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Comparison of NT-ProBNP Changes in Heart Failure Patients Following ACEI vs ARB Therapy

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ABSTRACT

NT-proBNP is a specific biomarker synthesized directly by the ventricular heart muscle under conditions of stretching or stress. The decrease in NT-proBNP levels correlates with clinical improvement in heart failure; a decrease exceeding the biological variation (>25%) indicates a good therapeutic response. Comparing effectiveness of ACEi and ARB therapies in outpatient heart failure patients in reducing NT-proBNP levels. This prospective study involved outpatient heart failure patients receiving ACEi or ARB therapy. Blood samples were taken at baseline and after two months of therapy from patients who met the inclusion criteria. The study included 27 subjects meeting inclusion criteria (13 ACEi group and 14 ARB group). The percentage change in NT-proBNP for ACEi was 29.47% (1.85 – 67.82) and for ARB was 40.53% (9.11-131.02), which was not statistically significant (p = 0.308). There were no significant changes in kidney function assessed by eGFR from baseline to post-therapy (p >0.05). The effectiveness of ACEi therapy compared to ARB in reducing NT-proBNP levels over two months was not significantly different.

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ABSTRAK

NT-proBNP merupakan biomarker spesifik yang disintesis langsung oleh otot ventrikel jantung dalam kondisi meregang atau stress. Biomarker ini direkomendasikan oleh American Colledge of Cardiology/American Heart Association untuk diagnosa awal, stratifikasi keparahan gagal jantung dan menilai prognosa gagal jantung. Penurunan kadar NT-proBNP berbanding lurus dengan perbaikan kondisi klinis pada pasien gagal jantung, dimana penurunan kadar melebihi variasi biologis (>25%) mengindikasi bahwa ada respon terapi yang baik. Penelitian ini dilakukan secara prospektif observasional pada pasien rawat jalan yang menerima terapi ACEi dan ARB. Dilakukan pengambilan sampel darah pada pasien yang memenuhi kriteria inklusi saat baseline dan setelah 2 bulan terapi. Nilai Nt-proBNP sebagai parameter primer diukur menggunakan alat IMMULITE dan serum kreatinin diukur sebagai parameter sekunder. Pada penelitian diperoleh 27 subyek yang memenuhi kriteri inklusia (13 pasien dalam terapi ACEi dan 14 pasien dalam terapi ARB). Setelah 2 bulan terapi, prosentase perubahan NT-proBNP pada terapi ACEi sebesar 29,47 % (1,85 – 67,82 %) dan pada terapi ARB 40,53% (9,11-131,02%) tidak bermakna secara statistik (p = 0.308) dengan asumsi tidak ada perubahan fungsi ginjal yang signifikan pada eGFR baseline dengan post terapi (p = 0,161 pada kelompok ACEi dan p = 0,657 pada kelompok ARB). Sehingga pada penelitian ini, efektivitas pemberian terapi ACEi dibandingkan ARB) dapat menurunkan nilai NT-proBNP secara signifikan selama dua bulan dengan efektivitas yang tidak berbeda signifikan

Kata Kunci: NT-proBNP; Gagal Jantung; Angiotensin Receptor Blocker (ARB); Angiotensin Converting Enzyme Inhibitor (ACEi)

1. Introduction

Heart failure remains a significant non-communicable disease and health issue in Indonesia. According to the 2018 Riskesdas data, 1.5% of the Indonesian population was reported to suffer from heart disease [1]. The treatment of heart failure imposes a substantial financial burden, with healthcare costs reaching USD 139 million as per a 2020 study. This underscores the importance of preventive measures and strategies to enhance the effectiveness of heart failure therapy [2].

Heart failure is a multifaceted clinical condition characterized by symptoms and signs stemming from any structural or functional deficits in ventricular filling or blood ejection[3] . After a cardiac injury such as myocardial infarction, various cellular, structural and neurohormonal changes occur. These changes affect both intracellular and intercelluelar functions. Consequently, the sympathoadrenergic system and renin-angiotensin-aldosteron system are activated, leading to compensation mechanism by heart. These compensations result in volume overload, tachycardia, dyspnea and further worsening of cellular function, creating a vicious cycle [4].

Natriuretic peptides are markers secreted by heart muscle as cardioprotective components in heart failure patients, particularly the types BNP (Brain Natriuretic Peptide) and ANP (Atrial Natriuretic Peptide). They act as antagonists to angiotensin II. In most studies, BNP markers and their fragments (NT-proBNP) are widely used as specific markers or diagnostic tools in assessing the progression of heart failure, as these markers are specifically secreted by the stretching ventricular muscles. In addition to their diagnostic function, in several studies, BNP markers and their fragments (NT-proBNP) are also used to evaluate the effectiveness of pharmacological therapy in heart failure patients, with the assumption that higher NT-proBNP values indicate a worsening degree of heart failure [5][6].

The main principle in heart failure therapy is the inhibition of the renin-angiotensin-aldosterone (RAA) system and the sympathetic nervous system. Therefore, the primary components of therapy for heart failure patients are drugs based on Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs). This is in line with clinical practice recommendations issued by the American College of Cardiology/American Heart Association (AHA), which are based on evidence indicating that ACEI or ARB medications can reduce morbidity and mortality in patients[7]. Several previous studies have found that the therapeutic outcomes of ACEIs and ARBs are not significantly different, with both effectively reducing morbidity and mortality in patients with cardiovascular disorders [8][9]. This study will compare ACEI-based therapy with ARB-based therapy in heart failure patients using the NT-proBNP marker.

2. Methods

This research is a prospective observational study conducted at the Outpatient Cardiology Unit of RSUD Dr. Soetomo in Surabaya. The measurements of NT-proBNP levels and serum creatinine both pre-therapy and post-therapy were performed on heart failure patients who met the inclusion criteria. In this study, subjects divided into 2 main groups : ACEi-based group and ARB-based group. Ethical approval for the study was obtained from the Health Research Ethics Committee of RSUD Dr. Soetomo, with Ethical Clearance Certificate number 474/Panke.KKE/IX/2015.

Patients

Subjects were selected using nonrandom sampling and consecutive sampling methods. Both inclusion and exclusion criteria for subjects recruitment were determined based on several prior research [10] [11] [12]. The following are the criteria used in this research : Male or Female (aged 21 – 75 years), Diagnosed with Chronic Heart Failure class II – III, Receiving ACEi-based or ARB-based therapy in combination with diuretic and/or digoxin at a stable dose for a maximum of 3 months prior to the study (without β-blocker), and Willing to participate in the study. Exclusion criteria : End Stage Renal Disease (Glomerular Filtration Rate < 25 ml/minute) and Body Mass Index ≥ 30 kg/m^2. And if during the course of the study conducted, patients do not return for the second sampel collection or pass away, they will be considered as having dropped out.

Blood Sampling and Assay

Blood sampling for the measurement of NT-proBNP and serum creatinine was conducted in two stages: initially (pre-therapy) and two months later (post-therapy). Blood samples were collected from selected subjects and stored in vacutainers, followed by centrifugation and storage at 8-10°C. NT-proBNP measurements were performed using the Siemens (DPC) IMMULITE® 1000 Immunoassay Analyzer and the IMMULITE 1000 Turbo NT-proBNP kit.

Data Analysis.

Descriptive analysis was conducted on the demographic data, NT-proBNP profile and eGFR profile. Comparative analysis will be performed on the changes in NT-proBNP and eGFR values between both ACEi-ARB groups and pre-post therapy groups using statistical tests.

3. Results and Discussion

Throughout the study period, a total of 27 ambulatory heart failure patients met the inclusion criteria, with 13 patients receiving ACEi therapy and 14 patients receiving ARB therapy. The baseline and post-therapy patient characteristics data for both groups are presented in Table 1 below.

Table 1. Patients characteristic

Characteristics	ACEi group (n = 13)		ARB group (n = 14)		All (n = 27)	
	n	(%)	n	(%)	n	(%)
Sex						
Female	6	(46,2)	3	(21,4)	9	(33,3)
Male	7	(53,8)	1 1	(78,6)	1 8	(66,7)
Age						
< 50	4	(30,8)	4	(28,6)	8	(29,6)
50 - 75	8	(61,5)	1 0	(71,4)	1 9	(70,4)
Etiology						
Cardiomyopathy	3	(23,1)	3	(21,4)	6	(22,2)
Congenital Heart Disease	2	(15,4)	0	(0,0)	2	(7,4)
Coronary Heart Disease	6	(46,2)	5	(35,7)	1	(40,7)
Hypertensive Heart Disease	0	(0,0)	2	(14,3)	1	(7,4)
Valvular Heart Disease	2	(15,4)	4	(28,6)	2	(22,2)
Co-existing illness*						
Atrial Fibrillation	2	(15,4)	2	(14,3)	4	(14,8)
Diabetes Mellitus	0	(0,0)	3	(21,4)	3	(11,1)
Chronic Obstructive Pulmonary Disease (CPOD)	0	(0,0)	1	(7,1)	1	(3,7)
Pulmonal Hypertension	2	(15,4)	0	(0,0)	2	(7,4)

*One patient may have one or more coexisting illness

Heart Failure Patients Characteristics

Both groups ACEi and ARB were contained more male patients (66,7%) compared to female (33,3%). Regarding the age profile, incidence of heart failure was higher in patients aged 50 – 75 years (70,4%) compare to those under 50 years (29,6 %). Gender and age distribution from this study align with previous epidemiological

studies, which also present a higher incidence of heart failure ini males and an increase in incidence with advancing age [13] [14]. According to many epidemiological studies, majority of heart failure cases are instigated by coronary artery disease, involving myocardial infarction and chronic ischemia [15]. The progression of coronary artery disease involves the construction of atherosclerotic plaques, which result from the enlargement of fatty substances. These plaques can constricted the arterial lumen and impede blood flow to the heart, leading to ischemic conditions. Chronic ischemia can lessen blood flow to the heart muscle, adversely affecting the heart's pumping ability (ejection fraction)[16] [17]. The data in this study shows nearly half of the total patients (40,7%) had a history of coronary artery disease as the underlying cause of heart failure, either as Old Myocardial Infarction (OMI) or Acute Myocardial Infarction (AMI).

Drug Therapy Profile.

Therapy profile acquired in this study is depicted in Table 2. The ACEi therapy group used Captopril, Lisinopril, and Ramipril, while the ARB therapy group used Candesartan, Telmisartan, and Valsartan. The ACEI and ARB medications consumed by the patients are catalogued in the National Formulary, as all patients in this study were funded by the National Health Insurance (JKN). Ramipril was the most commonly used ACEI (66.7%), and Valsartan was the most commonly used ARB (66.7%).

Table 2. Drug therapy profile

Profil Terapi	Kelompok Terapi ACEI (n = 13)		Kelompok Terapi ARB (n = 14)		Keseluruhan (n = 24)	
	n	%	n	%	n	%
ACEI						
Captopril	1	(7,7)	-	-	-	-
Lisinopril	4	(30,8)	-	-	-	-
Ramipril	8	(61,5)	-	-	-	-
ARB					-	-
Candesartan	-	-	2	(14,3)	-	-
Telmisartan	-	-	3	(21,4)	-	-
Valsartan	-	-	9	(64,3)	-	-
Co-Therapy*						
Furosemide	10	(76,9)	13	(92,9)	23	(85,2)
Spironolactone	9	(69,2)	9	(64,3)	18	(66,7)
Digoxin	9	(69,2)	7	(50,0)	16	(59,3)
Acetosal	6	(46,2)	8	(57,1)	14	(51,9)
Clopidogrel	2	(15,4)	3	(21,4)	5	(18,5)
Isosorbide Dinitrat	6	(46,2)	3	(21,4)	9	(33,3)
Warfarin	4	(30,8)	4	(28,6)	8	(29,6)
Simvastatin	4	(30,8)	5	(35,7)	9	(33,3)
Beraprost	2	(15,4)	0	(0,0)	2	(7,4)

*One patient may have one or more co-therapy

Pharmacological treatment for heart failure does not depend solely on single-drug ACEI or ARB; it comprises a combination of medications based on principles of neurohormonal modulation, symptomatic treatment, and focusing the underlying causes. Among the non-ACEI and non-ARB therapies, Furosemide (85.2%) and Spironolactone (66.7%) were the most commonly used medications in the patient. Spironolactone, which works via neurohormonal modulation, and Furosemide, which decreases fluid excess to ease the burden on the heart, may affect alters in NT-proBNP levels in addition to the effects of ACEi and ARB therapies. Prior researches have shown that furosemide can enhance neurohormonal outcomes, evidenced by a reduction in NT-proBNP levels by more than 30% in patients with decongestion [18] [19].

In addition to furosemide, spironolactone is a frequently used as co-therapy for patients in both the ACEi and ARB groups. Like furosemide, spironolactone is a diuretic, but it has a weaker diuretic effect compared to loop diuretics like furosemide, resulting in minimal hemodynamic effects. However, spironolactone is an aldosterone antagonist that acts on the neurohormonal modulation pathway in the RAA system, potentially influencing NT-proBNP levels. HOMAGE studies have found that standard doses of spironolactone can reduce BNP levels in patients with an ejection fraction below 60% during therapy. Other studies have also showed that both low (40 mg) and high (80 mg) doses of spironolactone can quickly decrease BNP and NT-proBNP levels in patients with chronic heart failure [20][21].

In this study, the impact of both furosemide and spironolactone on NT-proBNP levels was statistically tested within each ACEi and ARB group, as presented in Table 3. Statistical analysis shows that furosemide and spironolactone did not affect significantly the percentage change in NT-proBNP at both ACEi group and ARB group.

Table 3. Co-therapy statistical analysis

Group	Co-Therapy Analysis	p-value
ACEi	Percentage change in NT-proBNP with furosemide vs without furosemide	p> 0,05 (p = 0.506)
ARB		p> 0,05 (p = 0.429)
ACEi	Percentage change in NT-proBNP with furosemide vs without Spironolakton	p> 0,05 (p = 0.948)
ARB		P > 0,05 (p = 0.947)

Estimated Glomerular Filtration Rate (eGFR) Profile and Analysis

The secondary parameter obtained was serum creatinine, then converted to estimated Glomerular Filtration Rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula. The analysis of eGFR profiles was considered because NT-proBNP clearance primarily occurs through the kidneys. Therefore, renal impairment could decrease NT-proBNP clearance, leading to increased or prolonged levels of NT-proBNP in the blood [22] [23]. In this study, a statistical analysis was conducted on the changes in eGFR of patients at baseline and two months after therapy in the ACEi and ARB groups, as shown in Table 4.

Table 4. eGFR profile analysis

	ACEi group	**ARB group**
Baseline eGFR (ml/minute)	72,82 (44,26 – 112,47)	73,33 (37,05 – 266,68)
Post therapy eGFR (ml/minute)	86.28 (48.54 – 109.66)	90.74 (39.31 – 167.02)
p-value (Baseline Vs Post Therapy)	p > 0,05 (p = 0,161)	p > 0,05 (p = 0,657)

The data above presents that patients in both the ACEi and ARB groups did not experience significant changes in kidney function. Therefore, renal function did not influence the NT-proBNP levels measured and analyzed in this study.

NT-proBNP Profile and Analysis

Before comparing the ACEi and ARB groups, an analysis of NT-proBNP levels was conducted within each group at baseline and after two months of therapy. The data and analysis are presented in Table 5.

Table 5. NT-proBNP baseline – post therapy profile

	ACEi group	**ARB group**
Baseline NT-proBNP (pg/ml)	2045,85 (486 - 5243)	7126,79 (216 - 32112)
Post therapy NT-proBNP (pg/ml)	1476,85 (477 - 2670)	4188,07 (486 - 5243)
p-value (Baseline Vs Post Therapy)	p < 0,05 (p = 0,003)	p < 0,05 (p = 0,011)

From the analysis of Table 5, it was found that in both the ACEi and ARB groups, the NT-proBNP levels at baseline compared to after two months of ACEi/ARB-based therapy showed significant changes ($p<0.05$). This indicates that both ACEi and ARB-based therapies are effective in reducing NT-proBNP levels. Previous studies have similarly reported that ACEi, ARB, or their combination significantly reduce NT-proBNP levels after at least two months of therapy, correlating well with improved prognosis in heart failure patients. Additionally, past research has highlighted that besides effectively lowering NT-proBNP, ACEi and ARB use can reduce cardiac remodeling and improve patient mortality [24][25] [26][27].

The situation above shows that there is a statistically significant change in NT-proBNP levels (a downward trend from baseline); however, it is important to consider the biological variation present in each individual. NT-proBNP levels exhibit considerable biological variability among individuals. In serial NT-proBNP measurements, a decrease exceeding the biological variation can show a positive therapeutic response in heart failure patients. The Frankenstein study demonstrated that when NT-proBNP is measured serially at 14 days, 1 month, 2 months, and 4 months, the biological variation ranges from 11% to 20%. Existing research suggests that clinical improvement in heart failure patients with a good therapeutic response is indicated by a change greater than 25% [28] [29] [10].

The comparison of the effectiveness of ACEi and ARB in changing NT-proBNP levels is expressed as the percentage change from baseline to post-therapy, as shown in Table 6 below.

Table 6. Percentage of change in NT-proBNP

	ACEi group (n = 13)	**ARB group (n = 14)**
Percentage of Change on NT-proBNP (%)Table 6.	29,47 (1,85 - 67,82)	40,53 (9,11 - 131,02)
p-value (ACEi Vs ARB)	p > 0,05 (p = 0,308)	
Number of Patients with >25% Change in NT-proBNP	5 (34.86%)	7 (50%)

The statistical comparison between the ACEi and ARB groups implies that the ability of ACE inhibitors and Angiotensin II receptor blockers to alter or reduce NT-proBNP levels does not significantly differ ($p > 0.05$). This suggests that the efficacy of ACE inhibitors and ARB treatments is similar. Clinical guidelines from the American College of Cardiology/American Heart Association recommend using either ACE inhibitors or ARBs as primary treatments for heart failure, based on evidence from numerous studies. Many research attempts have shown that ARBs are not superior to ACE inhibitors when used as initial therapy, with both being equally effective in improving cardiovascular outcomes (such as acute myocardial infarction, ischemic or hemorrhagic stroke, heart failure hospitalization, and cardiac mortality). However, some studies suggest that ARBs may be inferior to ACE inhibitors [30],[31], [32].

4. Conclusion

This study concludes that therapy with ACEIs (Angiotensin Converting Enzyme Inhibitors) compared to ARBs (Angiotensin Receptor Blockers) significantly reduces NT-proBNP levels over two months, with both treatments demonstrating equal effectiveness.

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