A Prospective Assessment on Clinical Experience with ARNI in Patients Having HFrEF in a Tertiary Care Hospital

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ABSTRACT

AIM

To evaluate the clinical improvement with ARNI (Angiotensin Receptor Neprilysin Inhibitor) compared to ACEI (Angiotensin Converting Enzyme Inhibitor) in patients having HFrEF.

METHODOLOGY

The prospective observational study was conducted in tertiary care teaching hospital located in Elayampalayam. The duration of study was six months (December- June). The clinical experience with ARNI and ACEI were compared for the primary outcome, secondary outcome, extrapolatory outcome and was computed by using Microsoft Excel 2007 and GraphPad Prism 9.

RESULTS

Out of 70 patients about 39 male patients (55.71%) were predominantly affected with Heart failure rather than female. The highest frequency of heart failure was among the age group of 51-60 (41.43%). Most of the patients 27 (38.58%) were found to be associated with co-morbidities of hypertension step down to diabetes mellitus 26 (37.14%). NT-pro BNP of patients taking sacubitril/valsartan showed a gradual decrease of 586.043 ± 390.533 than ACEI. Ejection fractions among the patients with ARNI were elevated widely 37.91 ± 4.009 than ACEI. Systolic blood pressure and Diastolic blood pressure among ARNI patients showed an improvement than ACEI after a period of 3 months.

CONCLUSION

The study concluded that ARNI in patients having HFrEF, is superior to ACEI in the aspect of clinical improvement, in terms of parameters like NT Pro BNP, ejection fraction and blood pressure.

***Keywords:** Heart Failure, Sacubitril/Valsartan, ACEI.*

INTRODUCTION

American heart association defines heart failure as a complex clinical syndrome that result from any structural or functional impairment of ventricular filling (diastole) or ejection of blood (systole).

Heart Failure is a pathophysiologic state in which the impaired cardiac function, unable to maintain an adequate circulation for the metabolic needs of the tissues of the body (Huffman & Prabhakaran, 2010, & Chaturvedi, 2016).

Heart failure can sometimes be mentioned as a clinical syndrome that is caused by structural defect in the myocardium. This may ultimately result in impairment of ventricular filling and reduced ejection fraction. It may be acute or chronic. Heart failure patients showan evidence of congestion of peripheral circulation and lungs. Chronic heart failure (CHF) is the end result of various forms of serious heart diseases (Urvashi, 2015).

The major cause of heart failure is reduced left ventricular myocardial function, dysfunction of pericardium, endocardium, heart valves or great vessels (aorta). The abnormal mechanism which results in the genesis of heart failurein the body isby the elevation of resistance to the blood flow by the factors likelack of oxygen which may be the result of dysfunction of heart, changes in the structure of ventricles, elevation in the neurohumoral mechanism, abnormal myocyte, calcium cycling, excessive or inadequate proliferation of extra cellular matrix, accelerated apoptosis and genetic mutation. (Huffman & Prabhakaran, 2010, & Borlaug & Paulus, 2011).

In patients with reduced ejection fraction, the left ventricular cavity is typically dilated and the ratio of left ventricular mass by end diastolic volume is either normal or reduced. The miscellaneous factors which contribute to heart failure are anemia, vascular shunting, hyperthyroidism, vitamin B1 deficiency. These occur as a result of ineffective blood volume and pressure, which stimulate the sympathetic nervous system, renin-angiotensin aldosterone system (RAAS) and release of anti-diuretic hormone (ADH). All together contribute to the ventricular enlargement, negative ventricular remodeling, and heart failure. The objective of the study include to evaluate the clinical improvement

with ARNI (Sacubitril/Valsartan) in heart failure patients with reduced ejection fraction, to evaluate the clinical improvement with ACEI in heart failure patients with reduced ejection fraction, and to compare clinical improvement of ARNI and ACEI in heart failure patients with reduced ejection fraction.

MATERIALS AND METHODS
STUDY TYPE
Prospective Observational Study
STUDY SITE
The study was conducted in the Cardiology department of more than 300 bedded multi-specialty hospital in Namakkal
STUDY PERIOD
The study was carried out for 6 months. (December 2019 - June 2020).
STUDY POPULATION
About 103 patients were screened and based on inclusion and exclusion criteria, 70 patients were recruited in our study after getting the patient consent (Annexure- 2) and the data was collected in a specially designed data entry form (Annexure- 3).
INCLUSION CRITERIA:
- Patients within 35 to 80 years of age.
- Both Male and Female patients have been included.
- Patients with reduced ejection fraction (less than 40%) in ECHO.
- Patients who are hemodynamically stable.
- Heart failure patients in NYHA class II, III and IV.
- Patients with abnormality in blood pressure
- Patients with NT-pro BNP greater than 600pg/ml.
EXCLUSION CRITERIA
- Previous history of angioedema.
- Liver and renal failure patients.
- Pregnant and lactating mothers.
- History of malignancy.
- Patients with an electrolyte abnormality.
- Hypotensive patients.
- History of taking RAAS inhibitor, Potassium sparing diuretics.

STUDY TOOLS

- Patient's case report
- Designed data entry form
- Imaging study report of each of the patient for the evaluation of ejection fraction
- Lab report of the patient, especially NT-Pro BNP
- Medication chart
- Patient and patient's caretaker interview

METHOD OF STUDY

Consent was obtained from each subject in patient consent form before initiating the study. Structured patient case form was used to collect various clinical and demographic details of patient such as age, gender, vital signs, lab investigations, primary diagnosis and treatment chart. The study started with screening of about 103 patients out of which 86 were included in the study. Only 70 of them came for follow up. Patients were categorized into three groups based on heart failure therapies. 27(38%) patients were included in Group A (under regular treatment on ARNI), 23(33%) patients were included in Group B (under regular treatment on ACEI) and 20(29%) patients were included in Control group (under irregular heart failure therapies).

DATA ANALYSIS

Data were analyzed by Student - t test to detect significant differences between before and after treatment by using Microsoft Excel 2007, GraphPad Prism 9.

RESULTS

Out of 102 patients, 70 were enrolled in the study. Among this, 20 patients were grouped as control (subject under HF treatment), 23 patients into group A (subject under ARNI treatment) and 27 patients into group B (under ACEI treatment).

1. GENDER WISE DISTRIBUTION

Gender wise distribution of heart failure patients showed that 39 (55.71 %) were male and 31(44.29 %) females. (**Figure1).**

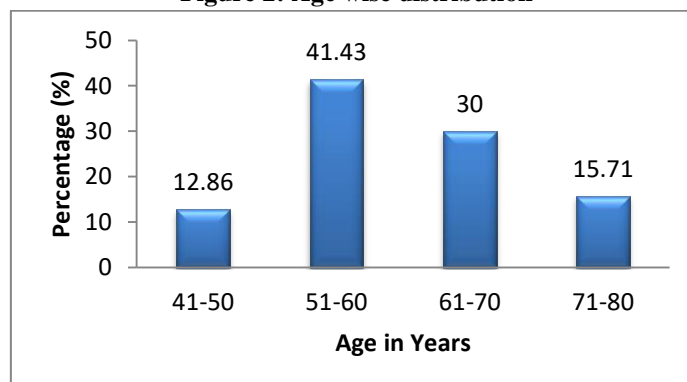**Figure 1: Gender wise distribution**
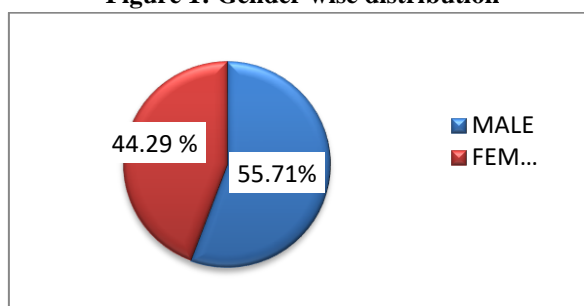
2. AGE WISE DISTRIBUTION

Based on age wise categorization, 9 (12.86 %) patients were within the age group of 41-50 years, 29 (41.43 %) patients were within 51-60 years, 21 (30 %) patients were within 61-70 years and 11 (15.71%) patients were within 71-80 years. In our study, the highest frequency of CHF patients was from the age group of 51-60 years. **(Figure2).**

Figure 2: Age wise distribution

3. GENDER WISE DISTRIBUTION AMONG AGE GROUP

Categorization based on gender- wise distribution among age groups was done. Out of 70 patients, 8 (20.5%) male patients and 1 (3.22%) female patient belonged to first category (41-50 years), 21 (53.85%) male patients and 8 (25.8%) female patients were within 51-60 years, 8 (20.51%) male patients and 13 (41.93%) were within the age group of 61-70 years, 2 (5.12%) male patients and 9 (29.05%) female patients were within the age group of 71-80 years. (**Figure3**).

**Figure 3: Gender wise distribution among age groups**
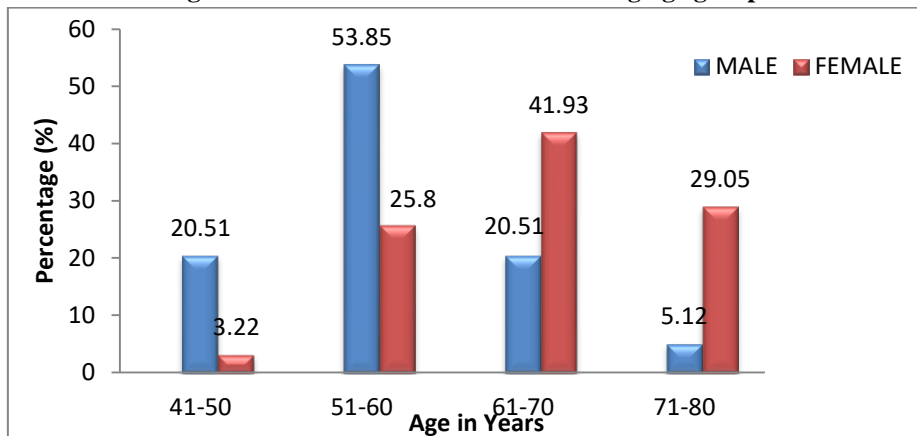
4. CATEGORIZATION BASED ON HEART FAILURE THERAPY

Patients were categorized into three groups based on heart failure therapies. Out of 70 patients 27(38%) patients were included in Group A (under regular treatment on ARNI), 23(33%) patients were included in Group B (under regular treatment on ACEI) and 20(29%) patients were included in the Control group (under irregular heart failure therapies) (**Figure4**).

**Figure 4: Categorization based on Heart Failure Therapy**
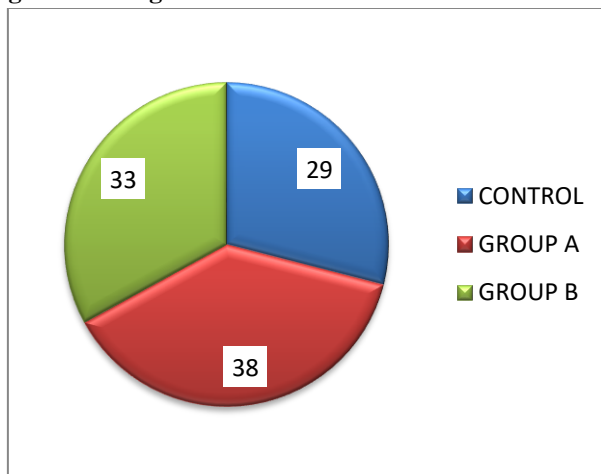
5. CATERGORIZATION BASED ON NYHA CLASS

Out of 70 patients, classification based on NYHA shows that 45 patients categorized in NYHA II class, 34 patients categorized in NYHA III and 11 in NYHA IV class. Among the 45 patients of NYHA II, 14 were grouped as control, 15 were grouped in ARNI and 16 were grouped in ACEI. Among the 34 patients 10 were grouped in control, 11 in ARNI and 13 in ACEI. NYHA III shows that 3 in control group, 4 in ARNI, 4 in ACEI. (**Figure5**).

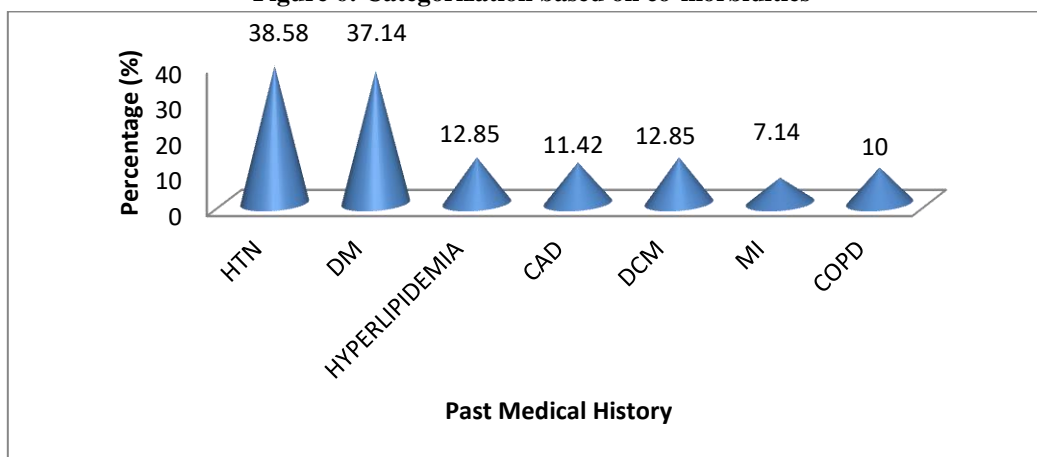**Figure 5: Categorization based on NYHA class**
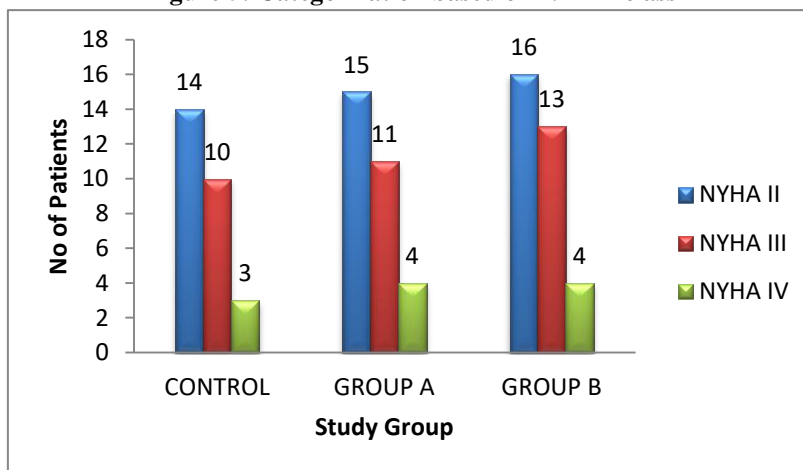
6. CATEGORIZATION BASED ON CO-MORBIDITIES

Out of all the co-morbidities observed, HTN 27 (38.58%) stands first. Next comes diabetes mellitus 26 (37.14%) followed by Hyperlipidemia 9 (12.85%), CAD 8 (11.42%), DCM 9 (12.85%), MI 5 (7.14%) and COPD 7 (10%) **(Figure6)**.

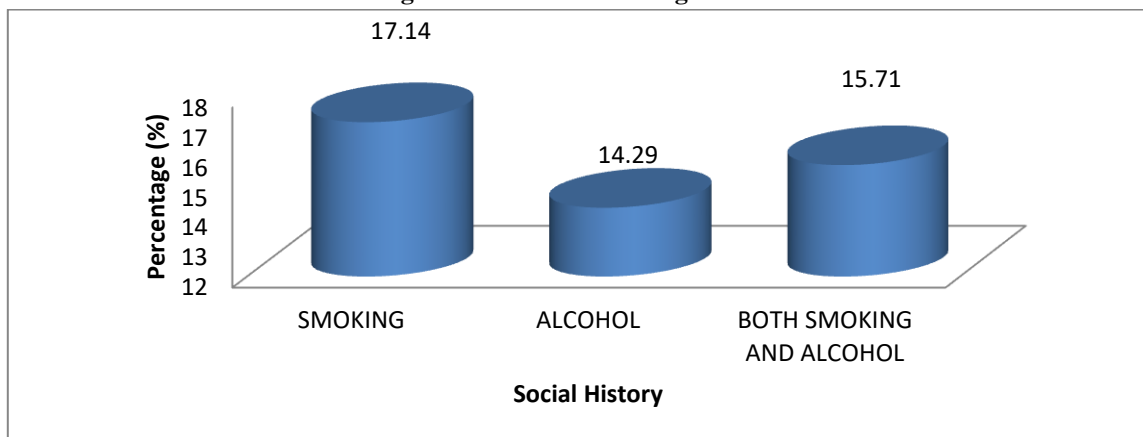**Figure 6: Categorization based on co-morbidities**

7. SOCIAL HABIT CATEGORIZATION

Among 70 patients 12 (17.14%) were smokers, 10 (14.29%) alcoholics and 11 (15.71%) had a habit of both smoking and alcohol consumption. **(Figure7).**

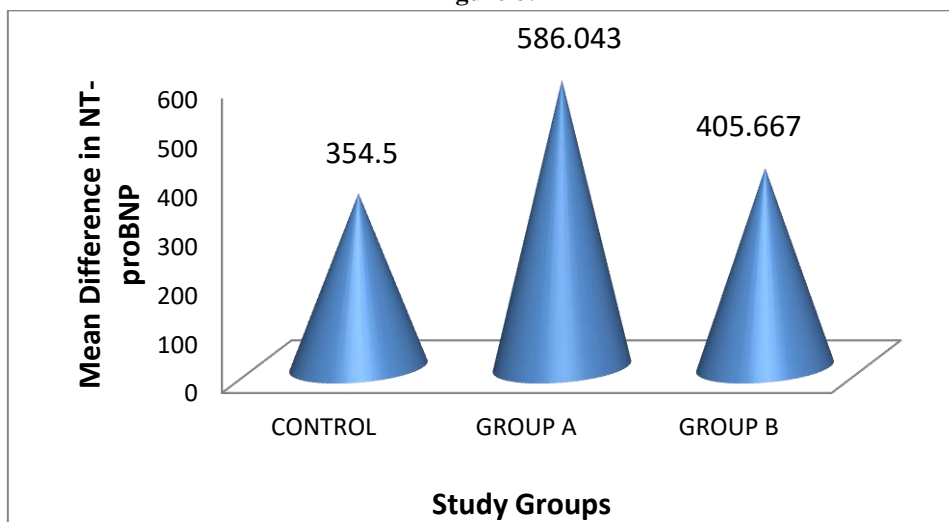**Figure 7: Social habit categorization**

8 DIAGNOSTIC BIOMARKER VARIATION AMONG PATIENTS
8.1 CHANGES IN NT-pro BNP LEVEL

The changes in NT-pro BNP level among Group A was found to be more significant compared to group B followed by the control group **(Figure8).**
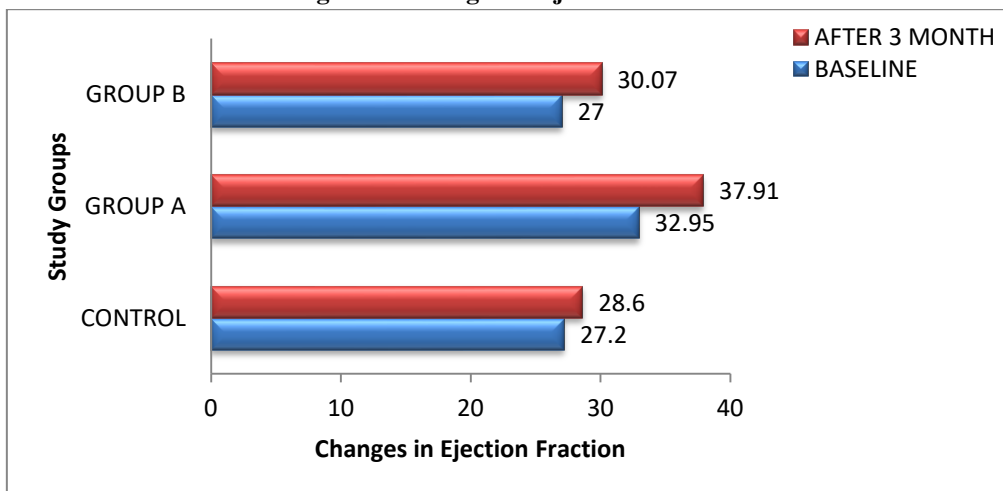
Figure 8:

9 ECHOCARDIOGRAPHIC CHANGES IN EJECTION FRACTION
9.1 CHANGES IN EJECTION FRACTION

The Echocardiographic variations of study groups were compared. CHF patients had significantly reduced ejection fraction (most patients had < 40%) compared to normal patients. **(Figure9).**

Figure 9: Changes in Ejection fraction

9.2 MEAN DIFFERENCE IN EJECTION FRACTION

The echocardiographic variations among the study groups were compared. Ejection fraction levels were analysed before the initiation of therapy (considered as baseline) and after three months. Group A shows a significant increase in ejection fraction followed by Group B and Control group **(Figure10).**

Figure 10: Mean Difference in Ejection Fraction
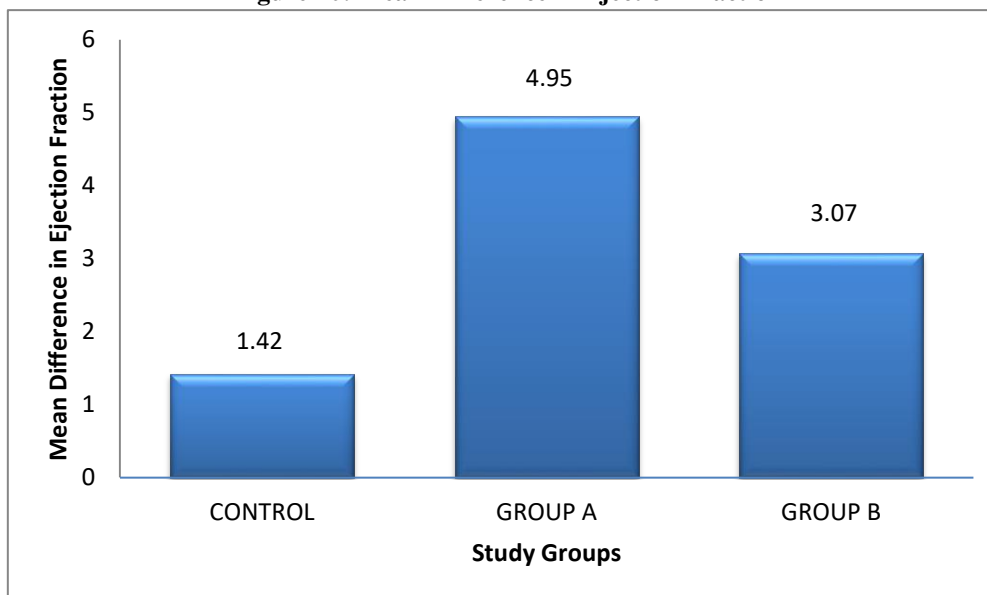
10   EXPLORATORY   ENDPOINT VARIATION AMONG PATIENTS

The exploratory endpoint of the study was blood pressure. Both systolic and diastolic blood pressure was analysed. CHF patients show abnormality in blood pressure.

10.1 MEAN DIFFERENCE IN SYSTOLIC BLOOD PRESSURE

From the comparison of systolic blood pressure among three groups of CHF patients, there was a significant improvement in mean difference in Group A compared to other groups. **(Figure11).**

Figure 11: Mean difference in Systolic Blood Pressure
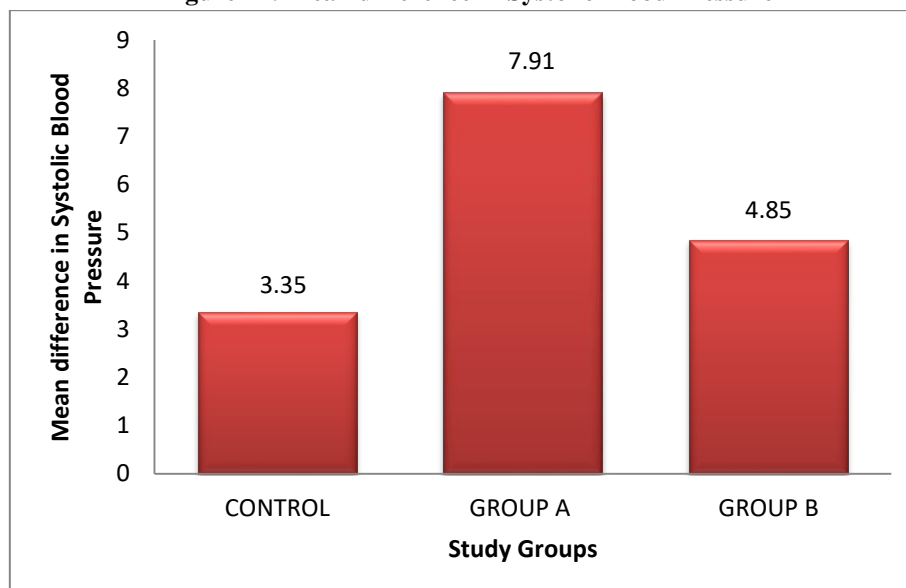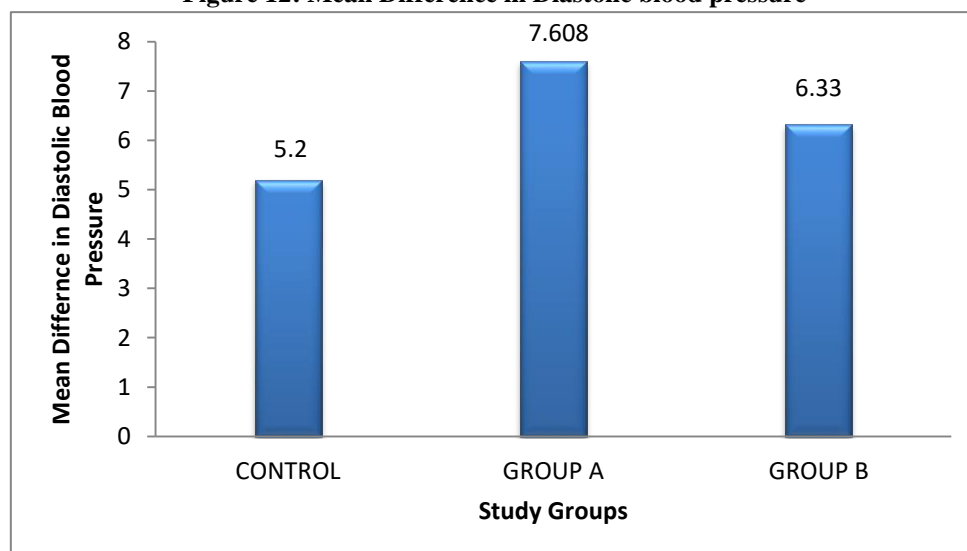

10.2   MEAN   DIFFERENCE   IN DIASTOLIC BLOOD PRESSURE

From the comparison of diastolic blood pressure among CHF patients, there was a significant improvement in the mean difference in Group A compared to others. **(Figure12).**

Figure 12: Mean Difference in Diastolic blood pressure

DISCUSSION

Heart failure is a chronic progressive condition in which heart muscles are unable to pump blood to meet the body's need. In this condition, the heart's pumping action cannot deliver the oxygen and nutrition-rich blood to the body cells, resulting in fatigue, shortness of breath, cough and other symptoms associated with heart failure. There are majorly three types of heart failure - left-sided heart failure, right-sided heart failure, and congestive heart failure. Left-sided heart failure is majorly expressed in two types i.e. heart failure with reduced ejection fraction (HFrEF) – systolic failure, heart failure with preserved ejection fraction (HFpEF) – diastolic failure. Both of these require different therapeutical management. Right-sided heart failure occurs as a result of left-sided heart failure. Congestive heart failure requires urgent medical attention and is accompanied by symptoms like edema (swelling of legs, ankles, pulmonary edema). The risk factors of heart failure include high blood pressure, diabetes mellitus, hyperlipidimia, smoking, age, gender or family history.

The study started with the screening of about 102 patients out of which 86 were included in the study. Only 70 of them came for followup. Patients were categorized into three groups based on heart failure therapies. 27(38%) patients were included in Group A (under regular treatment on ARNI), 23(33%) patients were included in Group B (under regular treatment on ACEI) and 20(29%) patients were included in the Control group (under irregular heart failure therapies excluding ARNI and ACEI).

In the current study, the heart failure showed high incidence among males (55.71%) than the female (44.29%) and showed similar observation from the study conducted by Franz Duca et al. in 2018 named Gender-related differences in heart failure with preserved ejection fraction.

Based on age wise distribution the patients with in the age group of 51 – 60 were predominant (41.43%) to the development of heart failure than other groups which were also observed in the study conducted by Ragnar Danielsen et al. "Prevalence of heart failure in the elderly and future projections: the AGES-Reykjavík".

Based on the gender-wise distribution among age groups, male with an age group of 51 – 60 and female with an age group of 61 - 70 were predominantly associated than another category. Similar observation was also displayed in the studies conducted by Franz Duca et al. titled Gender and heart failure: a population perspective.

A total of 38.58% of patients who enrolled in the study had a history of systemic hypertension and 37.14% with a history of DM. The observation made in the study was similar to that conducted by Maya Guglin et al. in 2014 "Heart Failure as a Risk Factor for Diabetes Mellitus" (Danielsen, 2017).

Out of 70 patients, 17.14% were smokers and 14.29% were alcoholics. This states that smoking is one of the major risk factors for the development of heart failure. This observation was supported in "Influence of Smoking Status on Risk of Incident Heart Failure: A Systematic Review and Meta-Analysis of Prospective Cohort Studies" by Hyeonju Lee et al. (2019).

In assessing the mean difference in ejection fraction among treatment groups, ARNI showed a significant improvement (4.95 ± 2.386) than ACEI. Similar result was also observed in the study conducted by Jeffrey Marbach et al. "Ejection fraction improvement and reverse remodeling achieved with sacubitril/valsartan in heart failure with reduced ejection fraction patients" (Almufleh, 2017).

The reduction in NT-proBNP among the patients treated with ARNI (586.043 ± 390.533) is more than ACEI (405.667 ± 52.410) and control group (354.5 ± 106.075) supported in "ARNI and the natriuretic peptide axis" by Spencer Carter et al. in (2020).

The mean systolic blood pressure among the patients treated with ARNI displayed better improvement (7.91 ± 0.281) than ACEI (4.85 ± 0.704) and control group (3.35 ± 0.726). The total improvement of diastolic blood pressure was observed more among ARNI group (7.608 ± 0.488) than ACEI (6.33 ± 0.544) and control group (5.2 ± 0.411). Similar result was observed under the study conducted by Geng Q et al. "Effect of LCZ696 (Sacubitril/Valsartan) on blood pressure in patients with hypertension: a meta-analysis of a randomized controlled trial" (Geng et al., 2020).

CONCLUSION

The study entitled "A PROSPECTIVE ASSESSMENT ON CLINICAL EXPERIENCE WITH ARNI IN PATIENTS HAVING HFrEF IN A TERTIARY CARE HOSPITAL" concluded that heart failure affects both male and female at any age. It showed that heart failure is usually related with comorbidities like hypertension, diabetes mellitus, hyperlipidemia etc. On relating angiotensin receptor neprilysin inhibitor with angiotensin converting enzyme inhibitor, the patients treated with ARNI exhibited a significant improvement in parameters like NT-pro BNP, ejection fraction and blood pressure than patients treated with ACEI. Hence ARNI proved as an efficient therapeutic approach for heart failure. The future outlook of the study ARNI is one of the developing therapeutic approaches in heart failure. The safety, efficacy, and tolerability of this drug make it as a preferable drug of choice for heart failure in present and future. Further benefits of ARNI should be discovered and explored.

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