Quick Response Code:

Study of pattern & distribution of adverse drug reactions in acute coronary syndrome patients in a tertiary care hospital

Manjappa Mahadevappa[1], Chinmay Meher[2], N.B. Pushpa[3], Prashanth Kulkarni[1,4], K.S. Poornima[1] & Nagaraj Desai[1]

Departments of [1]Cardiology, [2]Clinical Pharmacy Practice, JSS Pharmacy College, [3]Anatomy, JSS Medical College Hospital, JSS Academy of Higher Education and Research, Mysuru, Karnataka & [4]Department of Cardiology, CARE Hospitals, Hi-tech City, Hyderabad, Telangana, India

Background & objectives: With the availability of a wide range of drugs to treat patients with acute coronary syndrome (ACS), adverse drug reactions (ADRs) have become inevitable in clinical practice. Thorough knowledge of such reactions is essential for the treating physician for optimal treatment and better outcomes. There are many scales to define, measure and assess the ADRs, but there is a dearth of data available on such drug reactions among ACS patients. Hence, this study attempted to analyze the pattern, causality, severity, predictability and preventability of ADRs in ACS patients. All the ADRs reported during the study period were analyzed for causality by the World Health Organization–Uppsala Monitoring Centre (WHO-UMC), Naranjo's and Karch and Lasagna scales; severity by modified Hartwig and Siegel scale; predictability by Rawlins and Thompson criterion and preventability by Schumock and Thornton scale.

Methods: A single-centre, record-based analysis for the occurrence of ADRs was done among ACS patients admitted to the department of Cardiology between January and October 2017. Demographic data, comorbid conditions, reported ADRs and ADR assessment details were noted from the hospital case records and ADR monitoring centre (AMC) records. The data were analyzed and presented in a descriptive manner using percentages, mean and standard deviation. The Pearson's chi-squared test was used to ascertain the significance of the association between different groups.

Results: Out of 324 patients under evaluation, 67 had developed one or more ADRs. There were 30 different types of ADRs reported, headache being the most common. Among the drugs, heparin was the most common factor, causing 27 per cent of ADRs. Definite causality of a suspected drug causing ADRs was seen in 11.9 (n=8), nine (n=6) and 7.5 (n=5) per cent cases as per WHO-UMC, Naranjo (Naranjo algorithm) and Karch and Lasagna scales, respectively. In the severity of ADRs, the most severe reactions according to the modified Hartwig-Siegel scale (level 4a in our study) were seen in 17.5 (n=12) per cent of patients, and the rest were either level 2 or 3 reactions. Nearly 92.5 (n=62) per cent of reactions were predictable according to the Rawlins and Thompson criterion. Application of the modified Schumock-Thornton scale showed that 22.4 per cent of ACS patients had preventable reactions, and the rest were not preventable.

Interpretation & conclusions: The study results suggest that ADRs are relatively common among ACS patients. Most of these can be identified and assessed for causality, severity, predictability and preventability using various available scales. Diligent pharmacovigilance for identifying and assessing ADRs may help manage and mitigate morbidity associated with these in high-risk ACS patients.

Coronary artery disease and acute coronary syndrome (ACS) are on the rise globally[1]. Cardiovascular diseases (CVD) have become the leading cause of mortality in India at the turn of the century[2,3]. With the evolution of more sophisticated treatment options, adverse drug reactions (ADRs) have become more common. An ADR is defined as 'any noxious, unintended or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis or therapy'[4]. Such ADRs frequently happen in clinical practice and pose a significant challenge for treating physicians[5]. In critical illnesses such as ACS, multiple factors influence susceptibility to develop ADRs, such as advancing age, types of medications, use of multiple drugs (polypharmacy), the complexity of the disease and comorbidities that have added to the inevitable occurrence of ADRs[6,7]. Many studies have demonstrated ADRs as a significant health service problem related to morbidity, mortality and increasing healthcare costs[8].

ACS includes ST-elevation myocardial infarction (STEMI), unstable angina (UA) and non-STEMI (NSTEMI). ACS is a clinical condition where multiple drugs are used with a similar goal to treat the underlying disease process, which unduly predisposes the patient to develop frequent and severe ADRs. Cardiovascular drugs have been cited as one of the most common drugs associated with medication errors and ADRs, which need to be monitored from time to time[9]. Meticulous diagnosis and management of ADRs definitively is a challenge among these high-risk patients. Hence, thorough knowledge of ADRs is essential for treating physicians, which will help in minimizing the associated mortality and morbidity.

The World Health Organization (WHO) has advocated a pharmacovigilance (PV) programme, which is a scientific activity related to the early detection, assessment, understanding, management, and prevention of any drug-related problem or adverse effect termed as ADR[10]. Although India has a nationwide ADR monitoring programme called the Pharmacovigilance Programme of India (PvPI), which operates through AMCs[11], the availability of ADR-related data on Indian patients with ACS is sparse. Hence, this record-based study was undertaken to know the pattern of ADRs in ACS patients, assessing causality, severity, predictability and preventability in a tertiary care hospital and AMC in southern India.

Material & Methods

A single-centre record-based analysis was done for ADRs among ACS patients admitted to the department of Cardiology JSS Medical College Hospital, Mysuru, Karnataka, India, between January and October 2017 for a duration of 10 months after procuring permission from the Institutional Ethics Committee.

Collection of data: Data on demographic characteristics such as patient identification, age, sex, weight, primary diagnosis, date of admission, date of discharge, number of days of hospital stay, history of comorbidities such as diabetes mellitus (DM), hypertension (HTN), hypothyroidism, prior ischaemic heart disease, chronic obstructive pulmonary disease (COPD), cerebrovascular accidents, prior history of drug allergy, number and type of medications used during index admission, investigation reports such as cardiac biomarkers, two-dimensional echocardiogram, any ADRs reported, brief description of the ADRs such as date of onset and subsidence, duration, specific treatment given, predisposing factors, other possible non-pharmacological causes, fate of the medication, any de-challenge and re-challenge done, progression and recovery, length of hospital stay, whether an alert card was provided at the time of discharge, any morbidity or mortality associated with the ADRs, were noted as recorded in the case files and AMC records of the institution.

Consecutive ACS patients admitted for management who developed at least one ADR during index hospitalization during the study period were analyzed for pattern; causality by WHO-Uppsala

Monitoring Centre (UMC)[12], Naranjo's[13] and Karch and Lasagna[14] scales; severity by modified Hartwig and Siegel scale[15]; predictability by Rawlins and Thompson criterion[16] and preventability by Schumock and Thornton scale[17].

Causality assessment of adverse drug reactions (ADRs): Causality or probability assessment denotes the causal relationship between the suspected drug and ADR, which was established using the following scales.

The WHO-UMC scale of causality assessment[12] used six different terms for causality categorization, with set definitions into (*i*) certain, (*ii*) probable, (*iii*) possible, (*iv*) unlikely, (*v*) conditional and (*vi*) un-assessable.

Naranjo's scale for causality assessment[13] is another simple and reproducible method to assess the causality of ADRs related to drug therapy in various clinical scenarios. Based on the total score, the ADR is said to be related to the drug as definite or highly probable if the total score is >9; probable if the total score is 5-8; possible if the total score is 1-4; doubtful if the score is 0.

Karch and Lasagna scale[14] employs five questions with an answer of either yes (Score 1) or no (Score 0) to each of them. The causal relationship is assigned based on the score as definite: 4/5, probable: 3/5 with no alternate explanation, possible: 2/5 with no re-challenge and alternate explanation and conditional: irrespective of the score if there is an alternative explanation available. The questions are as follows:
(*i*)   Is there a reasonable temporal sequence?
(*ii*) Is it a known response pattern to the drug?
(*iii*) Whether reaction improved on de-challenge?
(*iv*) Whether reaction return after a re-challenge?
(*v*)   Whether an alternate explanation present for the reaction?

Severity assessment of adverse drug reactions (ADRs): The intensity of a medical event like ADR is denoted by the term severity, which Modified Hartwig and Siegel scale[15] categorized as mild, moderate, and severe based on the management. The ADR is said to be mild (level 1 and level 2): suspected drug not withdrawn with symptomatic treatment or the suspected drug withdrawn with symptomatic treatment; moderate (level 3, 4a and 4b): the suspected drug was withdrawn with a specific treatment or increasing the hospital stay by at least one day or ADRs becoming the reason for hospitalization and severe (level 5, 6 and 7): requiring intensive medical care or causing permanent damage or death of the patient, respectively.

Predictability assessment of ADRs: The predictability of the reported ADRs was assessed using Rawlins and Thompson criterion[16] which categorizes adverse events into type A: dose-dependent and predictable forms; and type B: dose-independent diosyncratic, non-predictable forms.

Preventability assessment of ADRs: Preventability criteria according to the Schumock and Thornton scale[17] were employed and categorized ADRs into (*i*) definitely preventable, (*ii*) probably preventable and (*iii*) not preventable. Most of the dose-, time- and dose–time-dependent ADRs fall under preventable reactions, whereas idiosyncratic or unpredictable reactions fall under the not preventable category.

Statistical analysis: The data were entered into Microsoft Excel version 2019 (Microsoft Corp., Seattle, Washington, USA) and analyzed using Statistical Package for Social Sciences for windows version 25 (IBM Corp., IL, USA; licensed to the institution). Continuous variables were presented as mean±standard deviation. The categorical variables were presented in percentages and were also analyzed using the Chi-squared test to ascertain the significance of the association between different groups.

Results

The data of 324 consecutive patients admitted with ACS were evaluated for the occurrence of at least one ADR during their hospitalization. Of these, 67 patients had suffered from one or more ADRs. These ADRs were analyzed further for occurrence, pattern, causality, severity, predictability and preventability using appropriate scales listed in the materials and methods section.

Demographic characteristics showed the mean age of the analyzed patients to be 56.4±12.9 yr, and 74.6 per cent (n=50) were male. The average duration of hospital stay was 6.36±3.0 days. STEMI was diagnosed in 67.2 per cent (n=45) of patients, and the rest were with either NSTEMI or UA 32.8 per cent (n=22). The most common presenting symptom was angina (59.7%), followed by angina and dyspnoea in 26.9 per cent of the patients. HTN 58.2 per cent (n=39) and DM 53.7 per cent (n=36) were the most prevailing comorbid conditions, followed by prior ischaemic

heart disease, observed in 19.4 per cent (n=13) of patients. Only six per cent (n=4) of the patients had a prior history of drug allergy to a particular class of medication. The remaining demographic details are shown in Table I.

The most commonly prescribed oral antiplatelet drug combination was aspirin and ticagrelor (65%), followed by aspirin and clopidogrel (35%). 79.1 per cent of patients received atorvastatin, and the rest received rosuvastatin. Beta-blockers were either continued or prescribed newly to 67.2 per cent of the patients, and angiotensin-converting enzyme inhibitors/ARBs were prescribed to 82.1 per cent, and nearly 58.2 per cent of the patients received a diuretic. The most commonly employed intravenous anticoagulation was heparin, either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), used in 100 per cent of patients. Nearly 90 per cent (89.6%) of patients received a proton-pump inhibitor. The average number of medications used was 10.13±2.3 per ACS patient, and the range is six to 19 depending on the need, associated comorbidities and complications arising out of the illness or ADRs. The most commonly prescribed medications as per the current recommendations, hospital protocol and treating physicians' discretion are listed in Table II.

Nearly 20 different medications caused more than 30 different types of ADRs. The most commonly employed intravenous anticoagulant, heparin, was responsible for the most number of ADRs by a single drug (UFH and LMWH causing 14.9 and 12 per cent, respectively, with a total of 27 per cent of reactions between them). Most of the heparin-related ADRs were haematologic abnormalities and bleeding manifestations. The next highest number of ADRs was by antianginals (15%), causing constitutional symptoms such as headache and diuretics causing 15 per cent of ADRs related to dyselectrolytaemia (furosemide) and gastrointestinal disturbances (spironolactone). However, the most commonly reported ADR was a headache, 20.9 per cent (n=14), followed by nine per cent (n=6), thrombocytopenia, 7.5 per cent (n=5), abdominal discomfort and hyponatraemia, respectively. Table III lists the medications causing various ADRs, the number of ADRs caused by incriminated drugs and the description of the ADRs.

The haematological system was the most frequently affected with abnormalities like thrombocytopaenia, thrombocytosis, and bleeding manifestations in 23.9 per cent (n=16) of cases reporting ADRs. Constitutional

Table I. Demographic characteristics of acute coronary syndrome patients experiencing adverse drug reactions		
Characteristics	Range	Number of patients (n=67)
Age (yr), mean±SD	26-85	56.4±12.9
Gender, n (%)		
Male	-	50 (74.6)
Female	-	17 (25.4)
Weight (kg), mean±SD	49-87	68.29±8.4
Duration of hospital stay (days)	01-16	06.36±3.0
Trop T (ng/dl), mean±SD	0.002-13.300	01.72±02.22
Ejection fraction (%), mean±SD	15-62	42.90±9.05
Diagnosis, n (%)		
STEMI	-	45 (67.2)
NSTEMI/UA	-	22 (32.8)
Past medical history, n (%)		
DM	-	36 (53.7)
HTN	-	39 (58.2)
IHD	-	13 (19.4)
COPD	-	06 (09.0)
CKD	-	06 (09.0)
Hypothyroidism	-	01 (01.5)
Other illness	-	03 (04.5)
Known allergy to a drug	-	04 (06.0)
Symptoms on admission, n (%)		
Angina	-	40 (59.7)
Angina and dyspnoea	-	18 (26.9)
Dyspnoea	-	03 (04.5)
Fatigue	-	01 (01.5)
Others	-	05 (07.5)

SD, standard deviation; STEMI, ST-elevation myocardial infarction; NSTEMI, Non-ST-elevation myocardial infarction; UA, unstable angina; DM, diabetes mellitus; HTN, hypertension; IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease

symptoms, 20.9 per cent (n=14), were the second most common, followed by electrolyte imbalances and gastrointestinal system 14.9 per cent (10 each) involvement. The other organ systems involved are shown in Table IV.

The occurrence of ADRs was 20.68 per cent (67 out of 324), with an average number of ADRs per patient being 1.3±0.5. The majority of the patients, 79.1 per cent (n=53), reported one ADR, and three per cent (n=2) of the patients reported a maximum number

Table II. Medication utilization amongst acute coronary syndrome patients experiencing adverse drug reactions		
Medications/drugs utilized amongst patients reporting ADRs	Number of patients receiving the drug, n (%)	χ^2, *P*
Aspirin 150 mg+clopidogrel 75 mg od (MD)	24 (35.8)	5.39, 0.020
Aspirin 75 mg+ticagrelor 90 mg bid (MD)	43 (64.2)	
Atorvastatin	53 (79.1)	22.70, 0.001
Rosuvastatin	14 (20.9)	
BB	45 (67.2)	7.90, 0.005
No BB	22 (32.8)	
ACE/ARB inhibitors	55 (82.1)	27.60, 0.005
No ACE/ARB inhibitors	12 (18.9)	
CCB	08 (11.9)	38.82, 0.005
No CCB	59 (88.1)	
DU	39 (58.2)	1.81, 0.179
No DU	28 (41.8)	
UFH	58 (86.6)	35.84, 0.001
LMWH	09 (13.4)	
Spironolactone	40 (59.7)	2.52, 0.112
No spironolactone	27 (40.3)	
Proton-pump inhibitor	60 (89.6)	41.93, 0.001
No proton-pump inhibitor	07 (10.4)	
Antiemetics	20 (29.8)	10.88, 0.001
No antiemetics	47 (70.2)	
Salbutamol/ipratropium bromide	30 (44.8)	
Steroid-budesonide/fluticasone	21 (31.3)	4.51, 0.105
No nebulization	16 (23.9)	
Nicoumalone	02 (02.9)	59.24, 0.001
No nicoumalone	65 (97.1)	
Cephalosporins	32 (47.8)	
Other antibiotics	07 (10.4)	16.15, 0.001
No antibiotics	28 (41.8)	
Other medications: Insulin, OHAs, morphine/pethidine, alprazolam, lactulose and others	41 (61.2)	3.36, 0.067
No other medications	26 (38.8)	
The average number of medications used, mean±SD	10.13±2.30	-
MD, maintenance dose; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; ADRs, adverse drug reactions; OHAs, oral hypoglycaemic agents; BB, beta-blockers; DU, diuretics		

of three ADRs. In this study, around 68.7 per cent of patients had de-challenge (withdrawal of causative drug), and only 16.4 per cent (n=11) had re-challenge. Most of the re-challenge were seen with diuretics and antianginals. In 64.2 per cent (n=43) of patients, the offending drug had to be withdrawn to treat the ADR; in 20.9 per cent (n=14) of patients, the drug dose had to be adjusted to reduce the severity of the ADR. Only 14.9 per cent (n=10) of patients tolerated the continuation of

the drug-causing ADRs. As per treatment of ADRs was concerned specific therapy with another medication was required in 34.3 per cent (n=23) patients, and the rest responded to either symptomatic (44.8%) or no treatment (20.9%) at all. 98.5 per cent (n=66) of patients fully recovered from the ADRs by the time they were discharged. In one patient, the fate of ADR was not known as he left the hospital against medical advice. Details are shown in Table V.

Medications incriminated in causing ADRs	Number of ADRs attributed to the drug, n (%)	ADR description (n)
Alprazolam	1 (1.5)	Constipation, loose stools and ataxia
Aspirin	2 (3.0)	Dyspeptic symptoms/epigastric discomfort/eructation/flatulence/vomiting
Aspirin/ticagrelor	1 (1.5)	Generalized petechiae
Aspirin/clopidogrel	1 (1.5)	Generalized petechiae
Atorvastatin	3 (4.5)	Diarrhoea (2) and hyperpigmented papules over the neck and back (1)
Budesonide	1 (1.5)	Abdominal cramps
Carvedilol	2 (3.0)	Bradycardia (1), hypotension, bradycardia and giddiness (2)
Cefoperazone	1 (1.5)	Generalized urticaria and rashes
Ciprofloxacin	1 (1.5)	Tachycardia
Clopidogrel	5 (7.5)	Generalized urticaria and rashes (4) Headache
Dopamine	1 (1.5)	Vomiting and tachycardia
Furosemide	8 (12)	Hypernatraemia (1) Hypokalaemia (1) Hyponatraemia (50) Hyponatraemia plus hypochloraemia (1)
Heparin (UFH)	10 (15)	Bleeding from gums (3) Thrombocytopenia (3) Thrombocytosis (2) Haematuria (1) Haematoma (1)
Isosorbide mononitrate	5 (7.5)	Headache
LMWH	8 (12)	Thrombocytopenia (3) Thrombocytosis (1) Haematuria (3) Hyperkalaemia (1)
Metoprolol	5 (7.5)	Headache (5) Bronchospasm (1) Constipation (1)
Morphine	1 (1.5)	Abdominal cramps
NTG	2 (3.0)	Headache
Nicorandil	3 (4.5)	Headache
Ramipril	1 (1.5)	Dry cough
Spironolactone	2 (3.0)	Abdominal cramps (1) Hyperkalaemia (1)
Ticagrelor	3 (4.5)	Breathlessness
Test statistics	χ^2=49.57; P=0.001	

Table III. The list of medications incriminated in causing adverse drug reactions

χ^2: Chi-squared test was applied to the test statistics to ascertain the significance of reported ADRs, which showed a P value of 0.001, denoting significance. NTG, nitroglycerin

Definite causality of a suspected drug causing ADR was seen in 11.9 (n=8), nine (n=6) and 7.5 per cent (n=5) cases as per WHO-UMC, Naranjo (Naranjo algorithm) and Karch and Lasagna scales, respectively. In the severity of ADRs, the most severe reactions according to the modified Hartwig-Siegel scale (level 4a in this study) were seen in 17.5 per cent (n=12) of patients, and the rest were either level 2 or level 3 reactions. Nearly 92.5 per cent (n=62) of reactions were a predictable form of ADRs belonging to type A, and only 7.5 per cent of the reactions belonged to type B, which were unpredictable and

Table IV. The frequency of organ systems involved and the attributed category of medications causing adverse drug reactions (ADRs)

Category of medications	Organ system involved due to ADRs							Total ADRs
	CVS	RS	GI	Haematologic/ bleeding	Dyselec- trolytaemia	Skin/ genitalia	Constitutional	
AP, n (%)	0 (0.0)	3 (60.0)	2 (20.0)	2 (10.5)	0 (0.0)	4 (66.7)	1 (7.1)	12 (17.9)
Statins, n (%)	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	3 (4.5)
BB, n (%)	2 (66.7)	1 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (21.4)	7 (10.4)
AA, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (71.4)	10 (14.9)
DU, n (%)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	9 (90.0)	0 (0.0)	0 (0.0)	10 (14.9)
ACEI/ARBs, n (%)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
AC, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	17 (89.5)	1 (10.0)	0 (0.0)	0 (0.0)	18 (26.9)
Others, n (%)	1 (33.3)	0 (0.0)	4 (40.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	6 (9.0)
Total, n (%)	3 (100)	5 (100)	10 (100)	19 (100)	10 (100)	6 (100)	14 (100)	67 (100)
Test statistics (category of medications)	χ^2=24.10; *P*=0.001							
Test statistics (organ system involved)	χ^2=19.40; *P*=0.004							
Test statistics (association with ADRs)	χ^2=195.83; *P*=0.001							

χ^2: Chi-squared test was applied to ascertain the significant association between different groups. CVS, cardiovascular system; RS, respiratory system; GI, gastrointestinal system; BB, beta-blockers; AP, antiplatelets; AC; anticoagulants; AA, antianginal; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DU, diuretics

Table V. Pattern, distribution, treatment and outcomes of adverse drug reaction (ADR)

Number of patients with ADR out of 324 consecutive ACS patients, n (%)	67 (20.68)	χ^2, *P*
Average number of ADRs reported per patient, mean±SD	1.3±0.5	-
Number of ADRs reported, n (%)		
One ADR	53 (79.1)	3.36, 0.001
Two ADRs	12 (17.9)	
Three ADRs	02 (03.0)	
Fate of the suspected drug, n (%)		
No change	10 (14.9)	29.05, 0.001
Drug withdrawn	43 (64.2)	
Dose adjusted	14 (20.9)	
Treatment given, n (%)		
No Rx given	14 (20.9)	5.76, 0.001
Symptomatic Rx	30 (44.8)	
Specific Rx	23 (34.3)	
De-challenge/re-challenge/no challenge, n (%)		
De-challenge	46 (68.7)	37.64, 0.001
Re-challenge	11 (16.4)	
No challenge	10 (14.9)	
Outcome, n (%)		
Recovered	66 (98.5)	63.06, 0.001
Unknown	01 (1.5)	

χ^2: Chi-squared test was applied to ascertain the significant association between different groups. $P \leq 0.005$ was considered significant for different groups. Rx, treatment

idiosyncratic according to the Rawlins and Thompson criterion. The modified Schumock-Thornton scale to study patients showed that 22.4 per cent of ACS patients had definitely preventable reactions and the rest were not preventable. The details of the pattern, distribution, treatment and outcomes of ADRs are listed in Table VI.

Discussion

Ever-increasing ACS in the general population and its rapidly evolving management strategy, the availability of a significant number of more potent medications predisposes ACS patients to ADRs. Low-income countries, including India, have much higher case fatalities due to CVDs and ACS than in the middle- and high-income countries[18,19]. The additional

burden of undetected, untreated or partially treated ADRs can disproportionately increase morbidity, mortality and healthcare costs.

Several factors such as dose, frequency of administration, genetic polymorphism, pharmacokinetics, extremes of age and associated hepatic or renal impairment influence the risk of developing an ADR to drug therapy. As ADRs are frequent in clinical practice with potentially serious consequences, their impact on clinical practice and economic perspective are dramatic[20,21]. Polypharmacy and drug-drug interactions are essential causes of severe ADRs[22].

In the current study, ADRs were documented carefully as part of the institutional PV programme,

Table VI. Assessment of adverse drug reactions for causality, severity, predictability and preventability as per different scales		
Assessment of ADRs (characteristics)	n (%)	χ^2, P
Causality assessment		
WHO-UMC Scale		
Certain	08 (11.9)	13.82, 0.001
Probable/likely	37 (55.2)	
Possible	22 (32.8)	
Naranjo Scale		
Total score >9 definite	06 (09)	29.76, 0.001
Total score 5-8 probable	42 (62.7)	
Total score 1-4 possible	19 (28.4)	
Karch and Lasagna Scale		
Definite	05 (7.5)	25.91, 0.001
Probable	39 (58.2)	
Possible	23 (34.3)	
Severity assessment		
Modified Hartwig-Siegel scale		
Level 2: Stop the drug/symptomatic Rx/No Rx	15 (22.4)	21.16, 0.001
Level 3: Stopped/changed the drug/specific Rx	40 (59.7)	
Level 4a: Extension of hospital stay by at least one day	12 (17.5)	
Predictability assessment		
Rawlins and Thompson's criterion		
Non-predictable	05 (7.5)	48.49, 0.001
Predictable	62 (92.5)	
Preventability assessment		
Modified Schumock-Thornton scale		
Not preventable	52 (77.6)	20.43, 0.001
Definitely preventable	15 (22.4)	
χ^2: Chi-squared test was applied to ascertain the significant association between different groups. $P \leq 0.005$ was considered significant for different groups. WHO-UMC, World Health Organization-Uppsala Monitoring Centre		

based on patient reporting, symptoms, signs, laboratory investigations, and temporal relation to drug intake and events.

The proportion of these ADRs was 20.68 per cent (n=67) in the current study, comparable with Kaur *et al*[9] among Indian patients hospitalized with CVD (incidence of 21.5%). However, another study from Indonesia by Amalia *et al*[23] reported an incidence of 54.72 per cent, which may be because the reference study included only STEMI patients who underwent mainly thrombolytic therapy and/or PCI. Whereas our study included the entire spectrum of ACS patients (STEMI, NSTEMI and UA), and the treatment offered to STEMI patients was mainly primary PCI, which could be the reason for fewer adverse events such as bleeding, hypotension and others, as no patients were undergoing thrombolytic therapy. Patients reporting single ADRs in this study accounted for 79.1 per cent (n=53), while the rest had two or a maximum of three ADRs.

The most commonly reported ADR in the present study was headache, mainly caused by antianginals. A similar pattern of ADRs with antianginals (both in frequency and severity) has been reported[9,24,25]. This may also be because antianginals were commonly employed at optimal doses in our study. This study also reveals the most common system involved to be the haematologic system with abnormalities in platelet count and bleeding manifestations contributed by anticoagulants[26], in this case, UFH and LMWH, which are known to cause increased events when used at a relatively high dose along with antiplatelets in patients with ACS. Diuretics were attributed to a significant number of ADRs, which are also reported in the literature[27].

Similarly, although patients reporting single ADR were the most in Amalia *et al*[23], the proportion was lesser compared to our study, which could be due to fibrinolysis employed by the other trialists for the treatment of STEMI. All of our patients (100%) received dual antiplatelet therapy for loading and maintenance doses.

When it comes to causality or probability assessment, the majority of the ADRs in our study fell into the category of probable or likely 55.2 per cent (WHO-UMC), 62.7 per cent (Naranjo's scale) and 58.2 per cent (Karch and Lasagna) – an average of three scales being 58.7 per cent when compared to Amalia *et al*[23] who reported 69.39 per cent and another

study from India by Tarun *et al*[28] reported 20 per cent as probable. Both studies used only the WHO-UMC scale, whereas our study employed three different scales to assess this parameter.

In the category of definite/certain causal relationship to the drug and ADRs, our study had 11.9 (WHO-UMC), nine (Naranjo's) and 7.5 per cent (Karch and Lasagna), respectively (average of three, 9.46%), whereas previous studies have reported 5.38[28] and 14.29 per cent[23], respectively. Although the trend could imply that the WHO-UMC scale may be more sensitive in picking up a definite relationship when compared to the other two scales, this cannot be conclusively said, given the small sample size of the current study.

In severity assessment, most reactions fell in moderately severe category level 3, 59.7 per cent, comparable to Amalia *et al*[23], who reported 53.06 per cent in the same category. Around 17.5 per cent of patients in our study reported more severe level 4a reactions requiring at least a day's additional stay in the hospital.

92.5 per cent of the patients in the current study had predictable ADRs, implying that most of the reactions in ACS patients can be predicted if care is given. However, probably due to the obligatory use of many medications relatively at a higher dose implied that only 22.4 per cent could be prevented, and the rest were not preventable. In similar patients, the other Indian study by Tarun *et al*[28] documented only 16.14 per cent as preventable (definitely/probably) and 83.84 per cent as not preventable.

(*i*) Analysis of our data also revealed no particular association between the incidence of ADRs to age, gender and other associated comorbidities such as COPD, DM or HTN, which may be due to optimized use of drugs depending on the underlying comorbid conditions. However, this cannot be categorically deduced as this was only an observational record-based study with a relatively small sample size[29]. Furthermore, there were also certain limitations, including; (*i*) being a record-based analysis of ADRs reported to AMC and documented by the treating physician in case records, there was a possible under-reporting of ADRs; (*ii*) de-challenge and re-challenge were based on the treating physician's discretion and the clinical need of the drug for repeated use and not protocol driven; (*iii*) the sample size was small to

assess the actual incidence of ADRs among ACS patients, and lastly (*iv*) there were few studies available analyzing this category of ACS patients experiencing ADRs hence an in-depth comparison was also not possible.

Overall, ADRs are common among ACS patients due to polypharmacy and the combined use of different classes of medications with overlapping therapeutic effects. Most ADRs can be diagnosed and assessed for causality, severity, predictability and preventability using various scales, as done in the present study. Adequate care while prescribing multiple drugs in adjusting the dose, frequency, active PV, prompt recording and assessment of ADRs mass help manage and mitigate the morbidity associated with ADRs in this high-risk subset of ACS patients.

Conflicts of Interest: None.

References

1. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr., Ganiats TG, Holmes DR Jr., *et al*. 2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; *64* : e139-228.

2. Srinath Reddy K, Shah B, Varghese C, Ramadoss A. Responding to the threat of chronic diseases in India. *Lancet* 2005; *366* : 1744-9.

3. Gupta R. Burden of coronary heart disease in India. *Indian Heart J* 2005; *57* : 632-8.

4. World Health Organization. *International drug monitoring: The role of the hospital, report of a WHO meeting [held in Geneva from 18 to 23 November 1968]*. Available from: *https://apps.who.int/iris/handle/10665/40747,* accessed on March 25, 2020.

5. Juntti-Patinen L, Neuvonen PJ. Drug-related deaths in a university central hospital. *Eur J Clin Pharmacol* 2002; *58* : 479-82.

6. Kane-Gill SL, Jacobi J, Rothschild JM. Adverse drug events in Intensive Care Units: Risk factors, impact, and the role of team care. *Crit Care Med* 2010; *38* : S83-9.

7. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: A systematic review of prospective observational studies. *Ann Pharmacother* 2008; *42* : 1017-25.

8. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. *Lancet* 2000; *356* : 1255-9.

9. Kaur S, Kapoor V, Mahajan R, Lal M, Gupta S. Monitoring of incidence, severity, and causality of adverse drug reactions in hospitalized patients with cardiovascular disease. *Indian J Pharmacol* 2011; *43* : 22-6.

10. Lobo MGAA, Pinheiro SMB, Castro JGD, Momenté VG, Pranchevicius MCS. Adverse drug reaction monitoring: Support for pharmacovigilance at a tertiary care hospital in Northern Brazil. *BMC Pharmacol Toxicol* 2013; *14* : 5.

11. Indian Pharmacopoeia Commission, National Coordination Centre - Pharmacovigilance Programme of India (PvPI). Ministry of Health & Family Welfare, Government of India. *Guidance document for spontaneous adverse drug reaction reporting*. Available from: *https://who-umc.org/media/1075/india.pdf*, accessed on March 25, 2020.

12. Uppsala Monitoring Centre. *The use of the WHO–UMC system for standardized case causality assessment*. Available from: *http://www.WHO-UMC.org/graphics/4409.pdf*, accessed on March 25, 2020.

13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; *30* : 239-45.

14. Karch FE, Lasagna L. Adverse drug reactions. A critical review. *JAMA* 1975; *234* : 1236-41.

15. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm* 1992; *49* : 2229-32.

16. Raut AL, Patel P, Patel C, Pawar A. Preventability, predictability and seriousness of adverse drug reactions amongst medicine inpatients in a teaching hospital: A prospective observational study. *Int J Pharm Chem Sci* 2012; *1* : 1293-9.

17. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp Pharm* 1992; *27* : 538.

18. Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, *et al*. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med* 2014; *371* : 818-27.

19. Prabhakaran D, Yusuf S, Mehta S, Pogue J, Avezum A, Budaj A, *et al*. Two-year outcomes in patients admitted with non-ST elevation acute coronary syndrome: Results of the OASIS registry 1 and 2. *Indian Heart J* 2005; *57* : 217-25.

20. Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother* 2013; *4* : S73-7.

21. Harpaz R, Chase HS, Friedman C. Mining multi-item drug adverse effect associations in spontaneous reporting systems. *BMC Bioinformatics* 2010; *11* (Suppl 9) : S7.

22. Yang H, Yang CC. Discovering drug-drug Interactions and Associated Adverse Drug Reactions with Triad Prediction in Heterogeneous Healthcare Networks. In: Computer Science 2016: Proceedings of the IEEE International Conference on Healthcare Informatics (ICHI) Chicago. IEEE; 2016. p. 244-54.

23. Amalia L, Anggadireja K, Aprami TM, Septiani V. Prevalence of adverse drug reactions in CAD STEMI patients treated in the cardiac Intensive Care Unit at the public hospital in Bandung, Indonesia. *Sci Pharm* 2016; *84* : 167-79.

24. Mandavi, D'Cruz S, Sachdev A, Tiwari P. Adverse drug reactions & their risk factors among Indian ambulatory elderly patients. *Indian J Med Res* 2012; *136* : 404-10.

25. Horinaka S. Use of nicorandil in cardiovascular disease and its optimization. *Drugs* 2011; *71* : 1105-19.

26. Piazza G, Nguyen TN, Cios D, Labreche M, Hohlfelder B, Fanikos J, *et al*. Anticoagulation-associated adverse drug events. *Am J Med* 2011; *124* : 1136-42.

27. Prichard BN, Owens CW, Woolf AS. Adverse reactions to diuretics. *Eur Heart J* 1992; *13* (Suppl G) : 96-103.

28. Tarun W, Patil PA, Suresh VP. Monitoring of adverse drug reactions in coronary thrombosis patients admitted to the intensive cardiac care unit in a tertiary care hospital. *Indian J Pharm Pract* 2013; *6* : 6-12.

29. Sultana J, Trifirò G. The potential role of big data in the detection of adverse drug reactions. *Expert Rev Clin Pharmacol* 2020; *13* : 201-4.

For correspondence: Dr Manjappa Mahadevappa, Department of Cardiology, JSS Medical College Hospital, JSS Academy of Higher
                            Education and Research, Mysuru 570 004, Karnataka, India
                            e-mail: manjappam@jssuni.edu.in