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# Pattern And Incidence Of Adverse Drug Reactions Observed Due To Cardiovascular Drugs

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**ABSTRACT**

**Background:** Cardiovascular diseases (CVD) are one of the leading causes of non-communicable disease related deaths globally. Patients with cardiovascular diseases are often prescribed multiple drugs and have higher risk for developing more adverse drug reactions. The present study aimed to monitor the incidence and pattern of adverse drug reactions (ADRs) in the cardiac care unit.

**Methods**: This was a prospective surveillance study that included patients of either gender who were hospitalized and prescribed at least one cardiovascular drug. The study was conducted with the permission of the Institutional Ethics Committee. Patients visiting the medicine outpatient department, cardiac clinic, medical ward, and emergency departments over a period of 24 months were recruited. ADRs were recorded on the prescribed form. A causality assessment was done using the WHO probability scale.

**Results:** A total of 325 patients were enrolled in the present study. Male preponderance was observed over female. Patients with age 51- 60 years experienced 83 ADRs. The most common drug class implicated in ADRs was observed due to Sacubitril/valsartan.

**Conclusion:** Intensive approach towards monitoring and reporting of ADRs could help healthcare professionals in minimizing preventable ADRs. There is a need for conducting such studies in more and more patients to see the pattern of ADRs in cardiac patients. More information will help in reducing the ADR occurrence and making drug use more rational and safe for patients.

**KEYWORDS** Adverse drug reaction, Coronary artery disease, Cardiovascular, Pharmacovigilance program of India

## INTRODUCTION

**Cardiovascular diseases** (CVDs) are considered multifactorial conditions that especially affect the essential components of the circulatory system of the human body such as the heart, blood vessels, and blood itself. CVDs can be congenital or acquired throughout people's lifespan. Atherosclerosis, rheumatic heart disease, and cardiovascular inflammation are the main and more prevalent cardiovascular acquired problems.[1]Cardiovascular disease is the leading cause of death worldwide and in all regions except Africa. In 2008, 30% of all global death was attributed to cardiovascular diseases.

Death caused by cardiovascular diseases are also higher in low- and middle-income countries as over 80% of all global deaths caused by cardiovascular diseases occurred in those countries. It is also estimated that by 2030, over 23 million people will die from cardiovascular diseases each year. CVD is a broad term for a range of diseases affecting the heart and blood vessels. CVD affects not only high-income but also low and middle-income countries. It is estimated that in 2030 in the world, the leading causes of death will be ischemic heart disease and cerebrovascular disease, both components of CVD.[2-3] Hypertension and cardiovascular diseases (CVD) remain one of the leading causes of mortality and morbidity. 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. Since the data on ADRs in cardiovascular diseases in India is limited, the present study aims to see the incidence and pattern of ADRs in cardiovascular diseases at the tertiary hospital level. The number of risk factors tends to increase with the consumption of various medicines.

World Health Organization defines an adverse drug reaction (ADR) as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or modification of physiological function"[4]. Pharmacovigilance is particularly concerned with ADRs, which are drug responses that are noxious and unintended, and which occur at doses normally used for the prophylaxis, diagnosis or therapy of disease, or the modification of physiological function. Continuous monitoring of drug effects, side effects, contraindications, and outright harmful effects that could result in a high degree of morbidity, and in some cases, even mortality, is essential to maximize benefits and minimize risks. The increased complexity of drug therapy requires strict vigilance by health care professionals. Hence, it is of utmost importance for healthcare professionals to safeguard their patients from preventable ADRs. Pharmacovigilance plays a key role in the healthcare system through assessment, monitoring, and discovery of interactions amongst drugs and their effects on human. Improvement of patient care and safety concerning the use of medicines with medical and paramedical interventions remains to be an important parameter. The main objectives of pharmacovigilance involve exhibiting the efficacy of drugs by monitoring their adverse effect profile for many years from the lab to the pharmacy; tracking any drastic effects of drugs improving public health and safety in relation to the use of medicines; encouraging the safe, rational and cost-effective use of drugs; promoting understanding, education and clinical training in pharmacovigilance; and effective communication to the generic public. Besides, providing information to consumers, practitioners, and regulators on the effective use of drugs along with designing programs and procedures for collecting and analyzing reports from patients and clinicians conclude to the objectives of pharmacovigilance studies.

**METHODS**

The present study was initiated with the enrolment of patients based on inclusion and exclusion criteria. Patients were monitored from the day of admission till the day of discharge for the occurrence of ADRs due to cardiovascular drugs by attending clinical meetings, ward rounds, reviewing patients' medical records and electronic medical records. If ADR was detected, the case details were documented in the patient profile form and ADR related details in the ADR monitoring and documentation form designed for the study purpose. The disease history and demographic details of all the patients were taken and entered individually in a case report form by the attending researcher.

Adverse drug reactions were evaluated for various clinical parameters such as demographics, individual drug implicated, drug class implicated, type of ADRs, risk factors, etc.

**Number of Patients:**

The present study was carried out to monitor ADRs in 325 patients with cardiovascular diseases using antihypertensives drugs for stable coronary artery disease. Adverse Drug Reaction Monitoring was carried out at Institute

For some newly approved cardiovascular drugs the pharmacovigilance study has been carried out as; Ticagrelor, Amlodipine, Telmisartan, Apixaban, Sacubitril/valsartan, Midodrine , Azilsartan, Efonidipine, Macitentan and Riociguat.

**Study criteria**:

**Inclusion criteria**: Patients with ADR, of any age of either sex, have reported to the clinical pharmacist from the outpatient department in India.
**Exclusion criteria**: The ADR that due to Medication errors, overprescribing, overdosing/excess consumption, drug-drug interaction, drug-food interaction, drug interaction with the use of the alternative system of medicine

**Data collection**:

Data on the reported ADRs were evaluated to understand the pattern of the ADRs with respect to patient demographic disease, nature of the reactions, characteristics of the drugs involved, and outcome of the reactions. The collected data was analyzed using descriptive statistics, showing numbers and percentages respectively.

The data collected by the informants regarding the use of their data on adverse drug reaction for research purpose and their assurance that their identity shall not reveal at any stage without their due concurrence. The informants were also assuring their identities too shall not be disclosed while making a pharmacovigilance reporting in the research work as well as data basis. This is standard practice under the pharmacovigilance programme of India.

**Analysis of ADRs:**

The severity of adverse drug reactions was assessed using the WHO-UMC scale (Edwards, 2012). According to the WHO-UMC scale (Edwards, 2012) causality assessment scale, ADRs were classified into certain, probable, possible, unlikely, unclassified, and unclassifiable.

**Statistical analysis**

Binomial logistic regression analysis was used to correlate whether age and gender is a cofactor for ADR. Statistical significance was determined at a 95% level of confidence. The data were analyzed using software STATA version 12.1.

**RESULTS**

cardiovascular diseases are one of the major concerns and cardiac drugs can cause a multitude of ADRs, development of a robust network for detection and reporting of ADRs is of utmost importance. The study involves the spontaneous reporting of the ADRs in patients (causality and ward) and

outpatients with hypertension and coronary artery diseases visiting the Hospital. In this study, 325 patients with Cardiovascular diseases were enrolled. Out of the total 223 patients, 204 were males and 121 were females. The highest number (25.53%) of ADRs encountered between 51 to 60 year age group and lowest (0.00%) in 91 to 100 and 1-10 year age group.

**Drug class implicated in ADR**

Sacubitril/valsartan has shown the highest number of adverse drug reaction reported 15.69% followed by Amlodipine 15.07%, Ticagrelor 12.61%, Riociguat 10.46%, Azilsartan 9.84%, Apixaban 8.61%, Efonidipine 8%, Telmisartan 7.07%, Midodrine 7.07%, and Macitentan 5.53% as shown in table no.1

**Table No. 1- Distribution of ADRs by the class of Suspected Drugs**

| S. No. | Class of suspected drugs | No. of Patients Reports | Percentage |
|---|---|---|---|
| 1. | Ticagrelor | 41 | 12.61% |
| 2 | Amlodipine | 49 | 15.07% |
| 3. | Telmisartan | 23 | 7.07% |
| 4. | Apixaban | 28 | 8.61% |
| 5. | Sacubitril/valsartan | 51 | 15.69% |
| 6. | Midodrine | 23 | 7.07% |
| 7. | Azilsartan | 32 | 9.84% |
| 8. | Efonidipine | 26 | 8% |
| 9. | Macitentan | 18 | 5.53% |
| 10. | Riociguat | 34 | 10.46% |

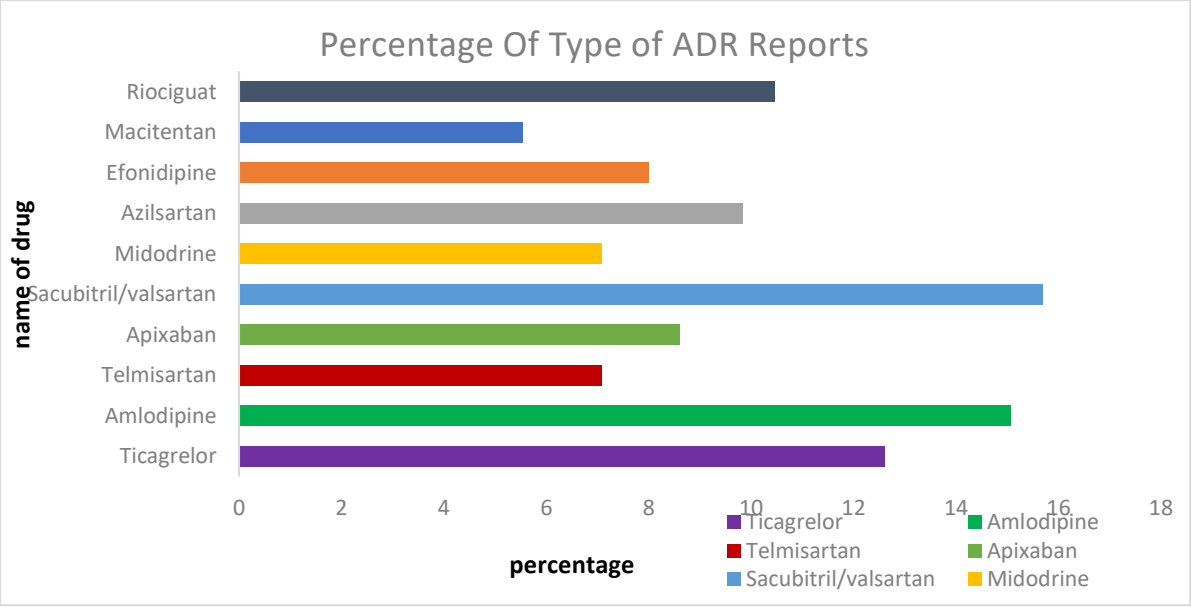


**Fig. No. 1: Data clearly explains the ADR reported by class of suspected drugs**

**Suspected adverse drug reaction**

Bleeding, Bradyarrhythmia's and Dyspnoea, Dizziness, Nausea, Headache, Pain, and Edema are the adverse drug reaction reported by the patients in the case of Ticagrelor. Amlodipine has shown ADR like flushing, headache, and dizziness. The adverse drug reactions reported for Telmisartan are Headache, Cough, Dizziness, Fatigue, Insomnia, and body ache. The adverse drug reported for Apixaban is Headache, dizziness, and arterial fibrillation.

The ADR shown by Sacubitril/valsartan is Hypotension, Hyperkalemia, Cough, Dizziness, and Renal failure. Midodrine is a vasopressor, anti-hypotensive agent. The adverse drug reactions reported are Dyspnoea, Dizziness, Headache, Pruritis, Hypertension, and Urinary tract disorders. Azilsartan shows adverse drug reactions like Hypotension, Diarrhoea, Fatigue, Muscle pain, and Dizziness. Efonidipine is a dihydropyridine calcium channel blocker. The adverse drug reactions reported in our study are Nausea, Dizziness, Headache, and pruritis. Macitentan is an endothelin receptor antagonist approved for the treatment of pulmonary arterial hypertension. The adverse drug reaction reported in our study are Headache, Dizziness, and Nausea and the adverse drug reaction reported for Riociguat are Headache, Dizziness, and Nausea.

**Table No. 2- ADRs reported for the Class of Suspected Drugs**

| S. No. | Class of suspected drugs | ADR reported |
|---|---|---|
| 1. | Ticagrelor | Bleeding, Bradyarrhythmia's and Dyspnoea, Dizziness, Nausea, Headache, Pain, and Edema |
| 2 | Amlodipine | Dizziness, Swelling, Nausea, Fatigue, and Edema |
| 3. | Telmisartan | Headache, Cough, Dizziness, Fatigue, Insomnia, and body ache. |
| 4. | Apixaban | Headache, Dizziness, and Arterial fibrillation. |
| 5. | Sacubitril/valsartan | Hypotension, Hyperkalemia, Cough, Dizziness, and Renal failure. |
| 6. | Midodrine | Dyspnoea, Dizziness, Headache, Pruritis, Hypertension, and Urinary tract disorders. |
| 7. | Azilsartan | Hypotension, Diarrhoea, Fatigue, Muscle pain, and Dizziness. |
| 8. | Efonidipine | Nausea, Dizziness, Headache, and pruritis. |
| 9. | Macitentan | Headache, Dizziness, and Nausea. |
| 10. | Riociguat | Headache, Dyspepsia/gastritis, Dizziness, Nausea, Diarrhoea, Hypotension, Vomiting, Anaemia, and Constipation. |

**Causality assessment**

Headache, Nausea, and dizziness were the most frequent ADRs reported in cardiac patients. Telmisartan, Apixaban, Riociguat, Macitentan, Efonidipine, and Ticagrelor were the most frequently

suspected drugs causing the headache. Out of the total 325 ADRs 39, ADRs were categorized as probable and, 53 as possible as shown in fig no. 2.

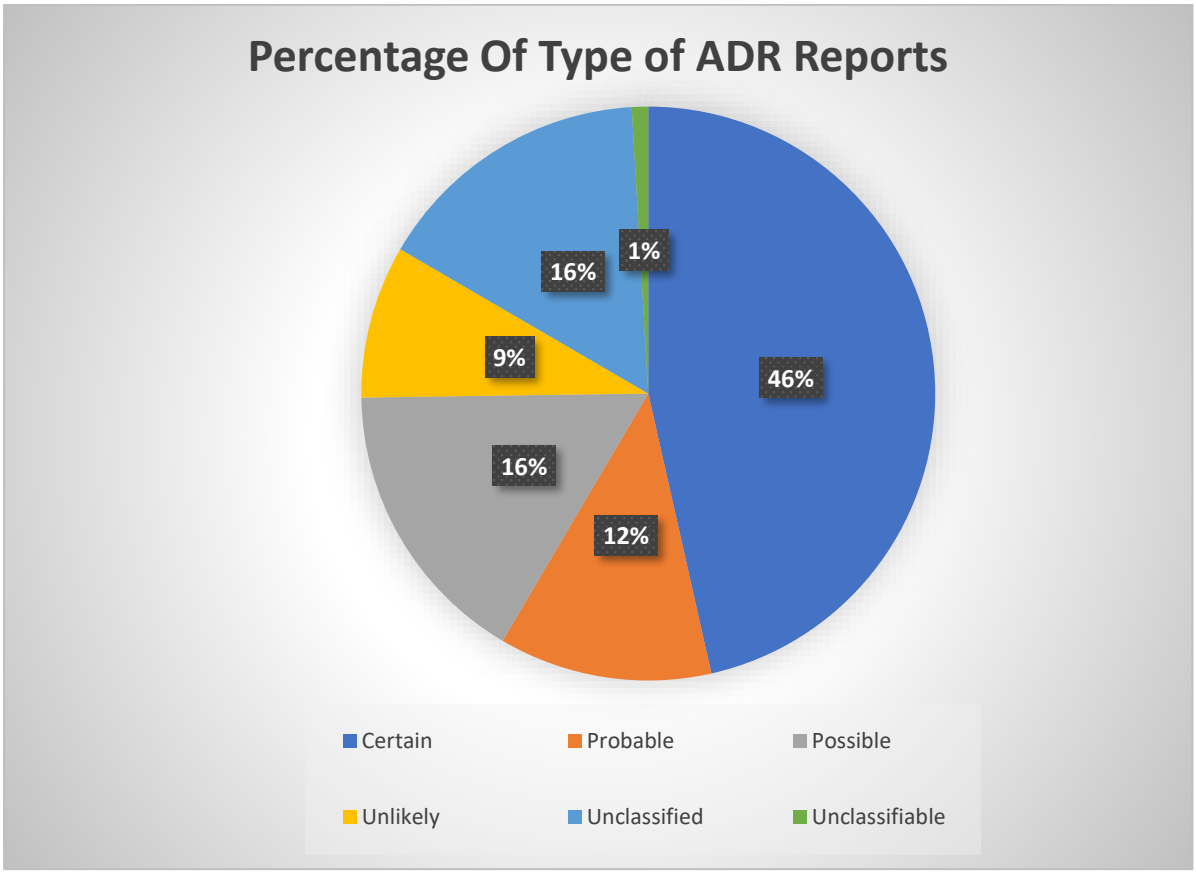


**Fig. No. 2: Data clearly explains the WHO-UMC causality assessment parameters**

**Management and outcome**

During management In 26.15% drug is withdrawn, 6.76% drug is reduced, 12% does not change, 8.61% not applicable, and in 46.46% untraced as shown in table no. 4.10

**Table No. 3- Distribution of ADRs by management and outcome**

| S. No. | Action taken | No. of Patients Reports | Percentage |
|---|---|---|---|
| 1. | Drug withdraw | 85 | 26.15% |
| 2 | Dose reduced | 22 | 6.76% |
| 3. | Does not changed | 39 | 12% |
| 4. | Not applicable | 28 | 8.61% |
| 5. | Untraced | 151 | 46.46% |

**Management of the Reaction**

In 26.46% (86) cases adverse drug reaction is cured by Self-care, in 37.53% (121) by Medical Treatment, in 27.38% (89) cases no treatment is taken.

**Severity assessment**

On severity assessment, it was found that in 47.07% cases adverse drug reaction is mild, 45.84% moderate and 7.07% is severe as shown in table no. 4

**Table No. 4- Distribution of ADRs by Severity**

| S. No. | Severity | No. of Patients Reports | Percentage |
|---|---|---|---|
| 1. | Mild | 153 | 47.07% |
| 2 | Moderate | 149 | 45.84% |
| 3. | Severe | 23 | 7.07% |

**Preventability assessment**

On evaluation, it was observed that 32.69% of cases are definitely preventable, 33.23% are probably preventable, and 43.38%are non-preventable as shown in table no. 5

**Table No. 5-Distribution of ADRs by Preventability**

| S. No. | Preventability | No. of Patients Reports | Percentage |
|---|---|---|---|
| 1. | Definitely Preventable | 103 | 32.69% |
| 2 | Probably preventable | 108 | 33.23% |
| 3. | Not preventable | 141 | 43.38% |

**DISCUSSION**

To estimate the incidence of ADRs, the present study was conducted. A total of 325 patients who were on cardiovascular drugs were enrolled in the present study. Gender distribution of patients who had encountered ADRs during the study period was more in males (62.76%) and low in females (37.23%). The causality assessment revealed 16.30% were possible, 12.0% probable, 8.61% unlikely, 46.46% certain, 15.69% unclassified and 0.92% unclassifiable type of ADRs reports. Severity assessment of ADRs showed a high incidence of mild reactions in the present study. According to preventability out of 325 ADRs, most of the ADRs were probably preventable, followed by definitely preventable. In the case of Sacubitril/valsartan; most of the ADRs were reported and headache, nausea, and dizziness were observed in most of the cases. The present study demonstrated a high incidence of ADRs among patients on cardiovascular drugs. The design and duration of the study were restricted to the generalization of the findings. However, an intensive approach towards monitoring and reporting of ADRs could help healthcare professionals in minimizing preventable ADRs. The present study was done to evaluate the pattern of ADRs among patients who received cardiovascular drugs. Amlodipine has shown some other adverse effects like headache, dizziness, backache, muscle pain, hypotension, chest pain were reported in other studies. Major adverse effects of CCBs are Dizziness, light-headedness, swelling ankles/feet, or flushing may occur[5]. Apart from that Peripheral edema, nausea, palpitation, dizziness, headache, and pruritus are also reported in other studies.[6] Majority of patients taking amlodipine developed more than one adverse drug reaction which may be dose-related. Fatigue and insomnia come under the possible category, dizziness and palpitation come under probable category[7-10] Some common adverse drug reactions reported for Telmisartan in other studies

are headache, upper respiratory tract infection, dizziness, pain, back pain, fatigue, etc. Some other adverse reactions reported are Insomnia, Impotence, Migraine, Gas, Constipation, Dry mouth, Depression, Middle ear infection, Asthma, Vision problems, and Serious breakdown of muscle[11]. A case reported of a woman who is 60-year-old followed for permanent atrial fibrillation who was prescribed apixaban. She rapidly developed worsening neurologic symptoms of imbalance and non-vertiginous dizziness preventing her from walking, headache, diplopia, and confusion/disorientation[12]. Apixaban leads to one or more manifestations of heightened bleeding risk. Reports have also been published documenting rare idiosyncratic drug-induced liver injury, which is usually but not always reversible with drug discontinuation. However, an extensive search of the peer-reviewed literature failed to identify any neurologic adverse events due to apixaban, save those associated with hemorrhage or hematoma formation. The FDA's Adverse Reporting System Public Dashboard of reports received from 2011 to January 2018 listed 19 reports of diplopia, 163 of confusion, 27 of disorientation, 894 of dizziness, 718 of headache, and 86 of balance disorders[13,14]. In another study, a 78-year-old female patient who was being followed for hypertension and atrial fibrillation was referred due to a pruritic skin eruption. Her physical examination revealed thick, scaly, hyperkeratotic, erythematous, and desquamative plaques of various sizes on the palmoplantar areas, suggestive of a psoriasiform eruption.[14] Apixaban also leads to increased risk of haemorrhage or thromboembolic events due to a drug-drug interaction[15]. Hypo-tension and orthostatic hypotension were the most common AEs leading to discontinuation of therapy[16].

Cardiovascular diseases are multifactorial and several modifiable and non-modifiable risk factors and unhealthy lifestyles are involved; however, these risks and behaviors cannot completely explain the incidence of cardiovascular events. Healthcare professionals are the main reports of the ADRs; however, there are high percentages of under-reporting reported globally. It is the major challenge for today. Despite those limitations, the spontaneous reporting system remains the most widely used method to report ADRs and can generate a signal of rare and very rare types of ADRs. The study relates to the pattern and incidence of ADRs in the cardiac clinic of a tertiary care hospital. Pharmacovigilance plays a role in the scientific understanding of the safety profile of drugs and the issuance of advisory to the regulatory authorities. Detecting signals is one of the important aspects of pharmacovigilance. The spontaneous reporting system of ADRs is one of the commonest methods of detecting a signal in pharmacovigilance. According to the WHO, pharmacovigilance signal is "reported information on a possible causal association between an adverse event and a drug, the relationship being unclear or incompletely documented previously."

**CONCLUSIONS**

Adverse drug reactions to cardiovascular drugs are a matter of importance as they are used as the first line of treatment for cardiac diseases. Effective reporting might bring down the causalities. The most common drugs which cause ADRs can be meticulously used. Modification and redesigning of protocols from time to time based on the data recorded will bring about the best for saving lives, improving quality, and reduction in individual costs towards health. The study indicates the incidence and pattern of ADRs in patients with hypertension and coronary artery disease attending the cardiac clinic of tertiary care hospital. The mortality and morbidity due to cardiovascular diseases are increasing at an alarming rate. Since the patients are on polypharmacy for a longer duration, risks of ADRs always exist. There is a need of conducting such studies in more and more patients to obtain more data on the pattern and incidence of ADRs. The awareness can be created in the physicians treating the patients

to prescribe medicines accordingly and thus help in avoiding the ADRs. The more information we get will help in reducing the ADR occurrence and making the drug use more rational and safe for the patient. To ensure a better treatment regimen and improve patients' compliance, it is essential to reduce and prevent adverse drug reactions. Implementation of pharmacovigilance programs in the hospitals is thus essential to enhance the awareness regarding early detection, reporting, management, and further prevention of Adverse Drug Reactions.

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