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Relationship Between Potential Antihypertensive Drug Interactions and Target Blood Pressure in Outpatients with Chronic Kidney Disease

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ABSTRACT

Background: Chronic kidney disease (CKD) is an increasingly prevalent condition globally and is strongly associated with cardiovascular disease (CVD). Hypertension frequently occurs during the development of kidney disease and is a leading cause of its progression. CKD patients with complications and comorbidities often require combination therapy. However, some drug combinations can cause adverse drug reactions and reduce the efficacy of therapy. One such reaction is failing to achieve the blood pressure target; **Method**: This research is a non-experimental, analytical study with retrospective sampling. The sample for this study consisted of 71 patients. Potential drug interactions were analyzed using the drug interaction checker application on drug.com. Univariate analysis was performed to describe patient characteristics, and bivariate analysis using the Chi-square statistical test was performed to examine the relationship between the potential interactions of antihypertensive drugs and blood pressure targets; **Results**: The correlation analysis test results showed no relationship between the potential interaction of antihypertensive drugs and the target blood pressure of CKD patients (p-value = 0.607); **Conclusion**: There is potential for antihypertensive drug interactions in CKD patients, but they do not statistically affect blood pressure targets.

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Introduction

Chronic Kidney Disease (CKD) is an abnormality in the anatomy and physiology of the kidneys that occur for more than three months and has a negative impact on health [1]. CKD is a progressive condition affecting over 10% of the global population, or more than 800 million people. It is increasingly recognized as a major cause of death worldwide. According to Global Burden of Disease (GBD) data, CKD-related mortality rose by 41.5% between 1990 and 2017. CKD advanced from the 36th to the 12th leading cause of death and is projected to become the fifth leading cause of years of life lost (YLL) by 2040 [2]. Statistical data on the epidemiology of CKD in Indonesia remain limited. However, data from the 2018 Riset Kesehatan Dasar (RISKESDAS) show an increase in CKD prevalence from 0.2% in 2013 to 0.3% in 2018, accompanied by a significant rise in the number of patients undergoing kidney replacement therapy, primarily through hemodialysis [3]. The Special Region of Yogyakarta is one of the provinces with the third-highest prevalence of CKD in Indonesia [4]. Data from the Indonesian Renal Registry (IRR) in 2020 shows that the most common etiology of CKD undergoing hemodialysis is hypertension, namely 35% [5]. Hypertension is one of the main risk factors for CKD which can damage the blood vessels in the kidneys, thereby reducing the kidneys' capacity to filter blood [6–9]. Research about

the description of complications of non-dialysis CKD at the Kidney-Hypertension Polyclinic, RSUP Prof. Dr. R. D. Kandou pointed out several complications that often occur in CKD patients, namely anemia, uncontrolled hypertension, dyslipidemia, hyperuricemia, electrolyte disorders (hyponatremia and hypernatremia), and hypokalemia [10]. Several complications and the presence of comorbid diseases mean that treatment of CKD often requires several types of drugs, which is called polypharmacy [11,12]. Although administration of this combination therapy is generally planned to provide beneficial effects, drug interactions may occur in some cases that eliminate the therapeutic effect or cause unexpected events. Drug interactions are considered clinically significant if they result in increased toxicity or reduced efficacy of interacting drugs so that the effects and outcomes of therapy can change, especially for drugs with a narrow therapeutic index [13–16].

Research at the Bandung Special Kidney Hospital regarding the potential for antihypertensive drug interactions in patients with CKD showed that the highest potential drug interactions were interactions between antihypertensive drugs, namely the use of amlodipine and bisoprolol with moderate severity (74.42% of cases) [17]. Another study about the description of drug interactions in CKD patients on hemodialysis shows that antihypertensive drugs are the type most used in CKD patients. In terms of frequency, there were 21 cases, or 36.21% of drug interactions with pharmacokinetic mechanisms, while 6 cases, or 10.34% had drug interactions whose mechanism was unknown. The drug interaction that most often occurs in the pharmacokinetic mechanism is between furosemide and omeprazole, with 8 cases [18].

Drug interactions in CKD remain a common clinical concern, particularly involving antihypertensive medications, which are frequently prescribed due to the high prevalence of hypertension as both a cause and complication of CKD. Several studies have identified a significant proportion of drug interactions among antihypertensive agents, potentially affecting therapeutic outcomes and patient safety. Considering the high prevalence of CKD in the Special Region of Yogyakarta and the frequent use of antihypertensive drugs in this population, this study was conducted at a hospital in Yogyakarta. The aim is to evaluate the relationship between the potential for antihypertensive drug interactions and clinical outcomes, specifically the achievement of target blood pressure in outpatient CKD patients.

Materials and Method

The design used was analytical observational with retrospective sampling. This research was carried out from May to June 2024 at the Medical Records Installation of a hospital in Yogyakarta City. The study population consisted of 249 CKD patients with antihypertensive prescriptions who underwent outpatient treatment at the hospital during the period from January to December 2023. The research sample consisted of 71 CKD patients from the study population who met the inclusion criteria. The following are the inclusion criteria and exclusion criteria:

a. Inclusion criteria
   CKD patients undergoing outpatient care at a hospital in Yogyakarta City, with or without comorbidities and complications, who have received antihypertensive medication for at least 1 month, aged ≥18 years, with or without hemodialysis, and who have complete medical history data.
b. Exclusion criteria
   CKD patients have incomplete medical record data, have prescriptions that cannot be read clearly, and CKD patients receive antihypertensive drugs whose names are not available on drugs.com.

This research has received ethical approval number 00165/KT.7.4/V/2024. The data analysis used is univariate analysis to determine the characteristics of the sample and bivariate analysis to see the relationship between two variables using the Chi-Square test.

Results and Discussion

This study aims to determine the relationship between potential interactions between antihypertensive drugs and blood pressure targets in outpatient CKD patients at a hospital in Yogyakarta in the period January to December 2023. The population in this study was 249 patients, with a minimum number of samples from the calculation results and having met the inclusion criteria of 71 patients. The results of this study include patient characteristics (age, gender, CKD stage, as well as comorbidities and complications), description of potential drug interactions, and the relationship between potential drug interactions and blood pressure targets in CKD patients.

Results

Characteristics of CKD patients as shown in Table 1. Most outpatient CKD patients were male, namely 37 patients (52.1%), aged ≥60 years as many as 40 patients (56.3%), the highest stage of CKD was stage 5 as many as 48 patients (67.6%), patients who had comorbidities or complications as many as 52 patients (73.2%).

Table 1. Characteristics of CKD Patients (n=71)

Variables	Total	
	n	%
Gender		
Male	37	52.1
Female	34	47.9
Age (Years)		
< 60	31	43.7
≥ 60	40	56.3
Chronic Kidney Disease Stage		
Stage 1	0	0
Stage 2	4	5.6
Stage 3	11	15.5
Stage 4	8	11.3
Stage 5	48	67.6
Co-morbidities		
Yes	52	73.2
No	19	26.8

Based on patient prescriptions, it was found that 48 outpatient PGK patients (67.6%) had the potential to experience drug interactions with antihypertensive drugs, and 23 patients (32.4%) did not have the potential to experience drug interactions with antihypertensive drugs (table 2).

Table 2. Potential Drug Interactions (n=71)

Potential Drug Interactions	Total	
	n	%
Yes	48	67.6
No	23	32.4

The severity level of potential antihypertensive drug interactions is divided into three, as shown in Table 3. Moderate severity is the level of severity most often experienced by outpatient CKD patients, namely in 137 patients (81.5%), minor in 26 patients (15.5%), and major in 5 patients (3.0%).

Table 3. Severity of Drug Interactions (n=168)

Category	Total	
	n	%
Major	5	3.0
Moderate	137	81.5
Minor	26	15.5

Based on the drug interaction mechanism, the potential drug interactions that outpatient GGK patients can experience are as shown in Table 4. 136 patients (81.0%) have the potential to experience drug interactions with pharmacodynamic mechanisms, and 32 patients (19.0%) have the potential to experience drug interactions with pharmacokinetic mechanisms.

Table 4. Mechanism of Interactions (n=168)

Mechanism	Total	
	n	%
Pharmacodynamic	136	81.0
Pharmacokinetic	32	19.0

Bivariate analysis was used to determine the relationship between potential drug interactions and the achievement of patient blood pressure targets. The results of the analysis using the Chi-

square test (Table 5) obtained a p-value of 0.607 (p ≥ 0.05) so that it can be stated that the potential for antihypertensive drug interactions is not related to the blood pressure targets of CKD patients**.**

Table 5. Analysis of the Relationship Between Potential Drug Interactions and Blood Pressure Targets (n=71)

		Blood Pressure Targets		Total	*p-value*
		Controlled BP	Uncontrolled BP		
Potential Drug Interactions	Yes	24 (50.0%)	24 (50.0%)	48 (100.0%)	0.607
	No	13 (56.5%)	10 (43.5%)	23 (100.0%)	
Total		**37 (52.1%)**	**34 (47.9%)**	**71 (100.0%)**	

Discussion

1. Patient Characteristics

Based on Table 1, it is known that outpatient GGK patients in one of the hospitals in Yogyakarta are mostly male. This is in line with the research of Hardianti & Herliany (2023) at the Bandung Kidney Specialist Hospital which showed that outpatient GGK patients were dominated by men, amounting to 142 patients (63.11%) [17] Men tend to be at risk of experiencing GGK due to several factors, namely hormonal and lifestyle. Hormonal factors are related to high levels of the testosterone hormone which works on androgen receptors in the kidneys. Activation of these receptors can increase sodium and water reabsorption, thereby increasing blood pressure and impaired kidney function. Lifestyle and behavioral factors that cause men to be at risk of experiencing GGK include smoking habits [19].

Most of the patients in this study were aged ≥60 years (Table 1). This is in line with the results of research at Sanglah Central Hospital, Denpasar, which showed that outpatient GGK patients were dominated by those aged ≥41 years, namely 23 patients (51%) [20]. Clinically, kidney function will decrease with age. At the age of 60, kidney function can decrease by up to 50% of normal conditions due to a decrease in the number and inability to regenerate nephron cells, so that at that age they are more susceptible to GGK [21].

Based on the GGK stage, most patients are stage 5 GGK. This is in line with research at Ulin Banjarmasin Hospital which showed the same results, namely that outpatient GGK patients were dominated by stage 5, namely 313 patients (100%) [22]. GGK is a silent killer that develops without showing clear symptoms, so patients tend to seek treatment when the condition has reached the final stage [23]. In the early stages of GGK, patients often do not seek medical care because the symptoms they experience are not yet visible. However, in stages 4-5, GGK symptoms have begun to appear and encourage patients to seek treatment [24].

Based on Table 1, it is also known that most outpatient GGK patients have comorbidities and complications. Study at the Abdoel Wahab Sjahranie Samarinda Regional Hospital which showed that most outpatient GGK patients had comorbidities and complications of 52 patients (78.46%) [25]. Another study at the Sleman Yogyakarta Regional Hospital also showed that most outpatient GGK patients had comorbidities and complications of 131 patients (90.97%) [26].

2. Potential drug interactions

Based on Table 2, it is known that 48 patients (67.6%) of outpatient GGK have the potential to experience drug interactions. This result is in line with the research at Prof. Dr. W.Z. Johannes Kupang Hospital, which showed that most outpatient GGK patients have the potential to experience drug interactions of 72 patients (85.7%) [27]. Several complications and the presence of comorbidities result in GGK treatment often requiring several types of drugs. The use of 5 or more drugs simultaneously is called polypharmacy. The results of the research at Sleman Yogyakarta Hospital showed that there was a relationship between polypharmacy and the incidence of drug interactions [28].

Based on Table 3, the order of severity of potential drug interactions from the most experienced outpatient GGK patients is moderate, minor, and major. These results are in line with research at Dr. M.M Dunda Limboto Hospital, which showed that most outpatient GGK patients experienced drug interactions with moderate severity levels of 39 patients (75.86%) [18]. Moderate severity is the severity of the interaction where two or more drugs taken together can cause significant but non-life-threatening effects [29].

Based on Table 4, it is known that the potential for drug interactions is most often experienced by outpatient GGK patients with interaction mechanisms, namely pharmacodynamics of 136 patients (81.0%), and pharmacokinetics of 32 patients (19.0%). Previous research showed that most GGK patients experienced drug interaction mechanisms, namely pharmacodynamic mechanisms, in 27 patients (53.45%) [18]. Pharmacodynamic interactions are interactions involving the receptor system and the physiological system that have additive, synergistic, and antagonistic effects without changing the pharmacokinetics of the drug [30].

3. The relationship between potential drug interactions and clinical outcomes

Based on the results of the analysis using the Chi-square test (table 5), a p-value of 0.607 (p≥0.05) was obtained, so it can be stated that there is no relationship between the potential for antihypertensive drug interactions and the target blood pressure of CKD patients. These results are in line with the research of Setyoningsih & Zaini at Dr. R. Soetrasno Rembang Hospital which showed no significant relationship between the occurrence of drug interactions and the effectiveness of antihypertensive drug use with a p-value of 0.807 [31].

Drug interactions are one of the factors that can affect clinical outcomes, both interactions that occur between drugs or drug interactions with food. Other factors can affect the clinical outcome of a treatment but were not studied and are limitations in this study, namely drug interaction factors with food, and lifestyle factors such as diet, physical activity, smoking habits, and stress. The results of this study are still potential because the data was taken retrospectively, so it cannot directly monitor the patient's clinical outcomes. This study used the Drugs.com instrument. The weaknesses of this instrument are the limitations in analyzing the mechanism of drug interactions so that in-depth analysis is needed, and the name of the drug (glycidone) is not included in this instrument, so a lot of data is excluded.

Conclusion

Outpatients with CKD in one of the hospitals in Yogyakarta are predominantly male, aged ≥60 years, stage 5 CKD, and have comorbidities or complications. Most patients have the potential to experience anti-hypertensive drug interactions with the highest severity level, namely moderate, and the mechanism of drug interactions is pharmacodynamic (81.0%). There is no relationship between the potential for anti-hypertensive drug interactions and blood pressure targets in CKD patients undergoing outpatient care.

Declaration

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Conflicts of Interest: This study has no conflict of interest.

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