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POTENTIAL AND ACTUAL DRUG-DRUG INTERACTIONS AMONG PATIENTS WITH CARDIOVASCULAR DISEASE: A COMPREHENSIVE ANALYSIS OF DATA FROM A TERTIARY CARE HOSPITAL IN SOUTH INDIA

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Keywords:

Antithrombotic agents, Cardiovascular disease, Drug-drug interactions, South India

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ABSTRACT: Context: Drug-drug interactions (DDIs) are frequently observed in hospitalized cardiac patients and associated with alteration in the effectiveness of cardiovascular therapy. **Aim:** The study was conducted to identify the incidence and nature of DDIs and their associated risk factors among patients with cardiovascular disease (CVD). **Materials and Method:** A prospective interventional study was conducted between August 2018 and April 2019 in the Department of Cardiology of a tertiary care South Indian hospital. Patients admitted with CVD on a minimum of two medications were enrolled in the study and their prescriptions were evaluated for DDIs using Micromedex interaction checker version 2.8. **Results:** A total of 258 patients with CVD were enrolled in the study with a mean age of 60.11±12.07 years. On average, each patient was prescribed 11.35±3.30 medications. The incidence of potential DDIs (pDDIs) was 99.61%, with 7.59±4.10 as a mean number of pDDIs per prescription. The majority of the interactions were significant in severity (50.69%), pharmacodynamic (68.24%) in nature, of unspecified onset (69.97%), and with fair documentation status (61.79%). The incidence of actual DDIs (aDDIs) was found to be 1.16%. The number of medications per prescription, duration of hospital stays, number and type of comorbidities, and presence of narrow therapeutic index drugs in the prescription were the significant risk factors for the occurrence of the higher number of interactions. **Conclusion:** The occurrence of a more significant number of DDIs in patients with CVD highlights the need for accurate monitoring, evaluation, and planning of the individual patients' drug therapies.

INTRODUCTION: Cardiovascular disease (CVD) is the leading cause of mortality globally which affects both developed and developing countries.

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In the year 2016, CVD accounted for around 18 million deaths which were 31% of all worldwide deaths and 85% of the deaths were because of heart attack and stroke. By 2030, the death toll is predicted to exceed 23.6 million [1, 2]. In India, the prevalence of CVD was estimated to be 54.5 million in 2016, and is increasing every year with CVD being the cause for one in four deaths in India [3, 4].

Cardiovascular patients are more often reported with potential drug-drug interactions (pDDIs) and cardiac drugs are observed to have a higher

potential for drug interactions [5, 6]. Patients with CVD are particularly vulnerable to DDIs due to multimorbidity, a more significant number of drugs prescribed (polypharmacy), longer duration of hospital stay, the complexity of the disease, physiological changes with advancing age or conditions such as renal failure, shock, hepatic disease like cirrhosis or acute viral hepatitis, stages of the disease and the influence of heart disease on drug metabolism [7-12].

Alteration in the effect of a drug (object drug) when it is simultaneously administered with another drug (precipitant drug) is considered as drug-drug interaction (DDI) [13]. When the simultaneously administered drugs have the potential to interact with each other but may not result in any clinical manifestations, it is referred to as pDDI. However, any clinical manifestations in the patient while on concurrent use of medications is actual DDI (aDDI). The aDDIs may results in adverse patient outcomes (*e.g.* adverse drug reactions (ADRs), diminished therapeutic effect), hence, also known as adverse drug interactions (ADIs) [14]. Different studies conducted show that bleeding manifestations were a significant concern of DDIs and DDIs may lead to an increased risk of hospitalization and higher healthcare costs [15-17].

Recent studies around the world had shown the incidence of DDIs to be in the range of 21.3%-98% [16, 18-20]. Although a large number of studies have been conducted throughout the world assessing the DDIs in patients with CVD, there are variations in the reported rates of pDDIs. With this background, the current study is carried out to identify the pDDIs and aDDIs, assess the causality of aDDIs, and identify risk factors associated with pDDIs among patients with CVD in a tertiary hospital of South India.

MATERIALS AND METHODS:

Study Design: The study was a prospective interventional study.

Study Site: This study was carried out in the Department of Cardiology, JSS Hospital, Mysuru. It is an 1800 bedded multispecialty tertiary care teaching hospital established to provide healthcare services to people in and around Mysuru city, South India.

Study Period: The study was conducted over nine months, from August 2018 to April 2019.

Study Population: Patients of either gender with an age of more than 18 years diagnosed with CVD and admitted to the Department of Cardiology of JSS Hospital, Mysuru were included in the study. Patients prescribed with a minimum of two medications were included in this study. We have excluded pregnant women with CVD from this study.

Ethical Approval: Ethical approval for this study was obtained from the Institutional Human Ethics Committee of JSS College of Pharmacy, Mysuru. The permission to conduct the study was also taken from the department head of cardiology. The verbal consent was taken from the enrolled patients.

Data Collection and Procedure: A suitable data collection form was designed, and all the relevant and necessary data were collected from the patient's case notes, patient treatment charts, laboratory reports, and patient and cardiologist interviews. The prescribed drugs for patients were assessed for the pDDIs using Micromedex version 2.8 drug interaction checker daily (by considering the addition and discontinuation of the drugs on regular follow-up), and a brief description of interactions was recorded whenever present.

Interventions were provided for the identified DDIs whenever necessary. The 24 h interval between administrations of two drugs was considered while assessing pDDIs, *i.e.* the pDDIs between two drugs were taken into considerations if the interval between their administrations was within 24 h. Incidence of pDDIs and aDDIs were estimated. The identified pDDIs were classified based on severity (contraindicated, major, moderate, minor and unknown), onset (rapid, delayed and not specified), the mechanism (pharmacodynamic, pharmacokinetic and unknown) and documentation (excellent, good, fair and unknown).

On observation of pDDIs, the required interventions were provided and recorded along with a description of the ADIs. The causality of the identified ADIs was assessed by using the drug interaction probability scale (DIPS) and was given a score. The interactions were categorized as highly

probable, probable, possible and doubtful with a score of >8, 5-8, 2-4 and <2 respectively.

Data Analysis: The data collected was analyzed using descriptive statistics, namely mean with standard deviation for continuous variables and number with percentage for categorical variables. Binary logistic regression analysis was used to identify the risk factors for the DDIs. Results were considered statistically significant at a standard of $p<0.05$. All the analyses were carried out by using Statistical Package for the Social Sciences (SPSS) version 21.0.

RESULTS:

Demographic and Clinical Characteristics of the Study Population: Tables 1 and **2** show the demographic and clinical characteristics of the study population, respectively. A total of 258 patients with CVD were enrolled in the study. The mean age of patients was 60.11±12.07 years, the majority were males (n = 199, 77.00%) and in the age group of 41-60 years (n=119, 46.12%).

TABLE 1: DEMOGRAPHIC CHARACTERISTICS OF STUDY POPULATION

Demographic Characteristics		No. of patients (%) (N = 258)
Sex	Male	199 (77)
	Female	59 (23)
	Mean ± SD	60.11 ± 12.07
Age	21-40	16 (6.20)
	41-60	119 (46.12)
	61-80	111 (43.02)
	81-100	12 (4.65)

A total of 208 patients (80.62%) had one or more comorbidities with a mean of 1.70 ± 1.34. The majority of the patients were observed to have 1-4 (n=199, 77.13%) comorbidities. A greater number of CVD patients were found to have diabetes and hypertension (n=79, 30.62%) as comorbid conditions. Among the study population, the common cardiovascular diagnoses were Non-ST Elevation Myocardial Infarction (NSTEMI) (n=85, 32.95%) and ST-Elevation Myocardial Infarction (STEMI) (n=67, 25.97%). The mean duration of hospital stay of the patients was 4.76±2.40 (range 1-18) days.

TABLE 2: CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

Clinical Characteristics		No. of patients (%), (N = 258)
Disease conditions	CVD	58 (22.48)
	CVD + HTN	48 (18.60)
	CVD + DM	36 (13.95)
	CVD + DM+ HTN	79 (30.62)
	CVD + DM+ HTN + Kidney disease	10 (3.87)
	CVD + Kidney disease	1 (0.39)
	CVD + HTN + Kidney disease	11 (4.27)
	CVD + DM + Kidney disease	1 (0.39)
	CVD + Other disease conditions*	14 (5.43)
CVD observed (N= 294#)	ACS-NSTEMI	85 (32.95)
	ACS-STEMI	67 (25.97)
	ACS-Unstable angina	29 (11.24)
	Acute decompensated heart failure	28 (10.85)
	Atrial fibrillation	23 (8.91)
	Complete heart block	12 (4.66)
	Dilated cardiomyopathy	11 (4.26)
	IHD-Stable angina	11 (4.26)
	Acute Left ventricular failure	10 (3.88)
	Congestive cardiac failure	9 (3.49)
	Rheumatic heart disease	9 (3.49)
No. of comorbidities	None	50 (19.38)
	1-4	199 (77.13)
	5-8	9 (3.49)

*Other disease conditions: Chronic obstructive pulmonary disease, asthma, infections, benign prostatic hyperplasia, thyroid disorders, cerebrovascular disease, stroke, pneumonia, peripheral vascular disease, deep vein thrombosis, urinary tract infections; #A single patient presented with more than one cardiovascular disease resulting in more number of observed cardiovascular diseases than the total no. of patients. HTN-Hypertension; DM-Diabetes; ACS-Acute coronary syndrome; STEMIST-elevation myocardial infarction; NSTEMI-NonST-segment elevation myocardial infarction

Pattern of Medication usage in Cardiovascular Disease: Fig. 1 shows the distribution of patients according to the number of medications prescribed. A total of 2840 medications containing 207 active ingredients were prescribed to the study participants. On average, each patient was prescribed

11.35 ± 3.30 (range 4-22) medications. The majority of the patients (n=143, 55.53%) were prescribed 9-13 medications.

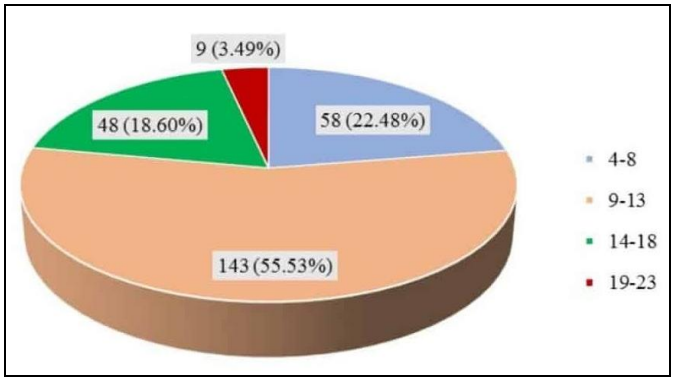

FIG. 1: DISTRIBUTION OF PATIENTS ACCORDING TO THE NUMBER OF MEDICATIONS PRESCRIBED

Medications under the Anatomical Therapeutic Chemical (ATC) category 'cardiovascular system (*class C)'* were seen to be frequently prescribed (n=1171, 41.23%) followed by drugs under the 'blood and blood-forming organs (*class B*)' (n=647, 22.78%) **Table 3**. Antithrombotic agents (n=631, 22.22%), including antiplatelets and anticoagulants, were widely prescribed medications under blood and blood-forming organs. Under cardiovascular system, lipid-modifying agents (n=242, 8.52%), diuretics (n=206, 7.25%) and vasodilators (n=188, 6.62%) were prescribed commonly.

TABLE 3: MEDICATIONS CLASSIFICATION AS PER ANATOMICAL THERAPEUTIC CHEMICAL (ATC) CLASSIFICATION SYSTEM

ATC Code	ATC Class	Number of medications (%) (N= 2840)
C	Cardiovascular system	1171 (41.23)
B	Blood and blood-forming organs	647 (22.78)
A	Alimentary tract and metabolism	563 (19.82)
R	Respiratory system	162 (5.70)
N	Nervous system	132 (4.65)
J	Anti-infectives for systemic use	125 (4.40)
G	Genito-urinary system and sex hormones	13 (0.46)
H	Systemic hormonal preparations, excl. sex hormones and insulins	11 (0.39)
M	Musculoskeletal system	8 (0.28)
V	Various	6 (0.21)
L	Antineoplastic and immunomodulating agents	1 (0.04)
P	Antiparasitic products, insecticides and repellents	1 (0.04)

Common antiplatelets seen in the prescription were aspirin (n=199, 77.13%), clopidogrel (n=105, 40.70%) and ticagrelor (n=103, 39.92%). As anti-coagulant, heparin (n=175, 67.83%) was commonly prescribed. Around 76% (n=195) of the total study population were observed to be prescribed with atorvastatin as lipid lowering agent. Beside these medications, trimetazidine (n=142, 55.04%), nicorandil (n=127, 49.22%), furosemide (n=110, 42.63%), metoprolol (n=86, 33.33%), spirono-lactone (n=56, 21.71%), digoxin (n=38, 14.73%), ramipril (n=32, 12.40%), cilnidipine (n=32, 12.40%), dobutamine (n=27, 10.46%) were the most commonly prescribed medications among patients with CVD.

Incidence and Nature of pDDIs: Out of 258 patients' prescriptions, 257 had at least one pDDI with an overall incidence rate of 99.61%. A total of 1955 pDDIs containing 250 drug pairs were identified in 257 patients' prescriptions. The mean number of pDDIs per prescription was 7.59±4.10 (range 1-20). Majority of the patients (n=101, 39.30%) had 6-10 interactions **Fig. 2**.

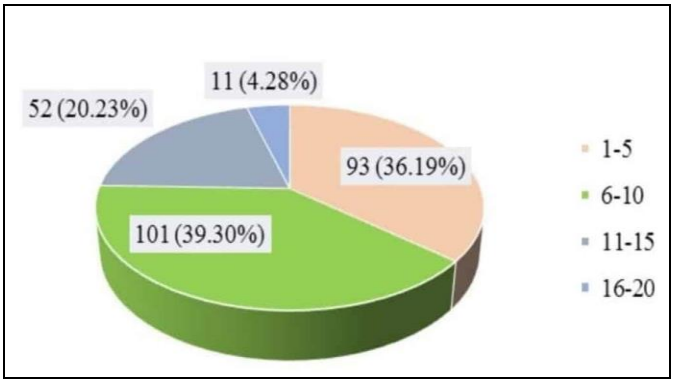

FIG. 2: NUMBER OF INTERACTIONS IN STUDY POPULATION

Table 4 shows the categorization of pDDIs based on severity, onset, mechanism, and documentation. Among 1955 identified pDDIs, most of them were major in severity (n= 991, 50.69%). Most of the pDDIs (n=1368, 69.97%) had unspecified onset and the pDDIs with fair documentation status were common (n=1208, 61.79%).

In terms of mechanism, most pDDIs were found to be pharmacodynamic (n=1334, 68.24%) and among the pharmacokinetic interactions, metabolism (n=197, 47.93%) related interactions were common.

TABLE 4: CATEGORIZATION OF pDDIs BASED ON SEVERITY, ONSET, MECHANISM AND DOCUMENTATION

Characteristics			No. of interactions (%), N=1955
Severity	Major		991 (50.69)
	Moderate		938 (47.98)
	Minor		26 (1.33)
Onset	Rapid		173 (8.85)
	Delayed		414 (21.18)
	Not specified		1368 (69.97)
Documentation	Excellent		166 (8.49)
	Good		581 (29.72)
	Fair		1208 (61.79)
Mechanism	Pharmacokinetic, n=411 (21.02%)	Absorption	58 (14.11)
		Distribution	5 (1.22)
		Metabolism	197 (47.93)
		Excretion	151 (36.74)
	Pharmacodynamic		1334 (68.24)
	Unknown		210 (10.74)

Interactions Observed based on the Severity: Among major interactions (N=991), the interactions with antithrombotic agents (n=550, 55.50%) were frequently observed, followed by interactions with diuretics (n=181, 18.26%). The heparin-aspirin (n=160, 16.14%) and clopidogrel-aspirin (n=116, 11.70%) drug pair interactions were commonly identified major interactions. Interactions with antithrombotic agents (n=291, 31.02%) and oral hypoglycemic agents (n=245, 26.12%) were widely seen moderate interactions. The most common moderate interaction was between clopidogrel and atorvastatin (n=115, 12.26%), followed by ticagrelor and heparin (n=73, 7.78%) drug pairs. A total of 26 (1.33%) minor interactions were identified among the study patients, and the common minor interaction was between furosemide and hydralazine (n=8, 30.76%).

Top Five Classes of Medications with pDDIs: In the majority of the interactions, antithrombotic agents (n=843, 43.12%) were involved. Likewise, interactions with diuretics (n=235, 12.02%) and cardiac glycoside (n=174, 8.90%) were frequently observed. The top five classes of medications with pDDIs are enlisted in **Table 5**.

TABLE 5: TOP FIVE CLASSES OF MEDICATIONS WITH pDDIs

Interacting class of medications*	No. of interactions (%) (N=1955)
Antithrombotic agents	843 (43.12)
Diuretics	235 (12.02)
Cardiac glycosides	174 (8.90)
Beta-blockers	136 (6.96)
Agents acting on the renin-angiotensin system	100 (5.11)

* Drug of these classes were present as object drug in the identified pDDIs

Top Ten Drugs Involved in pDDIs: The most common medication involved in the identified pDDIs was clopidogrel (n=333, 17.03%) followed by others as represented in Table 6.

TABLE 6: TOP TEN DRUGS INVOLVED IN pDDIs

S. no.	Medications	No. of interactions (%) (N=1955)
1	Clopidogrel	333 (17.03%)
2	Insulin	194 (9.92%)
3	Heparin	185 (9.46%)
4	Ticagrelor	182 (9.31%)
5	Digoxin	174 (8.90%)
6	Furosemide	143 (7.31%)
7	Aspirin	103 (5.27%)
8	Metoprolol	96 (4.91%)
9	Ramipril	62 (3.17%)
10	Metformin	58 (2.97%)

Top Ten pDDIs Identified: Among all the identified pDDIs, the common interacting drug pairs were heparin-aspirin (n=160, 8.18%), followed by clopidogrel-heparin (n=116, 5.93%) and clopidogrel-atorvastatin (n=115, 5.88%), as depicted in **Table 7**.

TABLE 7: TOP TEN pDDIs IDENTIFIED

S. no.	Interacting drug pairs	Category of interaction	Number of interactions (%) (N=1955)	Potential outcome of an interaction
1	Heparin + aspirin	Major	160 (8.18)	Increase the risk of bleeding
2	Clopidogrel + Aspirin	Major	116 (5.93)	Increase the risk of bleeding
3	Clopidogrel + Atorvastatin	Moderate	115 (5.88)	Decrease formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity
4	Ticagrelor + Aspirin	Major	102 (5.22)	Increase the risk of bleeding and decrease ticagrelor efficacy with the higher dose of aspirin
5	Furosemide + Aspirin	Major	93 (4.76)	Reduce diuretic effectiveness and possible nephrotoxicity
6	Clopidogrel + Heparin	Major	82 (4.19)	Increase the risk of bleeding

7	Metoprolol + Aspirin	Moderate	81 (4.14)	Increase BP
8	Insulin + Aspirin	Moderate	75 (3.84)	Increase the risk of hypoglycemia
9	Ticagrelor + Heparin	Moderate	73 (3.73)	Increase the risk of bleeding
10	Aspirin + Magnesium hydroxide	Moderate	63 (3.22)	Decrease salicylate effectiveness

Incidence and Nature of a DDIs: Among the total of 1955 pDDIs, only three resulted in ADIs with an incidence of 1.16%. Interactions between furosemide-levosalbutamol and torsemide-levosalbutamol resulting in hypokalemia, and nebivolol-clonidine resulting in bradycardia were observed. Patients with hypokalemia were treated symptomatically with potassium chloride supplement and the dose of nebivolol was decreased as a management approach in bradycardia. The causality assessment was done for the ADIs using DIPS. The interaction between drug pair furosemide-levosalbutamol and torsemide-levosalbutamol each was probable with a DIPS score of five, whereas the interaction between Nebivolol and Clonidine was identified as possible with DIPS score of four.

Risk Factors for pDDIs: To identify the risk factors for DDIs, the study population was divided into two groups as patients with less than or equal to seven pDDIs and patients with more than seven pDDIs.

Binary logistic regression showed that the risk of having more than seven pDDIs was significantly higher when patients stayed at the hospital for 5-12 days compared to 1-4 days, among patients prescribed with more than nine medications compared to patients prescribed with 1-8 medications, patients having comorbid conditions compared to patients without comorbid conditions, patients with comorbid conditions like hypertension and diabetes mellitus (HTN + DM) and diabetes mellitus (DM) only compared to patients with CVD alone, and patients prescribed with narrow therapeutic index medications compared to patients not prescribed with narrow therapeutic index medications **Table 8**.

TABLE 8: RISK FACTORS FOR pDDIs

Risk factors		No. of Interactions > 7(%)	No. of Interactions ≤ 7(%)	Odds Ratio (95% CI)	p-value
Gender	Male	86 (43.22)	113 (56.78)	Reference	
	Female	32 (55.17)	26 (44.83)	1.62 (0.90-2.91)	0.108
Age	21-60	55 (40.74)	80 (59.26)	Reference	
	61-100	63 (51.64)	59 (48.36)	1.55 (0.95-2.55)	0.080
Length of hospital stay	1-4	43 (30.93)	96 (69.06)	Reference	
	5-8	58 (58)	42 (42)	3.08 (1.80-5.27)	<0.001
	9-12	14 (100)	0	--	<0.001
	13-16	2 (66.67)	1 (33.34)	4.47 (0.39-50.58)	0.236
	17-20	1 (100)	0	--	0.314
No. of medications prescribed	4-8	5 (8.77)	52 (91.23)	Reference	
	9-13	69 (48.25)	74 (51.75)	9.70 (3.66-25.70)	<0.001
	14-18	35 (72.92)	13 (27.08)	28.00 (9.16-85.55)	<0.001
	19-23	9 (100)	0	--	<0.001
No. of comorbid conditions	None	12 (24)	38 (76)	Reference	
	1-4	98 (49.50)	100 (50.50)	3.10 (1.53-6.29)	0.001
	5-8	8 (88.89)	1 (11.11)	25.33(2.87-223.62)	0.003
Narrow therapeutic drugs*	Absent	80 (39.80)	121 (60.20)	Reference	
	Present	38 (67.86)	18 (32.14)	3.19 (1.70-5.98)	<0.001
Disease conditions	CVD	15 (25.86)	43 (74.14)	Reference	
	CVD + HTN	15 (31.25)	33 (68.75)	1.30 (0.56-3.04)	0.540
	CVD + DM	20 (55.56)	16 (44.44)	3.58 (1.48-8.66)	0.004
	CVD + DM + HTN	50 (64.10)	28 (35.91)	5.12 (2.42-10.82)	<0.001

*Narrow therapeutic drugs: Levothyroxine, Theophylline (combination and alone), Digoxin, Phenytoin, Phenobarbitone, Rifampicin

Suggestions like monitoring the blood glucose level, electrolytes, interval between medication administration, heart rate and blood pressure were provided wherever necessary. Monitoring vital parameters [like blood pressure, heart rate, glucose level, renal function test (RFT), liver function Test (LFT), prothrombin time-international normalized ratio (PT-INR), electrolyte level, *etc*. of patients

was the common management option for most of the identified pDDIs, which were routinely monitored as a part of the patient management within the hospital.

DISCUSSION: DM with HTN was the most common comorbid condition in the study population, followed by DM and HTN alone. The finding differs from another study from Mysuru, where dyslipidemia (57%) and DM (27.5%) were the most common comorbidities [20]. These medical conditions seem to have a pathophysiological association with each other and are often observed to occur in the presence of one another, which might be the reason for a higher number of patients with DM and HTN as comorbidities [21].

The average number of medications per prescription was found to be 11.35±3.30, which is higher than found in other studies from Morocco and Mysuru, with the average number of medications per prescription to be 5.2 and 8.4 respectively [16, 18]. As most of the enrolled patients presented with comorbidities, the number of medications per prescription was higher in the current study.

The study showed the incidence of pDDIs to be 99.6%, which is higher than studies conducted in India, Nepal, Serbia, and Pakistan, revealing the incidence of 21.3%-98% [6, 18, 19, 20, 22]. These variabilities in the data may be due to different tools used to assess the DDIs, variation in the study population, and the prescribing pattern in different settings. Considering all the grades of pDDIs with the inclusion of patients from the coronary care unit and the general cardiology wards might have led to a high incidence of DDIs in this study.

With the total of 1955 pDDIs identified in 257 study population involving 207 different drugs, pDDIs per prescription was found to be 7.59±4.09 the study. This was slightly higher than the number of pDDIs found in other studies carried out in Mysuru (6±3.1) and Jaipur (5.69±4.87) [20, 23]. The higher number of interactions might be because of the more significant number of drugs (11.35±3.30) prescribed in the present study compared to others.

Most of the interactions were significant in severity (n=991, 50.69%), followed by moderate (n=938, 47.98%). This distribution was in contrast to the studies' findings in a South Indian hospital and in Morocco, where most of the interactions were moderate and minor in severity, respectively [16, 18]. A study carried out in Pakistan showed 55% of moderate interactions and 45% of major interactions [6]. Most of the patients being prescribed with cardiovascular drugs that tend to cause significant interactions might have led to a higher number of it in the study population.

The onset of most of the pDDIs (n=1368, 69.97%) was unspecified, implying that onset of most pDDIs are not predictable, which was in contrast with Patel's findings that showed 52% of the delayed and 43% of rapid onset interactions [16]. The majority of the interactions were identified to have pharmacodynamic (n=1334, 68.24%) mechanisms followed by pharmacokinetic (n=411, 21.02%). These findings are consistent with the studies from South India, which reported 64.69% and 76.3% of interactions were pharmacodynamic, and 20.1% and 15.8% of interactions were pharmacokinetics [16, 20].

Majority of the identified pDDIs involved clopidogrel (n=333, 17.03%) in this study which is in contrast to the finding of a study in Nepal which showed atorvastatin (33.3%) as the first drug found to be involved [22]. As clopidogrel (n=105, 40.70%) was one of the most commonly prescribed medications in the current study, the interactions involving clopidogrel were in higher number.

Frequent interactions were observed with antithrombotic agents (anticoagulants and antiplatelets) and diuretics. These two classes of drugs were responsible for 55.14% of the total identified pDDIs. The most common interacting drug pairs were heparin/aspirin (n=160, 8.18%) and clopidogrel/heparin (n=116, 5.93%), which was consistent with the study conducted by Patel VK where the frequent potential interactions were between aspirin & heparin (29.38%), and clopidogrel & heparin (7.21%), and antiplatelets, anticoagulants, and diuretics as common drug classes involved in the occurrence of pDDIs [16]. Frequent prescription of antithrombotic agents and diuretics among cardiac patients in this study might have led to a higher number of interactions involving these drugs.

Out of 1955 pDDIs, three resulted in ADIs giving an incidence of 1.16% which is very less compared

to 68 ADIs among the 388 identified pDDIs with the incidence of 17.53% in the study by Patel VK [16].

Binary logistic regression analysis for the associated risk factors of pDDIs among the study population revealed several medications per prescription, length of hospital stays, number and type of comorbidities, presence of narrow therapeutic index drugs in the prescription are the significant ones for the occurrence of a higher number of interactions. These findings are comparable to the studies showing the positive association between pDDIs and the number of drugs, comorbidities, and duration of hospital stay [6, 15-17, 20]. With increased comorbid conditions, the number of drug intake also increases, and those prescribed with the more significant number of medications have a higher chance of developing DDIs because the probability of each drug encountering the other for interaction is increased with a higher number of simultaneous drug administration. Exposure to the more significant number of drugs with a prolonged hospital stay can be correlated with the increased number of pDDIs [13, 23, 24], and this justifies the fact that patients with a length of hospital stay of 5-12 days were seen to be at higher risk of having pDDIs compared to those who stayed for less than five days in this study. Alteration in the concentrations of narrow therapeutic index drugs by the precipitant drugs might have led to a higher number of interactions in those prescribed with them.

Study Limitations: The current study could not include all the patients admitted to the cardiology department as some of them got discharged on the same day of hospitalization. Also, delayed drug-drug interactions and their consequences were not assessed as the patients were not followed up after discharge.

Recommendations: Similar studies need to be carried out in larger populations to obtain more information on the exact pattern and risk factors associated with developing potential drug-drug interactions. Studies involving the development and implementation of strategies to prevent drug-drug interactions can be conducted. Furthermore, the economic burden on patients due to interaction can be assessed.

CONCLUSION: The occurrence of a greater number of DDIs in patients with CVD highlights the need for accurate monitoring, evaluation, and planning of the patients' drug therapies. Some of the potential consequences of the identified pDDIs were haemorrhage, alteration in serum potassium levels, hypoglycemia, digoxin toxicity, nephrotoxicity and reduced efficacy of specific antihypertensive agents. To prevent the occurrence of adverse events from DDIs, strategic medication management with collaborative efforts from multidisciplinary healthcare professionals is necessary.

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