Assessment of Drug-Drug interaction in patients on cardiovascular medication

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Received: 25th May, 2026; **Revised:** 6th June, 2026; **Accepted:** 8th June, 2026; **Available Online:** 09th June, 2026

ABSTRACT
Background: The prescription of cardiovascular patients contains multiple medication. These pharmacological interventions can lead to Drug-Drug interaction (DDI). These interactions can be beneficial or hazardous. Polypharmacy may increase the disease burden, increase the chance of occurrence of adverse drug reaction and lead to therapeutic failure.
Materials and method: This study analyzed prescriptions of 265 patients with cardiovascular disease. It was a cross-sectional study. Micromedex software was employed to analyze the DDI.
Results: The 168(63%) patient prescriptions had DDI. A total of 308 DDIs were identified, of which , 166(53%) interactions were major and 142 (46%) interactions were moderate.
Conclusion: The prescription containing more than one drug is to be analyzed to prevent DDI. Hence this promotes rationale prescribing of drugs, improves the drug compliance and minimizes occurrence of adverse drug reaction.
Key words: Drug-Drug interaction, cardiovascular drugs, polypharmacy
How to cite this article: Sneha C, Karthik A. Assessment of drug-drug interaction in patients on cardiovascular medication. Int J Drug Deliv Technol. 2026;16(74s): 618-622. DOI: 10.25258/ijddt.16.74s.74
Source of support: Nil.
Conflict of interest: Nil

INTRODUCTION

Cardiovascular diseases are one of the leading causes of global mortality and morbidity. According to world heart federation report 2023, more than half a billion around the world are affected by cardiovascular disease.[1] By 2025 WHO targets to treat at least 50% of patients with cardiovascular disease to prevent morbidity and mortality.[2]

Drug is prescribed to treat the aliments, but often the same drugs may cause harm if they interact with one another. Drug-drug interaction is defined as "an alteration in the effectiveness or toxicity of one drug by another drug administered simultaneously"[2] These interactions can occur for pharmacokinetic or pharmacodynamic reasons. They may contribute to beneficial effects or may also harm the patient by increasing the risk of adverse events. It is postulated that about 33% patients admitted to hospital and 67% of intensive care patients experienced DDI during their hospital stay .[4]Sometimes the DDI may interfere with diagnostic tests leading to misdiagnosis. Example: In neuroendocrine tumors there is an elevated level of chromogranin A. Patients on long term prescription of proton pump inhibitors, also have elevated levels chromogranin A. This is due to stimulation of the gastric enterochromaffin-like cells and can lead to misdiagnosis of neuroendocrine tumours.[5] One of the common sources of diagnostic error is the lack of knowledge of the presence of drug-laboratory test inter actions (DLTIs). Misinterpretation of test results may lead to an erroneous diagnosis, unnecessary extra diagnostic tests, therapy or follow-up.[6]The chances of the DDI is more in

neonates, elderly population, in patient with multiple co-morbid condition, organ dysfunction. The risk of pharmacokinetic DDI is more when two or more co-administered drugs are metabolized by the same enzyme. In patients with cardiovascular disorder, multiple drugs are used for treatment. In patients with co-existing life diseases like diabetes, thyroid disorder and dyslipidemia, patients are on multiple medication and hence there can be DDI leading to morbidity and mortality. Approximately 22% of drug withdrawal and adverse drug reactions-related hospital admissions are due to DDI. They are one of the preventable drug related problems with the risk of deteriorating the therapeutic effect, causing adverse drug reactions resulting in treatment failure or even death.[7] Sometimes deprescribing of the polypharmacy prescription may be required for preventing drug induced morbidity and mortality.[8]This study was conducted with the objective of identifying pattern of drug interaction in patients on cardiovascular drugs.

MATERIALS AND METHODS:

The data was prospectively obtained from the 265 inpatients in the department of Internal Medicine at

a tertiary care center over a period of 2 years. All inpatients above 18 years on cardiovascular drugs were included in the study. Informed consent was obtained. The study was approved by the Institutional Ethics Committee. The prescription of patients fulfilling the inclusion criteria were analyzed. The demographic data, pre-existing diseases, no of drugs in the prescription were recorded. Drug interactions were assessed using Micromedex software (Truven Health Analytics).[9]
The severity of the reaction severity of drug interaction was characterized as follows [9]

- Contraindicated: The combination of drugs should be avoided to prevent severe harm
- Major drug interaction: This interaction led to serious reaction which required medical intervention to prevent or minimize harm.
- Moderate drug interaction: Monitoring required to minimize the harm.
- Minor drug interaction: the interaction has little or no evidence on clinical concern if used concomitantly.

Statistical analysis

All the quantitative variables like age, number of male and patients, number of drugs were expressed as mean± SD. Chi square test was used for comparing the occurrence of DDI between male and female patients. Logistic regression analysis was done to check the associating factors with DDI. Descriptive statistics were done in MS Excel 2010. Pearsons's correlation and Regression analysis were done using SPSS v 20.

RESULTS:

A total of 265 patients were recruited in this study. Table 1 shows the details of patient demography. All the quantitative variables like age were expressed as mean and standard deviation. All the qualitative variables were expressed as proportion. Chi square test was used to compare the occurrence of potential DDI among male and female. However, there was no statistical significance.

Out of 265 patients, the prescription of 168 patients (63%) had DDI. The types of potential adverse drug reaction are depicted in table 3. The number of DDIs per prescription ranged from 1 to 10. Only one prescription had 16 DDI. Pearsons's correlation test was used to analyze the correlation between the number of drugs in the prescription and risk of occurrence of DDI. A statistically significant association was established between the number of drugs in the prescription and the potential DDI, R score 0.7, result is significant at $p < .05$.

All 265 patients on cardiovascular drug had at least one co morbid condition. On univariate analysis, patients with more than 41 years of age and those prescribed with more than 3 drugs had higher risk of development of DDI (OR = 11.3; 95% CI: 8.2-16.8; $p < .05$). Amongst the cardiovascular drugs, the antiplatelet drugs like aspirin 34 %, (n=92) and clopidogrel 29%, (n=78) were the most common drug contributing to the interaction. A total of 308 drug interactions were predicted. Around 16 ADRs seen in these patients were because of the DDI (Table 2). The causality assessment of all these 16 ADRs were done according to WHO scale and were possibly associated with the DDI.

DISCUSSION

This study identified about 17 pairs of potential DDI involved with cardiovascular drugs in 265 patient prescriptions. According to this study the prevalence of DDI in patients on drugs acting on the cardiovascular system is 63%. This is lower than those reported in other studies (73%-100%).[10-12]The prevalence of potential DDI was in a study conducted by Ahamad et al was about 20%, for cardiovascular drugs.[13] The minimum number of DDI per patient was one in 58 patients and the maximum number of DDIs was 16 in one patient who was on 11 drugs (figure 1 and 2). In this study the minimum of 3 drugs in prescription contributed to DDI. But in a retrospective study conducted b 2y Sahoo et al had more than 10 drugs in the prescription per day to cause significant DDI.[14] This study noted that age more than 45 years, with more than 3 drugs were significantly associated with DDI. According to Diksis et al, age more than 56 years and minimum of 2 drugs in the prescription have also contributed to DDI.[15] And patient age more than 60 years and prescription containing more than 12 drugs were associated with DDI according to Akbar et al.[16] Another study analyzed that age above 70 years was associated with the drug interactions.[17]This study highlights that out of the 308 drug interactions, 166(53%) interactions were major and 142 (46%) interactions were moderate, which is similar to the study conducted by Khatiwada et al.[18]

There were 16 hospitalizations as a result of adverse event that occurred because of DDI. This observation is similar to study results of Kang et al.[19] Among them hypoglycemia was the commonest symptom. There were 51 DDI which predicted the occurrence of hypoglycemia as DDI (table 3). While the actual incidence of hypoglycemia was11%(n=6). However, another study done at South India had 1% actual incidence of DDI.[18] This study had aspirin and clopidogrel (n=163, 53%) as common interaction drug leading to DDI. This was concurrent with retrospective study conducted by Iyer et al.[20] However in this study we did not corelate the occurrence of DDI with dose of aspirin and clopidogrel. Huang et al noted that higher doses of aspirin were associated with more DDI.[21]In our study, out of the total 308 DDI, about 40%(n=123) was pharmacodynamic interactions and 60% (n=145) were pharmacokinetic interactions. While Kapadia et al study reported higher pharmacodynamic interactions.[22]

Hence this study results suggests that DDIs can have serious clinical consequences that can alter the

therapeutic outcome. The research finding give an insight that with increasing number of drugs in the prescription, potential occurrence of DDI is to be considered for patient safety. And most of the DDI can be avoided by slight modification in the dosage regimen and frequency of drug administration. The possibility of potential DDI is to be evaluated in treatment failure.

In our study we have used Micromedex for checking the DDI. Kheshti et al, concluded that Lexi-Interact and Epocrates, ranked first and second in providing accurate drug interaction software programs. Micromedex, Medscape, and iFacts ranked third, fourth, and fifth.[23]

Limitations of the study

The occurrence potential DDI as predicted by the software were not actively monitored in the patients. The relationship between the dose of the drug and occurrence were not recorded. Estimation of therapeutic drug levels in the body with the therapeutic outcome and drug-drug- gene interactions were beyond the scope of the study.

CONCLUSION

Among the cardiovascular drugs, aspirin and clopidogrel have a higher risk of interaction with the other drugs in the prescription. In case of diabetics, the likelihood of drug induced hypoglycaemia is also to be considered and the patient should be educated regarding the same before modifying the dosage of antidiabetic drugs. In case of polypharmacy, patients should be closely monitored for prevention of adverse effects related to drug interaction. The DDI checking software plays a significant role in predicting the potential occurrence of interactions, deprescribing drugs or dosage modification of the drugs.

CONFLICT OF INTEREST: There are no conflicts of interest declared with this study

ACKNOWLEDGEMENT

We would like to acknowledge the department of Pharmacology Faculty, staff and post graduates for all the support and coordination for carrying out the research activity.

Table:1 Age and gender distribution of patients		
1	Total number of patients	265
2	Total number of females	101
3	Total number of males	164
4	Age range	41-87y
5	Mean age	62y±10.2y
6	Number of drugs per prescription*	
	<2 drugs	33
	3-5 drugs	51
	6-9 drugs	21
	≥10	5
7	Total number of prescriptions with DDI	168(63%)

*Pearsons's correlation test was used to analyse the correlation between the number of drugs in the prescription and risk of occurrence of DDI. There was a statistically significant correlation in prescriptions with more than 2 drugs. p<.

Table 2 : DDI leading to ADR in patients		
1	Hypoglycaemia	06
2	Minor bleed	02
3	Giddy	02
4	Inadequate BP control	01
5	Muscle cramp	01
6	Seizure	01
7	Fluid retention	01
8	Hyperkalaemia	01
9	Hypothyroidism	01
Total		16

Prescriptions with< 2 drugs group 1, prescriptions with 3-6 drugs were group 2 and prescriptions with > 7 drugs were in group 3. There were statistically significant correlation(p<.05) prescriptions more than 2 drugs had occurrence of DDI.

Table 3: Drugs causing potential DDI(According to software)

Sl no	Drugs	Interactions	Total no
1	Aspirin+ Clopidogrel	Increases risk of bleeding	51
2	Atorvastatin +Clopidogrel	Decreases antiplatelet effect	45
3	Insulin+ Aspirin	Increases hypo/hyperglycaemia risk	28
4	Aspirin+ Furosemide	Decreases diuretic efficacy	21
5	Aspirin+ Metoprolol	Decreases antihypertensive efficacy	18
6	Insulin+ Metoprolol	Masks symptoms of hypoglycaemia	14
7	Insulin+ Telmisartan	Increases risk of hypoglycaemia	15
7	Aspirin+ Ramipril	Decreases antihypertensive efficacy	14
8	Aspirin+ Cilostazol	Increases risk of bleeding	11
9	Amlodipine+ Clopidogrel	Decreases antiplatelet efficacy	12
10	Furosemide+ Metolazone	Increased electrolyte imbalance risk	23
11	Ramipril+ Metformin	Increases risk of hypoglycaemia	16
12	Aspirin+ Enalapril	Decreases antihypertensive efficacy	14
14	Aspirin+ Carvedilol	Decreases β blocker efficacy	11
15	Ramipril+ Spironolactone	Increased risk of hyperkalaemia	07
16	Aspirin+ Calcium	Decreased effectiveness of calcium	04
17	Pantoprazole+ Thyroxine	Increases TSH levels	04

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