Original Article

# Potential Drug-Drug Interactions in a Cardiac Center: Development of Simple Software for Pattern Identification

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## Abstract

***Background:*** *Patients with cardiovascular disorders (CVD) are at higher risk for potential drug-drug interactions (pDDIs) due to complex treatment regimens. This study aimed to evaluate pDDI patterns in physicians' prescriptions in a specialized heart center using simple software.*

***Methods:*** *This cross-sectional study identified severe and related interactions during a 2-stage survey of experts. The data collected included age, sex, the date of admission and discharge, the length of hospital stay, drug names, inpatient wards, and the final diagnosis. The extracted drug interactions were used as a source of software knowledge. The software was designed using the SQL Server and the C # programming language.*

***Results:*** *Of 24 875 patients included in the study, 14 695 (59.1%) were male. The average age was 62 years. Based on the survey of experts, only 57 pairs of severe pDDIs were identified. The designed software evaluated 185 516 prescriptions. The incidence of pDDIs was 10.5%. The average number of prescriptions per patient was 7.5. The highest frequency of pDDIs was detected in patients with lymphatic system disorders (15.0%). Aspirin with heparin (14.3%) and heparin with clopidogrel (11.7%) were the most common documented pDDIs.*

***Conclusion:*** *This study reports the prevalence of pDDIs in a cardiac center. Patients with lymphatic system disorders, male patients, and older patients were at higher risk of pDDIs. This study shows that pDDIs are common among CVD patients and highlights the need to use computer software to screen patients' prescriptions to assist in detection and prevention.*

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***Keywords:*** *Drug interactions; Cardiovascular diseases; Prevalence; Adverse effects; Software*

## Introduction

Adverse drug events have long been a concern for patients and healthcare providers.[1] Drug-drug interactions (DDIs) are considered a kind of adverse drug event.[2] When the presence of another drug alters the effects of a drug, this is known as a DDI. Drug interactions frequently reduce a drug's effectiveness and increase toxicity, illness,

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mortality, and medical costs, as well as impose high annual expenditures on a community's economy.[3] According to previous studies, DDIs were responsible for 17% to 27% of problems in inpatients.[4,5] A systematic review in Iran showed that the average incidence of potential drug-drug interactions (pDDIs) was 8.5% in the outpatient setting and 19.2% in the inpatient setting.[6]

In recent decades, the prevalence of cardiovascular illnesses has risen dramatically.[7] According to studies, patients with cardiovascular diseases (CVDs) have a higher prevalence of DDIs than other patient groups because of the amount and kind of medicines they take and the impact of cardiac disorders on the metabolism of drugs.[8,9] The prevalence of pDDIs among patients with CVDs has previously ranged from 21.3% to 96.9%.[1,7,10–15] Comorbidities, polypharmacy, old age, complex treatment regimens, and the types of drugs given to CVD patients make them a high-risk group for pDDIs.[10,16] Although pDDIs are common in cardiac patients, there is no practical method in Iranian government hospitals for reporting them. However, prescribers must have a general understanding of drug interactions to analyze pDDIs properly. Although healthcare providers can be expected to identify the most common and severe risks associated with pDDIs, a prescriber cannot maintain all information in mind and be up to date.[17]

Today, there is a strong emphasis on using information technology-based programs to increase patients' safety and prevent medication errors.[17,18] A study in Iran showed that information technology-based interventions positively affected the identification of pDDIs.[19] Still, one of the weaknesses of such programs is the report of minor drug interactions due to the lack of standard warning levels, causing user exhaustion and the non-use of the program.[20,21] Furthermore, a previous study showed that the results of drug interaction searches usually differ between different drug interaction database programs due to the lack of a single standard for defining DDIs.[3] Solving such problems needs more detailed research on the sources that classify the severity of drug interactions. Therefore, surveys of physicians as the primary users of these programs are crucial in determining drug interactions. Given the lack of accurate statistics on the prevalence of cardiac drug interactions in Iran, it is necessary to determine drug interactions in this area. Accordingly, this study aimed to develop a simple software system to identify pDDI patterns in physicians' prescriptions in a cardiac center.

## *Methods*

The present retrospective study, carried out in the inpatient wards of Shahid Chamran Hospital, a tertiary care teaching hospital in the Iranian province of Isfahan, included all the patients attending the cardiac center between December 2018 and January 2020. The inclusion criteria consisted of patients who received at least 2 drugs simultaneously during a cardiac department stay and had active electronic medical records. Patients who did not meet these criteria were excluded from this study. The Ethics Committee of Kashan University of Medical Sciences approved this study (IR.KAUMS.NUHEPM.REC.1398.017). The need for informed consent from the patients was waived because this was a retrospective study based on the analysis of electronic health records.

All prescriptions prescribed to patients admitted to the different wards of the cardiac center during the study period were recorded. Demographic and clinical information was extracted from the hospital information system (HIS) and electronic medical records. Physicians or nurses record all orders directly into the computer. There is no way to check pDDIs in this system. The data collected includes patients' medical record numbers, age, sex, the date of admission and discharge, the duration of hospital stay, prescription numbers, drug names, generic drug codes, prescription dates, final diagnoses (classified based on ICD-10), and the names of the hospital wards. In the present study, the clinical signs associated with DDIs were not evaluated, so the expression "pDDI" was used. Figure 1 demonstrates all the steps in the process of identifying and classifying the relevance of the pDDI types.

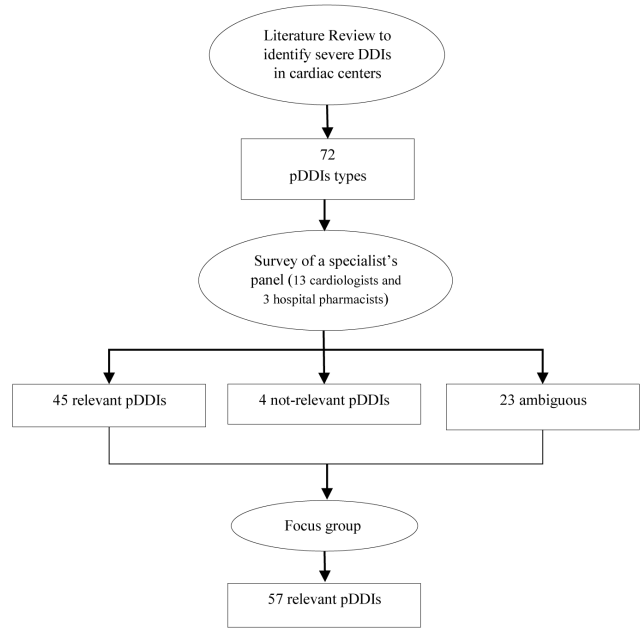


Figure 1. The image illustrates the flowchart of the identification and classification process of potential drug-drug interaction (pDDI) types.

This literature review was conducted via a search of electronic databases, including PubMed, ISI, Scopus, CINAHL, and ScienceDirect using keywords such as "drug interaction", "adverse drug event", "adverse drug reaction", "medication error", "prescription error", "cardiovascular

diseases", "heart diseases", "cardiovascular abnormalities", "heart disease risk factors", and "cardiovascular drugs". Two researchers conducted the article search process independently. All published studies related to cardiovascular drug interactions with any research method (systematic, experimental, or cross-sectional) published in English after 2010 were included in the present study. The selection process of studies, consisting of eliminating duplicate studies; evaluating the title, abstract, and full text of articles; and evaluating the reference list of eligible studies, was performed based on the inclusion and exclusion criteria. The quality of the included studies was assessed independently by 2 researchers.

A questionnaire was designed to classify the severity of drug interactions and create a standard definition based on the data extracted from the included studies in the previous step. A 5-faculty member panel of cardiologists, pharmacists, and medical informatics assessed this instrument and approved it, with a content validity ratio and content validity index above 0.8. Moreover, the reliability of this tool was confirmed through a pilot study, with a Cronbach's alpha of 0.8. The statistical population of the present study was 13 cardiovascular specialists and 3 hospital pharmacists working at Isfahan University of Medical Sciences, who were randomly assigned to the research. The criteria for selecting participants were 5 years of experience working in cardiac centers. The participants responded to the items of this tool based on a 6-point potential clinical severity scale ranging from "not very serious" to "potentially deadly" (Categories A–F). For data collection, the questionnaire was emailed to the cardiologists and pharmacists, who were asked to categorize each pDDI type separately. In the analysis, Categories A and B were considered "not relevant", while Categories C, D, and E were considered "relevant". (The risk rating scale is presented in Table 1.) If 66% of the physicians and pharmacists agreed on the interaction (Categories C, D, and E), the interaction would be considered severe and cardiovascular-related and was included in the final list. Four intensivists and a pharmacist met with a moderator and a facilitator in a focus group for 2 hours to discuss the identified interactions without agreement. If 3 of them agreed on the interaction, it would be accepted and added to the final list. Finally, the list of severe and cardiovascular-related interactions was prepared.

A pDDI software tool was designed using the SQL Server and C # programming language. Data required) drug orders, demographic, and clinical information (were extracted from the hospital information system and converted into Excel format. The output report of the software included a list of pDDIs by the type of interaction, the name of the prescribing physician, the final diagnosis, patients' age, patients' sex, and inpatient wards. The reporting system was based on the source of knowledge of the interactions created in the previous steps. The software developers and the research team were constantly in contact, discussing and improving the system's contents and user interfaces. During the software development process, a software prototype was created to collect more feedback on users' requirements. Furthermore, the software validation process (accuracy) was conducted by manually reviewing 100 randomly assigned prescriptions (system testing). The data were analyzed using descriptive statistics. Continuous variables were presented as the mean, and ordinal and nominal data were shown as numbers (n) and percentages (%).

Table 1. Risk rating scale of pDDIs

| Classification | Definition |
|---|---|
| A | The pDDI type is not relevant as it has no consequent effect on the patient. |
| B | It is not relevant because the consequences are acceptable for the patient. |
| C | It is relevant, but the intensivist can monitor the consequences by extra supplementary diagnosis or measurements. |
| D | It is relevant, but the consequences of a possible interaction are treatable. |
| E | The pDDI type is certainly relevant and life-threatening. |
| F | Implications of the pDDI type are unknown to the participant. |

pDDIs, Potential drug-drug interactions

## *Results*

After the assessment of the title, abstract, and full text of the articles, 72 pairs of pDDIs related to CVDs were extracted from 27 studies. A summary of our literature review is shown in Table 2.

During the 2-stage survey, severe and related interactions were identified for cardiovascular patients. In the first stage, the specialists agreed on 45 interactions (62.5%) as related interactions and 4 interactions (5.6%) as unrelated. In addition, they disagreed on 23 interferences (31.9%). In the second stage, 23 pairs of drugs that did not meet the specialists' required agreement (6.0%) were retested. At this stage, 12 pairs of drugs with at least 66.0% agreement were added to the interactions list; hence, 57 pairs (79.2%) were identified as severe and related, and 15 pairs (20.8%) were identified as unrelated interactions.

The results showed that out of the 24 875 patients included in the study, 14 695 (59.1%) were male, and 10 180 (40.9%) were female. The median age was 62 years, and the length of hospital stay was 3 days. A total of 185 516 prescriptions were evaluated. The average number of medicines prescriptions per patient was 7.5.

The highest prevalence of pDDIs was observed in cardiovascular patients aged 65 years and older. Table 3 presents the distribution of pDDIs according to the age group of the study population.

Common pDDIs belonged to the diseases of veins, lymphatic vessels, lymph nodes (15%), and ischemic heart disease (12.8%) (Table 4).

The cardiac surgery unit (23.8%), the intensive care unit (ICU) (14.8%), the coronary care unit (CCU) (14.2%), and the internal cardiac unit (14.2%) had the highest percentages of pDDI, respectively (Figure 2).

Fifty-seven different pairs of interacting drugs associated

Table 2. Severe and relevant pDDIs extracted from the literature review and survey of specialists

| Row | Drug Interacting Pairs | Agreement (×/√) | References | Row | Drug Interacting Pairs | Agreement (×/√) | References |
|---|---|---|---|---|---|---|---|
| 1 | Aspirin + Clopidogrel | × | 1,13,22,23 | 38 | Simvastatin + Ketoconazole | √ | 33 |
| 2 | Aspirin +Warfarin | √ | 26–1,9,22,24 | 39 | Simvastatin + Cyclosporine | √ | 33,34 |
| 3 | Aspirin + Heparin | √ | 22,24 | 40 | Simvastatin + Erythromycin | √ | 33,34 |
| 4 | Aspirin + Fondaparinux | √ | 10 | 41 | Simvastatin + Azithromycin | √ | 1,22 |
| 5 | Aspirin + Cimetidine | × | 22 | 42 | Simvastatin + Clarithromycin | √ | 7,34 |
| 6 | Aspirin + Ibuprofen | √ | 27 | 43 | Simvastatin + Gemfibrozil | √ | 25,33 |
| 7 | Aspirin + Enoxaparin | √ | 13,16,22,26 | 44 | Simvastatin + Nefazodone | √ | 33,34 |
| 8 | Aspirin + Omeprazole | × | 22 | 45 | Simvastatin+ Ciprofloxacin | √ | 22 |
| 9 | Aspirin + Fluoxetine | × | 22 | 46 | Furosemide + Gentamicin | √ | 7 |
| 10 | Amiodarone + Warfarin | √ | 28 | 47 | Carvedilol + Salbutamol | √ | 9 |
| 11 | Amiodarone + Digoxin | √ | 16 | 48 | Lovastatin + Cyclosporine | √ | 33,34 |
| 12 | Amiodarone + Edoxaban | × | 29 | 49 | Lovastatin + Clarithromycin | × | 33,34 |
| 13 | Amlodipine + Clarithromycin | √ | 1,22 | 50 | Lovastatin + Nefazodone | × | 35 |
| 14 | Spironolactone + Enalapril | √ | 1,22 | 51 | Lovastatin + Gemfibrozil | √ | 25,33 |
| 15 | Spironolactone + Captopril | √ | 14,25 | 52 | Lovastatin + Ketoconazole | × | 26 |
| 16 | Spironolactone + Ramipril | √ | 30 | 53 | Losartan + Spironolactone | √ | 24 |
| 17 | Spironolactone + Verapamil | √ | 15 | 54 | Midazolam + Morphine | √ | 14,24 |
| 18 | Enoxaparin + Spironolactone | × | 22 | 55 | Nifedipine + Clarithromycin | √ | 22 |
| 19 | Heparin + Enoxaparin | √ | 22 | 56 | Warfarin + Ceftazidime | √ | 24 |
| 20 | Spironolactone + Potassium chloride | √ | 14,22 | 57 | Warfarin + Clarithromycin | √ | 22 |
| 21 | Ramipril + Potassium chloride | √ | 31 | 58 | Warfarin + Metronidazole | √ | 1,7,22 |
| 22 | Enalapril + Potassium chloride | √ | 7,22 | 59 | Warfarin + Enoxaparin | √ | 24,26 |
| 23 | Clopidogrel + Warfarin | √ | 22,24 | 60 | Warfarin+ Cyclophosphamide | √ | 34 |
| 24 | Clopidogrel + Omeprazol | √ | 16 | 61 | Warfarin + Diclofenac | √ | 22 |
| 25 | Clopidogrel + Cimetidine | × | 22 | 62 | Warfarin + Ciprofloxacin | √ | 24 |
| 26 | Diclofenac + Clopidogrel | √ | 22,32 | 63 | Warfarin + Azithromycin | √ | 22 |
| 27 | Enoxaparin + Clopidogrel | √ | 13,14,16,24 | 64 | Verapamil + Carbamazepine | √ | 34 |
| 28 | Fondaparinux + Clopidogrel | √ | 10 | 65 | Verapamil + Edoxaban | √ | 26 |
| 29 | Rabeprazole + Clopidogrel | √ | 7 | 66 | Heparin + Clopidogrel | √ | 22,26 |
| 30 | Quinidine + Procainamide | √ | 15 | 67 | Heparin + Indomethacin | √ | 22 |
| 31 | Spironolactone + Digoxin | √ | 22 | 68 | Heparin + Diclofenac | √ | 22 |
| 32 | Alprazolam + Digoxin | √ | 7 | 69 | Heparin + Nitroglycerin | × | 36 |
| 33 | Clarithromycin + Digoxin | √ | 22 | 70 | ACE + Allopurinol | × | 34 |
| 34 | Digoxin + Furosemide | √ | 15,24 | 71 | ACE + Lithium | × | 34 |
| 35 | Ciprofloxacin + Insulin | × | 14,22,24 | 72 | Digoxin + Macrolide | √ | 37 |
| 36 | Ciprofloxacin + Amitriptyline | √ | 22 | | | | |

pDDIs, Potential drug-drug interactions
A and B= "×"
C, D, and E ="√"

Table 3. Distribution of pDDIs based on age groups

| Age Groups | Prescribed Prescriptions (n) | pDDIs n (%) |
|---|---|---|
| 0-14 years | 16825 | 695 (4.1) |
| 15-24 years | 1672 | 116 (6.9) |
| 25-64 years | 99623 | 10534 (10.6) |
| ≥65 years | 67396 | 8174 (12.1) |

Table 4. Distributions of pDDIs based on clinical diagnosis

| Diagnosis | Prescribed Prescriptions (n) | pDDIs n (%) |
|---|---|---|
| Ischemic heart disease | 78480 | 10061 (12.8) |
| Pulmonary heart disease and diseases of the pulmonary circulation | 3233 | 367 (11.4) |
| Other forms of heart disease | 48098 | 5304 (11.0) |
| Diseases of arteries, arterioles, and capillaries | 2777 | 296 (10.7) |
| Diseases of veins, lymphatic vessels, and lymph nodes | 820 | 123 (15.0) |
| Congestive heart failure | 11161 | 561 (5.0) |
| Others (hypertension and arrhythmias) | 40947 | 2807 (6.9) |
| Total | 185516 | 19519 (10.5) |

Table 5. Most common pairs of pDDIs in patients with cardiovascular diseases

| Interacting pair | | | |
|---|---|---|---|
| Drug 1 | Drug 2 | Percentage | Severity |
| Aspirin | Heparin | 14.4% | C |
| Heparin | Clopidogrel | 11.7 | C |
| Clopidogrel | Enoxaparin | 9.6 | D |
| Aspirin | Enoxaparin | 9.6 | C |
| Aspirin | Warfarin | 6.2 | C |
| Losartan | Spironolactone | 1.2 | D |

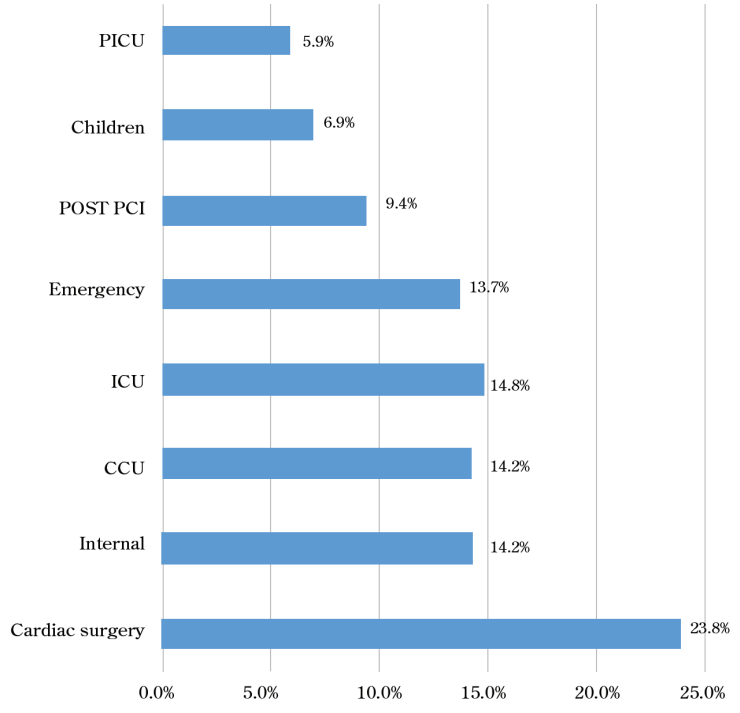


Figure 2. The image depicts the distribution of pDDIs based on the different wards of the hospital.
PICU, Pediatric intensive care unit; POST PCI, Post-percutaneous coronary intervention; ICU, Intensive care unit; CCU, Coronary care unit; pDDIs, potential drug-drug interactions

with cardiovascular medicines were detected. Aspirin with heparin (14.4%) and heparin with clopidogrel (11.7%) were the most commonly documented pDDIs. The most common pDDIs and the severity of pDDIs are enlisted in Table 5.

## *Discussion*

A very critical aspect of drug therapy is the identification of drug interactions. Drug interactions are still a significant issue for international healthcare decision-makers owing to the dramatic increase in the morbidity and mortality of patients. To our knowledge, the identification of pDDIs using software systems has not been previously investigated in CVD patients in Iran. Hence, the present study developed a software system for identifying pDDIs using the literature review and survey of a specialist panel. Based on the literature review, a questionnaire was designed to reclassify the severity of pDDIs. Participants responded to the items in this questionnaire, and 57 paired severe pDDIs for CVDs were identified. Further, the current study showed that among the 185 516 prescriptions screened by the designed software system, there were 10.5% interactions. Aspirin with heparin, followed by heparin with clopidogrel, was the most commonly documented pDDI.

Based on our literature review, we extracted 72 pairs of pDDIs related to CVDs in the present study. Then, during a 2-stage survey and based on a survey of a panel of experts (cardiologists and pharmacists), only 57 pairs of severe pDDIs for CVDs were identified. This method was consistent with a study in the Netherlands that used a team of 9 local pharmacists and intensivists to reclassify the identified pDDI types for the ICU. Their results showed that they agreed on 53 drug pairs with severe interactions.[29]

The present study considered only severe drug interactions in the designed software because one of the weaknesses of DDI database programs is the report of minor drug interactions, causing user exhaustion and the non-use of the program.[20,21] Therefore, correct information[38] and interaction classification according to their severity level[19] are required to optimize alerts, leading to the better management of computer systems. Despite efforts to improve the selection of DDI evidence, there is no accepted standard for defining pDDI risk. Thus, it is necessary to study pDDIs and create knowledge of interactions in different diseases. In addition, computer systems should focus on a limited list of the most important drug interactions to avoid unnecessary interruptions, as well as false and irrelevant warnings.

The majority of patients with CVDs were male, which is in line with the fact that men are more prone to cardiac disease than women.[39] Additionally, pDDIs were found to be more frequent in males than in females, which is consistent with some previously published reports[10,16,40] and contrary to the findings of 1 study.[41] This disparity can be attributed to the fact that the number of male patients in the present study was more than female patients. Another reason could be that men have a higher risk of CVDs than women, necessitating various medicines, which can lead to pDDIs. The present study's findings showed that the majority of the patients belonged to the age group of 65 years or above and pDDIs were widely seen in patients of the same age group. These findings are similar to those reported in Ethiopia[1] and Nepal.[7] This finding can be explained by the fact that older people are exposed to multiple regimens compared with younger people, increasing the risk of pDDIs.

The average number of prescribed medications per patient was 7.5. The value obtained was relatively similar to that in a study in Nepal,[7] which reported that the average number of medicines prescribed per patient was 6.9. Nonetheless, it had a higher value than studies conducted in Pakistan[10] and Morocco.[42] It can be explained by the fact that these patients are likely to take several prescriptions on account of multiple comorbidities. The current study revealed the prevalence of pDDIs in 10.5% of CVD admissions. The value achieved in the current research is relatively low compared with that in the study conducted in Western Nepal, which stated an incidence rate of 21.3%.[7] Furthermore, a similar study conducted in India among hospitalized cardiac patients showed an incidence rate of 30.2%.[43] These differences might be because the current study considered only pDDIs with moderate-to-major severity in contrast to the other research that considered drug interactions of all severity. Moreover, the other possible reasons for the discrepancy in different studies could be differences in the classification of DDI severity, the use of various screening tools, prescribing patterns, the nature of drugs, the methods applied in each study, settings, and subjects, and the availability of clinical pharmacists in the study settings.

The current study showed that the most common interactions were in patients with diseases of veins, lymphatic vessels, and lymph nodes, as well as ischemic heart disease. Nonetheless, no studies have shown the exact pattern of the pDDI prevalence based on the type of CVD. Hence, this discussion requires more detailed studies in the future to trace the prevalence of drug interactions in these categories of cardiac diseases. The cardiac surgery unit, the ICU, the CCU, and the internal cardiac care unit had the highest number of pDDIs. Our study showed similar results to those from the United States, which reported that the prevalence of drug interactions was 29.0% in the ICU and 27.3% in the CCU.[44] It seems that the high rate of pDDIs in these wards compared with other wards is probably due to the long-term hospitalization of these patients and the severity of the disease. The most common interacting pairs identified in this study were aspirin with heparin and heparin with clopidogrel. These results are consistent with findings from previous studies conducted in India,[43] which reported that bleeding was the most common consequence of the

concomitant use of these drugs in cardiovascular patients.

This study has several strong points. Firstly, it is a literature review and a survey of a panel of specialists to classify the severity of pDDIs in patients with CVDs. Secondly, in addition to detecting patterns of drug interactions in prescriptions, the designed software provided periodic reports on the performance of each of the center's physicians. Thirdly, the investigation of the drug profiles of a large number of patients over a long period is another salient strength. Be that as it may, the present study has several limitations. One of the weaknesses is its single-institution study design rather than a prospective interventional study design. Due to the retrospective design, the potential clinical outcome is unknown. Other limitations are the obsolescence of some drugs mentioned in the present study and the use of new drugs that physicians had not yet examined for interference.

It is recommended to use pDDI knowledge resources with the standard definitions of the intensity of interactions by clinical guidelines and expert surveys for other diseases. Furthermore, given the insufficiency of definitive proof regarding the influence of information technology-based interventions on clinical consequences related to pDDIs, there is a need for more investigations with high methodological quality. In addition, to decrease the burden of DDI alerts on prescribers, further studies are needed to determine when and how they should be directed to the appropriate recipient and what features of alerts are most effective for different recipients.

## Conclusion

The current study revealed the prevalence of pDDIs in 10.5% of CVD admissions to the cardiac center. The highest prevalence of pDDIs was observed in ages 65 years and older. Additionally, the results of this study revealed that cardiologists and pharmacists had considerable consensus on the severity of drug interactions in patients with CVDs. Therefore, it can be concluded that the collaboration of these 2 groups in developing drug interaction knowledge and implementing that knowledge in information technology-based interventions can improve drug therapy management and prevent the consequences of pDDIs.

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