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Cardiovascular drugs and pharmacovigilance-a comprehensive study in India

Prashant Ashok Pawar[1], Tushar Atmaram Deshmukh[2], Jitendra B Naik[3]
[1] Scholar, University Institute of Chemical Technology, KBC North Maharashtra, Jalgaon, Maharashtra, India
[2] Principal, Shellino Education Society's Arunamai College of Pharmacy Mamurabad, Jalgaon, Maharashtra, India
[3] Professor, University Institute of Chemical Technology, KBC North Maharashtra, Jalgaon, Maharashtra, India

Abstract
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 a higher risk for developing more adverse drug reactions due to polypharmacy. Adverse drug reactions (ADRs) can result in several consequences, ranging from allergic reactions to permanent harm thereby causing morbidity and mortality leading to an increase in the health care cost. The main objective of the present study was to assess the prevalence of adverse drug reactions due to cardiovascular drugs. The common ADRs due to cardiovascular drugs can be reduced by improving the prescription pattern. Cough, gastritis, fatigue, and myalgia by enalapril, aspirin, β-blockers, and atorvastatin respectively were found to be the most commonly reported ADRs among the cardiovascular drugs**.** This review highlights the importance of systematic evaluation of adverse drug reactions and highlights the new directions that pharmacovigilance has taken.

Keywords: adverse drug reaction, pharmacovigilance, coronary artery disease, cardiovascular

Introduction
Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems [1] 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. Pharmacovigilance is indispensable because ADRs are significant causes of potentially preventable morbidity and mortality worldwide [2]. The concept of Pharmacovigilance and its significance enhances the impact of pharmacovigilance on patient welfare and public health and to know what is pharmacovigilance. The role of pharmacovigilance in guiding drug regulation and in facilitating informed, rational prescribing has been recognized only recently in our country [3]. Pharmacovigilance is a pharmacological science relating to the detection, assessment, understanding, and prevention of adverse effects, particularly long-term and short-term side effects, of medicines [4]. While not well understood by those outsides of the drug safety world, pharmacovigilance plays a pivotal role in helping to ensure patient safety for both newly released drugs and those that are well-established in the market. Pharmacovigilance involves consumers, health care professionals (HCPs), pharmaceutical companies, and global regulatory agencies, each of whom plays a unique and critical role in this process. Pharmacovigilance activities guide regulatory interventions to maintain drug safety in populations and promote informed, rational pharmacotherapy in individual patients [5].
Pharmacovigilance playing an important role in drug regulation for protecting public health by identifying, evaluating, and minimizing safety issues to ensure that the overall benefits of medicines outweigh the risks. That is to monitoring the post-marketing surveillance, drug safety, efficacy, and quality of drugs, as well as the accuracy and appropriateness of the drug information available to the public to reduce the adverse drug reactions.

Pharmacovigilance in India
Pharmacovigilance was first introduced in the year 1961 with a publication of a letter which was a case report in the Lancet journal by McBride W, who first suspected the cause of phocomelia to be thalidomide, a drug used as an anti-emetic in pregnant women introduced in the market in 1957. In this regard, WHO launched ‘programme for international drug monitoring’ in 1968 with a vision of compiling the global data on ADR [6]. In particular, the main aim of the “WHO Programme” was to identify the earliest possible PV signals. The term PV was proposed in the mid-70s by a French group of pharmacologists and toxicologists to define the activities promoting “The assessment of the risks of side effects potentially associated with drug treatment” [7]. In 1998, India became a part of it which is managed by uppsala monitoring centre in Sweden [8].
PvPI also conducts various workshops for pharmacy institutions, regional trainings on PV system, establishment and capacity building at pharma industries, skill development programme on pharmacovigilance [9] Drug safety alerts are also a part of PvPI where HCP, consumers or patients can closely monitor the possibility of adverse

events while the warning drug has been prescribed [10]. Multiple events are conducted by PvPI in order to widen the horizon of the programme. In May 2017, PvPI decided to introduce pharmacovigilance system in drug supply chain helping in maintaining quality assurance. First intensive drug monitoring programme was launched in 2017 to monitor sodium glucose co-transporter-2 (SGLT2) inhibitors, pioglitazone and sofosbuvir in India [11]. MvPI was launched by Drug Controller General of India (DCGI) on 6 th July 2015 at IPC, Ghaziabad. There was a incidence of loss of lives after a 8-minute power cut in dialysis unit in premier hospital in Puducherry, India [12]. Hemovigilance programme of India (HvPI), was launched in 2012 under PvPI in collaboration with National Institute of Biologicals, Noida, UP under MOHFW in order to track the ADR related to blood and blood products thus contributing to improvement of patient safety [13] Adverse event following immunization (AEFI) AEFI is any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. PvPI coordinated with AEFI Secretariat (universal immunization programme) since 28th Feb 2013 to monitor the safety of vaccines [14].

The national pharmacovigilance system plays a vital role in increasing public awareness of drug safety. However, minimum requirements for a functional national pharmacovigilance system are required which include a national pharmacovigilance centre with designated staff, stable basic funding, clear mandates, well defined structures and roles and collaborating with the WHO programme for international drug monitoring; the existence of a national spontaneous reporting system with a national individual case safety report (ICSR) form; a national database or system for collating and managing adverse drug reaction reports; a national pharmacovigilance advisory committee able to provide technical assistance on causality assessment, risk assessment, risk management, case investigation; and a clear communication strategy for routine communication and crises communication

Cardiovascular Diseases

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 [15]. Heart failure (heart is unable to pump the blood through the body), disorders of the heart muscle (cardiomyopathy), and alterations in the heart rhythm (arrhythmias) are also considered types of CVDs; however, they are less frequent than IHD and stroke. Most of these cardiovascular risk factors are a result of people's lifestyles and behaviors; therefore, they could be modifiable and avoidable [16]. Most of these cardiovascular risk factors are a result of people's lifestyles and behaviors; therefore, they could be modifiable and avoidable[17]. In the last few decades, new factors such as those related to inflammatory and metabolic processes as well as people's behaviors and psychological and socioeconomic conditions have been linked to CVDs [18-21].

Pharmacovigilance in Cardiovascular Therapeutics

Pharmacovigilance is especially relevant to cardiovascular therapeutics because patients with CVD are usually on multiple drugs and have co-morbid disorders increasing their susceptibility to ADRs and drug interactions. Unsurprisingly ADRs to drugs used in CVD are frequently being reported to pharmacovigilance databases. Cardiovascular diseases (CVDs) are the leading cause of death according to American Heart Association (AHA) [22] and account for over a third of all deaths in Australia each year [23]. Drugs used for the management of cardiovascular diseases are not devoid of adverse effects but could lead to adverse consequences if not monitored properly. With the increased number of medicines for cardiac patients, there is a tendency to cause drug-related problems such as ADRs, drug-drug Interactions (DDIs), etc. Since cardiovascular diseases are one of the major concerns and cardiac drugs can cause a multitude of ADRs, the development of a robust network for detection and reporting of ADRs is of utmost importance.

Adverse drug reactions (ADRs) are considered as one of the major public health concern which may contribute for increasing healthcare burden. The keystone of all pharmacovigilance programs is spontaneous reporting of ADRs by doctors, nurses, pharmacists, and allied healthcare professionals. It is done by filling ADR forms which are designed specifically for healthcare professionals. A complex and vital relationship exists between wide ranges of partners in the practice of drug safety monitoring such as government, industry, health care centers, hospitals, academia, medical and pharmaceutical associations, poisons information centers, health professionals, patients, consumers, and media. Sustained collaboration and commitment are vital if future challenges in pharmacovigilance are to be met to develop and flourish. Pharmacovigilance and all drug safety issues are relevant for everyone whose life is touched in any way by medical interventions. The evolution of Pharmacovigilance in recent years has grown in importance as a science critical to effective clinical practice and public health science. Pharmacovigilance is now firmly based on sound scientific principles and is integral to effective clinical practice.

A study that includes more than 2000 notifications of adverse reactions from 10 teaching hospitals is that cardiovascular adverse reactions were caused most frequently by non-cardiovascular drugs and that cardiovascular drug caused most frequently non-cardiovascular side effects. Of 151 reports of cardiovascular adverse reactions produced by all ATC classes of drugs, 22 (14.6%) were serious including 6 life-threatening conditions. It should be noted that there were 3 reported cases of cardiac arrest (which occurred during anesthetic

procedures), but none of these resulted in death. Patients with adverse cardiovascular reactions had an average age of 57.9 years, and 82 of them (54.3%) were female. Cardiovascular reactions occurred more frequently in females. Female sex is an independent risk factor for drug-induced QT prolongation and adverse drug reactions. Also, symptoms or findings of the clinical examination were the most common clue to adverse reactions in this subset of patients. This underscores the need to exclude non-cardiac drugs as a cause of cardiovascular complaint. The main tool to do this is a comprehensive evaluation of drug utilization [24]. However in another study on the administration of Enalapril 81 ADR was reported related to Cough and Angioedema and in the case of Atorvastatin 69 which includes Constipation, Arthralgia, Dry skin. Aspirin leads to Tinnitus, Malena and Gastritis; Metoprolol leads to Fatigue, Insomnia, and Giddiness; Atenolol leads to Fatigue, Giddiness, and Insomnia; Ranolazine leads to Palpitation, Arthralgia, and Constipation; Amlodipine leads to Pedal edema, Facial edema; Isosorbide mononitrate leads to headache and dizziness; Trimetazidine leads to Constipation, Weakness, Abdominal pain and Spironolactone leads to Gynecomastia and Metabolic alkalosis. A total of 463 ADRs related to the cardiovascular system were reported [25]. Mohebbi et al reported adverse drug reactions related to Nervous system disorders, GI system disorders on the administration of Nitroglycerin, and Amiodarone [26]. According to Singhal et al., Headache and dry cough were observed as the most common ADR on the administration of Calcium channel blockers and Nitrates [27]. On administration of Digoxin and Nitroglycerine, Fanak et al. reported ADR related to GI system disorders, Respiratory system disorders [28]. In another study, a 78-year-old female patient who was being followed for hypertension and atrial fibrillation, medicated with Apixaban 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 [29].

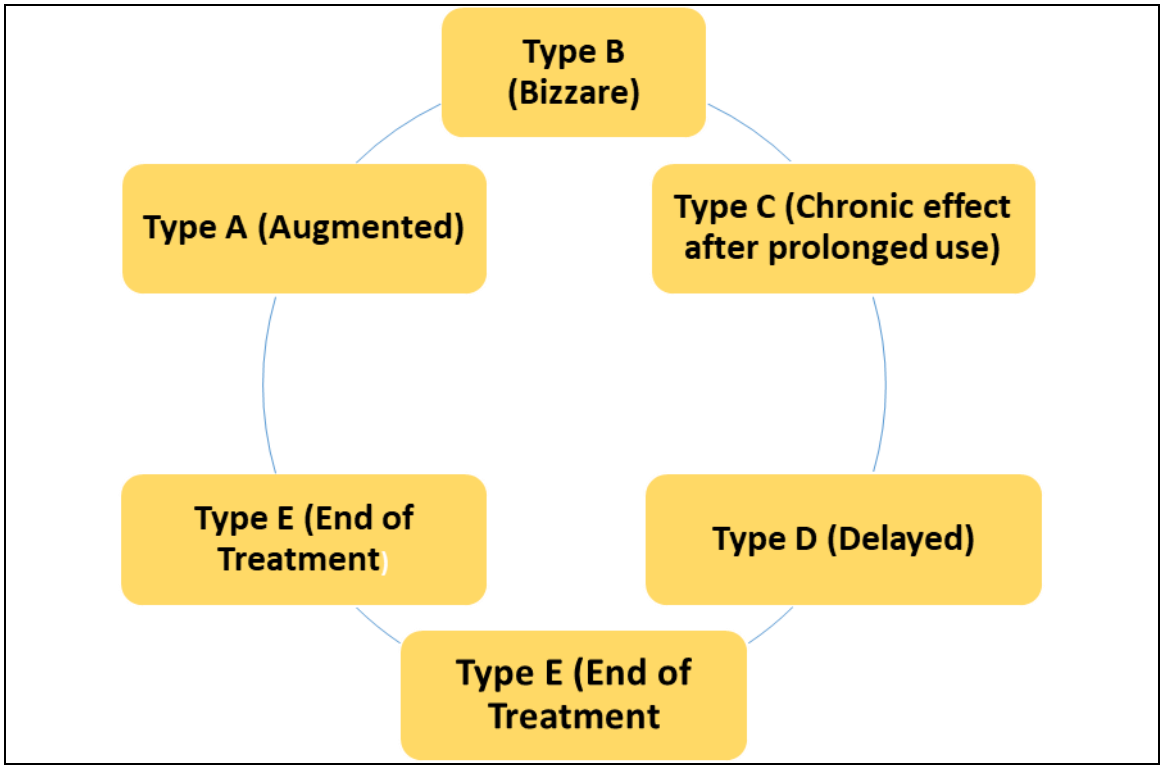

Fig 1: Classification of Adverse Drug Reactions

Prevention of Cardiovascular ADRs

Pharmacovigilance is an arm of patient care. It aims at getting the best outcome of treatment with medicines. No one wants to harm patients, but unfortunately, because of many different factors, any medicine will sometimes do this. Good pharmacovigilance will identify the risks in the shortest possible time after the medicine has been marketed and will help to establish and/or identify risk factors.

Underreporting of ADRs by the healthcare professional to the national pharmacovigilance center is a challenge in India and globally. The role of healthcare professionals is vital in recording and reporting suspected ADRs so that regulatory agencies are alerted of emerging safety concerns and therefore facilitating timely and appropriate action. To deal with the adverse drug reactions firstly the patient's medication history will identify any previous ADRs and therefore preclude re-exposure to the drug. In other cases, susceptibility factors such as age, gender, pregnancy status, and ethnicity can help predict the risk of an ADR occurring. Clinical decision support systems available at the point of care can inform practitioners of any patient specific cautions to treatment or additional monitoring requirements to reduce the risk of harm. Overall a systems approach, involving multiple strategies and including the patient and all healthcare professionals, is required to reduce the risk of an ADR and prevent

those 'avoidable' reactions occurring in practice. Therefore, all the members of the healthcare team are required to be aware of the importance of ADR reporting and that they are competent to provide practical information for reporting ADRs. They should have a familiarity with the policy and procedures of ADRs reporting and guidance as to how and when to report and where to send it. Healthcare professionals usually consider that they have a major responsibility to be a Pharmacovigilance partner by reporting suspected ADRs [30].

Pharmacovigilance A Tool for Safety and Monitoring

Pharmacovigilance is majorly known as drug safety. Pharmacovigilance gives information to assess the safety profile of a drug; the success of pharmacovigilance is largely dependent on the participation of professionals of health care countrywide to report ADRs/AEs, Current progress in Pharmacovigilance is marked by an increase in the use of databases to make the process more proactive and organized. New, unexpected, and rare ADRs are often discovered when drugs are used in larger or in a different population than studied during initial clinical trials which are conducted in a controlled environment in a limited number of patients. Therefore, reports from patients/consumers will be an extra source of information that may help in reducing the limitation imposed by underreporting. The World Health Organization (WHO) stated that reporting routes should be made readily accessible and cheap. Patients/ consumers may submit their reports by telephone, or through fax, e-mail, e-forms, and paper forms which can be submitted in a pre-paid post. Paper forms should be available at local pharmacies, healthcare facilities, or offices or in magazines produced by patients' organizations [31].

The pharmacovigilance programme of India was officially started on 23rd November 2004 at New Delhi, is under the control of CDSCO (Central Drug Standard Control Organization), Directorate general of health services, Indian pharmacopeia commission (Ghaziabad) [32]. The program is conducting by NCC (National Coordinating Centre) to ensure that the benefits of the use of medicine against the risks [33]. The information collected in the center was broadened to include hospitals and practitioners from nearby areas. Direct information collection from consumers has also been practiced. The standard protocol to analyze ADRs has been applied and elaborated. There has, however, been grass disparities in reporting pattern from diverse specialties. The same would reflect in the collected data giving indications for the betterment of ADR reporting and Pharmacovigilance activity at institutional and regional center levels. The national pharmacovigilance system plays a vital role in increasing public awareness of drug safety. However, the national pharmacovigilance system has been known to exhibit various functions which include, promoting pharmacovigilance in the country in order to collect and manage adverse drug reaction; reporting of medication errors and suspected substandard drugs; collaborating and harmonizing with existing adverse reaction collection activities within the country; identifying signals of medicine safety; undertaking assessment of risk and options for risk management; identifying the possible quality problems in medicines resulting in adverse reactions; supporting the identification of medicine quality issues; providing effective communication on aspects related to medicine safety; applying resulting information from pharmacovigilance for the benefit of public health programmes, individual patients and national medicines policies and treatment guidelines; developing and maintaining drug utilization information; and identifying issues associated with unregulated prescribing and dispensing of medicines.

A complex and vital relationship exists between wide ranges of partners in the practice of drug safety monitoring such as government, industry, health care centers, hospitals, academia, medical and pharmaceutical associations, poisons information centers, health professionals, patients, consumers and media. But more is required for the integration of the discipline into clinical practice and public policy. To fulfill the PV obligations for its marketed products as per regulations, a pharmaceutical company in India has to essentially carry out activities such as collection, and expedited reporting of serious unexpected ADRs [34-37].

At present, the DCGI should act quickly to improve PV so as to integrate Good Pharmacovigilance Practice (GPP) into the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety and post marketing surveillance. An appropriately working PV system is essential if medicines are to be used carefully. It will benefit healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It helps pharmaceutical companies to monitor their medicines for risk.[38] Thus, healthcare settings should be targeted to change the concept of considering ADR reporting as a common accepted daily routine practice.[39] Pharmacovigilance should be included in curriculum on a large basis in undergraduate and postgraduate pharmacology. The amount of time dedicated to pharmacovigilance teaching in undergraduate and postgraduate courses is low. Factors discouraging reporting of ADR also included uncertainty about causality assessment between ADR and drug, forgetfulness, diffidence and lack of time.[40]

Pharmacovigilance incorporates and provides training in the identification of adverse reactions, data collection, processing, and analysis. The information collected also provides the tools for the effective management of problems. These include communication and minimization of risk. In spite of this, it is not widely practiced in Indian hospitals. The idea that pharmacovigilance programme can be set up and effectively implemented only in the developed countries should be replaced by the realization that a reliable system of pharmacovigilance is extremely essential for the rational, safe, and cost-effective use of medicines even in developing countries like India. So in the future, a comprehensive sensitization Programme is required in each step of the health care system right from treating doctors, nurses, paramedics, and drug dispensing pharmacists to ensure better and safe pharmacotherapy and improve compliance of patients. Many latest drugs are being introduced in the country, so there is a vast need to advance the Pharmacovigilance system to protect the Indian population from potential harm that may be caused by various new drugs.[41] A single countrywide specific adverse event reporting form

needs to be considered should not only be used by the National Pharmacovigilance Centers, but also by all registered hospitals (both private and government), teaching hospitals, Drug Information Centers and pharmacies all over the country.[42] The relations with the IT sector in building a robust Pharmacovigilance system for India Software programs developed can be used for collection and analyses of data sets, determining trends of drug usage in various disease areas, compliance, medication errors and drug interactions leading to ADRs[43] ADR can occur with herbal drugs also if they are compounded and dispensed improperly. Hence, to put PV for Ayurveda, Siddha, Unani (ASU) was highly essential to provide ADR data of AYUSH drugs as per WHO guidelines[44].

Conclusion

The Cardiovascular system was one of the most prominent organ systems affected by drugs. The major challenge of cardiovascular prevention consists of setting up multidisciplinary approaches that combine interventions oriented towards reducing cardiovascular risk such as promoting lifestyle changes, optimal medical treatment and care services, health education as well as improvements to the environmental and social conditions in which individuals live during their lifetime. The majority of significant adverse reactions involving cardiovascular drugs are predictable and therefore preventable. The ever-present underreporting of adverse events highlights the need to continue to promote the specialty of pharmacovigilance and to help HCPs understand the role that pharmacovigilance plays to help ensure patient safety. As prospects increase, PV systems capable to detect new ADRs, and taking regulatory actions are needed to protect public health. Little emphasis has been put on generating information that can assist a healthcare professional or a patient in the decision-making process. The safe use of medicines is perhaps the single most important criteria that any regulatory authority within a given country has to ensure in order both to protect the public health and the integrity of its health care system.

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