

PHARMACOVIGILANCE IN CARDIOLOGY DEPARTMENT OF A TERTIARY CARE HOSPITAL

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ABSTRACT

Cardiovascular diseases are one of the leading cause of non-communicable disease related death globally. Increased age, comorbidity and smoking were found to be the risk factors for development of cardiovascular diseases. Cardiovascular medications have been cited as the most common class of drug associated with adverse drug reaction and medication error. A total of 267 ADRs were reported from 261 patients. Common ADRs observed were headache, gastritis and GI bleed and contrast nephropathy. According to Hart-wig severity scale majority of the reports were moderate. A system wise classification of ADRs showed that central and peripheral nervous

system related reactions were the most frequently observed adverse reactions followed by platelet, clotting, bleeding system related adverse effects. Since most patients with cardiovascular diseases are on multiple drugs it is not uncommon to see adverse drug reactions and it is important to monitor and alter therapy as and when the situation arises. Pharmacovigilance is needed in tertiary care hospitals were relatively high volume of adverse drug reactions are being detected.

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INTRODUCTION

Modern medicines have changed the way in which diseases are managed and controlled. However, despite all their benefits, evidence continues to mount that adverse reactions to medicines are a common, yet often preventable cause of illness, disability and even death.^[1]

In order to prevent or reduce harm to patients and thus improve public health, mechanisms for evaluating and monitoring the safety of medicines in clinical use are vital. In practice this means having in place a well-organized pharmacovigilance system.^[2]

Globally Cardiovascular disease has led to 17.5 million death in 2012. More than 75% death occurred in developing countries. In contrast to developed countries where mortality from CHD is rapidly declining, it is increasing in developing countries. This increase is driven by factors such as industrialization, urbanization and related lifestyle changes and called as epidemiological transition.^[3] Patients with cardiovascular disease are particularly vulnerable to ADRs due to their advanced age, polypharmacy, longer duration of therapy, and the influence of heart disease on drug metabolism.^[4] Moreover, cardiovascular disease itself may alter the frequency and characteristics of drug-related toxicity by modifying pharmacokinetics parameters such as volume of distribution and intestinal absorption.^[5] Side effects of cardiovascular drugs are frequent and this may be related to the high prevalence of cardiovascular disorders, co morbidities and advanced age of most of cardiovascular patients and narrow therapeutic index of cardiovascular drugs used in the inpatient setting, patients treated with drugs should be monitored and followed and report any possible adverse event to appropriate pharmacovigilance agents.^[6]

MATERIALS AND METHODS

Prospective observational study, by spontaneous reporting of Adverse Drug Reaction in patients admitted to Cardiac care unit. All cardiovascular drugs including diagnostic agents receiving patients were followed during 6 month time period. Patient were monitored daily throughout their hospital stay, and medical records reviewed. Any ADR developed during the period were identified. Data of each patient was collected using structured data collection form. Causality assessment of ADR was carried out using Naranjo's scale which categorizes the causality relationship into definite, probable, possible, unlikely. Severity of ADR was graded as per scale developed by Hartwig et al. The management strategies used for the

ADRs were considered as drug withdrawal, dose reduction, and additional treatment for the ADR or no change in regimen with no additional treatment.

The study was approved by the Institutional Human Ethical Committee of Academy of Pharmaceutical Sciences, Pariyaram Medical College filed under (Ref no.A1/1839/2016/APSC/IEC05/2016).

Statistical Analysis used: The study used descriptive statistics and the values were expressed in numbers and percentages.

RESULTS AND DISCUSSION

During the study period of 6 months in CCU, 502 patients were followed, of which 299 (59.56%) were males and 203 (40.43%) were females. The age of the patients ranged from 20 to 80 years, with majority belonging to the age group 60–69 years followed by 70-79 and 50-59 years.

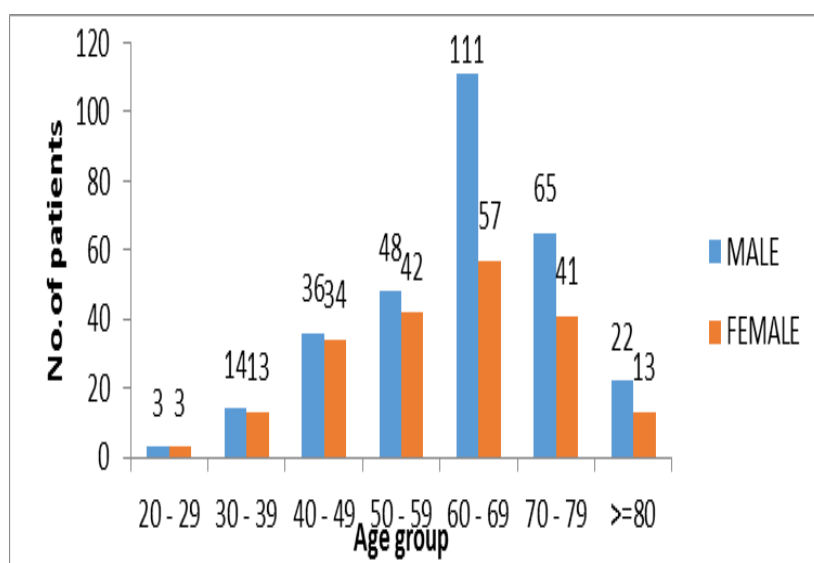


Fig 1: Age and sexwise distribution of patients.

5.1 CO-MORBIDITY

Among the 502 patients followed, 355 (70.71%) patients had co-morbidities and 147 patients were without any known co-morbidities, the presence or absence of co-morbidities in our study is shown in the fig 2.

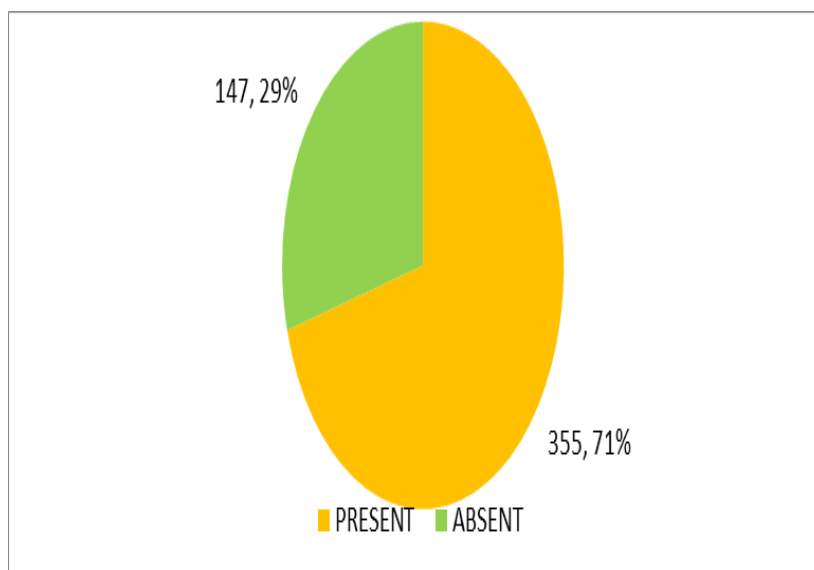


Fig 2; Presence of co-morbidities.

The important co-morbidities were hypertension, diabetes mellitus, chronic kidney disease, thyroid dysfunction (hypo or hyperthyroidism), and dyslipidemia. Among the co-morbidities, hypertension and DM were found to be in greater proportion that is 190 (53.52%) patients were hypertensive and 152 (52.67%) patients were having concomitant diabetes mellitus as depicted in fig 3. Diabetes and hypertension seems to be the major risk factors for the cardiovascular diseases. Other risk factors include smoking, hypercholesterolemia, Stress etc. Pekka Jousilathi *et. Al*^[7] conducted a prospective observational study, according to the study the determined cardiovascular risk factors found to be smoking, diabetes mellitus, hypertension, hypercholesterolemia and age.

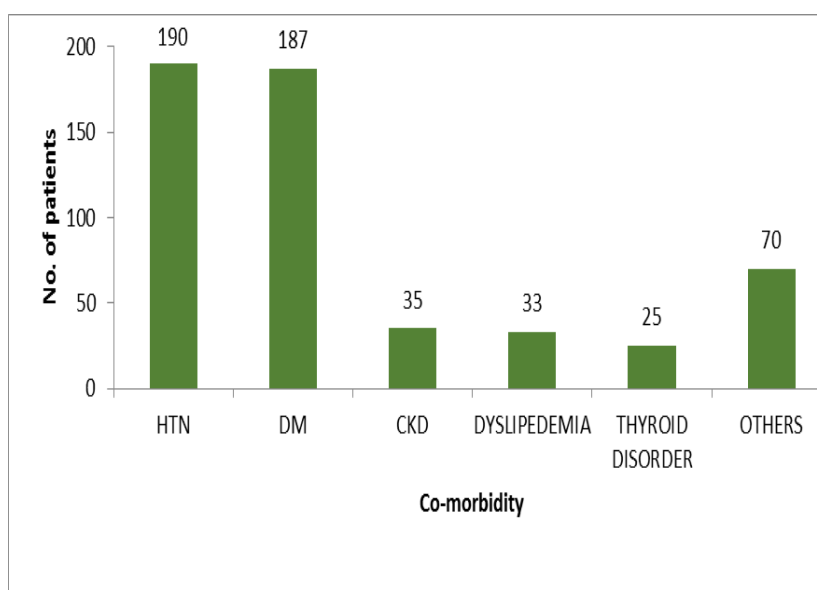


Fig 3: Pattern of co-morbidity.

5.2 PRIMARY DIAGNOSIS

The patients were admitted to CCU for various cardiac related diseases with varying symptoms. Major number of patients had coronary artery diseases contributing 78.08% of the total study population. 12.94%(65) were admitted due to arrhythmia which include bradycardia, atrial fibrillation, 4.98%(25) patients were admitted due to valvular heart disease, which include congenital valvular disease which need intervention, and 3.98%(20) patients were presented with congestive cardiac failure. Primary admission diagnosis of patients are shown in Fig:5.

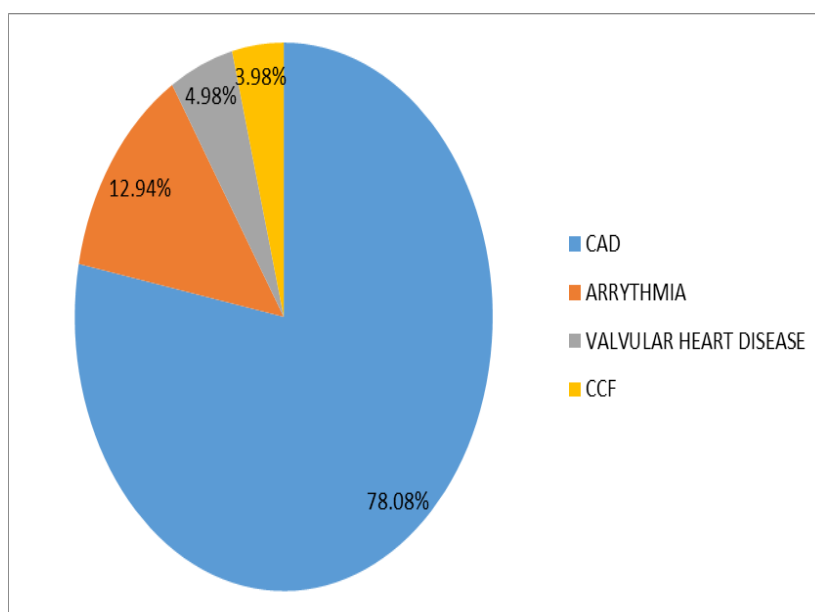


Fig 4: Primary diagnosis of the patient admitted in CCU.

5.3 Commonly Used Medications In Cardiology Department

The most frequent cardiovascular medication administered during CCU stay was Antiplatelet agents, out of which Aspirin (71.1%), followed by Clopidogrel(60.35%), statins (67.92%) (commonly used are Atorvastatin and Rosuvastatin), Anticoagulants include Heparin(47.41%) and warfarin(4.78%), Anti anginal include Nitrates(47.41%), nicorandil(19.32%), ranolazine (3.98%), Anti arrhythmic agents include Amiodarone (4.78%) and dobutamine(1.19%), Beta blockers (31.07%), diuretics (70.71%), ACE inhibitors(12.94%) and the contrast dye (used in diagnosis and interventional procedures in CAD patients).

5.4 Adverse Drug Reaction Reported

Out of 502 patients followed in CCU admissions, total 267 adverse drug reactions were recorded in 216 patients including both males and females,. Among these patients most of them had only one ADR and some had experienced 2 or 3 adverse drug reactions simultaneously.

Headache was the most frequent adverse drug reaction noted (20.59%), followed by gastritis (13.85%) and contrast nephropathy (13.48%). Nitrates and nikorandil contribute to the maximum ADR, nitroglycerine which was administered as infusion produced more number of headache, gastritis in patients were caused by drugs such as antiplatelet including aspirin and clopidogrel were as contrast dye induced nephropathy which is the 3rd leading cause (fig 6), Contrast-induced nephropathy (CIN) is defined as the impairment of renal function—measured as either a 25% increase in serum creatinine (SCr) from baseline or a 0.5 mg/dL (44 μ mol/L) increase in absolute SCr value—within 48-72 hours of intravenous contrast administration, Thadani U and Rodgers T^[8], study reveals that Headache is the most common side effect of nitrates; often dose-related and reported by up to 82% of patients in placebo-controlled trials. Nearly 10% of patients are unable to tolerate nitrates due to disabling headaches or dizziness. Aly Kasem^[9] conducted a study on contrast induced nephropathy in cardiac patients, The overall incidence of (CIN) was 12.5%.(CIN) increased with older age, particularly above the age of 60 years. There was an increase in the incidence of (CIN) in diabetic versus non diabetic patients (20.5% and 6.7%). There was a highly significant increase in incidence of CIN in patients with CHF versus those without CHF (100% and 71%).

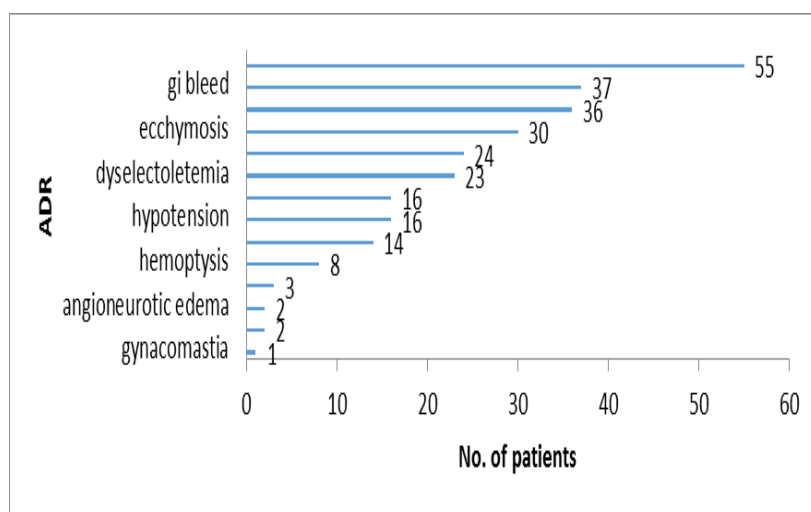


Fig 6: ADR and its pattern in patients.

Our study also reveals that there was a significant association between the drug administered and adverse drug reaction produced in seen case of drugs such as nikorandil nitrates with p value 0.005 and 0.002 respectively and contrast dye used for diagnostic purpose and intervention with p value of <0.001, shown in table 1.

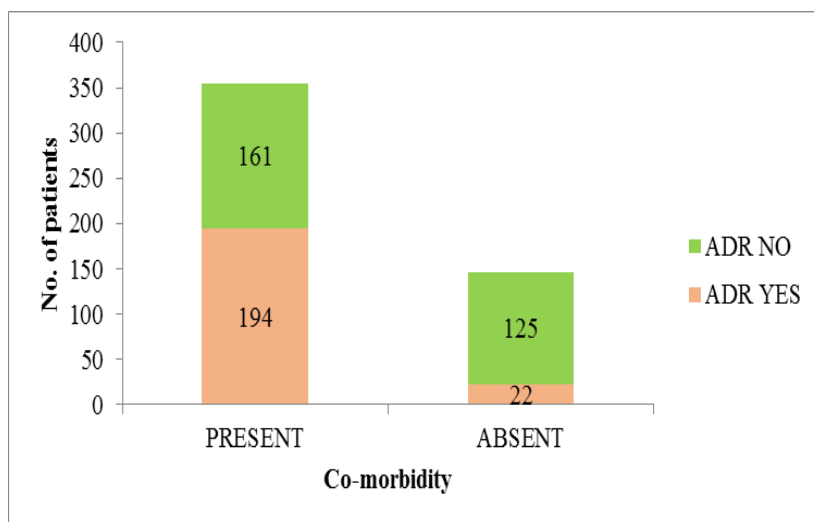
Table 1: Association between drug administered & ADR.

Adverse effects	Drug caused	Number of adverse effect caused by the drug	%	Number of adverse effect occurred not caused by the drug	%	P value
Headache	Nitrates	36	15	19	7	0.005*
	Nicorandil	19	20	36	9	0.002*
Nausea & vomiting	Dopamine	14	26	0	0	<0.001*
Hematuria	Heparin	16	7	0	0	<0.001*
Hemoptysis	Heparin	8	3	0	0	0.002*
Hematoma	Heparin	30	13	0	0	<0.001*
GI bleed	Aspirin	34	10	3	2	0.004*
	Clopidogrel	37	12	0	0	<0.001*
Dyselectrolytemia	Spironolactone	8	12	15	4	0.008*
	Diuretics	13	5	10	4	0.548
	Ace inhibitors	9	14	14	3.2	0.001*
Myalgia	Statins	3	1	0	0	0.555
Bradycardia, AV block	Beta blockers	24	17	0	0	<0.001*
Contrast nephropathy	Contrast dye	36	10	0	0	<0.001*
Angioneurotic edema	Ace inhibitors	2	3	0	0	0.017*
gynaecomastia	Spironolactone	1	1	0	0	0.137
hypotension	Nitrates	16	7	0	0	<0.001*
CHB	Amiodarone	2	8	0	0	<0.001*

*-significant

5.5 Association Between Co-Morbidity And Development of Adr

355 patient had co-morbidity in our study and 194 ADR were reported, thus a significant association exist between patients with concomitant disease in development of ADR when compared to patient without co-morbidities as given in fig.7. A review article published by Muaed Jamal Alomar^[10] says about co-morbid disease conditions one among the factors contributing to development of adverse drug reaction and other important factors are age, sex genetic variations etc.



Association significant ($p < 0.001$)

Fig.7 Association between co-morbidity and development of ADR.

5.6 Age-Groupwise Distribution of Adr

From our total study population adverse drug reactions were found to be in increased proportion in age group between 70-79 (65.09%), followed by 60-69 years(63.69%). Geriatric populations (above 60) are reported with greater ADR with Significance when compared to populations below 60. According to the study by C. R. Jayanthi et al^[11] adverse drug reactions are frequently encountered in the elderly (> 60 years) population and the important etiology quoted being , multifactorial and often interplay of many factors like polypharmacy, altered drug pharmacokinetic and pharmacodynamics responses, drug interactions that increase their risk for ADR, making them a vulnerable population. Age group wise distribution of ADR is given in figure 8.

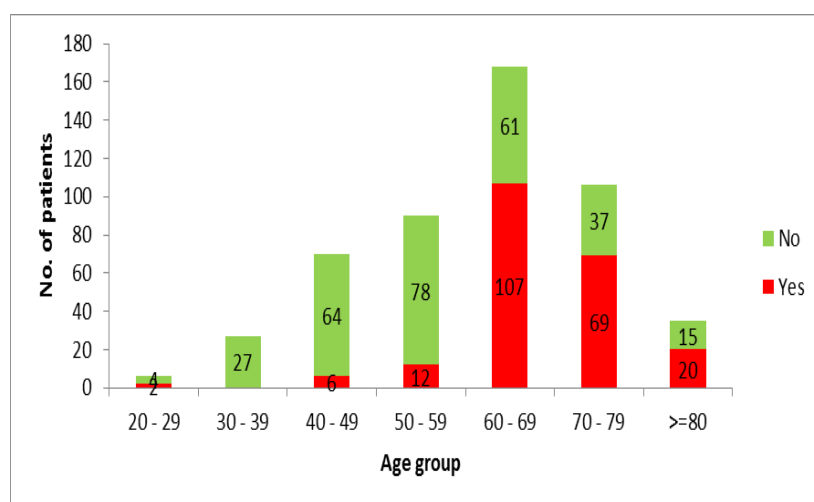


Fig 8: Age-group wise distribution of ADR.

5.7 Causality Assessment of Adr

Causality assessment of ADR was carried out using Naranjo's scale which categorizes the causality relationship into definite, probable, possible, unlikely (figure9). Assessment of ADRs using Naranjo's Causality Assessment scale revealed that definite comprises 28.4% (76) much more increased number had been observed in case of probable ie, 39.32% (105) and the possible category ie, 24.71% (66), and 7.49% (20) comes under the category of unlikely.

Corresponding to this data, Shaminder Kaur^[12] in his study revealed that majority of ADR were rated as probable (56.7%) of the reactions, whereas 43.3% were possible. Another study by Palanysamy S^[13]; revealed that most of the ADR comes under the category of Probable (90.62%), 4.17% were possible and 5.21% were definite.

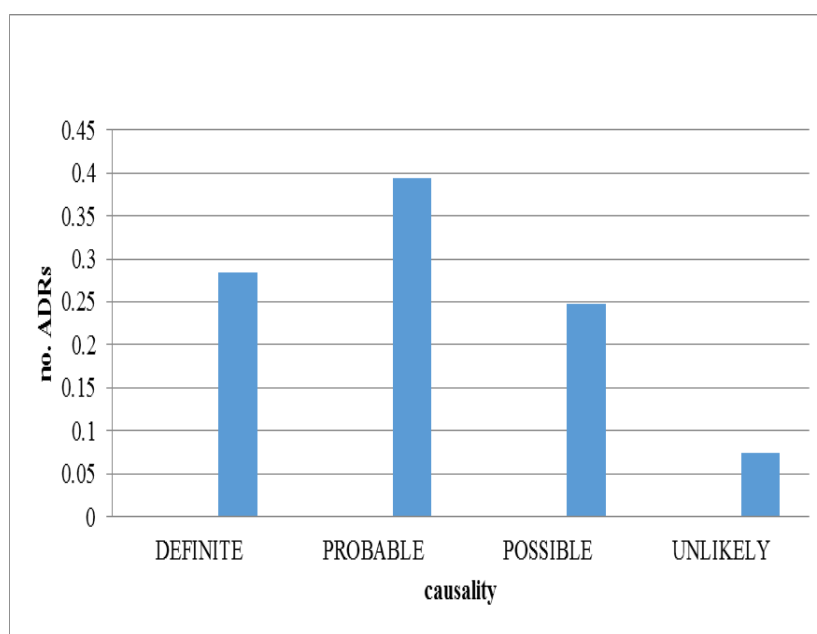


Fig 9: Naranjo's Causality Assessment of ADR.

CONCLUSION

Cardiovascular diseases remains leading cause of mortality and morbidity. Increased age, co-morbidity and smoking were found to be the risk factors for development of cardiovascular diseases. Cardiovascular medications have been cited as the most common class of drug associated with adverse drug reaction and medication error. The most frequently reported adverse reactions were headache, gastritis, hematuria, hemoptysis and ecchymosis. The most commonly implicated cardiovascular drugs causing these adverse reactions were nitrates, heparin and aspirin. Increased proportion of adverse drug reactions were found to be in

geriatrics when compared to that of other age group. Most patients with cardiovascular diseases were on multiple drugs therapy, predisposing them to development of adverse drug reactions, thus it is important to monitor and alter therapy as and when the situation arises. In this scenario, Pharmacovigilance play an important role in tertiary care hospitals were relatively high volume of adverse drug reactions were being detected. Clinical Pharmacists with their immense knowledge of medication use can play role in the detection, prevention, and management of adverse drug reactions.

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