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Original Article

ACE inhibitors versus angiotensin receptor-neprilysin inhibitors for *HFrEF* management: A prospective cohort study from Indonesia

Teuku Heriansyah[1*], Nova D. Lestari[2], Tjut F. Hadi[1], Rizki Novia[1], Iffah Munawarah[1], Taufiqurrahman Taufiqurrahman[1], Shahcoga L. Yuvhendmindo[1] and Ahmad A. Bashori[1]

[1]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia; [2]Department of Neurology, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia

*Corresponding author: teuku_hery@usk.ac.id

Abstract

Previous studies have reported that angiotensin receptor-neprilysin inhibitors (ARNI) are superior to angiotensin-converting enzyme inhibitors (ACEI) in treating heart failure with reduced ejection fraction (HFrEF). Unfortunately, previously published studies predominantly focused on Western populations, while the data remains insufficient in developing countries. The aim of this study was to compare the efficacies of ARNI and ACEI on patients with HFrEF in Indonesia. A prospective cohort study was conducted among heart failure patients at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. Both ACEI and ARNI each consisted of 40 subjects receiving standard treatment for heart failure. Left ventricular ejection fraction (LVEF), quality of life (QoL), suppression of tumorigenicity 2 (ST2), and troponin T were measured upon admission and at the end of the follow-up. In addition, the occurrence of major adverse cardiac events (MACE) was observed during 6 months of follow-up. Paired *t*-test was used to compare the outcomes of ACEI and ARNI. The results revealed that KKCQ score and LVEF were improved in both ARNI and ACEI groups (each with $p<0.001$). A higher KCCQ overall score was observed in the ARNI group in contrast to the ACEI group ($p=0.01$). ARNI demonstrated superior results in improving the ejection fraction as compared with ACEI ($p=0.001$). Troponin T and ST2 levels exhibited no significant difference between the two groups ($p=0.07$ and 0.286, respectively). MACE-associated mortality ($p=0.696$) and rehospitalization ($p=0.955$) were identical between both groups. In conclusion, ARNI was more efficacious than ACEI in improving the quality of life and left ventricular ejection fraction of patients with HFrEF. However, the efficacy was not significantly different in reducing the risk of MACE.

Keywords: Heart failure, ARNI, ACEI, ST2, quality of life

Introduction

Heart failure remains one of the leading causes of hospitalization, with the incidence rate still high—an estimated 26 million people globally suffer from heart failure. It is the primary condition requiring treatment in individuals over the age of 60 [1]. A recent study in Indonesia reported that the average age of heart failure patients was 54.65±10.75 years, with 83.3% male and 16.7% female [2]. The readmission rate for heart failure is also notably high, reaching 30% within 60 to 90 days of discharge, and up to 30% of patients experience mortality within one year after treatment [1]. The heart's inability to pump blood efficiently manifests in symptoms such as

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fatigue, breathlessness, and fluid retention [3,4]. These symptoms can significantly affect the patient's quality of life (QoL). Frequent rehospitalizations, long-term treatment, and the severity of the disease, as categorized by the New York Heart Association (NYHA), also negatively impact QoL [5]. Other studies have shown that older age, female sex, marital status, and comorbidities are linked to poorer QoL [5,6].

The focus on improving heart failure patients' QoL has gained increasing importance, expanding beyond just morbidity and mortality. Treatment now aims not only to extend life but also to alleviate symptoms and improve overall daily function [6]. Common clinical symptoms of heart failure—breathlessness, fatigue, and fluid retention—are known to affect physical function, cause treatment side effects, and lead to social limitations. These factors often drive patients to withdraw from social activities, resulting in reduced social support and relationships [6,7].

Biomarker evaluation is essential for risk stratification in heart failure patients. Commonly used cardiac biomarkers include troponin and N-terminal (NT)-pro-brain natriuretic peptide (NT-proBNP) [7,8]. However, patient comorbidities may reduce the accuracy of these biomarkers, complicating their interpretation. A novel biomarker, Suppression of Tumorigenicity 2 (ST2), has been introduced for heart failure patients. As part of the interleukin (IL) receptor superfamily, ST2 is involved in biological processes related to cardiovascular disease. In heart failure, cardiomyocytes and fibroblasts release excessive ST2 in response to stress caused by increased ventricular volume. This process underscores the importance of myocardial remodeling and fibrosis, both of which are closely associated with ST2. Currently, ST2 has been validated as a predictive biomarker for heart failure [9]. Studies further emphasize that elevated ST2 levels are linked to a higher risk of cardiovascular death [9,10].

One of the most effective treatments for heart failure is the angiotensin-converting enzyme inhibitor (ACEI) class of drugs [11,12]. ACEIs can reduce symptoms such as fatigue and breathlessness, leading to an overall improvement in QoL. Patients often feel more in control of their symptoms and find it easier to perform everyday activities [11,12]. Another class of medication, angiotensin receptor-neprilysin inhibitors (ARNI), is a combination of sacubitril and valsartan (also known as LCZ696) [12]. ARNIs offer several benefits for heart failure patients, including reduced mortality and hospitalizations, improved exercise tolerance, decreased symptoms, prevention of cardiac remodeling, and better neurohormonal balance [12]. By inhibiting the renin-angiotensin-aldosterone system (RAAS), ARNIs improve hemodynamics, lower testosterone levels, and prevent ventricular remodeling. Together with beta-blockers, mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 (SGLT2) inhibitors, these two drug classes are part of the European Society of Cardiology's (ESC) four key medications for heart failure treatment [4]. To the best of our knowledge, there have been no studies comparing the effects of ACEI and ARNI in Indonesia. Therefore, the aim of this study was to evaluate the effects of ARNIs and ACEIs on improving QoL in heart failure patients with reduced ejection fraction (HFrEF) in Indonesia.

Methods

Study design, setting and sampling

This prospective cohort study was conducted in the Intensive Coronary Care Unit (ICCU) and the Cardiology Ward of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, over a three-month period from February to April 2023. The study was designed to compare clinical outcomes in patients with HFrEF who were treated with either ACEIs or ARNIs. Prior to initiation, the study protocol received approval from the hospital's institutional review board and ethics committee, ensuring compliance with relevant ethical guidelines and principles.

Patients were selected through purposive sampling to ensure that the sample included patients meeting specific inclusion criteria related to HFrEF and their prescribed treatment regimen. The minimum sample size was determined using Slovin’s formula, which indicated that at least 31 patients were necessary for statistical validity. To account for potential dropouts or incomplete data, we increased the target sample size by 20%, setting a minimum goal of 40 patients in each treatment group.

Patients

This study enrolled patients aged 18 to 75 years who had been diagnosed with heart failure by a cardiologist. Eligible patients were required to have a left ventricular ejection fraction (LVEF) of less than 50%. To ensure the safety and integrity of the study, several exclusion criteria were established. Patients with congenital heart disease, severe valvular heart disease, chronic obstructive pulmonary disease (COPD), or those diagnosed with stage IV or V chronic kidney disease (CKD) were excluded from participation.

Study outcomes

In this study, we evaluated patients with HFrEF treated with either ACEIs or ARNIs. The primary outcomes were the QoL, LVEF, and the incidence of major adverse cardiac events (MACE). Secondary outcomes included laboratory biomarkers such as troponin T, ST2, blood urea nitrogen, and creatinine levels.

Data collection

Data collection was conducted among patients diagnosed with HFrEF. All eligible patients provided informed consent and shared their contact information. The baseline characteristics assessed included vital signs, such as systolic blood pressure (SBP) and diastolic blood pressure (DBP), Body Mass Index (BMI, kg/m^2), and LVEF. A GE Vivid E95 echocardiography machine (General Electric, Boston, USA) was used in transthoracic echocardiography (TTE) mode to measure the LVEF. The Teichholz method was employed, which involved obtaining M-mode measurements of the left ventricle in the parasternal long-axis view. The left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were measured at the level of the mitral valve chordae. LVEF was calculated using: LVEF (%) = (LVEDD^3−LVESD^3)/LVEDD^3.

All patients were imaged in the left lateral decubitus position to optimize the acoustic windows. Measurements adhered to the guidelines established by the American Society of Echocardiography and were averaged over three consecutive cardiac cycles.

Additionally, we recorded the patient's comorbidities, including hypertension, defined as an SBP of ≥140 mmHg and/or a DBP of ≥90 mmHg, and type 2 diabetes mellitus, defined as either a fasting plasma glucose level of ≥126 mg/dL, a 2-hour plasma glucose level of ≥200 mg/dL during an oral glucose tolerance test, or a hemoglobin A1c (HbA1c) level of ≥6.5%. Furthermore, a history of smoking was also recorded.

At the initiation of the study, blood samples were collected from the patient's brachial veins into pre-cooled tubes containing ethylenediaminetetraacetic acid (EDTA). Standard blood analyses were performed, including blood urea nitrogen, creatinine levels, and measurements of troponin T levels using the Roche cobas® h232 Troponin T system (Roche Diagnostics, Basel, Switzerland), in accordance with the manufacturer's instructions. The ST2 levels were measured using the Presage ST2 Assay (Critical Diagnostics, San Diego, USA) and the Presage ST2 Control Kit (BC–1066E), also following the manufacturer's guidelines. Blood urea nitrogen and creatinine levels were determined using the ion-selective electrode (ISE) method.

In addition, each patient underwent an interview to evaluate their QoL using the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) [13]. This disease-specific instrument consists of 12 questions divided into various domains, including physical and social limitations, symptoms, self-efficacy, and overall QoL. Each domain score is transformed to a range between 0 and 100, with higher scores indicating better health status. The clinical summary score combines measures of symptoms and social factors, while the overall summary score integrates all domains [13]. The questionnaire utilized was a translated version in Indonesian, which had already been validated in a previous study [14].

A follow-up assessment was conducted six months post-enrollment. During this period, participants were invited for a reevaluation of their QoL using the KCCQ-12, echocardiography reassessment, and another blood draw from the brachial vein for repeat analyses of standard blood parameters, troponin T, ST2, blood urea nitrogen, and creatinine levels. The follow-up also included a review of MACE, consisting of heart failure-associated mortality and hospitalization. The data were collected through medical records or interviews, following the suggestions from a previous study [15].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Baseline characteristics of the study population were reported, with categorical variables presented as the frequency (percentage) of patients and continuous variables summarized as medians. To assess the normality of continuous variables, the Shapiro-Wilk test was employed. A paired t-test was then used to compare outcomes between ACEI and ARNI groups. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 25 (SPSS Inc, Chicago, USA).

Results

Characteristics of the patients

Initially, a total of 110 patients diagnosed with HFrEF were deemed eligible for inclusion in the study. Following a thorough screening process, 17 patients were excluded due to various criteria, and an additional 13 patients declined to participate. After a six-month follow-up period, the occurrence of MACEs was documented, revealing seven cases in the ACEI group and six cases in the ARNI group. An illustration of the study flow is presented in **Figure 1**.

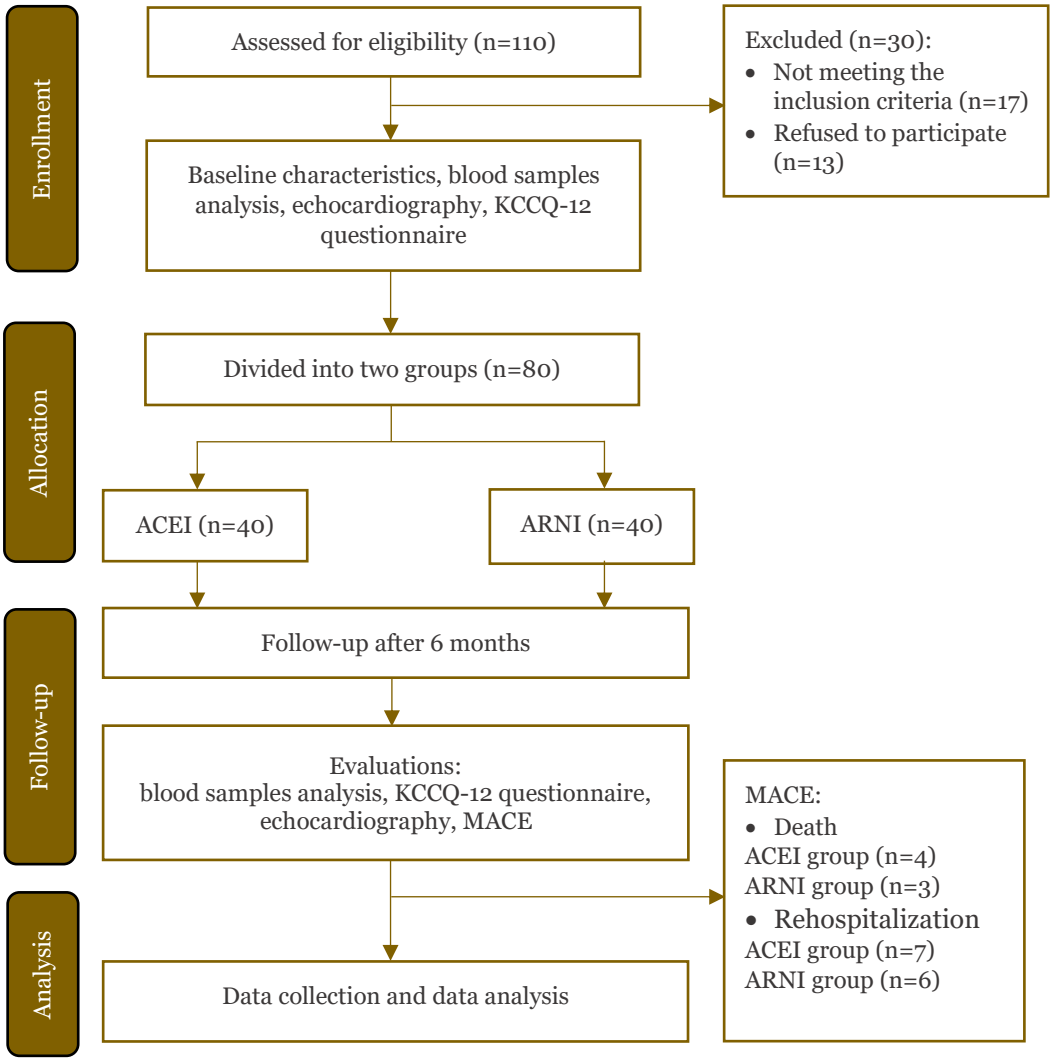

Figure 1. CONSORT flow diagram illustrating the recruitment and group allocation of the research subjects. ACEI: angiotensin-converting enzyme inhibitor; ARNI: angiotensin receptor-neprilysin inhibitor; KCCQ-12: Kansas City Cardiomyopathy Questionnaire; MACE: major adverse cardiac events.

A total of 80 patients with HFrEF were included in the study, where the subjects' characteristics are presented in **Table 1**. The ARNI group had a higher mean age (61.5±9 years) than the ACEI group (56±11 years), and males predominated in both groups. Blood pressure readings were similar, with slightly higher systolic values in the ARNI group (126.32±23.71 mmHg) compared to the ACEI group (122.25±23.77 mmHg). The prevalence of hypertension, type 2 diabetes mellitus, and smoking history were comparable across groups. Notably, a greater percentage of ACEI patients rated their QoL as "poor" (65%) compared to the ARNI group (30%), while the ARNI group had a higher proportion rating their QoL as "moderate." Major adverse cardiac events were slightly less frequent in the ARNI group, with three deaths (7.5%) versus four (10%) in the ACEI group and three rehospitalizations in both groups.

Table 1. Characteristics of the heart failure patients with reduced ejection fraction (n=80)

Characteristics	n (%)	
	ACEI (n=40)	ARNI (n=40)
Age, mean±SD (years)	56±11	61.5±9
Gender		
Male	31 (77.5)	32 (80.0)
Female	9 (22.5)	8 (20.0)
Systolic blood pressure, mean±SD (mmHg)	122.25±23.77	126.32±23.71
Diastolic blood pressure, mean±SD (mmHg)	70.83±0.96	69.35±10.23
Hypertension		
Yes	17 (42.5)	17 (42.5)
No	23 (57.5)	23 (57.5)
Type 2 diabetes mellitus		
Yes	17 (53.1)	15 (46.9)
No	23 (47.9)	25 (52.1)
Smoking		
Yes	27 (67.5)	27 (67.5)
No	13 (32.5)	13 (32.5)
Body mass index mean±SD, (kg/m^2)	25.39±2.33	24.97±2.76
Normal	10 (25.0)	20 (50.0)
Overweight	27 (67.5)	16 (40.0)
Obese	3 (7.5)	4 (10.0)
Quality of life (pretest)		
Very Poor	5 (12.5)	3 (7.5)
Poor	26 (65)	12 (30.0)
Moderate	2 (5.0)	18 (45.0)
Excellent	7 (17.5)	7 (17.5)
Major adverse cardiac events		
Mortality	4 (10)	3 (7.5)
Rehospitalization	3 (7.5)	3 (7.5)
None	33 (82.5)	34 (85.0)

ACEI: angiotensin-converting enzyme inhibitors; ARNI: angiotensin receptor-neprilysin inhibitors

Primary outcomes

There was a statistically significant increase in all parameter scores between baseline and follow-up in both the ACEI and ARNI groups (p=0.001). The mean improvement in the ACEI group was 10.62 (95%CI: 8.65–12.60), while the ARNI group showed a higher mean increase of 15.36 (12.43–18.29), with a p-value of 0.01. The ARNI group had a higher improvement compared to the ACEI group in terms of the social limitation domain (p=0.02). In terms of LVEF, significant improvements were observed in both the ACEI and ARNI groups (p=0.001). The mean increase in LVEF was 0.41 in the ACEI group and 0.97 in the ARNI group, with the difference between the two groups also being statistically significant (p=0.001). A comparison of QoL between the ARNI and ACEI groups revealed no significant difference (p=0.49) (**Table 2**).

Table 2. Comparison of quality of life and ejection fraction among groups

Variable	ACEI, mean±SD			ARNI, mean±SD			Mean difference (95%CI)		*p*-value[a]
	Before	After	*p*-value[a]	Before	After	*p*-value[a]	ACEI (n=40)	ARNI (n=40)	
KCCQ score									
Overall	47.51±17.59	58.13±14.94	0.001**	54.37±17.27	69.73±14.25	0.001**	10.62 (8.65–12.60)	15.36 (12.43–18.29)	0.01*
Physical limitations	49.19±25.85	59.25±21.75	0.001**	57.88±23.52	73.53±17.95	0.001**	10.07 (6.48–13.66)	15.65 (11.18–20.12)	0.05
Symptoms frequency	44.09±20.10	54.05±18.14	0.001**	52.30±19.12	65.88±18.27	0.001**	9.95 (6.82–13.09)	13.58 (8.69–18.47)	0.21
Social limitation	54.05±22.87	63.65±19.91	0.001**	60.69±24.22	77.70±19.59	0.001**	9.61 (6.17–13.04)	17.01 (11.96–22.05)	0.02*
Quality of life	42.70±22.43	55.55±21.43	0.001**	46.62±21.17	61.82±17.66	0.001**	12.85 (9.13–16.56)	15.20 (9.38–21.03)	0.49
Left ventricular ejection fraction (%)	40.39±6.21	40.81±6.11	0.001**	39.49±6.81	40.46±6.55	0.001**	0.41 (0.23–0.60)	0.97 (0.72–1.23)	0.001**
Suppression of tumorigenicity 2 (ng/mL)	41.82±29.48	32.18±44.79	0.308	51.37±32.99	64.59±48.06	0.123	9.64 (9.29–28.58)	13.22 (3.76–30.20)	0.07
Troponin T (ng/L)	0.28±0.38	0.29±0.36	0.638	0.43±0.50	0.45±0.51	0.045*	0.01 (0.02–0.03)	0.02 (0.01–0.04)	0.286
Blood urea nitrogen (mg/dL)	57.94±24.46	56.06±22.81	0.258	51.73±24.80	62.43±20.73	0.048*	1.89 (1.44–5.22)	10.70 (0.09–21.32)	0.027*
Creatinine (mg/dL)	1.15±0.27	0.87±0.14	0.001**	1.06±0.29	0.91±0.19	0.011*	0.28 (0.17–0.39)	0.15 (0.04–0.25)	0.08

ACEI: angiotensin-converting enzyme inhibitors; ARNI: angiotensin receptor-neprilysin inhibitors
[a] Analyzed using paired t-test
* Statistically significant at $p<0.05$; ** $p<0.01$

Secondary outcomes

Significant elevation of troponin T (p=0.045) and blood urea nitrogen (p=0.048) were observed in the ARNI group but not in the ACEI group (**Table 2**). The increase in BUN levels was significantly higher in the ARNI group (p=0.027). Creatinine levels were significantly reduced following treatment in both groups, with p-values of 0.001 and 0.011 for the ACEI and ARNI groups, respectively. No significant differences were observed in ST2 (p=0.07) and troponin T (p=0.286) between the two groups (**Table 2**).

Discussion

In this study, the male population predominated in both groups, a finding consistent with the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PIONEER-HF) and Study to Evaluate the Tolerability and Safety of Pre-Discharge Initiation of Sacubitril/Valsartan (TRANSITION) studies [15,16]. Over a six-month follow-up, heart failure (HF) hospitalization, mortality, QoL, biomarkers, and echocardiographic parameters were assessed. The KCCQ, a tool specifically designed to measure QoL in heart failure patients, has shown significant predictive relationships with health outcomes [17,18]. Previous studies indicated mean KCCQ scores between 25 and 35 for individuals with NYHA class IV heart failure [17,18]. Studies assessing the efficacy of heart failure treatments have demonstrated that patients receiving guideline-directed medical therapy (GDMT) show substantial improvement in QoL within three months compared to those on standard therapy [17,19]. A study found that in patients with preserved or mildly reduced LVEF (≥40%), HRQL was a stronger predictor of all-cause mortality and the combined outcome of death or heart failure hospitalization compared to those with reduced LVEF (<40%) [20]. These findings suggest that HRQL measures, such as the KCCQ-12, could be particularly valuable for risk stratification in clinical practice, especially in patients with lower LVEF or milder symptoms. HRQL offers a robust, easy-to-use risk predictor that can help identify patients who may require additional care to avoid adverse outcomes, making it applicable in most clinical settings worldwide [21,22]. In this study, the KCCQ facilitated the monitoring of QoL improvements, with better results observed in the ARNI group compared to the ACEI group regarding the KCCQ overall score. This outcome is similar to the PARADIGM-HF study, which reported higher overall KCCQ scores for patients treated with ARNI compared to those treated with ACE-I (20.5% vs. 12.1%, respectively) [22,23].

Suppression of ST2 is present in cardiac myocytes and fibroblasts and is part of the IL-1 receptor family [9]. According to the American Heart Association's statement on biomarkers in heart failure, ST2 has emerged as a novel cardiovascular biomarker for diagnosing acute heart failure and predicting the progression of chronic heart failure [24]. Other important biomarkers in this context include troponin, C-reactive protein, and natriuretic peptides, which are essential for diagnosing, managing, and prognosing patients with heart failure. However, in the Prospective Randomized study of Myocardial Infarction, Rehabilitation, and Heart Failure (PRIMA trial), medical therapy did not reduce mortality or morbidity, even though patient management guided by NT-proBNP levels had a positive effect [25]. Furthermore, treating patients with HFrEF based on NT-proBNP levels did not improve outcomes, leading to the early termination of the recent randomized controlled Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) trial [25,26].

Given that ST2 is a relatively new biomarker, few studies have focused on its use in heart failure [10,27]. Previous studies have indicated that ST2 is a powerful prognostic tool for patients with chronic heart failure [10,28]. In the present study, the initial change in ST2 levels was not significantly different between the ACEI and ARNI groups. In the case of troponin T, although the level was significantly reduced in the ARNI group, the change was not significantly different in comparison to that in the ACEI group. These results contrast with findings from previous studies [19,29]. In the PARADIGM trial, for instance, NT-proBNP levels were reduced more in the ARNI group than in the ACEI group [19]. Another study also demonstrated a greater reduction in ST2 levels from baseline in patients receiving ARNI compared to ACEI [29]. It is worth noting that ARNI prescription in the Indonesian population presents challenges due to its stronger hypotensive side effects [30]. Consequently, there was a hesitation to increase the ARNI

dosage when a patient's blood pressure fell below 100 mmHg. Discrepancies in dosing strategy could be the reason why the findings of the present studies were not aligned with previous trials [19,31,32].

In the present trial, the LVEF parameter showed a significant improvement in the ARNI group compared to the ACEI group. ARNI acts through dual mechanisms, inhibiting both angiotensin II receptors and the enzyme neprilysin (also known as enkephalinase) [33]. This inhibition allows ARNI to benefit the cardiovascular system by blocking neprilysin, which increases the levels of peptides, such as natriuretic peptides, that are normally broken down by this enzyme [33]. Consequently, ARNI promotes vasodilation, induces diuresis and natriuresis, enhances the protective effects of natriuretic peptides on the cardiovascular system, mitigates myocardial hypertrophy and fibrosis, reduces cardiac load, and ultimately improves cardiac function. These two complementary mechanisms work together to support and improve left ventricular function [33].

In this study, there was no statistically significant difference in adverse outcome incidence between the ARNI and ACEI groups. A total of 13 individuals (16.25%) encountered major adverse cardiovascular events (MACE). Among these, 7 subjects were in the ARNI group, comprising 4 deaths and 3 people who were re-hospitalized. Several factors may explain the observed greater risk of cardiovascular mortality in our study, including the lower prevalence of achieving maximum ARNI dosages and the advanced stage of heart failure in our study population. A previous study identified hypotension as the main adverse event, occurring in 21 patients in the ARNI group and 11 patients in the ACEI group [34]. A recent study also reported hypotension as the most frequent adverse event, with an overall incidence of 16% and symptomatic cases comprising 4% [30]. Specifically, symptomatic hypotension was observed in 2.3% of cases in the ARNI-TR trial and 14% in the PARADIGM-HF trial [19]. This is particularly important for patients with low baseline blood pressure who are being evaluated for ARNI initiation. For physically frail patients, slower titration and careful monitoring can improve drug tolerance, while reducing or discontinuing other antihypertensive medications may enhance ARNI tolerability. Additionally, impaired renal function and electrolyte imbalances are among the other expected side effects of ARNI [30].

This present study faced several limitations. Firstly, the initiation of ARNI therapy was generally delayed until patients exhibited signs of clinical decline. Consequently, the ARNI group demonstrated minimal improvement in key health parameters compared to the ACEI group, potentially impacting the comparative outcomes. Additionally, optimal dosage titration for ARNI was limited, as physicians expressed concerns over the drug's adverse side effects, resulting in suboptimal dosing. The most substantial limitation, however, was low patient adherence to prescribed medications. Various factors contributed to this, including limited access to healthcare facilities and the high cost of medications, both of which posed significant barriers to consistent patient follow-up and adherence.

Conclusion

This study revealed that both ACEI and ARNI can enhance QoL and LVEF, with the latter found to be more efficacious. No significant differences were observed in the improvements of ST2 and troponin T between the two groups. More importantly, no significant difference was observed in MACE incidences between the ACEI and ARNI groups. Further studies with rigorous methodology and cost-effectiveness analysis should be established for this population.

Ethics approval

The Declaration of Helsinki's guiding principles were followed in the conduct of this study. The Dr. Zainoel Abidin General Hospital Ethics Committee gave its approval (No. 124/ETIK-RSUDZA/2023).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

The corresponding author can provide the data that back up the study's findings upon request. The data are not accessible to the general public because of ethical and privacy concerns.

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