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Research Article

A STUDY OF ANGIOTENSIN–NEPRILYSIN INHIBITOR VERSUS ENALAPRIL IN HEART FAILURE WITH REDUCED EJECTION FRACTION IN A TERTIARY CARE HOSPITAL IN EASTERN INDIA

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A B S T R A C T

Angiotensin-converting–enzyme (ACE) inhibitors have been the cornerstone of the treatment for heart failure and a reduced ejection fraction for nearly 25 years, since enalapril was shown to reduce the risk of death in two trials.[1,2]. The effect of angiotensin-receptor blockers (ARBs) on mortality has been inconsistent,[3,4]. Combined inhibition of ACE and neprilysin was associated with serious angioedema. In our study we have compared the angiotensin receptor–neprilysin inhibitor (sacubitril- valsartan) with enalapril in patients who had heart failure with a reduced ejection fraction.

INTRODUCTION

Heart failure (HF) is a clinical syndrome that occurs in patients who, because of an inherited or acquired abnormality of cardiac structure and/or function, develop a constellation of clinical symptoms (dyspnoea and fatigue) and signs (oedema and rales) that lead to frequent hospitalizations, a poor quality of life, and a shortened life expectancy.[5]

Heart failure is a burgeoning problem worldwide, with more than 20 million peoples affected. The overall prevalence of HF in the adult population in developed countries is 2%. HF prevalence follows an exponential pattern, rising with age, and affects 6-10% of people over age 65. Reliable estimates of heart failure are lacking in India because of the absence of a surveillance programme to track incidence, prevalence, outcomes and key causes of heart failure.

The prevalence of heart failure in India due to coronary heart disease, hypertension, obesity, diabetes and rheumatic heart disease has been conservatively estimated to range from 1.3 to 4.6 million, with an annual incidence of 4, 91, 600–1.8 million. In spite of optimal medical therapy, heart failure (HF) may progress with unpredictable episodes of worsening.

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Angiotensin-converting–enzyme (ACE) inhibitors have been the cornerstone of the treatment for heart failure and a reduced ejection fraction for nearly 25 years, since enalapril was shown to reduce the risk of death in two trials.[2,3] Long-term treatment with enalapril decreased the relative risk of death by 16% among patients with mild-to-moderate symptoms.[2]

Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin.[6] Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling.[7] Combined inhibition of the renin–angiotensin system and neprilysin had effects that were superior to those of either approach alone in experimental studies,[8] but in clinical trials, the combined inhibition of ACE and neprilysin was associated with serious angioedema.[9]

LCZ696, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan, was designed to minimize the risk of serious angioedema.[10] In small trials involving patients who had hypertension or heart failure with a preserved ejection fraction, Sacubitril/Valsartan had hemodynamic and neurohormonal effects that were greater than those of an ARB alone.[11] We will examine whether the long-term effects of Sacubitril/Valsartan on morbidity and mortality were superior

to those of ACE inhibition with enalapril in patients with chronic heart failure and a reduced ejection fraction.
We will compare the angiotensin receptor–neprilysin inhibitor (sacubitril- valsartan) with enalapril in patients who had heart failure with a reduced ejection fraction.

Material and methods

Both OPD and Indoor Patients from Cardiology Departments, clinically diagnosed as Heart Failure supported by objective evidence of cardiac dysfunction: either a LVEF < 50% satisfying the inclusion & exclusion criteria had been taken as study population.

Inclusion Criteria

1. Age of at least 18 years.
2. New York Heart Association (NYHA) class II, III, or IV symptoms.
3. An ejection fraction of 50% or less

Exclusion Criteria

1. In patients with hypersensitivity to any component.
2. In patients with a history of angioedema related to previous ACE inhibitor or ARB therapy.
3. In patients who are pregnant given risk of foetal toxicity including foetal death.
4. Who are not willing to give consent.
5. Severe hepatic impairment.
6. Renal impairment
7. Breastfeeding mother.

Patients taking any dose of an ACE inhibitor or ARB are considered for participation, but for at least 4 weeks before screening, patients were required to take a stable dose of a beta-blocker and an ACE inhibitor (or ARB) equivalent to at least 10 mg of enalapril daily.

Detailed history was taken from the patient or patients' attendants attending Cardiology and Medicine OPD and Indoor satisfying the inclusion criteria.

d) Full clinical examination was done and was recorded in pre-designed schedule.
e) Reports of blood parameters was collected and reviewed.
f) Echocardiography (2D, M-mode and Doppler) was performed by following mentioned procedure and results were documented.
g) Patients were put on guideline directed medical therapy and followed up monthly, during emergency visits and hospitalizations with the parameters mentioned for six months.

Result and analysis

The mean level of LVEF of cases and controls at the start of the study were both 32.86%. That level at the end of the study was 40.12% and 35.9% respectively for cases and controls. This finding was statistically very much significant.

Mean changes in ejection fraction was 7.2% anongst patients receiving sacubitril/valsartan, compared to 3.04% changes in patients receiving enalapril, after the stipulated study end period. This was highly statistically significant.

Regarding no of hospitalisation(patient-year), it has been found that sacubitril/valsartan group has total 18 patient-year of hospitalisation in comparison with enalapril group which has 48 patient years of hospitalisation. This was satatistically significant as shown by Mann-whitney test.

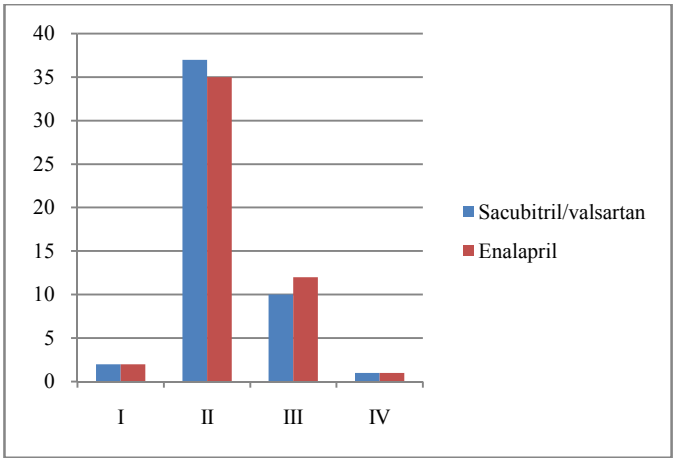

Fig 1 Distribution of NYHA class amongst the patients in both groups at the start of the study

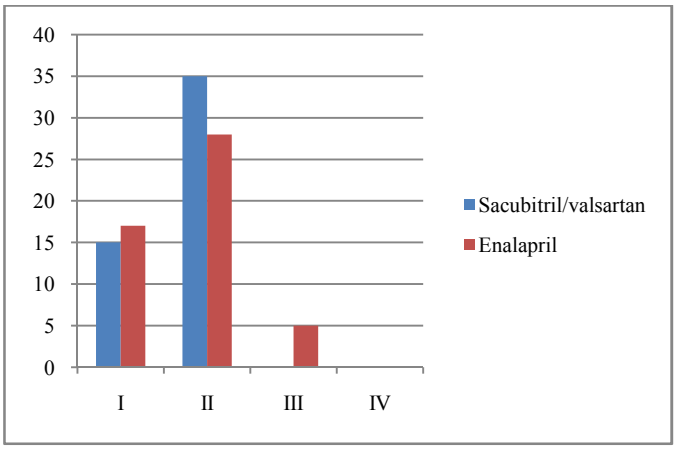

Fig 2 Distribution of NYHA class amongst the patients in both groups at the end of the study

This two chart (Fig 1, fig 2) shows that there is significant improvements in NYHA class in sacubitril/valsartan group in comparison with enalapril at the end of the study.

The mean level of serum K at the start of the study was 4.438 meq/ml while that of controls were 4.2 meq/ml. That level at the end of the study was 4.678meq/ml and 4.742meq/ml respectively**.**

The mean level of serum creatinine at the start of the study was 0.938mg/dl while that of controls were 0.94 mg/dl. That level at the end of the study was 1.10 and 1.09 mg/dl respectively**.**
There was few episodes of hypotension in both the groups, with slightly more in sacubitril/valsartan group, which was statistically insignificant.

DISCUSSION

The Prospective Comparison of ARNI with ACE inhibitors (ACEi) to Determine Impact on Global Mortality and Morbidity in Hart Failure Trial (PARADIGM-HF) [12] is a

randomized, double blind and event-driven trial designed to investigate the effect of sacubitril/valsartan compared with enalapril in patients with chronic and symptomatic HF.

50 cases and 50 controls were selected for this study using the selection criteria established in materials and methods. In this study 66% of cases were male and 34% of cases were female; whereas 62% of controls were male and 38% were female. Mean age of cases was 61.96 ± 11.80 year (mean ± 1S. D.) and that of control was 53.44 ± 11.03 year. The mean age of our cohort was almost similar to PARADIGM-HF trial[12]. Male sex is independent risk factor for congestive heart failure which is evident in this study as we can see that nearly two-third of cases was male.

56% of the cases were from middle socio-economic status, of them 67.85% were male and 32.15% were females. 44% of the cases were from low socio-economic status, of them 63.64% were males and 36.36% were females. Among controls 2%, 48%, and 50% were from upper, middle, and lower socio-economic status.

Cigarette smoking has been accepted as a risk factor for heart failure. There is a dose – response relationship, males and females are equally affected. The mechanism whereby smoking may exert these effects is by vessel wall changes (atherogenesis) and hematological effects and the relative impact of each of these mechanisms may vary depending on the age of the patient. Smoking may be a more potent risk factor in younger patients and in this group hematological effects may predominate. The duration of smoking may be more important than total daily dose and cessation of smoking may diminish but perhaps may not abolish the risk of heart failure. Healthcare settings provide an important teachable moment for smokingcessation intervention. Seventy-five percent of the adult populationvisits a physician at least once a year, with the average adultmaking five visits per year. In the physician's office, patients areoften conscious of their health and most receptive to risk factor intervention,providing an important opportunity for change. A number ofstudies have documented that physician-delivered counselingintervention for smoking cessation can be effective (*Ira S. Ockene et al*).

In our study among cases, 30 out of 33 male (90.99%) were smoker, whereas only 6 out of 17 female (35.29%) were smoker. In control group, 12 out of 31 (38.71%) male were smoker and 7 out of 19 (36.84%) female were smoker.

The baseline characteristics of both groups in our study were as follows: SBP (mmHg) was 122 ± 26 in sacubitril/valsartan group and 121 ±15 in enalapril group at the start of the study. Serum Creatinine (mg/dl) was 0.938±0.22 in sacubitril/valsartan group and 0.941±0.23 in enalapril group. LVEF (%) was 32.86±5.86 in sacubitril/valsartan group and 32.82±5.9 in enalapril group. This was very closely matched with the PARADIGM-HF trial[12]. Amongst the patients 60% in sacubitril/valsartan group and 58% in enalapril group had a diagnosis of ischemic cardiomyopathy and rest of the patients had a diagnosis of dilated cardiomyopathy. The incidence of atrial fibrillation was 36% and 38% in sacubitril/valsartan and enalapril group respectively. The incidence of DM was 34% and 38% in sacubitril/valsartan and enalapril group respectively. Pre-trial use ACEi, ARB, Beta blocker and MRA were 78%, 22%, 90%, 60% in sacubitril/valsartan group and 80%, 20%, 90%, 58% in enalapril group respectively. This characteristic also closely follows the PARADIGM-HF trial[12.] The NYHA functional class amongst sacubitril/valsartan group was 4%/74%/20%/2% for NYHA I, II, III, IV and it was 4%/70%/24%/2% for enalapril group. At the end of the study it has been shown that all the patients from sacubitril/valsartan was in within NYHA I/II category and none of them was in NYHA III/IV category. Whereas 10% of the patients were in NYHA III category in enalapril group after completion of study. These differences were statistically significant ($p<0.05$). The SBP after the end of the study was almost identical in both the groups. It was 116±26 mm of hg in sacubitril/valsartan group and 118± 18 mm of hg in enalapril group. However, in sacubitril/valsartan group 3 of the patients has to hold the therapy for symptomatic hypotension.

The mean level of urea at the start of the study was 30.70 mg/dl while that of controls were 30.44 mg/dl. That level at the end of the study was 31.80 and 31.64 mg/dl respectively. It does not show significant changes in both the groups.

The mean level of serum creatinine at the start of the study was 0.938mg/dl while that of controls were 0.94 mg/dl. That level at the end of the study was 1.10 and 1.09 mg/dl respectively. Both the groups has showed the tendency in increse of serum creatinine but there is very little difference between both the groups and it was statistically insignificant ($p > 0.05$). one interesting finding is that in sacubtril/valsartan group 5 patients has raised creatinine level more than 2.5mg/dl, whereas 3 patients has devaloped creatinine level of more than 2.5mg/dl in enalapril arm.

The mean level of serum Na at the start of the study was 133.86meq/ml while that of controls were 133.88meq/ml. That level at the end of the study was 133.72meq/ml and 134.46meq/ml respectively. There is little differences between both the groups here.

The mean level of serum K at the start of the study was 4.438meq/ml while that of controls were 4.2meq/ml. That level at the end of the study was 4.678meq/ml and 4.742meq/ml respectively. Both the groups has shown tendency to have raised serum potasium level. There is little differences between both the groups here. 8 patients from sacubitril/valsartan group and 10 patients from enalapril group has devaloped serum potassium level of more than 5.5 mg/dl and one patient from sacubitril/valsartan group needed to stop the drug due to symptomatic hyperkalemia with serum potasium level of more than 6mg/dl.

In PARADIGM-HF Trial[12] After randomization, symptomatic hypotension and nonserious angioedema were more common in the sacubitril/valsartan group but renal deterioration (creatinine level $\geqslant$ 2.5 mg/dl), cough and hyperkalemia (serum potassium $\geqslant$ 6.0 mmol/l) occurred more frequently with enalapril.

The mean level of LVEF of cases and controls at the start of the study were both 32.86%. That level at the end of the study was 40.12% and 35.9% respectively for cases and controls. Mean changes in ejection fraction was 7.2% anongst patients receiving sacubitril/valsartan, compared to 3.04% changes in

patients receiving enalapril, after the stipulated study end period. This was highly statistically significant($p<0.05$). LVEF was documented as a
significant and independent predictor of all outcomes and sacubitril/valsartan was effective across its entire spectrum and there was no evidence of heterogeneity for the primary endpoint (p interaction = 0.87), CV death (p interaction = 0.55), HF hospitalization (p interaction = 0.78) and all cause mortality (p interaction = 0.93) **[Solomon *et al*. 2016].**

Regarding no of hospitalisation(patient-year), it has been found that sacubitril/valsartan group has total 18 patient-year of hospitalisation in comparison with enalapril group which has 48 patient years of hospitalisation. This was satatistically significant as shown by Mann-whitney test ($p<0.05$). in PARADIGM-HF Trial it has been found that Patients treated with sacubitril/valsartan were less likely to be hospitalized for HF (one or multiple times) with 23% fewer hospitalizations for worsening HF ($p < 0.001$), 16% lesser hospitalizations for CV reason ($p < 0.001$), 15.6% lesser hospitalizations for any reason ($p < 0.001$) and 29% fewer HF hospitalizations (more than once; $p = 0.001$). Diminution in HFH with sacubitril/valsartan was patent within the first 30 days after randomization.

We do not found serious angioedema in both the groups. Intractable cough was more in the enalapril group than in sacubitril/valsartan group.

We have found that sacubtril/valsartan is superior to enalapril in improving ejection fraction, heart failure related hospitalisation and improvement of NYHA class of the patient. It is relatively safer than enalapril regarding cough, hyperkalemia. However symptomatic hypotension was common in sacubitril/valsartan group than in enalapril group. Incidence of serious angioedema was not significant in both the groups.

CONCLUSION

ACEis have been the cornerstone of HF with reduced EF treatment for more than 25 years since enalapril was found to improve survival which was the beginning of an 'effective disease modifying drugs' era [CONSESUS Trial Study Group, 1987; SOLVD Investigators, 1991]. Sacubitril/valsartan which consists of the NEP inhibitor sacubitril and the ARB valsartan has shown to be superior to the ACEi enalapril, reducing the risk of death and HFH, facts that were consistent all across different studied subgroups or populations. In addition, sacubitril/valsartan was more effective at improving symptoms and preventing clinical deterioration in surviving patients.

Our study is a small-scale study in the eastern region of India, where there is lack of constructive data regarding the use of sacubitril/valsartan and its benefits as proved in PARADIGM-HF study. We have concluded that

1. Sacubitril/valsartan is superior to enalapril in reducing heart failure related hospitalisation.
2. Sacubitril/valsartan is superior to enalapril in improvements of ejection fraction.
3. Sacubitril/valsartan is superior to enalapril in improvements of functional class of the patients.
4. We do not find serious angioedema in both the groups.
5. Intractable cough was more in the enalapril group than in sacubitril/valsartan group.
6. However symptomatic hypotension was common in sacubitril/valsartan group than in enalapril group.
7. More patients in the enalapril has devaloped hyperkalemia in enalapril group in comparison with sacubitril/valsartan group.
8. Both the groups has showed the tendency in increse of serum creatinine but there is very little difference between both the groups and it was statistically insignificant ($p > 0.05$).
9. Most of the findings closely relates with the PARADIGM-HF study.
10. There was no death reported in both the groups.
11. Therefore, it is our view that an ARNI should replace an ACE inhibitor (or an ARB) as a foundation of treatment for HF-REF and already this view is reflected in new guideline.

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Conflicts of interest:There is no conflicts of interest.
Legend for figures

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