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Effect of Angiotensin Receptor-Neprilysin Inhibitor versus Valsartan on Cardiac Status in Patients with Chronic Heart Failure with Reduced Ejection Fraction: A Randomized Clinical Trial in Rangpur Medical College Hospital, Bangladesh

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Abstract

Background: Heart failure with reduced ejection fraction has a significant association with considerable morbidity and mortality, but there is still inadequacy in appropriate treatment to prevent this condition. We observed the effect of angiotensin receptor neprilysin inhibitor (ARNi) with such disorder compared to valsartan. **Methods:** In this single-blind trial, the patients were enrolled with chronic HF aged on or above 40 years, symptomatic NYHA class II - IV, an elevated NT-proBNP above 400 pg/ml level and a reduced LVEF of 40% or less. The patients were randomly assigned 1:1 to the treatment arms either ARNi (50 mg titrated to 100 mg twice a day) or valsartan (40 mg titrated to 80 mg twice a day) and followed for a median of 88 days. The primary outcome was mode of cardiovascular death and re-hospitalization for heart failure. Changes in the level of NT-proBNP and rate of ejection fraction were also measured. **Results:** Cardiovascular deaths occurred 4 (8%) in the ARNi treatment arm, while 11 (22%) in the valsartan treatment arm with significant hazard ratio in the ARNi group [Hazard Ratio = 0.37; 95% CI: 0.34, 0.64; p = 0.042] during a median of 88 days of follow up period and 2 (4%) of the patients from the ARNi treatment arm were hospitalized due to HF, while in the valsartan treatment arm, 10 (20%) patients were hospitalized due to HF followed by receiving treatment respectively with hazard ratio in the ARNi group [Hazard Ratio = 0.80; 95% CI: 0.57, 0.92; p < 0.037]. Furthermore, a significant effect was found to have in LVEF and NT-proBNP at

95% level of significance ($p < 0.05$). These effects resulted from somewhat increased in LVEF (30.4% ± 6.7% to 38.8% ± 8.1%) and intensely decreased in NT-proBNP (3066.5 ± 1882.1 pg/ml to 808.2 ± 592.5 pg/ml) in the ARNi group, as compared to valsartan group in LVEF (30.6% ± 6.0% to 35% ± 7.9%) and in NT-proBNP (3488.2 ± 2912.2 pg/ml to 1886.4 ± 1017.8 pg/ml). **Conclusion:** Chronic treatment with the angiotensin receptor neprilysin inhibitor (ARNi) strongly decreases the NT-proBNP as well as morbidity and mortality and increases LVEF in patients with heart failure compared to valsartan.

Keywords

Chronic Heart Failure, Ejection Fraction, Angiotensin Receptor-Neprilysin Inhibitor (ARNi), NT-proBNP

1. Introduction

Heart failure (HF) is generally observed as clinical observation caused by different kinds of cardiac diseases [1]. The prevalence of HF has steadily been increasing in recent years and this trend is expected to continue due to a growing aging population with more cardiovascular risk factors [2] [3]. Heart failure with reduced ejection fraction responsible for 50% of the conditions [4] is complicated by means of considerable morbidity and mortality [5] [6]. Previously, a lot of clinical trials were conducted with the pharmacological treatments including β blockers [7] calcium-channel blockers [8] angiotensin-converting enzyme inhibitors (ACEi) [9] and angiotensin receptor blockers (ARBs) [10]. But it was not able to demonstrate absolute benefit as expected.

For patients with HF with reduced ejection fraction (HFrEF), no therapy has proven to be effective at reducing morbidity and mortality [11]. Consequently, there is an urgent need for new safe therapies to prevent and treat HFrEF. Angiotensin receptor neprilysin inhibitor (ARNi) is the new drug class and unprecedented scientifically which forms one compound with molecular moieties of the neprilysin (neutral endopeptidase 24) [11] inhibitor prodrug AHU377 and the ARB valsartan [12]. Enzymatic cleavage absorbs AHU377 to sacubitril at (LBQ657), the active inhibitor of neprilysin.

Except for biologically inactive NT-proBNP, biologically active natriuretic peptides as well as atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide are degraded by Neprilysin [13]. Assays for BNP and NT-proBNP which are both natriuretic peptide biomarkers, have been used increasingly to establish the presence and severity of HF. proBNP (108 amino acid) cleavage into NT-proBNP (76 amino acid) & BNP (32 amino acid). Notably, BNP but not NT-proBNP, is a substrate for Neprilysin; therefore, ARNi increases BNP level but not NT pro-BNP level. In two studies with ARNi, NT-proBNP level was reduced. With the reduction of NT-pro-BNP in one study

had associated with an improved clinical outcome. New data suggest that natriuretic peptide biomarkers screening and early intervention may prevent heart failure [11] [12] [13].

The Dual inhibition of ACE and neprilysin was connected with serious angioedema [14] [15] [16]. LCZ696 which consists of the neprilysin inhibitor Sacubitril (AHU 377) and the ARB was designed to minimize the risk of serious angioedema and fully additive reduction of blood pressure [17] [18]. There are no head to head comparisons of an ARB versus ARNi for HF. The current study will evaluate whether the short-term effects of ARNi on morbidity and mortality were superior to those of Valsartan in patients with chronic heart failure with reduced ejection fraction.

2. Methods and Materials

2.1. Study Design and Patient's Selection

We conducted a single-blind randomized controlled trial at the Department of Cardiology, Rangpur Medical College Hospital, Rangpur, Bangladesh. In this trail, the patients were unaware of the treatment but researchers are aware of it, where 100 patients were randomly assigned comparative treatment arms ARNi and Valsartan to know the efficacy of the study drug. A total of 242 patients were screened between May 10, 2018 and December 3, 2018. Out of which 142 patients were excluded due to not meeting inclusion and exclusion criteria, withdrawal of consent or adverse events (**Figure 1**). Exclusion Criteria:

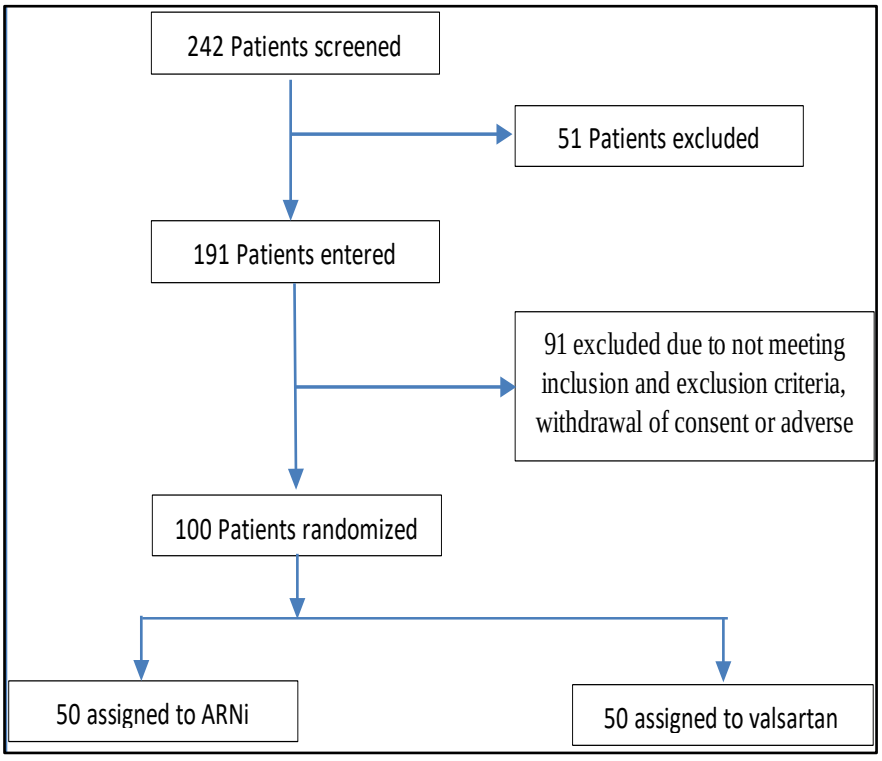

Figure 1. Sampling technique.

- Any prior measurement of LVEF < 40%.
- Acute coronary syndrome (including MI), cardiac surgery, other major CV surgery within 3 months, or urgent percutaneous coronary intervention within 3 months or and elective PCI within 30 days prior to entry.
- Any clinical event within the 6 months prior to entry could have reduced the LVEF (e.g., MI, CABG), unless an echo measurement performed after the event confirms a LVEF ≥ 45%.
- Current acute decompensated HF requiring therapy.
- Patients who require treatment with 2 or more of the following: an angiotensin converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB) or a renin inhibitor.

In this single-blind trial, the patients were enrolled with chronic HF aged on or above 40 years, considering based on NYHA class II - IV and LVEF 40% or less. Moreover, NT-proBNP was required to have 400 pg/ml or larger among the patients. In view of inclusion and exclusion criteria, 100 patients with heart failure were randomly assigned 1:1 to the treatment arms either angiotensin receptor neprilysin inhibitor (ARNi) or valsartan through purposive sampling technique and followed for a median of 88 days. The study was approved by ERC (Ethical Research Committee) and IRB (Institutional Review Board) of Rangpur Medical College authority, Rangpur, Bangladesh. The study was approved in April, 2018. All of the subjects were required to receive written informed consent prior to be included in the study. Each patient was prospectively included in the intention-to-treat analysis and study ended on March 3, 2019.

2.2. Procedures

Subsequent to randomization, the patients were underwent angiotensin receptor neprilysin inhibitor (ARNi) 50 mg and titrated to their final dose of 100 mg twice a day or valsartan 40 mg and titrated to the final dose of 80 mg twice a day to identify the effect of angiotensin receptor neprilysin inhibitor (ARNi) on cardiac status compared to valsartan in patients with chronic heart failure with reduced ejection fraction. Prior to be enrolled in the study, each of total of 100 patients was discontinued on their background treatments (ACE-I or ARB) 24 hour earlier.

Transthoracic echocardiography (LA diameter, LVIDD, LVIDS and left ventricular ejection fraction) test was performed at baseline, 30 days and 90 days or end of the study. All the echocardiographys were performed in the Department of Cardiology, Rangpur Medical College Hospital, Rangpur, Bangladesh. Measurement is made in accordance with the recommendation of the American society of Echocardiography. Echo was performed by using Philip iE-33 echo machine. NT-proBNP was measured at screening/baseline and 90 days or at early termination of visits by Getein 1100 immunofluorescence Quantitative Analyzer. Level of blood sugar, serum creatinine, eGFR (estimated glomerular filtration rate) and level of serum electrolytes were also examined at

baseline, 30 days and 90 days or at early termination of visit or end of the study [19]. To define the functional capacity, the New York Heart Association (NYHA) functional classification (I, II, III, IV) was used.

Based on New York Heart Association (NYHA) Classification:

1) Class I—No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.

2) Class II—Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

3) Class III—Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20 - 100 m). Comfortable only at rest.

4) Class IV—Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

5) No NYHA class listed or unable to determine.

The clinical composite assessment was done in accordance with the NYHA functional classification, patient-reported outcomes (PROs) or major adverse clinical events (or both) [20]. The patients were considered as improved based on improvement in NYHA functional classification or patient-reported outcomes (PROs) and no major cardiovascular event was reported. In contrast, at the endpoint of follow up, the patients who did have a major cardiovascular event or deteriorating of their NYHA class or patient-reported outcomes (PROs) during this single-blind treatment were adjudicated to be inferior. The primary outcome was mode of cardiovascular death and rate of hospitalization for heart failure or overall mortality.

2.3. Statistical Analysis

A total 100 patients were randomly assigned through system generated block randomization into two comparison treatment arms, considering 80% power and at 5% level of significance, to perceive 25% in the ratio of the NT-proBNP at a median of 88 days over baseline between ARNi and valsartan group, we used a two-sided t-test on the logarithm of this ratio (**Table 1**).

Table 1. Demographic characteristics and clinical profile at baseline.

Characteristics	ARNi (n = 50)	Valsartan (n = 50)
Age (years)	60.8 ± 11.4	61.9 ± 12.5
Age group (years)		
(40 - 50)	11 (22)	10 (20)
(51 - 60)	13 (26)	15 (30)
(61 - 70)	16 (32)	16 (32)
(71 - 80)	9 (18)	8 (16)
(81 - 90)	1 (2)	0 (0)
(90 - 100)	0 (0)	1 (2)

Continued

Female sex no. (%)	17 (34.0)	16 (32.0)
LA Diameter	43.3 ± 3.7	43.4 ± 7.6
LVIDD (mm)	63.7 ± 7.2	61.9 ± 6.8
LVIDS (mm)	53.00 ± 8.95	51.1 ± 7.4
LVEF (%)	30.44 ± 6.707	30.57 ± 6.047
Blood sugar (mmol/L)	8.14 ± 3.039	8.97 ± 7.826
Serum creatinine (mg/dl)	1.20 ± 0.4	1.48 ± 0.6
e GFR (ml/min/1.73m^2)	53.42 ± 18.15	46.62 ± 18.85
NT-proBNP (pg/ml)	3066.5 ± 1882.15	3488.18 ± 2912.219
Median NT-proBNP (pg/ml)-IQR	2386	2041.5
NYHA functional class no. (%)		
II	1 (2)	4 (8)
III	48 (96)	46 (92)
IV	1 (2)	0 (0)
Clinical symptoms		
Chest pain	28 (56)	33 (66)
Shortness of breath	38 (76)	45 (90)
Medical History		
Systolic blood pressure (mmHg)	119.78 ± 19.8	124.4 ± 29.6
BMI	22.9 ± 3.2	23.5 ± 2.8
Hypertension no. (%)	14 (28)	11 (22)
Diabetes no. (%)	14 (28)	11 (22)
Pretrial use of medication no. (%)		
ACE inhibitor	11 (22)	5 (10)
ARB	11 (22)	5 (10)
BB	44 (88)	41 (82)
Diuretics	38 (76)	41 (82)
MRA (Spironolactone)	37 (74)	38 (76)
Risk factors		
Tobacco smoking/chewing	14 (28)	16 (32)
Obesity	6 (12)	4 (8)
Family H/O CAD	4 (8)	5 (10)
Dyslipidemia	4 (8)	5 (10)
Sedentary lifestyle	4 (8)	5 (10)

No significant difference was found to have between two groups. Plus-minus values indicate mean ± SD. IQR denotes interquartile range. The body-mass index is the weight in kilograms divided by the square of the height in meters.

We used statistical software STATA (version 13.0) for all of analysis according to intent-to-treat. For the primary endpoint of the single-blind trial, we per-

formed Cox-proportional hazards models and Kaplan-Meier estimates for comparing time-to-event cardiovascular deaths and rehospitalization due to heart failure between the treatment arms. We then adjusted the effect of all prespecified subgroups with dichotomas variables through Cox-proportional hazards models as well. To compare the occurrence of adverse event for undergoing both treatments, we performed Fisher's exact test.

3. Results

3.1. Patient's Demographic Information and Clinical Profiles

Finally, a total of 100 patients with chronic heart failure were recruited to equally distributed between two groups. The patients were predominantly male (67%). The majority of patients reclined in the age group of (61 - 70) years (32%). The most collective symptom was found to have shortness of breath (83%) followed by chest pain (61%). The trial found tobacco smoking/chewing (30%) as the major risk factor followed by hypertension and diabetes (25% each). The both treatment arms were well-adjusted with reference to patient's baseline characteristics.

3.2. Study Outcome

The primary endpoints, occurrence of cardiovascular deaths occurred 4 (8%) in the ARNi treatment arm, while 11 (22%) in the valsartan treatment arm with significant hazard ratio in the ARNi group [Hazard Ratio = 0.37; 95% CI: 0.34, 0.64; p = 0.042] during a median of 88 days of follow up period (Table 2(a) and Figure 2). 2 (4%) of the patients from the ARNi treatment arm were hospitalized due to HF, while in the valsartan treatment arm, 10 (20%) patients were hospitalized due to HF followed by receiving treatment respectively with hazard ratio in the ARNi group [Hazard Ratio = 0.80; 95% CI: 0.57, 0.92; p < 0.037] (Table 2(a)). The secondary outcomes of the trial were to examine the differences of ejection fraction, NT-proBNP and e-GFR between two groups.

A significant effect was found to have in both ejection fraction and NT-proBNP at 95% confidence interval (p < 0.05). These effects resulted from somewhat increased in ejection fraction (30.4% ± 6.7% to 38.8% ± 8.1%) and intensely decreased in NT-proBNP (3066.5 ± 1882.1 pg/ml to 808.2 ± 592.5 pg/ml) in the ARNi group, as compared to valsartan group in LVEF (30.6% ± 6.0% to 35% ± 7.9%) and in NT-proBNP (3488.2 ± 2912.2 pg/ml to 1886.4 ± 1017.8 pg/ml) respectively (Table 2(b)).

But no evidence of differences was found to have between the ARNi and valsartan groups with respect to the other echocardiography measurements (LA Diameter, p-value 0.53; LVIDD. p-value 0.78; LVIDS and p-value 0.50) except ejection fraction at a median of 88 days of follow up (Table 3). Similarly, the ARNi and valsartan groups did not differ with regard to the blood sugar (p-value = 0.38), potassium (K) (p-value = 0.23) and chloride (Cl) (p-value = 0.68) but sodium (Na) (p-value = 0.028) of serum electrolytes demonstrated the significance difference between ARNi and valsartan groups.

Table 2. Primary and secondary outcomes.

(a)

Primary outcome no. (%)	ARNi	Valsartan	Hazard Ratio	p-value
Cardiovascular death	4 (8)	11 (22)	0.37 (0.34, 0.64)	0.042
Hospitalization followed by receiving treatment	2 (4)	10 (20)	0.80 (0.57, 0.92)	0.037

(b)

Secondary outcome	ARNi			Valsartan			p-value
	n	Baseline	90 days	n	Baseline	90 days	
Elevated EF	50	30.4 ± 6.7	38.8 ± 8.1	50	30.6 ± 6.0	35.0 ± 7.9	0.017
Decreased NT-proBNP	50	3066.5 ± 1882.1	808.2 ± 592.5	50	3488.2 ± 2912.2	1886.4 ± 1017.8	0.000
Elevated e-GFR	50	53.4 ± 18.1	56.2 ± 16.6	48	46.6 ± 18.8	48.9 ± 22.3	0.045

EF denotes ejection fraction, e-GFR denotes estimated glomerular filtration rate and NT-proBNP denotes N-terminal prohormone of brain natriuretic peptide.

Table 3. Changes in echocardiographic measures and serum electrolytes at 90 days.

Clinical parameters	ARNi			Valsartan			p-value
	n	Baseline	90 days	n	Baseline	90 days	
LA Diameter	36	43.3 ± 3.7	41.6 ± 7.6	38	43.4 ± 7.6	41.8 ± 7.3	0.53
LVIDD	50	63.7 ± 7.2	59.7 ± 5.8	50	61.9 ± 6.8	58.3 ± 8.8	0.78
LVIDS	50	53.0 ± 8.9	49.8 ± 7.9	50	51.1 ± 7.4	49.8 ± 8.3	0.50
Blood sugar (mmol/L)	50	8.1 ± 3.0	7.4 ± 2.6	49	9.0 ± 7.8	7.7 ± 6.4	0.38
Sodium (Na)	48	139.1 ± 5.6	138.0 ± 6.0	48	137.0 ± 6.9	135.0 ± 8.5	0.028
Potassium (K)	48	4.1 ± 0.6	4.9 ± 6.7	48	4.0 ± 0.5	4.1 ± 0.6	0.23
Chloride (Cl)	48	99.7 ± 4.6	99.9 ± 3.6	48	98.9 ± 6.1	100.5 ± 8.4	0.68
S. Creatinine	50	1.2 ± 0.4	1.1 ± 0.2	50	1.4 ± 0.6	1.4 ± 0.7	0.000

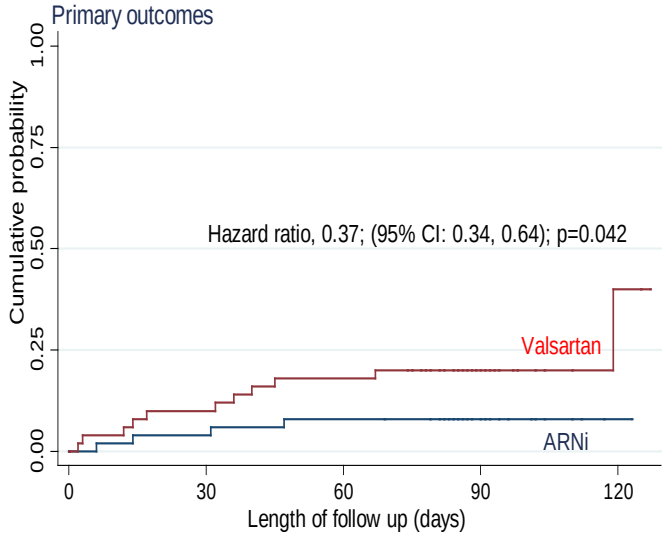

Figure 2. Kaplan-Meier mortality curves.

3.3. Adverse Event during Treatment

In the ARNi group, 2 patients (4%) were re-hospitalized followed by receiving treatment while ratio of re-hospitalized increased to a greater extent in the valsartan group, 10 patients (20%) (p-value = 0.014). No adverse effect was found in the ARNi group 0 (0%) with respect to renal impairment but in the valsartan group 4 patients (10.26%) did have the abnormal (≥2.5 mg/dl) level of serum creatinine (p-value = 0.026) (**Table 5**). The number of patients with elevated potassium or elevated blood sugar did not differ between the groups.

4. Discussion

The study revealed that participated patients with chronic heart failure by means of reduced ejection fraction, the angiotensin receptor neprilysin inhibitor (ARNi) was to a greater extent effective in dropping the risk of cardiovascular deaths and re-hospitalization resulting from heart failure than did valsartan followed by a median of 88 days. ARNi was also found as superior in powerfully reducing NT-proBNP and increasing ejection fraction compared to valsartan which was consistent with a few studies previously conducted [21] [22]. The results of these extensive benefits of angiotensin receptor neprilysin inhibitor compared to valsartan were found to have a strong significant effect. In the ARNi group, improvement of NYHA class was significant compared to valsartan. To inhibit deteriorating of clinical condition in patients with heart failure, previously conducted few trials have reported advances in exercise tolerance or functional class or reductions in the risk of hospitalization for heart failure [23] [24]. In accordance with these generated findings, this trial recommends that the patients of heart failure with reduced ejection fraction have a greater chance of having a beneficial effect who receive ARNi. In patients with this disorder, further testing of this composite could be justified. Current treatment of heart failure with reduced ejection fraction is continued through both symptom-based and empiric without acceptance of specific treatment for this indication [25]. Even though ACE inhibitors and ARBs have the evidence improving the symptoms, increasing the functional capacity and reduction of hospitalization in patients with this condition [9] [10]. Existing guidelines announced that to decrease morbidity or mortality, current treatment could not show the credibility [26].

Our study aimed to reveal the credible evidence in management of cardiovascular diseases with ARNi in adding with existing treatment. This study observed a benefit with regard to reduce cardiovascular mortality, was one of our primary endpoints which were met by the study (**Table 4**).

The patients who received ARNi did have consistently much lower levels of NT-proBNP (reflecting reduced cardiac wall stress) all over the trial in comparison with valsartan which is consistent with the evidence previously reported [27]. NT-proBNP is an indicator of left ventricular tension and decreases in NT-proBNP were associated with better-quality outcomes in patients with heart failure, which was our secondary outcome and achieved expectedly.

Table 4. Sub group analysis with multiple adjustments for all variables shown in Cox proportional Hazards Models with time dependent coverable.

Sub group	ARNi n (%)	Valsartan n (%)	Hazard Ratio	p-value
Age				
<65 years	31 (62)	25 (50)		
≥65 years	19 (38)	25 (50)	1.00 (0.79 1.86)	0.997
Age				
<75 years	41 (82)	41 (82)		
≥75 years	9 (18)	9 (18)	0.48 (0.42 2.62)	0.326
Sex				
Male	33 (66)	16 (32)		
Female	17 (34)	34 (68)	0.60 (0.15 2.41)	0.475
NYHA class				
II	1 (2)	4 (8)		
III or IV	49 (98)	46 (92)	0.51 (0.57 0.82)	0.047
Estimated e GFR				
<60 ml/min/1.73 m^2	34 (68)	37 (74)		
≥60 ml/min/1.73 m^2	16 (32)	13 (26)	0.17 (0.26 1.14)	0.076
LA Diameter				
≤Median	9 (25)	12 (31.6)		
>Median	27 (75)	26 (68.4)	1.77 (0.23 3.19)	0.579
LVIDD				
≤Median	25 (50)	27 (54)		
>Median	25 (50)	23 (46)	1.47 (0.22 9.78)	0.688
LVIDS				
≤Median	24 (48)	33 (66)		
>Median	26 (52)	17 (34)	0.30 (0.04 2.07)	0.222
Ejection fraction (%)				
≤Median	28 (56)	26 (52)		
>Median	22 (44)	24 (48)	0.14 (0.03 0.79)	0.034
NT-proBNP (pg/ml)				
≤Median	22 (44)	28 (56)		
>Median	28 (56)	22 (44)	9.01 (1.10 3.56)	0.040

ARNi was found sound endurable as a whole and its adverse-effect profile was less frequent in comparison with valsartan in this study. Fewer patients of the study participants underwent the adverse events in the ARNi with respect to re-hospitalization and no adverse event was found in regard to renal impairment while in the valsartan group, significant increase in the level of serum creatinine (≥2.5 mg/dl) and re-hospitalization was more frequent (Table 5).

Table 5. Adverse events during treatment.

Events	ARNi	Valsartan	p-value
Re-hospitalization	2 (4)	10 (20)	0.014
Elevated s. creatinine ≥2.5 mg/dl	0 (0)	4 (10.26)	0.026
Elevated Potassium ≥5.5 (mEq/L)	1 (2.22)	1 (2.56)	0.918
Elevated Blood sugar ≥10.2 (mmol/l)	7 (15.22)	3 (7.69)	0.283

This outcome of ARNi on renal impairment is found consistent in the experimental studies [28] [29]. Biomarkers and substitute endpoints were the major determinants for this result of the study, whether the experimental outcomes will interpret into better clinical consequences need to conduct further prospective testing in an appropriately sampled outcomes study.

Limitation of the Study: The study had a limitation on sample size. Based on geographic consideration and traditional perspective, study sample size was limited.

5. Conclusion

Chronic treatment with the angiotensin receptor neprilysin inhibitor (ARNi) significantly decreases the progressive NT-proBNP, slightly changes sodium (Na) and e-GFR levels [30]. ARNi also increases ejection fraction including decreasing the risks and rates of a number of indicators of clinical worsening of enduring patients with heart failure compared to valsartan. As a result, ARNi has a greater impact on reducing morbidity and mortality in patients with chronic heart failure than valsartan. Besides the treatment effect of ARNi, it steady the progression of heart failure is likely to have significant effect for quality of life in this disorder.

Sponsor

General Pharmaceuticals Limited, Bangladesh.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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