The risk of adverse drug drug interactions for stable angina pectoris patients with heart failure complication prescribed polypharmacy

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Submission date: 03-Nov-2023 10:39AM (UTC+0700)
Submission ID: 2215912489
File name: ents_with_heart_failure_complication_prescribed_polypharmacy.pdf (337.96K)
Word count: 4040
Character count: 23821

BERKALA KEDOKTERAN
doi: 10.20527/jbk.v19i2.17404
RESEARCH ARTICLE
OPEN ACCES

The Risk of Adverse Drug-Drug Interactions for Stable Angina Pectoris Patients with Heart Failure Complication Prescribed Polypharmacy

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Abstract:

Stable angina pectoris (SAP) is an imbalance that occurs when myocardial oxygen need increases disproportionally, causing complaints of chest pain. Uncontrolled SAP can lead to a complication of heart failure (HF). Polypharmacy treatment frequently given to SAP patients with HF complications can be potentially detrimental for them. This study aims to determine the risk of adverse drug-drug interactions in SAP patients with HF complications prescribed polypharmacy. This was an analytic observational study with a cross-sectional approach using retrospective data from medical record data from 2020-2021 among hospitalized patients in cardiology ward Ulin General Hospital, Banjarmasin. Potential drug-drug interactions were determined using the Lexicomp tool from the UpToDate® site. Prevalence Odds Ratio (POR) and 95% Confidence Interval (95%CI) were determined using the Logistic Regression test at the 95% level of confidence. Twenty-four SAP patients with HF were recruited. According to its potential interactions, the most interactions were under category C (82.6%), followed by category B (11.3%) and category D (6.0%). Based on its level of severity, the most common was moderate (77.4%), followed by minor (13.0%) and major (9.5%). SAP patients with HF who were not prescribed polypharmacy had a lower risk of adverse drug-drug interactions by 64.7% compared to polypharmacy users, although it was not statistically difference (crude POR 0.353, 95% CI; 0.360-3.421; p-value = 0.369). This study shows that there is a tendency of lower risk of adverse drug-drug interactions in SAP patients with HF complication prescribed polypharmacy compared to those without polypharmacy, but the association is not statistically significant.

Keywords: polypharmacy; adverse drug-drug interactions; stable angina pectoris; heart failure, Ulin General Hospital; Banjarmasin.

Introduction

World Health Organization (WHO) defines a cardiovascular disease (CVD) as a disease caused by the impaired function of heart and blood vessels. There are many types of CVDs, but the most common are coronary heart disease and stroke. According to the WHO, CVDs are the number one cause of death globally, and more people die from these diseases compared to other causes, leading to 17.5 million deaths per year. The Centers for Disease Control and Prevention (CDC) also ranked CVDs as the first cause of death for 3 consecutive years from 2009 to 2011. The Indonesia Basic Health Research (Riskedas) in 2013 concluded that death caused by CVDs, cancers, chronic obstructive pulmonary disease (COPD) together are responsible for 59% of the total deaths.[1,2,3]

Coronary heart disease (CHD) is a clinical condition that occurs due to the accumulation of atherosclerotic plaque in the pericardial arteries leading to myocardial ischemia. Among several CHD spectra, Stable Angina Pectoris (SAP) or Classic Angina is a type of spectrum mostly found. [4,5,6]

SAP that is not well controlled can lead to heart failure (HF) complications. Heart failure currently becomes a global epidemic problem for health services and the leading causes of death and disability in worldwide. More than 23 million people with HF were recorded in the world and this figure continues to increase. In the United States documented 5 million HF patients, and 550,000 newly diagnosed HF patients by doctors every year. [4,5,6]

In SAP patients with HF complications, multi-drug is usually used for therapy (polypharmacy). Polypharmacy is defined as the regular use of ≥5 kinds of drugs simultaneously. Currently polypharmacy is commonly prescribed. More than half of the elderly patient population is taking 5 or more drugs concurrently. The higher the number of patients who take multiple drugs (polypharmacy), the higher risk and highly susceptible to drug interactions. Drug interactions are the changes that occur in the drug due to the presence of other drugs, herbal medicines, food, or other chemical agents. Drug interactions are included in the category of drug related problems which may affect the patient's clinical outcome. These interactions are considered clinically important when it increases the toxicity and/or reduces the effectiveness of the interacted drugs especially for drugs with narrow therapeutic index. Drug interactions can cause both unwanted side effects such as reducing drug effectiveness, increasing drug adverse events and drug toxicity which can lead to an increased risk of hospitalization and treatment costs. In certain circumstances, the effects of drug interactions can be life threatening. [7,8,9]

In the clinical setting, the incidence of important drug interactions is difficult to estimate due to (1) the documentation is still very sparse; (2) often escapes from observation because of the lack of knowledge of doctors on the mechanism and the possibility of occurrence. Drug interactions in the form of increased toxicity are often considered as a idiosyncratic towards one drug while the interaction in the form of a decreased effectiveness is often suspected due to increased disease severity; Besides that many drugs that interact with each other are difficult to remember; and finally (3) the occurrence or severity of interactions is influenced by individual variation (population, certain individuals are more sensitive or

susceptible, for example the elderly or those with severe disease, differences in metabolic capacity between individuals), certain diseases (especially renal failure or severe liver disease), and other factors (large doses, medications swallowed together, and chronic administration). [7,8,9]

From the current conditions and data on the incidence of polypharmacy in SAP patients with HF complications in Indonesia, especially in South Kalimantan, as well as there is no data and research yet, we then performed a study to calculate the risk of adverse drug-drug interaction in APS patients with HF complications prescribed polypharmacy hospitalized at Ulin General Hospital, Banjarmasin.

Research Method

Study Design and Data Source (Setting)

We conducted an analytical observational study with a cross sectional approach among SAP inpatients with complication of HF at the cardiology ward Ulin General Hospital, Banjarmasin by using medical record data from 2020-2021. Ulin General Hospital is a tertiary referral hospital for South Kalimantan and neighbour provinces. All patients were included in this study. The information on demographic data (age and sex) and drugs used were then collected. This study protocol has been approved by the Ethic Committee for Health Research, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia under the number of No. 565/KEPK-FK ULM/EC/XII/2022.

Variable of Interest

Variables of interest for this study were number of drugs prescribed by the doctor for SAP patients with HF complication and the potency of adverse drug-drug interaction. The patients prescribed with 5 drugs or more were categorized as those with polypharmacy, whereas the patients prescribed with less than 5 drugs were categorized as those without polypharmacy. Drug-drug interaction was determined by using UpToDate® website under Lexicomp tool. There are 5 categories of drug-drug interactions, i.e., Category A (no interaction known), Category B (no action needed), Category C (benefits are outweigh of the risks, but the therapy should be under strict supervision to avoid a potency of harm), Category D (considered to modify the therapy and to take the proper action in order to reduce its toxicity), and Category X (contraindicated, should be avoided). The adverse drug-drug interactions were then categorized into "*low risk*" (Category A, B, and C) and "*high risk*" (Category D and X). Meanwhile, the severity of adverse drug-drug interaction was classified into *major* (life threatening or permanent disability), *moderate* (interaction might deteriorate patients' clinical conditions), and *minor* (minimal effects).

Statistical Analyses

Demographic and medical data of all participants were collected. Logistic regression test was then used to estimate crude Prevalence Odds Ratios (PORs) and 95% Confidence Intervals (95%CIs) of the risk of adverse drug-drug interaction for those prescribed polypharmacy among SAP patients with complication of HF. All analyses were conducted by using a statistical software IBM SPSS version 26 with a statistically significance of 5% (p-value of <0.05).

Results

Characteristics of the study population

We found 138 hospitalized patients with SAP in the Cardiology ward at Ulin General Hospital Banjarmasin between 2020-2021.

Among them, only 24 patients had a complication of HF. Most of them were males (15 patient, 62.5%), with aged between 56-55 years old (12 patients; 50.0%), and had no diabetes mellitus and normal blood pressure, i.e. 17 patients (70.8%) and 15 patients (62.5%), respectively. In average each patient was prescribed 4.79 drugs (**Table 1**).

A number of 115 drug-drug interactions were identified among 24 SAP patients with HF complication. Based on the category of interactions, most of drug-drug interaction was under category C (95 interactions, 82.6%) followed by category B (13 interactions, 11.3%) and then category D (7 interactions, 6.0%). However, no interaction (0 interaction; 0%) was found under category A and X (**Table 2**). According to the level of severity, most of drug-drug interaction was moderate (89 interactions; 77.4%), followed by minor interaction (15 interactions; 13.0%) and finally major interaction (11 interactions; 9.5%) (**Table 3**). Under category B, minor drug-drug interaction between clopidogrel and atorvastatin most frequently was found (8 prescriptions). Meanwhile, under category C, moderate drug-drug interaction between isosorbide dinitrate and candesartan was commonly found (9 prescriptions). Finally, major drug-drug interaction under category D was most likely found for ticagrelor and acetylsalicylic acid (3 prescriptions)(Appendices).

Table 1. Baseline characteristics of participants

Characteristics	n=24
Sex, n (%)	
● Males	15 (62.5)
● Females	9 (37.5)
Age, n (%)	
● Adults	
■ 26-35 years	0 (0.0)
■ 36-45 years	4 (16.6)
■ 46-55 years	5 (20.8)
■ 56-65 years	12 (50.0)
● Elderly (>65 years)	3 (12.5)
Diabetes Mellitus, n (%)	
● Yes, diagnosed	7 (29.1)
● Not diagnosed	17 (70.8)
Hypertension, n (%)	
● Normal	15 (62.5)
● High normal	2 (8.3)
● Hypertension grade I	4 (16.6)
● Hypertension grade II	1 (4.2)
● Hypertension grade III	2 (8.3)
Number of drugs prescribed, average	4.79

Table 2. Categories of drug-drug interaction

Category	n (%)
• A (no interaction known)	0 (0.0)
• B (no action needed)	13 (11.3)
• C (benefits are outweigh of the risks, but the therapy should be under strict supervision to avoid a potency of harm)	95 (82.6)
• D (considered to modify the therapy and to take the proper action in order to reduce its toxicity)	7 (6.0)
• X (contraindicated, should be avoided)	0 (0.0)
Total	115 (100.0)

Table 3. Level of severity

Category	n (%)
• Minor (minimal effects)	15 (13.0)
• Moderate (interaction might deteriorate patients' clinical conditions)	89 (77.4)
• Major (life threatening or permanent disability)	11 (9.5)
Total	115 (100.0)

Risk of the adverse drug-drug interaction

For those who had no risk of adverse drug-drug interaction, most of them were prescribed polypharmacy (102 patients; 94.4%) as well as for high risk of adverse drug-drug interactions (6 patients; 85.7%). Even though SAP patients with HF complication prescribed no polypharmacy was associated with a lower risk of adverse drug-drug interaction by about 65% compared to their counterparts prescribed polypharmacy, this risk was not statistically significant of crude POR 0.353, 95%CI; 0.360-3.421 (p=0.369) (**Table 4**).

Table 4 Prevalence odds ratio for the risk of adverse drug-drug interaction for stable angina pectors patients with heart failure complication prescribed polypharmacy compared to those without polypharmacy

Polypharmacy, n (%)	Adverse drug-drug interactions, n (%)		p-value	Crude POR (95%CI)
	No risk	High Risk		
Yes	102 (94.4)	6 (85.7)	0.369	1
No	6 (5.6)	1 (14.3)		0.353 (0.360-3.421)

CI= confidence intervals; POR = prevalence odds ratio

Discussion

A potential drug interaction is a situation in which drugs' effect may be altered by a concomitant use with other drugs and may be observed under pharmacokinetic and pharmacodynamic conditions. An interaction occurs when the effect of one drug is altered by the presence of either another drug, herbal remedy, food, beverages, or other chemical agents. Drug interactions are one of eight categories of drug-related problems identified as a drug-related event or condition that could affect patients' clinical outcomes. In pharmacokinetic interventions, drugs alter absorption, distribution, metabolism, and

excretion of other drugs. Drug interactions are considered clinically important when it results in an increased toxicity and/or reduced the effectiveness of interacting drugs, especially when it comes to drugs with narrow safety margins (low therapeutic index).[7,8,10,11]

Most of our participants were between 56-65 years old. Other than polypharmacy, older age is also a risk factor for drug interaction along with genetic polymorphism, comorbidity, drug dosage, number of physicians prescribing the drugs, and prescription itself. More than 80% of elderly patients consume at least 1 prescribed drug, and more than 50% of elderly population consume 5 or more prescription drugs concomitantly. The more of patients take the higher number of drugs and a complex regimen therapy, the risk of drug interactions are also increased. [12]

In this study, a combination between clopidogrel and atorvastatin may lead to a minor interaction. Atorvastatin can reduce anti-platelet effect of clopidogrel. The use of isosorbide dinitrate and candesartan altogether might lead to a moderate interaction. The combination potentiates hypotensive effect of these drugs. A major interaction between ticagrelor and acetylsalysilic acid might threat life or lead to permanent disability. Acetylsalysilic acid can increase antiplatelet effect of ticagrelor. Furthermore, for adults who take clopidogrel and aspirin with daily dose of aspirin of >100-150 mg, the effect of ticagrelor on clopidogrel is reduced.

In Indonesia, rational use of drugs is still a problem for health services. For example, the use of polypharmacy is one of the common problems along with the overuse of antibiotics, short consultation times (3 minutes in average), lack of patients' compliance in taking the drug with the increasing complexity of drug used in current medicine and the development of polypharmacy. Then the possibility of drug interactions is greater. Drug interactions need to be considered because they can affect the response body on treatment. [13]

Clinical Implication

We found many SAP patients with HF complication were prescribed polypharmacy and most of them were under category C and moderate severity. Even though our findings demonstrated that the risk of adverse drug-drug interaction are similar for SAP patients with HF complication prescribed polypharmacy and those without polypharmacy, prescription of more than 5 drugs should be done properly and wisely. Most of the drugs combination indeed gives benefits more than the risks, but physicians should still strictly monitor the regimen therapy to avoid a potency of harm and worsening patients' clinical conditions.

Strengths and Limitation

We identified several strengths in this study. First, to the best of our knowledge this was the first study assessing the risk of adverse drug-drug interaction in Ulin General Hospital, especially for SAP patients with HF complication prescribed polypharmacy. Second, Lexicomp® is built to classify drugs interaction based on its level of severity or risks. It is a high sensitivity and specificity tool.

Nevertheless, we also need to acknowledge several weakness in our study. First, we included a small number of participants. Hence, we lost the power to detect a small risk or difference. Second, we did not adjust for several potential confounder such as sex, age, comorbidity, and life style factors that might contribute to the risk of adverse drug-drug interactions other

than number of drugs prescribed. Finally, the tool Lexicomp® is not able to detect the interaction between more than 2 drugs as well as less reliable.

Conclusion

In conclusion, there is no significant decreased risk of adverse drug-drug interaction for SAP patients with HF complication prescribed no polypharmacy compared to those prescribed polypharmacy.

Acknowledgements

We thank all participants who involved in this study.

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Appendices

Category	Drug-drug Interaction	Quantity (n)	Level of severity	Effect(s)
A	-	0	-	-
B	Clopidogrel - Atorvastatin	8	Minor	Atorvastatin decreases antiplatelet effect of clopidogrel
	Atorvastatin - Amlodipine	3	Minor	Atorvastatin decreases serum amlodipine concentration
	Nitroglycerin - Acetylcalicylic acid	2	Minor	Aspirin increases serum nitroglycerin concentration
C	Isosorbide dinitrate - Candesartan	9	Moderate	Hypotensive agents increase hypotensive effect of other hypotensive agents
	Isosorbide dinitrate - Bisoprolol	7	Moderate	Hypotensive agents increase hypotensive effect of other hypotensive agents
	Clopidogrel - Lansoprazole	7	Major	Lansoprazole reduces serum concentration of active metabolite of clopidogrel
	Acetylsalicylic acid - Clopidogrel	6	Moderate	Agents with antiplatelet properties increases antiplatelet and detrimental/toxic effects of other agents such as salycylic. Risk of bleeding is increased
	Clopidogrel - Amlodipine	6	Moderate	Calcium channel blockers decrease therapeutic effect of clopidogrel
	Isosorbide dinitrate - Amlodipine	5	Moderate	Hypotensive agents increase hypotensive effect of other hypotensive agents
	Candesartan - Furosemide	5	Moderate	Loop diuretics increase hypotensive and nephrotoxic effects of Angiotensin II Receptor Blockers
	Isosorbide dinitrate - Furosemide	4	Moderate	Hypotensive agents increase hypotensive effect of other hypotensive agents
	Bisoprolol - Furosemide	4	Moderate	Loop diuretics increase hypotensive effect of other hypotensive agents
	Spironolacton - Furosemide	3	Moderate	Loop diuretics increase hypotensive effect of other hypotensive agents

Category	Drug-drug Interaction	Quantity (n)	Level of severity	Effect(s)
	Nitroglycerin - Spironolacton	3	Moderate	Hypotensive agents increase hypotensive effect of other hypotensive agents
	Amlodipine - Furosemide	2	Moderate	Loop diuretics increase hypotensive effect of other hypotensive agents
	Isosorbide dinitrate - Bisoprolol	2	Moderate	Hypotensive agents increase hypotensive effect of other hypotensive agents
	Isosorbide dinitrate - Candesartan	2	Moderate	Hypotensive agents increase hypotensive effect of other hypotensive agents
	Nitroglycerin - Furosemide	2	Moderate	Hypotensive agents increase hypotensive effect of other hypotensive agents
	Spironolcaton - Atorvastatin	2	Moderate	Atorvastatin increases detrimental/toxic effects of spironolcaton. Specifically, theoretically there is a potency to increase the decreased effect of steroid endogen activity
	Nebivolol - Furosemide	1	Moderate	Loop diuretics increase hypotensive effect of other hypotensive agents
	Clopidogrel - Diltiazem	1	Moderate	Calcium channel blockers decrease therapeutic effect of clopidogrel
	Isosorbide dinitrate - Ramipril	1	Moderate	Hypotensive agents increase hypotensive effect of other hypotensive agents
	Isosorbide dinitrate - Diltiazem	1	Moderate	Hypotensive agents increase hypotensive effect of other hypotensive agents
	Isosorbide dinitrate - Nebivolol	1	Moderate	Hypotensive agents increase hypotensive effect of other hypotensive agents
	Furosemide - Codein	1	Moderate	Opioid agonists increase adverse/toxic effects of diuretics and decrease therapeutic effect of diuretics
	Spironolacton - Codein	1	Moderate	Opioid agonists increase adverse/toxic effects of diuretics

Category	Drug-drug Interaction	Quantity (n)	Level of severity	Effect(s)
				and decrease therapeutic effect of diuretics
	Bisoprolol - Ketorolac	1	Moderate	NSAID agents decrease anti-hypertensive effect of beta blockers
	Ketorolac - Ramipril	1	Moderate	Angiotensin Converting Enzyme Inhibitors increase adverse/toxic effects of NSAIDs. This combination decreases significantly renal function. NSAID agents decrease anti-hypertensive of Angiotensin Converting Enzyme Inhibitors
	Ramipril - Furosemide	1	Moderate	Loop diuretics increase hypotensive and nephrotoxic effects of Angiotensin Converting Enzyme Inhibitors.
	Metformin - Bisoprolol	1	Moderate	Beta blockers (Selective Beta 1) increase hypoglycemic effect of anti diabetic agents
	Spironolacton - Candesartan	1	Major	Angiotensin II Receptor Blockers increase hyperkalemia effect of Potassium-sparing diuretics
	Atorvastatin - Brilinta	1	Moderate	Ticaglerol increase serum atorvastatin concentrasion
	Acetylsalicylic acid - Diltiazem	1	Moderate	Calcium channel blockers (non dihydropyridine) increase antiplatelet effect of aspirin
	Brilinta - Diltiazem	1	Moderate	CYP3A4 inhibitors (moderate) decrease serum concentration of active metabolite of and increase serum concentration of ticaglerol
	Amlodipine - Calcium carbonate	1	Moderate	Calcium salts decrease therapeutic effect of Calcium Channel Blockers
	Digoxin - Atorvastatin	1	Moderate	Atorvastatin increases serum concentration of digoxin
	Spironolacton - Acetylsalicylic acid	1	Minor	Aspirin reduces therapeutic effect of spironolacton

Category	Drug-drug Interaction	Quantity (n)	Level of severity	Effect(s)
	Furosemide - Acetylsalicylic acid	1	Moderate	Calycylate decreases diuretic effect of loop diuretics. Loopd diuretics increase serum concentration of calycylate.
	Amlodipine - Diltiazem	1	Minor	CYP3A4 inhibitors (moderate) increase serum concentration of amlodipine
	Atorvastatin - Diltiazem	1	Moderate	CYP3A4 inhibitors (moderate) increase serum concentration of atorvastatine
	Bisoprolol - Diltiazem	1	Moderate	Bradycardia agents increase bradycardia effects of other agents
	Acarbose - Acetylsalicylic acid	1	Moderate	Calycylate increases hypoglycemic effect of blood sugar lowering agents
	Glimepiride - Acetylsalicylic acid	1	Moderate	Calycylate increases hypoglycemic effect of blood sugar lowering agents
	Glimepiride - Furosemide	1	Moderate	Hyperglyecmia associated agents decrease therapeutic effect of anti-diabetic agents
	Glimepiride - Bisoprolol	1	Moderate	Beta blockers (Selective Beta 1) increase hypoglycemic effect of anti-diabetic agents. Beta blockers increase hypoglycemic effect of anti-diabetic sulfonilurea. Cardioseletive beta blockers (such as acebutolol, atenolol, metoprolol, and penbutolol) might be safer than non selective beta blockers. All beta blockers seem to hinder early symptoms of hypogycemia. Topical beta blocker for eye might be associated with the lower risks than the systemic agents.
D	Brilianta - Acetylsalicylic acid	3	Major	Aspirin increases antiplatelet and decreases therapeutic effects of ticagrelor. Specifically, the benefits of ticagrelor for clopidogrel might

Category	Drug-drug Interaction	Quantity (n)	Level of severity	Effect(s)
				be decreased for adult patients taken daily dose of aspirin by 100-150 mg
	Furosemide - Ketorolac	1	Moderate	NSAID agents decrease diuretic effect. Diuretics increase nephrotoxic effec of NSAIDs
	Furosemide - Sucralfate	1	Moderate	Sucralfate decreases serum concentration of furosemide
	Simvastatin - Brilianta	1	Moderate	Ticagrelor increases serum concentration of simvastatin
	Glimepiride - Acarbose	1	Moderate	Alpha Glucosidase Inhbitor increase hypoglycemic effect of Sulfonilurea
X	-	0	-	-

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