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Should We Retain Half-Dose ARNIs in HFrEF? Lessons Learned from Reverse Remodeling using CORE-HF Real-World Data

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ABSTRACT

Background: Heart failure (HF) is a progressive health problem with high mortality and morbidity rates in both developed and developing countries. Patients with HF who develop reverse remodeling during treatment have better outcomes and lower mortality. Real-world data on the reverse remodeling effects of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor-neprilysin inhibitors (ARNIs) in Indonesians are yet to be available.

Objectives: This study aimed to compare the reverse cardiac remodeling of patients with heart failure with reduced ejection fraction (HFrEF) treated for six months with an ARNI or ACEI based on the CORE-HF registry.

Methods: We conducted a non-experimental, sub-analysis study of the CORE-HF database at the Heart Failure Clinic of Universitas Sebelas Maret Hospital from 2018 to 2021. One group had been treated with ARNIs, while the other was administered with the optimal tolerated ACEI. A six-month follow-up was carried out to determine left ventricle reverse remodeling (LVRR) and functional class alteration as endpoints.

Results: While 89.2% of those in the ACEI group could tolerate the maximum dose, only one person in the ARNI group received the maximum dose, with the majority receiving half the maximum dose (100 mg BID). After six months, LVRR occurred at a similar rate in both groups (26.31% for ARNI and 26.15% for ACEI; P = 0.989). However, the New York Heart Association functional class improved more in the ARNI group (mean 0.95 ± 0.7 vs. 0.62 ± 0.86; P = 0.128).

Conclusions: Despite similar LVRR and functional capacity improvements, a slightly better echocardiography improvement was observed in the ACEI arm. We postulate that full intervention of the renin-angiotensin-aldosterone system should still be the main goal, together with other guideline-directed medical therapies for HF. Hence, cost-effective full-dose of ACEi should be chosen for low- to middle-income countries whose ARNI was not easily available yet due to several issues.

1. Background

Heart failure (HF) is a progressive disease with high morbidity and mortality rates in both developed and developing countries. It affects nearly 26 million people worldwide (1). Despite the scarcity of data on HF in Indonesia, one study revealed high 30-day readmission and mortality rates, with this country having the least expenditure on HF in Asia (2). While coronary artery disease has become the most prominent etiology of HF in Asia, data from CORE-HF (COmprehensive Registry and rEsearch on Heart Failure) depict most patients in Surakarta as men, smokers, hypertensive, and diabetic (1, 3).

Among patients within the HF spectrum, some have preserved (≥ 50%) left ventricular ejection fraction (LVEF), while others have reduced LVEF (< 40%) or mid-range LVEF (4). Heart failure with reduced ejection fraction (HFrEF) has a higher in-hospital and 90-day mortality rate than other spectrums, as also appreciated by CORE-HF in which cumulative all-cause mortality within 24 months of HFrEF was more than twice as high as HFpEF.(1, 3)

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Several important neurohormonal compensatory mechanisms are activated in response to decreased cardiac output. Striking of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) are the first things to happen; although they are initially beneficial, they eventually lead to maladaptive cardiac remodeling (5, 6).

Reverse remodeling (RR) is defined as decreased left ventricular (LV) size combined with improved systolic function. During treatment, RR leads to better outcomes and reduces mortality (7). Angiotensin-converting enzyme inhibitors (ACEIs) can induce RR in patients with chronic HF and post-myocardial infarction (8). On the other hand, PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling during Sacubitril/Valsartan therapy for Heart Failure) evidenced reduction of N terminal pro–b-type natriuretic peptide (NT-proBNP) concentration by angiotensin receptor-neprilysin inhibitors (ARNIs), correlating with improvements of cardiac volume and function of patients with HFrEF after 12 months of treatment (9).

The patient's response to the drug is influenced by several factors, including race and ethnicity (10, 11). For example, monotherapy with ACEIs or angiotensin receptor blockers (ARBs) for hypertension is less effective in the Afro-American race because of genetic predisposition (12, 13). Real-world data on the RR effects of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor-neprilysin inhibitors (ARNIs) in Indonesians are yet to be available.

2. Objectives

This study aims to compare the RR of patients with HFrEF treated for six months with ARNI or ACEIs based on the CORE-HF registry.

3. Patients and Methods

3.1. Study Design and Subjects

This was a non-experimental study that recruited samples from the CORE-HF database. CORE-HF is a continuous real-world registry on chronic HF, and its two-year epidemiological data were published in late 2021. All these studies were conducted at the Heart Failure Clinic of Universitas Sebelas Maret Hospital, commencing in 2018. All patients who showed up at the outpatient HF Clinic with HFrEF were treated based on current ESC (4), ACC/AHA (14), and IHA Guidelines (15) by a cardiologist certified by the Indonesian Heart Failure working group (InaHF-IHA).

We included subjects aged > 18 years with LVEF < 40% on the initial echocardiography. One group comprised subjects treated with an ARNI, while the other consisted of subjects administered with an optimal tolerated ACEI, including ramipril, perindopril, or lisinopril. All subjects were on an optimal tolerated beta blocker and mineralocorticoid antagonist (MRA) therapy. Analysis was made after six months of treatment.

3.2. Primary & Secondary Endpoints

This study's primary endpoint was the occurrence of Left Ventricle Reverse Remodeling (LVRR), appreciated by positive echocardiography results from baseline to six months after therapy. The secondary endpoint was the functional class alteration.

3.3. Echocardiography and Functional Class

Parameters measured at the beginning and end of the study were LVEDD (Left Ventricle End-Diastolic Diameter), LVESD (Left Ventricle End-Systolic Diameter), IVSD (Interventricular Septum Diameter), and LVEF (Left Ventricular Ejection Fraction). Left Ventricle Reverse Remodeling (LVRR) was defined as a 10% reduction of LVEDD and LVESD and a 10% improvement of LVEF. All echocardiography parameters were taken by a cardiologist of the HF Clinic using the ASE Guidelines (16) that prevailed in our hospital practice at that time.

The New York Heart Association (NYHA) functional class was categorized by the usual classification provided by ESC and ACC/AHA Guidelines on Heart Failure. Subjective NYHA classification was used in this article.

3.4. Statistical Analysis

SPSS program version 24 was used to analyze all data. Baseline characteristics are expressed as numbers and percentages for categorical data or mean ± standard deviation for continuous data. Levene's test was used for the equality analysis of variances. Continuous data were compared with the independent t-test, while Pearson's chi-squared test was used for categorical comparison analysis. Some results were analyzed using Fisher's exact test where appropriate. A level of $P < 0.05$ was considered statistically significant.

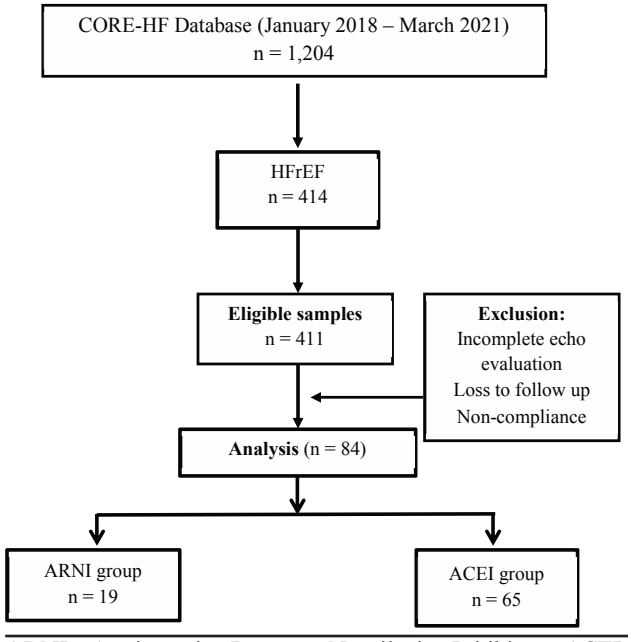
4. Results

Despite the difficulty in ARNI prescription due to its unavailability in our national health insurance coverage, we managed to include 19 patients with ARNI use in our analysis. On the other hand, 65 patients in the ACEI group were eligible as per the inclusion and exclusion criteria (Figure 1). Subjects in the ACEI group were taking either ramipril (95.38%), lisinopril (3.07%), or perindopril (1.53%). Overall, statistics exhibited equality of baseline characteristics between both groups.

While 89.2% of those in the ACEI group could tolerate the maximum dose, only one person in the ARNI group received the maximum dose, with the majority receiving half the maximum dose (100 mg BID). Both groups received indistinguishable proportions of beta blockers, MRAs, and ivabradine, as shown in Table 1. We also appreciate that the ARNI group consumed considerably more loop diuretics than the ACEI group (89.47% vs. 66.15%; $P = 0.048$), which could be the effect of a slightly worse functional class at admission. No significant difference was seen in comorbidities.

On the initial echocardiography, the ARNI group had insignificantly larger LVEDD and LVESD, thinner IVSD, and lower LVEF (Table 2). After six months, there was a slightly better clinical benefit in the ACEI group in terms of LVEDD and LVESD size reduction and LVEF improvement. Most importantly, there was no difference in the LVRR between groups (26.31% for ARNI and 26.15% for ACEi; $P = 0.989$).

Figure 1. Study Flow Chart.



ARNI, Angiotensin Receptor-Neprilysin Inhibitor; ACEI, Angiotensin-Converting Enzyme Inhibitor; HFrEF, Heart Failure with reduced Ejection Fraction

Both groups had no difference in NYHA class at the beginning of medication introduction, as depicted by Table 3, with around three-fourths of them coming to the outpatient HF Clinic with NYHA I-II. The secondary outcome of NYHA showed a superior functional class improvement with ARNI (mean improvement 0.95 ± 0.7 vs. 0.62 ± 0.86; P = 0.128), leaving one patient with ACEi still at NYHA III-IV.

5. Discussion

In heart failure (HF), reduction of cardiac output leads to the intensification of neurohormonal activity as an adaptive and compensatory mechanism (5, 6, 17). Its persistency becomes a source of cardiac remodeling related to negative long-term consequences (8). Thus, sufficient blockade of the systems involved is crucial. The occurrence of LVRR in HF is a predictor of lower mortality, better prognosis, and improved quality of life (7, 18, 19). LVRR is indicated by several criteria such as left ventricular fractional shortening, LVEDD reduction, LVESD reduction, and LVEF improvement (8, 20).

Studies on treating HFrEF with ARNI commenced with the PARADIGM-HF trial in 2014, where 200 mg BID of an ARNI was superior to enalapril in reducing the risks of HF-related hospitalization and death (21). Right after that, more studies were published, strengthening the evidence. Considering the numerous obstacles in up-titrating the ARNI dose, several studies have concluded that a low dose of ARNI still yielded clinical benefits. Corrado et al. (22) determined that a one-year < 75 mg BID dose of ARNI is as effective as a higher dose, though the latter had a shorter time to benefit. According to real-world data from Asia, low-dose ARNI (25 mg BID) for six months provoked beneficial cardiac reverse remodeling and functional class improvement (23). Aside from those clinical benefits, one meta-analysis also showed an advantageous cost-effectiveness ratio of ARNI usage in Europe, America, and Australia compared to ACEIs.(24) However, a ten-year simulated model in Singapore and a study from Thailand indicated otherwise (25, 26). Whether cost-efficiency could be replicated in Asia, where it remains difficult to prescribe the maximal dose of ARNI, is still questionable.

This study compared the occurrence of LVRR in HFrEF patients treated with an ARNI or ACEI for six months. While another study revealed the superior effect of ARNI in LVRR compared to ACEI or ARB even at a low dose (27-29), this study, based on real-world data, failed to show the same outcome. This is possibly due to the dose-dependent effect proposed by several studies, in which a higher dose would

Table 1. Baseline Characteristics of the Two Groups

Baseline Characteristic	ARNI [n = 19]	ACEI [n = 65]	P-value
Demographics			
Age	55.79 ± 12.34	54.55 ± 11.61	0.680
Gender, Male	11 (57.89)	45 (69.23)	0.356
Functional class			
NYHA I-II	14 (73.6)	56 (86.2)	
NYHA III-IV	5 (26.4)	9 (13.8)	0.200
Comorbidities			
CAD	16 (84.21)	47 (72.30)	0.292
Hypertension	9 (47.37)	46 (70.77)	0.059
Diabetes mellitus	6 (31.58)	16 (24.61)	0.544
Atrial fibrillation	1 (5.26)	3 (4.61)	0.907
Smoking	8 (42.1)	37 (56.9)	0.255
Pharmacological treatment			
Beta-blocker	19 (100)	65 (100)	-
MRA	9 (47.37)	34 (52.3)	0.705
Ivabradine	2 (10.52)	1 (1.53)	0.063
Loop diuretic	17 (89.47)	43 (66.15)	0.048
Maximum dose of ARNI/ACEI *	1 (5.2)	58 (89.2)	0.001

Data are presented as mean ± SD or n (%)

Abbreviations: ARNI, Angiotensin Receptor-Neprilysin Inhibitor; ACEI, Angiotensin-Converting Enzyme Inhibitor; NYHA, New York Heart Association; CAD, Coronary Artery Disease; MRA, Mineralocorticoids-Receptor Antagonist.

*Maximum dose of ARNI: 200 mg BID; ACEI: ramipril 10 mg QD, perindopril 10 mg QD, lisinopril 40 mg QD.

Table 2. Echocardiography Profiles among Groups

Echocardiography Parameters	ARNI [n = 19]	ACEI [n = 65]	P-value
Initial			
LVEDD	62.78 ± 8.02	58.84 ± 9.24	0.097
LVESD	55.04 ± 7.32	50.30 ± 10.75	0.076
IVSD	10.21 ± 2.09	11.03 ± 2.44	0.221
EF	23.53 ± 9.56	25.39 ± 8.66	0.423
Echocardiography at 6 months follow up			
LVEDD reduction	-3.55 ± 7.17	-4.17 ± 6.71	0.726
LVESD reduction	-6.88 ± 9.38	-7.76 ± 9.27	0.716
EF improvement	13.44 ± 13.15	14.85 ± 12.46	0.671
LVRR	5 (26.31)	17 (26.15)	0.989

Data are presented as mean ± SD or n (%)
Abbreviations: ARNI, Angiotensin Receptor Blocker-Neprilysin Inhibitor; ACEI, Angiotensin-Converting Enzyme Inhibitor; LVEDD, Left Ventricle End-Diastolic Diameter; LVESD, Left Ventricle End-Systolic Diameter; IVSD, Interventricular Septum Diameter; EF, Ejection Fraction; LVRR, Left Ventricular Reverse Remodeling.

Table 3. Functional Class Profile among Groups

Functional Class	ARNI [n = 19]	ACEI [n = 65]	P-value
Initial			
NYHA I-II	14 (73.69)	56 (86.15)	
NYHA III-IV	5 (26.31)	9 (13.85)	0.200
After 6 months			
NYHA I-II	19 (100)	64 (98.46)	
NYHA III-IV	0	1 (1.54)	0.989 *
Delta NYHA change after 6 months	0.95 ± 0.7	0.62 ± 0.86	0.128

Data are presented as mean ± SD or n (%); * Fisher's exact test
Abbreviations: ARNI, Angiotensin Receptor-Neprilysin Inhibitor; ACEI, Angiotensin-Converting Enzyme Inhibitor; NYHA, New York Heart Association

induce greater LVRR (27). It was unfortunate that only one patient experienced a maximum dose of ARNI, which we believe contributed to this issue. Starting, up-titrating, and maintaining the maximum dose of ARNI in Indonesia, particularly Surakarta, became a noteworthy challenge for the HF Clinic, considering its minimal insurance coverage and the low income per capita of the population. Thus, the small number of samples and number of samples with maximum dose in the ARNI arm might eventually interfere with the head-to-head results of our primary and secondary outcomes.

A recent meta-analysis showed a minimum 5% increase in LVEF, as well as improved LVEDD and LVRR, in patients who used an ARNI compared with an ACEI for nine months (17). Even in a short period of three months, ARNIs still distinctly improved cardiac reserve remodeling compared with ACEIs (27). In our registry, echocardiography findings on follow-up revealed no difference in LVEDD and LVESD reduction, as well as LVEF improvement and LVRR, between the two groups, though from a clinical point of view, the former three variables were better in the ACEI arm. Better neurohormonal suppression with a higher neurohormonal blockage dose can explain this result. On the other hand, worse initial LVEDD, LVESD, IVSD, and LVEF in the ARNI group were in line with the worse initial functional class, meaning that the potential recovery capacity of the ARNI group could have been less.

On the secondary outcome, functional class improvement between groups after six months was not significantly different. However, the ARNI group clinically generated better functional class improvement (mean 0.95 ± 0.7 vs. 0.62 ± 0.86 for the ACEI group), with no one left on NYHA III-IV. Our data failed to reproduce the results of other studies citing a greater NYHA improvement on several months follow-up following ARNI use.(17, 30) Likewise to our primary outcome, it might be due to inadequate blockage produced by under-dosage of ARNI in our registry samples.

With regards to the limitations of our HF Clinic to give guidelines-directed medical therapy with the maximum tolerated dose, we assume that the maximum dose of ACEI was comparable to the half-dose of ARNI in producing LVRR on HFrEF patients within six months. It is in line with previous historical studies in which ACEIs have been proven to prevent cardiac remodeling and promote LVRR in LV dysfunction and HF (31-33). Since our national insurance coverage is yet to fully cover ARNIs, we postulate that a full dose of an ACEI still suffices in ensuring clinical improvement in HFrEF patients.

5.1. Conclusion

This is the first Indonesian study based on real-world data to compare LVRR between half-dose ARNI and full-dose ACEI administration on top of optimal beta-blockers and MRAs in HFrEF. Despite LVRR and functional capacity improvement occurring at the same degree between both groups after six months, a slightly better echocardiography improvement was observed on the ACEI side. We postulate that full intervention of RAAS should still be the main goal, together with other HF guidelines-directed medical therapies. Hence, the cost-effective, full dose of an ACEI should be chosen for low-

to middle-income countries where ARNIs are not easily available due to several issues. Considering population-based differences, further real-world data with larger sample sizes, head-to-head maximum dose comparisons, and longer follow-ups are needed in Indonesia to attain more conclusive results.

5.2. Limitations

This was a sub-analysis of non-randomized CORE-HF real-world data, and ARNIs are still not fully covered by our national health insurance. As a result, only a handful of people use ARNIs, mostly at a sub-optimal dose, since its price is still a concern for almost all of our patients. As most of our patients refused to continue the ARNI after six months, we believe switching from an underdose ARNI to an optimal full-dose ACEI will benefit them.

5.3. New Insights

In HFrEF, adequate blockade of the renin-angiotensin-aldosterone system by the maximally tolerated dose should still be the main treatment goal, alongside other essential drugs.

According to real-life data, patients with low per-capita income tend to use a sub-optimal dose of ARNIs.

The cost-effective full dose of an ACEI should be chosen in low- to middle-income countries where ARNIs can not be adequately prescribed.

5.4. Ethics Approval

The Health Research Ethics Committee of the Faculty of Medicine Universitas Sebelas Maret, Surakarta, Indonesia, approved this study as a part of CORE-HF (No:57/UN27.06.6.1/KEP/EC2021).

5.5. Informed Consent

The Informed Consent form was uploaded in the supplementary files during submission (file name: Informed Consent CORE-HF.pdf)

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Authors' Contribution

Study concept and design: II and HA; Acquisition of data: IHR and TW; Analysis and interpretation of data: II, IHR, and HA; Drafting of the manuscript: II and IHR; Critical revision of the manuscript for important intellectual content: II, and TW; Statistical analysis: IR and HA; Administrative, technical, and material support: II, IR, and HA; Study supervision: II and TW.

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The authors declare no conflicts of interest for this article; all authors have read and approved the final manuscript.

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