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ARNI vs ACE Inhibitors in Improving Left Ventricular Geometry, Diastolic Function, and Cardiac Power Output in HFrEF Patients: A Prospective Cohort Study among Acehnese, Indonesia

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Abstract: Heart failure with reduced ejection fraction (HFrEF) is a condition associated with high morbidity and mortality. Changes in left ventricular geometry, diastolic function, and cardiac power output (CPO) are key indicators in the management of heart failure. ARNI and ACE inhibitors have been proven effective to treat this condition, but comparative studies on these therapies in the Asian population remain limited. This study was conducted to assess changes in left ventricular geometry, diastolic function, and CPO in heart failure patients following ARNI therapy compared to ACE inhibitors among Indonesian. This observational study employed a prospective cohort design involving 73 heart failure patients divided into two groups: the ARNI group and the ACE inhibitor group. Evaluations were conducted at first admission/recruitment and after three months period of therapy using echocardiography to assess parameters of left ventricular geometry (LVMI and RWT), diastolic function (E/e' ratio), and CPO. The use of ARNI or ACE inhibitors over three months showed a significant reduction in LVMI, accompanied by an improvement in diastolic function marked by a significant decrease in the E/e' ratio ($p < 0.05$). However, no significant differences were observed between the two groups. CPO values increased in both groups with a p-value < 0.05, where ARNI therapy showed a greater improvement compared to ACE inhibitors ($p = 0.048$). The use of ARNI and ACE inhibitors in heart failure patients can improve CPO, left ventricular geometry, and diastolic function, with ARNI therapy providing a better enhancement in CPO compared to ACE inhibitors.

Keywords: ACE inhibitors; ARNI; Cardiac power output; Diastolic function; Heart failure; Left ventricular geometry

Introduction

Heart failure is a complex clinical syndrome characterized by shortness of breath and limitations in physical activity due to impaired ventricular filling, pumping function (ejection), or a combination of both. This condition is a significant cause of morbidity and mortality, with a 7.2% mortality rate and a 31.9% rehospitalization rate within one year in patients with chronic heart failure (Murphy et al., 2020; Rashid et al., 2023; Kourek et al., 2024). Globally, heart failure affects approximately 64 million people, with a mortality rate

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reaching 15–18%. In Indonesia, according to the Ministry of Health's 2013 report, the prevalence of heart disease is 0.13%, while in Aceh is 0.10%. Among patients with chronic heart failure, the 30-day mortality rate reaches 17%, in-hospital mortality stands at 3%, and rehospitalization rates are as high as 29%. The economic burden of heart failure is substantial, primarily due to the rising rates of hospital admissions, and it is projected to continue increasing globally (Nauli et al., 2023).

Based on ejection fraction, heart failure is categorized into three types: heart failure with preserved ejection fraction (HFpEF, EF≥50%), heart failure with mildly reduced ejection fraction (HFmrEF, EF 41–49%), and heart failure with reduced ejection fraction (HFrEF, EF≤40%). Optimal management for patients with reduced ejection fraction continues to evolve, driven by advancements in pharmacological therapies and the utilization of the latest medical devices (Dowling et al., 2020; Cikes & Solomon, 2015; Turgeon & Barry, 2020; Hayley & Burwash, 2012).

Cardiac power output (CPO) is a physiological parameter commonly used as a measure of the heart's ability to pump blood effectively. CPO values can be influenced by changes in left ventricular geometry, which are often observed in heart failure patients. Patients with heart failure tend to experience alterations in left ventricular geometry due to impairments in contractility and left ventricular remodeling. These changes may include dilation, hypertrophy, and alterations in the shape and volume of the left ventricle. Meanwhile, diastolic function, which reflects the ventricle's ability to fill with blood before contraction, also plays a significant role in determining cardiac output. In heart failure patients, diastolic dysfunction is closely linked to symptoms like shortness of breath, caused by increased pressure in the lungs and reduced blood flow from the left ventricle. The more severe the diastolic dysfunction, the worse the heart failure symptoms (Harada et al., 2022; Shah et al., 2019; Stokes & Sanders, 2019).

Management of heart failure patients with reduced ejection fraction include the use of medications. Angiotensin-converting enzyme inhibitors (ACE inhibitors) has been proven effective in heart failure therapy by reducing afterload, preload, and systolic wall stress, which results in improved cardiac output without an increase in heart rate. A study reported that the use of ACE inhibitors can reduce mortality rates in this population (Tai et al., 2017; Cheng et al., 2014; Bangalore et al., 2016; Zou et al., 2016). In recent years, a novel treatment involving angiotensin receptor-neprilysin inhibitors (ARNI) has shown promising outcomes for heart failure patients. ARNI therapy has been clinically proven to reduce morbidity and mortality in heart failure patients. Moreover, both ARNI and ACE inhibitors are believed to inhibit cardiac remodeling processes, with their use being associated with cardiac reverse remodeling (CRR). ACE inhibitors and ARNI contribute to CRR at rates of approximately 1–4% and 9–15%, respectively (Haydock et al., 2022; Zhang et al., 2022; Sanderson et al., 2006; Gohar et al., 2019).

However, previous studies have primarily focused on Caucasian populations, resulting in limited data on Asian populations. Differences in genetic patterns, lifestyle, and body mass index between Caucasian and Asian are likely to influence phenotypic factors, which may contribute to variations in pathophysiological mechanisms and therapeutic responses in heart failure patients within this group. This study aims to compare the efficacy of ACE inhibitors and ARNI in heart failure patients with reduced ejection fraction, as assessed by echocardiographic parameters, including left ventricular geometry, diastolic function, and cardiac power output among Indonesian, especially Acehnese.

Method

Study Design

This study was an analytical observational research design with a prospective cohort approach. This research was conducted at cardiac inpatient room and echocardiography polyclinic of Dr. Zainoel Abidin Banda Aceh Hospital from July-September 2023. Patients admitted to the cardiology ward, according to the reduced ejection fraction criteria based on the European Society of Cardiology guidelines, will be included in the study. Patients who have threatening arrhythmias, severe heart valve disorders, congenital heart disease, COPD, and end-stage renal disease will be excluded from this study. The sample size was estimated using the Lameshow formula and based on previous studies (Williams et al., 2022; Tam et al., 2023; Smith et al., 2021; Oyanguren et al., 2020; Kaplinsky, 2015), the minimum sample size is 25 participants for each group.

Variables

The dependent variables in this study are left ventricular geometry, diastolic function, and cardiac power output measured by echocardiography, while the independent variables are the type of treatment (ARNI or ACE inhibitors).

Left Ventricular Geometry

Measurements of left ventricular geometry can be performed using transthoracal echocardiography, using the GE vivid E95 probe M5S echocardiography machine. The technique used in this examination is to place the probe on the patient's left chest and the operator gets a view of the parasternal long-axis position, then

measurements are made using 2D M mode, and the thickness of the posterior wall of the left ventricle, the thickness of the intraventricular septal and the diameter of the left ventricular diastole is calculated. The final results were LVMI (Left-Ventricular Mass Index) and RWT (Regional Wall Thickness) data.

Diastolic Function

Examination of the diastolic function of the left ventricle can be done by positioning the probe on the 4-chamber position display, then the peak velocity peak is assessed at the initial fast charging wave (E) using pulsed Doppler mitral flow by positioning the cursor on the anterior mitral annulus, then to obtain the velocity value of e' septal and e' lateral with the echocardiography feature, namely Tissue Doppler Imaging. For e' septal the cursor position remains on the anterior mitral annulus but for e' lateral the cursor is placed in the posterior mitral annulus. Furthermore, after getting the e' septal and e' lateral values, we take the average value, and then calculate the average ratio of E/e'.

Cardiac Power Output

Cardiac power output (CPO) examination can be done by calculating cardiac output first which is done by positioning the probe on the parasternal long axis position display and calculating the LVOT diameter. Next, the probe is positioned on the display of the 5-chamber position, then an assessment is carried out using a pulsed Doppler by placing the cursor over the LVOT. Then tracing the LVOT VTI and adjusting the patient's heart rate so that the cardiac output value is obtained. Next, calculate CPO using the formula: Cardiac output (liters/minute) x MAP/451. CPO is measured in watts.

Data Collection

Participant received a comprehensive explanation of the study and provided informed consent. Baseline data collection included measurements of blood pressure, height, weight, body mass index (BMI), and echocardiographic evaluations to assess left ventricular geometry, diastolic function, and cardiac power output (CPO). Then the participants were divided into two groups: one group received ACE inhibitor, and the other group received ARNI, as part of optimal medical therapy for heart failure. Monthly evaluations of treatment and vital signs were conducted. After 3 months, a follow-up assessment of left ventricular geometry, diastolic function, and CPO was performed using echocardiographic examinations, and the collected data was analyzed.

Statistical Analysis

Data analysis and processing were carried out using Microsoft Excel version 16.66 and SPSS Statistic 25. Continuous data is tested for normality using Shapiro Wilk and presented in the form of an average value with a standard deviation if the data is normally distributed or a middle value and a minimum-maximum value if the data distribution is abnormal. The statistical test used is the chi-square test on categorical data. For numerical data, statistical tests were performed using paired T-tests to assess changes before and after therapy using ACE inhibitors and ARNI, and unpaired T-tests were used to compare ACE inhibitors to ARNI. $P < 0.05$ was considered statistically significant throughout the analyses.

Ethics Approval

All actions were performed with informed consent and ethical approval from the Ethical Committee of Dr. Zainoel Abidin Banda Aceh Hospital (No.124/ETIK-RSUDZA/2023, protocol 23-02-043), ensuring secure data storage and confidentiality.

Result and Discussion

Baseline Characteristics

The sample of this study consisted of 57 males (78.1%) and 16 females (21.9%) with an average age of 59.21±10.6 years. A total of 31 (42.5%) subjects had hypertension, 4 subjects (5.5%) were obese and 48 subjects (65.8%) smoked. The average body mass index (BMI) in the ACE inhibitor group was 24.97 kg/m², while in the ARNI group was 25.1 kg/m², with no significant difference observed between the two groups ($p = 0.156$). Similarly, systolic and diastolic blood pressure showed no significant differences between the groups. The average systolic blood pressure in the ACE inhibitor group was 125 mmHg compared to 114 mmHg in the ARNI group, while the average diastolic blood pressure was 63 mmHg in the ACE inhibitor group and 68 mmHg in the ARNI group.

Based on the initial recruitment data, the examination of left ventricular diastolic function parameters and CPO revealed a median CPO value of 0.4 watts (range 0.39–0.94), a median E/A ratio of 1.4 (range 0.5–2.5), a median e' value of 6 (range 2–9) cm/s, and a median E/e' ratio of 14 (range 9–24). No significant differences were found in the echocardiographic parameters between the two groups. Regarding left ventricular geometry parameters, the average RWT was 0.37±0.03%, and the median LVMI was 110 (range 88–127) g/m². However, no statistically significant differences were found between the ACE inhibitor and ARNI groups in this study ($p > 0.05$). The basic

characteristics of the research are presented in full in Table 1.

Table 1. Baseline Characteristics

Variable	ARNI N=36 (49.3)	ACEi N=37 (50.7)	Total	p
Age (years)	55.89±10.55	62.43±9.78	59.21±10.6	0.07
Sex				1.00
Male	28 (38.4)	29 (39.7)	57 (78.1)	
Female	8 (11)	8 (11)	16 (21.9)	
Height (cm)	166 (150-170)	167 (155-170)	167 (150-170)	0.032
Weight (kg)	70 (45-86)	70 (55-87)	70 (45-87)	0.402
BMI	25.1 (18.73-31.11)	24.97 (19.03-30.82)	25.1 (18.73-31.11)	0.156
Hypertension	15 (20.5)	16 (21.9)	31 (42.5)	1.000
Obesity	1 (1.4)	3 (4.1)	4 (5.5)	0.615
Smoking	24 (32.9)	24 (32.9)	48 (65.8)	1.000
SBP (mmHg)	114 (90-170)	125 (90-176)	125 (90-176)	0.459
DBP (mmHg)	68 (60-100)	63 (60-94)	65 (60-100)	0.706
CPO (watt)	0.63 (0.39-0.86)	0.64 (0.42-0.94)	0.4 (0.39-0.94)	0.493
E/A	1.4 (0.5-2.5)	1.4 (0.5-2.4)	1.4 (0.5-2.5)	0.539
e′ (cm/s)	6 (2-9)	6 (3-7)	6 (2-9)	0.991
E/e′	14 (9-22)	14 (9-24)	14 (9-24)	0.531
RWT (%)	0.37±0.03	0.37±0.03	0.37±0.03	0.836
LVMI (g/m²)	110 (88-127)	110 (91-124)	110 (88-127)	0.723

Echocardiography Parameters Before and After Administration of ACE inhibitors or ARNI in HFrEF Patients

From the analysis of cardiac power output, a significant increase was observed after the administration of ACE inhibitors and ARNI, with p-values of 0.032 and 0.041, respectively. The parameters of diastolic function showed a significant decrease in the ratio of E/A. and E/e' in both groups and a significant increase in e' was obtained in both groups with a p-value of <0.001. LVMI showed a significant decrease after administration of ACE inhibitors and ARNI for 3 months with p values of <0.001 and 0.002, respectively (Table 2).

Table 2. Echocardiography Parameters Before and After Administration of ACE Inhibitors or ARNI in HfrEF Patients

Variable	ACEi N=36 (49.3)			ARNI N=37 (50.7)		
	Pre	Post	p	Pre	Post	p
CPO (watt)	0.63 (0.39-0.86)	0.64 (0.45-84)	0.032	0.64 (0.42-0.94)	0.68 (0.54-0.9)	0.041
E/A	1.4 (0.5-2.5)	1.05 (0.7-2)	0.005	1.4 (0.5-2.4)	1.3 (0.6-2)	<0.001
e′ (cm/s)	6 (2-9)	7 (3-10)	<0.001	6 (3-7)	7 (5-9)	<0.001
E/e′	14 (9-22)	11 (8-16)	<0.001	14 (9-4)	12 (8-15)	<0.001
RWT (%)	0.37±0.03	0.37±0.03]	0.692	0.37±0.3	0.37±0.02	0.475
LVMI (g/m²)	110 (88-127)	108 (90-125)	<0.001	110 (91-124)	108 (90-120)	0.002

ACE inhibitors vs ARNI in Improving LV Geometry, Diastolic Function and CPO in HFrEF Patients

A significantly higher median value of CPO was obtained in the ARNI group compared to the ACE inhibitors group (0.68 vs 0.64, p=0.048). The parameters of the diastolic function and the left ventricle geometry did not show any significant difference between the two groups after 3 months of therapy (Table 3).

Table 3. Effect of ACE Inhibitors vs ARNI in HFrEF Patients

Variable	ACEi N=36 (49.3)	ARNI N=37 (50.7)	p
CPO (watt)	0.64 (0.45-84)	0.68 (0.54-0.9)	0.048
E/A	1.05 (0.7-2)	1.3 (0.6-2)	0.374
e′ (cm/s)	7 (3-10)	7 (5-9)	0.944
E/e′	11 (8-16)	12 (8-15)	0.296
RWT (%)	0.37±0.03	0.37±0.02	0.843

Variable	ACEi N=36 (49.3)	ARNI N=37 (50.7)	p
LVMI (g/m²)	108 (90-125)	108 (90-120)	1.00

This study demonstrate improvements in left ventricular geometry, diastolic function and CPO in HFrEF patients after 3 months of treatment with either ARNI or ACE inhibitors. This confirms the cardioprotective and anti-remodeling effects of ARNI and ACE inhibitors. The improvement in diastolic function observed in this study is consistent with findings from Pericas et al., who reported a decrease in the median E/A ratio and a reduction in the median E/e' ratio, along with an increase in the average e' value after the use of ARNI (Pericas et al., 2021). Martens et al. reported that in 125 heart failure subjects with reduced ejection fraction, treatment with sacubitril/valsartan during the follow-up period led to improvements in diastolic function parameters, including a reduction in the E/A ratio (Martens et al., 2018). Meanwhile, Brilla et al. noted that the use of lisinopril improved left ventricular diastolic function, as evidenced by an improvement in the E/A ratio (Brilla et al., 2000).

This study demonstrates an improvement in left ventricular geometry, as indicated by a reduction in LVMI after 3 months of therapy with either ARNI or ACE inhibitors. This is consistent with the findings of Monosilio et al., who reported a significant reduction in LV mass after 6 months of ARNI therapy (Monosilio et al., 2022). Similar results were also noted in the study by Mantegazza et al. where there was a significant reduction in LV mass after 6 months of ARNI therapy (Mantegazza et al., 2021). Meanwhile, Beck concluded that the use of enalapril can reduce the relative thickness of the left ventricle and LVMI (Beck et al., 2012). Another study reported a 13% reduction in the left ventricular systolic index following captopril therapy (Gotzsche et al., 1992).

A study by Gentile et al. in patients with advanced heart failure reported a slight decrease in cardiac power output from 0.64 to 0.63 after 6 ± 2 months of ARNI therapy, though this change was not statistically significant ($p = 0.61$) (Gentile et al., 2022). In contrast, the results of this study demonstrate that after 3 months of ARNI or ACE inhibitors therapy, there was a notable improvement in CPO. This enhancement in cardiac output is a reflection of the reduced preload and afterload, leading to more efficient stroke volume and better overall heart function.

The ability of ARNI to prevent remodelling and improve heart performance is due to the dual action of the combination of valsartan and sacubitril. Sacubitril inhibits neprilysin, increasing the levels of natriuretic peptides such as BNP, which have vasodilatory, natriuretic, and antifibrotic effects. These effects help reduce pressure on the ventricles and prevent hypertrophy and myocardial fibrosis, thus inhibiting cardiac remodeling. Valsartan, as an angiotensin II type 1 (AT1) receptor blocker, reduces vasoconstriction, fluid retention, and hypertrophy induced by angiotensin II. Improvement in diastolic function is achieved by reducing ventricular filling pressure and enhancing myocardial relaxation due to the reduction in preload and afterload. Furthermore, by reducing the heart's workload and improving blood flow efficiency, ARNI helps the heart produce more optimal output, as seen in the increase in CPO (Mcmurray et al., 2014).

ACE inhibitors work by blocking the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor that contributes to increased afterload, myocardial stress, and maladaptive cardiac remodelling. By lowering angiotensin II levels, ACE inhibitors prevent ventricular hypertrophy and fibrosis, thereby preventing pathological remodelling and maintaining left ventricular geometry. Improvement in diastolic function with ACE inhibitors occurs due to reduced myocardial stiffness and enhanced ventricular relaxation, resulting from decreased fibrotic changes and oxidative stress in the heart tissue. Additionally, by reducing afterload and improving myocardial efficiency, ACE inhibitors contribute to an increase in cardiac power output (CPO). This increase reflects the heart's enhanced ability to generate output against systemic vascular resistance, ultimately leading to better clinical outcomes for heart failure patients (Greenberg, 2002).

ARNI vs ACE Inhibitors in HFrEF Patients

The results of this study indicate that both ARNI and ACE inhibitors can improve left ventricular geometry and diastolic function, but there was no significant difference in the effectiveness between the two treatments. Our findings differ from previous research by Desai et al., which compared the effects of ARNI and ACE inhibitors in heart failure patients with reduced ejection fraction. They reported a greater reduction in the E/e' ratio in the ARNI group compared to the ACE inhibitor group over a 12-week period. Specifically, the mitral E/e' ratio changed from 13.8 to 12.3 in the ARNI group, while in the enalapril group, it changed from 13.4 to 13.8, with a group difference of -1.8 (95% CI -2.8 to -0.8; $p = 0.001$). Additionally, Elshafey found significant differences in diastolic function parameters between the ARNI group and the traditional heart failure treatment group over 6 months (Elshafey et

al., 2021; Li at al., 2024; Febiani et al., 2023; Erdogan et al., 2023).

This study is the first to compare the effects of ARNI and ACE inhibitors on changes in left ventricular geometry and CPO. These findings show that both ARNI and ACE inhibitors are equally effective in improving left ventricular geometry; however, ARNI demonstrates superior efficacy in enhancing CPO compared to ACE inhibitors. Compared to ACE inhibitors, ARNI has a more pronounced cardiac anti-remodeling effect, particularly on ejection fraction and volume reduction, which is clinically reflected in lower NYHA functional class and better performance in the 6-minute walking test (6MWT). Heriansyah et al. revealed that both ACE inhibitors and ARNI can enhance QoL and LVEF, with the latter found to be more efficacious (Heriansyah et al., 2024; Taufik et al., 2024).

In this study, both ACE inhibitors and ARNI were found to have similar effects in mitigating cardiac remodeling. The disparity in results to the previous research could be attributed to several factors, including differences in race, BMI, follow up duration and the dosage administered to patients. In the study by Desai et al., the subjects consisted of individuals from the United States, with an average BMI of 30 kg/m², and the ARNI dosage was titrated up to 97/103 mg. In contrast, this study focused on Indonesian with an average BMI of 25 kg/m², and the ARNI dosage did not reach the maximum dose. This is because the hypotensive response in Indonesian is assumed to be more pronounced than in Caucasian, making it difficult to titrate to the maximum dose.

There are limitations in this study, including: (1) small sample size and data collected from only one center, (2) relatively short follow-up duration, (3) study did not include or analyze the effect of drug dosage on the results, (4) other standard cardiac therapies provided to patients were not presented.

Conclusion

The use of ARNI or ACE inhibitors for three months in heart failure patients with reduced ejection fraction can improve CPO, enhance left ventricular geometry and diastolic function, with ARNI showing a more significant improvement in CPO compared to ACE inhibitors.

Author Contributions

Conceptualization, methodology, formal analysis, investigation, resources, data curation, and original draftwriting: T.; validation, review and editing, and visualization: T.H., A.P., N and Z. All authors have read and approved the published version of the manuscript.

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Conflict of Interest

All author declares that there is no conflict of interest.

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