Innovative Journal of Medical and Health Science
Received 05 April 2022 | Revised 02 May 2022 | Accepted 15 May 2022 | Published Online 28 May 2022

DOI: https://doi.org/10.15520/ijmhs.v12i05.3440
Inno J of Med Health Sci 12 (05), 1903-1909 (2022)

ISSN (P) 2589-9341 | (O) 2277-4939 IF:1.6

RESEARCH ARTICLE

Prospective Study to Ascertain the Advantages of Adding Neprilysin Inhibitor to Standard Care Among Patients with Congestive Cardiac Failure

Dr.Vivekananda Chood O.M | Dr.Sriram.K | Associate Professor Dr.Thilagar

Junior Resident, Dept of General Medicine, Sree Mookambika Institute ofmedical sciences, kulasekharam, kanyakumari

Professor: Dept of General medicine, Sree mookambika institute of medical sciences, kulasekharam, kanyakumari

Abstract

Neprilysin, a neural endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal over activation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling. Sacubitril-Valsartan, a angiotensin neprilysin inhibitor when added to standard care among congestive heart failure patients, reduces the risk of cardiovascular death, heart failure hospitalizations and also it incrementally improves symptoms and physical limitations due to heart failure. There are many studies in western countries which showed neprilysin inhibition added to standard care reduces mortality and morbidity in patients with heart failure with reduced ejection fraction. But in India studies were limited, to show these facts. In this study we will compare the angiotensin receptor neprilysin inhibitor (sacubitril- valsartan) with telmisartan in patients who had heart failure with a borderline reduced ejection fraction

Methods:

Patients with heart failure those who met the inclusion criteria for the study were randomly divided into two groups namely Group one, receiving Telmisartan(40mg od) and other Group receiving sacubitril – valsartan(100mg BD) therapy in addition to standard care of heart failure. Two groups were followed up for a period of 8months and the improvement in LVEF, rehospitalisation for heart failure, reduction in NT-ProBNP levels, improvement in NYHA class, adverse events and other key parameters were observed in both the groups.

Statistical Analysis:

The data was analysed by SPSS 20.0 with unpaired t test and chi square test.

Results:

We found that the sacubitril/valsartan group has significant improvement in EF, reduced hospitalization for HF, improved quality of life in patients of Heart failure with EF <40%, against Telmisartan group.. Sacubitril/valsartan group has total no of hospitalisation of 5 against 16 of Telmisartan group during study period, with p value of <0.05. Sacubitril/valsartan group has an average 10% improvements in EF against 5% in Telmisartan group, which is statistically significant with p value of <0.05. The average NT-proBNP level decreased from 1259 pg/mL to 343 pg/mL in sacubitril/valsartan group with p value of <0.05.

Conclusion:

The study showed that, there is significant improvement in EF, REDUCED hospitalization for HF, improved quality of life, improvement in NYHA class and a significant reduction in NT-ProBNP levels among patients with HF with reduced EF<40% initiated on sacubitril-valsartan compared to telmisartan group. Results support the use of sacubitril/valsartan in Indian patients with chronic HF with reduced ejection fraction with acceptable safety profile and treatment benefits.

Keywords:

SACUBITRIL-VALSARTAN, NT-Probnp, NEPRILYSIN INHIBITOR, TELMISARTAN, EJECTION FRACTION

Corresponding Author: Dr. Sriram K , Dr.Vivekananda Chood O.M, Junior Resident, Department of General Medicine Sree Mookambika Institute of Medical Sciences , Kulasekharam, Kanyakumari

1 | INTRODUCTION

Heart failure is a major problem in developed as well as developing countries and has become a major problem in india as our longeivity increases. World over heart failure is the commonest cause for hospital admissions in the older age group3

The angiotensin converting enzyme inhibitors, beta-blockers, angiotensin II receptor blockers are the standard care of management of heart failure, for almost two decades. But these standard treatment, despite efficacious were unable to reduce events of rehospitalisation. Several studies had shown that neprilysin inhibition has several beneficial effects in heart failure. Sacubitril/valsartan which has been referred to as angiotensin receptor- neprilysin inhibitors is the new class 0f drugs. Sacubitril/valsartan combination therapy is more efficacious. It has lesser adverse effect. It improves overall quality of life in patients with HF reduced ejection fraction, when compared to other classes of drugs. Many studies in western countries showed neprilysin inhibition when added to standard care reduces mortality and morbidity in patients with heart failure with reduced ejection fraction. This study is aimed to assess the outcome of adding neprilysin inhibition to standard care.

2 | AIMS AND OBJECTIVES

To access the outcome of adding neprilysin inhibition to standard care among patients with cStudy design: Longitudinal Study

3 | MATERIALS AND METHODS

Study setting : Department of Cardiology, Sree Mookambika institute of Medical sciences.

Study period : 8 months.

a. Inclusion criteria:

Patients 18year or older were eligible for inclusion in the study if they had a

- Left ventricular ejection fraction of 40% or less within the past 6months by ECHO
- N-terminal pro-B-type natriueretic peptide concentration of >450 pg per milliliter or more(or BNP >150)
- Had received a primary clinical diagnosis of acute decompensated heart failure
- Patients who had NYHA CLASS II – IV Symptoms
- Systolic blood pressure >95mmhg, eGFR >30ml/min/1.73m2 and serum K<5.4mEq/L at randomization.

b) Exclusion criteria

- 1.History of intolerance/hypersensitivity to ACE inhibitors or angiotensin receptor blockers/sacubitril.
- 2.Hemodynamically unstable patients
- 3.Patients with worsening renal function/renal disease/dysfunction were also excluded from the study or with eGFR,30ml/min1.73m2.

c. Number of groups to be studied: Two group

- 1st group – Patients who met the inclusion criteria after randomization receiving

Telmisartan 40mg along with other medication in the standard care of congestive heart failure

- 2nd group – Patients who met the inclusion criteria after randomization receiving

sacubitril – valsartan combination (100mg bd) along with other medication in the

standard of care of congestive heart failure

Study procedure:

- After approval of the study protocol by our Institutional research & human

ethical Committee, study will be conducted in our department.

- All the patients will be explained in detail about the procedure and informed consent will be obtained.
- Patients with heart failure those who met the inclusion criteria for the study were randomly divided into two groups namely Group one, receiving Telmisartan(40mg od) and other Group receiving sacubitril – valsartan(100mg BD) therapy in addition to standard care of heart failure. The patient in Group two, who is already on ACE inhibitors, a 48hrs washout period will be given, and then only they will be started on valsartan-sacubitril. If the patient in Group two who is on ARBs, then the next dose of ARBs will be stopped and sacubitril/valsartan will be started. In other group one, if the patient is on ACE inhibitor or any other ARBs it will be converted to Telmisartan40mg OD.
- Two groups were followed up for a period of 8months with subsequent visits planned at 2weeks, 6weeks, 14weeks and at 32 weeks and advantage of adding neprilysin inhibition to standard care of heart failure were assessed using the key parameters compared between the two groups at the time of randomisation and during their subsequent visits after randomisation.
- NT-Pro BNP/BNP measured at the time of randomization, at 4weeks and at 8weeks.
- LV Ejection fraction measured at the time of randomization and at 6 months..

iii. Software(s) to be used for statistical analysis: SPSS version 20.0

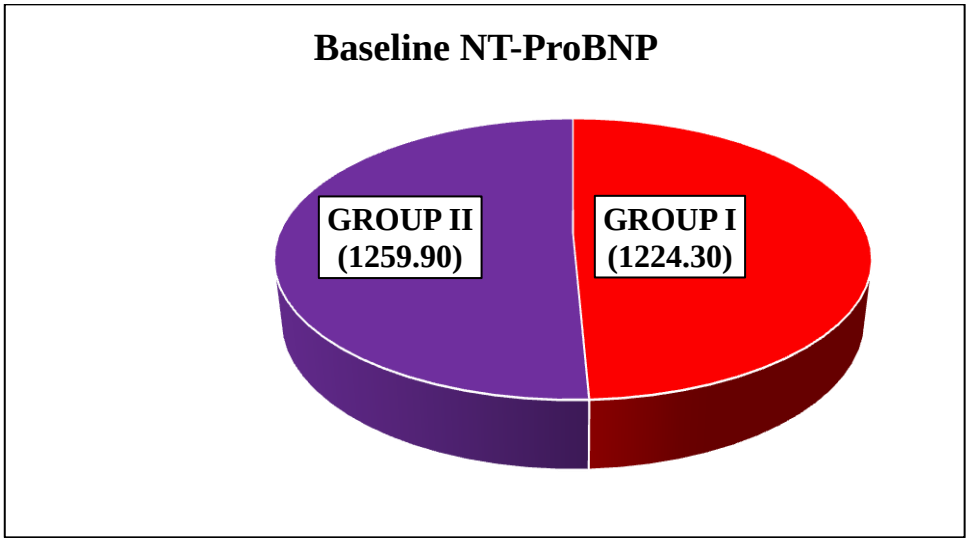
4 | RESULTS

Table-3: Comparison of mean baseline NT-ProBNP values between the groups

Groups	Baseline NT-ProBNP (MEAN±SD)
Group-I	1224.30±3.13
Group-II	1259.90±3.28*

(*p<0.05 significant compared between group-I with group-II)

Graph-3: Comparison of mean baseline NT-ProBNP values between the groups



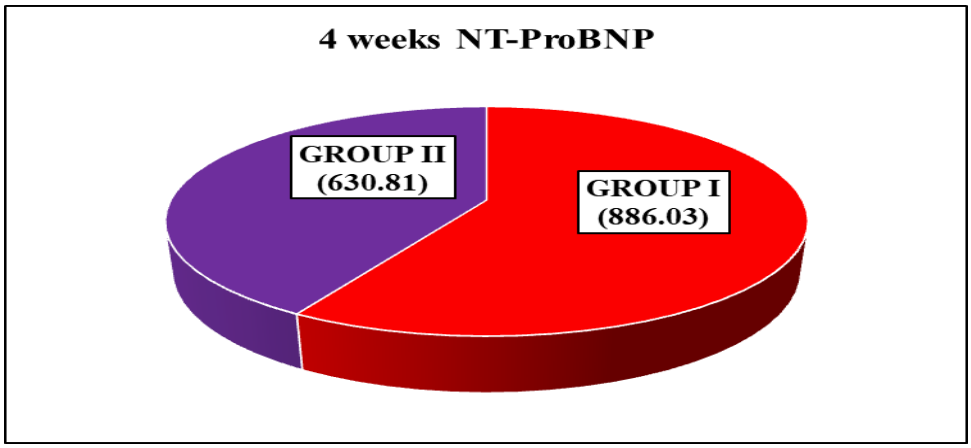
Mean NT-ProBNP baseline values showed significant difference between the groups with p value <0.05. Group-II had higher value compare

Table-4: Comparison of mean 4 weeks NT-ProBNP values between the groups to group-I.

Groups	4 weeks NT-ProBNP (MEAN±SD)
Group-I	886.03±2.51
Group-II	630.81±1.89*

(*p<0.05 significant compared between group-I with group-II)

Graph-4: Comparison of mean 4 weeks NT-ProBNP values between the groups



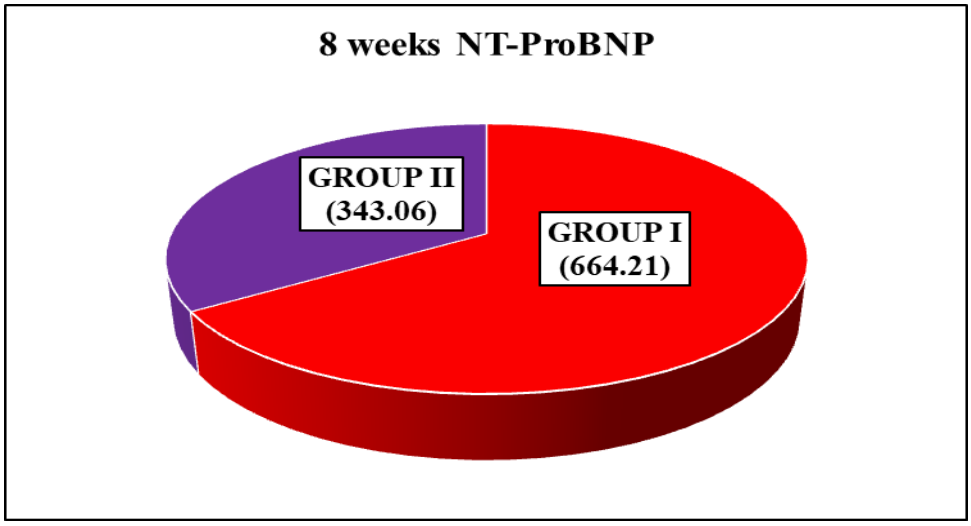
Group-II showed significant (p<0.05) reduction compared to group-I at 4 weeks NT-ProBNP values. Group-I showed high mean values (886.03) compared to group-II (630.81).

Table-5: Comparison of mean8 weeks NT-ProBNP values between the groups

Groups	8 weeks NT-ProBNP (MEAN±SD)
Group-I	664.21±2.32
Group-II	343.06±1.34*

(*p<0.05 significant compared between group-I with group-II)

Table-5: Comparison of mean8 weeks NT-ProBNP values between the patients



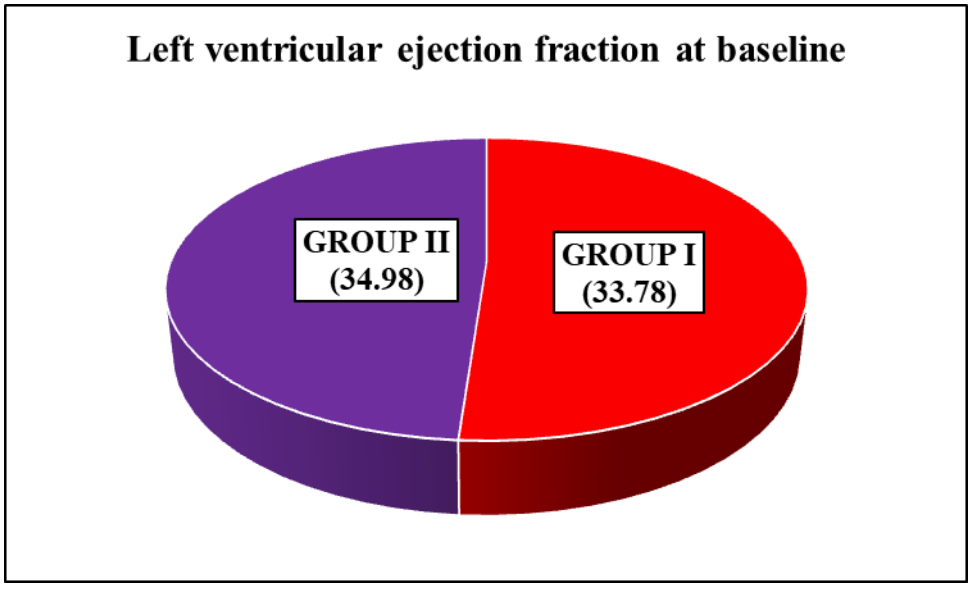
Comparison of mean NT-ProBNP values at 8 weeks showed significant ($p<0.05$) between the group-I and II. High value was observed in group-I compared group-I.

Table-21: Comparison of left ventricular ejection fraction of base line between the groups

Groups	Left ventricular ejection fraction at baseline (MEAN±SD)
Group-I	33.78±5.10
Group-II	34.98±4.90

($p>0.05$ no significant difference compared group-I with group-II)

Graph-21: Comparison of left ventricular ejection fraction of base line between the groups



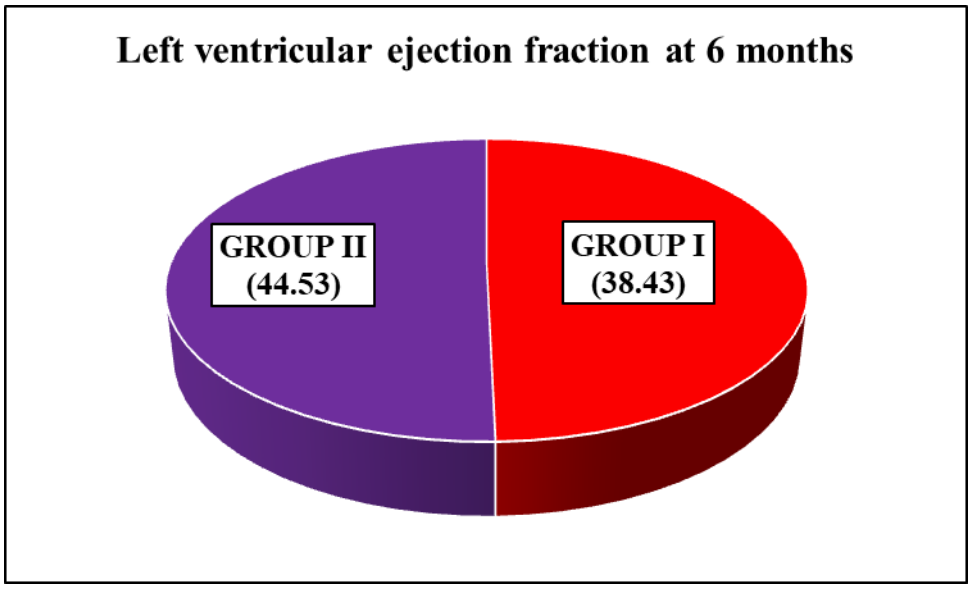
Comparison of left ventricular ejection fraction at baseline between the group-I and II not showed any significant ($p>0.05$) difference. Group-II showed low ejection fraction (36.70) compared to group-I (38.45).

Table-22: Comparison of left ventricular ejection fraction at 6months between the groups

Groups	Left ventricular ejection fraction at 6 months (MEAN±SD)
Group-I	38.43±7.39
Group-II	44.53±6.53*

(*$p<0.05$ significant difference compared group-I with group-II)

Graph-22: Comparison of left ventricular ejection fraction at 6months between the groups



Comparison of left ventricular ejection fraction at 6 months showed significant ($p<0.05$) difference. Group-I had low mean (38.43) ejection fraction compared to group-II (44.33)

5 | DISCUSSION

Medications for heart failure and controlling the underlying condition concomitantly are equally important in the management of heart failure. The rate of decrease in NTproBNP levels in patients on sacubitril/valsartan may have improved the clinical condition, in our study,. The mean serum NT-proBNP level at baseline was 1224 pg/mL in group 1, and 1259 pg/ml in group 2. It was noted that there is significant reduction in mean serum NT-ProBNP levels at week 4(630pg/ml) and week 8(343pg/ml) in sacubitril/valsartan group compared to telmisartan group.Comparison of mean NT-ProBNP values at 8 weeks showed significant ($p<0.05$) between the group-I and II. High value was observed in group-I compared group-II. Natriuretic peptide can reduce blood pressure by decreasing plasma volume and inducing vasodilatation through endothelial nitric oxide synthesis. Sacubitril/valsartan theraphy when initiated led to a greater reduction in the NT-ProBNP concentration than telmisartan theraphy. The time averaged reduction in the NT-proBNP concentration was significantly greater in the sacubitril-valsartan group than in the telmisartan group. In the study conducted by *Li-Wei Liu in 2020* The average NT-proBNP level decreased from 6379 pg/mL to 1661 pg/dL.from baseline to 65 days of follow-up.

In our study, LV EF measured at baseline and after 6months when compared between group 1 and group 2, mean ejection fraction improved from baseline 34$\pm$ 4.90 to 44$\pm$ 4.1 at 6months in group 2 ie, patient on sacubitril/valsartan. Improvement in LVEF is much significant in sacubitril/valsartan group than in telmisartan group.

Reverse remodelling could be one of the most important mechanisms by which sacubitril/valsartan improves mortality and morbidity in patients with HFrEF. In the study conducted by *Li-Wei Liu in 2020* The mean ejection fraction improved from 35 $\pm$6.1% to 50 $\pm$8.8% at 6 months of sacubitril/valsartan treatment. In the study of Almufleh et al., 48 patients with HFrEF were treated with sacubitril/valsartan, there was an increase in the mean EF of 5.09 ± 1.36% in the medium/high sacubitril/ valsartan dose cohort, and 4.03 ± 3.17% in low dose cohort, respectively. They concluded that sacubitril/valsartan was found to improve LVEF above and beyond the effect of pre-existing optimal medical therapy. It was the first study to describe improvements in LVEF after treatment with sacubitril/ valsartan. Our study agrees with the study of Almufleh et al. showing EF improvement following sacubitril/valsartan treatment. It is noted that there was significant reduction in heart failure symptoms among patients in group 2 treated with sacubitril/valsartan

6 | LIMITATIONS

The important limitations are

1. In this study, the enrolled patients included those with both acute and chronic heart failure.
2. The maximum recommended dose of sacubitril/valsartan for the treatment of HFrEF was not used in this study.

7 | CONCLUSION

From the outcome in our study it is evident that, there is significant improvement in EF, and a significant reduction in NT-ProBNP levels among patients with HF with reduced EF initiated on sacubitril-valsartan compared to telmisartan group. Results support the use of sacubitril/valsartan in Indian patients with chronic HF with reduced ejection fraction with treatment benefits similar to global trial.

8 | BIBLIOGRAPHY

1. Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D.,M.H.S., et al. Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure . N Engl J Med 2019; 380:539-548, DOI: 10.1056/NEJMoa1812851.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland J, Coats A,*et al*. 2016 ESC Guidelines for the diagnosis and treatment ofacute and chronic heart failure: The task force for the diagnosisand treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC.Eur Heart J 2016;37:2129-200. doi: 10.1093/eurheartj/ehw128.
3. McMurray JJ, Petrie MC, Murdoch DR, Davie AP. Clinical epidemiology of heartfailure: public and private health burden. **Eur Heart J**. 1998; *19*(suppl P):Mann D L, Chakinala M. Heart failure:pathophysiology and diagnosis.In:Harrison‘s principles of internal medicine 19th ed, McGraw-Hill; Longo DL,Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J eds. Vol 2, Chap 279:2112
4. Butler J, Braunwald E, Gheorghiade M. Recognizing worsening chronic heart failure as anentity and an end point in clinical trials. JAMA. 2014;312:789–790
5. Cleland JG. How to assess new treatments for the management of heart failure: composite scoring systems to assess the patients’ clinical journey. ur J Heart Fail. 2002;4:243–247. with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991;325:293–302.
6. Mann D L. Pathophysiology of heart failure. In: Braunwald's heart disease: A textbook of cardiovascular medicine. 9th ed. Elsevier; Chap 25:487-503
7. Mann DL: Mechanisms and models in HF: A combinatorial approach.Circulation 100:99, 1999; and Kaye DM, Krum H: Drug discovery for heart failure: A new era or the end of the pipeline? Nat Rev Drug Discov 6:127,2007.
8. Robb D. Kociol. Heart Failure Editors' Picks: Most Important Papers in Pathophysiology and genetics. Circ Heart Fail. 2012;5:e32-e49
9. Mann DL, Bristow MR: Mechanisms and models in heart failure: The biomechanical model and beyond. Circulation 111:2837, 2005
10. Dell‘Italia L, Sabri A: Activation of the renin-angiotensin system in hypertrophy and heart failure. *In* Mann DL (ed): Heart Failure: A Companion to Braunwald‘s Heart Disease. Philadelphia, Saunders, 2004, pp 129-143