

STUDY OF POTENTIAL DRUG INTERACTIONS IN HYPERTENSION PATIENS AT THE INPATIENT INSTALLATION OF PERMATA CIREBON HOSPITAL

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ABSTRACT

Identification of drug interactions in hypertensive patients needs to be performed because they affect the achievement of therapeutic effects and can increase the risk of side effects. This study aimed to determine patient characteristics (age, gender, drug items used, and comorbidities), the potential for drug interactions in hypertensive patients, the severity of potential drug interactions, and the type and number of drugs that interact in hypertensive patients at the time of installation. Inpatient at Permata Cirebon Hospital. The sample in this study included patients diagnosed with hypertension at the Inpatient Installation of Permata Cirebon Hospital in 2022 who met the inclusion criteria. This was a descriptive analytical study with retrospective data on patient characteristics (age, sex, drug items used, and comorbidities). The results were analyzed in the form of an overview of potential drug interactions using the Medscape application in the form of percentages and tables. The results of the study of 264 samples of hypertension patients taken by random sampling obtained for drug interaction based on severity events were as many as 149 patients (56,44%) with the highest number of gender, namely women as many as 154 patients (58,33%), the level of severity at most, namely monitors as many as 261 events (82,33%). The most interacting drug was Amlodipine with Metformin, with 27 monitored interactions (8,52%). Drug interactions can occur due to the number of drug therapies used and the presence of comorbidities.

Keywords: Hypertension, Drug Interactions, Permata Cirebon Hospital.

INTRODUCTION

Hypertension is defined as a state of systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mmHg after two separate measurements. Increased blood pressure is usually the result of modified causes (diet, obesity, smoking, and DM disease) and those that cannot be modified (age, race, gender and genetics) (Kesehatan, 2017).

According to RISKESDAS in 2018, there is a prevalence of hypertension of 34,11% in people aged ≥18 years in Indonesia, which has increased significantly compared to the results of RISKESDAS in 2013, which stated that the incidence of hypertension based on the result of blood pressure measurements in Indonesian people aged ≥18 years old was 25,8% (Risksedas, 2018).

Drug interaction is the effect of a drug caused by another given at first or given simultaneously to ensure the effectiveness or toxicity of one or more drugs (Iskandar et al., 2021). The potential for drug interactions in hypertensive patients can affect the therapeutic effects and increase the risk of side effects (Indriani & Oktaviani, 2020).

Maulia et al. (2022) reported 34% or 39 incidents (minor), 65% or 76 incidents (moderate), and 1% of as many as one incident (major). Based on its severity, the most frequent interaction of the drug use of Amlodipin with Simvastatin occurred in 36 incidents.

RESEARCH METHODS

The research is a type of non-experimental approach with a retrospective approach, using data drawn from hypertensive patient prescriptions at the inpatient installation of Permata Cirebon Hospital in 2022. Data were obtained using descriptive analysis and are presented in tables and pictures. Assessment of potential drug interactions using Medscape applications.

The population used in this study was a prescription for hypertension at the inpatient installation of Permata Cirebon Hospital in 2022, with 776 prescriptions. The sample in this study was a prescription for hypertension at the inpatient installation of Permata Cirebon Hospital in 2022 that meets the criteria for inclusion. A total of 264 samples were randomly selected using the Slovin formula.

The slovin formula:

$$n = \frac{N}{1 + (N \times e^2)}$$

$$\text{Number of sample} = \frac{776}{1 + (776 \times (0,05)^2)} = 263,9 \approx 264 \text{ Sample.}$$

Information:

n = number of sampel

N = number of population

e = error tolerance limit = 5% = 0,05

Equipment and Materials

The device used in this research was the Medscape application, which contains information about drug interactions, drug side effects, and drug mechanisms. Patient characteristics were collected from the hospital system, after which they were recorded on a data collection sheet for analysis. The research materials used were patient characteristics (age, sex, drug items used, and comorbidities) at the inpatient installation of the Permata Cirebon Hospital in 2022.

The Course of Research

1. Data Collection Technique
 - a. Administrative preparation (research permits and codes of ethics).
 - b. Determining the population size and patient prescriptions in the Prescription Installation Room at Permata Cirebon Hospital.
 - c. Determination of samples that met the inclusion criteria.
 - d. Data recording (age, gender, drug items used, drug name, and comorbides)
 - e. Asses potential drug interactions on Medscape.
 - f. Categorize the severity of potential drug interactions.
 - g. The results were analyzed in the form of percentages and tables.
2. Recording data on Patient Characteristics included the following:
 - a. Age;
 - b. Gender;
 - c. Drugs items used;
 - d. Co-morbidities.

Research Procedure

1. Research permits and ethical codes
2. Preliminary study to determine the research sample

3. Data collection on hypertension patient prescription sheets at inpatient installation at the Permata Cirebon Hospital in 2022.
4. We analyzed whether there were potential drug interactions using Medscape.
5. Data processing.

Data Analysis

After collecting data from the inpatient installation of Permata Cirebon Hospital in 2022, which complies with the inclusion criteria, the data were analyzed using the Medscape Drug Interaction Checker application, and drug interactions were then grouped based on severity (contraindications, serious, strict monitoring, and minor) presented in the form tables and figures. The evaluation of drug interactions that occur is carried out with supporting literature, such as books and journals.

RESULTS AND DISCUSSION

Description of Patient Characteristics

In research on the inpatient installation of Permata Cirebon Hospital, 264 samples were used. Patient data included age, gender, medication used, and comorbidities. Based on the research results, characteristics patient were obtained as shown in [Table I](#).

Table I. Characteristics of Hypertension Patient at the Inpatient Installation at Permata Cirebon Hospital in 2022

Characteristics Patient	Group Variables	Number of Recipe Sheets	Percentage (%)	Amount Interaction
Gender	Male	110	41,67%	-
	Female	154	58,33%	-
	Total	264	100%	-
Age	20-39	12	4,54%	-
	40-59	150	56,81%	-
	≥60	102	38,63%	-
	Total	264	100%	-
Drugs items used	2-4	174	65,91%	137 Incidents
	≥5 drugs	90	34,09%	180 Incidents
	Total	264	100%	317 Incidents
Co-morbidities	Patiens with co-morbidities	131	49,62%	-
	Patients without co-morbidities	133	50,38%	-
	Total	264	100%	-

Hypertension is mostly affected by women due to the influence of estrogen. Postmenopausal women have less estrogen decrease, which causes thickening of the arterial walls, which is a factor for hypertension. Reduced estrogen production can cause the body to maintain vasodilation, which regulates blood pressure ([Indriani & Oktaviani, 2020](#)).

The characteristics of hypertensive patients at the Inpatient Installation at Permata Cirebon Hospital in 2022 based on gender are shown in [Figure 1](#).

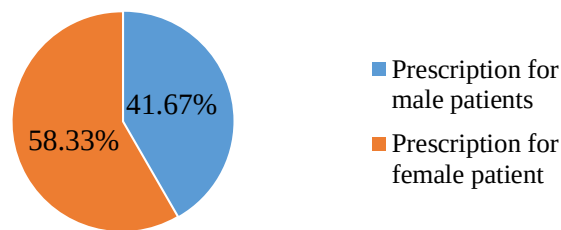


Figure 1. Gender Characteristics of Hypertension Patients in the Inpatient Installation of Permata Cirebon Hospital in 2022

Based on Figure 1, there were 110 prescriptions for male patients (41,67% and 154 prescriptions for female percentage (58,33% who received antihypertensive drug therapy. These results are in accordance with the research conducted by (Indriani & Oktaviani, (2020) entitled Study of Potential Interactions of Antihypertensive Drugs in Inpatients at One of the Hospitals in Bogor. The results showed that 29 patients were male, with a percentage of 39, 2%, while there were 45 female patients (60,8%. Characteristics of hypertensive patients at the Inpatient Installation at Permata Cirebon Hospital in 2022 based on age are shown in Table II.

Table II. Age Characteristics of Hypertension Patients in the Inpatient Installation of Permata Cirebon Hospital in 2022

Age Patient	Group Variables	Prescription Sheet for	Percentage (%)
20-39 Years old	Male	8	66,67%
	Female	4	33,33%
	Total	12	100%
40-59 Years old	Male	60	40%
	Female	90	60%
	Total	150	100%
≥60 Years old	Male	42	41,17%
	Female	60	58,82%
	Total	102	100%

Based on research results obtained from prescription data, it is known that the age group 40-59 years old received the most antihypertensive drug therapy with a total of 150 patients (56,82%), followed by those aged ≥60 years with a total of 102 patients (38,64%), and the least was in the age group of 20-39 years old with a total of 12 patiens (4,54%).

In the 20-39 years old group, young adult men were five times more likely to experience increased blood pressure, which can occur due to smoking habits, excessive alcohol consumption, and lifestyle (Jasmine et al., 2022).

In the age group 40-59 years old, more women experience hypertension when heading to menopause due to decreased estrogen hormone levels (Kusumawaty & Hidayat, 2016).

In the age group ≥60 years, women experience hypertension at a higher rate, which is influenced by estrogen levels that play a role in protecting blood vessels from damage (Kusumawaty & Hidayat, 2016). The characteristics of drug items used by hypertension patients in the inpatient installation of Permata Cirebon Hospital in 2022 are shown in Figure 2.

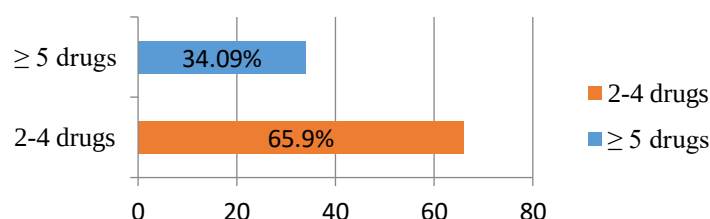


Figure 2. Characteristics of Drugs Items Used by Hypertension Patients in the Inpatient Installation of Permata Cirebon Hospital in 2022

These data can be grouped into 2 groups: those containing 2-4 drugs and those containing ≥ 5 drugs. The results of the study indicated that the drug item group was used the most, with 174 prescriptions in the 2-4 drugs group (65,90%), whereas the ≥ 5 drug group received the lowest number was 90 prescriptions (34,09%). Of all the drug items used a maximum of 9 items of medicine were obtained, and at least 2 items of medicine are prescribed in on prescription. Characteristics of comorbidities in hypertension patients in the inpatient installation of Permata Cirebon Hospital in 2022 are shown in Figure 3.

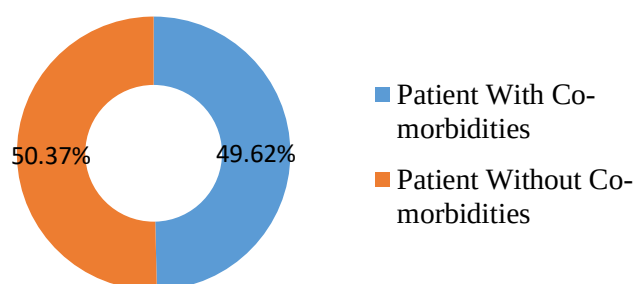


Figure 3. Characteristics of Co-morbidities in Hypertension Patients in the Inpatient Installation of Permata Cirebon Hospital in 2022

Based on Figure 3, patients who were diagnosed with hypertension at the Inpatient Installation of Permata Cirebon Hospital in 2022 showed that most results were in patients without comorbidities, as many as 133 patients (50,37%), and the least were in patients with comorbidities, namely as many as 131 patients (49,62%). Comorbidities in hypertensive patients at Permata Cirebon Hospital are Diabetes Mellitus and Cardiovascular disease, as seen from the specialist doctor listed on the RM number given by the hospital, which is then through the system.

Description of the Number of Potential Drug Interaction Incident

Descriptions of the number of potential drug interaction incidents are presented in Table III.

Table III. Description of the Number of Potential Drug Interaction Incident

Criteria	Number of Prescription	Percentage (%)
Number of prescription that have the potential drug interactions	149	56,44%
Number of prescription that do not have the potential for drug interactions	115	43,56%
Total	264	100%

Table III shows that 149 patients (56,44%) had the potential for drug interactions and the number of patients who did not have the potential for drug interactions was 115 prescription (43,56%). This is in accordance with the research conducted by Maulia et al., (2022), who obtained 116 drug interaction incidents from 134 prescription sheets.

Drug interactions that occur in hypertensive patients can be due to the drug items used and the presence of comorbidities (Herdaningsih et al., 2016). A description of the Average Potential Drug Interactions is shown in Table IV.

Table IV. Description of the Average Potential Drug Interactions

Criteria	Amount
Number of drug interaction incidents	317 incidents
Number of prescriptions with potential drug interactions	149 prescription sheets
The average occurrence of interactions in the prescription sheet potential drug interactions	2,12$\approx$2

Table IV shows that out of 264 hypertensive patients, there is a potential for incidents of drug interactions in 149 patients, with drug interactions based on severity, namely 317 drug interaction incidents. The data included the number of drug interaction incidents on each patient's prescription sheet that have the potential for drug interactions, namely, as many as 2 potential drug interaction incidents.

Description of Severity of Potential Drug Interactions

Description of Severity of Potential Drug Interactions as shown in Table V.

Table V. Description of Severity of Potential Drug Interactions

Criteria	Amount	Percentage (%)
Contraindications	0	0,00%
<i>Serious</i>	22	6,94%
<i>Monitor</i>	261	82,33%
<i>Minor</i>	34	10,73%
Total	317	100%

Based on Table V, the potential for drug interactions based on the severity of the monitor occurred the most, namely 261 interactions (82,33%). Monitor interactions, which have effects that may cause a decrease in patients' clinical status, where additional inpatient therapy may be needed (Medscape, 2016).

The severity of further drug interactions was minor, with as many as 34 interactions (10,73%). Minor interactions have a mild effect on the patients (Supriyadi et al., 2019).

The least severe drug interactions occurred in serious interactions, where 22 interactions (6,94%) were obtained, for example, Ramipril and Aspirin. Serious interactions have effects that are potentially life-threatening or capable of causing permanent damage (Supriyadi et al., 2019).

Description of the Types and Amount of Drugs that Interact in Hypertension Patients

Based on the results of research that has been carried out, it shows that out of 264 hypertensive patients in the Inpatient Installation at Permata Cirebon Hospital in 2022, 149 patients (56,44%) were found with potential drug interaction incidents.

The number of severity levels of drug interactions that occurred was 317 interactions, namely 261 incidents of drug interactions (strictly monitored), 34 incidents of drug interactions (minor), and 22 incidents of drug interactions (serious). Descriptions of the types and numbers of interacting drugs are shown in Table VI.

Table VI. Description of Type and Number of Interacting Drugs

No.	Drugs Name	Severity Level	Number og Drugs	Percentage (%)
1.	Ramipril + Aspirin	<i>Serious</i>	7	2,21%
2.	Amlodipin + Simvastatin	<i>Serious</i>	4	1,26%
3.	Spironolactone + KSR	<i>Serious</i>	1	0,32%
4.	Candesartan + Captopril	<i>Serious</i>	1	0,32%
5.	Bisoprolol + Digoxin	<i>Serious</i>	1	0,32%
6.	Bisoprolol + Clonidine	<i>Serious</i>	1	0,32%
7.	Ramipril + Meloxicam	<i>Serious</i>	1	0,32%
8.	Diltiazem + Simvastatin	<i>Serious</i>	1	0,32%
9.	Diltiazem + Bisoprolol	<i>Serious</i>	1	0,32%
10.	Ramipril + Natrium Diclofenac	<i>Serious</i>	1	0,32%
11.	Digoxin + Eritromisin	<i>Serious</i>	1	0,32%
12.	Ramipril + Celecoxib	<i>Serious</i>	1	0,32%
13.	Phenytoin + Lansoprazole	<i>Serious</i>	1	0,32%
14.	Amlodipin + Metformin	Monitor	27	8,52%
15.	Amlodipin + Bisoprolol	Monitor	20	6,31%
16.	Bisoprolol + Furosemide	Monitor	16	5,05%
17.	Bisoprolol + Candesartan	Monitor	15	4,73%
18.	Furosemide + Spironolactone	Monitor	14	4,42%
19.	Bisoprolol + Aspirin	Monitor	14	4,42%
20.	Ramipril + Spironolactone	Monitor	14	4,42%
21.	Candesartan + Furosemide	Monitor	12	3,79%
22.	Bisoprolol + Spironolactone	Monitor	12	3,79%
23.	Ramipril + Furosemide	Monitor	12	3,79%
24.	Candesartan + Hidroklortiazide	Monitor	9	2,84%
25.	Candesartan + Spironolactone	Monitor	8	2,52%
26.	Spironolactone + Aspirin	Monitor	8	2,52%
27.	Clopidogrel + Lansoprazole	Monitor	5	1,58%
28.	Candesartan + Novorapid Flexpen	Monitor	4	1,26%
29.	Natrium Bicarbonat + Anemolat	Monitor	4	1,26%
30.	Aspirin + Clopidogrel	Monitor	4	1,26%
31.	Ramipril + Aspirin	Monitor	7	2,21%
32.	Candesartan + Aspirin	Monitor	4	1,26%
33.	Spironolactone + Digoxin	Monitor	3	0,95%
34.	Candesartan + KSR	Monitor	3	0,95%
35.	Gabapentin + Amitryptiline	Monitor	2	0,63%
36.	Ciprofloxacin + Zinc	Monitor	2	0,63%
37.	Aspirin + Furosemide	Monitor	2	0,63%
38.	Omeprazole + Anemolat	Monitor	2	0,63%
39.	Metformin + Novorapid Flexpen	Monitor	2	0,63%
40.	Glimepiride + Natrium Diclofenac	Monitor	2	0,63%
41.	Metformin + Ondansentron	Monitor	2	0,63%
42.	Glimepiride + Ketorolac	Monitor	2	0,63%
43.	Ramipril + Digoxin	Monitor	2	0,63%
44.	Furosemide + Ketorolac	Monitor	2	0,63%
45.	Amlodipin + Phenytoin	Monitor	1	0,32%

No.	Drugs Name	Severity Level	Number og Drugs	Percentage (%)
46.	Ramipril + Celecoxib	Monitor	1	0,32%
47.	Clopidogrel + Celecoxib	Monitor	1	0,32%
48.	Omeprazole + Ciprofloxacin	Monitor	1	0,32%
49.	Eritromisin + Digoxin	Monitor	1	0,32%
50.	Furosemide + Digoxin	Monitor	1	0,32%
51.	Candesartan + Tizanidine	Monitor	1	0,32%
52.	Bisoprolol + Natrium Diclofenac	Monitor	1	0,32%
53.	Meloxicam + Aspirin	Monitor	1	0,32%
54.	Clopidogrel + Aspirin	Monitor	1	0,32%
55.	Gabapentin + Codein	Monitor	1	0,32%
56.	Bisoprolol + Diltiazem	Monitor	1	0,32%
57.	Ramipril + Meloxicam	Monitor	1	0,32%
58.	Bisoprolol + Clonidine	Monitor	1	0,32%
59.	Furosemide + Captopril	Monitor	1	0,32%
60.	Ramipril + KSR	Monitor	1	0,32%
61.	Bisoprolol + Natrium Bicarbonat	Monitor	1	0,32%
62.	Candesartan + Digoxin	Monitor	1	0,32%
63.	Bisoprolol + Digoxin	Monitor	1	0,32%
64.	Bisoprolol + Ketorolac	Monitor	1	0,32%
65.	Candesartan + Ketorolac	Monitor	1	0,32%
66.	Glimepiride + Ciprofloxacin	Monitor	1	0,32%
67.	Captopril + Metformin	Monitor	1	0,32%
68.	Analsik + Braxidin	Monitor	1	0,32%
69.	Acarbose + Novorapid Flexpen	Monitor	1	0,32%
70.	Furosemide + Aspirin	Monitor	1	0,32%
71.	Metformin + Folic Acid	Minor	8	2,52%
72.	Gabapentin + Mecobalamin	Minor	5	1,58%
73.	Omeprazole + Mecobalamine	Minor	3	0,95%
74.	Aspirin + Furosemide	Minor	3	0,95%
75.	Furosemide + Ketorolac	Minor	2	0,63%
76.	Metformin + Mecobalamin	Minor	2	0,63%
77.	Omeprazole + Analsik	Minor	1	0,32%
78.	Furosemide + Asam Tranexamat	Minor	1	0,32%
79.	Amlodipin + Tizanidine	Minor	1	0,32%
80.	Omeprazole + Alprazolam	Minor	1	0,32%
81.	Omeprazole + Braxidin	Minor	1	0,32%
82.	Meloxicam + Asam Tranexamat	Minor	1	0,32%
83.	Diltiazem + Asam Tranexamat	Minor	1	0,32%
84.	Hidroklortiazide + Glimepiride	Minor	1	0,32%
85.	Furosemide + Folic Acid	Minor	1	0,32%
86.	Cefadroxil + Ketorolac	Minor	1	0,32%
87.	Cefadroxil + Furosemide	Minor	1	0,32%
Total			317	100%

As shown in [Table VI](#), of the 317 drug interactions that occurred in hypertensive patients, it is known that the type and number of drugs that interacted most were drug

interactions between Amlodipine and Metformin: 27 incidents (8,52%), Amlodipine and Bisoprolol: 20 incidents (6,31%), and Bisoprolol and Furosemide: 16 incidents (5,05%). At the serious severity level, the most frequent interactions between Ramipril and Aspirin were 7 incidents (2,21%), Amlodipine and Simvastatin were 4 incidents (1,26%).

Based on research result. The level of severity that occurred most frequently in the severity monitor was for the drugs Amlodipine and Metformin. This is because amlodipine reduces the effects of metformin as a pharmacodynamic antagonist; patients receiving metformin should be closely observed for hypoglycemia ([Medscape, 2016](#)).

The most frequent interactions were Amlodipine and Bisoprolol, with 20 incidents (6,31%). The combination of Amlodipine and Bisoprolol can enhance other pharmacodynamic synergistic effects. Both drugs can lower the blood pressure ([Medscape, 2016](#)). This is in accordance with research [Oktianti et al., \(2023\)](#) where drug interactions often occur with Amlodipine and Bisoprolol, where Amlodipine has good effectiveness and safety for treating hypertension and preventing cardiovascular-related incidents. Bisoprolol is used in patients with hypertension accompanied by heart failure.

The next most frequent interaction was between Bisoprolol and Furosemide, with 16 incidents (5,05%). The combination of Bisoprolol and Furosemide can increase the effect of Bisoprolol and furosemide in reducing serum potassium levels ([Medscape, 2016](#)). This is in accordance with previous research ([Ramdani et al., 2022](#)), namely that the most frequent drug interactions occur between Bisoprolol and furosemide. Interactions in this combination of drugs can increase the risk of hyperglycemia and hypertriglyceridemia. Furosemide increases the effectiveness of Bisoprolol while reducing its side effects. A combination of these drugs will be beneficial but requires monitoring of serum potassium levels, blood pressure, and blood glucose.

This research received an Ethical Exemption statement from Permata Cirebon Hospital (No. 773/SRT/DIR/RSPC/VI/2023). The weakness of this study was that the samples were taken retrospectively, so that information could not be obtained directly from patients.

CONCLUSION

Based on the results of this study, it can be concluded that hypertension patients at the Inpatient Installation of Permata Cirebon Hospital in 2022 from the characteristics of age commonly occur in the age group 40-59 years old; gender most commonly occurs in females; the most common drug items used were 2-4 drug items: 174 prescription sheets, the presence of comorbidities was 131 prescription sheets, and without comorbidities were 133 prescription sheets were not present. The number of potential drug interaction incidents in hypertensive patients at the Inpatient Installation of Permata Cirebon Hospital in 2022 was 149. The severity of the potential for drug interactions in hypertensive patients at the Inpatient Installation of Permata Cirebon Hospital in 2022 is the highest, namely at the severity level of monitoring potential drug interactions. Description of the type and number of drugs that interact in hypertensive patients in the Inpatient Installation of Permata Cirebon Hospital in 2022. Most cases of Amlodipine and Metformin were monitored.

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