARNI or Enalapril (Table 1).

Characteristic	ARNI(N=256)	Enalapril(N=256)
Age-yr	57.6 ± 09.4	58.2 ± 9.8
Female sex-no. (%)	49(19.1)	52(20.3)
Systolic blood pressure-mm Hg	117 ± 13	116 ± 14

Heart rate-beats/min	78 ± 11	77 ± 12
Serum creatinine-mg/dl	1.08 ± 0.6	1.09 ± 0.6
Clinical features of heart failure		
Ischemic cardiomyopathy-no. (%)	97(37.8)	99(38.6)
Left ventricular ejection fraction-%	28.3 ± 7.2	28.6 ± 6.9
NYHA functional class-no. (%)		
II	62(24.4)	65(25.4)
III	194(75.6)	191(74.6)
Medical history-no. (%)		
Hypertension	130(50.7)	131(51.2)
Diabetes	77(30.0)	76(29.6)
Myocardial infarction	82(32.0)	84(32.8)
Pretrial use of ACE inhibitor	164(64.0)	162 (63.2)
Pretrial use of ARB	87(33.9)	88(34.3)

### Study outcomes

The primary outcome was a composite of death from cardiovascular causes or a first hospitalization for heart failure.

The secondary outcomes were the time to death from any cause, the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) [5] (on a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure), and the time to the first occurrence of a decline in renal function (which was defined as end-stage renal disease or as a decrease in the eGFR of at least 50%).

### Statistical analysis

Statistical significance of differences among the groups of patients was tested using the Fischer exact or chi-square test. Effect of Sacubitril/valsartan vs. Enalapril with respect to end points. All the analysis was carried out by using SPSS 21.0 version (Chicago Inc. USA). We analyzed the total symptom score on the Kansas City Cardiomyopathy Questionnaire [5] as a composite, rank-based outcome, incorporating patient vital status at 8 months along with a change in score from baseline to 8 months (Table 2).

**Table 2:** Primary and secondary outcomes.

Outcome	ARNI(N=256)	Enalapril(N=256)	Hazard Ratio or Difference (95% CI)	P-Value
Primary composite outcome-no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	42(16.4)	63(24.6)	0.67(0.47-0.94)	0.022
Death from cardiovascular causes	23(9.0)	31(12.1)	0.74(0.44-1.23)	0.251
First hospitalization for worsening heart failure	26(10.1)	36(14.0)	0.72(0.45-1.16)	0.177
Secondary outcomes-no. (%)				
Death from any cause	33(12.8)	45 (17.6)	0.74(0.49-1.11)	0.141
Change in KCCQ clinical summary score at 8 mo	-1.56 ± 0.72	-2.34 ± 0.64	0.78 ± 0.68	0.089
Decline in renal function	04(1.5)	05(1.9)	0.80(0.22-2.94)	0.737

## Results

Death from cardiovascular causes or hospitalization for heart failure (the primary endpoint) occurred in 42 patients in ARNI group compared to 63 in enalapril group (hazard ratio, 0.67; 95% CI, 0.47 to 0.94;  $p=0.022$ ). 23 people died in ARNI and 31 in enalapril group due to cardiovascular causes (hazard ratio, 0.74; 95% CI, 0.44 to 1.21;  $p=0.251$ ). 26 patients were hospitalized for heart failure in ARNI group, as compared with 36 patients receiving enalapril (hazard ratio, 0.72; 95%CI, 0.45 to 1.16;  $p=0.177$ ). 33 patients in the ARNI group and 45 patients in the enalapril group died (hazard ratio for death from any cause, 0.74; 95% CI, 0.49 to 1.11;  $p=0.141$ ).

The mean change from baseline to month 8 in the KCCQ clinical summary score was a reduction of 1.56 points in the ARNI group and a reduction of 2.34 points in the enalapril group (between-group difference, 1.64 points; 95% CI, 0.78 to 1.46;  $p=0.089$ ). 4 patients in the ARNI group and 5 patients in the enalapril group had a decline in renal function ( $p=0.737$ ).

## Safety

Symptomatic hypotension was reported more frequently in the ARNI arm compared to enalapril arm (16% vs. 4.6%) but discontinuation of medication was rarely required. Cough was reported more frequently in the enalapril arm than the ARNI group.

There were no significant changes from baseline in heart rate or serum creatinine level between the two groups. The benefit of ARNI seen in this trial is significant in the sense that these individuals were already on Optimal Medical Therapy and in relatively sicker cohort and specific to the Indian population (Table 3).

**Table 3:** Adverse events during randomized treatment.

Event	ARNI(N =256)	Enalapril(N= 256)
Hypotension symptomatic	41 (16.0)	12(4.6)
Elevated serum creatinine		
≥ 2.0 mg/dl	04(1.5)	05(1.9)
Cough	474(11.3)	601(14.3)

## Discussion

A strategy of dual RAAS blockade and natriuretic peptide augmentation [10,11] is theoretically attractive in heart failure and was tried previously with the dual neprilysin/ACE inhibitor omapatrilat in the Omapatrilat vs. Enalapril Randomized Trial of Utility in Reducing Events trial (OVERTURE) [4]. Although omapatrilat did not reduce the primary endpoint of death or hospitalization for heart failure requiring intravenous treatment, compared with enalapril 10 mg b.i.d., it was superior to enalapril in relation to the secondary end point of CV death or CV hospitalization. Furthermore, when the effect of omapatrilat on the primary endpoint was evaluated, retrospectively, using the same definition of hospitalization for heart failure as had been used in the Studies of Left Ventricular Dysfunction Treatment-trial (SOLVD-Treatment), where the use of intravenous therapy was not required for positive adjudication, omapatrilat was superior to the use of enalapril. Furthermore, administration of a single, large, dose of omapatrilat once daily may have on the one hand caused excessive post-dose hypotension and on the other not provided complete 24 hr RAAS blockade or 24 hr neprilysin inhibition. Ultimately, however, because omapatrilat caused an unacceptable incidence of angioedema in patients with hypertension, its development was halted. And then studies with ARNI or LCZ696 were conducted and the results were heartening.

The first major trial with LCZ696 was the PARADIGM-HF trial [3]. Results from PARADIGM-HF were extremely promising and overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome occurred in 21.8% patients in the LCZ696 group and 26.5% patients in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% Confidence Interval [CI], 0.73 to 0.87;  $p < 0.001$ ). About 17.0% patients receiving LCZ696 and 19.8% patients receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93;  $p < 0.001$ ); of these 13.3% patients and 16.5% respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89;  $p < 0.001$ ). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% ( $p < 0.001$ ) and decreased the symptoms.

Our study design is quite similar to PARADIGM-HF and our purpose was to see whether ARNI has similar benefits in Indians and in our patient cohorts. In our small study of patients with heart failure and reduced ejection fraction, the primary endpoints of the risk of death from cardiovascular causes or hospitalization for heart failure was significantly less in the ARNI group compared to patients on Enalapril. There was a trend towards lower cardiovascular mortality and hospitalization in the ARNI arm but it did not reach statistical significance unlike the PARADIGM-HF [12,13].

No serious side effects were noted in the ARNI arm which warranted drug withdrawal. As expected, symptomatic hypotension was numerically more in the ARNI group but this too did not lead to any additional drug termination. There was no increase in renal complications like rise in the levels of creatinine.

### Conclusion

Most of our patients received full doses of the drugs whether on enalapril or ARNI, as these dosages have been found to provide mortality benefit in Heart failure patients though the doses were slowly uptitrated.

But unlike PARADIGM-HF a larger percentage of our patients were in Class III, almost 75% because we enrolled our patients mainly from the admitted cohort as they are more receptive to novel therapies and easier to convince. So definitely our patients were sicker and probably that is the reason that we do not see the kind of benefits accrued in PARADIGM-HF.

Though our trial was small, but it has significance in that probably it's first of its kind in this part of the world and holds value for our indigenous patients. And we can safely conclude that ARNI

is as good and safe as ACE I in HFrEF with probable additional mortality benefit and improved quality of life.

### Financial Support

None

### Conflicts of Interest

The authors have no conflicts to disclose.

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## Research Article

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