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Polypharmacy, Drug-drug Interaction and Potentially Inappropriate Medication in Hospitalized Elderly Patients with Cardiovascular Diseases in Wangaya Hospital

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ABSTRACT
Cardiovascular diseases (CVDs) are common diseases in the elderly as aging can cause changes in the heart and blood vessels. Patients with CVD are prone to multimorbid conditions which lead to the use of multiple medications (polypharmacy). Polypharmacy is susceptible to drug-drug interaction (DDI) and potentially inappropriate medication (PIM). This study aimed to identify polypharmacy, DDI and PIM in hospitalized elderly patients with CVD. The design of this study is retrospective cohort. A number of 100 medical records were employed and analyzed decriptively. Polypharmacy is defined as administering multiple medications at the same time or excessive medication administration ≥4 drugs or ≥5 drugs. Potential DDI was detected by Lexicomp Application. PIM was identified based on Beers criteria 2019. The findings showed that most of the patients were male (55%) and aged 61-70 (72%). Most of the patients (48%) were categorized as moderate polypharmacy (8-10 medications/day). Potential DDI revealed 97% patients, and Beers criteria 2019 identified 280 cases of PIM. The study showed that polypharmacy, DDI, and PIM frequently occured in hospitalized elderly patients with CVD. Pharmacists should pay more attention to review the prescription. Therefore, the process of pharmacotherapy can be optimized and increase safety for elderly patients with CVDs.
Keywords: Cardiovascular Diseases; Drug-drug Interaction; Elderly Patients; Polypharmacy; Potentially Inappropriate Medication.

INTRODUCTION
People aged 65 years or older are projected to grow from the estimation of 524 million in 2010 to be almost 1.5 billion by 2050 and mostly live in the developing countries (Rodrigues and Oliveira, 2016). Almost half of the elderly in Indonesia (48.14%) had health problems, both physically or psychologically, and the percentage of elderly getting ill was almost a quarter of the whole elderly population, i.e. (24.35%) (Statistics Indonesia, 2020). Hence, a significant increase in life expectancy of the elderly is necessary and considered to be one of the greatest social achievements (Błeszyńska *et al.,* 2020).

Elderly people have higher probability of suffering from multiple health disorders caused by their reduced physical and mental functions (Khaje-Bishak *et al.,* 2014). This condition is commonly called as comorbidity. Comorbidity is defined as the condition when a person has more than one disease or condition at the same time (Theis *et al.,* 2017). Comorbidities in elderly leads to the use of multiple medications; a condition known as polypharmacy (Krishnaswami *et al*., 2019).

Polypharmacy, defined by WHO as administering multiple medications at the same time (WHO, 2019). Some studies defined polypharmacy as ≥4 drugs or ≥5 drugs (Schenker *et al.,* 2019). Polypharmacy is common in elderly hospitalized patients and may lead to the use of potentially inappropriate medications for older adults (Veloso *et al.,*2019). International estimates suggest that more than 60% of the older population receive five or more drugs concomitantly, which cause polypharmacy and, in many cases, it may be due to inappropriate prescription of medications and preventable problems (Zazzara *et al.,* 2021).

Cardiovascular diseases (CVDs) are a group of disorders which are interrelated with each other as one disorder could appear as a complication of the other. Consequently, patients with CVDs are more prone to multimorbid conditions which makes them as well exposed to polypharmacy.

A study found that the prevalence of polypharmacy was 24.8% in cardiovascular outpatients and elderly patients (aged ≥ 65 years and above) were nearly two times more likely to had polypharmacy prescriptions (Tefera *et al.,* 2020).

Polypharmacy becomes more vivid in cardiovascular patients due to the complexity of the disease nature and multimorbid vulnerability which may lead to multiple medications. Several factors have been shown to be associated with polypharmacy in CVDs such as the development of complications, presence of various morbidities, advanced disease stage and increasing age are among others (Tefera *et al.,* 2020).

According to estimates, one in six elderly patients may be at risk of a significant drug interaction (Błeszyńska *et al.,* 2020). The use of multiple medications increases the probability of unwanted interaction and effects of drugs, and elderly people are the most prone to develop ADR (Oscanoa *et al.,* 2017). ADR is the most common cause of hospital admission and the fourth or sixth leading cause of death (Montastruc *et al.,* 2021). It is more common with the increasing of age because the older age is frequently accompanied by polypharmacy, comorbidity and frailty (Davies and O'Mahony, 2015).

In addition, the use of multiple medications might also cause potentially inappropriate medication (PIM). PIM refers to medication with greater risks than its benefits, especially when a safer or more effective alternative treatment is available for the same medical condition (Li *et al.,* 2023). Identifying and taking more effort to reduce PIM n elderly patients with CVD is pivotal as the burden of PIM appears high in older adults with chronic polypharmacy and multimorbidity (Zhao *et al.,* 2021).

This study aimed to identify polypharmacy, drug-drug interaction (DDI) and potentially inappropriate medications (PIM) in elderly patients with cardiovascular diseases. The information of polypharmacy, DDI, and PIM in elderly patients with CVD could help health practitioners especially for pharmacist to optimize the process of pharmacotherapy, and thus increase safety of elderly patients, especially those with cardiovascular diseases. Therefore, the quality of life of the elderly can be improved as well as the life expectancy in Indonesia.

METHODS

Study design

A retrospective cohort was used as the design of this study. This study took place at Medical Records Department in Wangaya Hospital from March to June 2022. The study was obtaining ethical clearance from Wangaya Hospital Ethical Committees, REC reference No. 015/II.3/KEP/RSW/2022.

Study population

The subjects of this study were hospitalized elderly patients with CVD treated in Wangaya Hospital within the period 2020-2022. The subjects were selected by implementing the inclusion criteria, namely aged >60 years old, admitted with cardiovascular diseases include coronary artery disease and heart failure, and possessed complete medical records, including complete medical records, including the patient identity, clinical laboratory test result and examination result. However, the subjects were excluded if they were diagnosed with cancer and received immunosuppressive therapy. After applying the inclusion and exclusion criteria, the total sample for this study were 100 hospitalized elderly patients with CVD.

The size of the sample for this study was calculated by using this formula (Huley *et al.,* 2013):

$$n = \frac{\left[Z_{a/2} + Z_{\beta}\right]^2}{0.5 \ln[(1+r)/(1-r)]} + 3$$

n = Sample size for each group; Z = Normal curve coefficient; α = Threshold probability for rejecting the null hypothesis. Type I error rate (0.05); β = Probability of failing to reject the null hypothesis under the alternative hypothesis. Type II error rate (0.20); r = The expected correlation coefficient.

Outcome of the study

The data were classified under four classifications, namely non-polypharmacy defined as patients who received therapy <5 medications per day; minor polypharmacy defined as patients who

received 5-7 medications per day; moderate polypharmacy defined as patients who received 8-10 medications per day; and major polypharmacy defined as patients who received >10 medications per day.

Drug-drug interaction (DDI) was detected by using Lexicomp application, and potentially inappropriate medication (PIM) was identified by using Beers criteria 2019. Beers criteria 2019 has five categories, namely potentially inappropriate medciation use in older adults, potentially inappropriate medication use in older adults due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome, potentially inappropriate medications to be used with caution in older adults, and medication that should be avoided or have their dosage reduced with varying levels of kidney function in older adults. In terms of the quality of evidence, there are three categories, namely high-quality evidence, moderate-quality evidence and low-quality evidence. Meanwhile, in terms of the strength of recommendation, there are two categories, namely strong which means harms, adverse events, and risks clearly outweigh the benefits and weak, which means harms, adverse events, and risks may not putweigh the benefits.

Data analysis

The data in this study were analyzed decriptively.

FINDINGS AND DISCUSSION

The characteristics of the subjects of this study can be seen in Table I. Most of the patients were male (55%) and 61-70 years old (72%). The most frequently found cardiovascular diseases were heart failure (100%), coronary artery disease (31%), and atrial fibrillation (14%). Meanwhile, the most common other diseases were infection disease (27%), renal disease (27%) and type 2 diabetes mellitus (22%). One patient might have more than one comorbidity.

Similarly with this study, studies conducted by Gao *et al.* (2019) and Suman *et al.* (2023) stated that women generally have a lower prevalence of CVD than men. This is due to the differences in gene expression from the sex chromosomes and posterior differences in sex hormones.

The characteristics of the subjects also show that most of the patients were 61-70 years old. It was supported by the statement from NHS (2022) stating that CVD is the most common in people over 50 and the risk of developing increases as they get older. In addition, the life expectancy in Indonesia was 72.14 years old, which was also the reason why most of the patients of CVDs ranged between 61 and 70 years old.

The most common other diseases found in this study were infection disease (27%), renal disease (27%) and type 2 diabetes mellitus (22%). One patient might have more than one comorbidity. It was in line with a statement stated that nearly half of people over 65 years old have at least three chronic diseases (Błeszyńska *et al.,* 2020). A number of studies found that ADR were more likely in patients with higher comorbidities score (Davies and O'Mahony, 2015; Zhou and Rupa, 2018).

There were several possible mechanisms that might occur due to comorbidity. The first possible mechanism is drug-disease interaction where a drug given to treat a disease can worsen a co-existing disease. The second possible mechanism is the condition that alter the drugs metabolism; it is mentioned that kidney and liver disease can alter drug metabolism. The last possible mechanisms are disorders determining non-metabolic reaction, such as depression or other mental illness (Zazzara *et al.,* 2021). The use of cardiovascular disease medication in this study is presented in Table II.

Table II shows that the most frequently used cardiovascular medications are diuretic furosemide (88%), bisoprolol (71%), and clopidogrel as antiplatelet (55%). Antiplatelet agents are proven to reduce risk of major cardiovascular events in patients with cardiovascular disease and normal kidney function. Low-dose aspirin monotherapy should be used cautiously for secondary prevention of future cardiovascular events in CKD patients. Clopidogrel is more commonly used as dual Antiplatelet agents' therapy with aspirin in secondary prevention and monotherapy for primary prevention in those allergic to aspirin (Jain *et al.,* 2013). Aspirin remains the first line option as monotherapy for long-term (>12 months) treatment in all categories of patients in sinus rhythm. In patients with combined coronary disease and atrial fibrillation at low bleeding risk, combination

Table I. Characteristics of Elderly Patients with CVD in Wangaya Hospital 2020-2022

Characteristics	Total	Percentage
Sex		
Male	55	55%
Female	45	45%
Age (years)		
61-70	72	72%
71-80	19	19%
≥81	9	9%
Type of Cardiovascular Diseases		
Coronary artery disease (CAD)	31	31%
Heart Failure	100	100%
Atrial fibrillation (AF)	14	14%
Hypertension	7	7%
Valvular heart Disease	3	3%
Stroke	2	2%
Cardiomyopathy	1	1%
Deep vein thrombosis (DVT)	1	1%
Right bundle-branch block (RBBB)	2	2%
Other Diseases		
Infection disease; Sepsis, pneumonia, Urinary tract infection	27	27%
Renal disease; CKD, AKI, Kidney stone, Anemia	27	27%
Gastrointestinal disorder; Dyspepsia, Gastritis, Constipation	5	5%
Electrolyte imbalance; Hypokalemia, Hyperkalemia	8	8%
Type 2 diabetes mellitus (T2DM)	22	22%
Pleural effusion	5	5%
Cirrhosis	4	4%
Melena	2	2%
Hypoalbuminemia	2	2%
Cardiogenic shock	1	1%
Benign prostatic hyperplasia (BPH)	1	1%
Edema	1	1%
Hypoglycemia	1	1%

Note: CKD (Chronic kidney disease); AKI (Acute kidney disease)

antiplatelet and anticoagulant therapy may be considered (Passacquale *et al.,* 2022). Dyslipidemia was diagnosed in individuals who met one of the three following criteria: a low-density lipoprotein cholesterol level ≥160 mg/dL, a high-density lipoprotein cholesterol level <40 mg/dL, or a triglyceride level ≥200 mg/dL (Rhee, 2020). The drugs that decrease LDL-cholesterol more than 50% are rosuvastatin 20 to 40 mg, atorvastatin 40 to 80 mg, and simvastatin 20 to 80 mg (Horodinschi *et al.,* 2019). The Eighth Joint National Committee guidelines recommend a target BP of 150/90 mm Hg in patients 60 years and older, the decision to attempt a lower BP target should be individualized. An angiotensin-converting enzyme ACEI, CCB, thiazide diuretic, or ARB is recommended for initial therapy and the presence of diabetes ACEI or ARBs are preferred (Whelton *et al.,* 2018).

In this study, patients also received the other medications in addition to cardiovascular medications. Table III shows the five most frequently additional medications received by the patients. The most frequently used is Acetylcysteine (35%). Acetylcysteine is a molecule classically known for its mucolytic effect, but it also has direct and indirect antioxidant activity as a precursor of reduced glutathione. Acetylcysteine is safe, tolerable, affordable, and easily available, patients with severe disease and respiratory compromise, the use of intravenous Acetylcysteine at a dose of 100 mg/kg for a minimum of three days may be indicated. This dose can be increased in the first 24 h to 150 mg/kg in situations of acute respiratory distress syndrome (Izquierdo-Alonso *et al*., 2022). Proton pump inhibitors (PPIs) are an antacid drug often used in acid-related disorders. As of 2015, the FDA

Table II. The use of cardiovascular disease medications in hospitalized elderly patients

No	Medication		Total	Percentage
1	**Antiplatelet**	Clopidogrel	55	55%
2		Acetylsalicylic acid	38	38%
3	**Anticoagulant**	Enoxaparin	11	11%
4		Fondaparinux	2	2%
5		Warfarin	10	10%
6	**Statin**	Atorvastatin	37	37%
7		Simvastatin	31	31%
8	**ACEI**	Ramipril	41	41%
9		Captopril	11	11%
10		Lisinopril	2	2%
11	**CCB**	Amlodipine	13	13%
12		Nifedipine	1	1%
13		Diltiazem	1	1%
14	**Beta Blocker**	Bisoprolol	71	71%
15		Carvedilol	4	4%
16		Nebivolol	1	1%
17	**ARB**	Valsartan	9	9%
18		Irbesartan	2	2%
19		Candesartan	19	19%
20	**Diuretic**	Furosemide	88	88%
21		Spironolactone	26	26%
22		Hydrochlorothiazide	2	2%
23	**Nitrate**	Isosorbide dinitrate	13	13%
24		Nitroglycerin	18	18%
25	**Other**	Dobutamine	3	3%
26		Dopamine	2	2%
27		Trimetazidine	10	10%
28		Amiodaron	15	15%
29		Ivabradine	2	2%
30		Digoxin	27	27%
31		Potassium Chloride	12	12%
32		Clonidine	1	1%
33		Calcium polystyrene sulphonate	3	3%
34		Sacubitril Valsartan	1	1%

Note: ACEI (Angiotensin-converting enzyme); CCB (Calcium-channel blockers); ARB (Angiotensin II receptor blockers)

Table III. The five most frequently used additional medications in the elderly patient with cardiovascular diseases

No	Medication	Total	Percentage
1	Acetylcysteine	35	35%
2	Omeprazole	33	33%
3	Levofloxacin	33	33%
4	Acetaminophen	22	22%
5	Cefoperazone	22	22%

has already approved six drugs of this class (omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole and rabeprazole) (Lespessailles and Toumi, 2022). PPIs are indicated for treatment of ulcers with or without Helicobacter pylori infection, for treatment of gastroesophageal reflux, Zollinger-Ellison disease, dyspepsia, esophagitis and gastritis; and for prevention of peptic ulcers in patients receiving nonsteroidal inflammatory agents (NSAIDs) and in patients with upper gastrointestinal bleeding. Omeprazole is effective and safe most of the time

Table IV. Polypharmacy in elderly patients with CVD treated in Wangaya Hospital within the period 2020-2022

Category	Total	Percentage
Non-polypharmacy (< 5 medication/day)	12	12%
Polypharmacy		
Minor (5-7 medications/day)	28	28%
Moderate (8-10 medications/day)	48	48%
Major (> 10 medications/day)	12	12%
Total	100	100%

(Forgerini *et al*., 2018). Acetaminophen may provide short-term relief of rhinorrhea and nasal obstruction but has no effect on sore throat, malaise, sneezing, or cough (DeGeorge *et al*., 2019). Community-acquired pneumonia (CAP) is a common type of infection that can be caused by a variety of microorganisms. In the face of the high morbidity and mortality of this disease, an appropriate antibiotic is the key to treatment. Respiratory quinolones, including levofloxacin and moxifloxacin, have good in vitro and in vivo activity against typical and atypical CAP pathogens and are recommended for treatment (Chang *et al*., 2019).

Comorbidities in elderly lead to the use of multiple medications; a condition known as polypharmacy. Because one patient might develop more than one comorbidity, they were treated with more than one medication. The data were categorized into four groups, namely those who received less than 5 medications/day (non-polypharmacy), those who received 5-7 medications/day (minor polypharmacy), those who received 8-10 medications/day (moderate polypharmacy), and those who received more than 10 medications/day (major polypharmacy). The distribution of polypharmacy in elderly patients with CVD can be seen in Table IV.

From Table IV it can be seen that most of the patients (48%) was categorized as moderate polypharmacy. It means that the patients received 8-10 medications/day. Polypharmacy can lead to increased risks of adverse drug-drug and drug-disease interactions, inappropriate medication use, under-use of effective treatment, poor medication adherence, and most importantly adverse drug events (Woo *et al*., 2020). In an observational cohort study in a geriatric hospital, polypharmacy (having 6–9 drug prescriptions in the last 3 months) and excessive polypharmacy (ten or more drug prescriptions in the last 3 months) were both associated with emergency department revisit and hospital admission (Pazan and Wehling, 2021).

In this study, the potential drug-drug interaction was detected by using Lexicomp application. The study showed there were 97% potential drug-drug interaction. The number of potential drug-drug interaction can be seen in Table V.

Potential drug-drug interactions due to inappropriate prescribing is another severe problem. Approximately 3–26% of adverse reactions related to hospital admissions are due to drug-drug interactions (Mugada *et al*., 2021). This study found 97% patients who were at risk of potential drug-drug interaction, where the highest percentage was found in patients who received ≥10 DDI. The most frequently found DDI was the combination of bisoprolol and furosemide where Loop Diuretics may enhance the hypotensive effect of Antihypertensive Agents. However, it can be overcome by monitoring blood pressure during co-administration of loop diuretics and antihypertensives. Antihypertensive dose adjustments may be required (Lacy *et al*., 2008). Elderly patients are considered as high-risk population for DDIs. The prevalence of DDIs in elderly outpatients with multimorbidity was recently reported to be between 25.1% and 100% (De Oliveira *et al*., 2021).

The potentially inappropriate medications (PIM) identified based on the Beers Criteria 2019. The category of medications in Beers criteria was presented in Table VI.

The total of 280 cases of potentially inappropriate medications was identified by applying Beers criteria 2019. One patient might pose more than one PIM. In the first category, there were 11 potentially inappropriate medications, namely clonidine, amiodarone, digoxin, nifedipine, insulin, glimepiride, omeprazole, lansoprazrole, meloxicam, katorolac and diazepam. Subsequently, in the second category there were three potentially inappropriate medications, namely meloxicam, ketorolac, and diltiazem. Furthermore, in the third category, there were 4 potentially inappropriate

Table V. Percentage of potential drug-drug interaction based on lexicomp application

Description	Total	Percentage
Potential dug-dug interaction	97	97%
1-3 DDI	15	15%
4-6 DDI	25	25%
7-9 DDI	23	23%
≥10 DDI	34	34%
No drug-drug interaction	3	3%

Table VI. Medications Category in Beers Criteria 2019

Category	Drug	Quality of Evidence	Strength of Recommendation	Total (n)	Percentage (%)
1	Clonidine	Low	Strong	1	0.35
	Amiodarone	High	Strong	15	5.36
	Digoxin	Low	Strong	27	9.64
	Nifedipine	High	Strong	1	0.35
	Insulin	Moderate	Strong	21	7.50
	Glimepiride	High	Strong	3	1.07
	Omeprazole	High	Strong	33	11.8
	Lansoprazole	High	Strong	3	1.07
	Meloxicam	Moderate	Strong	4	1.43
	Ketorolac	Moderate	Strong	3	1.07
	Diazepam	Moderate	Strong	1	0.35
2	Meloxicam + Cardiovascular (Heart failure)	Moderate	Strong	4	1.43
	Ketorolac + Cardiovascular (Heart failure)	Moderate	Strong	3	1.07
	Diltiazem + Cardiovascular (Heart failure)	Moderate	Strong	1	0.35
3	Acetylsalicylic acid	Moderate	Strong	38	13.57
	Furosemide	Moderate	Strong	88	31.43
	Spironolactone	Moderate	Strong	26	9.29
	Hydrochlorothiazide	Moderate	Strong	2	0.71
4	Ramipril + Candesartan	Moderate	Strong	1	0.35
	Captopril +Candesartan	Moderate	Strong	1	0.35
	Warfarin + Amiodarone	Moderate	Strong	4	1.43
				280	100%

medications, namely acetylsalicylic acid, furosemide, spironolactone and hydrochlorothiazide. Lastly, in the fourth category there were 2 types of interaction, namely interactions between ACEI and ARB, i.e. ramipril+candesartan, captopril+candesartan, and warfarin+amiodarone. From this study, there was no case included in the fifth category due to the lack of information related to clearance creatinine score of the patients.

The medication included in the first category was clonidine. According to Beers criteria 2019, it is not recommended as the routine treatment for patients with hypertension because it might cause bradycardia and orthostatic hypotension. Nifedipin can potentially cause hypotension, and insulin can potentially cause hypoglycemia. Similarly, glimipiride also have higher risk to cause severe and

prolonged hypoglycemia in elderly patients. Proton pump inhibitor class drugs have a risk of bone loss and fractures, so the use should not be more than 8 weeks. Taking meloxicam and ketorolac can also potentially cause gastrointestinal bleeding or peptic ulcer. The use of benzodiazepine in geriatric patients should also be avoided because it can increase sensitivity to benzodiazepines and decrease metabolism of long-acting agents.

In the second category, the use of NSAID and CCB (Diltiazem) in geriatric patients with cardiovascular disease (heart failure) should be avoided because it can potentially increase fluid retention and/or exacerbate heart failure.

The medications included in the third category are acetylsalicylic acid, furosemide, spironolactone and hydrochlorothiazide. According to Beers criteria 2019, the use of acetylsalicylic acid in geriatric patients ≥70 years old has high risk of major bleeding. Furthermore, the use of diuretic can deteriorate and cause syndrome of inappropriate antidiuretic hormone or hyponatremia. However, this medication might still be used by monitoring the sodium level of the patients.

Referring to the fourth category in Beers criteria 2019, the interaction between ACEI and ARB can increase the risk of hyperkalemia, and the interaction between warfarin and amiodarone can increase the risk of bleeding.

From table VI, it can be seen that the most frequently PIM was found in the third category, namely potentially inappropriate medications to be used with caution in older adults, where the specific medication being the most frequently found was Furosemide (31.43%), where the quality of evidence identified as moderate and the strength of recoomendation is classified as strong.

From the analysis by using Beers criteria 2019, there was one patient who received clodine therapy which was identified as adverse drug reactions (ADR), i.e. bradycardia. Clonidine is an imidazoline derivative drug that acts by positively stimulating alpha receptors. From virtue of its mechanism of action, bradycardia was thought to be a prominent side effect of clonidine use. However, later with increase is its usage, it was discovered that bradycardia appears only in case of clonidine overdose or in case of poisoning or infusion therapy or clonidine addiction (Chande *et al*., 2021). ADR analysis was conducted by using WHO-UMC and Hartwig & Siegel scale which resulted that ADR in this patient was categorized as possible and the severity was mild.

CONCLUSION

Most of the hospitalized elderly patients have potential DDI (97%) and are categorized in moderate polypharmacy (8-10 medications/day). The analysis by using Beers criteria 2019 identified 280 cases of potentially inappropriate medications (PIM). Polypharmacy, DDI, and PIM were frequently found in hospitalized elderly patients with CVD. Pharmacists should pay more attention to the prescription. Therefore, the process of pharmacotherapy can be optimized and increase safety for elderly patients with CVDs.

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