ORIGINAL RESEARCH PAPER

Pharmaceutical Science

A STUDY ON DRUG UTILIZATION PATTERN OF CARDIOVASCULAR DRUGS IN INTENSIVE CARE UNIT OF DEPARTMENT OF MEDICINE IN A TERTIARY CARE TEACHING HOSPITAL

KEY WORDS: Cardiovascular diseases (CVDs), Adverse Drug Reactions(ADR), Drug-Drug Interactions(DDI).

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ABSTRACT

Introduction: Cardiovascular diseases (CVDs) are leading cause of death and disability in the world. Medical intensive care unit represents most critically ill patients. The interplay of multiple co-morbidities and polypharmacy in intensive care settings is a risk factor for ADRs, DDIs & Prescription errors, so the research was planned to study utilization pattern of cardiovascular drugs. **Objectives:** To study the drug utilization pattern of cardiovascular drugs & to evaluate the prescriptions according to WHO drug use indicators. To study the occurrence & management of adverse drug reactions and drug-drug interactions. **Method:** This is a prospective, observational study, conducted in patients having cardiovascular disease and admitted to medical intensive care unit. **Results:** Total 222 patients suffering from cardiovascular disease with or without co-morbidities participated in the study. Out of 222 patients 75% were associated with some risk factors for CVDs and 14% were with some non-cardiovascular co-morbidity. Most common diagnosis was acute coronary syndrome and most common cardiovascular drug prescribed was Aspirin. Polypharmacy was present in 96.3% of prescriptions. Drugs prescribed by generic names were 38% and those from the National List of Essential Medicines were 87.5%. DDI occurred in 9 patients. 8 drugs in 18 Patients were found to be responsible for ADR. **Conclusion:** The results of this study suggested: polypharmacy, overuse of injections and low prescribing habits by generic names. Though antiplatelet, hypolipidemic use was higher, these are an essential part of treatment of certain CVDs. To prevent DDIs and ADRs prescriber should be vigilant before prescribing drugs to the patients.

INTRODUCTION

Cardiovascular diseases (CVDs) are a group of disorders of the heart and Blood vessels which include coronary artery diseases, cerebrovascular diseases, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism etc.[1]. According to World Health Organization (WHO), CVDs are the leading non-communicable diseases and also leading cause of death and disability in the world. An estimated 17.7 million people died due to CVDs in 2015, representing 31% of the deaths worldwide. More people die annually from CVDs than from any other cause[2]

The major risk factors for a fatal cardiovascular disease are high blood cholesterol, high blood pressure, smoking, diabetes, poor diet and overweight[3] Many times cardiovascular disease patients have multiple co-morbid conditions, thus they are prescribed with multiple drugs. Drug interaction is defined as when the effect of one drug is changed by the presence of another drug, food or by some environmental chemical agent[4]. Drug interactions create a significant challenge to health care providers and may affect mortality, morbidity and a quality life of patients.

Studies of prescribing patterns and drug utilization are useful to identify the problems and provide feedback to prescribers so as to create awareness about rational use of drugs[5]. Importance of drug utilization studies in pharmaco-epidemiology has been increasing due to their close association to other areas like public health, pharmaco-vigilance, pharmacoeconomics and pharmacogenetics[6].

The Medical intensive care unit (MICU) represents the critically ill patients with multiple co-morbidities in whom judicious and appropriate pharmacotherapy can be lifesaving while irrational use of medications can be life threatening. Also drug therapies in critically ill patients are often complicated by the altered physiology and co-existence of multiple co-morbidities that warrants polypharmacy, which increased risk of drug–drug interactions, adverse drug reactions, medication errors and non-compliance with treatment[7]. It has been reported that patients with adverse drug events spend an average of 2.2 days longer in hospitals.[8]

In this context, the study was planned to get deeper knowledge of drug utilization, ADRs, drug-drug interactions which allows us to prescribe efficient treatment and to eliminate inappropriate drugs according to the patient's needs.

MATERIALS AND METHODS

Study design: This was a prospective, observational study.
Study Site: The Medical Intensive care unit of a tertiary care teaching hospital.
Study duration: The total duration of the study was one year which included screening, recruitment of participant and data analysis.
Study population: Patients having cardiovascular disease and admitted to the MICU were recruited.

Sample size calculation: Prevalence of most commonly utilized cardiovascular drug was 88.88%[9] Sample size was calculated using following formula[10] based on prevalence.

Inclusion criteria: Patients in age group of 18 to 80 years who have diagnosis of cardiovascular disease with or without co-morbidities, prescribed with cardiovascular drugs and are admitted for >24 hrs, in the intensive care unit of department of medicine.
Exclusion criteria: Patients discharged within 24 hours of their admission. Patients not willing to be a part of study or refusing informed consent form.

METHODOLOGY:

The study started after getting approval from an Institutional Ethics Committee (Reference number D-1019121-21 dated 15-10-2019). Permission of in-charge of Medicine department was taken to conduct the study in their Medical Intensive Care Unit (MICU). Cardiovascular disease patients admitted in MICU were assessed for eligibility as per the inclusion/ exclusion and provided written informed consent document.

Demographic details like registration number, age, sex and medication details were recorded in the Case Record Form. Participants were enquired regarding any cardiovascular risk factors and non-cardiovascular co-morbid conditions. Any DDI and adverse drug reaction related to the ongoing therapy with its management was noted.

ADR was documented in suspected adverse drug reaction reporting form and causality assessment was done using the Naranjo Scale. Reporting of ADR was done to PvPI.

Prescribing indicators evaluated as per WHO [11] were

1. Age-wise and gender wise distributions of patients
2. Risk factors for cardiovascular diseases and prevalence of non cardiovascular co-morbidities among patients was noted.
3. Diagnosis wise distribution of patients.
4. Distribution of the patients based on drug therapy prescribed from NLEM and hospital pharmacy.
5. The number of drugs per prescription was observed.
6. The number of drugs prescribed by generic / branded name.
7. Drugs categorized according to class they belong.
8. Distribution of antibiotics, fixed dose combinations was noted.
9. Drug-drug interactions and ADRs were noted.

Statistical Analysis: All responses were tabulated and analysed using Microsoft- Excel 2007 Software and SPSS software version 21.

Continuous data [age] was expressed as mean ± standard deviation. Categorical data [Gender] were expressed as a percentage.

OBSERVATIONS AND RESULTS:

Demographic profile of study participants:

A total of 222 patients suffering from cardiovascular disease with or without co-morbidities participated in the study. The mean age of patients was 54.12 ± 16.09 years (mean ± standard deviation). Minimum age of the patient recruited was 25 years and the maximum age was 80 years.

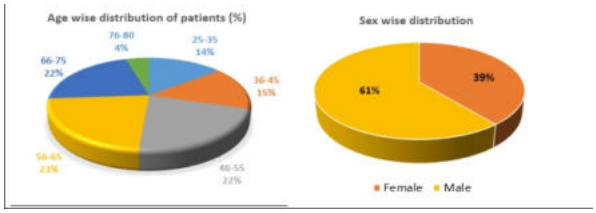

Fig.1: Pie diagram showing age wise & sex wise distribution of the patients

Table no.1: Types of risk factor & co-morbidity wise distribution of patients.

Sr. No.	Risk Factors	No. of patients	Co-morbidity	No. of patients
1	Diabetes mellitus	44 (18.80%)	Covid-19	9 (25.71%)
2	High Blood Pressure	65 (27.7%)	Anemia	2 (5.71%)
3	Family history of heart disease	23 (9.82%)	AKI	4 (11.42%)
4	Smoking	15 (6.41%)	Hypothyroidism	6 (17.14%)
5	Tobacco Chewing	23 (9.82%)	COPD	6 (17.14%)
6	Obesity	20 (8.54%)	Hyperhomocysteinemia, CKD,TB	1 (2.85%) each
7	High cholesterol	10 (4.27%)	Epilepsy	3 (8.57%)
8	More than one risk factors	34 (14.52%)	More than one co-morbidity	2 (5.71%)

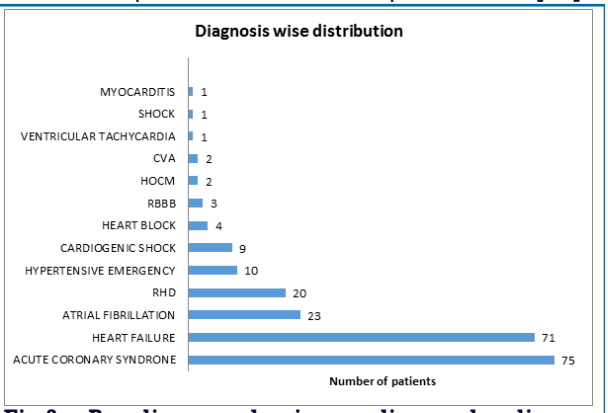

Fig.2: Bar diagram showing cardiovascular disease diagnosis wise distribution of patients.

Drug use indicators: A total of 1828 (cardiovascular and non-cardiovascular) drugs were prescribed in the 222 prescriptions that were analyzed.

Table no. 2: Results of WHO prescribing indicators.

Sr. no.	Prescribing indicator	Results
1	Total number of prescriptions	222
2	Total number of drugs	1828
3	Average no of drugs per prescription	1828/222(8.23)
4	% of drugs prescribed from hospital pharmacy	1627/1828 (89%)
5	% of prescriptions with polypharmacy ≥5 drugs	214/222 (96.3%)
6	% of drugs prescribed from NLEM	1600/1828 (87.5%)
7	% of drugs prescribed by generic name	695/1828 (38%)
8	% of prescriptions with an antimicrobial agent	89/222 (40%)
9	% of prescription with an injection	210/222 (94.5%)

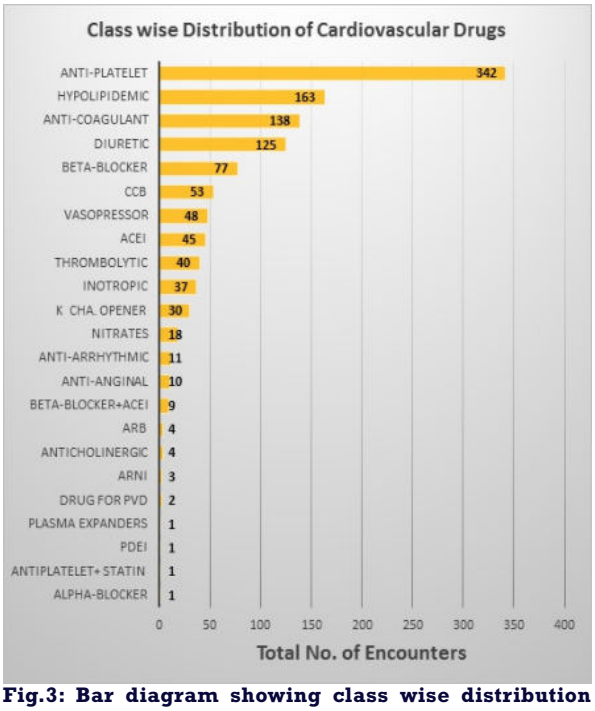

Fig.3: Bar diagram showing class wise distribution cardiovascular drugs (n=1163).

Total 1163 cardiovascular drugs were prescribed to 222

patients. Antiplatelet drugs were prescribed more commonly (342/1163, 29.40%) followed by hypolipidemic drugs 163/1163(14.01%). Least commonly prescribed drugs were alpha-blockers, phosphodiesterase inhibitors, plasma expanders etc.

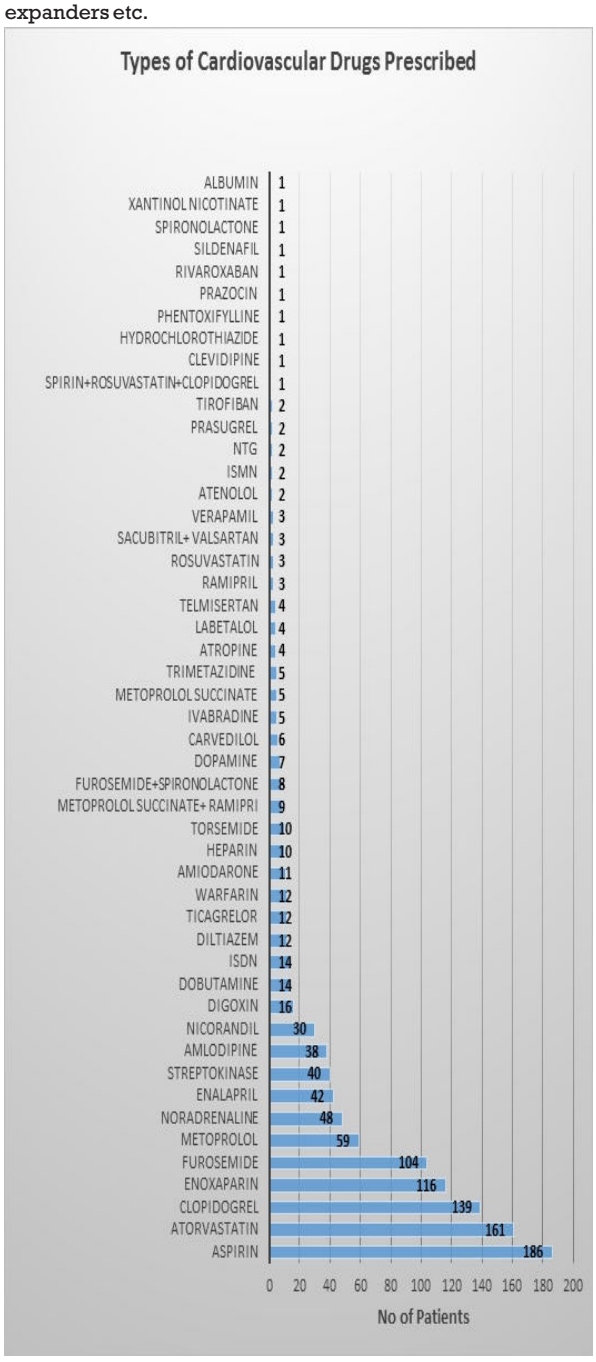

Fig.4: Types of Cardiovascular drugs prescribed (n=1163).

Table no.3: Showing FDCs prescribed to patients.

Sr. No.	Fixed dose combination prescribed	Number of patients
1	Aspirin+Rosuvastatin+Clopidogrel	1
2	Nicotinamide+Cynocobalamin+Folic acid	1
3	Sacubitril+ Valsartan	1
4	Etophylline+Theophylline	2
5	Metoprolol succinate+ Ramipril	2
6	Teneligliptin+Metformin	3
7	Piperacillin - Tazobactam	5
8	Metoprolol+Ramipril	6
9	Furosemide+Spironolactone	8
10	Amoxicillin & Clavulanic acid	28
11	Liquid Paraffin- Milk of magnesia	47
	Total	104

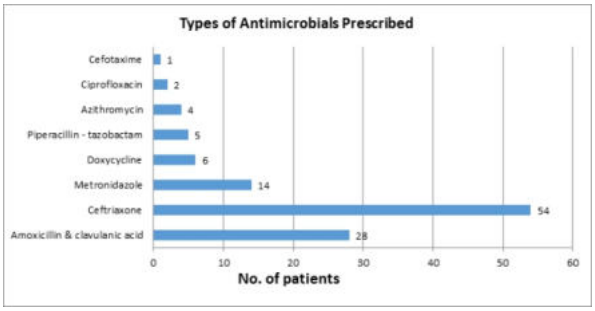

Fig.5: Bar diagram showing types of antimicrobials prescribed (n=114)

Table no. 4: Drug-Drug Interactions and their management

Sr. No	Drug-Drug Interaction (DDI)	Drugs Causing DDI	Management	No. of patients
1	Nasal bleeding	Warfarin, Streptokinase	Symptomatic treatment, Dose reduced	1
2	Bradycardia	Digoxin, Metoprolol, Ramipril, Ivabradine	Symptomatic treatment, Drug stopped	1
3	GI bleeding	Warfarin, Aspirin	Drug stopped, symptomatic treatment	1
4	Bleeding piles	Warfarin, Ceftriaxone	Dose reduced, Symptomatic treatment	1
5	Nasal Bleeding	Enoxaparin, Warfarin Aspirin, Clopidogrel.	Dose reduced, Symptomatic treatment	1
6	Bleeding piles	Streptokinase, Enoxaparin, Aspirin, Clopidogrel	Symptomatic treatment Dose reduced	4

Table no.5: Drugs causing ADRs, Causality Assessments and Management

Sr. No.	Drug Prescribed to (no. of pts)	ADR type	No. Of patients With ADR	Management	Causality assessment
1	Metoprolol (59)	Weakness	1	Symptomatic treatment, Drug continued	Possible
2	Warfarin (12)	GI bleed	1	symptomatic treatment, Drug stopped	Possible
		Bleeding piles	1	Symptomatic treatment, Dose reduced	Possible
		Nasal bleeding	1	Symptomatic treatment, Dose reduced	Possible
3	Streptokinase (40)	Nasal bleeding	1	Symptomatic treatment, Drug continued	Possible

		Bleeding piles	4	Symptomatic treatment Drug continued	Possible
4	Digoxin (16)	Nausea	1	Symptomatic treatment Drug continued	Possible
		Bradycardia	1	symptomatic treatment, Drug stopped	Possible
5	Aspirin (186)	Gastritis	3	Symptomatic treatment Drug continued	Possible
6	Nicorandil (30)	Headache	2	Symptomatic treatment Drug continued	Possible
7	Atorvastatin (161)	Myalgia	1	Symptomatic treatment Drug continued	Possible
8	Furosemide (104)	Hypotension	1	Symptomatic treatment Drug continued	Possible

DISCUSSION

Management of patients with the major cardiac events is challenging and it demands utmost care considering the life threatening condition and the immediate measures that need to be taken, leaves no room for any error. Physician has to consider risks and benefits of the drug therapy given, prior to their administration.

Demographic profile of study participants

The mean age of participants was 54.12 ± 16.09 years (mean ± standard deviation). The similar finding was observed by Madhuri D Kulkarni et al[12]. wherein mean age was 55.68 +13.54 years, and Nooreen, et al[1].where most of the patients were in the age group of 51 to 60 years.

Majority of the patients were male (61%) and only (39%) were female. Similar findings were observed in the study done by Madhuri D Kulkarni et al[12]. This shows that cardiovascular diseases are more prevalent in males as compared to females. These results are in adherence with standard literature, which states that estrogen increases high-density lipoproteins (HDL) and lowers low-density lipoproteins (LDL), whereas the androgens have the opposite effect. Estrogen in addition has a direct vasodilator effect. Thus endogenous estrogens exert a cardio protective influence.[13]

High blood pressure was the most prevalent risk factors for cardiovascular diseases followed by diabetes mellitus, these finding were similar to the study done by Nooreen, et al.[1]

In the present study Covid-19 infection was the most common co-morbidity, maybe because the study was conducted during the period of Covid-19 pandemic.

It was seen that majority of the patients (33.78%) admitted to MICU were of Acute coronary syndrome followed by Heart failure (31.98%). Acute coronary syndrome includes unstable angina (UA), Non–ST-segment elevated myocardial infarction (NSTEMI), ST- segment elevated MI (STEMI). Similar findings were observed in the study done by Madhuri D Kulkarni et al[12] and Pendhari S R et al[2]. Where MI was the most common diagnosis in the patients admitted in ICU.

WHO Prescribing Indicators

In the present study total 222 prescriptions containing total 1828 drugs were analyzed.

Average no of drugs per prescription was found to be 8.23. Majority of the patients received 5 cardiovascular and 2 non-cardiovascular drugs per patients. These findings indicate presence of polypharmacy. Similar studies done in India shows average 10.9 drugs per prescription (Madhuri D Kulkarni et al[12]), 7.8±2.2 drugs per prescription (Nagabushan H et al[14]). This suggests that polypharmacy is common in cardiac intensive care unit and could be because of the fact that cardiovascular diseases are a combination of risk factors resulting in clinical events that increase morbidity and mortality and Intensive care unit (ICU) care for the most seriously ill patients. Therefore, higher numbers of drugs are employed to save these patients, of which some are therapeutic, whereas others are prophylactic in nature.

In the present study the most commonly prescribed class of cardiovascular drug was antiplatelet agents (29.40%) followed by hypolipidemic agents (14.01%). Third most commonly prescribed class was Anticoagulants.
This result was as expected because most common diagnosis were ACS and Heart failure and the findings correlate with the standard guidelines mentioned for use of drugs in cardiovascular emergencies. These results were found to be similar to various studies conducted by Madhuri D Kulkarni et al[12] and Nagabushan et al[14].

In this study, majority of the drugs (62%) were prescribed by their branded names and only (38%) drugs were prescribed by their generic names. The findings of the study done by Biswal et al.[15]wasalso coherent to this study.

89% of the drugs were prescribed from hospital pharmacy which indicates maximum drugs were available in the tertiary care hospital where the study was conducted.

According to WHO 100% drugs should be prescribed from NLEM. In the present study 87.5 % of the prescribed drugs were mentioned in National list of Essential medicine -2021 (NLEM) and 12.5% were not mentioned in NLEM. This is quite expected, considering the severity of illness of the patients in the ICU which may warrants use of some of the drugs not mentioned in NLEM.

As per WHO antimicrobial use should be less than 30%. In study use of antimicrobial agent was 40%, this may be because patients treated in ICUs are 5 to 10 times more prone to develop nosocomial infections.[16] and ACS patient may need surgical intervention which warrants use of antimicrobial prophylaxis.

Drug-Drug Interactions

Approximately 3–26% of all adverse drug reactions that require hospital admission are caused by drug–drug interactions.[17] DDI constitute a significant fraction of preventable ADRs.

Results of the current study revealed that among the 222 patients 4 types of DDIs occurred in 9 patients. Out of 4 types 3 were minor bleeding related DDIs and one major DDI occurred. Most common DDI was bleeding piles (5 patients) followed by nasal bleeding (2 patients) and gastrointestinal bleed (1patient).

One major DDI occurred in 1 patient due to concurrent use of Digoxin, Metoprolol, Ivabradine and Ramipril resulting in bradycardia for which symptomatic treatment was given and drug was stopped. Streptokinase–Enoxaparin-Aspirin-Clopidogrel use was most commonly associated with minor bleeding piles, Warfarin-Aspirin, Warfarin-Streptokinase, Warfarin-Ceftriaxone was associated with minor bleeding related DDIs.

Majority of DDIs found in the study could be because of pharmacodynamic synergism. Whereas DDI occurred between Warfarin – Ceftriaxone could be because of inhibition of gut microbiota by Ceftriaxone resulting increased the pharmacological action of Warfarin.

This highlights the importance of careful selection of patients, clinical and laboratory monitoring and dose adjustment based on it.

Adverse Drug Reactions (ADRs)

In our study, 18 participants experienced some side effects with the prescribed medication.

Among thrombolytics, Streptokinase is the most commonly used and studied due to its availability and lower cost in comparison to other agents in this pharmacologic class. Many studies have reported frequent causes of ADRs in the use of streptokinase, among thrombolytic drugs in hospitals.[18] Literature review done by Mansouri et al[19] noted after allergic reactions second most prevalent ADR associated with Streptokinase was bleeding.

Warfarin was given to 12 patients and out of which 3 patients experienced bleeding (25%) but since these patients were also receiving antiplatelet drugs these ADRs could be because of the DDIs.

Limitations

Since the study was done in a single tertiary care teaching hospital, extrapolation of results to the general population would be better if the study conducted in more number of patients and multicenteric set ups.

CONCLUSION

The present study concluded that most common cardiovascular emergency in MICU was acute coronary syndrome and most commonly prescribed drugs were Antiplatelet agents. Majority of the drugs prescribed in the present study were from the Hospital pharmacy and National List of Essential Medicines (NLEM). It is advisable to keep the number of drugs per prescription as low as possible to avoid polypharmacy. Prescribing of drugs by brand names was higher in study hence there is need to encourage the physicians to avoid economical burden on patients.

Finally our study recommends each hospital to compare their drug usage with standard treatment guidelines or frame the guidelines if not existent. All these will help to bring better clinical outcomes.

Conflict of Interest:

There is no conflict of interest.

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