Review Article

Acute Coronary Syndrome – Exploring the Evidences Clinical Pharmacist Driven Cardiac Review

Aftab Alam[1], Tarun Wadhwa[1,*], Elwaleed Hassan[2]

[1]Department of Clinical Pharmacy and Pharmacology, RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, Ras Al Khaimah, UAE.
[2]Specialist, Cardiology, Ibrahim Bin Hamad Obaidallah Hospital, Ras Al Khaimah, UAE.

ABSTRACT

Acute Coronary Syndrome is the most common type of coronary artery disease. Coronary artery disease and acute coronary syndrome together responsible for approx. 7 million deaths which accounts for around half of the global burden. World Health Organization report exemplified that 17.9 million deaths occurred in 2016 due to cardiovascular diseases which represents 31% of all global deaths. Known family history, age, male gender, hypercholesterolemia, diabetes mellitus, hypertension, lack of physical activity, abdominal obesity, cigarette smoking, psychosocial factors, consumption of too much alcohol and consumption of less fruits, vegetables and polyunsaturated fatty acids are some of the risk factors associated with coronary artery disease. Patients' sign and symptoms, past medical history, ECG changes and determination of cardiac markers (Troponin and CK MB) are used to stratify patients into low, medium or high risk of death or MI, likelihood of failure of pharmacotherapy and need for immediate coronary angiography or percutaneous coronary intervention. For the management of acute coronary syndrome, cardiac drugs are recommended in addition to surgical interventions with specific goals for short and long term of treatment. Cardiac drugs need to be used cautiously in patients with coronary thrombosis as these category of drugs are responsible for increased incidence of adverse drug reactions thereby affecting the patient's health status and economic condition. Therapeutic interventions like smoking cessation, managing dyslipidaemia and controlling blood pressure not only prevent coronary artery disease but also delays its progression and complications.

Key words: Acute Coronary Syndrome, Adverse Drug Events, Adverse Drug Reactions, Cardiac Drugs, Coronary Artery Disease, Ischemic Heart Disease, Risk Factors, World Health Organization.

INTRODUCTION

Coronary arteries are responsible for supplying oxygen rich blood and nutrients to the heart for effective functioning. They control the supply of oxygen rich blood based on the requirements of the heart as shown by heart rate, blood pressure and force of contraction of heart.[1] Ischemic Heart Disease (IHD) occurs when arteries of the heart are unable to supply sufficient amount of oxygen rich blood to the heart. The most common type of ischemic heart disease is coronary artery disease (CAD) (Figure 1 and 2).[2]

World Health Organization (WHO) report exemplified that 17.9 million deaths occurred in 2016 due to cardiovascular diseases which represents 31% of all global deaths. Out of these, 85% of deaths are reported due to heart attack and stroke.[3] Based on the recent data from 2016, the report states that 121.5 million US adults are living with some form of cardiovascular disease, which affects 48% of American adults (Figure 3).[4]

Epidemiology

According to a recent report, published in February 2019, by American College of Cardiology (ACC), approximately after every 40 seconds, an American will have myocardial infarction. In the US in 2019, a total of 1,055,000 coronary events are expected to occur which will consist of 7,20,000 new and 3,35,000 recurrent cases.[5]

Prevalence of CAD in the Middle East region has been reported in the range of 5.4% to 13.4%.[6] A report from the Ministry of Health and Prevention (MoHAP) showed

DOI: 10.5530/ijopp.13.4.52

Address for correspondence:
Dr. Tarun Wadhwa
Assistant Professor, Department of Clinical Pharmacy and Pharmacology, RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, Ras Al Khaimah, UAE.
Phone no: +971 503747342
Email Id: tarun@rakmhsu.ac.ae

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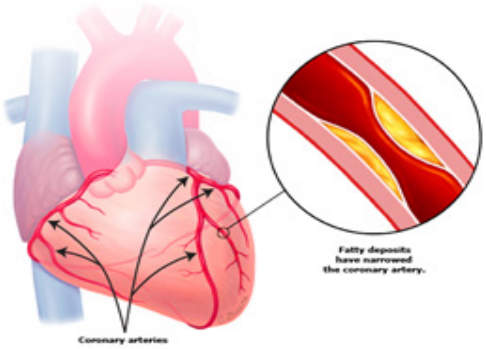


Figure 1: Coronary Arteries and Atherosclerosis.

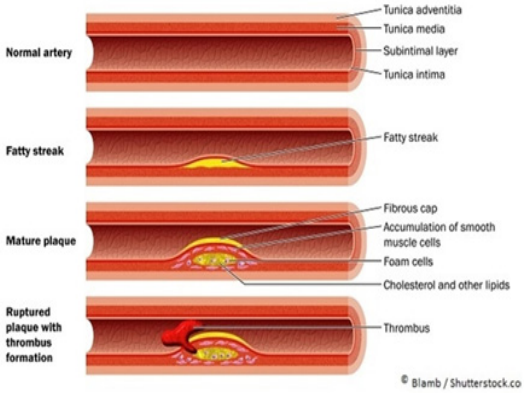


Figure 2: Status of Coronary Arteries in Coronary Artery Disease.

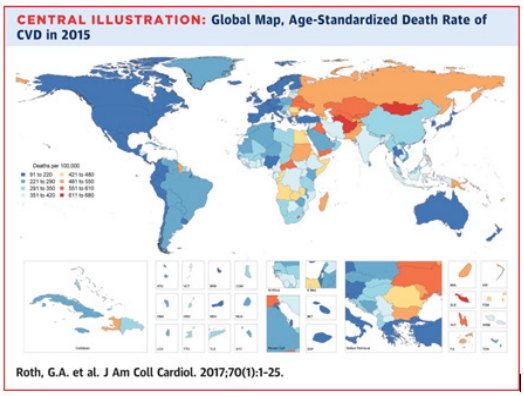


Figure 3: Global Map, Age Standardized Death Rate of CVD.

the fact that one of the leading causes of mortality in United Arab Emirates (UAE) is cardiovascular disease (CVD). Of all deaths, 22% were due to acute myocardial infarction, 16% due to cerebrovascular disease, 6% due to ischemic heart disease and 5% due to hypertension.[7]

Based on a report published by WHO in The Atlas of Heart Disease and Stroke, annual number of deaths expected to occur globally due to Cardiovascular Disease (CVD) by 2020 and 2030 is 20.5 million and 24.2 million respectively which was 18.1 million in 2010. Percentage of all deaths due to CVD expected to occur worldwide by 2020 and 2030 is 31.5% and 32.5% respectively compared to 30.8% in 2010.[8]

Coronary artery disease

Coronary artery disease (CAD) is the main cause of fatality in the United States and worldwide.[2,9,10] It occurs due to formation of plaques inside the coronary arteries. Fat, cholesterol, calcium and other substances available in the blood form plaques. Over a period of time, plaques become hard and make the arteries narrow which results in decreased supply of oxygen rich blood to the heart. Sometimes, the plaque ruptures and forms a clot on its surface. The clot size in the coronary arteries, if large enough, interrupt the blood flow to certain part of the heart muscle leading to angina or heart attack.[10] (Figure 1,2)

Acute Coronary Syndrome

Acute Coronary Syndrome (ACS) refers to a condition when the blood supply to the heart is blocked suddenly. It is considered as a medical emergency. Acute Coronary Syndrome is the most common type of CAD. Coronary artery disease and acute coronary syndrome together responsible for approx. 7 million deaths which accounts for around half of the global burden.[11,12]

Stratification of Acute Coronary Syndrome

Acute Coronary Syndrome has been classified into three clinical categories based on the presence/ absence of ST-segment elevation of the electrocardiogram (ECG) and estimation of myocardial biomarkers (such as troponin or creatine kinase) (Table 1).

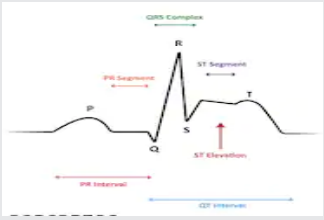
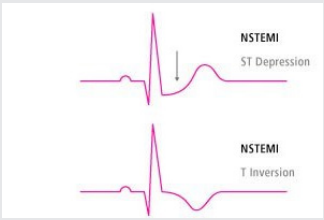
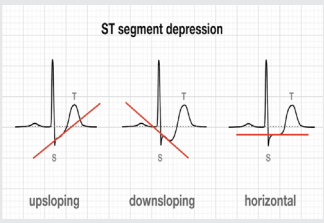
ST-elevation myocardial infarction represents complete occlusion of the coronary artery. In case of STEMI, the ECG shows persistent elevation in two or more anatomically contiguous leads of ST-segment.

Unstable angina and NSTEMI represents partial occlusion of coronary artery. In such cases, ECG shows changes such as ST-segment depression and T-wave inversion or may be normal. Unstable angina and NSTEMI are differentiated by the serial measurement of cardiac biomarkers (troponin and creatine kinase-MB), which are elevated at presentation or after several hours in case of NSTEMI but are normal in case of UA.[13]

Clinical Features

Major signs and symptoms of myocardial infarction include chest pain or discomfort, pain or discomfort in the arms or shoulder, shortness of breath, feeling light

Table 1: Stratification of ACS based on ECG characteristics.

S.No.	Clinical Category	ECG findings
1.	ST-elevation Myocardial Infarction (STEMI)	
2.	Non-ST-elevation Myocardial Infarction (NSTEMI)	
3.	Unstable Angina (UA)	

headed or faint, vomiting, syncope or sudden death due to arrhythmia and pain or discomfort in the jaw, neck or back. Sometimes myocardial infarction may be painless especially in elderly and diabetic patients.[14,15]

Risk Factors

Risk factors of CAD include positive family history, age, male gender, hypercholesterolaemia, diabetes mellitus, hypertension, lack of physical activity, abdominal obesity, cigarette smoking, psychosocial factors, consumption of too much alcohol and consumption of less fruits, vegetables and polyunsaturated fatty acids.[9,15,16]

Although many among the risk factors are non-modifiable, it has been reported that interventions such as smoking cessation, managing high blood pressure and treating dyslipidemia can prevent CAD and delay its progression or complication.[15]

Stratification of Risk Groups

Patients' sign and symptoms, past medical history, ECG changes and determination of cardiac markers (Troponin and CK MB) are used to stratify patients into low, medium or high risk of death or MI, likelihood of failure of pharmacotherapy and need for immediate coronary angiography or Percutaneous Coronary Intervention (PCI). Patients with STEMI need immediate initiation of reperfusion strategy as they are at high risk of death. Risk stratification of patients with NSTEMI is more complex because of variable outcomes.[17,18]

GRACE Risk Score

GRACE risk score is used to stratify the risk in acute coronary syndrome. Clinical features of grace score are heart failure, systolic blood pressure, heart rate, age (years), serum creatinine (μmol/L), cardiac arrest at admission, ST-segment deviation and elevated cardiac enzyme levels.[15]

TIMI Risk Score

Another method used for the risk stratification is TIMI risk score. It consists of seven variables namely age (≥ 65 years), three or more cardiac risk factors, previous coronary stenosis 50% or more, ST-segment deviation, two anginal events in past 24 hr, use of aspirin in prior seven days and elevated cardiac markers.[9] TIMI score 0-2 points indicates low risk, 3-4 points indicates medium risk and 5-7 points indicates high risk.[18]

The presence of various risk factors, cardiac disease status, use of complex regimen and intensive management may enhance the exposure and thereby risk of developing adverse drug reactions.

Evidence related to adverse drug reactions (ADRs) is mainly gathered from hospitals as the risk is comparatively higher as compared to other healthcare settings. Certain predisposing factors such as elderly age, gender, polypharmacy, co-morbidity, past history of allergy, drug-drug interactions, genetic factors etc. are associated with increased occurrence of ADRs. Factors that affect the occurrence of ADRs can be classified into five groups namely, patient related factors, social factors, drug related factors, disease related factors and ADR related factors.[19]

Adverse Drug Events

Adverse Drug Events (ADEs) can be life threatening for patients who are critically ill. Life threatening adverse events occur in 26% of intensive care unit (ICU) patients as compared to 11% in case of non-ICU patients. The rate of preventable and potential adverse drug events in ICU and general care units is reported as 19 events and 10 events per 1000 patient days respectively. Alteration in organ function, complex drug regimens and quick decision-making in critically ill patients make them more vulnerable to develop ADRs.[20]

Adverse drug reaction definition (WHO)

According to WHO definition, an adverse drug reaction

(ADR) is any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy. The use of any medicine may cause unwanted effect. According to Centre for Health Policy Research, more than 50% of the approved drugs in the United States are known to cause some kind of ADR that was undetected prior to approval of these drugs.[21]

Adverse drug reactions are associated with significant morbidity and mortality. It has been estimated that 11% of hospital admissions are due to ADRs. A meta-analysis reported that worldwide incidence of serious ADRs is 6.7 % whereas fatal ADRs is 0.32 % among hospitalized patients. Many hospitalizations and emergency visits due to ADRs are preventable.[21]

Cardiovascular Medications and Adverse Drug Events

One of the most common drug class, that is considered to be associated with ADRs, is cardiovascular medications. Therefore, these medications require close and continuous monitoring. Based on a report from adverse drug event prevention group, odds ratio of cardiovascular medications are 2.4 times higher than that of other class of medications.[22,23]

Adverse drug events (ADEs) include errors of administration and adverse drug reactions. In-hospital medication errors cause 770,000 injuries or deaths each year in US. An average prolongation in hospitalization due to ADEs are 1.2 to 3.8 days. According to a meta-analysis by Lazarou *et al*. ADRs are fourth to sixth leading cause of death. A Canadian retrospective study highlighted that 42% patients need hospitalization because of ADEs and 29% of those were considered as preventable ADEs. A retrospective study carried out in Britain unveiled ADRs were the cause of 6% hospital admissions.[23]

VigiBase is global database of WHO for international drug monitoring. It contains more than 18 million safety reports from 131 countries. Analysis of individual case safety reports collected between 1967 and 2018, revealed gender specific differences related to ADRs among males and females. According to a report, females are more prone to develop ADRs than males especially during their reproductive years whereas proportion of serious and fatal ADRs are higher in males as compared to females.[24]

Analysis of in-patient data collected from Western Australia hospital between 1981 to 2002 by Burgess *et al*. revealed that there is an increase in the incidence of ADRs from 2.5 to 12.9 per 1000 patients aged 60 years and above. Of all episodes related to ADRs, 45% were males and 55% were females with vast majority were in the age range of 65-84 years (45.6%) followed by 45-64 years (21.1%) and 85 years and above (16.1%). Of all patients hospitalized due to ADRs, 3.3% died during the course of care which accounts for 2.4% increase per year. The study shown that anticoagulants were responsible for 13.5% of all hospitalizations.[25]

According to a research study carried out in a tertiary care emergency medicine ward in Sweden, the most common organ system affected by ADRs was cardiovascular, followed by electrolyte imbalance and haemorrhage. Adverse drug reaction was the reason for admission in 18% of patient population out of which 24% ADRs were preventable.[26]

Another study conducted by Palaniappan *et al*. (2015) in a tertiary care teaching hospital in India, stated that ADRs related to cardiovascular drugs accounted for 18.1% of the total reported ADRs during study period. Common cardiovascular drugs found to be associated with ADRs were enalapril (17.5%), atorvastatin (14.9%), aspirin (8.4%) and metoprolol (8.4%).[27]

A prospective cohort study carried out in Saudi Arabia by Aljadhey *et al*. reported 30% of ADEs among hospitalized patients which were definitely or probably preventable.[28] Another prospective cohort study demonstrated 6.1% incidence of adverse drug events (ADEs). The occurrence of ADEs in ICU, medical and surgical units were 60.8%, 27.3% and 11.8% respectively. Out of total, 52.7% of ADEs were reported to be significant, serious (37.1%), life threatening (9%) and fatal (1.2%).[29]

A prospective observational study carried out in United Arab Emirates (UAE) demonstrated that the most common drugs associated with ADR-related hospitalizations were diuretics (32%), anticoagulants (9%) and antiplatelets (6%). The study reported that one third of hospital admissions to cardiac unit were related to ADRs that are preventable.[30]

A prospective observational study was conducted in a secondary care hospital in northern emirates demonstrated high incidence of ADRs due to cardiovascular drugs. Bisoprolol was the most common drug implicated in causing ADRs, specifically, bradycardia as an adverse effect.[31]

According to a news article published in Khaleej times in April 19, 2017, there is a significant increase in the number of cases of adverse drug reactions in UAE. Ministry of Health and Prevention, UAE noticed increase number of ADR cases varying from 59 in 2013 to 825 in 2016.[32]

Cardiac drugs need to be used cautiously in patients with coronary thrombosis as these category of drugs are responsible for increased incidence of ADRs thereby affecting the patient's health status and economic condition.

Evidence Based Treatment

For the management of ACS, cardiac drugs are recommended in addition to surgical intervention with specific goals for short and long term of treatment. Goals of treatment for short term include early restoration of blood flow to prevent expansion of infarct, prevention of death and other complications, prevention of re-occlusion of coronary artery and relief of ischemic chest discomfort. Long term goals of treatment are to control cardiovascular risk factors, prevention of further cardiovascular events and improvement in quality of life.[18]

All patients presenting to emergency department with symptoms suggestive of acute myocardial infarction should be thoroughly assessed for history, physical examination, ECG and intravenous (IV) access should be established. Continuous monitoring of oxygen saturation by pulse oximetry is required. Supplemental oxygen should be given if oxygen saturation is below 90%.[33]

All patients presenting with ACS should receive aspirin in a dose range of 162-325 mg. Nitrates should be given as sublingual tablet in a dose of 0.4 mg for reducing cardiac pain. Nitrates should not be used if a patient presents with hypotension or bradycardia as it is one of the side effects of nitrates. For refractory or severe pain, intravenous morphine in a dose range of 2-4 mg should be given. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided if possible as it is associated with adverse cardiovascular events.[33]

Various group of medications are required in order to improve survival, decrease recurrent ischemia and provide relief from symptoms. In patients with STEMI, the most important goal is to provide reperfusion therapy on time with the aim that ischemic time (time from onset of symptoms to administration of reperfusion modality) being less than 120 min. Reperfusion therapy can be either fibrinolytic agent or Percutaneous Coronary Intervention (PCI), which depends upon estimation of time necessary for selection of a particular intervention. Door-to-needle time is referred for fibrinolysis whereas Door-to-balloon time is considered for PCI. For patients with STEMI, presenting within 12 hr from the onset of symptoms, PCI is preferred. European guidelines 2017 suggests placement of drug eluting stent (DES) in the culprit artery. Radial access should be preferred over femoral access.[34]

Fibrinolytic therapy is contraindicated in some patients such as patients with previous intracranial haemorrhage, ischemic stroke within past three months, known central nervous system neoplasm, major head surgery within past two months, known active bleeding except menses, suspected aortic dissection, severe uncontrolled hypertension which is not responsive to therapy and use of streptokinase in the past six months.[33,34]

For the acute management of STEMI, Coronary Artery Bypass Grafting (CABG) should not be opted as initial treatment modality. It is recommended in case of failure of PCI, cardiogenic shock, high risk anatomy and ventricular septal rupture.[35]

Anticoagulants are used as an adjunctive therapy to reperfusion therapy (primary PCI or fibrinolytic therapy). For patients receiving primary PCI, unfractionated heparin (e.g. bivalirudin) and low molecular weight heparin (e.g. enoxaparin) is used. For patients receiving fibrinolytic therapy, anticoagulants should be prescribed until performing revascularization. All STEMI patients should be prescribed with dual antiplatelet agents. Examples of these agents are aspirin and P2Y12 receptor inhibitors (clopidogrel, ticagrelor and prasugrel). Latest European society guidelines recommend unfractionated heparin as a preferred anticoagulant but enoxaparin is a safe and alternative option.[33] A meta-analysis in 2018 conducted by Wang Hai-long *et al*. demonstrated that there is reduction in death and myocardial infarction if STEMI patients are treated with enoxaparin instead of unfractionated heparin. The study also showed that there is no major difference in the occurrence of bleeding events.[36]

All patients presented with STEMI should be advised to use beta blocker if there is no contraindication. Nitrates should be recommended for chest pain due to ischemia. Routine use of nitrates is not strongly recommended if there is no angina pain. Studies have shown beneficial effects of Angiotensin Converting Enzyme (ACE) inhibitors in cardiac patients. Angiotensin receptor blockers (ARBs) should be advised alternatively if the patient is unable to tolerate ACE inhibitors. ACE Inhibitors/ARBs are usually started after 24 hr of admission.[37] For severe chest pain not responding to nitrates, IV morphine is recommended. The common side effects of nitrates are hypotension and bradycardia.[38]

Statins are recommended as a lipid lowering agent in patients having elevated lipid profile. Beneficial effects of early treatment with statin have been demonstrated in the SECURE-PCI trial.[39] If a patient cannot tolerate statin therapy or is contraindicated, ezetimibe should

be considered which is demonstrated by IMPROVE-IT trial.[40]

For the management of NSTEMI or UA, early invasive strategy should be followed, which means performing coronary angiography within 48 hr of presentation and then PCI or CABG or only conventional line of management. All patients after diagnosis should receive the loading dose of aspirin and subsequent maintenance dose. Current European and American guidelines recommend the use of P2Y12 immediately after diagnosis. Anticoagulants such as enoxaparin, UFH and fondaparinux are Class-I recommendation. For patients who have developed heparin-induced thrombocytopenia, Bivalirudin is recommended. Use of nitrates, morphine and beta blockers for the symptomatic management remains the same as that in case of STEMI. Statin therapy should be initiated as soon as possible after hospitalization. ACE inhibitors/ ARBs should be used as long term therapy based on the tolerability and convenience of patients.[34]

Therapeutic Interventions

Therapeutic interventions like smoking cessation, managing dyslipidaemia and controlling blood pressure not only prevent CAD but also delays its progression and complications. Many clinical trials have shown the efficacy of statins in the prevention of death, coronary events and strokes. IMPROVE-IT trial demonstrated that the use of ezetimibe 10 mg in combination with simvastatin is better than that of using simvastatin alone in reducing the risk of myocardial infarction. All patients who are at risk of cardiovascular events should be treated with statins regardless of their cholesterol levels. Recommended target LDL level should be less than 70 mg/dl for those patients who have previous cardiovascular events. The role of aspirin including its dose remains controversial in the primary prevention. Effectiveness of clopidogrel has been demonstrated in preventing vascular events for 9 to 12 months after ACS. CHARISMA trial showed that the long term treatment of aspirin and clopidogrel in combination was not effective in preventing vascular events. COMPASS trial shown the effectiveness of rivaroxaban (direct factor Xa inhibitor) 2.5 mg twice daily with 100 mg aspirin in reducing cardiovascular death, myocardial infarction (MI) and stroke by 24% as compared to 100 mg aspirin monotherapy in stable patients with CHD and peripheral artery disease. The HOPE trial and EUROPA trial demonstrated the effectiveness of ramipril 10 mg per day and perindopril 8 mg per day respectively in reducing the cardiovascular deaths and non-fatal MI by 20-25% among patients who are at high risk and have diabetes mellitus.[9]

Complications of Acute Coronary Syndrome

Complications of acute coronary syndrome include arrhythmias, post-infarction ischaemia, acute circulatory failure, pericarditis, papillary muscle rupture, rupture of the interventricular septum, rupture of the ventricle, mural thrombus and development of ventricular aneurysm.[9,15]

Prognosis in ACS patients

Evaluation of therapeutic outcomes can be performed for STEMI, NSTEMI and UA patients by monitoring the efficacy of pharmacological and non-pharmacological therapy in relation to common parameters such as relief from chest discomfort, reversal of abnormal ECG findings to normal and absence of signs of heart failure. Most common ADRs associated with the use of ACS medications are hypotension and bleeding. Management of these ADRs can be achieved by cessation of causative agents until resolution of symptoms.[17]

CONCLUSION

Acute coronary syndrome is a type of coronary artery disease which requires thorough assessment by healthcare professionals based on clinical features, ECG characteristics, cardiac biomarkers and risk stratification. Evidence based medicine should be adopted for therapeutic management of ACS considering the effectiveness, safety and cost of interventions. Cardiac drugs need to be used cautiously in patients with coronary thrombosis as these drugs are responsible for high incidence of adverse drug reactions. Therapeutic interventions like smoking cessation, managing dyslipidaemia and controlling blood pressure not only prevent coronary artery disease but also delays its progression and complications. Clinical pharmacist driven approach, for monitoring adverse drug reactions and its timely management in order to enhance quality of care for patients with ACS, is of utmost importance.

ACKNOWLEDGEMENT

Authors wish to thank RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, Ras Al Khaimah, UAE for their constant support and encouragement.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ACC: American College of Cardiology; **ACE:** Angiotensin

Converting Enzyme; **ACS:** Acute Coronary Syndrome; **ADEs:** Adverse Drug Events; **ADRs:** Adverse Drug Reactions; **AHA:** American Heart Association; **ARB:** Angiotensin Receptor Blocker; **CABG:** Coronary Artery Bypass Grafting; **CAD:** Coronary Artery Disease; **CVD:** Cardiovascular Disease; **DES:** Drug Eluting Stent; **ECG:** Electrocardiogram; **ICU:** Intensive Care Unit; **IHD:** Ischemic Heart Disease; **IV:** Intravenous; **MoHAP:** Ministry of Health and Prevention; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **NSTEMI:** Non-ST Elevation Myocardial Infarction; **PCI:** Percutaneous Coronary Intervention; **STEMI:** ST Elevation Myocardial Infarction; **UA:** Unstable Angina; **UAE:** United Arab Emirates; **WHO:** World Health Organization.

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