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Pharmacotherapy of Hypertension in Chronic Dialysis Patients in USU Hospital Medan

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ABSTRACT.

Background: Hypertension is closely related to chronic kidney disease (CKD) patients because hypertension can be a cause or a result of hemodialysis (HD). The way that can be done to control blood pressure is the administration of antihypertensive drugs. The use of antihypertensive drugs in CKD on HD patients in hospitals is needed as an evaluation material in terms of the accuracy and optimization of drug administration. This study aims to know the administration pattern of antihypertensive drugs used by the HD unit in USU Hospital Medan.

Method: Descriptive statistics were used to present the antihypertensive drug prescription pattern of CKD in HD patients. This study used data in the form of medical records and also direct interviews with patients and nurses of the HD Unit at USU Hospital in 2022.

Results: The most common single drug antihypertensive used was Calcium Channel Blocker (CCB) as amlodipine 67.4% either alone or in combination. The most common 2 drugs antihypertensive combination were Angiotensin Receptor Blocker (ARB) as candesartan and CCB as amlodipine 19.5%.

Conclusion: The most common single drug antihypertensive used was CCB, and the most common drugs antihypertensive in combination 2 drugs were CCB and ARB.

Keywords: Antihypertensives, Chronic Kidney Disease, Hemodialysis

ABSTRAK.

***Latar Belakang**: Hipertensi erat kaitannya dengan pasien penyakit ginjal kronis (PGK) karena hipertensi dapat menjadi penyebab atau akibat hemodialisis (HD).*

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Cara yang dapat dilakukan adalah mengontrol tekanan darah dengan pemberian obat antihipertensi. Penggunaan obat antihipertensi pada PGK pada pasien HD di rumah sakit diperlukan sebagai bahan evaluasi dalam hal akurasi dan optimalisasi pemberian obat. Penelitian ini bertujuan untuk mengetahui pola pemberian obat antihipertensi yang digunakan oleh unit HD di RS USU Medan.

***Metode**: Statistik deskriptif digunakan untuk menyajikan pola resep obat antihipertensi CKD pada pasien HD. Penelitian ini menggunakan data berupa rekam medis dan juga wawancara langsung dengan pasien dan perawat Unit HD RS USU tahun 2022.*

***Hasil:** Obat tunggal antihipertensi yang paling umum digunakan adalah Calcium Channel Blocker (CCB) sebagai amlodipine 67,4% baik sendiri atau dalam kombinasi. Obat antihipertensi yang paling umum pada kombinasi 2 obat adalah Angiotensin Receptor Blocker (ARB) seperti candesartan dan CCB seperti amlodipine 19,5%.*

***Kesimpulan**: Obat tunggal antihipertensi yang paling umum digunakan adalah CCB, dan obat kombinasi 2 antihipertensi yang paling umum adalah CCB dengan ARB.*

***Kata kunci**: Antihipertensi, Penyakit Ginjal Kronis, Hemodialisis*

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1 Introduction

Chronic kidney disease (CKD) is a clinical syndrome characterized by a progressive and irreversible decline in kidney function and/or structure. An adult patient is diagnosed with CKD if there is a decrease in the glomerular filtration rate (GFR) to less than 60 mL/minute/1.73 m² for three months or more, or if the GFR is more than 60 mL/minute/1.73 m² with signs of kidney damage such as albuminuria, hematuria/leukocyturia, changes in renal imaging, histological changes in kidney biopsies, persistent hydro electrolyte disturbances, or a history of kidney transplantation. [1]

According to the Kidney Disease: Improving Global Outcomes (KDIGO) classification from 2012, CKD is categorized into five stages based on GFR calculations. Stage 1 is kidney damage with normal GFR (more than 90 ml/min); Stage 2 is a mild decrease in GFR (60-89 mL/min); Stage 3a is a moderate decrease in GFR (45-59 mL/min); Stage 3b is a moderate decrease in GFR (30-44 mL/min); Stage 4 is a severe decrease in GFR (15-29 mL/min); and Stage 5 is renal failure (GFR below 15 mL/min).[1]

The overall global prevalence of the five stages of CKD is 13.4%, with the prevalence of each stage as follows: Stage 1 (3.5%), Stage 2 (3.9%), Stage 3 (7.6%), Stage 4 (0.4%), and Stage 5

(0.1%). [2] In Indonesia, the prevalence of CKD among individuals aged 15 years and older has increased from 2.0% per 1000 population (499,800 individuals) to 3.8% per 1000 population. In North Sumatra alone, the prevalence of chronic kidney failure (Stage 5 CKD) in 2018 reached 0.33% of the total population aged 15 years and older, which corresponds to around 36,410 people. This data indicates a significant increase from 0.2% of the population in 2013.[3]

Management of chronic kidney disease includes specific therapy for the underlying disease, prevention, and treatment of comorbid conditions, slowing down the deterioration of kidney function, prevention and treatment of cardiovascular disease, prevention and treatment of complications, and, if the disease is at an advanced stage or End Stage Renal Disease (ESRD), kidney replacement therapy such as dialysis or kidney transplantation.[4]

Renal replacement therapy (RRT) can be performed intermittently or continuously using extracorporeal methods such as HD or para-corporeal methods such as peritoneal dialysis. The choice of replacement therapy is based on the patient's preference, medical and surgical contraindications, cost considerations, and available dialysis facilities. Currently, HD is more economical than peritoneal dialysis.[5] However, no definitive studies are showing the superiority of one method over the other. According to the Indonesian Society of Nephrology (Pernefri) in 2018, the number of CKD patients undergoing regular HD (CKD-HD) in Indonesia has increased significantly. In 2018, there were 66,433 new patients and 132,142 active patients undergoing HD. CKD-HD also has a high mortality rate, with cardiovascular disorders accounting for the highest mortality rate (47%).[6]

Hypertension is defined as high blood pressure with a systolic pressure of 140 mmHg or higher, a diastolic pressure of 90 mmHg or higher, or both.[7] Hypertension is both a cause and a complication of CKD, whether on HD or not. In Indonesia, hypertension is reported as a comorbidity in 51% of stage 5 CKD patients. The etiology of hypertension in CKD-HD patients is multifactorial, including factors such as excess fluid volume, increased activation of the sympathetic nervous system, endothelial dysfunction, non-suppression of the renin-angiotensin-aldosterone system, and electrolyte imbalance during the HD process.[8]

An epidemiological study conducted in the United States on 2,173 hypertensive patients undergoing HD revealed that only 30% of the hypertensive patients had controlled blood pressure, while the remaining patients had untreated hypertension (12%) or treated but inadequately controlled hypertension (58%).[9] Uncontrolled hypertension in this condition increases the prevalence of cardiovascular disease. Cardiovascular complications are the leading cause of mortality and morbidity in CKD-HD patients. Therefore, controlling blood pressure according to the Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations (<130/85) is crucial in reducing the severity of the disease and improving the patient's quality of life.[1]

The administration of antihypertensive drugs (AHT) such as ACE (Angiotensin Converting Enzyme) inhibitors or ARB (Angiotensin Receptor Blocker) is recommended for blood pressure management in CKD-HD patients. For stage 1 hypertension (BP 140-159/90-99 mmHg), ARBs or ACE inhibitors are given, and for stage 2 hypertension (BP >160/100 mmHg), a combination of ARB or ACE inhibitor with a CCB is recommended. If the target blood pressure is not achieved, β-Blockers or Clonidine can also be given, and Minoxidil can be considered if the target is still not reached. [10]

Different regions in Indonesia may have their patterns of antihypertensive drug administration for controlling blood pressure in CKD-HD patients. For example, at Toto Kabila Hospital in Bone Bolango District, Gorontalo, during the 2017-2018 period, monotherapy with CCB or ARB, combination therapy with two ARBs + CCB, ARB + ACE Inhibitor, ARB + β-Blocker, ARB + Diuretic, and triple therapy with ARB + CCB + Diuretic were used.[11] At Bhayangkara Hospital HS Samsoeri Mertojoso Surabaya, most patients received combination therapy with ARB and CCB, either 1 ARB + 1 CCB or 1 ARB + 2 CCB.[12] There is a close relationship between hypertension and CKD, especially in patients undergoing HD. However, there is limited research on the patterns of antihypertensive drug use in CKD-HD patients at USU Hospital Medan. The purpose of the study was to evaluate how the pattern of use of antihypertensive drugs in CKD patients with regular HD at USU Hospital Medan.Top of Form

2 Method

The population for this study consisted of all regular CKD on HD patients with hypertension who received antihypertensive therapy at the USU Hospital in 2022. The study sample was derived from secondary data, which included medical records of regular CKD in HD patients treated at the hospital in 2022.

3 Result

In this study, there were 59 patients undergoing regular HD at USU Hospital Medan, and 46 patients met the inclusion criteria. The most distribution of patients across these age groups was patients aged 56-65 (28.3%) years. The most duration of regular HD among patients was 16 (34.8%) patients had undergone HD for over 36 months. The most classification of hypertension severity was 36 (78.3%) patients who had grade 2 hypertension. Additionally, 31 (67.4%) patients had their blood pressure successfully controlled (Table 1).

Table 1 Patients Distribution

Parameters	Frequency	(%)
Gender		
Male	24	52.2
Female	22	47.8
Age		
25-35	6	13.0
36-45	7	15.2
46-55	11	23.9
56-65	13	28.3
> 65	9	19.6
Length of HD		
3-12	15	32.6
12-36	15	32.6
>36	16	34.8
Type of Hypertension		
Hypertension type 1	10 (21.7)	7 (15.2)[1]
Hypertension type 2	36(78.3)	24 (52.1)[1]

Abbreviation: [1]Controlled hypertension

Based on Tabel 2, Among the 46 samples analyzed, the utilization of antihypertensive medications in CKD on HD patients at USU Hospital Medan during the 2022 period revealed that 5 (11%) patients received monotherapy, 23 (50%) combination of 2 antihypertensive drugs, 14 (30.4%) patients combination 3 antihypertensive drugs, and 4 (8.6%) patients the combination of 4 antihypertensive drugs.

Table 2 Amount of Antihypertensive drugs

Amount of Drugs	Type of Hypertension (n=46)		Total (%)
	Stage 1	Stage 2	
Monotherapy	2	3	5 (11)
Polytherapy 2 Drugs	5	18	23 (50)
Polytherapy 3 Drugs	2	12	14 (30.4)
Polytherapy 4 Drugs	0	4	4 (8.6)

Abbreviations: ARB: Angiotensin receptor blockers, ACE: Angiotensin-converting enzyme, CCB: Calcium channel blocker

Based on Table 3, the most combination was ARB with CCB administered to 13 individuals (28.2%) with 2 drugs.

Table 3 Therapy 2 Combinations of Antihypertensive

Classes of 2 Drugs	n (%)
ARB + Beta Blocker	
Candesartan + Bisoprolol	3 (6.5)
ARB + CCB	
Candersartan + Amlodipine	9 (19.5)
Telmisartan + Amlodipine	3 (6.5)
Telmisartan + Nifedipine	1 (2.2)
ARB + Diuretic	
Candersartan + Furosemide	1 (2.2)
Beta Blocker + CCB	
Bisoprolol + Amlodipine	2 (4.3)
Beta Blocker + Diuretic	
Bisoprolol + Furosemide	2 (4.3)
CCB + Diuretic	
Amlodipine + Furosemide	2 (4.3)

Abbreviations: ARB: Angiotensin receptor blockers, ACE: Angiotensin-converting enzyme, CCB: Calcium channel blocker

Based on Table 4, the polytherapy regimen involving the use of 3 antihypertensive drugs was observed. The combination of ARB + Beta Blocker + CCB was administered to 11 individuals (28.2%). Among the polytherapy regimens with 3 drugs, the most commonly prescribed combination, based on the drug names, was Candesartan + Bisoprolol + Amlodipine, which was utilized by 8 patients (17.3%).

Table 4 Therapy 3 combinations of antihypertensives

Classes combination 3 drugs	**n (%)**
ACE Inhibitor + CCB + Diuretic	
Ramipril + Amlodipine + Furosemide	1 (2.2)
ARB + Beta Blocker + CCB	
Candesartan + Bisoprolol + Amlodipine	8 (17.3)
Candesartan + Bisoprolol + Nifedipine	2 (4.3)
Telmisartan + Bisoprolol + Amlodipine	1 (2.2)
ARB + Beta Blocker + Diuretic	
Candesartan + Bisoprolol + Furosemide	1 (2.1)
Beta Blocker + CCB + Diuretic	
Bisoprolol + Amlodipine + Furosemide	1 (2.1)

Abbreviations: ARB: Angiotensin receptor blockers, ACE: Angiotensin-converting enzyme, CCB: Calcium channel blocker

Based on Table 5, the polytherapy drug regimen with the most used 4 drugs was the combination of ARB + Beta Blocker + CCB + Diuretic in 3 people (6.5%).

Table 5 Therapy 4 combinations of antihypertensives drugs

Classes and Names of Polytherapy 4 Drugs	n (%)
ARB + ACE Inhibitor + Beta blocker + Diuretic	
Candesartan + Ramipril + Bisoprolol + Furosemide	1 (2.2)
ARB + Beta Blocker + CCB + Diuretic	
Candesartan + Beta blocker + Amlodipine + Furosemide	1 (2.2)
Candesartan + Carvedilol + Amlodipine + Furosemide	1 (2.2)
Valsartan + Beta blocker + Amlodipine + Furosemide	1 (2.2)

Abbreviations: ARB: Angiotensin receptor blockers, ACE: Angiotensin-converting enzyme, CCB: Calcium channel blocker

Based on Figure 1, the class of antihypertensive drugs that was most widely used by patients was the CCB as amlodipine in 31 patients (67.4%) either alone or in combination with other antihypertensive drugs.

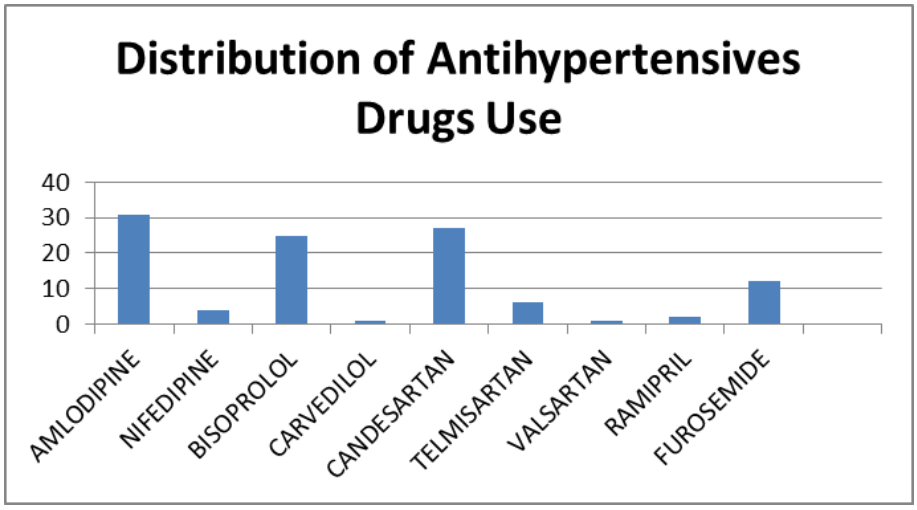

Figure 1 Distribution of Antihypertensives Drugs Use

4 Discussion

The findings of the study conducted at the USU Hospital in 2022 on CKD HD patients receiving antihypertensive therapy revealed that the majority of CKD HD patients were male, accounting for 24 individuals (52.2%). This finding aligns with a study conducted at the Bhayangkara HS Samsoeri Mertojoso Hospital in Surabaya, which reported that 74% (n=14) of CKD HD patients receiving anti-hypertensive drugs were predominantly male.[12] However, contrasting results were observed in similar studies, where 51.6% of CKD HD patients were female (n=43).[13] This observation may be attributed to the global disparity in the prevalence of dialysis, with more men undergoing this treatment worldwide.[14] Levey et al., in 2007, also suggested that men are more prone to systemic diseases and have a greater familial history of such conditions.[13]

Regarding the age distribution, the study found that CKD HD patients receiving antihypertensive drug therapy were mostly in the age range of 46-55 years, accounting for 23.9% (11 individuals), followed by 56-65 years at 28.3% (13 individuals). Among the elderly population (>65 years), 19.6% of patients were included (9 individuals). A similar study conducted at the Jakarta Islamic

Hospital Cempaka Putih also reported comparable findings, with 42.27% of patients falling within the age range of 40-59 years (n=67) and 44.78% being older than 60 years.[15] This observation can be attributed to the age-related decline in kidney function, where the estimated glomerular filtration rate (eGFR) decreases by approximately 0.82 ml/minute per 1.73 m2 annually.[16] Furthermore, a significant proportion of CKD patients at the USU Hospital had undergone regular HD for more than 36 months, accounting for 34.8% (n=46). A study conducted at RSUP by Dr. Soeradji Tirtonegoro Klaten also reported that 66.9% (n=72) of CKD HD patients had undergone HD for more than 36 months.[17] Kidney replacement therapy, including dialysis or transplantation, serves as an option for CKD patients with end-stage renal disease (ESRD), and it can be performed intermittently or continuously, aiming to replace the impaired kidney function and filter metabolic waste and excess water from the patient's blood. [5]

The severity of hypertension among the CKD HD patients included in this study was assessed based on different grades. Among the 46 samples, grade 2 hypertension accounted for the majority at 78.3%, while grade 1 hypertension was observed in 21.7% of the patients. Notably, 67.4% of patients with hypertension had successfully achieved blood pressure control. A similar study conducted in the United States, involving 10,813 HD patients, reported that 86.2% of the patients had hypertension, with only 13.2% having their hypertension effectively controlled.[18] Hypertension is highly prevalent in patients with chronic kidney disease (CKD), particularly those with end-stage renal disease (ESRD) undergoing HD.[19]

5 Antihypertensive Drugs in CKD Patients with Hypertension

The study findings indicated that regular CKD patients received various treatment approaches, including monotherapy, and polytherapy with two, three, or four drugs, encompassing all classes of antihypertensive drugs. The results revealed that a higher proportion of patients were treated with polytherapy (89.1%, n=41) compared to monotherapy (10.8%, n=5). These findings are consistent with previous studies conducted in Surabaya, Yogyakarta, and Gorontalo.[11], [12], [20]

Regarding monotherapy, the most commonly utilized drugs were Beta Blockers and CCBs, each accounting for 2 patients (4.3%), followed by 1 patient (2.1%) in the ARB group. According to guidelines such as NKF-KDIGO, initiating hypertension therapy should involve monotherapy, which can reduce systolic blood pressure by approximately 7-13 mmHg and diastolic blood pressure by around 4-8 mmHg.[21] However, the findings of this study did not align with the NKF-KDIGO guidelines, which recommend combination therapy for CKD patients with stage two hypertension,[10] as there were still 3 patients (6.5%) with stage 2 hypertension who were treated with monotherapy.

The most commonly utilized polytherapy involved the combination of two drugs, specifically ARB + CCB, represented by Candesartan + Amlodipine in 9 patients (19.5%). Consistent with

the NKF-KDIGO recommendations, patients with CKD HD and stage 2 hypertension typically initiate treatment with ACE inhibitors or ARB + CCB combination therapy.[10] A similar study also reported similar findings, with 95% of patients (n=19) being treated with a combination of ARB + CCB drugs at the Bhayangkara HS Samsoeri Mertojoso Hospital in Surabaya.[12]

Among the different classes of drugs, CCBs were the most frequently prescribed, being used by 35 patients (76%), with amlodipine being the most commonly prescribed drug, utilized by 31 patients (67.4%) either as monotherapy or in combination with other drugs. Similar results were found in a study conducted by Nadia Husna and Niken Larasati at PKU Muhammadiyah Gamping Hospital, Yogyakarta, between June and August 2018. The CCB group was the most widely used antihypertensive group, accounting for 29.14% (88 individuals, n=302), with amlodipine being the most frequently prescribed drug in this group, used by 20.86% of patients (63 individuals, n=302).[20] Dihydropyridine (CCB) is commonly employed to lower blood pressure in hypertensive patients undergoing HD, with a randomized trial demonstrating that amlodipine significantly reduces blood pressure compared to placebo in this patient population.[22] Previous research conducted by Rahman and Griffin in 2004, as cited by Diana Laila Ramatillah and Widayati, also indicated that amlodipine is commonly used as an antihypertensive drug in hypertensive patients undergoing HD. The principle of antihypertensive therapy in HD patients involves utilizing various types of antihypertensive drugs.[15]

6 Conclusion

In conclusion, the study conducted at the USU Hospital HD Unit in 2022 provided valuable insights into the characteristics and treatment patterns of CKD HD patients receiving antihypertensive therapy. The majority of patients were male, with a significant proportion in the age range of 46-65 years. Hypertension, particularly grade 2, was prevalent among these patients, but a notable percentage achieved successful blood pressure control. Polytherapy, including combinations of ARB with CCB, was the preferred approach for treating hypertension, while CCBs, especially amlodipine, emerged as the most commonly used class of drugs. These findings underscore the importance of individualized treatment strategies to effectively manage hypertension in CKD HD patients and improve their overall health outcomes.

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