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A PROSPECTIVE OBSERVATIONAL STUDY ON DRUG-DRUG INTERACTIONS IN CARDIAC PATIENTS AT A TERTIARY CARE HOSPITAL

Javed Akhtar Ansari (javed.ansari47@gmail.com),
Farheen Fatima(farheenfatima995@yahoo.com),
Syeda Amtul Raqiba(raqibazaki182k19@gmail.com),
Qanita Munazza(qanitamun@gmail.com),
Mohammed Afanullah Khan(mdafankhan14@gmail.com)
MESCO college of pharmacy, hyderabad-500006

Abstract:
Aims and objectives: *Drug–drug interactions (DDIs) are defined as two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered. Patients with cardiovascular disorders are at higher risk for drug- drug interactions because of the types and number of drugs they receive. The aim of the present study was to assess the incidence and prevalence of DDIs in cardiac patients*
Subjects and methods: *A prospective observational study was carried out for a period of 6 months at Osmania General Hospital, a Tertiary Care Teaching Hospital. Cardiac patients taking at least two drugs and who had a hospital stay of at least 24 hours were included in the study. The prescription was analyzed for possible interactions using - Micromedex -2 (Thomson Reuters) × 2.0.*
Results: *A total of 150 patients were included in the study in which 719 drug-drug interactions were found. Among these males 72% were predominant. Majority of interactions were of moderate severity (68.98%) and pharmacodynamic (73.99%) in nature. Among the clinical consequences, the incidence of bleeding (55.39%) was found to be highest. CAD's were found to be the major cause of hospitalizations (43.34%). The class of drugs most commonly involved in drug-drug interactions was found to be Anticoagulants & Antiplatelet (34.18%).*
Conclusion: *This study highlights the need for screening prescriptions of cardiovascular patients for DDIs and proactive monitoring of patients who have identified risk factors; this helps in detection and prevention of possible adverse drug interactions.*
Keywords: *Cardiovascular disorders, Drug–drug interactions, Interaction severity, Micromedex*

Corresponding author:
Dr.JavedAkhtar Ansari,
13-5-741, Dept of pharmacy practice,
MESCO college of pharmacy, hyderabad-500006
Mailing address: javed.ansari47@gmail .com
.

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INTRODUCTION:

Safer use of modern and traditional medicines is an ambitious goal for all of us. Medicines have brought enormous benefits, but no medicine is 100% safe for all people in all situations. While some medicines can seriously injure or even kill, most have predominantly beneficial effects for most people - even while they may cause occasional minor harm (such as headache, rash or tiredness.[1]

With the increasing burden of patients with multiple disease states, the drug therapy has grown more complex.[2]Drug related problems such as adverse drug reactions, drug– drug interactions, idiosyncratic reactions, and hypersensitivity reactions remained a major challenge in clinical practice.[3]

An interaction is said to occur when the effects of one drug are altered by the co-administration of another drug, herbal medicine, food, drink or other environmental chemical agents. The net effect of the combination may manifest as an additive or enhanced effect of one or more drugs, antagonism of the effect of one or more drugs, or any other alteration in the effect of one or more drugs. [4]

Conditions such as multiple disorders, chronic diseases and polypharmacy may increase the risk of pDDIs . Drug therapies in critically ill patients are often complicated by the altered physiology and coexistence of multiple co-morbidities that warrants polypharmacy. Polypharmacy may increase the risk of adverse drug reactions (ADRs), medication errors and patient non-compliance with treatment. [5]

The treatment of disease usually requires the use of more than one drug. When patients have multiple symptoms, it becomes necessary to prescribe a number of drugs. DDI's usually occur among drugs with low therapeutic index having a small difference between their therapeutic and toxic or lethal dose. [6]

In the Harvard Medical Practice Study of adverse events, 20% of events in an acute hospital in-patient setting were drug related. Of these, 8% were considered to be due to Drug- Drug Interactions.[7] Therefore many adverse events can be prevented by identifying pDDIs.[8]

Various studies suggest that cardiovascular patients are more often reported with pDDIs as compared to patients with other diseases.[9]The incidence of cardiovascular diseases (CVDs) has increased in recent decades they are considered as the primary cause of mortality in the world i.e. 17.9 million people die each year from CVD's, an estimated 31% of deaths worldwide.(WHO). The mortality data from first phase of the Million Death Study showed CVDs as the largest cause of deaths in India leading to 1.7–2 million deaths annually.[10] According to the Global burden of diseases study in India, coronary artery disease is the largest contributor to CVD accounting for over 35% of disease burden.[11]

Some studies have found that up to 11% of patients experience symptoms associated with DDIs and that DDIs are responsible for up to 2.8% of hospital admissions.[12]Research has also shown that DDIs are associated with increased health care use.[13]

The aim and objective of the present study was to assess the incidence and prevalence of DDIs in cardiac patients andto identify and evaluate the impact of significant drug-drug interactions in cardiac patients.

METHODOLOGY:

The prospective observational study was conducted for a period of 6 months at Osmania General Hospital, Hyderabad. All patients diagnosed to have cardiovascular diseases and undergoing treatment in the General Medicine and Cardiology unit were included in the study based on the study criteria.
Ethical clearance has been accorded by the Institutional Ethics Committee.

Patients of age greater than 18, both gender and cardiac patients taking at least two drugs and who had a hospital stay of at least 24 hours were included. Patients with incomplete data, visiting outpatient department, pregnant and lactating women were excluded from the study

Their demographic and medical details were properly documented in the self-designed patient profile form. The medications taken by the cardiac patients during their hospital stay were analyzed for possible DDIs via electronic database - Micromedex x 2.0. The data obtained was used to categorize interactions based on the mechanism as pharmacokinetic or pharmacodynamic. The pharmacokinetic drug interactions were further categorized into interactions based on absorption, distribution, metabolism and elimination.

The DDIs of major moderate and minor severity were documented. Certain demographic characteristics were studied to find out the predictors of DDIs, such as patient characteristics [gender, age (more than 18 years old), concurrent morbidities and length of stay] and drug characteristic (number of drugs). These interactions were also classified in terms of their mechanism. Available data on prescriptions included

are: Physicians identification, name, strength, frequency and quantity of medications dispensed. Due to greater clinical importance of Drug Interactions, all the three types of interactions – Major, Moderate and minor were considered in the present study.

Drug interaction checker:
Drug Interactions have been identified using a computerized DDI database system (Micromedex). This program describes all potential interactions and states whether information is available on specific drugs within a class of drugs

The drug interaction check was also performed using the www.drugs.com database.

Data analysis/ statistical analysis:
Data was analyzed by Microsoft Excel and Graph Pad Prism software. The correlation between two variables was done by Karl Pearson's correlation test for continuous data. All p-values less than 0.05 were considered as statistically significant. Wherever necessary, the results were represented in the form of percentages, graphs and tables using Microsoft Excel 2010.

Distribution of subjects based on age:

RESULTS:

A total of 150 prescriptions were analysed during the study period, with a male predominance of (72%). The average stay in hospital was 6.57 days. Most patients had cardiovascular diseases with a predominance of CAD (43.34%) followed by HF (26.66%) and cardiomyopathy (17.34%). The analysis of prescriptions allowed us to identify 719 interactions among 134 patients, with an average number of drugs taken of 9.5. The prevalence of DDIs was estimated to be 89.3%. Among the 1425 prescribed drugs, 749 (52.56%) were drugs of the cardiovascular system.

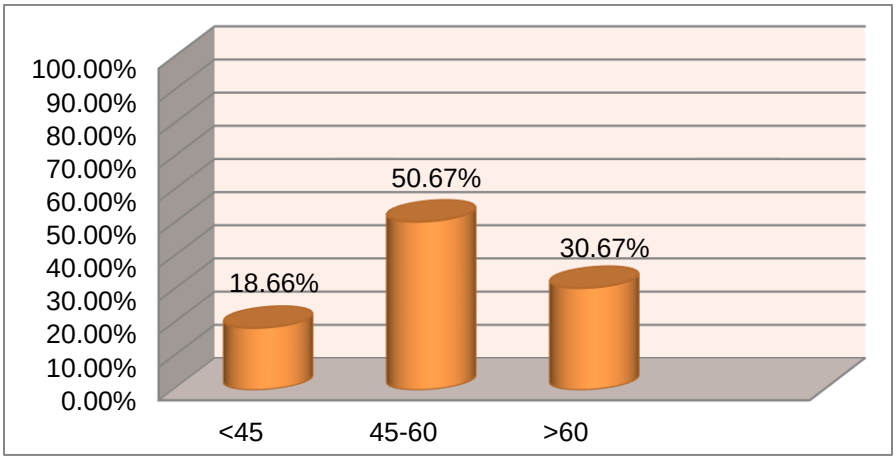

Figure 1: Distribution of subjects based on age

A total of 150 subjects were evaluated. Among which the age group affected more commonly are from 45-60 years of age (50.67%) .

Gender distribution based on DDI's:

Table 1: Distribution of gender based on the occurrence of DDI's

GENDER	No. Of Patients	% Of Patients	No. Of DDIs	% Of DDIs
MALE	108	72%	548	76.22%
FEMALE	42	28%	171	23.78%

Of the total study population, the number of males was predominant. Hence the number of DDI's was found to be significantly greater in males.

Categorization of number of drugs per prescription:

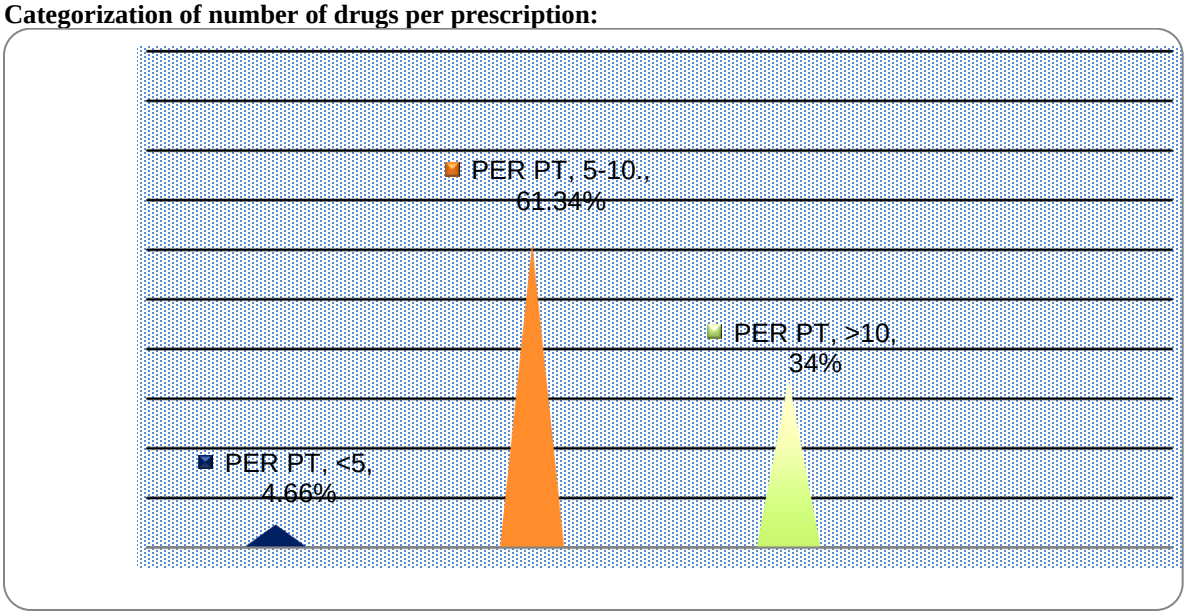

Figure 2: Column graph showing number of drugs prescribed to the patients

The distribution of subjects based on the number of drugs prescribed to each patient shows that greater number of cardiac patients were prescribed with more than 5 drugs which indicates the prominence of polypharmacy among the cardiac patients.

Distribution of subjects based on diagnosis:

Table 2: Distribution of sample based on diagnosis

Diagnosis	Frequency	Percentage
Coronary Artery Disease	65	43.34%
Atrial Fibrillations	6	4%
Congestive Heart Failure	40	26.66%
Rheumatic Heart Disease	7	4.66%
Cardiomyopathy	26	17.34%
Others	6	4%
Total	150	100%

The highest number of subjects in our sample were found to be suffering from CAD (42.50%) followed by CHF(21.25%) and cardiomyopathy(21.25%).

Distribution of cardiovascular drugs prescribed:

Table 3: List of cardiovascular drugs prescribed

Cardiovascular drugs	Frequency	Percentage
Anticoagulants & antiplatelet	256	34.18%
Diuretics	128	17.1%
Anti hyperlipidemics	97	12.95%
CCBs	31	4.13%
ACEI	74	9.87%
Vasodilators	32	4.28%
Adrenergic blockers	80	10.68%
ARBs	10	1.34%
Inotropic agents	41	5.47%

The most common drug class prescribed to the cardiac patients was Anticoagulants & Antiplatelet (34.18%) followed by diuretics (17.10%).

Categorization of DDI's based on severity:

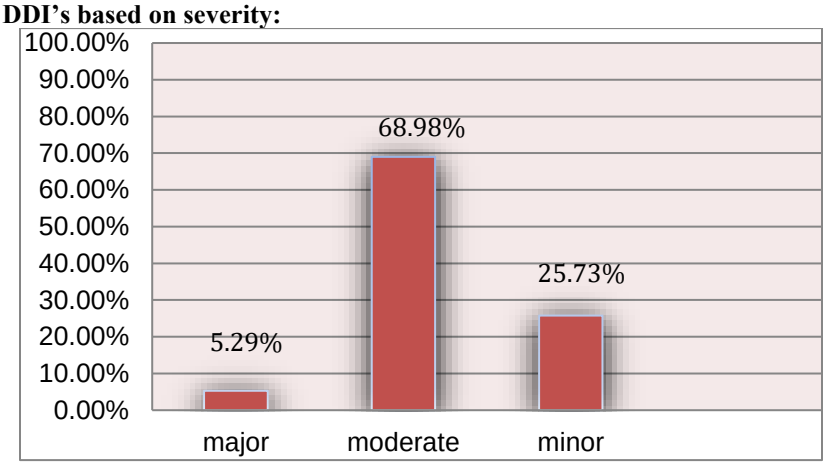

Figure 3: Column graph showing DDI's based on severity

Of the total DDI's identified, the interacting combination of moderate severity (68.98%) constituted majority of DDI's.

Interacting pairs of major severity:

Table 4: List of drug interactions of major severity

Interacting pairs	No of encounter	Consequences
Enalapril /spironolactone	14	Hyperkalemia
Enoxaparin /Acenocoumarol	3	Increased bleeding
Enoxaparin /diclofenac	1	Increased bleeding
Enoxaparin / clopidogrel	3	Increased bleeding
Carvedilol / digoxin	2	bradycardia
Metronidazole / ondansetron	1	QT prolongation
Digoxin / amlodipine	5	Heart block
Ranolazine / atorvastatin	1	Myopathy
Digoxin / calcium gluconate	1	Cardiac arrhythmias
Enalapril / potassium chloride	1	Hyperkalemia
Esomeprazole / clopidogrel	1	Decreased clopidogrel action

Categorisation DDI's based on mechanism of interaction:

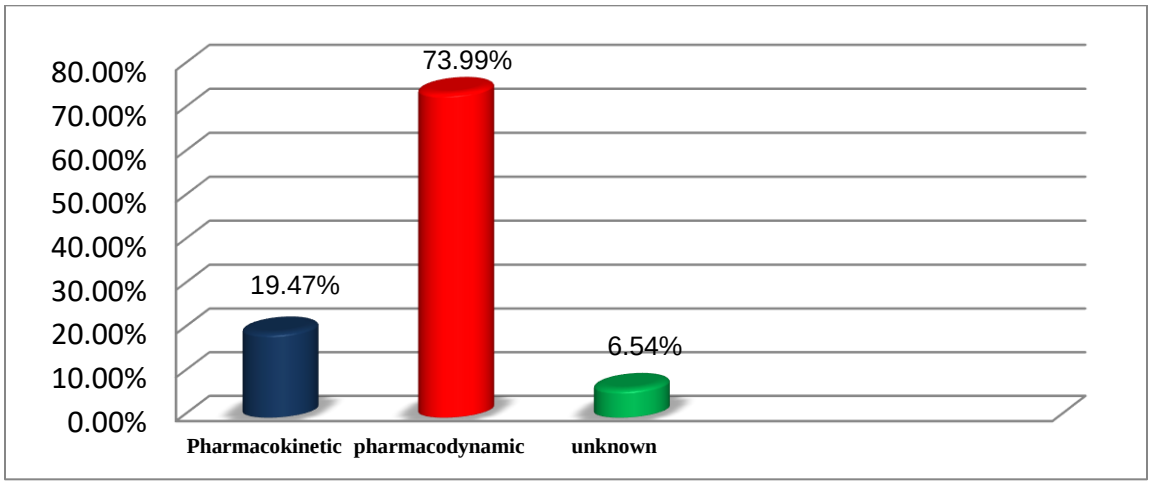

Figure 4: Column graph showing the distribution of DDI's based on mechanism.

Among the total number of DDI's identified, pharmacodynamics type of interactions (73.99%) were found in higher number

Distribution of number of DDI's in each patient:

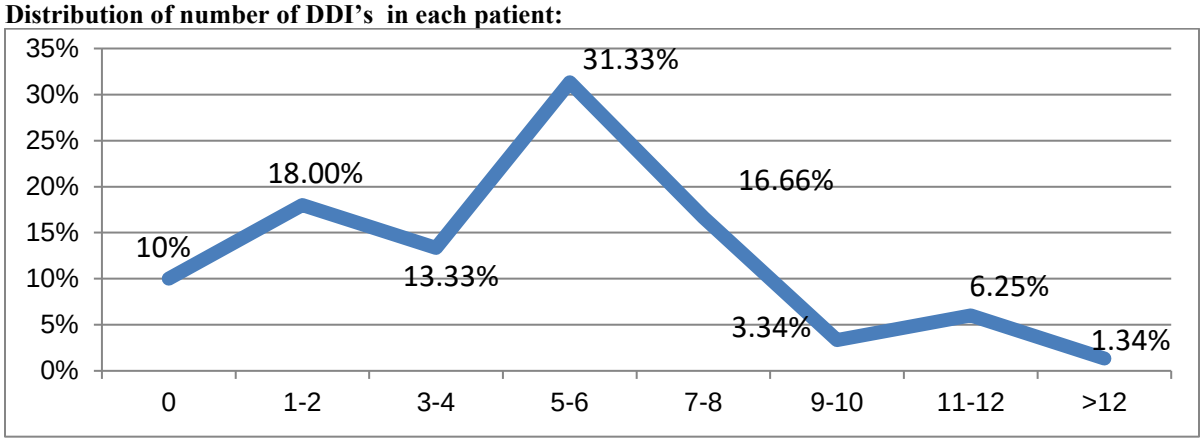

Figure 5: Line graph showing distribution of interactions per patients.

In maximum number of Cardiac patients, 5-6 drug-drug interactions were found.

Drug-drug interactions most commonly found:

Table 5: List of commonly occurring DDI's

Interacting pair	Consequences
Enalapril / furosemide	Risk of hypotension
Digoxin / furosemide	Increased risk of digoxin toxicity
Enalapril / aspirin	Decreased effectiveness of enalapril
Aspirin / furosemide	Decreased diuretic effectiveness
Heparin / aspirin	Increased risk of bleeding
Metoprolol / aspirin	Risk of decrease in blood pressure

Clinical consequences of DDI's:

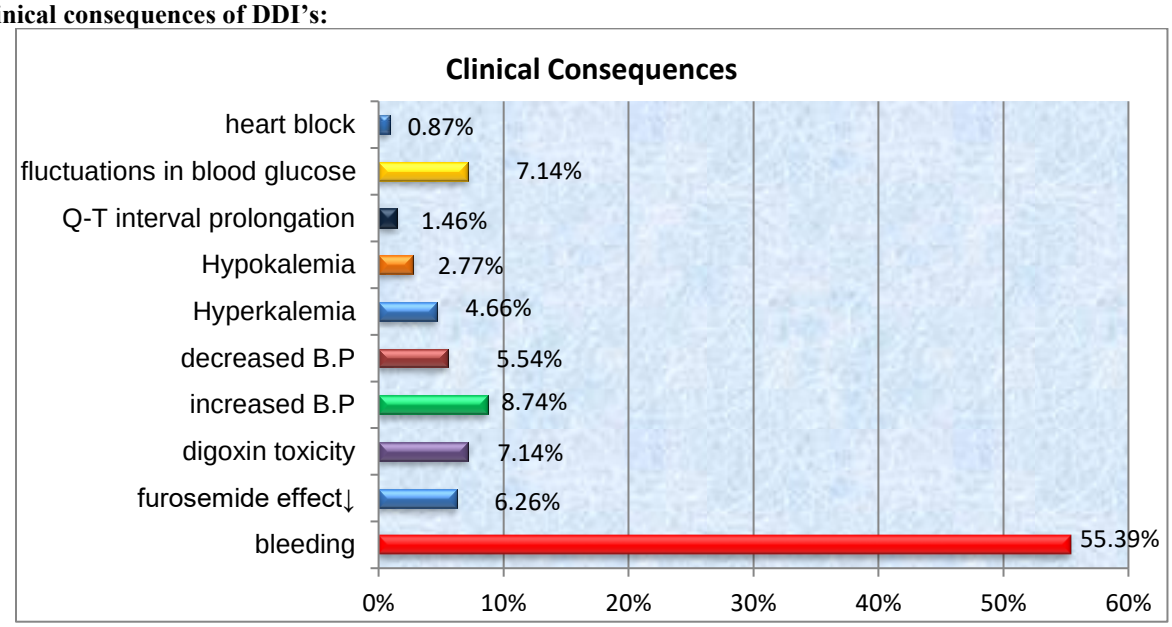

Figure 6: Bar graph showing various clinical consequences occurring due to DDI's.

Among the various clinical consequences, the incidence of bleeding (55.39%) was found to be highest.

Management requirements for the drug-drug interactions:

Table 6: Management options required for DDI's

Management	Number of DDI's	Percentage
Dose adjustment	111	14.13%
No management required	14	2.31%
Monitor for signs and symptoms	95	15.93%
Monitor for drug levels	54	10.79%
Monitor for biochemical parameters	203	28.53%
Avoid the combination or substitute	48	7.45%
Monitor for electrolytes levels	75	10.79%
Dose titration	30	3.85%
Risk benefit analysis	21	2.82%

The most common management plan found for most of the DDIs was monitoring Biochemical parameters (28.53%).

Relationship between the risk factors and occurrence of DDI's in cardiac patients:

Length of hospital stay and number of medicines were assessed to determine their association with the likelihood of occurrence of DDIs. Statistical analysis by Karl Pearson's correlation test revealed there is a significant correlation between these factors and the occurrence of DDI's.

Table 7: The correlation between length of hospital stay and number of DDI's

Parameters	*N*	*Minimum*	*Maximum*	*Mean*	*SD*	*r-value*	*P-value*
Length of hospital stay	150	2	17	6.573	3.159	0.751	<0.0001
No. of DDI's	150	0	15	4.793	3.031		

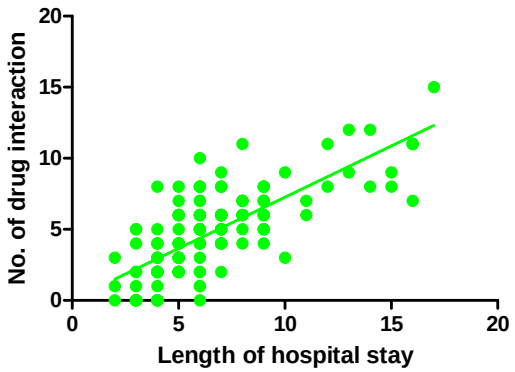

Figure 7: The scatter diagram for the correlation between length of hospital stay and number of DDI

Therefore, there is significant correlation between length of hospital stay and number of drug interaction.

Table 8: The correlation between number of medicines and number of DDI's

Parameters	*N*	*Minimum*	*Maximum*	*Mean*	*SD*	*r-value*	*P-value*
No. of medicines	150	4	19	9.50	2.95	0.645	<0.0001
No. of DDI's	150	0	15	4.793	3.031		

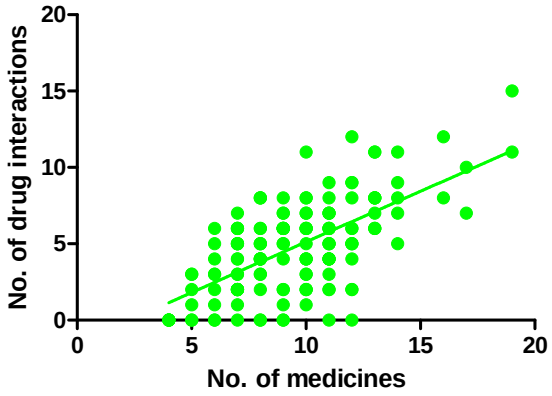

Figure 8: The scatter diagram for the correlation between number of medicines and number of DDI's

Therefore**,** there is significant correlation between number of medicines and number of drug interactions

DISCUSSION:

Drug-drug interactions (DDI's) are a concern for all the stake holders, especially patients and this risk increases as greater numbers of medications are commonly used to manage complex conditions. It has been observed that the use of polypharmacy was related to widely increased risk of unsafe drug-drug combinations.[14] Therefore, there is a need to raise the awareness of possible DDI's and all DDI's should be identified, managed and recorded.

The present study identified the pattern of DDI's in cardiac patients admitted to the tertiary care teaching hospital. The incidence rate of DDI was 89.3%. The value obtained in the present study is relatively more when compared with the study by Youssef *et al*.(2018)[15] in Morocco who reported an incidence rate of 68.11% and comparatively less compared to the study by Kulkarni *et al*.(2013).[16] These differences might be because our study took into consideration all the drug interactions of moderate and minor severity and also the database used for identifying drug interactions in contrast to others studies.

A total 719 drug-drug interactions were found in 150 patients. Among 150 Patients that were included, 108 patients were male which accounts for 72% and 42 patients were females which accounts for 28%.

Therefore, the predominance of males was similar when compared to the study by Sushmita *et al.* (2014).[17]

On analysing the mechanism of drug interaction identified, pharmacodynamics type of interactions (73.99%) were found in higher number compared to pharmacokinetic type of drug interactions (19.47%) followed by the interactions of unknown mechanism (6.54%). This trend is found to be similar when compared to the study by Patel *et al*. (2011).[18]

Of the total DDI's identified, the interacting combination of moderate severity (68.98%) constituted majority of DDI's. This finding is similar to most of the DDI studies conducted worldwide. This was followed by interacting combinations of minor severity (25.73%). The interactions of major severity were found to be least. Therefore, this trend of severity assessment of drug-drug interactions was found to be similar when compared with the study of Kulkarni *et.al.*(2013).[14]

The incidence of cardiovascular diseases (CVDs) has increased in recent decades. In India, coronary artery

disease is the largest contributor to CVD accounting for over all disease burden.[11] Similarly, among the various cardiovascular diseases in our study Coronary Artery Diseases (CAD) (43.34%) was found to be predominant. This was subsequently followed by Heart failure (26.66%), cardiomyopathy (17.34%), Rheumatic heart disease (4.66%), Atrial fibrillations and others (4%) respectively.

Many of the commonly used cardiovascular drugs interact with one another. These drugs can be used together to treat cardiac conditions following a risk benefit assessment. It is likely that many clinicians balance the risks of DDI against the benefit when prescribing patients with multidrug regimen. An example would be combined anticoagulant-antiplatelet therapy where an increase in the risk of haemorrhage with the combined therapy needs to be considered against the risk of thromboembolism without it. Benefits with multidrug regimens are unlikely to always outweigh their risks; therefore, decisions regarding prescriptions must always be tailored to suit each patient.

The class of drugs most commonly involved in drug-drug interactions was found to be Anticoagulants & Antiplatelet (34.18%).This result correlates with the results of another study of Matet*iet al*.(2011)[19]. The most common interacting pairs identified in our study were aspirin/clopidogrel, enalapril/furosemide, heparin/aspirin, digoxin/furosemide and metoprolol/aspirin.

The average duration of hospital stay in the current study was 6.57 days. It was also seen that there is preponderance for increased incidence of DDIs in the population as the duration of stay increases. Available studies also have shown that increased length of stay increases the probability of occurrences DDIs.[17] This might be because the chance of getting multiple drug increases with longer stays in the hospital which in turn increase the risk for pDDIs.

A significant positive linear relationship was found between the length of hospital stay and DDIs (r = 0.751, P < 0.0001). Our finding well resembles to the finding by several studies which have also shown that increased incidence of DDI's corresponds with an increase in duration of hospital stay. The reason might be that the likelihood of getting the multiple drugs increases with the increased length of hospital stay which in turn will increase the likelihood of DDI's. Similar positive linear relationship was also found between the number of medicines prescribed and DDI's (r = 0.645, P < 0.0001). The findings well correlate with the fact that polypharmacy increases the likelihood of DDIs to a great extent as shown by study of Sushmita *et.al*.(2014).[17]

The National Patient Safety Agency risk assessment of anticoagulation therapy highlighted co-prescribing of NSAIDs and other interacting medicines in cardiac patients as one of the 15 key high-risk prescribing practices. The potential consequence of such prescribing practice leads to an increase in the risk of bleeding complication therefore, the incidence of bleeding (55.39%) in our study was found to be highest. (Matet*iet al*. 2011).[19]

Caution must be exercised by maintaining the normal range of activated partial thromboplastin time (aPTT) and INR value because even slight increase or decrease in plasma drug concentration can have profound clinical effects. The most common management plan found for most of the DDIs was monitoring Biochemical parameters (28.53%).This finding was different from another study reported in the literature where the dosage adjustment was most common. (Kulkarni *et al.* 2013). [16] The suggested action to be taken in most cases was monitoring drug levels, signs and symptoms, electrolyte levels.

Hence, consistent with previous research it was observed in this study that the use of multiple medications was associated with significantly increased risk of drug-drug interactions. Therefore, there is a need to increase the awareness of possible DDI's in all hospital departments, especially the cardiology department as a sizeable number of DDI's have been recorded in it.

CONCLUSION:

This study reports the incidence of DDI's in patients admitted to the cardiology department of a tertiary care hospital. It was observed that prevalence of DDI"s increased linearly with number of drugs and length of stay. Patients with cardiovascular disease are at high risk for drug-drug interaction because of the types and number of drugs they receive. As a result number of drug-drug interactions increases with increase in number of drugs prescribed.

Therefore, in this study most of the interactions found were of moderate severity. CAD's were found to be the major cause of hospitalizations. The class of drugs most commonly involved in drug-drug interactions were found to be Anticoagulants & Antiplatelet. The incidence of bleeding was found to be highest. The most common management plan found for most of the DDIs was monitoring Biochemical parameters.

The present study shows that DDI's are frequent among hospitalized cardiac patients and highlights the need to screen prescriptions of cardiovascular patients for DDI's, as this helps in detection and prevention of possible adverse drug interactions.

Thus, this study assists in understanding the factors associated with DDI's that can help in safe and effective use of drugs in future.

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