ISSN 2745-455X (Online)
Indonesian Journal of Pharmacology and Therapy

The use of antihypertension in hypertension patients with chronic kidney failure at the Universitas Gadjah Mada (UGM) Academic Hospital, Yogyakarta

Syifa Indi Wijaya[1], Anggraini Citra Ryshang Bathari[2], Chairun Wiedyaningsih[1]*

[1]Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, [2]Department of Pharmacy, Universitas Gadjah Mada Academic Hospital, Yogyakarta

https://doi.org/10.22146/ijpther.10453

Submitted: 07-11-2023
Accepted : 22-12-2023

Keywords:
antihypertension; hypertension; chronic kidney failure; rational drugs use; health insurance

ABSTRACT

According to the 2018 Indonesian Basic Health Research data, the prevalence of hypertension in the Yogyakarta Special Region (11.0%) is higher than the national average of 8.8%. Hypertension with chronic kidney failure is currently a prevalent and increasing issue. This study aimed to investigate the pattern and rationality of antihypertensive use in hypertension patients with chronic kidney failure (CKF) participating in the National Health Insurance (*Jaminan Kesehatan Nasional*/JKN) program at Universitas Gadjah Mada (UGM) Academic Hospital period of 2020 to 2022. The study was conducted using quantitative descriptive non-experimental methods. Data collection was carried out retrospectively through medical records of patients diagnosed with hypertension with CKF (ICD I12.0). Samples were selected using purposive techniques and analyzed by comparing the suitability of drug selection with standard hypertension therapy with CKF based on JNC 8 and NKF-K/DOQI, including the rationality of their use. A total of 68 patients over the age of 18 were used as samples. The results showed that a combination of 2 drugs is more dominant (52.9%) compared to monotherapy (29.4%) and a combination of 3 drugs (17.6%). The majority of drug groups used were angiotensin receptor blockers (ARBs), specifically candesartan (45%), ARB and calcium channel blockers (CCB), specifically nifedipine + amlodipine (50%), and ARB + CCB + diuretic, specifically nifedipine + amlodipine + furosemide (33.3%). The rationality of drug use showed that 66.2% in the right indications, 89.7% the right drugs, 100% in the right patients and 85% the right doses. Therefore, health workers still need to make efforts to encourage rational drug use.

ABSTRAK

Menurut data Riset Kesehatan Dasar (Riskesdas) tahun 2018, prevalensi hipertensi di Daerah Istimewa Yogyakarta (11,0%) lebih tinggi dari angka nasional (8,8%). Penyakit hipertensi dengan gagal ginjal kronis sampai saat ini sering terjadi dan terus meningkat. Penelitian ini bertujuan mengkaji gambaran pengobatan dan rasionalitas penggunaan antihipertensi pada pasien hipertensi dengan gagal ginjal kronis (GGK) peserta Jaminan Kesehatan Nasional (JKN) di instalasi rawat jalan RS Akademik UGM periode tahun 2020-2022. Penelitian dilakukan dengan metode non-eksperimental deskriptif kuantitatif. Pengambilan data dilakukan secara retrospektif melalui rekam medis pasien yang terdiagnosa hipertensi dengan GGK (ICD I12.0). Pemilihan sampel dilakukan dengan teknik purposive sampling dan dianalisis dengan membandingkan kesesuaian pemilihan obat terhadap standar terapi hipertensi dengan GGK berupa JNC 8 dan NKF-K/DOQI, termasuk rasionalitas penggunannya. Sampel yang digunakan sebanyak 68 pasien dengan usia lebih dari 18 tahun. Hasil penelitian menunjukan kombinasi 2 obat lebih dominan dengan persentase (52,9%) dibandingkan monoterapi (29,4%) dan kombinasi 3 obat (17,6%). Mayoritas golongan obat yang digunakan adalah ARB yaitu candesartan (45%); ARB + CCB yaitu nifedipine + amlodipine (50%); dan ARB + CCB + diuretik yaitu nifedipine + amlodipine + furosemide (33,3%). Evaluasi rasionalitas penggunaan obat didapatkan hasil, tepat indikasi (66,2%), tepat obat (89,7%), tepat pasien (100%) dan tepat dosis (95,6%). Oleh karena itu, tenaga kesehatan masih perlu melakukan upaya untuk mendorong penggunaan obat yang lebih rasional.

*corresponding author: chairun_wied@ugm.ac.id

INTRODUCTION

The World Health Organization (WHO) in 2021 reported that 1.28 billion people worldwide suffer from hypertension, most of them or two-thirds living in low- and middle-income countries[1]. An estimated 46% of adults with hypertension are unaware that they have the disease.[1] Hypertension is both a cause and effect of chronic kidney diseases (CKD) and affects the vast majority of chronic failure patients. The 2018 Indonesian Basic Health Research (*Riset Kesehatan Dasar*/Riskesdas) reported showed that the hypertension cases in Indonesia is 63,309,620 people, with 427,218 deaths.[2] According to Riskesdas in 2018, the prevalence of hypertension in the Special Region Yogyakarta (DIY) (11.0%) is higher compared with the national average (8.85%).[2] This prevalence places DIY in 4th place in provinces with high cases of hypertension.

Chronic and uncontrolled hypertension can cause organs damage if it is not treated properly. Chronic kidney failure is one of the complications caused by the chronic hypertension. High blood pressure can constrict blood vessels, which ultimately damages and weakens blood vessels throughout the body, including in the kidneys.[3] Uncontrolled hypertension can be a health burden for a country. According to the Regulation of the Minister of Health of the Republic of Indonesia No. 72 of 2016 concerning Standards for Pharmaceutical Services in Hospitals[4], quality of pharmaceutical care in hospitals must carry out monitoring and evaluation of drug quality control including management and drug use. In supporting the implementation of health care, the Directorate General of Development Pharmaceuticals and Medical Devices strives to guarantee the availability, affordability, and accessibility of medicines by compiling the National Formulary that is used as a reference in health services in all health facilities.[5]

Guidelines for the treatment of hypertension patients in the the National Health Insurance (*Jaminan Kesehatan Nasional*/JKN) era have been stipulated in the National Formulary which is revised every 2 years. Blood pressure control is basic care for patients with kidney failure and is associated with all stages of CKF. Studies concerning evaluation of antihypertension drug use in hypertension patients with kidney failure is limited. Tuloli *et al.*[6] reported that the antihypertension drug use in hypertension patients with kidney failure does not fully meet the requirements criteria for appropriates indication and dosage. Their study concerning antihypertensive drugs in hypertensive patients with kidney failure undergoing hemodialysis at Toto Kabila Regional Hospital in the period January 2017-October 2018 resulted in the right patient (100%), the right drug (86.05%), the right indication (83.72%) and the right dose (53.49%).[6]

The high number of cases of hypertensions and many causes of kidney failure due to uncontrolled hypertension in Yogyakarta were reported. A study to evaluate the rational use of drugs in hypertension patients with CKD is needed. This study aimed to investigate the pattern and rationality of antihypertensive use in hypertension patients with CKF participating in the JKN UGM) Academic Hospital, Yogyakarta.

MATERIAL AND METHODS

Study design

This is an observational study to evaluate the pattern and rationality of antihypertensive use of JKN hypertension outpatients diagnosed with CRF (ICD I12.0) for the 2020 to 2022. The study was conducted at the UGM Academic Hospital, Yogyakarta during January

2023, to collect data retrospectively on the medical records.

Protocol of study

The inclusion criteria were outpatients with hypertension and CKF (ICD I12.0) as the principal diagnosis, aged ≥18 years, and those who JKN participants. The exclusion criteria were patients with incomplete or unreadable medical records (no data on gender, age, diagnosis, and medication). Sampling was carried out by purposive sampling and the minimum number of samples taken was calculated using the Slovin formula,[7] with precision set at 10% and a confidence level of 90%. Based on the results of these calculations, if the total population was 106 (data on the medical records, number of hypertensive patients with chronic kidney failure that met the inclusion and exclusion criteria at the UGM Academic Hospital during the 2020 to 2022), then the minimum sample size required is 52 samples. The electronic medical record data used was patient data including identity, gender, age, body weight, diagnosis, complaints, disease history, history of allergies, and history of drug use, as well as physical examination data which included blood pressure data when the patient was diagnosed with primary hypertension with kidney failure and one month after therapy or during control. When patients were controlled, researchers only looked at the blood pressure results after one month of therapy use without evaluating the use of prescribed medication again.

Data analysis

Patient medical record data were recorded on a data collection sheet, and processed against patterns of antihypertensive drug use based on the choice of drug class, type of monotherapy or polytherapy drug use, and evaluated quantitatively regarding the rationality of drug use including accuracy of indication, accuracy of drug choice for the patient and appropriate dosage based on JNC 8,[8] and NKF-K/DOQI 2004.[9] The data were analyzed univariate, and the results were presented descriptively supported by tables.

Ethics approval

This study has been approved by the Medical and Health Research Ethic Committee, Faculty of Medicine, Public Health and Nursing, UGM with Number KE/FK/1660/EC/2022. This study has also received a permit to carry out research at the UGM Academic Hospital, Yogyakarta with number 368/UNI/RSA.2/AR/SB/2023.

RESULTS

A total of 68 samples who met the inclusion and exclusion criteria were obtained during the study. The characteristics of hypertensive outpatients with kidney failure at UGM Academic Hospital, Yogyakarta for the period 2020-2022 are presented in TABLE 1. Based on the gender characteristics presented in TABLE 1, the number of male patients was greater than the number of female patients. In 2015, the WHO under the United Nations officially revised the age standards.[10] The age of the patients in this study was categorized into 3 groups i.e. young age < 45 yr, middle age 45-60 yr, and the elderly category > 60 yr.[10] The results show that patient characteristics based on age were generally over 45 y.o. and there were 17 categories of comorbidities experienced by patients. The JNC 8 classifies blood pressure into four levels, i.e., normal, normal-high, stage 1 hypertension and stage 2 hypertension.[10] The results show majority of hypertensive patients with renal failure had stage 2 hypertension.

TABLE 1. Characteristics of hypertension outpatients with kidney failure, JKN participants at the UGM Academic Hospital during the 2020-2022 period

Category	n (%)
Gender	
• Female	20 (29.4)
• Nale	48 (70.6)
Age (yr)	
• <45	6 (8.8)
• 45-60	30 (44.1)
• >60	32 (47.1)
Comorbidities	
• No- comorbidities	21 (30.9)
• T2DMT	17 (25.0)
• Gout	9 (13.2)
• Gout, hypercholesterolemia	3 (4.4)
• T2DM, hypercholesterolemia	3 (4.4)
• T2DM, gout	2 (2.9)
• T2DM, gout, hypoalbuminemia	1 (1.5)
• T2DM, anaemia	1 (1.5)
• T2DM, hypercholesterolemia, proteinuria	1 (1.5)
• CIHD	1 (1.5)
• Arrhythmia, CIHD	1 (1.5)
• Asthma, dyspepsia	1 (1.5)
• Epistaxis	1 (1.5)
• Hyperplasia prostate	1 (1.5)
• Hypoalbuminemia	1 (1.5)
• Low back pain	1 (1.5)
• Proteinuria	1 (1.5)
• Gastritis	1 (1.5)
Initial blood pressure diagnosed ICD I12.0*	
• Normal** (<130/85)	11 (16.2)
• Normal-High** (130/85-139/89)	15 (22.1)
• Hypertension stage 1** (140/90-159/99)	15 (22.1)
• Hypertension stage 2** (≥ 160/100)	27 (39.7)
Total	68 (100)

CIHD: chronic, ischaemic heart disease; *: hypertension with renal failure; **: Systolic blood pressure is the main measurement as a basis for determining the diagnosis of the degree of hypertension.

TABLE 2 shows the types of antihypertensive therapy, including monotherapy, a combination of 2 drugs, and a combination of 3 drugs. The results showed that the use of therapy was dominated by a combination of two drugs in 36 cases (52.9%). There are 6 types of antihypertensive drugs in kidney failure hypertension patients: ACE-I [angiotensin-converting enzyme (ACE) inhibitor], ARB (angiotensin receptor blocker), BB (beta blocker), CCB

(calcium channel blocker), diuretics, and ∝-agonists (TABLE 2). The most commonly used in hypertensive patients with kidney failure as monotherapy was ARB (candesartan), while the highest use for a combination of 2 drugs, was the ARB + CCB group (candesartan + amlodipine). Furthermore, the highest use of 3 drug combinations was the use of ARB + CCB + diuretic (candesartan + amlodipine + furosemide).

TABLE 2. Pattern of antihypertensive drug use in hypertensive outpatients with kidney failure of JKN participants at the UGM Academic Hospital for the 2020-2022 period

Drug class	Drug	n (%)
Monotherapy		
• ACEI	Ramipril	1 (5)
• ARB	Candesartan	9 (45)
	Telmisartan	1 (5)
	Valsartan	2 (10)
	Irbesartan	1 (5)
• BB	-	0 (0)
• CCB	Amlodipine	2 (10)
	Nifedipine	1 (5)
	Diltiazem	2 (10)
• Diuretic	Furosemide	1 (5)
Total		20 (100)
Combination of 2 drugs		
• ARB + CCB	Irbesartan + amlodipine	3 (8.3)
	Candesartan + amlodipine	18 (50)
	Candesartan + nifedipine	3 (8.3)
	Valsartan + amlodipine	3 (8.3)
	Telmisartan + amlodipine	1 (2.8)
• ARB + BB	Candesartan + bisoprolol	1 (2.8)
	Valsartan + bisoprolol	1 (2.8)
• ARB + diuretic	Candesartan + furosemide	2 (5.6)
	Irbesartan + furosemide	1 (2.8)
• CCB + diuretic	Diltiazem + spironolactone	1 (2.8)
	Amlodipine + furosemide	1 (2.8)
• ACEI + CCB	Lisinopril + amlodipine	1 (2.8)
Total		36 (100)
Combination of 3 drugs		
• α-agonist +ARB+ CCB	Clonidine + candesartan + ciltiazem	3 (25)
• ARB + CCB + diuretic	Candesartan + amlodipine + hidroklorotiazid	1 (8.3)
	Candesartan + amlodipine + furosemide	4 (33.3)
	Candesartan + diltiazem + hidroklorotiazid	1 (8.3)
• ARB + BB + diuretic	Candesartan + bisoprolol + furosemide	1 (8.3)
• ARB + BB + CCB	Candesartan + bisoprolol + amlodipine	1 (8.3)
• ARB + CCB + CCB	Candesartan + diltiazem + nifedipine	1 (8.3)
Total		12 (100)

*CCB (calcium channel blocker); ACEI (angiotensin-converting enzyme inhibitor); ARB (angiotensin receptor blocker); BB (beta blocker)

The present study shows 23 patients (33.8%) were administered antihypertensive therapy with inappropriate indication criteria (TABLE 3). The decision to prescribe a drug was not entirely based on medical rationale and drug therapy for effective and safe treatment. The data obtained from the patient's medical record showed initial blood pressure level in the normal range but receiving antihypertensive drugs. While in the medical records (the data was taken retrospectively) was also no data on previous drugs use or data on diagnoses from the previous Primary Health Centre (*Puskesmas*) before referral. Therefore, these patients should be advised to change their lifestyle first.

TABLE 3. Distribution of hypertension with kidney failure outpatients of JKN Participants with inappropriate indication at the UGM Academic Hospital for the 2020-2022 period

Comorbidities (Case no.)	Initial BP (mmHg)	Antihypertensive
No comorbidities		
• 19	100/80	ARB + CCB
• 40	130/90	ACEI + CCB
• 45	120/80	ARB
• 49	130/80	ARB + CCB
• 50	130/80	ARB + CCB
• 56	120/70	ARB + diuretic
• 58	130/90	ARB
• 60	120/07	ARB + CCB
T2DM		
• 5	130/70	ARB + diuretic
• 18	130/80	ARB + CCB
• 21	130/80	ARB
• 24	120/70	ARB + BB
• 28	94/60	ARB + diuretic
• 32	130/70	ARB + CCB + diuretic
• 62	130/70	ARB + CCB
• 67	130/70	ARB + CCB + diuretic
Gout		
• 10	110/70	CCB
• 31	130/80	ARB
• 34	138/89	ARB
• 36	120/70	ACEI
• 42	130/90	CCB
• 22	120/70	CCB
• 15	130/80	ARB

* ARB (angiotensin receptor blocker); CCB (calcium channel blocker); ACEI (angiotensin-converting enzyme inhibitor).

Evaluation of the rationality of drug use in terms of patient accuracy was the accuracy of drug selection based on the patient's individual condition and the absence of contraindications. The present study shows no contraindications were found, and all the drugs given were appropriate to the patient's pathological and physiological conditions. Evaluation of the rationality of drug use in terms of appropriate drug was the choice of antihypertensive for patients with chronic kidney failure based on JNC 8 and NKF-K/DOQI 2004 recommendations as well have the desired therapeutic effect. The presence of antihypertensive drugs that were not listed in the guidelines were stated as inappropriate drugs. Those results show that 61 (89.7%) patients were in the appropriate drug choice, while 7 (10.3%) patients were in the inappropriate drug choice categories (TABLE 4).

Furthermore, the accuracy of the dose was evaluated based on the suitability of the drug dose given to the JNC 8 standard, and NKF-K/DOQI 2004. The drug dose was the strength of the drug that the patient was taking to get the desired therapeutic effect. The results show 65 patients (95.6%) had the appropriate dose, while 3 patients (4.4%) had an inappropriate dose (TABLE 5).

TABLE 4. Distribution of hypertension with kidney failure outpatients of JKN Participants with inappropriate drug at the UGM Academic Hospital for the 2020-2022 period

Case no.	Initial BP* (mmHg)	BP after 1 month** (mmHg)	Antihypertension drug	Comorbidity	Suggestion
6	140/80	155/80	BB+diuretic+ARB	T2DM; hyper-cholesterolemic; proteinuria	Add another drug group/titrate dose
11	160/90	190/100	CCB+ARB + **α**-gonist	T2DM; gout	Add another drug group/titrate dose
27	200/110	210/100	ARB+CCB+**α**-ago-nist	T2DM	Add another drug group/titrate dose
30	160/80	180/100	ARB+CCB	-	Add another drug group/titrate dose
41	187/99	180/88	Diuretic	-	Combination of 2 drugs
43	160/80	160/90	ARB+CBB+CCB	T2DM	Duplication of therapy (use different groups)
47	160/100	160/100	CCB	-	Combination of 2 drugs

*: systolic blood pressure is the main measurement as a basis for determining the diagnosis of the degree of hypertension

TABLE 5. Distribution of hypertension with kidney failure outpatients of JKN Participants based on the accuracy of dose at the UGM Academic Hospital for the 2020-2022 period

Case no.	Drug	Clcr adjustment	Clcr patient (mL/min)	Dose
35	Spironolactone	CLcr 31-50 mL/ min the dose is reduced to 12.5 mg 1/d, CLcr < 30 mL/min was not recommended	40	100 mg/d, dose should be reduced to 12.5 mg/d.[11]
36	Ramipril	For CLcr < 40 mL/ minutes, give 25% of the normal dose	32,4	5 mg/day (the dose should be 25% of 5 mg, 1.25 mg/d.[11]
40	Lisinopril	CLcr>30 mL/ min, initial dose 5 mg/d	65	10 mg/d, because it was for the first time, the dose used was 5 mg/d.[11]

DISCUSSION

Of the total 68 cases involved this study, the number of male patients suffering from hypertension and kidney disease was greater than female patients. Although overall hypertension is more common in men, women experience a much sharper decline in blood pressure from the third decade of life and as a result, the prevalence of hypertension increases with age.[12] Hypertension confers about a fifth lower excess risk of incident chronic kidney disease or end-stage renal disease in women than men.[13] Murphy *et al.*[14] reported that kidney failure's prevalence was higher in women than men and Albertus *et al.*[15] indicated that the lifetime risk of end-stage kidney failure is higher in men than women. Chang *et al.*[16] showed that proteinuria is the most important risk factor in male patients. However, further research is needed to demonstrate the mechanisms responsible for the observed sex differences.[13]

Hypertension is a highly prevalent condition with numerous health risks, and the incidence of hypertension is greatest among older adults. These current results are in line with the Indonesian Ministry of Health's report that the prevalence of hypertension at risk of kidney failure in Indonesia increases with age.[2] Patients aged over 50 or 60 yr are more at risk of developing hypertension complications,[17,18] since increasing age, the arteries tend to become more rigid, reducing the elasticity of blood vessels so that blood vessels become narrower and stiffer.[19,20] Although there is no synergistic effect between diabetes and hypertension on the incidence of kidney failure,[21] the study results show that T2DM was the most common comorbidity. The results show that T2DM was in the first place as a comorbid disease, but it was found only in 25% of comorbidities, while 30% of patients had no comorbidities and the rest had various comorbidities.

Treatment guidelines for hypertensive patients with kidney disease are widely available.[22-24] The current study shows the most commonly used in hypertensive patients with kidney failure as monotherapy was ARB (candesartan), while the highest use for a combination of 2 drugs, was the ARB + CCB group (candesartan + amlodipine). Furthermore, the highest use of 3 drug combinations was the use of ARB + CCB + diuretic (candesartan + amlodipine + furosemide), and ∝-agonist + ARB + CCB (clonidine + candesartan + diltiazem). Hypertension is both a cause and effect of CKD and affects the vast majority of CKD patients.[22,25] Rational use of drugs is very important to increase therapeutic success. If hypertensive patients

with kidney failure do not receive appropriate treatment, it will cause the disease to get worse and possibly cause other disease complications worsening the patient's condition and even the potential for death is greater. Control of hypertension is important in those patients with chronic kidney disease as it leads to slowing of disease progression.[22] They will often require a combination of antihypertensive medications to achieve target blood pressure.[22] Therapy customized for individuals is extremely important, especially for patients with high blood pressure who are at increased risk of end-organ damage. This study showed that candesartan was the most commonly used monotherapy option. According to a meta-analysis, ARBs are the most effective antihypertensive agents for the prevention of end-stage renal disease.[26] Candesartan is a potent angiotensin II type 1 receptor blocker (ARB) that binds more tightly to the AT_1-receptor and dissociates more slowly than earlier members of the class.[27] Candesartan provides cardiovascular protection even in those patients who may occasionally miss doses.[28] The Study on Evaluation of Candesartan Cilexetil after Renal Transplantation (SECRET) provides evidence of the utility of candesartan, showing good safety and tolerability, improved blood pressure control, and reduced proteinuria in kidney transplant recipients.[29]

Controlling hypertension in those patients with chronic kidney disease not only slows the progression of renal damage but reduces the risk of cardiovascular disease.[22] To achieve target blood pressure, patients with CKD usually require two or more antihypertensive agents.[22,25] Some guidelines recommend initiating treatment with two drugs in those patients with a systolic blood pressure >20 mmHg and/or a diastolic blood pressure >10 mmHg above the goals.[30] In addition, approximately 25% of patients will require three antihypertensive agents to achieve the therapeutic targets.[30] The study showed that the most common choice of drugs used to achieve target blood pressure levels was a combination of 2 drugs. The results are supported by previously available data showing that at least 75% of patients require combination therapy to achieve blood pressure targets.[31] The choice of specific combinations may be individualized according to demographics, comorbid conditions, response to previous treatments, and cost, as well as physician preference.[31,32] Using drug combination has superior ability to control blood pressure in patients with difficult-to-treat hypertension.[33] In addition, combination treatment allows for easier (and faster) blood pressure control compared with monotherapy.[33] Although antihypertensive monotherapy is commonly used, it does not address the multifactorial nature of hypertension as a disease with many pathways.[34] The use of more than one drug makes more sense in therapy because combination drugs cover more than one pathway.[34] Using a drug dose combination with two different classes of antihypertensive agents will achieve the goal of blood pressures.[34,35] The advantages of combinations include 1) greater blood pressure decrease and response rates than monotherapy; 2) fewer side effects with small doses of two drugs than with large doses of one agent; 3) improved treatment adherence; and 4) possibly lower cost of therapy.[35] Angiotensin receptor blockers are among the recommended first-line treatment options in patients with hypertension and chronic kidney disease.[36] A study using meta-analysis demonstrated ARB as monotherapy or in combination with other antihypertensive drugs had a favorable impact on blood pressure and renal parameters such as protein, highlighting their potential benefits in patients with hypertension and chronic kidney diseases.[36] These data suggest that ARB fulfilled two important criteria to be recommended as first-line therapy in hypertension and chronic kidney diseases.[36] Individualization of therapy is necessary, and patient comorbidities

must be considered.[37]including missed dialysis treatments, intradialytic changes in BP, medication removal with dialysis, and poor correlation of BPs obtained in the dialysis unit with those at home and with CV outcomes. Control of extracellular volume with ultrafiltration and dietary sodium restriction represents the principal strategy to manage hypertension in ESRD, and antihypertensive medications are subsequently added if this strategy is inadequate. While reduction in BP with medication improves CV outcomes, few head-to-head clinical trials have been performed to firmly establish the superiority of one antihypertensive medication class over another. Therefore, individualization of therapy is necessary, and patient comorbidities must be considered. Angiotensin-converting enzyme (ACE Angiotensin-converting enzyme inhibitors, ARBs, and BB are reasonable first-line medications for most patients.[37] Kumolosari *et al*[38] conducted research to determine the effectiveness of a combination of antihypertensive drugs in hypertensive patients with end-stage renal failure at one of the tertiary hospitals in Malaysia. The combination of BB and CCB is the most common combination given to hypertensive patients with end-stage renal failure.[38]

Rational use of medicine encourages safe, efficient, and cost-effective utilization of drug. In this study, an evaluation has been carried out on the accuracy of selecting the right antihypertensive drug for chronic kidney failure patients based on JNC 88 and NKF-K/DOQI 20049 recommendations. The results showed that 23 patients (33.8%) were given antihypertensive therapy with inappropriate indication criteria. Modifying lifestyle should be the first choice. There were still patients who received drugs that were not in accordance with indications. The evaluation was based on medical record data which showed that the patients' initial blood pressure was within the normal range but they were given antihypertensive drugs. However, the results still have limitations considering that the data was taken retrospectively and there was still limited data related to previous drug use or diagnostic data from previous health centers before referral. Indeed, although treatment with pharmacological agents is commonplace, lifestyle management to delay the progression of chronic kidney disease must also be carried out.[39] There is increasing evidence that lifestyle factors impact the risk and progression of chronic kidney disease.[40] Lifestyle factors that aggravate progression include, among others, smoking, obesity, and dietary salt intake.[40] Wakasugi *et al.*[41] also stated the importance of a healthy lifestyle in preventing chronic kidney disease.

If a patient was given an antihypertensive drug that was not included in the preferred drugs in the guidelines, it was stated that the drug was not appropriate. The study showed that there were 61 (89.7%) patients in the appropriate drugs category, while there were 7 (10.3%) patients in the inappropriate drugs category. Inappropriate drugs in this study occurred due to combinations, group selection, and therapeutic effects that did not comply with JNC 8[8] and NKF-K/DOQI 2004[9] standards. The JNC 8 recommends the use of combination therapy as first-line therapy for stage 2 hypertension (>160/100 mmHg) or if systolic blood pressure >20 mmHg increases above target (<140 mmHg) and diastolic blood pressure >10 mmHg above target (<90 mmHg). Monotherapy is used in patients with stage one hypertension and is also recommended for patients at high risk of adverse effects side.[8] Inappropriate drugs occurred in patients with case numbers 41, 43, and 47. Patients with case no. 41 and no.47 had stage two hypertension with blood pressure ≥160. Based on JNC 8,[8] patients with stage 2 hypertension are recommended to use combination therapy. Patient case no.

43 used drugs in the same class (CCB: diltiazem and nifedipine). Combinations of antihypertensive drugs should be chosen from different class.[8] Patients with case no. 6, 11, 27, and 30 were found that the blood pressure achieved after using therapy for 1 month was not according to the target. Blood pressure achieved in patients with case no. 6, 11, 27, and 30 was not on target after using therapy for 1 month. This was because the patient experienced an increase in blood pressure based on the patient's initial physical examination. Therefore, it was necessary to titrate the dose or add other classes of drugs that have not been used.[8] The recommended drugs were thiazide diuretics, ACE-I, ARB, or CCB (note: use of the initial drug should not be repeated, and avoid the combination of ACE-I and ARB). If blood pressure still has not reached the desired therapeutic target, then another class of antihypertensive drugs, such as β-blockers, aldosterone antagonists, and/or another consultation was carried out for hypertension therapy management.[8]

Dosage is an important aspect in determining drug efficacy. If the dose given does not match the therapeutic range, the expected therapeutic effect will not be achieved. The dose was considered correct if the dose given to the patient was based on the JNC 8[8] and NKF-K/DOQI 2004[9] standards. The results showed that 65 (95.6%) patients received the correct dose and 3 (4.4%) patients received the incorrect dose. The dosage of spironolactone, ramipril, and lisinopril was not inappropriate. Inaccuracies in dosage categories due to antihypertensive drugs should be adjusted to the Clearance creatinine (Cl_{Cr}) value.

This study was conducted retrospectively with limited completeness of data in medical records. Reseacrhers did not know the doctors' considerations in choosing treatment strategies for patients, so it was difficult to ensure that the treatment given to patients was truly appropriate. Apart from that, researchers also did not know the incidence of side effects because this data is not listed in the patient's medical record. Researchers only found out the results of the therapeutic effect by achieving the blood pressure target within 1 month of antihypertension drug use. In this study there were differences in the standard guidelines used, therefore, the decision on the right indication, the right drug, the right patient, and the right dose of the study was only based on the JNC 8 and NKF-K/DOQI 2004 standards.

CONCLUSION

The use of antihypertensive drugs in hypertensive outpatients with renal failure of JKN participants at the UGM Academic Hospital, Yogyakarta is a combination of 2 drugs in 36 patients (52.9%), followed by monotherapy in 20 patients (29.4%), a combination of 3 drugs. in 12 patients (17.6%). The monotherapy group is dominated by ARBs (candesartan (45%)); while the combination of 2 drugs is ARB + CCB, (nifedipine + amlodipine (50%)); and the combination of 3 drugs is ARB + CCB + diuretic (nifedipine + amlodipine + furosemide (33.3%). Evaluation of rationality based on the JNC 8 and NKF-K/DOQI 2004 guidelines obtains 66.2% correct indication, 89.7% correct drug, 100% correct patient and 95.6% correct dose.

ACKNOWLEDGEMENT

Authors would like to thank the Director of UGM Academic Hospital for the permission to conduct this study.

REFERENCES

1. World Health Organization. Hypertension [Internet]. [cited 2023 Oct 28]. https://www.who.int/news-room-fact-sheets/detail/hypertension
2. Kemenkes RI. Hasil Riset Kesehatan

Dasar Tahun 2018. Kementrian Kesehat RI. 2018; 53(9):1689-99.
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet 2017; 389(10064):37-55. https://doi.org/10.1016/S0140-6736(16)31919-5
4. Kemenkes RI. Peraturan Menteri Kesehatan Republik Indonesia Nomor 72 Tahun 2016 Tentang Standar Pelayanan Kefarmasian di Rumah sakit. Kementeri Kesehat Republik Indones. 2016;
5. Kemenkes RI. Keputusan Menteri Kesehatan Republik Indonesia Nomor Hk.01.07/Menkes/1970/2022 Tentang Perubahan Atas Keputusan Menteri Kesehatan Nomor Hk.01.07/Menkes/6485/2021 Tentang Formularium Nasional. Kementeri Kesehat Republik Indones [Internet]. 2022; 2021:4-92. https://e-fornas.kemkes.go.id/files/pdf/KMK No. HK.01.07-MENKES-1970-2022 tentang Perubahan atas Formularium Nasional.pdf
6. Tuloli TS, Madania M, Mustapa MA, Tuli EP. Evaluasi Penggunaan Obat Pada Pasien Gagal Ginjal Kronik Yang Menjalani Hemodialisis Di Rsud Toto Kabila Periode 2017-2018. Parapemikir J Ilm Farm 2019; 8(2):25. https://doi.org/10.30591/pjif.v8i2.1470
7. Ellen S. Slovin's Formula Sampling Techniques [Internet]. [cited 2023 Oct 30]. https://sciencing.com/slovins-formula-sampling-techniques-5475547.html
8. Schmieder S. JNC 8 Hypertension Guidline Algorithm. St Cl Comput High - Technol Law J 2004; 21(1):163-234.
9. National Kidney Foundation. K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease [Internet]. 2004 [cited 2023 Nov 6]. https://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_bp/index.htm
10. Dyussenbayev A. Age Periods Of Human Life. Adv Soc Sci Res J 2017; 4(6):258-63. https://doi.org/10.14738/assrj.46.2924
11. Lacy CF, Amstrong LL, Goldman MP, Lance LL. Drug Information Handbook: A Comprehensive aaaaaresource for All Clinicians and Healthcare Professionals (Lexi-Comp's Drug Reference Handbooks). Vol. 17, Lexi-Comp Inc. 2009.
12. Connelly PJ, Currie G, Delles C. Sex Differences in the Prevalence, Outcomes and Management of Hypertension. Curr Hypertens Rep 2022; 24(6):185-92. https://doi.org/10.1007/s11906-022-01183-8
13. Weldegiorgis M, Woodward M. The impact of hypertension on chronic kidney disease and end-stage renal disease is greater in men than women: a systematic review and meta-analysis. BMC Nephrol 2020; 21(506):1-9. https://doi.org/10.1186/s12882-020-02151-7
14. Murphy D, Mcculloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, *et al*. Trends in prevalence of chronic kidney disease in the United States for the Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team HHS Public Access. Ann Intern Med 2016; 165(7):473-81. https://doi.org/10.7326/M16-0273
15. Albertus P, Morgenstern H, Robinson B SR. Risk of ESRD in the United States. Am J Kidney Dis 2016; 68(6):862-72. https://doi.org/10.1053/j.ajkd.2016.05.030
16. Chang PY, Chien LN, Lin YF, Wu MS, Chiu WT, Chiou HY. Risk factors of gender for renal progression in patients with early chronic kidney disease. Med (United States). 2016; 95(30). https://doi.org/10.1097/

MD.0000000000004203
17. Haller H. Effective management of hypertension with dihydropyridine calcium channel blocker-based combination therapy in patients at high cardiovascular risk. Int J Clin Pract 2008; 62(5):781-90. https://doi.org/10.1111/j.1742-1241.2008.01713.x
18. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, *et al*. Clinical Practice Guidelines for the Management of Hypertension in the Community: A Statement by the American Society of Hypertension and the International Society of Hypertension Clinical Practice Guidelines for the Management of Hypertension in the Comm. J Clin Hypertens 2014; 16(1):14-26. https://doi.org/10.1111/jch.12237
19. Laurent S, Boutouyrie P. Arterial Stiffness and Hypertension in the Elderly. Front Cardiovasc Med 2020; 7:1-13. https://doi.org/10.3389/fcvm.2020.544302
20. Kohn JC, Lampi MC, Reinhart-King CA. Age-related vascular stiffening: Causes and consequences. Front Genet 2015; 6:1-17. https://doi.org/10.3389/fgene.2015.00112
21. Erfanpoor S, Etemad K, Kazempour S, Hadaegh F, Hasani J, Azizi F, *et al*. Diabetes, hypertension, and incidence of chronic kidney disease: Is there any multiplicative or additive interaction? Int J Endocrinol Metab 2021; 19(1):1-8. https://doi.org/10.5812/ijem.101061
22. Pugh D, Gallacher PJ, Dhaun N. Management of Hypertension in Chronic Kidney Disease. Drugs 2019; 79(4):365-79. https://doi.org/10.1007/s40265-019-1064-1
23. Hebert SA, Ibrahim HN. Hypertension Management in Patients with Chronic Kidney Disease. Methodist Debakey Cardiovasc J 2022; 18(4):41-9. https://doi.org/10.14797/mdcvj.1119
24. Polychronopoulou E, Wuerzner G, Burnier M. How do I manage hypertension in patients with advanced chronic kidney disease not on dialysis? Perspectives from clinical practice. Vasc Health Risk Manag 2021; 17:1-11. https://doi.org/10.2147/VHRM.S292522
25. Palmer BF, Fenves AZ. Optimizing Blood Pressure Control in Patients with Chronic Kidney Disease. Baylor Univ Med Cent Proc 2010; 23(3):239-45. https://doi.org/10.1080/08998280.2010.11928626
26. Palmer SC, Mavridis D, Navarese E, Craig JC, Tonelli M, Salanti G, *et al*. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: A network meta-analysis. Lancet 2015; 385(9982):2047-56. https://doi.org/10.1016/S0140-6736(14)62459-4
27. Lacourcie Y, Asmar R. A Comparison of the Efficacy and Duration of Action of Candesartan Cilexetil and Losartan as Assessed by Clinic and Ambulatory Blood Pressure After a Missed Dose, in Truly Hypertensive Patients. Am J Hypertens 1999; 12(12):1181-7. https://doi.org/10.1016/S0895-7061(99)00142-9
28. Meredith P. Achieving quality 24-h blood pressure control with candesartan cilexetil. Blood Press Suppl 2000; 9(1):23-6. https://doi.org/10.1080/080370500439182
29. Philipp T, Martinez F, Geiger H, Moulin B, Mourad G, Schmieder R, *et al*. Candesartan improves blood pressure control and reduces proteinuria in renal transplant recipients: Results from SECRET. Nephrol Dial Transplant 2010; 25(3):967-76. https://doi.org/10.1093/ndt/gfp581
30. Guerrero-García C, Rubio-Guerra AF. Combination therapy in the treatment of hypertension. Drugs Context 2018; 7:1-9. https://doi.org/10.7573/dic.212531
31. Gradman AH, Basile JN, Carter BL, Bakris GL. Combination therapy in hypertension. J Am Soc Hypertens

2010; 4(1):42-50. https://doi.org/10.1016/j.jash.2010.02.005
32. Kalra S, Kalra B, Agrawal N. Combination therapy in hypertension: An update. Diabetol Metab Syndr 2010; 2(44):1-11. https://doi.org/10.1186/1758-5996-2-44
33. Mancia G, Rea F, Corrao G, Grassi G. Two-Drug Combinations as First-Step Antihypertensive Treatment. Circ Res 2019; 124(7):1113-23. https://doi.org/10.1161/CIRCRESAHA.118.313294
34. NeutelJM.Low-doseantihypertensive combination therapy: Its rationale and role in cardiovascular risk management. Am J Hypertens 1999; 12(8 SUPPL. 1):73-9. https://doi.org/10.1016/S0895-7061(99)00112-0
35. Moser M, Black HR. The Role of Combination Therapy in the Treatment of Hypertension. Am J Hypertens 1998; 11:73S-78S. https://doi.org/10.1016/S0895-7061(98)00060-0
36. Burnier M, Lin S, Ruilope L, Bader G, Durg S, Brunel P. Effect of angiotensin receptor blockers on blood pressure and renal function in patients with concomitant hypertension and chronic kidney disease: a systematic review and meta-analysis. Blood Press 2019; 28(6):358-74. https://doi.org/10.1080/08037051.2019.1644155
37. Denker MG, Cohen DL. Antihypertensive Medications in End-Stage Renal Disease. Semin Dial 2015; 28(4):330-6. https://doi.org/10.1111/sdi.12369
38. Kumolosasi E, Ng W Bin, Aziz SAA. Effectiveness of antihypertensive drugs in hypertensive patients with end stage renal failure. Med J Malaysia 2012; 67(4):379-85.
39. Williams AD, Fassett RG, Howden EJ, Coombes JS. Effect of lifestyle modifications on patients with chronic kidney disease [Internet]. Goldsmith DJ, Turner NN, Turner NN, Lameire N, Goldsmith DJ, Winearls CG, *et al.*, editors. Oxford Textbook of Clinical Nephrology. Oxford University Press; 2015. p. 824-9. https://doi.org/10.1093/med/9780199592548.003.0105_update_001
40. Ritz E, Schwenger V. Lifestyle modification and progressive renal failure. Nephrology 2005; 10(4):387-92. https://doi.org/10.1111/j.1440-1797.2005.00439.x
41. Wakasugi M, Kazama JJ, Yamamoto S, Kawamura K, Narita I. A combination of healthy lifestyle factors is associated with a decreased incidence of chronic kidney disease: a population-based cohort study. Hypertens Res 2013; 36(4):328-33. https://doi.org/10.1038/hr.2012.186