Received : 2020-08-26 Revised : 2020-11-24 Acceptance : 2020-12-05 Publish : 2020-12-07

STUDY OF THE USE AND POTENTIAL DRUG INTERACTION ON THE TREATMENT OF HYPERTENSIONS AT X HOSPITALS CILACAP IN 2020

Mika Tri Kumala Swandari[1], Dwi Maryanti[2]
[1]Bachelor of Pharmacy Program, STIKES Al Irsyad Al Islamiyyah Cilacap, Indonesia
[2]Diploma of Midwifery Program, STIKES Al Irsyad Al Islamiyyah Cilacap, Indonesia

*E-mail : bidandwimaryanti@gmail.com

ABSTRACT

Hypertension is a state of increasing systolic blood pressure of more than 140 mmHg and diastolic blood pressure of more than 90 mmHg on 2 measurements with an interval of 5 minutes in a calm state. Pharmacological management of hypertension refers to the Guideline Joint National Committee (JNC) 8 on 2014. The use of pharmacological therapy can cause problems, such as drug interactions. The complexity of using drugs tends to increase drug interactions. In this study, a potential drug interaction study was conducted to determine the magnitude of the potential interactions that might occur between drugs. The method used is descriptive method. The population in this study were medical records of hypertensive drug users diagnosed. Data analysis used univariate data analysis and the use of the Lexicom application. The results of the characteristics of hypertension drug users were 57,69% women and 42,31% men. Characteristics based on age were 40 years (0.77%), 74 years (0.77%) and the average age 61 (9.23%) years. The class of drugs used was 53.71% Calcium Channel Blocker (CCB), 28% Angiotensin Receptor Blocker (ARB), 8.57% Angiotensin Converting Enzyme Inhibitor (ACEI), 8% Beta Blocker and 1.71% Diuretic. The severity of hypertension medication was moderate 63.11%, major 3.88%, minor 33.01%. Based on the results obtained, the majority of women using hypertension drug characteristics were 58% and the average age was 61 (8.9%) years. The majority of the drugs used were 54% Calcium Channel Blockers with a moderate majority of 64%.

Keywords: Hypertension Drugs, Drug Interaction, Severity Level, Data Validity, Onset.

INTRODUCTION

Hypertension is a state of increasing systolic blood pressure of more than 140 mmHg and diastolic blood pressure of more than 90 mmHg at 2 measurements with an interval of 5 minutes in a calm state[1]. The classification of hypertension consists of normal blood pressure (systole <120 mmHg and diastole <80 mmHg), Prehypertension (120-139 mmHg systole and 80-89 mmHg diastole), Stage I hypertension (140-159 mmHg systole and 90-99 mmHg diastole), Stage II hypertension (160 or >160 mmHg systole and 100 or >100 mmHg diastole)[1].

Based on data from the World Health Organization (WHO), the estimate of hypertension sufferers worldwide is 1.13 billion, with 2/3 living in low and middle-income countries. In 2015,

1 from 4 men and 1 from 5 women had hypertension. Hypertension is the main cause of premature death worldwide[2]. In Indonesia, data on hypertension is obtained from the results of the 2018 Basic Health Research (Riskesdas). It is known that the prevalence of hypertension in Indonesia based on doctor's diagnosis at ≥18 years of age is at 13.2% (8.4%) with the most prevalence in North Sulawesi. Hypertension patience in Indonesia when viewed from several aspects, are as follows age characteristics, many suffer from those aged 75 years and over (69.5%); the gender aspect is more female (36.9%) than male (31.3%); the aspect of living is more from urban (34.4%) than rural (33.7%); education aspect, the majority have never attended school (51.6%); Aspect of work, the majority do not work (39.7%) [3].

The high rate of hypertension cannot be underestimated, moreover, the condition of high blood pressure significantly increases the risk of heart, brain, kidney and other diseases[4]. Meanwhile, hypertension management can be done by taking medications and lifestyle modifications. It is known that the proportion of taking medication in s with hypertension is the majority in the routine category (54.4%), does not routine 32,2% and does not take medication 13,3%. It's known that 59,8% of hypertension patients category doesn't routine take medication feel healthy[3].

The pharmacological management of hypertension refers to the Guideline Joint National Committee (JNC) 8 of 2014. JNC 8 guideline recommendations are based on the age population, such as ≥60 years: pharmacological therapy used to lower blood pressure, if systole is ≥150mmHg and diastole ≥90 mmHg; age <60 years, pharmacological therapy to lower blood pressure, if diastolic ≥90 mmHg, with target diastolic <90 mmHg; age <60 years, pharmacological therapy used to lower blood pressure, if systole ≥140 mmHg with a target systole <140 mmHg; age ≥18 years with diabetes, pharmacological therapy used to lower blood pressure, if systole ≥140 mmgh or diastole ≥90 mmHg with a target blood pressure systole <140 mmHg and diastole <90 mmHg; age ≥18 years with chronic kidney disease, initial antihypertensive therapy including ACEI or ARB used to improve renal outcome. The main goal of hypertension therapy is to achieve and maintain blood pressure targets. If the target blood pressure is not reached within 1 month of treatment, it is necessary to increase the initial drug dose or add a second drug from one of the recommended classes[5].

The use of pharmacological therapy can cause problems, one of which is drug interactions. The complexity of using drugs tends to increase drug interactions. Previous research conducted at the RSP pharmacy installation in Ario Wirawan Salatiga for the period January-March 2019, it was known that 51.39% had drug interactions, with 53.9% with pharmacokinetic mechanism patterns and the highest severity level was minor (42.86 %) and there is a significant correlation between the number of drugs and the incidence of interactions[6].

In this study, a potential drug interaction study was conducted to determine the magnitude of the potential interactions that might occur between drugs, because not all interactions produce positive effects. Adverse interactions can cause serious to fatal disorders, for example in combination. Hopefully, the results of this study can be an evaluation of the use

of hypertension drugs that have been running so far and can be the basis for the use of antihypertensives and the occurrence of drug interactions in out Hypertension Drug Users.

METHOD

The research used descriptive method with a documentation study design. The data is taken from a prescription at the Pharmacy Installation at a hospital X in Cilacap Regency. Hypertension patients are patients who go to the Pharmacy Installation at one of the hospitals in Cilacap Regency. After the data is taken, an editing process is carried out to ensure the completeness of the data. Incomplete data are excluded data. After the editing process, 130 data were processed. The inclusion criteria were prescription for hypertension drugs with complete data in December 2019. Data analysis using Univariate and recipe sheets was identified through trusted literature, namely Lexicomp made by Wolters Kluwer Health.

RESULT AND DISCUSSION

A. Characteristic of Hypertension Drug of Users

1. Gender

In Figure 1, it can be seen that the frequency distribution of hypertension drug users based on the majority gender is 75 (57.69%) women and 55 (42.31%) men.

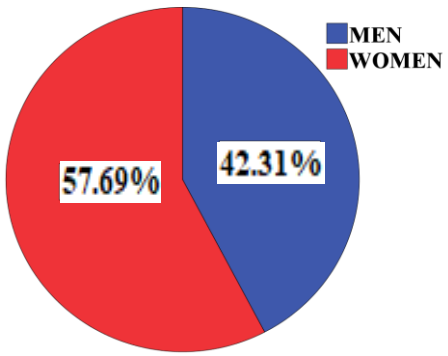

Figure 1. Percentage of Hypertension Drug Users based on Gender

This results of study are accordance with the 2018 Riskesdas, that the prevalence of hypertension in female Hypertension Drug Users is higher than male Hypertension Drug Users [3]. In line with some previous studies, that the majority of hypertension sufferers are female [6–8]. Women who have not experienced menopause will be more protected from cardiovascular disease than women who have experienced menopause, because they have the hormone estrogen which plays a role in increasing levels of High Density Lipoprotein (HDL). Women have the hormone estrogen in their bodies. One of the functions of estrogen is to increase High Density Lipoprotein (HDL). However, entering menopause the number of

follicles in the ovaries that produce estrogen decreases. This decrease in estrogen causes a decrease in HDL which provides an opportunity for the formation of aterosleros is which can damage the endothelial and increase blood pressure.

2. Ages

Based on Figure 2, it can be seen that the youngest age is 40 years (0.77%) and the oldest is 74 years (0.77%) with an average user aged 61 years (9.23%). Age 61 years is old age. In the elderly, the tendency is that there is a decrease in the function of the entire body, in this case the blood vessels. In the elderly there is a degenerative state, changes in blood vessels that become narrow and stiff, so that it is burdensome to work the heart. This can occur due to decreased levels of hormones, one of which is estrogen. This estrogen functions to maintain the flexibility of blood vessels, so when estrogen falls, the elasticity of the blood vessels drops to become stiff and narrow.

The prevalence of hypertension based on the results of Basic Health Research in 2018 illustrates that the largest percentage of Hypertension Drug Users is >75 years (69.5%), followed by 65-74 years (63.2%), 55-64 years (55.2%), 45 -54 years (45.3%), 35-44 years (31.6%), 25-34 years (20.1%), and the lowest is 18-24 years (13.2%) [3]. Age is a risk factor that cannot be controlled among other risk factors for hypertension. This results of the study on the majority of hypertension drug users were in line with other research that the majority of hypertensive s aged 56-65 years [6,7].

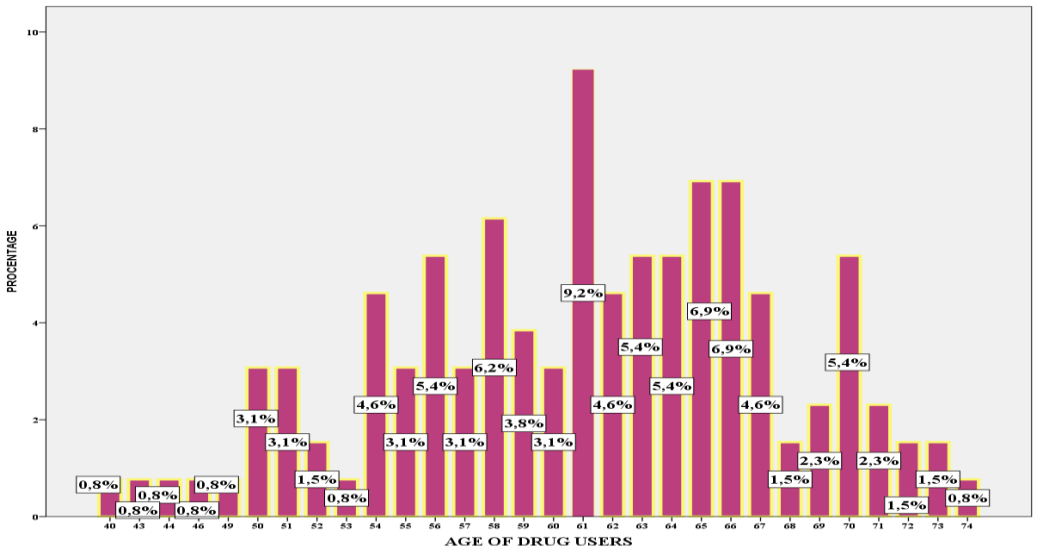

Figure 2. Characteristics of Hypertension Drug Users based on Age.

B. Class of Hypertension Drugs

Based on the results of this research on hypertension treatment in out Hypertension Drug Users at X Hospital Cilacap for the period of December 2019, the drugs received by Hypertension patience are in the form of single and combination antihypertensive drugs. The

classes of drugs used are Calcium Channel Blockers (CCB), Angiotensin Converting Enzyme Inhibitor (ACEI), Beta Blockers, Angiotensin Receptor Blockers (ARB), and Diuretics.

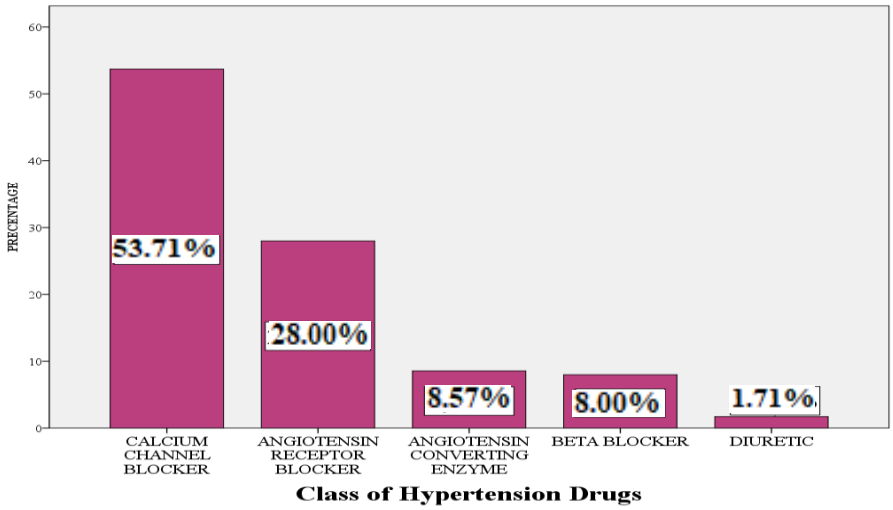

Figure 3. Frequency Distribution of Antihypertensive Drugs

For the CCB hypertension drug class there are 94 prescriptions. The most widely used drugs were Amlodipine (97.8%) and 2 (2.2%) prescription alone Nifedipine. The use of the CCB group is possible because of the ability of CCB to lower blood pressure through peripheral vasodilation and simultaneously activate Sympathetic Nervous System (SNS). From the Network meta-analysis, it is found that the combination of CCB or ACEI occupies the first rank because of its various advantages in terms of reducing mortality[9]. Another possibility of using CCB is based on indications, namely stage 1 hypertension[7]. Calcium channel blocker is used to treat hypertension with the heart coronary and diabetes mellitus. The use of Nifedipine in this case is only 2 prescriptions, it can be possible because there are only 2 s with hypertension with angina pectoris. Indications for nifedipine are prophylaxis and treatment of angina pectoris[10].

The ARB group was prescribed 49 prescriptions. The majority were Irbesartan at 69.4% and Candesartan at 30.6%. In Europe, the use of initial dose drugs in hypertension is recommended ARB. The use of ARBs is possible because patients who come less than 55 years, are not pregnant and as the initial dose of hypertension drug use. The ARB class directly inhibits the more selective angiotensin receptors such as ATI. For patients who experience side effects after using ACE-I, the recommended therapy is to use ARB. Although actually in terms of financing, this ARB is 45 times more expensive than the ACE-I [11].

The drugs used in the ACE-Inhibitor class were Ramipril 73.3% and Captopril 26.6%. The use of the ACE-I class was possible because of the indication that the patient was less than 55 years of age and not black RAS. The ACE-I class can be used as monotherapy and plays a role in preventing the mortality of patients at high risk of heart complications [11].

The beta blockers used in this study were Bisoprolol 64.2% and Carvedilol 35.7%. While the use of the Diuretic group, 66.7% were Furosemide and 33.3% were Spironolactone. The use of BB drugs can be used for stage I or Stage II hypertension for combination therapy. In Stage II hypertension it is recommended to use a diuretic combination therapy with a weight of **[7,9].**

C. **Severity Based on the Type of Hypertension Drugs**

Drug interactions can occur with the use of combination drugs or polypharmacy. The consequences of the interactions between these drugs can be various, namely Major, Moderate and Minor. Likewise, the use of combination hypertension drugs can occur among anti-hypertensive drugs as well as with other drugs. The interactions that occur can cause several effects, such as affecting the absorption, distribution, metabolism, excretion and reduction and increase in the effect of a drug. Antihypertensive drug interactions can be classified based on the level of severity, namely:

1. Major is an interaction between drugs that can cause clinical consequences and death.
2. Moderate is an interaction that causes changes in the 's clinical status.
3. Minor is an interaction that is still tolerable because if it is found in the recipe sheet, there is no need for change in therapy [12].

The table above shows the drug interactions based on the hypertension drug class. It is known that the occurrence of potential drug interactions with Amlodipinee and simvastatin is the most common occurrence with moderate severity. The number of interactions between Amlodipinee and simvastatin was 29.1%. This combination of drugs causes an increase in simvastatin levels, thereby increasing toxicity in the presence of myositis and rhabdomyolysis[13]. The mechanism of interaction that occurs is that Amlodipinee inhibits the cytochrome P450 enzyme isoenzyme CYP3A4. Management to overcome these interactions is to avoid doses of simvastatin use >20 mg/day and monitoring signs of poisoning such as myositis and rhabdomyolis.

The incidence of potential antihypertensive drug interactions with candesartan and isosorbide dinitrate had a moderate severity (1.9%) resulting in an increased hypotensive effect. The hypotensive effect increases because they both have the same mechanism. The management done is monitoring blood pressure. Another moderate severity occurred with candesartan and meloxicam (3.9%). Meloxicam is a class of NSAIDs that work by inhibiting prostaglandin synthesis, thereby causing decreased blood flow and salt retention. Therapeutic management to overcome these interactions is to monitor kidney function**[14].**

The incidence of potential drug interactions between captopril and allopurinol (1%) has a major severity of **[14].** The potential for drug interactions in captopril with allopurinol is an increase in hypersensitivity reactions to allopurinol, leukopenia, and serious infections. The interaction mechanism that occurs is that captopril can induce a hypersensitivity reaction of allopurinol. Management of therapy that can be done is by monitoring the hypersensitivity reactions such as redness of the skin, fever, sore throat **[15].** Other potential interactions, namely

captopril with acetylsalicylic acid (1%) have moderate severity. The effect that occurs is an increase in the potential effect of hypotension due to the same mechanism of action. Therapeutic management that can be done is monitoring blood pressure [14].

Table 1. List of Drug Interactions on Prescription at Hospital X in Cilacap Regency

No.	Antihypertensive Drugs and Other Drugs	Antihypertensive Drug Class	Severity Level	Percentage
1	Amlodipine + Simvastatin	Antihypertensive Drug Amlodipine	Moderate	29,1%
2	Amlodipine + Mefenamic Acid	Antihypertensive Drug Amlodipine	Minor	2,9%
3	Amlodipine+ Meloxicam	Antihypertensive Drug Amlodipine	Minor	20,4%
4	Amlodipine + Sodium Diclofenac	Antihypertensive Drug Amlodipine	Minor	5,8%
5	Amlodipine + Isosorbide Dinitrat	Antihypertensive Drug Amlodipine	Moderate	1,9%
6	Bisoprolol+ ISDN	Antihypertensive Drug Bisoprolol	Moderate	1%
7	Bisoprolol+Meloxicam	Antihypertensive Drug Bisoprolol	Meloxicam	1%
8	Carvedilol+ Meloxicam	Antihypertensive Drug Carvedilol	Moderate	1%
9	Candesartan+ Meloxicam	Antihypertensive Drug Candesartan	Moderate	3,9%
10	Candesartan+ ISDN	Antihypertensive Drug Candesartan	Moderate	1,9%
11	Captopril+ Allopurinol	Antihypertensive Drug Captopril	Mayor	1%
12	Captopril+Acetylsalicylic Acid	Antihypertensive Drug Captopril	Moderate	1%
13	Captopril+ Acarbose	Antihypertensive Drug Captopril	Minor	1%
14	Furosemide + Sucralfate	Antihypertensive Drug Captopril	Mayor	1%
15	Irbesartan+ Meloxicam	Antihypertensive Drug Irbesartan	Moderate	5,8%
16	Irbesartan+ Sodium Diclofenac	Antihypertensive Drug Irbesartan	Moderate	1,9%
17	Irbesartan+ Pipemidic Acid	Antihypertensive Drug Irbesartan	Moderate	1,9%
18	Irbesartan+ Mefenamic Acid	Antihypertensive Drug Irbesartan	Moderate	1%
19	Nifedipin+ Meloxicam	Antihypertensive Drug Nifedipin	Minor	1%
20	Ramipril + Metformin	Antihypertensive Drug Ramipril	Moderate	2,9%
21	Ramipril + Mefenamic Acid	Antihypertensive Drug Ramipril	Moderate	1%
22	Ramipril + Acetylsalicylic Acid	Antihypertensive Drug Ramipril	Moderate	2,9%
23	Ramipril + Glimepirid	Antihypertensive Drug Ramipril	Minor	1,9%
24	Ramipril + Meloxicam	Antihypertensive Drug Ramipril	Moderate	1%
25	Ramipril+ Allopurinol	Antihypertensive Drug Ramipril	Mayor	1,9%
26	Bisoprolol+ Carvedilol	Combination of Antihypertensive Drug	Moderate	1%
27	Captopril+ Irbesartan	Combination of Antihypertensive Drug	Moderate	1,9%
28	Furosemide+ Ramipril	Combination of Antihypertensive Drug	Moderate	1%
				100%

The potential interactions that occur between furosemide and sucralfate (1%) have a major severity. Sucralfate works by attaching to proteins on the surface of the ulcer by forming a stable solution complex. This complex functions as a barrier and protector of the

ulcer surface, this is what causes the absorption of furosemide to be not maximal and reduces its antihypertensive effect.[16]. Treatment of therapy for the effects arising from the interaction of these two drugs is to provide a pause at the time of drug administration. Sucralfate as a mucoprotector drug must be given first, 2 hours later then furosemide is given.

The potential incidence of drug interactions between irbesartan and meloxicam (5.8%) is a potential occurrence, namely 6 events. Meloxicam is a class of NSAIDs that work by inhibiting prostaglandin synthesis, thereby causing decreased blood flow and salt retention. The potential occurrence of drug interactions between nifedipine and meloxicam and mefenamic acid is of minor severity. Meloxicam and mefenamic acid are a class of NSAIDs that work by inhibiting prostaglandin synthesis, thereby causing decreased blood flow and salt fluid retention. Therapeutic management to overcome these interactions is to monitor kidney function[14].

The most frequent interaction was between ramipril and metformin (2.9%). In an unknown mechanism, the use of ramipril and metformin together can increase the effect of metformin in lowering blood sugar so that it can cause hypoglycemia 16. Treatment that needs to be done is monitoring sugar blood [14].

The incidence of potential drug interactions between ramipril and acetylsalicylic acid had a moderate severity of 2.9%. The interaction mechanism that occurs is that acetylsalicylic acid causes fluid and salt retention as opposed to the effect produced by ramipril. Therapeutic management that can be done is monitoring blood pressure. The most potential occurrence of interactions between antihypertensives and antihypertensives was captopril and irbesartan (1.9%). The combination of the two can cause an increase in the toxicity of captopril. Therapeutic management that can be done is monitoring blood pressure and kidney function[14].

Overall, of the 130 prescriptions received, it was known that 103 (79.2%) had drug interactions with the majority of the severity being 63.11% moderate.

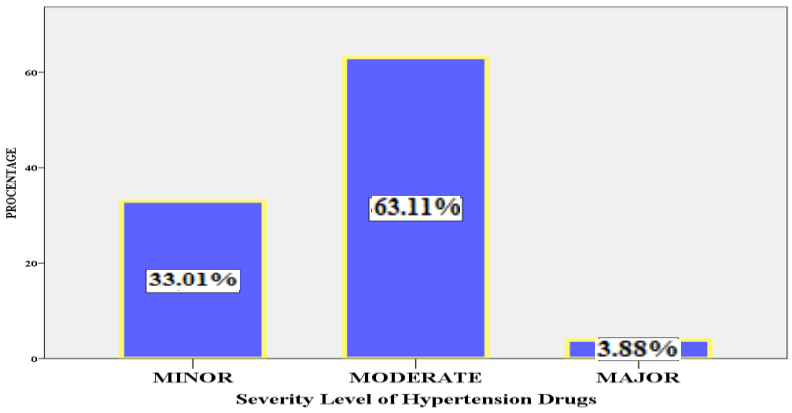

Figure 4. Severity Level of Hypertension Drugs.

CONCLUSSION

Based on the results and discussion above, it can be concluded that the characteristics of hypertension drug users are 58% women and the average age is 61 (8.9%) years. The majority of the drugs used were 54% Calcium Channel Blockers. The majority of the severity was moderate 64%.

ACKNOWLEDGEMENT

This research was funded by STIKES AL IRSYAD AL ISLAMIYYAH CILACAP.

REFERENCES

1. Kemenkes.RI. Pusdatin Hipertensi. *Infodatin*. 2014;(Hipertensi):1-7. doi:10.1177/109019817400200403
2. WHO. Hypertension. https://www.who.int/health-topics/hypertension/#tab=tab_2. Accessed August 9, 2020.
3. Balitbangkes Kemenkes RI. Hasil Utama Riskesdas Penyakit Tidak Menular 2018. *Has Utama Riskesdas Penyakit Tidak Menular*. 2018:8.
4. WHO. Hypertension. https://www.who.int/news-room/fact-sheets/detail/hypertension. Published 2019. Accessed August 9, 2020.
5. Armstrong C. JNC 8 guidelines for the management of hypertension in adults. *Am Fam Physician*. 2014.
6. Parulian L, Listyanti E, Hati[1] AK, Sunnah[1] I. Analisis Hubungan Polifarmasi Dan Interaksi Obat Pada Pasien Rawat JalanYang Mendapat Obat Hipertensi Di Rsp. Dr. Ario Wirawan Periode Januari-Maret 2019. 2019;02(July):79-86.
7. Fajarini H, Studi P, Fakultas F, Kesehatan I, Muhadi U, Siwuluh P. Pola penggunaan antihipertensi pada pasien rawat jalan di Puskesmas Siwuluh Kabupaten Brebes. *J Pharm*. 2019;01(1):1-6.
8. Indriani L, Oktaviani E. Kajian Interaksi Obat Antihipertensi Pada Pasien Rawat Inap di Salah Satu Rumah Sakit di Bogor, Indonesia. *Maj Farmasetika*. 2020;4(Suppl 1):212-219. doi:10.24198/mfarmasetika.v4i0.25884
9. Kandarini Y. Strategi Pemilihan Terapi kombinasi Obat Anti Hipertensi. 2013.
10. PIONAS BPOM. NIFEDIPIN | PIO Nas. http://pionas.pom.go.id/monografi/nifedipin. Published 2015. Accessed August 17, 2020.
11. Sonya.A.P, Bagus J. Gambaran Pola Penggunaan Obat Antihipertensi Pada Pasien Hipertensi Di Instalasi Rawat Inap Rsup Sanglah Denpasar Tahun 2016. *J Med Udayana*. 2019;8(6):ISSN 2597-8012. https://ojs.unud.ac.id/index.php/eum.
12. Agustina R, Annisa N, Prabowo WC. Potensi Interaksi Obat Resep Pasien Hipertensi di Salah Satu Rumah Sakit Pemerintah di Kota Samarinda. *J Sains dan Kesehat*. 2015;1(4):208-213. doi:10.25026/jsk.v1i4.41
13. Mahamudu YS, Citraningtyas G, Rotinsulu H. Kajian Potensi Interaksi Obat Antihipertensi Pada Pasien Hipertensi Primer Di Instalasi Rawat Jalan Rsud Luwuk Periode Januari – Maret 2016. 2017;6(3):1-9. doi:10.35799/pha.6.2017.16418
14. Lexicomp. Lexi-CLINICAL Site [App],s.l.: Wolters Kluwer,. 2018;(2):2-5. https://eur-lex.europa.eu/legal-content/PT/TXT/PDF/?uri=CELEX:32016R0679&from=PT%0Ahttp://eur-

lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52012PC0011:pt:NOT.
15. Fitriyani F. Identifikasi Drug Related Problems (DRPs) Kategori Interaksi Obat dengan Obat terhadap Pasien Hipertensi di RSUD HajiMakassar Prov. Sul-Sel Tahun 2016. 2017.
16. Nefrialdi A. Farmakologi Dan Terapi Edisi 6. FK UI.