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# Drug Interactions in Coronary Heart Disease Patients : a Literature Review

**Elok Tamarah[1] , Handayani [2*] , Andik Ferdiantoro[2]**

[1]Harapan Bhakti Vocational High School, Balikpapan, Indonesia
[2]Faculty of Medicine, Universitas Nahdlatul Ulama Surabaya, Surabaya, Indonesia
*Corresponding Author: yanikustyadji@gmail.com
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**ABSTRACT**

**Background:** Patients with coronary heart disease generally receive many drugs, such as hypercholesterolemia, antianginal, antiplatelet, anticoagulants, and medications for comorbid illnesses such as antihypertension and diabetes mellitus. Concomitant administration of several types of drugs may result in drug interactions.
**Objective :** This study aims to figure out drug interactions that might occur in using combination drugs in patients with coronary heart disease.
**Methods:** This article review uses the Google Scholar database, published 2017-2022. The keywords used were "coronary heart disease and drug interactions." The PRISMA flowchart is used to summarize the article selection process.
**Results:** Administration of aspirin with clopidogrel causes a moderate synergistic interaction, whereas administration of antiplatelet agents with anticoagulants causes a significant synergistic interaction on bleeding. And the administration of nifedipine with atorvastatin causes a synergistic pharmacodynamic interaction.
**Conclusions:** Drug interactions occur in patients with coronary heart disease, either synergistic or antagonistic pharmacodynamic interactions with minor, moderate, and significant classifications.

## Introduction

Cardiovascular disease is the leading cause of death worldwide, according to WHO. However, coronary heart disease (CHD) accounts for 31.9% of deaths in Indonesia. Coronary heart disease begins with endothelial dysfunction, which causes LDL cholesterol to be in the subendothelial layer, then it will be phagocytized by monocytes to form foam cells. If broken, foam cells have a fibrous shield that will trigger platelet aggregation. This aggregation will clog the coronary arteries. Total blockage of the coronary arteries will result in a sudden heart attack and can end in death if not treated immediately (Wahidah dan Harahap RA. 2021).

Patients with coronary heart disease generally receive many types of drugs, such as hypercholesterolemia and anti anginal drugs, drugs that may be given from anti- hypercholesterolemia, namely

atorvastatin, rosuvastatin, simvastatin, while for anti-angina medications such as nitrates, beta-blockers, and calcium channel blockers, antiplatelets such as aspirin, clopidogrel or ticagrelor, anticoagulants such as fondaparinux, enoxaparin or heparin. In addition, patients usually also receive drugs for comorbid diseases such as hypertension and diabetes mellitus drugs. Administering several types of drugs together may result in drug interactions (PERKI. 2018). Therefore, based on the problems above, it is necessary to analyze drug interactions that might occur in using combination drugs in patients with coronary heart disease.

## Methods

This article review uses the Google Scholar database, published 2017-2022. The keywords used were "coronary heart disease and drug interactions." The PRISMA flowchart is used to summarize the article selection process.

## Results and Discussion

The results of the review article found that the most synergic drug interactions for coronary heart disease occurred in the co-administration of aspirin with clopidogrel in 43 patients (51%), followed by the administration of enoxaparin with clopidogrel (Figure 1).

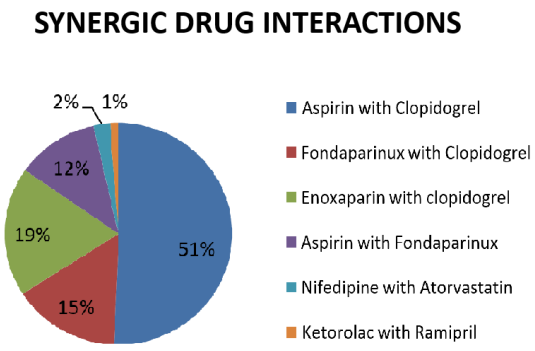


**Figure 1. Synergistic Drug Interactions for Coronary Heart Disease**

Meanwhile, antagonistic interactions with coronary heart disease drugs occurred in the administration of aspirin and bisoprolol in 23 patients (43%), followed by the administration of aspirin with furosemide (Figure 2).

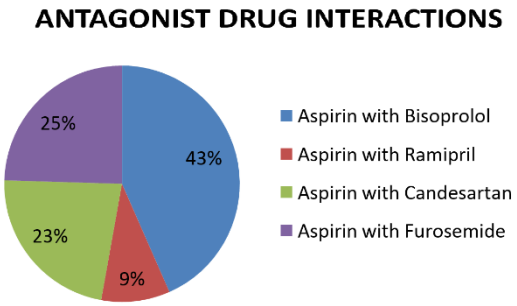


**Figure 2. Coronary Heart Disease Antagonist Drug Interactions**

Synergistic interactions that increase the occurrence of bleeding occur a lot in the administration of aspirin with clopidogrel, an antiplatelet group, followed by the administration of enoxaparin with clopidogrel, fondaparinux with clopidogrel and fondaparinux with aspirin which is an anticoagulant and antiplatelet group (Table 1).

## Table 1. Literature Review Results

| No | Article Title | Source | Source | Result | Conclusion |
|---|---|---|---|---|---|
| 1 | Gambaran interaksi obat penyakit jantung koroner dengan sindrom metabolik pada pasien rawat jalan di RS TK II DR. Soepraoen Malang | Google scholar | Descriptive study, with retrospective observation, Extraction of data from medical records, the population of all outpatient coronary heart disease medical record data at the Cardiac Polyclinic of RS Tk II dr. Soepraoen Malang. Purposive sampling was used to collect samples that met the inclusion criteria. Eighty-nine patients constituted the entire sample. | The results showed that 22 patients who were given the combination of aspirin + bisoprolol experienced minor classification antagonist pharmacodynamic interactions, three patients who were given the variety of aspirin + ramipril drugs experienced moderate classification antagonist pharmacodynamic interactions, 12 patients who were given the combination of aspirin + candesartan drugs experienced classified antagonist pharmacodynamic interactions moderate and ten patients who were given the variety of aspirin + clopidogrel drugs experienced a moderate classification of synergistic pharmacodynamic interactions. | The interaction of aspirin-bisoprolol, categorized as a minor antagonist pharmacodynamic interaction, is the most common drug interaction. The aspirincandesartan interaction, which is classified as a moderate antagonistic pharmacodynamic interaction, is the next most common drug interaction. |
| 2 | Kajian interaksi obat aktual pada pasien jantung koroner di Rumah Sakit X Kota Tasikmalaya | Google scholar, Jurnal farmasi Muhammadiyah Kuninga n | The study design was cross-sectional, and prospective data collection was used. According to the 2009 Drug Interaction Facts Tatro, literature studies with significant, moderate, or minor severity levels are used for drug interaction analysis. One hundred patients met the inclusion criteria for the study. | The results showed that three patients who were given the combination of aspirin + clopidogrel drugs experienced a significant synergistic pharmacodynamic interaction, one patient who was given the variety of Fondaparinux + Clopidogrel drugs experienced a synergistic pharmacodynamic interaction, one patient who was given the combination of drugs Ketorolac + Ramipril experienced a synergistic pharmacodynamic interaction and two patients who were given a variety of medications given a combination of drugs Aspirin + Ramipril experienced drug interactions. | The aspirin-clopidogrel interaction, categorized as a significant synergistic pharmacodynamic interaction, is the most common drug interaction. |

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|---|---|---|---|---|---|
| 3 | Kajian Interaksi Obat Potensial Pada Pasien Penyakit Jantung Koroner Rawat Inap di RSUD Moewardi Tahun 2018 | Google scholar, Urecol | This non-experimental study used medical record data from patients diagnosed with CHD who met the inclusion criteria retrospectively. A descriptive analysis was performed, and a purposive sampling strategy was used in this study. There were 100 patients who met the inclusion criteria for the study. | The results of the study showed that 16 patients who were given the drug combination Enoxaparin +clopidogrel experienced significant synergistic pharmacodynamic interactions, 12 patients who were given the drug combination clopidogrel +fondaparinux experienced meaningful synergistic pharmacodynamic interactions, ten patients who were given the drug combination aspirin+ fondaparinux experienced significant synergistic pharmacodynamic interactions, 30 patients who were given the combination of aspirin + clopidogrel experienced moderate synergistic pharmacodynamic interactions and 13 patients who were given the variety of aspirin + furosemide experienced minor antagonistic pharmacodynamic interactions. | The aspirin-clopidogrel interaction, categorized as a moderate synergistic pharmacodynamic interaction, is the most common drug interaction, followed by the enoxaparin-clopidogrel interaction, which is classified as a significant synergistic pharmacodynamic interaction.. |
| 4 | Evaluasi interaksi obat jantung koroner pada pasien rawat inap di rumah sakit umum Imelda pekerja Indonesia Medan | Google scholar | Research-based on Descriptve observation. They utilized information from the medical records of CHD patients treated at RSU Imelda. The population includes all CHD patient medical records from January to December 2020. Total sampling was used to select 71 people for the study sample. | The results showed that two patients who were given the combination of nifedipine + atorvastatin experienced moderate synergistic pharmacodynamic interactions, and one patient who was given the variety of drugs aspirin + bisoprolol experienced minor antagonistic pharmacodynamic interactions. | Nifedipine and atorvastatin have moderate synergistic pharmacodynamic interactions, making them the most common drug interactions |

The results of the four journals studied, three of which reported that the concomitant administration of aspirin and clopidogrel resulted in moderate synergistic pharmacodynamic drug interactions, that is drug effects that mutually reinforce each other when given simultaneously. Although the combination of aspirin and clopidogrel increases the risk of bleeding, it also reduces the risk of ischemic complications, myocardial infarction, and acute attack mortality. Therefore, this drug combination is used in patients in critical condition with close monitoring (Rahmawati DU and Mutmainah N. 2021). If a bleeding side effect occurs due to the use of the two drugs, it can be prevented by pausing the administration of the two drugs.

Two of the four journals observed concurrent administration of anticoagulant drugs with antiplatelet drugs (fodaparinux+clopidogrel/ fodaparinux+aspirin/enoxaparin+clopidogrel) led to significant synergistic pharmacodynamic interactions, meaning that if these two classes of drugs were given together, it would increase the occurrence of more substantial bleeding compared to double administration antiplatelet. Suppose the patient is in bad condition and must be given a combination of anticoagulants and antiplatelets. In that case, this can be done by reducing the dose of anticoagulants and paying attention to the INR (PERKI, 2016). Clopidogrel and Fondafarinux interact with each other. It inhibits factor Xa through its specific activity. Fondaparinux binds to antithrombin and alters the formation of antithrombin reactive sites, activating factor Xa inhibition. After that, antithrombin is started by releasing fondaparinux so that bleeding occurs. (Robiyatul S. et al. 2021). In addition, the combination of NSAIDs can cause gastrointestinal bleeding if given together with Ramipril.

Two of the four journals that studied the administration of Aspirin and bisoprolol caused minor antagonist pharmacodynamic drug interactions. The interactions of these drugs can reduce the effect of bisoprolol in lowering blood pressure, and the interactions between drugs work on the receptor system. The exchange of Aspirin together with Ramipril will increase the antihypertensive effect so that acute hypotension can occur and decreased kidney function, this also appears in the administration of Aspirin with candesartan, so it is necessary to monitor the patient's blood pressure and kidney function (Aprilianti RG. et al. 2022: Robiyatul S. et al. 2021).

Administration of aspirin with Furosemide causes minor antagonistic pharmacodynamic interactions. The interaction mechanism is that aspirin can reduce the effects of loop diuretic drugs,

one of which is Furosemide, and the exchange of Nifedipine with Atorvastatin, Nifedipine will increase the impact of atorvastatin with hepatic/intestinal enzyme CYP3A4 metabolism.

Administration of aspirin with clopidogrel causes a moderate synergistic interaction, whereas administration of antiplatelet agents with anticoagulants causes a significant synergistic interaction on bleeding. And the administration of nifedipine with atorvastatin causes a synergistic pharmacodynamic interaction.

## Conclusion

Drug interactions occur in patients with coronary heart disease, either synergistic or antagonistic pharmacodynamic interactions with minor, moderate, and significant classifications.

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