Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Original Article

Renal function and potassium changes in HFrEF patients treated with ACEI vs. ARNI: A prospective cohort study among Acehnese, Indonesia

Iffah Munawarah[1], Teuku Heriansyah[1*], Maimun Syukri[2], Adi Purnawarman[1], Buchari Buchari[3]

[1] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia
[2] Department of Internal Medicine, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia
[3] Department of Clinical pathology, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia

ARTICLE INFO

Keyword :
ACEI;
ARNI;
Heart Failure;
Potassium;
Renal Function.

ABSTRACT

Background: Renin-Angiotensin-Aldosterone System (RAAS) acceleration commonly occur in Heart Failure (HF). Drugs such as Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor-Neprilysin Inhibitors (ARNI) become essential part of HF treatment. Long-term consumption may impair kidney function and potassium imbalance, which could potentially limit the therapy, therefore we conducted this study to assess the effects of ACEI and ARNI on renal function and potassium level in Indonesian patients with heart failure with reduced ejection fraction (HFrEF), as no local studies exist.
Method: A prospective cohort was performed in Banda Aceh, which comprise of 40 ACEI and 40 ARNI patients on standard therapy. Left ventricular ejection fraction (LVEF), serum creatinine level then converted into estimated Glomerular Filtration Rate (eGFR), and serum potassium level were measured at baseline and after 3 months into the therapy. Independent t-test was applied to compare groups.
Result: Both ARNI and ACEI groups showed significant improvement in eGFR ($p < 0.005$). The intergroup difference was 11 mg/dL ($p = 0.038$) showed that ACEI had a better outcome in eGFR improvement compare with ARNI. Potassium rose slightly in both groups, with an intergroup difference of 0.082 mmol/L ($p = 0.623$), indicating no meaningful difference.
Conclusion: Both ACEI and ARNI improved eGFR after 3 months, with a modest potassium increase.

1. Introduction

Heart failure (HF) affects over 20 million population worldwide and recognized as a global health problem due to high mortality and poor quality of life. The incidence of HF rises yearly, with frequent hospital readmissions, making it a major burden.[1] About one in four hospitalized patients are readmitted within 30 days, and almost half within six months. Khan et al. reported increase of readmissions (30–90 days) between 2010–2017.[2] HF results from impaired systolic and diastolic function, reducing the heart's ability to provide enough blood for body and meet metabolic needs.[3] Left ventricular ejection fraction (LVEF) is widely used to assess cardiac function and predict outcomes in HF, particularly in reduced ejection fraction (HFrEF).[4]

The Renin-Angiotensin-Aldosterone System (RAAS) regulate sodium and fluid balance, influencing blood pressure through the heart, kidneys, and vessels.[5] In HFrEF, RAAS activity is elevated.[6] Reduced sodium delivery to the distal tubule causes glomerular hypoperfusion and sympathetic activation, leading to renin release and a cascade of vasoconstriction, fluid retention, and potassium excretion.[5] ACE inhibitors (ACEIs) block angiotensin I to II conversion, lowering angiotensin II levels and RAAS activation.[6] Those mechanism reduces preload, afterload, improves natriuresis, and lowers vascular pressures, lead to improving clinical outcomes in HF.[7] For this reason, ACEIs remain a cornerstone in HF therapy.

Angiotensin receptor-neprilysin inhibitors (ARNIs) combine neprilysin inhibition with RAAS blockade (sacubitril/valsartan).[8] They enhance remodeling, diuresis, and natriuresis while reducing vasoconstriction and fluid retention. Trials show ARNI lowers HF readmission and mortality, particularly in HFrEF.[8] Consequently, ARNI is now among the four pillars of HFrEF therapy with ACEI, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2 inhibitors.[9]

Despite the benefit, RAAS inhibitors can impair kidney function which lead to hyperkalemia. The effect could cause dose adjustments or discontinuation of the therapy.[10] Schmidt et al. found >30% serum creatinine rise in over 120,000 ACEI users, highlighting renal risks.[11] ACEIs may also increase potassium, and both hyperkalemia and hypokalemia raise mortality risk.[10,12,13] Nevertheless, ACEI benefits often outweigh risks.

ARNI can also affect renal outcomes. Some studies reported increased urinary albumin-to-creatinine ratiol.[14] Major clinical studies including PARADIGM-HF and PIONEER-HF showed ARNI exceeds ACEI in enhancing survival and lowering morbidity in HFrEF patients.[8–15]

Most evidence derives from Caucasian cohorts, while Asian populations remain underrepresented. Genetic, lifestyle, and metabolic differences may influence disease expression and treatment response.

* Corresponding author at: Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia
E-mail address: teuku_hery@usk.ac.id (T.Heriansyah).

https://doi.org/10.21776/ub.hsj.2026.007.02.10
Received 25 December 2025; Received in revised form 16 March 2026; Accepted 30 March 2026
Available online 26 April 2026

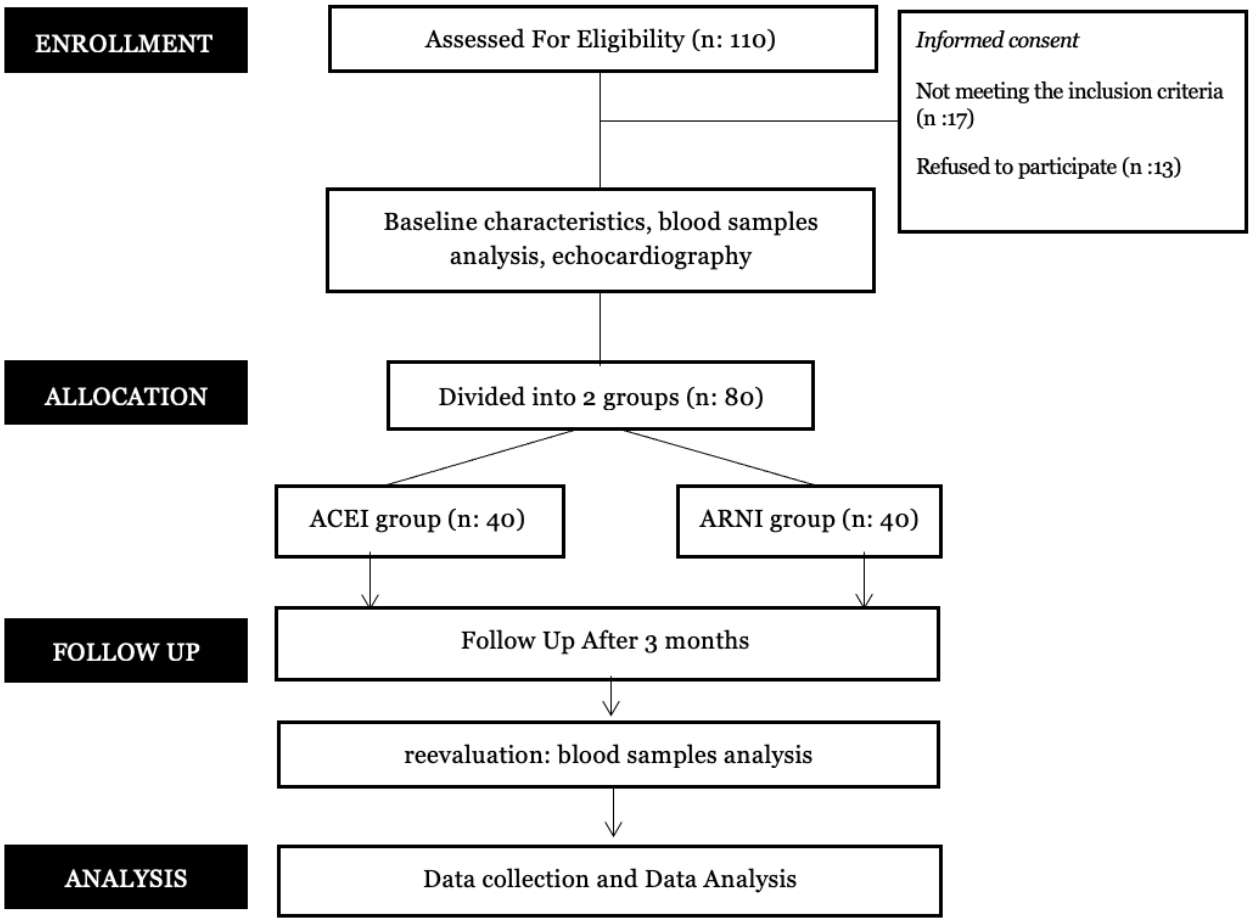


Figure 1. Consort flow of the study

Hence, this study investigates the outcome of ACEI and ARNI on renal function and potassium level in Indonesian HFrEF patients, focusing on Acehnese ethnicity.

2. Methods

Study design

This prospective cohort study was carried out from February to April 2023 at Intensive Coronary Care Unit (ICCU) and Cardiology Ward of Dr. Zainoel Abidin General Hospital, Banda Aceh, Indonesia. It evaluated the outcomes of ACEIs and ARNIs on renal function and serum potassium in HFrEF patients.

Ethical approval

Following the ethical guidelines of the Declaration of Helsinki's, The Dr. Zainoel Abidin General Hospital Ethics Committee granted approval for this study (No. 124/ETIK-RSUDZA/2023).

Study population

Purposive sampling identified HFrEF patients receiving ACEI or ARNI therapy. Using Slovin's formula, a minimum of 31 participants was required; this was increased by 20% to 40 per group. Inclusion criteria is adults aged 18–75 with cardiologist-confirmed HFrEF (LVEF <50%). With patient with congenital heart disease, severe valvular disease, COPD, or late-stage chronic kidney disease {stage IV – V or estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73m^2 were not included in this study

Data collection

Baseline data included demographics, vital signs (blood pressure, heart rate), body mass index (BMI), and LVEF. Echocardiography used the Simpson method (GE Vivid E95), calculating ejection fraction. Comorbidities such as hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg) and diabetes (fasting glucose ≥126 mg/dL, 2-hour glucose ≥200 mg/dL, or HbA1c ≥6.5%) were noted. Smoking history was recorded. Blood specimens were taken from the brachial vein at baseline and 3 months to measure creatinine and potassium. All renal data were converted into eGFR to provide standardized assessment of renal function.

Measure

To examining renal function, serum creatinine was first measured. Serum creatinine level was measured using Jaffe kinetic method (Indiko analyzer). Samples were placed in heparin tubes (avoiding EDTA, citrate, fluoride). Calibration used ScaI calibrators and Nortrol controls, with aliquots stored at –20°C. Values were reported in mg/dL. The obtained serum creatinine level was then converted to eGFR using the CKD – EPI formula. Results were expressed in mL/min/1.73m^2.

Potassium was analyzed using Ion Selective Electrodes (ISE) on the Nova 5 CRT Electrolyte Analyzer. Sample preparation was similar to creatinine testing. Calibration involved replacing reagent tubes and adjusting parameters. Results were expressed in mmol/L.

Data analysis

Baseline characteristics were presented descriptively. Continuous data are summarized using mean ± SD or median (min–max), whereas categorical data were described using frequency and percentage. Normality was tested by Shapiro-Wilk. Paired t-tests were implemented for normally distributed data, Mann-Whitney U or Wilcoxon tests otherwise. A p-value <0.05 indicated significance. Analysis used SPSS version 25 (SPSS Inc., Chicago, IL, USA).

3. Result

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

Characteristics	N (%)		P-Value
	ACEI (n=40)	ARNI (n=40)	
Age, mean±SD (years)	56±11	61.5±9	0.007
Sex			1.00
Male	31 (77.5)	32 (80.0)	
Female	9 (22.5)	8 (20.0)	
Systolic blood pressure (SDP), mean±SD (mmHg)	122.25±23.77	126.32±23.71	0.459
Diastolic blood pressure (DBP), mean±SD (mmHg)	70.83±0.96	69.35±10.23	0,706
Hypertension			1.00
Yes	17 (42.5)	17 (42.5)	
No	23 (57.5)	23 (57.5)	
Type 2 diabetes mellitus			0.924
Yes	17 (53.1)	15 (46.9)	
No	23 (47.9)	25 (52.1)	
Smoking			1.00
Yes	27 (67.5)	27 (67.5)	
No	13 (32.5)	13 (32.5)	
Body mass index (BMI), (kg/m^2)			1.00
Mean±SD	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)	
Creatinine Pre	1.05±0.28	1.15±0.27	0.146
Pottasium Pre	4.1±0.54	4.08±0.59	0.854
eGFR Pre	72 (39 – 134)	82 (30 – 120)	0.312

Table 2. Effect of ACEI and ARNI administration on eGFR among HFrEF patients (n=80)

Groups	mL/min/1.73m^2		*p*-value
	Pre	Post	
ARNI (n=40)	78.24±21.90	87.05±17.10	0.002[a]
ACEI (n=40)	72(39–134)	99(60 - 114)	0.001[b]

[a] Analyzed with Paired T-test
[b] Analyzed with Wilcoxon test

Table 3. Comparison of eGFR after ACEI and ARNI administration among HFrEF patients (n=80)

Groups	Delta (Mean ± SD)	Difference	*p*-value[a]
ARNI	8.81±22.0	11.05	0.038
ACEI	19,86 ± 22.7		

[a] Analyzed with Independent sample T-test

Table 4. Effect of ACEI and ARNI administration on potassium levels among HFrEF patients (n=80)

Groups	Potassium levels (mmol/L)		*p*-value[a]
	Pre	Post	
ARNI (n=40)	4.0 ± 0.59	4.4 ± 0.60	0.015[a]
ACEI (n=40)	4.1 (3.2–5.5)	4.1 (3.2–5.4)	0,036[b]

[a] Analyzed with Independent sample T-test
[b] Analyzed with Wilcoxon test

Table 5. Comparison of potassium levels after ACEI and ARNI administration among HFrEF patients (n=80)

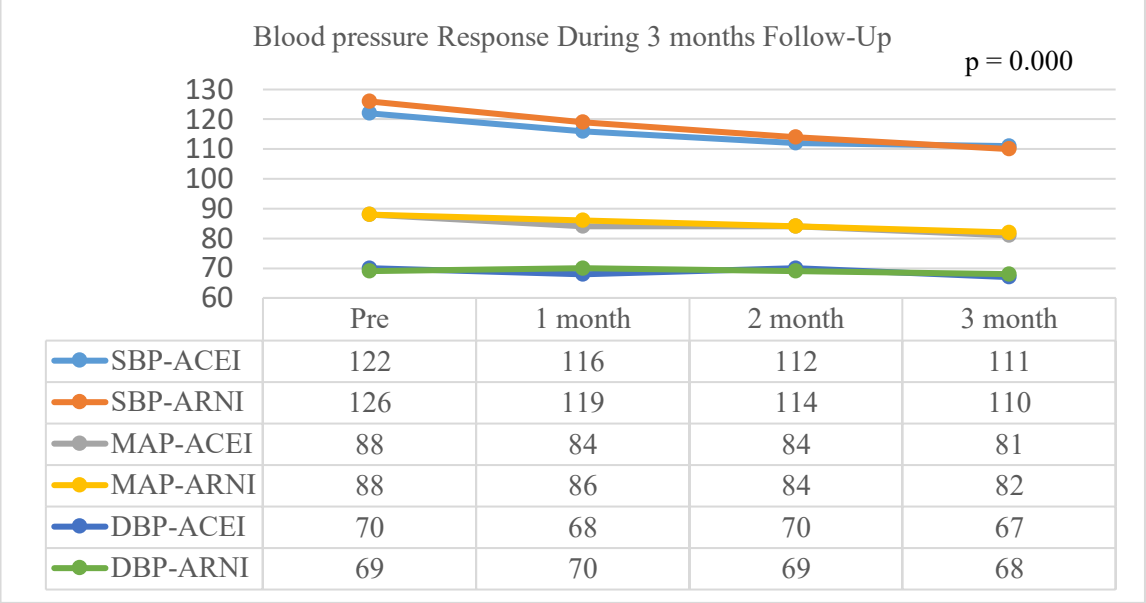
Groups	Delta (Mean ± SD)	Difference	*p*-value[a]
ARNI	0.33 ± 0.79	0.082	0.623
ACEI	0.25 ± 0.69		

[a] Analyzed with Independent sample T-test

Table. 6 Metabolic and demographic factors to eGFR changes

Cofounding Factors	B	SE	*p*-value[a]	B CI 95%
Age	0.475	0.267	0.080	-0.058, 1.008
Type 2 Diabetes	1.270	5.447	0.013	-9.600, 12.139
Hypertension	-6.643	5.373	0.816	-17.363, 4.078
RAAS Inhibitor	-14.005	5.477	0.013	-24.935, -3.076
Constant	-4.449	14.915		

[a] Analyzed with Linier Regression test



	Pre	1 month	2 month	3 month
SBP-ACEI	122	116	112	111
SBP-ARNI	126	119	114	110
MAP-ACEI	88	84	84	81
MAP-ARNI	88	86	84	82
DBP-ACEI	70	68	70	67
DBP-ARNI	69	70	69	68

Figure 2. Blood Pressure Response during 3 months follow up periode.

Patient selection

From 110 screened HFrEF patients, 17 excluded and 13 declined, leaving 80 participants. They were allocated into ACEI (n=40) and ARNI (n=40) groups. **Figure 1** outlines the recruitment process.

Baseline characteristics

Baseline characteristics illustrated in **Table 1**. The ARNI group was older than the ACEI group. Both groups were predominantly male. Blood pressure was comparable, though systolic values were slightly higher in ARNI patients (126.32±23.71 vs 122.25±23.77 mmHg). Hypertension, diabetes, and smoking prevalence were similar. BMI distribution was also not significantly different. Baseline characteristics showed a statistically significant difference in age; therefore, multivariate analysis was subsequently performed (**Table 6 and 7**)

Blood pressure changes

Monthly blood pressure monitoring is shown in Figure 2. Wilcoxon analysis revealed significant reductions in systolic, diastolic, and mean arterial pressure (MAP) after 3 months in both groups ($p < 0.001$).

Main findings

A total of 40 ACEI and 40 ARNI groups was enrolled in our study. **Table 2** shows eGFR results. Both groups demonstrated improvement in eGFR ($p < 0.005$). As shown in **Table 4**, potassium rose significantly in both groups after 3 months ($p < 0.05$). Seven patients in each group developed mild hyperkalemia (max 5.4 mmol/L). The intergroup difference in eGFR was 11 mL/min/1.73m^2 ($p = 0.038$), ACEI demonstrated greater improvement in eGFR compared with ARNI. Potassium rose slightly in both groups, with an intergroup difference of 0.082 mmol/L ($p = 0.623$), indicating no meaningful difference (**Table 3** and **Table 5)**. Despite the slight increase in potassium levels, no dangerous symptoms were observed, hence the therapy was continued.

4. Discussion

RAAS inhibitors remain essential in HFrEF therapy, but increase of kidney function level and dyskalemia often leads to discontinuation.[16,17] Making regular monitoring of kidney function and potassium important

This study showed ARNI improved patient's serum creatinine level compared to the baseline, consistent with trials such as PARADIGM-HF.[7] The nephroprotective effect is linked to enhance the natriuretic peptide activity, reducing inflammation, fibrosis, and improving renal perfusion through the decrease of blood pressure and arteriole vasodilation.[18] Furthermore, ARNI improves renal hemodynamics by inducing systemic blood pressure reduction, dilatation of afferent arterioles, and relative vasoconstriction of efferent arterioles, which collectively enhance renal blood flow[18]. Improved cardiac output may also support renal function, as reported in various study such as PARADIGM-HF, PARAGON-HF, and PIONEER-HF.[7,14,19]

Patients with ACEI also showed improved serum creatinine, contrary to earlier reports of increased levels.[4,20–22] Rise of serum creatinine are often considered as "pre-renal success," reflecting renal protection.[4,22] Increase of serum creatinine level up to 30% which will stabilize within the next four weeks are still acceptable. Long-term ACEI benefits include reduced intraglomerular pressure, improved filtration, and lower albuminuria. Usage of ARNI enhance renal flow via natriuretic peptides, dilating afferent arterioles and relaxing mesangial cells, while ACEI dilates efferent arterioles, reducing hyperfiltration but risking transient GFR decline and hyperkalemia.[23]

Hyperkalemia is a concern in patient with RAAS inhibitors, especially in older patients, diabetics, and those with Chronic kidney disease (CKD).[24] Reduced cardiac output decreases renal perfusion, activating RAAS and sympathetic pathways. While initially adaptive, this contributes to electrolyte imbalance. ACEI and ARNI both suppress aldosterone, limiting potassium excretion. Adding MRAs further increases risk by directly blocking aldosterone-driven sodium reabsorption and potassium elimination.[25,26]

In this study, potassium rose significantly in both groups, with mild hyperkalemia (potassium level was > 5 to ≤ 6 mmol/L) found in 14 patients. No difference was found between ACEI and ARNI, consistent with PARADIGM-HF and PIONEER-HF studies where hyperkalemia rates were similar.[7,14,24] Severe hyperkalemia (potassium level > 7 mmol/L) was rare in both groups.[7] Although Mineralocorticoid Receptor Antagonists (MRAs) increase the risk further, ARNI may carry a slightly lower risk than ACEI, but close monitoring is essential.

This is the first Indonesian study to compare both ARNI and ACEI on renal function and potassium level as the side effect of the therapy. Both groups improved serum creatinine level, with no difference in hyperkalemia or MACE incidence, consistent with Heriansyah et al.[27]

Various factors may explain the differences between the findings of this study and those of earlier research, including variations in patient ethnicity, age, body mass index (BMI), metabolic factors such as hypertension and diabetes mellitus, treatment duration, and medication dosing. For example, Desai et al. conducted their research in a U.S. cohort with a mean BMI of 30 kg/m^2, and ARNI therapy was

escalated to the target dose of 97/103 mg. Conversely, the current study involved Indonesian participants with an average BMI of 25 kg/m^2, and the ARNI dosage remained below the maximum. Moderation in ARNI dosage is likely due to a more pronounced blood pressure-lowering effect observed in the Indonesian population compared to Caucasians, which may present challenges in achieving full titration. The Acehnese population has a distinct regional dietary pattern characterized by high intake of sodium, fat, and sugar. This pattern may affect their metabolic profile; therefore, the changes in eGFR and potassium levels observed in this study were likely influenced not only by medication but also by other factors, including metabolic conditions.

This study has several limitations: (1) the sample size was limited and from a single institution; Future studies are recommended to use a randomized controlled trial (RCT) design to ensure better control of the study population and minimize potential bias, (2) the follow-up duration was short; (3) the influence of dosage variations on outcomes did not evaluate in this study; and (4) information regarding additional heart failure therapies administered to patients was not reported.

5. Conclusion

Significant improvement in eGFR was observed in HFrEF patients received with both ACEI and ARNI after three months of therapy. Additionally, while both therapies demonstrated improved eGFR during the 3 months follow-up period, a slight increase in serum potassium levels was observed in both groups.

6. Declaration

6.1 Ethics Approval and Consent to participate
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).

6.2. Consent for publication
Not applicable.

6.3 Availibility of data and materials
Data used in our study were presented in the main text.

6.4 Competing interests
Not applicable.

6.5 Funding Source
This research was supported by the Ministry of Higher Education through Universitas Syiah Kuala, under Grant Number 381/UN11.2.1/PG.01.05/2023.

6.6 Authors contributions
Idea/concept: TH, IM. Design: TH,IM Control/supervision: TH, IM, MS, AP, BC. Data collection/processing: TH, IM. Analysis/interpretation:TH, IM, MS, AP, BC. Literature review: TH, IM. Writing the article: IM. Critical review: TH, MS, AP, BC.. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

6.7 Acknowledgements
Authors express their gratitude to the staffs of cardiac center ward of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia.

References

1. Bhat TS, Hafeez I, Tak SF, Mattoo A, Patigaroo AR, Khan A, et al. Safety and efficacy of ARNI (valsartan/sacubitril) vs ACEI (enalapril) in acute heart failure – A prospective observational study. *Indian Heart J*. 2022;74(3):178-181. doi:10.1016/j.ihj.2022.04.003

2. Khan MS, Sreenivasan J, Lateef N, Abougergi MS, Greene SJ, Ahmad T, et al. Trends in 30- and 90-Day Readmission Rates for Heart Failure. *Circ Heart Fail*. 2021;14(4). doi:10.1161/CIRCHEARTFAILURE.121.008335

3. Solomon SD, Claggett B, Desai AS, Packer M, Zile M, Swedberg K, et al. Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction. *Circ Heart Fail*. 2016;9(3). doi:10.1161/CIRCHEARTFAILURE.115.002744

4. Momoniat T, Ilyas D, Bhandari S. ACE inhibitors and ARBs: Managing potassium and renal function. *Cleve Clin J Med*. 2019;86(9):601-607. doi:10.3949/ccjm.86a.18024

5. Tan NY, Deng Y, Yao X, Sangaralingham LR, Shah ND, Rule AD, et al. Renal Outcomes in Patients with Systolic Heart Failure Treated With Sacubitril-Valsartan or Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker. *Mayo Clin Proc Innov Qual Outcomes*. 2021;5(2):286-297. doi:10.1016/j.mayocpiqo.2020.10.008

6. Raebel MA. Hyperkalemia Associated with Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers. *Cardiovasc Ther*. 2012;30(3). doi:10.1111/j.1755-5922.2010.00258.x

7. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *New England Journal of Medicine*. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077

8. Bauersachs J. Heart failure drug treatment: the fantastic four. *Eur Heart J*. 2021;42(6):681-683. doi:10.1093/eurheartj/ehaa1012

9. Clark AL, Kalra PR, Petrie MC, Mark PB, Tomlinson LA, Tomson CR. Change in renal function associated with drug treatment in heart failure: national guidance. *Heart*. 2019;105(12):904-910. doi:10.1136/heartjnl-2018-314158

10. Schmidt M, Mansfield KE, Bhaskaran K, Nitsch D, Sorensen HT, Smeeth L, et al. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. *BMJ*. Published online March 9, 2017:j791. doi:10.1136/bmj.j791

11. Ferreira JP, Mogensen UM, Jhund PS, Desai AS, Rouleau JL, Zile MR, et al. Serum potassium in the PARADIGM-HF trial. *Eur J Heart Fail*. 2020;22(11):2056-2064. doi:10.1002/ejhf.1987

12. Rossignol P, Dobre D, McMurray JJV, Swedberg K, Krum H, Veldhuisen DJ, et al. Incidence, Determinants, and Prognostic Significance of Hyperkalemia and Worsening Renal Function in Patients With Heart Failure Receiving the Mineralocorticoid Receptor Antagonist Eplerenone or Placebo in Addition to Optimal Medical Therapy. *Circ Heart Fail*. 2014;7(1):51-58. doi:10.1161/CIRCHEARTFAILURE.113.000792

13. Voors AA, Gori M, Liu LCY, Claggett B, Zile MR, Pieske B, et al. Renal effects of the angiotensin receptor neprilysin inhibitor LCZ696 in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail*. 2015;17(5):510-517. doi:10.1002/ejhf.232

14. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure. *New England Journal of Medicine*. 2019;380(6):539-548. doi:10.1056/NEJMoa1812851

15. Tamargo J, Kaski JC, Kimura T, Barton JC, Yamamoto K, Komiyama M, et al. Racial and ethnic differences in pharmacotherapy to prevent coronary artery disease and thrombotic events. *Eur Heart J Cardiovasc Pharmacother*. 2022;8(7):738-751. doi:10.1093/ehjcvp/pvac040

16. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland. JGF, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;21(10):1169-1186. doi:10.1002/ejhf.1531

17. Drumm K, Kress TR, Gassner B, Krug AW, Gekle M. Aldosterone Stimulates Activity and Surface Expression of NHE3 in Human Primary Proximal Tubule Epithelial Cells (RPTEC). *Cellular Physiology and Biochemistry*. 2006;17(1-2):21-28. doi:10.1159/000091456

18. Pascual-Figal D, Bayés-Genis A, Beltrán-Troncoso P, Caravaca-Perez P, Conde-Martel A, Crespo – Leiro MG, et al. Sacubitril-Valsartan, Clinical Benefits and Related Mechanisms of Action in Heart Failure With Reduced Ejection Fraction. A Review. *Front Cardiovasc Med*. 2021;8. doi:10.3389/fcvm.2021.754499

19. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *New England Journal of Medicine*. 2019;381(17):1609-1620. doi:10.1056/NEJMoa1908655

20. Rouleau JL, Pfeffer MA, Stewart DJ, Isaac D, Sestier F, Kerut EK, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *The Lancet*. 2000;356(9230):615-620. doi:10.1016/S0140-6736(00)02602-7

21. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, et al. Comparison of Omapatrilat and Enalapril in Patients With Chronic Heart Failure. *Circulation*. 2002;106(8):920-926. doi:10.1161/01.CIR.0000029801.86489.50

22. Ahmed A. Use of Angiotensin-Converting Enzyme Inhibitors in Patients with Heart Failure and Renal Insufficiency: How Concerned Should We Be by the Rise in Serum Creatinine? *J Am Geriatr Soc*. 2002;50(7):1297-1300. doi:10.1046/j.1532-5415.2002.50321.x

23. Tsukamoto S, Uehara T, Azushima K, Wakui H, Tamura K. Updates for Cardio-Kidney Protective Effects by Angiotensin Receptor-Neprilysin Inhibitor: Requirement for Additional Evidence of Kidney Protection. *J Am Heart Assoc*. 2023;12(8). doi:10.1161/JAHA.122.029565

24. Ferreira JP, Butler J, Rossignol P, Pitt B, Anker SD, Kosiborod M, et al. Abnormalities of Potassium in Heart Failure. *J Am Coll Cardiol*. 2020;75(22):2836-2850. doi:10.1016/j.jacc.2020.04.021

25. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. *New England Journal of Medicine*. 1999;341(10):709-717. doi:10.1056/NEJM199909023411001

26. Desai AS, Vardeny O, Claggett B, McMurray JJ, Packer M, Swedberg K, et al. Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril. *JAMA Cardiol*. 2017;2(1):79. doi:10.1001/jamacardio.2016.4733

27. Heriansyah T, Lestari ND, Hadi TF, Novia R, Munawarah I, Taufiqurrahman T, et al. ACE inhibitors versus angiotensin receptor-neprilysin inhibitors for HFrEF management: A prospective cohort study from Indonesia. *Narra J*. 2024;4(3):e978. doi:10.52225/narra.v4i3.978