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Potential Drug–Drug Interactions in Ambulatory Patients with Hypertension: a Retrospective Study

Marcha Debby Saraswati[1,2], Shafira Muti Ardiana[3], Budi Suprapti[2,3]*, M. Yusuf Assegaf[2,4], Suharjono[3], Khusnul Fitri Hamidah[2]

[1]Magister of Clinical Pharmacy, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[2]Universitas Airlangga Teaching Hospital, Surabaya, Indonesia
[3]Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[4]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

*Corresponding author: budi-s@ff.unair.ac.id

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Abstract

Background*: Patients with cardiovascular diseases (CVD) are vulnerable to experiencing drug-drug interactions (DDIs). DDIs are a concern among patients receiving multiple drug regimens but they are also an avoidable cause of adverse drug reactions. The study of potential DDIs (pDDIs) would make it easier for the healthcare provider to deliver better patient care and mitigate pDDIs incidence.* ***Objective****: This study aimed to assess the frequency, severity level and risk factors associated with pDDIs among medications used to treat hypertensive ambulatory patients in Universitas Airlangga hospital.* ***Methods****: A retrospective observational study was carried out from electronic prescriptions received by hypertensive patients in March 2021. Data collection includes demographic data, the profile of antihypertensive drug use, and pDDIs. pDDIs were identified by severity using Lexicomp Drug Interaction Checker (Application). Univariate logistic regression analysis was used to find associated factors of major pDDIs. A p-value less than 0.05 (≤ 0.05) was considered statistically significant.* ***Results****: From 704 patients, 53.98% women and 46.02% men, 89.06% (n = 627) patients had minor to major pDDIs; 1354 pDDIs were identified, 89.4% (n = 1,210) were moderate and 9.8% (n = 133) were major class. Multiple antihypertensive drug regimens had significance associated with the major pDDIs occurrence.* ***Conclusion****: We found a high prevalence of pDDIs among hypertensive patients. The majority of pDDIs were of moderate severity. Multiple antihypertensive drug regimens were associated factors in the presence of major pDDIs.*

Keywords*: ambulatory patient, cardiovascular diseases, hypertension, potential drug-drug interaction*

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INTRODUCTION

Non-communicable diseases (NCDs) accounted for the most significant proportion of global deaths, contributing to 73.4% of causes of death of total deaths in 2017. It was estimated that the most significant number of deaths was from cardiovascular diseases (CVDs) (17.8 million). Hypertension is one of the CVDs. Deaths between 2007 and 2017 increased by 46.6% (Roth *et al.*, 2018). By causing an estimated 9.4 million deaths worldwide annually, hypertension has been shown to be one of the leading causes of death (WHO, 2019). In Indonesia, from 2013 to 2018, the prevalence of hypertension increased from 25.8% to 34.1% (Indonesia Ministry of Health, 2013; 2018).

Due to multiple comorbidities and complications, patients with hypertension need to be treated with a different treatment plan, including various drugs. A study on a combination of antihypertensive medications showed that most hypertensive patients use between two and five medications, which vary according to comorbidities. The most common antihypertensive regimens are angiotensin-converting-enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB) with thiazide (Johansen *et al*., 2020). A significant increase in hypertension among people on polytherapy regimenshas shown to meet their blood pressure goal (Gu *et al*., 2012). In hypertensive patients, comorbidities, complex drug treatment plans, and polypharmacy have raised the risk of incidence of drug-drug interaction (DDI) (Akbar *et al*., 2021).

DDI incidence is defined as a different pharmacological or clinical response to administering two or more drugs than one drug alone. This interaction can lead to a decrease or increase in the drug effects. The combination of drugs was considered potential drug-drug interactions (pDDIs) when the theoretical interactions in the prescription are evaluated rather than actual occurrence (Rodrigues *et al.*, 2017). Identification and management of pDDIs are important to prevent the associated risk (Ismail *et al*., 2013). A study of pDDIs in ambulatory patients from the internal medicine department has shown 292 (83.42%) prescriptions, with at least one identifiable pDDIs (Rana *et al*., 2014). Because of the differences in the study population, environment, design and drug interaction software platform used in these studies, the prevalence of pDDIs in various studies varied from 16% to 91% (Mistry *et al*., 2017; Al-Qerem *et al*., 2018; Ismail *et al.*, 2018;). In Indonesia, the study of antihypertensive drugs' problems held from March to May 2012 at Geriatric Department RSUD Dr. Soetomo reported 62% pDDIs incidence (Suprapti *et al*., 2014).

Therefore, this study was conducted to provide information on the frequency levels of discovered pDDIs and a list of frequently relevant interactions among the ambulatory patients of the Cardiology Department at Universitas Airlangga Teaching Hospital. Information about potential drug-drug interaction in any clinical setting will help the healthcare providers to improve patients' therapeutic outcomes.

MATERIALS AND METHODS

The study was designed as an observational retrospective study by observing the pDDIs of hypertensive patients with or without comorbidities. This study aims to identify pDDIs among patients with hypertension at the outpatient cardiology department, Universitas Airlangga Teaching Hospital Surabaya, Indonesia, during March 2021.

Data collection procedures

A retrospective observational was carried out from electronic prescriptions received by the patients that met the inclusion criteria and recorded on the data collection sheet, including demographic data, diagnosis, the profile of antihypertensive drug use, and pDDIs. Electronic prescriptions were obtained for a total of 704 patients in March 2021. The inclusion criteria included patients with hypertensive diagnosis and antihypertensive agents. This study observed pDDIs among all prescribed drugs. The board has approved the methodology of this study of ethics of Universitas Airlangga Teaching Hospital number 139/KEP/2021.

Data analysis

Identification of pDDIs was carried out based on data recorded on the data collection sheet. pDDIs in each prescription were identified by severity (minor, moderate, and major) using Lexicomp Drug Interaction Checker (Application) (Lexicomp, 2021). Data were analyzed descriptively using SPSS version 25. Furthermore, univariate logistic regression analysis was used to find associated factors of major pDDIs. A p-value less than 0.05 (≤ 0.05) was considered statistically significant.

RESULTS AND DISCUSSION

The demographic and clinical characteristics of the patients are listed in Table 1. About 704 hypertensive patients included in this study, the mean age of patients was 63.15 ± 10.57 years. The majority of patients were females (n = 380, 54%), ≥ 60 years old (n = 483, 68.6%), hypertensive heart disease (HHD) (n = 608, 86,4%), and

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polytherapy hypertensive regiment (n = 659, 93.6%). Hypertension is attributed to one-fifth of the deaths of US women and is a more significant burden for women than men. Moreover, around 60% of the population has hypertension by 60 years of age, and about 65% of men and 75% of women acquire high blood pressure by 70 years (Franklin et al., 2001; Lloyd-Jones et al., 2009; Mozaffarian *et al*., 2016). A study conducted in Malang District, East Java Province, Indonesia, demonstrated that 55.8% CVD risk factor was hypertension (Maharani *et al*., 2019). The seventh JNC guideline showed that more hypertensive patients are on a polytherapy hypertensive regimen than a decade ago. Polytherapy is defined as a person using > 1 antihypertensive drug (Chobanian *et al*., 2003; Gu *et al*., 2012).

The study revealed that 89.06% of pDDIs in hypertensive patients were considerably higher than reported studies in the other countries (Sharma *et al*., 2014; Kovačević et al., 2017; Muhammad & Afridi, 2017; Diksis *et al*., 2019). Few studies have evaluated the frequency and severity level of pDDIs among CVD patients in Indonesia. This study raises the awareness of pDDIs in pharmacy and hospital services, especially for ambulatory services. Moreover, the observed findings were likely the differences in the pattern of prescriptions between different countries and the patient population included in these studies. Our study found 89.4% of moderate pDDIs and 9.8% of major pDDIs levels in hypertensive patients (Table 2). Other studies also reported t that the most common types of pDDIs in CVD patients were moderate level. A survey conducted in the cardiology departments of two tertiary care teaching hospitals in the Quetta, Balochistan indicated 74.06% of moderate pDDIs (Akbar *et al*., 2021). Another study found a higher frequency of severe pDDIs (45%) than our study (Murtaza *et al*., 2016). Drug combinations involved major pDDIs and their potential consequences are listed in Table 3.

Table 1. Sociodemographic and clinical characteristics of study participants

Gender	**n (%)**
Female	380 (53.98)
Male	324 (46.02)
Age (years)	
18 – 30	7 (0.99)
31 – 40	12 (1.70)
41 – 50	54 (7.67)
51 – 60	148 (21.02)
> 60	483 (68.61)
Type of CVD	
Hypertensive Heart Disease without (congestive) heart failure (HHD)	608 (86.36)
HHD + Coronary Artery Disease (CAD)	84 (11.93)
HHD + Atrial Fibrillation (AF)	6 (0.85)
Hypertensive Heart Disease with (congestive) heart failure (HHF)	2 (0.30)
HHD + CAD + AF	2 (0.28)
Hypertension + Valvular Heart Disease (VHD)	1 (0.14)
HHD + Peripheral Artery Disease (PAD)	1 (0.14)
Number of hypertensive drugs prescribed	
Monotherapy	45 (6.39)
Polytherapy	659 (93.61)

Table 2. Category of pDDIs

Category	**pDDIs n (%)**
Severity	
Minor	11 (0.8)
Moderate	1210 (89.4)
Major	133 (9.8)

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Table 3. Drug combination involved in class major pDDIs and their potential consequences

Category	Drug combination	Frequency	Potential consequence
Major	Candesartan-Spironolakton	110	Increased risk of hyperkalemia
	Lisinopril-Spironolakton	8	Increased risk of hyperkalemia
	Ramipril-Spironolakton	7	Increased risk of hyperkalemia
	Lisinopril-Allopurinol	3	Increased potential for hypersensitivity
	Diltiazem-Bisoprolol	2	Increased risk of bradycardia
	Diltiazem-Simvastatin	2	Increased potential for rhabdomyolysis and myopathy
	Ramipril-Allopurinol	1	Increased potential for hypersensitivity

Table 4. Associated factors of major class pDDIs

Variables	Major class pDDIs	Univariate analysis	
	No. (%)	OR (95% Cl)	*p-value*
Gender			
Female	71 (56.80)	Referent	
Male	54 (43.20)	1.149 (0.778 – 1.696)	0.485
Age			
< 60	41 (32.80)	Referent	
≥ 60	84 (67.20)	1.082 (0.716 – 1.635)	0.708
Number of hypertensive drug prescribed			
Polytherapy			
2 - 3	40 (32.00)	Referent	
4 - 5	85 (68.00)	24.586 (15.143 – 39.919)	0.000

Table 4 showed that 125 (9,8%) patients had a significant severity of pDDIs. In univariate analysis, patients receiving 4-5 antihypertensive drug regimens (odd ratios (OR) 24.586, p-value – 0.000) were statistically associated with major pDDIs level. This study showed a significant association between an increased number of antihypertensive drugs prescribed (4 - 5) and the presence of major pDDIs levels is congruent with studies conducted in some countries and correlated with other studies which reported polypharmacy as a risk factor of the pDDIs prevalence (Murtaza *et al.*, 2016; Kovačević *et al*., 2017; Shakeel *et al.*, 2018; Diksis *et al*., 2019; Akbar *et al*., 2021). This present study also showed similarities to Subramanian et al. (2018) study in which hypertensive patients are vulnerable to DDI. The limitation of this study was conducted retrospectively and only in one institution. Prospective studies are required in the future to determine more associated factors of pDDIs.

CONCLUSION

There was a high prevalence of pDDIs in hypertensive ambulatory patients, and moderate severity was the most frequent pDDIs. Multiple antihypertensive drug regimens were demonstrated as associated factors of the significant pDDIs occurrence.

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AUTHOR CONTRIBUTIONS

Conceptualization, B.S., M.Y.A., S.S., M.D.S.; Methodology, B.S., M.Y.A., S.S., M.D.S.; Software, M.D.S., S.M.A.; Validation, B.S., M.Y.A., S.S.; Formal Analysis, M.D.S., K.F.H.; Investigation, M.D.S., S.M.A., K.F.H.; Resources, S.M.A., K.F.H.; Data Curation, M.D.S., S.M.A.; Writing - Original Draft, B.S., M.D.S., K.F.H.; Writing - Review & Editing, B.S., M.D.S.; Visualization, B.S., M.D.S.; Supervision, B.S., M.Y.A., S.S.; Project Administration, M.D.S., S.M.A.; Funding Acquisition, B.S.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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