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**RESEARCH ARTICLE**

# ANALYSIS OF KIDNEY FUNCTION PARAMETERS ON THE RENOPROTECTIVE EFFECTS OF ANTIHYPERTENSIVE THERAPY IN PATIENTS WITH CHRONIC KIDNEY FAILURE

## *(ANALISIS PARAMETER FUNGSI GINJAL TERHADAP EFEK RENOPROTEKTIF DARI ANTIHIPERTENSI PADA PASIEN GAGAL GINJAL KRONIK)*

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**ABSTRACT**

*The renoprotective effect in chronic kidney disease (CKD) patients can be induced by antihypertensive therapy, which provides a vasodilatory effect on the blood vessels leading to the kidneys. This resulting renoprotective function is considered to slow the decrease in kidney function in CKD patients. The purpose of this study was to examine the effectiveness of antihypertensive therapy as renoprotective agents through the analysis of kidney function parameters in CKD patients. A descriptive design with a cross-sectional method was used, and the study sample used data from patient medical records, specifically focusing on kidney function parameters of CKD patients during the January-June 2023 treatment period at RSUD Sultan Abdul Aziz Syah Peureulak. Of the 134 respondents, there were two groups of patients receiving antihypertensive therapy: ACE-Inhibitors (ACEIs) and (angiotensin receptor blockers) ARBs. After conducting the Wilcoxon test, there were significant changes in kidney function parameters (Urea, creatinine, and eGFR) between before and after antihypertensive therapy, with a p value <0.05. In the ACEI group, the mean urea level was 72.4 ± 48.3 mg/dL, creatinine 4.8 ± 4.3 mg/dL, and eGFR 30.6 ± 30.8 mL/min. In the ARB group, mean urea was were 85.2 ± 48.7 mg/dL, creatinine 6.1 ± 4.2 mg/dL, and eGFR 21.6 ± 26.7 mL/min. These findings indicate that ACEI and ARB antihypertensive therapies are effective as renoprotective agents in CKD patients.*

**Keywords:** *ACE-Inhibitor, antihypertensive, ARB, reno-protective effect*

*ABSTRAK*

*Efek renoprotektor pada pasien CKD dapat diinduksi dengan terapi antihipertensi yang akan memberikan efek vasodilatasi pada pembuluh darah ke renal. Fungsi renoprotektif yang*

*ditimbulkan dinilai memperlambat proses penurunan fungsi ginjal pasien CKD. Tujuan dari penelitian ini adalah untuk melihat efektifitas terapi antihipertensi kaitannya dengan agen renoprotektif melalui analisis parameter fungsi ginjal pada pasien CKD. Deskriptif desain dengan metode cross-sectonal digunakan, dengan sampel penelitian yang dipakai adalah data dari rekam medis pasien khususnya berfokus pada parameter fungsi ginjal pasien CKD perioede perawatan Januari-Juni 2023 di RSUD Sultan Abdul Aziz Peureulak. Dari 134 responden, terdapat dua kelompok pasien yang mendapat terapi antihipertensi berupa ACEI dan ARB. Setelah dilakukan uji Wilcoxon, terdapat perubahan signifikan antara sebelum dengan sesudah terapi antihipertensi pada parameter fungsi ginjal (Ureum, kreatinin, dan eGFR) dengan nilai p<0,05. Pada kelompok ACEI, nilai rerata ureum didapatkan sebesar 72,4 ± 48,3 mg/dL, kreatinin 4,8 ± 4,3 mg/dL, dan eGFR 30,6 ± 30,8 mL/menit. Sedangkan pada kelompok ARB, ilai rerata ureum adalah 85,2 ± 48,7 mg/dL, kreatinin 6,1 ± 4,2 mg/dL, dan eGFR 21,6 ± 26,7 mL/menit. Terapi antihipertensi ACE-Inhibitor dan ARB efektif sebagai agen renoprotektif pada pasien CKD.*

*Kata Kunci: ACE-inhibitor, antihipertensi, ARB, efek renoprotektif*

## INTRODUCTION

One of the diseases that with a relatively high prevalence in Indonesia is hypertension.[1] In 2019, the World Health Organization (WHO) estimated that there were around 1.28 million cases of hypertension in the world.[2] Data recorded in the National Basic Health Research (Riskesdas)[3] in 2018 showed that 34.11% of Indonesians over 18 years suffer from hypertension. Meanwhile, the prevalence of hypertension based on blood pressure measurements in the population over 18 years old in the Aceh region was 26.45%.[4] The percentage of incidents by age group was 10.48% (18-24 years), 15.45% (25-34 years), 26.88% (35-44 years), 38.05% (age 45-54 years), and 47.11% (55-64 years).[3,4]

Hypertension is a disease that occurs in blood circulation and is characterized by increased blood pressure. A continuous increase in blood pressure can trigger damage to the function and structure of various vital organs, including the kidneys.[1] Hypertension that has been going on for a long time or chronic can lead to a decrease in function or even kidney damage, eventually resulting in kidney failure. In contrast, a progressive decline in kidney function can also worsen hypertension. Barotrauma stimulation caused by hypertension that occurs in the kidney glomerulus can increase pressure on the glomerular structure and trigger glomerulosclerosis, which in turn stimulates hypoxia and damage to the kidney tissue.[5] This condition causes disturbances in kidney function that may lead to kidney failure. Therefore, if it persists over a long period, it can progress to chronic kidney failure. In this situation, changes in the kidney function parameters typically occur,

such as increased urea and creatinine levels, as well as decreased GFR values.

Several types of antihypertensive drug classes function to inhibit the Renin-Angiotensin-Aldosterone system (RAAS), including ACE and ARB enzyme inhibitors, diuretics, CCBs, and beta blockers. These therapies are commonly used in hypertensive patients. It is well known that the ACE-Inhibitor and ARB groups have reno-protective properties, which means they can slow the progression of kidney disease. The reno-protective effect of the ACE-Inhibitor and ARB groups is through the mechanism of vasodilation in the renal arterioles.[6] Currently, many studies have examined kidney function parameters by measuring urea, creatinine, and GFR values. However, relatively few studies specifically evaluate eGFR parameters as an indicator of kidney filtration and its relationship to hypertension patients. In a study by Fandinata SS, et al. (2022), a decrease in serum creatinine was found in CKD patients receiving ARB antihypertensives (candesartan, telmisartan and valsartan), in several results and the largest reduction was 0.33±0.20 mg/dL.[7] Meanwhile, a study by Zhao M, et al. (2021), reported no decrease in GFR in CKD patients receiving a combination of ACE-Inhibitor and ARB antihypertensive therapy.[8] This study aims to determine the effectiveness of antihypertensive drugs as reno-protective agents in CKD patients through the analysis of kidney function parameters

## METHODS

### Research Subjects and Settings

This study is a descriptive analytical study using a cross-sectional method. The study was conducted at RSUD Sultan Abdul Aziz Syah Peureulak by taking samples of medical record data from Chronic Kidney-Disease (CKD) patients treated during the January-June 2023 period. The inclusion criteria were patients diagnosed with CKD, aged >18 years, and receiving ACE-inhibitor and ARB antihypertensive therapy for ≥3 months. Patients who had been using antihypertensive therapy for <3 months were excluded.

The minimum sample size was determined using the proportion formula. In this study, the participants were divided into two antihypertensive groups, and based on the sample formula, n1 = n2 = 67 was obtained. Therefore, the total number of samples in both groups was 134.

### Data Collection and Statistical Analysis Procedure

The collected data were processed and analyzed using computer-based statistical software. The instrument used was an automatic chemistry analyzer for kidney function examination, which measured urea and serum creatinine levels

from blood samples. GFR values were obtained using the eGFR application with the CKD-EPI Creatinine equation method (2021), based on serum creatinine, gender, and age of the patient. Univariate analysis was performed to describe the socio-demographic characteristics of the patients. This was followed by bivariate analysis to assess the effectiveness of antihypertensive therapy as reno-protective agent, using the Wilcoxon test. This research was conducted in accordance with ethical standards and received ethical approval under number: 1122/KEPK/FKUMSU/2023.

## RESULTS

The secondary data obtained from the research were processed using statistical methods. The table below presents the sociodemographic characteristics of CKD patients at RSUD Sultan Abdul Aziz Syah Peureulak.

**Table 1** Sociodemographics of Participants

| Characteristics | Frequency (n) | Percentage (%) |
|---|---|---|
| **Gender** | | |
| Male | 61 | 45.5 |
| Female | 73 | 54.5 |
| **Age** | | |
| 36-45 | 22 | 16.4 |
| 46-55 | 50 | 37.3 |
| 56-65 | 46 | 34.3 |
| >65 | 16 | 11.9 |
| **Comorbidities** | | |
| Hypertension | 54 | 40.3 |
| DM 2 | 48 | 35.8 |
| CHD | 32 | 23.9 |
| Total | 134 | 100 |

*Abbreviation: DM 2 (Diabetes Mellitus 2); CHD (Coronary Heart-Disease).*

Based on the table above, the sociodemographic distribution of CKD patients in RSUD Sultan Abdul Aziz Syah Peureulak were dominated by women, with 73 patients (54.5%). The highest incidence occurred in the early elderly age group (46-55 years), with 50 patients (37.3%), while the lowest incidence was found in the elderly group (>65 years) with 16 patients (11.9%). The results also showed that the most common comorbidity among participants was hypertension (40.3%), followed by Type 2 Diabetes Mellitus (35.8%), and coronary heart disease (23.9%).

**Wilcoxon Different Tests**

The table below illustrates the mean urea, creatinine, and eGFR values before and after the administration of antihypertensive therapy, along with the corresponding Wilcoxon test results.

**Table 2** Mean urea, creatinine, and eGFR values before and after antihypertensive therapy

| Antihypertensive | Indicator | | p-Value |
|---|---|---|---|
| | **Urea (mg/dL)** | | |
| | Before | After | |
| ACE-*Inhibitor* | 88,6 ± 67 | 72,4 ± 48,3 | <0,001 |
| ARB | 106 ± 108,5 | 85,2 ± 48,7 | 0,012 |
| | **Creatinine (mg/dL)** | | |
| | Before | After | |
| ACE-*Inhibitor* | 5,6 ± 4,4 | 4,8 ± 4,3 | 0,007 |
| ARB | 8,6 ± 11,8 | 6,1 ± 4,2 | 0,012 |
| | **eGFR (mg/dL)** | | |
| | Before | After | |
| ACE-*Inhibitor* | 26,4 ± 28,8 | 30,6 ± 30,8 | 0,015 |
| ARB | 18,3 ± 24,7 | 21,6 ± 26,7 | 0,003 |

Based on Table 2 of the Wilcoxon Difference Test, the average decrease in urea levels in the ACE-Inhibitor group was -16.2 mg/dL, whereas the ARB showed a greater reduction of -20.8mg/dL, with a p-value <0.05 indicating a significant difference between pre- and post-therapy values. Similarly, creatinine levels showed a significant decline, with mean reduction of -0.8 mg/dL in the ACE-Inhibitor group and -2.5 mg/dL of -0.8 mg/dL (p <0.05). Furthermore, for eGFR parameter, the ACE-Inhibitor group exhibited an average increase of +4.2 mL/min, while the ARB group showed an increase of +3.3 mL/min, both with p value <0.05 indicating statistically significant difference following the therapy.

Sociodemographic data of CKD patients based on gender in Table 1show that the population in this study was dominated by women. These findings are in line with previous research in 2020, which reported 22 female patients (51.16%) and 21 male patients (48.84%).[9] The limited ability of women to control blood glucose levels affects the prognosis of CKD events. However, other studies have reported that the prevalence of CKD is higher in men than in women, which may be related to unhealthy lifestyles that are more commonly found in men, such as smoking and alcohol consumption.

In the sociodemographic data, the distribution of CKD patients by age in this study is consistent with the findings by Nurchayati S, et al. (2018), which reported

that the highest incidence of CKD occurred in the early elderly age group, accounting for 17 patients (36.2%).[10] This is in line with the results shown in Table 2, in which the early elderly group represents the largest proportion of participants. Increasing age is known to elevate the risk of CKD events, as it is directly associated with the progressive decline of kidney function. According to Ariyani H, et al. (2019), individuals aged > 40 years begin to experience gradual decrease renal filtration capacity over time. This decline is attributed to the deceleration in nephron regeneration, which subsequently affects the kidney filtration process.[11]

The group of comorbidities suffered by CKD patients in this study with the highest prevalence was hypertension, followed by Type 2 Diabetes Mellitus. These results are consistent with the research of Abyuta et al. (2019), who found that the highest comorbidity among CKD patients was hypertension, affecting 43 patients (43%), followed by diabetes mellitus (12 patients , 12%).[12] This condition is because chronic hypertension leads to continuous vasoconstriction in the blood vessels that can interfere with blood flow in the renal glomerulus, causing hypoxia and potentially resulting in global sclerosis. This condition certainly reduces or even damages kidney performance in filtering blood and metabolic waste.[13]

Diabetes is a significant risk factor for kidney disease because it can specifically cause diabetic nephropathy. Research indicates that approximately 20% to 40% of individuals diagnosed with diabetes are prone to diabetic nephropathy. The pathophysiology of diabetic nephropathy is driven by chronic hyperglycemia, which progressively damages the renal microvasculature.[14] This vascular disorder ultimately leads to impaired filtration and renal dysfunction.[15] In addition, persistent hyperglycemia can further trigger kidney damage and result in changes in the expression of vascular, metabolic, and hemodynamic factors.

Table 2 shows a significant difference in the average values parameters before and after treatment in both antihypertensive groups: ACE-Inhibitors and ARBs. These findings indicate that both groups of antihypertensives are effective as reno-protective. The vasodilatory effect of ACE-Inhibitors is known to play a greater role due to inhibition of bradykinin degradation, which increases nitric oxide and vasoactive prostaglandins levels and improves endothelial function. This mechanism is often considered an advantage of ACE-Inhibitors compared with ARBs. In contrast, ARBs selectively block angiotensin II type (AT1) receptors, allowing stimulation of type 2 (AT2)

receptors, which may promote vascular growth, fibrosis, and inflammation.[16]

ACE inhibitor therapy acts by interfering with the renin-angiotensin-aldosterone system (RAAS), although its effects are not directly related to blood renin levels. As the name suggests, ACE inhibitors block the angiotensin-converting enzyme responsible for converting angiotensin I to angiotensin II. Decreased production of angiotensin II increases natriuresis, lowers blood pressure, and prevents remodeling of smooth muscle and cardiac myocytes. The reduction in arterial and venous pressure reduces both preload and afterload. In addition, ACE inhibitors are believed to interfere with the degradation of bradykinin, a peptide that contributes to vasodilation.[17]

The angiotensin-converting enzyme (ACE) regulates the balance between the vasodilatory and natriuretic properties of bradykinin and the vasoconstrictive and salt-retaining properties of Angiotensin II. ACE inhibitors alter this balance by decreasing the formation of angiotensin II and limiting the degradation of bradykinin. These agents also alter the formation and degradation of several other vasoactive substances, such as substance P; however, the contribution of these compounds to the therapeutic effects or side effects of ACE inhibitors remains uncertain.[17]

The Wilcoxon test used in this study evaluates changes in values before and after treatment. The results presented in Table 2 show an average decrease in urea levels in both antihypertensive groups (-16.2 mg/dL and -20.8 mg/dL). It shows that antihypertensive therapy did not lead to worsening kidney function in CKD patients at RSUD Sultan Abdul Aziz Syah Peureulak. This result is in line with a study by Rachmaini F, et al. (2020), which also reported a decrease in urea values after three months of treatment, with an average decrease of -0.93 mg/dL.[9]

Agrawal A, et al. (2016) reported a decrease in creatinine values of 0.55 mg/dL following antihypertensives therapy.[18] This is in line with the findings in Table 2, which shows an average reduction in creatinine levels of -0.8 mg/dL and -2.5 mg/dL in both groups. This study also showed an increase in eGFR values of +12.88 mL/min, which is consistent with Table 2 which is consistent with eGFR improvements presented in Table 2 (+4.2 mL/min and +3.3 mL/minute). According to the previous studies, administration of ACE inhibitor or ARBs therapy is commonly associated with an increase in serum creatinine of up to ≤30% above baseline. This increase typically occurs within the first two weeks of treatment and stabilizes within 2-4 weeks.[19,20] Across 11 studies, the decline in GFR was found to be slower at the end of

the study compared to the initial period after starting ACEI therapy. Another study reported that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) increase serum creatinine levels by 20% to 30% due to pre-renal effects.[21]

The use of antihypertensives is important to slow the progression of nephron damage by reducing intraglomerular hypertension and glomerular hypertrophy.[22,23] ACE-inhibitors are more widely chosen because, in terms of safety, they do not induce metabolic side effects during long-term use. The ACE-inhibitor group promotes vasodilation of the renal arterioles and reduces proteinuria, thereby exerting a protective effect on the kidneys.[24]

However, in some individuals, ACEI may cause uncomfortable side effects. Data showed that up to 50% of patients experience cough intolerance, which is related to the the mechanism of ACE inhibitors in stimulating bradykinin accumulation, thereby triggering a cough responses. The ARB group is often used to treat patients with hypertension, especially for patients who are intolerant to ACE inhibitor therapy.[25]

The pharmacological target of the renin-angiotensin system is not only to regulate blood pressure but also to protect the vascular system. ARBs are more tolerable than ACE inhibitors and may serve as a practical therapeutic option. Clinical studies have demonstrated the efficacy of irbesartan, losartan, valsartan, and telmisartan in managing chronic kidney disease (CKD).[26] All ARBs are effective in improving several aspects of kidney dysfunction. Reduction in proteinuria with ARBs has also been associated with improved cardiovascular outcomes.[25]

## CONCLUSION

The results showed a significant difference in the average values of urea, creatinine, and eGFR before and after the administration of antihypertensive drugs, indicating that both ACE inhibitor and ARB antihypertensive drugs are effective as renoprotective agents in CKD patients. However, for individuals who are intolerant to ACEI therapy, ARBs remains an effective alternative for managing hypertension in CKD. Therefore, clinicians must be able to have good clinical judgment when selecting antihypertensive therapy to ensure patient comfort and optimize treatment. Appropriate therapy selection is expected to support better patient self-management and improve treatment compliance.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest to disclose.

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