



## The Use of Antihypertensive Drugs in Pre-Dialysis Chronic Kidney Disease Patients

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### ABSTRACT

In chronic kidney disease (CKD), hypertension plays a central role, acting as both a risk factor and a complication that contributes to disease progression. Effective control of blood pressure through antihypertensive therapy is essential for preserving kidney function and preventing clinical decline. Therefore, this study aimed to evaluate antihypertensive treatment and blood pressure target achievement in pre-dialysis CKD patients, with blood pressure targets defined as <130/80 mmHg and <140/80 mmHg in elderly patients. This study was a prospective observational study with a retrospective review of medical records over a 3-month period, and the data were subsequently analyzed using descriptive methods. Participants were pre-dialysis CKD patients aged 18 or older receiving antihypertensive therapy with complete blood pressure records. Among the 90 eligible patients, the most commonly used antihypertensive classes were angiotensin receptor blockers, particularly candesartan, and calcium channel blockers, specifically nifedipine, either as monotherapy or combined with two to five other antihypertensive drugs. Over three months, only an average of 23.3% of patients achieved blood pressure targets, and only 8.9% maintained that continuously. Therefore, a more effective blood pressure management strategy is needed to achieve the desired target blood pressure.



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## ABSTRAK

Pada penyakit ginjal kronik (PGK), hipertensi merupakan faktor risiko utama sekaligus komplikasi yang berkontribusi terhadap progresi penyakit. Pengendalian tekanan darah melalui terapi antihipertensi yang optimal sangat penting untuk mempertahankan fungsi ginjal dan mencegah perburukan kondisi klinis. Penelitian ini bertujuan untuk mengevaluasi terapi antihipertensi serta pencapaian target tekanan darah pada pasien PGK pra-dialisis, dengan target tekanan darah yaitu <130/80 mmHg dan <140/80 mmHg pada pasien usia lanjut. Penelitian ini merupakan studi observasional prospektif dengan tinjauan retrospektif rekam medis selama periode 3 bulan, kemudian data dianalisis menggunakan metode deskriptif. Subjek penelitian adalah pasien PGK pra-dialisis berusia  $\geq 18$  tahun yang menerima terapi antihipertensi dan memiliki catatan tekanan darah lengkap. Dari 90 pasien yang memenuhi kriteria, golongan obat antihipertensi yang paling banyak digunakan adalah angiotensin reseptor blocker yaitu candesartan dan calcium channel blocker terutama nifedipin, baik sebagai terapi tunggal maupun kombinasi dua hingga lima obat dengan antihipertensi lainnya. Selama periode tiga bulan, rata-rata hanya 23,3% pasien yang mencapai target tekanan darah, dan hanya 8,9% yang mampu mempertahankan target tekanan darah secara kontinu. Oleh karena itu, strategi pengelolaan tekanan darah yang lebih optimal dibutuhkan untuk mencapai target tekanan darah yang diharapkan.

**Kata Kunci:** Penyakit ginjal kronik; Pra-dialisis; Hipertensi; Antihipertensi; Tekanan darah

### 1. Introduction

Chronic kidney disease (CKD) is characterized by persistent kidney abnormalities over a period of at least three months and is classified based on etiology, glomerular filtration rate (GFR) stage, and albuminuria level. In CKD stages 1-3, kidney damage occurs with mild to moderate GFR reduction, while in stages 4-5, kidney damage happens with severe GFR reduction, leading to kidney failure [1].

In patients with CKD, hypertension is a frequently encountered complication. Declining kidney function contributes to elevated blood pressure through multiple mechanisms, including activation of the renin-angiotensin-aldosterone system (RAAS), imbalance in prostaglandin regulation, and reduced nitric oxide production. Compared to individuals without CKD, patients with CKD demonstrate a higher prevalence of hypertension, estimated at 80-85% [2].

Blood pressure management is an important component of CKD management, as suboptimal blood pressure control can accelerate the decline in kidney function and lead to vascular remodeling, atherosclerosis, and left ventricular hypertrophy, which are major risk factors for cardiovascular events [3]. According to the 2020 International Society of Hypertension (ISH) Global Hypertension Practice Guidelines, the recommended blood pressure target for patients with CKD is <130/80 mmHg and <140/80 mmHg in elderly patients [4]. Renin-angiotensin system (RAS) inhibitors, such as ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), are suggested for CKD patients with moderate to severe albuminuria, with or without diabetes [1].

Several studies emphasize the importance of blood pressure control in CKD patients. A study by Geng et al. [5] reported that CKD patients with well-managed blood pressure did not face a higher risk of death, myocardial infarction, or stroke compared

to individuals without CKD. Furthermore, Chen et al. showed that ACEIs/ARBs were linked to a lower risk of mortality, cardiovascular events, and progression to end-stage renal disease (ESRD) [6].

The majority of CKD patients require a regimen involving multiple blood pressure lowering medications, including calcium channel blockers (CCBs) and diuretics, to achieve optimal blood pressure control [2]. A study by Zhang et al. [7] showed that patients with uncontrolled blood pressure tend to use more types of antihypertensive drugs.

Therefore, this study aimed to examine antihypertensive therapy and blood pressure target achievement in pre-dialysis CKD patients. Optimal blood pressure control is essential to slow CKD progression and reduce the risk of progression to ESRD. This study provides data on antihypertensive therapy profiles and blood pressure target achievement in pre-dialysis CKD patients, which remain limited in previous studies.

## **2. Methods**

### **Study Design and Patients**

A prospectively designed observational study with descriptive analysis was performed at the Nephrology-Kidney Hypertension Outpatient Clinic, Universitas Airlangga Hospital, Surabaya, from June to July 2023. The population consisted of all pre-dialysis CKD patients with comorbidities and complications of hypertension who received antihypertensive therapy. The samples were selected based on inclusion criteria, such as CKD patients aged  $\geq 18$  years, documented blood pressure in their medical records, and currently on antihypertensive drugs. Exclusion criteria included patients who transferred hospitals, died, or were lost to follow-up before 3 months, and patients indicated for dialysis.

### **Data Collection**

This study started with selecting participants based on specific inclusion and exclusion criteria. Each participant received a clear explanation of the study objectives and provided written informed consent prior to participation. Data were collected from patients' medical records covering the study month and the two preceding months. These records included patient profiles, admission dates, medical record numbers, diagnoses, medical histories, clinical data, and all therapies administered. The information about antihypertensive drugs included the name, type, dosage, duration, frequency, time of administration, and achievement of blood pressure targets during each month of observation.

### **Data Analysis**

The collected information was documented in a data collection sheet, processed in Microsoft Excel, and analyzed descriptively. The results of the analysis were presented in tables, graphs, and narratives. The analysis included a description of patient characteristics by gender, age, medical history, and CKD stage, presented in tabular form.

Furthermore, an evaluation of antihypertensive therapy was performed, including the type of drugs, medications administered per patient, and whether patients achieved their target blood pressure. Blood pressure target achievement was defined according to 2020 ISH Guidelines, with targets for patients with CKD is  $<130/80$  mmHg and  $<140/80$  mmHg in elderly patients [4]. Patients who did not meet these targets were categorized as not achieving the target. Blood pressure achievement over the 3-month

observation period was analyzed by calculating the number and percentage of patients with consistent and non-consistent achievement.

**Ethical Statement**

This study was approved by the Ethics Committee of Universitas Airlangga Hospital (Approval number UA-02-23942).

**3. Results and Discussion**

**Characteristics of Participants**

In this study, 90 CKD patients with hypertension met the inclusion criteria. Table 1 shows a relatively balanced gender distribution, with 46 male patients (51.1%) and 44 female patients (48.9%). The slightly higher proportion of males is consistent with the results of Weldegiorgis and Woodward [8], who reported that hypertension has a greater impact on the development of CKD in men compared to women. In that study, women with hypertension exhibited a 23% lower relative risk of developing CKD compared with men. Biologically, estrogen in women is believed to have a protective effect on the kidneys, while testosterone in men contributes to kidney damage. Additionally, men tend to have lower adherence to antihypertensive therapy and engage in less healthy lifestyles.

**Table 1.** Participants’ Demographics, Comorbidities, and CKD Stages

<b>Demographic and Clinical Information</b>	<b>Frequency (n)</b>	<b>Percentage (%)</b>
<b>Gender</b>		
Male	46	51.1
Female	44	48.9
<b>Age Group</b>		
18 - 24 years	0	0.0
25 - 34 years	1	1.1
35 - 44 years	4	4.4
45 - 54 years	23	25.6
55 - 64 years	42	46.7
65 - 75 years	18	20.0
>75 years	2	2.2
<b>Comorbidities and Medical History*</b>		
Hypertension	90	100
Diabetes mellitus	70	77.8
Diabetic polyneuropathy	8	8.9
Hyperlipidemia	5	5.6
Atherosclerotic heart disease	5	5.6
Hyperuricemia	4	4.4
Acute renal failure	2	2.2
Hypertension secondary to endocrine diseases	2	2.2
Ischemic cardiomyopathy	2	2.2
Chronic ischemia	2	2.2
Dyspepsia	2	2.2
Hyperkalemia	1	1.1
Sequelae of cerebral infarction	1	1.1
Hypertensive emergencies	1	1.1
Atrial fibrillation and flutter	1	1.1

Inflammatory spondylopathy	1	1.1
<b>CKD Stages Based on GFR</b>		
CKD Stage 1 (GFR $\geq 90$ mL/min/1.73 m <sup>2</sup> )	0	0.0
CKD Stage 2 (GFR 60-89 mL/min/1.73 m <sup>2</sup> )	12	13.3
CKD Stage 3a (GFR 45-59 mL/min/1.73 m <sup>2</sup> )	28	31.1
CKD Stage 3b (GFR 30-44 mL/min/1.73 m <sup>2</sup> )	22	24.4
CKD Stage 4 (GFR 15-29 mL/min/1.73 m <sup>2</sup> )	20	22.2
CKD Stage 5 (GFR $< 15$ mL/min/1.73 m <sup>2</sup> )	8	8.9

\* - One patient may experience more than one type of disease.

- Percentages are calculated based on the total number of patients, which is 90.

Based on age distribution, most study subjects were in the 55-64 age range (42 patients, 46.7%), the next largest group was those aged 45-54 years (23 patients, 25.6%), and the 65-75 age group included 18 patients (20.0%). Meanwhile, the under 45 years age group had a very small proportion, and there were no subjects in the 18-24 age range. Consistent with the findings of Qin et al. [9], the majority of CKD cases were reported in individuals aged 55-74 years, and mortality due to CKD occurs mostly in individuals over 55 years. Age is a risk factor for CKD because the decline in GFR increases linearly with age [10].

All patients included in this study had hypertension (100%), as required by the study inclusion criteria, followed by diabetes mellitus in 70 patients (77.8%). Other conditions observed included diabetic polyneuropathy (8.9%), hyperlipidemia (5.6%), and atherosclerotic heart disease (5.6%), with several other diseases occurring in smaller proportions, less than 5%. Similar result were reported by Qureshi et al. [11], which identified hypertension as the primary risk factor for CKD, followed by diabetes mellitus as the second risk factor.

Chronic hypertension is a major cause of kidney damage, an organ that is particularly vulnerable to high blood pressure [12]. High blood pressure causes glomerular endothelial dysfunction, decreases GFR, and triggers RAAS activation, creating a repeating cycle of kidney damage [13]. Additionally, chronic hyperglycemia can cause glomerular hyperfiltration, increasing glomerular pressure and ultimately impairing kidney function. Large fluctuations in blood glucose levels further stress endothelial cells, thereby amplifying inflammatory responses and oxidative stress within the kidneys [14].

The distribution of CKD stages showed that most patients were in stage 3, with 28 patients (31.1%) in stage 3a and 22 patients (24.4%) in stage 3b. Moreover, 20 patients (22.2%) were in stage 4, and 8 patients (8.9%) were in stage 5. In addition, 12 patients (13.3%) were in stage 2, while none were in stage 1. These results are consistent with a study by Alshehri et al. [15], which reported that most CKD patients were in stage 3. This is likely because early-stage CKD is often asymptomatic, leading to low screening rates [16].

This study identified patients classified as stage 5 who were not receiving dialysis, showing that they remained in the conservative management phase. Dattolo et al. [17] reported that therapy with ACEI in advanced CKD, specifically in elderly patients, was effective at reducing the rate of kidney damage, thus postponing the start of dialysis.

### The Use of Antihypertensive Drugs

Both hypertension and CKD significantly increase the risk of cardiovascular events and mortality. The two conditions influence each other, as high blood pressure can accelerate kidney function decline, while reduced kidney function may worsen blood pressure control. Therefore, optimal blood pressure control is crucial for maintaining kidney function and improving cardiovascular outcomes [18].

According to **Table 2**, the most commonly used antihypertensive classes in CKD patients in this study were ARBs, particularly candesartan, and CCBs, specifically nifedipine, each with an average use of 54.8%, followed by  $\beta$ -blockers at 40.4%. Meanwhile, the use of other antihypertensive classes, such as ACE inhibitors, diuretics, and  $\alpha$ -2 agonists, was relatively lower, each accounting for less than 10%.

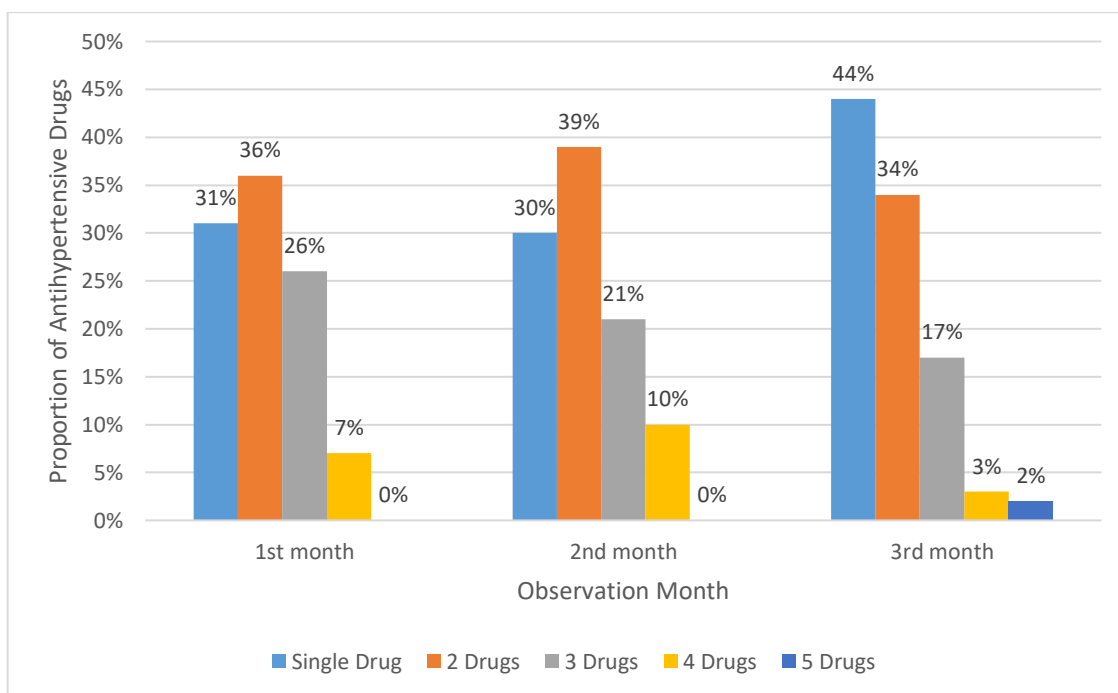
**Table 2.** Types of Antihypertensives Used by CKD Patients

Classes	Type of drug	Number of Patients (1 <sup>st</sup> Month)	% Usage	Number of Patients (2 <sup>nd</sup> Month)	% Usage	Number of Patients (3 <sup>rd</sup> Month)	% Usage	Total Usage	Average Percentage (%)
ACEI	Captopril	0	0.0	1	1.1	0	0.0	1	0.4
	Ramipril	4	4.4	1	1.1	1	1.1	6	2.2
	Lisinopril	6	6.7	4	4.4	8	8.9	18	6.7
	Imidapril	0	0.0	1	1.1	4	4.4	5	1.8
ARB	Candesartan	57	63.3	45	50.0	46	51.1	148	54.8
CCB	Nifedipine	40	44.4	55	61.1	53	58.9	148	54.8
	Amlodipine	24	26.7	16	17.8	14	15.6	54	20.0
	Diltiazem	1	1.1	1	1.1	1	1.1	3	1.1
$\beta$ -blocker	Bisoprolol	38	42.2	43	47.8	28	31.1	109	40.4
	Carvedilol	1	1.1	0	0.0	0	0.0	1	0.4
Loop diuretics	Furosemide	11	12.2	8	8.9	6	6.7	25	9.3
Potassium-sparing diuretics	Spironolactone	9	10.0	8	8.9	6	6.7	23	8.5
Thiazide diuretics	Hydrochlorothiazide	1	1.1	3	3.3	3	3.3	7	2.6
$\alpha$ -2 agonists	Methyldopa	0	0.0	2	2.2	4	4.4	6	2.2

Notes:

- One patient may receive more than one type of antihypertensive drug.
- The monthly percentage is calculated based on the number of patients, which is 90.
- Average percentage represents the average percentage of drug use over the 3-month observation period.

The results are in line with a study by Chinnadurai et al. [19], which showed that the most frequently prescribed antihypertensive class in non-dialysis CKD patients was RAS inhibitors. Moreover, Liu et al. [20] reported that the most commonly prescribed RAS inhibitor was ARB. Enhanced activation of the RAAS, combined with fluid overload are key contributors to poor blood pressure regulation in patients with CKD. Therefore, the use of RAS inhibitors is linked to improved blood pressure management in this population, as noted by Oladimeji et al. [21]. This study also found that CCBs were the antihypertensive class most commonly used in all CKD stages, either alone or in combination with other antihypertensive.



**Figure 1.** Proportion of Antihypertensive Drugs Used as Single and Combination per Month

**Figure 1** shows the proportion of antihypertensive drugs used by patients during the observation period, including both monotherapy and combinations of two to five drugs. **Table 3** then shows the details of the antihypertensive classes included in each treatment regimen.

**Table 3.** Single and Combination Antihypertensive Therapy Used

Therapy Used	Antihypertensive Classes
<b>Single Drug Therapy</b>	ARB
	ACEI
	CCB
	Beta Blocker
	Thiazide Diuretic
	Loop Diuretic
<b>Two Drugs Combination</b>	CCB + ARB
	CCB + ACEI
	CCB + Beta Blocker
	CCB + Loop Diuretic
	CCB + Thiazide Diuretic
	CCB + $\alpha$ -2 Receptor Agonist
	ARB + Beta Blocker
	ACEI + Beta Blocker

	Beta Blocker + Potassium-Sparing Diuretic
	Beta Blocker + Loop Diuretic
<b>Three Drugs Combination</b>	ARB + Beta Blocker + CCB
	ARB + Beta Blocker + Potassium-Sparing Diuretic
	ARB + Beta Blocker + Loop Diuretic
	ARB + Beta Blocker + Thiazide Diuretic
	ARB + CCB + Thiazide Diuretic
	ARB + Potassium-Sparing Diuretic + Loop Diuretic
	ACEI + Beta Blocker + CCB
	ACEI + Beta Blocker + Loop Diuretic
	ACEI + Beta Blocker + Potassium-Sparing Diuretic
	ACEI + CCB + Loop Diuretic
	Beta Blocker + CCB + Loop Diuretic
	Beta Blocker + CCB + Thiazide Diuretic
	$\alpha$ -2 Receptor Agonist + ARB + CCB
<b>Four Drugs Combination</b>	ARB + Beta Blocker + CCB + Loop Diuretic
	ARB + Beta Blocker + CCB + Potassium-Sparing Diuretic
	ARB + Beta Blocker + CCB + Thiazide Diuretic
	ARB + Beta Blocker + CCB + $\alpha$ -2 Receptor Agonist
	ARB + CCB + Loop Diuretic + Potassium-Sparing Diuretic
	ACEI + Beta Blocker + CCB + Potassium-Sparing Diuretic
<b>Five Drugs Combination</b>	CCB + ARB + Beta Blocker + Loop Diuretic + Potassium-Sparing Diuretic

Monotherapy with a single antihypertensive agent is generally recommended as the initial treatment strategy. RAS inhibitors are preferred first-line agents due to their ability to reduce albuminuria and lower blood pressure. However, monotherapy often proves insufficient to manage hypertension in CKD, thereby CCBs and diuretics may be added. Loop diuretics are indicated for individuals whose eGFR is under 30 ml/min/1.73 m<sup>2</sup> [2], [4].

According to Li et al. [22], approximately one-third of adult patients with CKD remained on antihypertensive monotherapy for many years, even though their blood pressure stayed uncontrolled. This large share of unchanged monotherapy is believed to be influenced by cost, patient preference, and tolerance for multiple drugs. Meanwhile, Derington et al. [23] found that achieving blood pressure control often requires a combination of two or more antihypertensive drug classes.

#### Achievement of Blood Pressure Targets

In this study, the evaluation of blood pressure achievement in CKD patients receiving antihypertensive therapy was based on blood pressure measurements over three months period after receiving therapy. The patients' blood pressure achievement profile over three months is presented in **Table 4**. In general, the percentage of patients achieving target blood pressure in the first month was 24.4%, increasing to 26.7% in the second month, but decreasing again to 18.9% in the third month. Conversely, the majority of patients did not achieve their target blood pressure, namely 75.6% in the first month, 73.3% in the second month, and 81.1% in the third month.

**Table 4.** Profile of Patients Blood Pressure Achievements Over 3 Months

Age Group (Years)	Comorbidities/Complications	Blood Pressure Target (mmHg)	1 <sup>st</sup> month		2 <sup>nd</sup> month		3 <sup>rd</sup> month	
			Achieved	Not Achieved	Achieved	Not Achieved	Achieved	Not Achieved
18-64	HT	<130/80	2	9	3	8	1	10
	HT + DM	<130/80	6	42	10	38	6	42
	HT + CHD	<130/80	1	1	0	2	0	2
	HT + Hyperuricemia	<130/80	0	1	1	0	1	0
	HT + DM + CHD	<130/80	0	4	0	4	0	4
	HT + DM + Hyperlipidemia	<130/80	1	1	1	1	0	2
	HT + DM + Hyperuricemia	<130/80	0	1	0	1	0	1
	HT + Hyperlipidemia + Hyperuricemia	<130/80	1	0	1	0	0	1
	65-79	HT	<140/80	2	0	2	0	2
HT + DM		<140/80	3	7	4	6	3	7
HT + CHD		<140/80	1	0	1	0	0	1
HT + Hyperkalemia		<140/80	1	0	0	1	0	1
HT + DM + CHD		<140/80	2	1	0	3	1	2
HT + DM + CHD + Hyperuricemia		<140/80	1	0	0	1	1	0
≥80		HT	<140/80	0	1	0	1	1
	HT + DM + CHD	<140/80	1	0	1	0	1	0
<b>Total Number</b>			<b>22</b>	<b>68</b>	<b>24</b>	<b>66</b>	<b>17</b>	<b>73</b>
<b>Percentage (%)</b>			<b>24.4</b>	<b>75.6</b>	<b>26.7</b>	<b>73.3</b>	<b>18.9</b>	<b>81.1</b>

Notes:

- A single patient may experience multiple comorbidities or complications.

- Target blood pressure values follow the 2020 ISH blood pressure targets [4].

**Table 5** shows the changes in blood pressure levels over the three months of observation. Only 8 patients (8.9%) consistently met their blood pressure targets for all three months, while 55 patients (61.1%) did not reach their targets during the observation period. The high rate of failure to achieve blood pressure targets is attributable not only to inadequate antihypertensive therapy but also to the underlying kidney disease. Reduced GFR complicates blood pressure control by stimulating RAAS activity and enhancing sympathetic nervous system activation [24]. The study by Katatwire and Meremo [25] showed that patients with stage 3 CKD have a 3.5 times more likely to develop uncontrolled hypertension.

Poor medication adherence plays an important role in inadequate blood pressure management among CKD patients. Polypharmacy is known to be a major influence on non-adherence to therapy [26]. Since CKD is a chronic condition requiring long-term treatment to slow disease progression, enhancing medication compliance in patients with CKD who are not on dialysis is essential [27].

**Table 5.** Profile of Fluctuations in Patients Blood Pressure Achievements

Blood Pressure Achievements			Number of Patients	Percentage (%)
1 <sup>st</sup> month	2 <sup>nd</sup> month	3 <sup>rd</sup> month		
+	+	+	8	8.9
+	-	+	3	3.3
+	-	-	5	5.6
+	+	-	7	7.8
-	+	-	4	4.4
-	+	+	5	5.6
-	-	+	3	3.3
-	-	-	55	61.1
<b>Total</b>			<b>90</b>	<b>100</b>

Notes: (+) Achieved, (-) Not achieved

In CKD patients, older age is associated with a higher risk of uncontrolled hypertension. The median age of patients with uncontrolled blood pressure is 55 years, and those aged 50 and above are five times more likely to experience uncontrolled blood pressure in early-stage CKD [25]. In addition, multiple factors influence the attainment of blood pressure targets, including limited availability of antihypertensive medications, restricted access to healthcare services, insufficient guidance on lifestyle changes, and economic constraints in obtaining antihypertensive drugs and personal blood pressure monitoring equipment [28].

The large number of CKD patients not reaching target blood pressure emphasizes the need for effective hypertension management to prevent progression of kidney injury to advanced stages. Furthermore, the high failure rate in achieving blood pressure targets and fluctuations in blood pressure underscore the importance of regular monitoring, adherence, and adequate knowledge of antihypertensive therapy.

These findings highlight the importance for regular blood pressure assessment and timely adjustment of antihypertensive therapy based on individual patient response. Optimization of combination therapy, routine blood pressure monitoring including home blood pressure monitoring, and a multidisciplinary approach are essential to improve blood pressure control in patients with CKD.

This study has several limitations. It was conducted at a single center, which may limit the generalizability of the findings to other clinical settings. In addition, blood pressure control is influenced not only by pharmacological therapy, but also by other factors such as patient adherence, lifestyle modification, and access to healthcare services, which were not fully assessed in this study.

#### 4. Conclusion

In conclusion, the use of antihypertensive drugs in pre-dialysis CKD patients is mainly focused on CCB and ARB, either monotherapy or in combination. Overall, 23.3% of patients achieved blood pressure targets, while only 8.9% were able to maintain that continuously, indicating that a significant proportion of patients fail to achieve and sustain blood pressure targets. These findings highlight the need for regular blood pressure monitoring, timely adjustment of antihypertensive therapy based on individual response, and a multidisciplinary approach to improve blood pressure control in patients with CKD.

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### Conflict of Interest:

The authors have no conflicts of interest to disclose.

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