ORIGINAL ARTICLE

The Management Outcome of Heart Failure Reduced Ejection Fraction with or without Angiotensin Receptor Neprilysin Inhibitor

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ABSTRACT

INTRODUCTION: Heart failure is associated with recurrent admission, higher mortality and low quality of life. Angiotensin receptor neprilysin inhibitor (ARNI) is a novel agent that has been used for treating heart failure reduced ejection fraction (HFrEF) patients. Thus, it is interesting to evaluate the effect of ARNI on the reverse cardiac remodelling, rehospitalization, cardiac biomarker and quality of life in HFrEF patients. **MATERIALS AND METHODS:** A case controlled study was conducted to assess the treatment outcome of HFrEF with or without ARNI. During the study, the patients' basic demography, co-morbidities, baseline echocardiography (ECHO) findings, NYHA classification, NT-pro BNP levels and KCCQ score were evaluated. The patients' admission history within 90 days from initiation of ARNI or non ARNI were obtained retrospectively. A follow up ECHO was obtained after at least 3 months of intervention. **RESULTS:** A total of 81 patients were recruited in which 54 patients were on ARNI and 27 were on non ARNI treatment. There was a statistically significant improvement of ejection fraction, left ventricular internal diameter end diastole and systole, and left ventricular end-systolic volume in ARNI group. The NYHA class was also noted to improve after ARNI treatment. The NT-proBNP value was lower whereas the KCCQ score was higher in ARNI group compared to non ARNI group. **CONCLUSION:** HFrEF patients with ARNI treatment had better reverse cardiac remodelling effect, cardiac biomarker and quality of life compared to non ARNI treatment. Furthermore, patient received ARNI demonstrated improved heart failure classification after treatment.

Keywords
Angiotensin Receptor Neprilysin Inhibitor (ARNI), Echocardiography, Heart Failure Reduced Ejection Fraction (HFrEF), N-terminal Pro-BNP, Quality of life.

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INTRODUCTION

Heart failure (HF) is a clinical syndrome of the end stage of most cardiac disease in which the typical symptoms during the presentation are shortness of breath, ankle swelling and fatigue.[1] The prevalence of HF in Malaysia is 6-10%.[2,3] Acute decompensated heart failure (ADHF) leads to 11.1% mortality and 24% rehospitalization within 30 days.[4] The survivals from ADHF may experience 35% mortality within 1 year without treatment.[5] On the other hand, readmission for ADHF causes a heavy burden to our health care services and national economy, which costs about RM 194 Million directly and indirectly.[6,7]

Our understanding and management of HF improved over the years with more research, which translated into a lower mortality rate. However, 50% mortality within 5 years is still considered deadlier than certain notorious cancers such as colorectal cancer (35.5%) and breast cancer (10%).[8,9] Clinical history, clinical symptoms with

physical examination combined with natriuretic peptides or chest radiograph is necessary for making diagnosis of HF.[10] Echocardiography (ECHO) use may further classify HF into HF with preserved ejection fraction (HFpEF), HF with mildly reduced ejection fraction (HFmrEF) and HF with reduced ejection fraction (HFrEF).

According to the latest guideline of American College of Cardiology (ACC) and European Society of Cardiology (ESC), angiotensin converting enzyme inhibitors (ACEi), beta-blockers, mineralocorticoid receptor antagonists (MRA) were found to have mortality and morbidity benefits in HF patients and had been recognized as part of the standard management of HF. Angiotensin receptor neprilysin inhibitor (ARNI) is a new novel agent for HF treatment. It is a combination of Angiotensin II receptor blockers and Neprilysin inhibitor which targets the neurohormonal activation pathway (Renin-Angiotensin-Aldosterone system and Vasopressin) in HF. This drug showed additional mortality and morbidity benefits on top of conventional standard therapy in previous studies.

In PARADIGM-HF study for HFrEF patients, there was 21% relative risk reduction in HF admission and 20% relative risk reduction in all-cause mortality.[11] Meanwhile PIONEER-HF study reported greater reduction of NT-proBNP concentration with ARNI than enalapril.[12] EVALUATE-HF study demonstrated reverse cardiac remodelling seen at 12 weeks of ARNI treatment in left ventricular end-systolic and end-diastolic volume indexes (LVEDVI and LVESVI),[13] while PROVE-HF study observed increased LVEF from 28.2% to 37.% by 12 months of ARNI treatment.[14] Those mentioned NT-proBNP markers and ECHO parameters were important prognosticating factor in HFrEF patients.[15,16] With that, ARNI had been widely recognized as part of standard/important therapy for HFrEF by European Society of Cardiology (ESC), American Heart Association (AHA), Malaysia clinical practice guidelines (CPG) and some other guidelines.

In our clinical practice, ARNI usage was associated with marked improvement of patients' general condition, functional class, and even reduced readmission rate. However, the drug is a non-standard medication and has to be purchased by majority of patients. Besides, we also found that there was paucity of relevant real-world experience in our country. Therefore, we conducted a local case control study, to observe the impact of ARNI on HFrEF treatment. In addition, we also aimed to observe the impact on simple ECHO parameters from conventional ECHO as a full conventional ECHO may took 15-20 minutes per person. Routine conventional ECHO had been found to be difficult to implement in a busy heart failure clinic. Hence POC ECHO with capability of assessing simple ECHO parameters may be the solution on time management.

MATERIALS AND METHODS

Study Design and Patients Selection

This study was a case controlled study conducted to assess the effect of ARNI compared with ACEi or ARB, on top of HFrEF standard management. The study populations were patients under the Cardiology clinic and Heart Failure clinic in Hospital Universiti Sains Malaysia (HUSM). Patients who fulfilled the criteria were identified during clinic consultation and case note review, using the following inclusion criteria: age between 18 to 80 years, confirmed diagnosis of HFrEF (ejection fraction, EF<40%) and latest ECHO done were not more than 2 years, taking ARNI or ACEi/ARB for more than 3 months (on top of guideline directed medical therapy including beta blockers/mineralocorticoid/ivabradine/ sodium glucose co-transporter 2 inhibitor), compliance to medication (defined as more than 2 visits to pharmacy department for drug collection in 2 months). On the other hand, patient with device therapy for HF treatment, severe valvular lesion pending surgery intervention, post mechanical valve implantation for valvular heart disease, end stage renal disease and pregnancy were excluded.

Data Collection

Patients who fulfilled the above-mentioned criteria were contacted and stratified into ARNI group and non ARNI group in a 2:1 ratio. Patients' basic demography, co-morbidities, the New York Heart Association (NYHA) class upon HF diagnosis, quality of life, N-terminal pro b-type natriuretic peptide (NT-pro BNP) levels and

baseline echocardiography (ECHO) findings were evaluated. Patients' admission history within 90 days from initiation of ARNI or ACEi/ARB were obtained retrospectively from the electronic health records or paper records. All comorbidities were confirmed based on latest guidelines using data obtained from the patients' folders and laboratory results. The ischemic heart disease (IHD) were defined based on conventional coronary angiogram or computed tomography coronary artery. The NYHA was used to classify the extent of HF and the quality of life of these patients was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The validated questionnaire in local language was used in this study. Serum NT-proBNP was measured using Cobas h 232 POC system (Roche Daignostics, Rotkreuz, Switzerland). Conventional ECHO were performed by certified cardiovascular technician using Philips EPIC or Philips Affiniti (Philips Healthcare, Selangor) with complete documentation of ejection fraction (EF) (simpson biplane), left ventricular internal diameter end diastole (LVIDd), left ventricular internal diameter end systole (LVIDs), end-diastolic volume (EDV) and end-systolic volume (ESV) were part of the selection criteria (ASE, updated 2018). The second ECHO was done at least 3 months apart from previous ECHO.

Statistical Analysis

All data was analysed using IBM SPPS software version 26 (Armonk, New York, USA). Data were presented in median (inter quartile range, IQR). The differences in median values between independent groups were assessed using MannWhitney Test and categorical variables were compared by chi-square test. The Wilcoxon Signed Ranks Test and McNemar Test were applied for two dependent variables analysis. A two tailed P-value of less than 0.05 was considered significant.

RESULTS

A total of 83 patients were screened but only 81 patients were recruited (2 patients in ARNI group were dropped out due to repetitive basic profile in study design). The recruited patients were divided into ARNI group (54 patients) and non ARNI group (27 patients). Majority of our study patients were male (81.4%) with the median age for ARNI group was 64.5 years (15.0) and non ARNI group was 62 years (13.0). The comorbidities were equally distributed in both ARNI group and non ARNI group and the concomitant HF medicines showed no significant difference between both groups. The systolic blood pressure (SBP) was not significantly differed between both groups while diastolic blood pressure (DBP) was higher in non ARNi group (Table I).

Table I: Baseline characteristics of study participants (n=81)

Parameters	ARNI (n=54)	Non ARNI (n=27)	P-value*
Age (years)	64.5 (15.0)	62.0 (13.0)	0.557^
Gender			
Male	44 (81.5%)	22 (81.5%)	1.000
Female	10 (18.5%)	5 (18.5%)	
Diabetes mellitus	35 (64.8%)	17 (63.0%)	0.870
Hypertension	36 (66.7%)	18 (66.7%)	1.000
Hyperlipidaemia	23 (42.6%)	11 (40.7%)	0.874
Ischemic heart disease	40 (74.1%)	19 (70.4%)	0.724
Atrial fibrillation	3 (5.6%)	1 (3.7%)	0.717
Chronic kidney disease	21 (38.9%)	11 (40.7%)	0.872
Beta blockers	41 (75.9%)	20 (74.1%)	0.855
Ivabradine	2 (3.7%)	1 (3.7%)	1.000
MRA	34 (63.0%)	48.0%)	0.203
SGLT2i	1 (1.9%)	1 (3.7%)	0.613
SBP, mmHg	110 (11.03)	111 (13.46)	0.070^
DBP, mmHg	58 (6.43)	62 (12.86)	0.005^

Data presented as Median (IQR) for continuous variables and Frequency (percentage) for categorical variables. *Chi-Square Test. ^Mann-Whitney U-Test. MRA=Mineralocorticoid receptor antagonists, SGLT2i=Sodium-glucose cotransporter 2 inhibitor, SBP=Systolic blood pressure, DBP=Diastolic blood pressure.

At the end of study, 9 patients (16.6%) received maximum dose of Entresto (200mg BD). 3 patients (5.6%) received 150mg BD, 15 patients (27.7%) were on 100mg BD, 17 patients (31.48%) remain on 50mg BD, and the last 10 patients (18.5%) only received 25mg BD. The median medication time upon enrolment in the study were 7 months. There were 13 patients (48.15%) received ACEi (individualized dose of Enalapril, Perindopril, Ramipril) whereas another 14 patients (51.85%) received ARB (individualized dose of Valsartan) in non ARNI group. Median exposure to non ARNI treatment were 9 months.

Second ECHO was done at 7.5 months in ARNI group and 9 months in non ARNI group after randomization. The repeated second EF at follow up was improved compared to baseline in ARNI group. However, there was no significant difference of EF changes in non ARNI treatment arm. The reduction of chamber size is statistically significant after ARNI treatment as indicated by the reduction of LVIDd. Cardiac volume was reduced in ARNI treatment group as showed in ESV reduction, albeit not statistically significant in EDV changes. However, the reverse cardiac remodelling changes was

not observed in non ARNI treatment arm as no changes in LVIDd. Furthermore, patient received non ARNI treatment did not showed significant cardiac volume reduction since no changes in EDV and ESV respectively (Table II).

Table II: Changes of echocardiographic parameters at baseline and follow up (n=81)

Parameters	ARNI (n=54)		P-value	Non ARNI (n=27)		P-value
	At Baseline	At Follow up		At Baseline	At Follow up	
EF	32.40 (9.25)	36.85 (10.10)	< 0.001	38.30 (8.80)	34.90 (11.30)	0.178
LVIDd	5.76 (1.14)	5.60 (0.96)	0.042	5.70 (0.96)	5.96 (1.23)	0.876
LVIDs	4.84 (1.42)	4.46 (0.95)	0.004	4.50 (0.90)	4.88 (1.09)	0.380
EDV	148.10 (65.71)	147.50 (59.50)	0.657	149.50 (62.49)	146.00 (63.00)	0.590
ESV	103.85 (48.54)	93.59 (42.94)	0.016	86.73 (44.00)	86.58 (46.04)	0.178

Data presented as Median (IQR). Wilcoxon Signed Ranks Test. EF = ejection fraction, LVIDd = Left ventricular internal diameter end diastole, LVIDs = Left ventricular internal diameter end systole, EDV = End-diastolic volume, ESV = End-systolic volume.

There was a statistically significant difference in the proportion of NYHA classes pre- and post-ARNI treatment. Meanwhile, patients in non-ARNI group also showed a statistically significant difference in the proportion of NYHA classes between baseline and after at least 3 months of treatment with non ARNI (Table III).

Table III: Changes of NYHA classification at baseline and follow up (n=81)

Parameters		At Baseline	At Follow Up	P-value
ARNI (n=54)	NYHA Class 1 & 2	5	33	< 0.001*
	NYHA Class 3 & 4	49	21	
Non ARNI (n=27)	NYHA Class 1 & 2	4	6	0.031*
	NYHA Class 3 & 4	23	17	

McNemar Test, *P < 0.05. NYHA = New York Heart Association.

With regards to the rate of hospitalization during the next 90 days from initiation of ARNI or non ARNI, there was no statistically significant median difference of length of admission between patient treated with or without ARNI treatment. NT-proBNP mean value in ARNI group showed significant lower value as compared to non ARNI group. While in the quality of life assessment, patient with ARNI treatment recorded better quality of life based on higher KCCQ score as opposed to non ARNI group (Table IV).

Table IV: Median difference in heart failure hospitalization, cardiac biomarker and quality of life (n=81)

Parameters	ARNI (n=54)	Non ARNI (n=27)	U-Stat	P-value
Length of Admission Between Treatment	1.32 (0.00)	10.06 (0.00)	617.0	0.050
NT-proBNP	1459.50 (3353)	3148.00 (6363)	478.50	0.012*
KCCQ	82.81 (29.43)	54.17 (52.08)	351.50	< 0.001*

Data presented as Median (IQR). Mann-Whitney U Test, *P<0.05. NT-proBNP= N-terminal pro b-type natriuretic peptide, KCCQ=Kansas City Cardiomyopathy Questionnaire.

DISCUSSION

This study was conducted to assess the treatment outcome of HFrEF with or without ARNI in local setting for about 3 months' duration. A total of 81 patients from HUSM were prospectively enrolled with stratified sampling method: 2:1 ratio (ARNI group, non-ARNI group). The EF and other ECHO parameters was performed during the clinical visit using conventional ECHO. Then patients were compared based on their rate of hospitalization at 90 days while measuring their mean NT-proBNP and KCCQ score.

Our study shown that male patients were found to be dominant, 66 (81.5%) in both treatment group and control group which similar to the findings in other landmark studies including PARADIGM-HF 77-79%, EVALUATE-HF 74-79% and PROVE-HF 71.5%.[11,13,14]

Our study population had a median age of (SD) 62-64.5 years (9.95), which was comparable to other studies such as PARADIGM-HF 63.8 year (SD 11.4), EVALUATE-HF 67.3 year (SD 9.15), PROVE-HF 65.1 year (SD 12.4) and real-world data Italy 66.5 year (SD 11.5), Taiwan 67 year (SD 12.4).[11,13,14,17,18] The heart failure patients median age in this study supports local data which Raja Shariff *et al.* reported that heart failure median age of 63 years in Klang valley.[19]

Ischemic heart disease was the most common co-morbid which shared by both groups of patients (74.1% vs70.4%). The finding was similar to other studies which shown that IHD was the most common cause of HF as reported by other studies: PARADIGM-HF 60%, EVALUATE-HF 63%, PROVE-HF 53.7%, Italy 67% and Taiwan 54%.[11,13,14,17,18] This higher number of IHD may be explained by significantly higher prevalence of diabetes mellitus in this study population: 64.2% whereas only less than 35% in other clinical studies (except PROVE-HF with 45.5% diabetes mellitus subjects). Otherwise, all other co-morbidities were similar between two groups. All p-value in between groups was >0.05.

Our study also found that there was a lower usage of beta blocker in local study (75.3%) among HFrEF patients in

comparison to other studies which shown >85% of study patients were on beta blocker, such as EVALUATE-HF (86.5%).[13] This was likely due to recruitment of higher NYHA class (NYHA III-IV) subjects in our study (88.9%). These group of patients were more ill and tend to have lower BP at baseline and throughout the study period (mean BP 109/58). However, guideline directed medical therapy were well balanced in both study groups with all p-value in between groups were >0.05.

Our study shown that both improvement of EF and reduction in heart size were observed in ARNI group. Left ventricular reverse remodelling is clearly an outcome of interest in HFrEF patients as it associated with poorer outcome.[15] These structural changes were paralleled with lower NT-proBNP value and better KCCQ scores.[16,20] These data suggested that clinical benefits of ARNI compared with non ARNI in HFrEF patients.

Our study revealed that there were no statistically significant difference in terms of NYHA class changes and hospitalization of heart failure in the first 90 days of treatment in both treatment group. The finding may be explained by the shorter study length in comparison to PARADIGM-HF trial which demonstrated admission benefits from ARNI over non ARNI at 180 days onwards. The lesser number of hospitalization in ARNI treatment group with a p-value of 0.05 also suggested more benefits in ARNI group than in on-ARNI group. However, we believed that some patient may be admitted to other hospital without our notice.

This study was comparable with other study such as PROVE-HF trial, which had effect on reverse cardiac remodelling effect from ARNI usage.[14] This study results shown homogenous ECHO result compared to the trial on using advanced ECHO parameters. The mean reduction of LVEDV in our study was 6.21 whereas in PROVE-HF was 6.65. The mean reduction of LVESV in our study whereas was 5.6 whereas in PROVE-HF was 8.67. However, the less complex ECHO parameters were not found in landmark trials. Our study results were comparable to study by Liu *et al,* in which the mean reduction of LVIDd was 0.16 in our study, whereas in Liu *et al* was. 0.3. The mean reduction of LVISd in our study was 0.38 whereas in Liu et al. was 0.5.[18]

Point of care (POC) ECGO is a simplified echocardiography with easy portability while providing high-quality image resolution.[21] Limited ECHO by trained personnel may provide information such as EF, less complex LV parameters and even assessing Doppler flow velocities and gradients.[22] A previous study found negligible deviations on LV measurements by POC ECHO while compared to routine ECHO.[23] This may potentiate usage of POC assessment during routine clinic review or heart failure clinic assessment as routine ECHO appointment may require longer period of time.

LIMITATION

This study has many limitations, due to patients' characteristic, co-morbidities, concomitant medication drugs, baseline ECHO findings were already fixed. Hence we had to screen more patients in order to keep both group balance, which explained 2 patients were dropped out from our study. In view of higher numbers of poor LVEF patients with borderline BP in our study, dosage of ARNI were individualized. Moreover, a single center study may not represent the whole population in Malaysia as well. Finally, this study only looked at 2 ECHO readings. An repeated measure ANOVA analysis would be better tool to analyze between ARNI and non ARNI group outcome however it requires 3 sets of ECHO readings.

CONCLUSION

In summary, the use of ARNI within 3 months in this study has showed positive reverse cardiac remodelling with improvement of EF as compared to non ARNI usage. However, the lack of significant result on non ARNI group may be an isolated one due to the limitation of this study. We expect ACEi/ARB also to have possible reverse remodelling but not as strong as ARNI. There was lower value of NT-proBNP, higher KCCQ score which translated into better QOL as well as improvement of NYHA class when ARNI was used compared to non ARNI users. However, benefits of hospitalization were not significant at 90 days from initiation of drugs even though there was positive

trend towards ARNI users with lesser days of stay. In conclusion, this study suggest ARNI usage has more benefits compared to non ARNI for advance HF patients attending HF clinic. A large scale study will further validate these outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

This study protocol was approved by the Human Research Ethics Committee Universiti Sains Malaysia, protocol code: USM/JEPeM/21020154. The study complied and conducted according to the Declaration of Helsinki. Permission from the HUSM management was also acquired before assessing the data and electronic health records. Signed informed consent form was obtained from the patients, prior their participation in this study.

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