"STUDY ON ANTICOAGULANT UTILIZATION EVALUATION AND RISK SCORE ASSESSMENT FOR PREDICTING BLEEDING AMONG PATIENTS WITH ACUTE CORONARY SYNDROME"

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CERTIFICATE

This is to certify that the M.Pharm Dissertation entitled **"Study on anticoagulant utilization evaluation and risk score assessment for predicting bleeding among patients with acute coronary syndrome"** being submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai was carried out by **Ms. Aparna.N (Reg. No. 261640101)** in the Department of Pharmacy Practice, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, under the direct supervision and guidance of **Dr. V.Shivashankar**, **M.Pharm., Ph.D**., Assistant Professor, Department of Pharmacy Practice, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore.

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ABBREVIATIONS

ACS	:	Acute Coronary Syndrome
UA	:	Unstable Angina
CHD	:	Coronary Heart Disease
CAD	:	Coronary Artery Disease
CVD	:	Cardiovascular Disease
STEMI	:	ST Elevated Myocardial Infarction
NSTEMI	:	Non ST Elevated Myocardial Infarction
GTN	:	Glyceryl Trinitrate
CRUSADE	:	Can Rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of ACC/AHA Guidelines
ACC/AHA	:	American College of Cardiology/ American Heart Association
eGFR	:	estimated Glomerular Filtration Rate
ACUITY HORIZONS	:	Acute Catheterization and Urgent Intervention Triage Strategy and Harmonizing Outcomes with Revascularization and Stent in Acute Myocardial Infarction
HAS-BLED	:	Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding, History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly

DAPT	:	Dual antiplatelet therapy
INR	:	International normalized ratio
GRACE	:	Global Registry for Acute Coronary Events
CBRS	:	CRUSADE Bleeding risk score
ACTION	:	Acute Coronary Treatment and Intervention Outcomes Network
TIMI	:	Thrombolysis In Myocardial Infarction
PURSUIT	:	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy
ECG	:	Electrocardiography
ADRs	:	Adverse Drug Reactions
WHO	:	World Health Organization
PCI	:	Percutaneous Coronary Intervention
DES	:	Drug Eluting Stent
BMS	:	Bare Metal Stent
GP IIb/IIIa	:	Glycoprotein IIb/IIIa
UFH	:	Unfractionated Heparin
LMWH	:	Low Molecular Weight Heparin
AF	:	Atrial Fibrillation
PTCA	:	Percutaneous Transluminal Coronary Intervention
ACE I	:	Angiotensin converting enzyme inhibitors
ARBs	:	Angiotensin receptor blockers

ABSTRACT

Coronary heart disease is responsible for more than half of all cardiovascular events in individuals less than 75 years of age. Among cardiovascular diseases (CVD), acute coronary syndrome is associated with substantial morbidity and mortality and places a large financial burden on the health care system. The Global Burden of Disease study estimate of age-standardized CVD death rate of 272 per 100,000 populations in India is higher than the global average of 235 per 100,000 populations. The World Health Organization (WHO) has estimated that, with the current burden of CVD, India would lose $237 billion from the loss of productivity and spending on health care over a 10-year period (2005–2015). Drug utilization evaluation of anticoagulant drugs is essential considering the spectrum of use and associated risk with their therapy. Early risk stratification with the help of various risk scores can assist Clinicians in determining appropriate pharmacologic therapies.

The objectives of the present study were to evaluate anticoagulant use patterns, identify and assess various drug interactions and ADRs and also to assess the prognostic value of CRUSADE (Can Rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) risk score in predicting risk of major bleeding among patients with acute coronary syndromes (ACS). A total of 122 patients of which 98 (80%) were males and 24 (20%) were females, from the Cardiology and General medicine department as per the inclusion criteria were included in this prospective, observational study conducted for duration of 10 months.

From the study, the mean age of the overall study population was found to be 55.63±10.02 and most predominant group was middle adulthood (34-59) 74(60.65%). Among the ACS patients, ST elevated myocardial infarction

103(84.42%) was the most commonly found followed by Unstable angina and Non ST elevated myocardial infarction. The most common non modifiable risk factor was found to be males 98(80%) and other modifiable risk factors was found to be diabetes, hypertension. Diabetes mellitus was the most common co-morbid condition among the study populations 30(32.96%). and majority of patients has received antiplatelets 242(19.29%) followed by anti-ulcerative agents and anticoagulants. A total of 721 drug-drug interactions were identified. 439(60.88%) interactions were major in severity.

Unfractionated heparin 114(96.61%) was found to be most extensively prescribed anticoagulants followed by Enoxaparin. More number of patients was in the very low bleeding risk category ≥ 20 (36.88%). The major bleeding risk factors were Age ($\geq$65yrs) followed by diabetes, Females etc. Patients at higher risk category are also at high risk of bleeding according to CRUSADE risk score. The overall incidence of bleeding rates was found to be 8(6.55%). The bleeding rate was more in the CRUSADE risk category (>40) (75%) and also in patients with ST elevated myocardial infarction (87.5%).

Across the ACS spectrum, CRUSADE risk score was able to identify patients at high bleeding risk and the future aspects of this research study can focus on the implementation of various bleeding reducing strategies including the dosage adjustments of anticoagulants based on international normalized ratio (INR) and activated partial thromboplastin time (ApTT) value, using alternative therapy with less bleeding risk, correcting bleeding risk factors, if possible.

1. INTRODUCTION

Coronary artery disease or Ischemic Heart disease is a complex chronic inflammatory disease, characterized by remodeling and narrowing of the coronary arteries supplying oxygen to the heart. Coronary artery disease is the leading cause of death and disability worldwide, and its prevalence is expected to increase in the coming years. It can have various clinical manifestations including stable angina, acute coronary syndrome, and sudden cardiac death. [1]Ischemia refers to a lack of oxygen due to inadequate perfusion of the myocardium, which causes an imbalance between oxygen supply and demand. The term Acute Coronary Syndrome refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes Unstable angina, Non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. [2]

Cardiovascular diseases have now become the leading cause of mortality in India. A quarter of all mortality is attributable to CVD. Ischemic heart disease and stroke are the world's biggest killers, accounting for a combined 15 million deaths in 2015. These diseases have remained the leading causes of death globally in the last 15 years. The Global Burden of Disease study estimate of age-standardized CVD death rate of 272 per 100,000 populations in India is higher than the global average of 235 per 100,000 populations. The World Health Organization has estimated that, with the current burden of CVD, India would lose $237 billion from the loss of productivity and spending on health care over a 10-year period (2005–2015).[3]

The American Heart Association and the American College of Cardiology recently updated practice guidelines and performance measures to help clinicians adhere to a standard of care for all patients who present with symptoms of ACS. Quantitative assessment of risk is useful for clinical decision making. Several scores have been developed from different populations to estimate ischemic and bleeding risks with different outcomes and time frames. In clinical practice,

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simple risk scores may be more convenient and preferred. It is recommended to use established risk scores for prognosis and bleeding with a class 1 recommendation.[5]

1.1 ETIOLOGY AND CLASSIFICATION OF ACUTE CORONARY SYNDROME

The vast majority of Coronary Heart Disease occurs in patients due to atherosclerosis of the coronary arteries. ACS begins when a disrupted atherosclerotic plaque in a coronary artery stimulates platelet aggregation and thrombus formation. The main coronary arteries are depicted in fig. no: 1. it's the thrombus occluding the vessel that prevents myocardial perfusion. Most cases of infarction are due to the formation of an occluding thrombus on the surface of the plaque.

Fig.1.The main coronary arteries of heart

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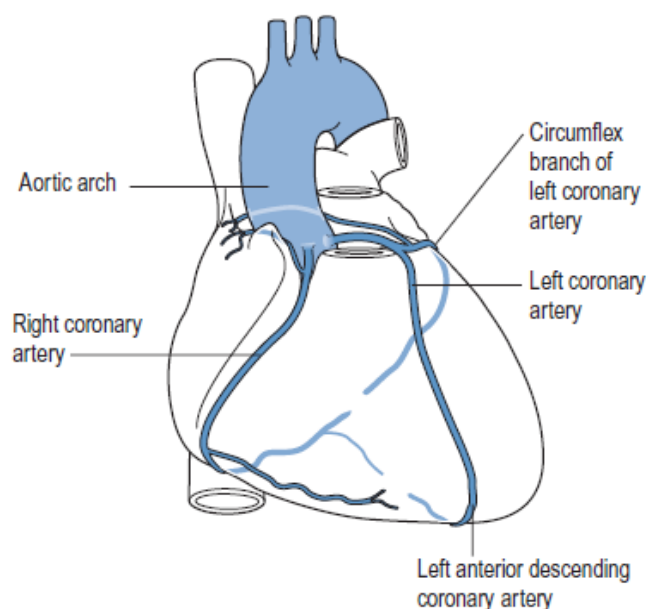
The AHA and the ACC recommend that a 12-lead electrocardiogram be performed in patients with symptoms consistent with ACS. ST elevation on a 12-lead ECG in two contiguous leads is diagnostic of STEMI. With STEMI, T-wave inversion may also be present. Electrocardiographic findings reflective of unstable angina or NSTEMI include ST-segment depression, inverted T waves and positive or negative cardiac markers. Unstable angina and NSTEMI normally result from a partially or intermittently occluded coronary artery, whereas STEMI results from a fully occluded coronary artery.

Coronary artery disease leads to the interruption of blood flow to cardiac muscle when the arteries are obstructed by plaque. Each artery supplies blood to a specific area of the heart. Depending on the degree to which an artery is blocked, the tissue that receives blood from it is at risk for ischemia, injury or infarction.

- ➤ If the left anterior descending artery is occluded, the anterior wall of the left ventricle, the interventricular septum, the right bundle branch, and the left anterior fasciculus of the left bundle branch may become ischemic, injured, or infarcted.

- ➤ If the right coronary artery is occluded, the right atrium and ventricle and part of the left ventricle may become ischemic, injured, or infarcted.

- ➤ If the circumflex artery is blocked, the lateral walls of the left ventricle, the left atrium, and the left posterior fasciculus of the left bundle branch may become ischemic, injured, or infarcted.[5]

1.2 RISK FACTORS OF ISCHEMIC HEART DISEASE

The World Health Organization has recognized obesity, diabetes mellitus, hypertension, chronic kidney disease, hypercholesterolemia, and smoking among the top10 traditional risk factors for premature death and morbidity.[6]

Traditional Framingham risk factors such as hypertension, hyperlipidemia, diabetes, smoking, as well as lifestyle habits such as unhealthy diet and sedentary lifestyle are all modifiable. Health care providers should be aware of emerging

cardiac risk factors in women such as adverse pregnancy outcomes, systemic autoimmune disorders, obstructive sleep apnea, and radiation induced heart disease. Psychological factors includes mental stress, depression, anxiety, low socioeconomic status, work and marital stress play an important role in Ischemic Heart disease in women.[7] The same was depicted below in Table.1.

Table.1. Ischemic Heart Disease risk factors

Framingham risk factors	Hypertension
	Hyperlipidemia
	Smoking
	Peripheral artery disease
	Chronic kidney disease
Non-Framingham risk factors	Overweight and obesity
	Family history of ischemic heart disease
	Metabolic syndrome: Dysregulation of metabolic factors such as tumor necrosis factor-α, leptin and adiponectin
	C-reactive protein
	Polycystic ovarian syndrome
	Radiation therapy
	Anemia
	Osteoporosis
Lifestyle factors	Alcohol
	Physical inactivity etc.

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1.3 MANAGEMENT OF ACUTE CORONARY SYNDROME

The short-term goals of treatment for the ACS patient are:

➤ Early restoration of blood flow to the infarct-related artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion

➤ Prevention of death and other complications

➤ Prevention of coronary artery reocclusion

➤ Relief of ischemic chest discomfort

Either fibrinolysis or immediate primary percutaneous coronary intervention is the treatment of choice for reestablishing coronary artery blood flow for patients with ST-segment-elevation ACS when the patient presents within 3 hours of symptom onset. For primary PCI, the patient is taken from the emergency department to the cardiac catheterization laboratory and undergoes coronary angiography with either balloon angioplasty or placement of a bare metal or drug-eluting stent.

According to the ACC/AHA ST-segment-elevation ACS practice guidelines, early pharmacotherapy of ST-segment elevation should include:

➤ Intranasal oxygen (if oxygen saturation is <90%)

➤ Sublingual followed by intravenous nitroglycerin, aspirin, an IV β-blocker, unfractionated heparin, and fibrinolysis in eligible candidates.

➤ Morphine is administered to patients with refractory angina as an analgesic and a venodilator that lowers preload.

Early pharmacotherapy for non-ST-segment-elevation ACS is similar to that for ST-segment-elevation ACS with four exceptions:

➤ Fibrinolytic therapy is not administered.

➤ Glycoprotein IIb/IIIa receptor blockers are administered to high-risk patients for medical therapy as well as for PCI patients.

➤ There are no standard quality indicators for patients with non-ST-segment-elevation ACS who are not diagnosed with MI.

1.4 PHARMACOLOGICAL THERAPY

1.4.1 IMMEDIATE CARE TO ALLEVIATE PAIN, PREVENT DETERIORATION AND IMPROVE CARDIAC FUNCTION

Patients with suspected STEMI should receive sublingual Glyceryl Trinitrate under the tongue, oxygen administered and intravenous access established immediately. If sublingual GTN fails to relieve the chest pain, intravenous morphine may be administered together with an antiemetic such as prochlorperazine or metoclopamide.

1.4.2 RESTORING CORONARY FLOW AND MYOCARDIAL TISSUE PERFUSION

a) Fibrinolytics

➢ Administration of a fibrinolytic agent is indicated in patients with ST-segment-elevation ACS presenting to hospital within 24 hours of the onset of chest discomfort who have at least 1 mm of ST-segment elevation in two or more contiguous ECG leads.

➢ According to ACC/AHA ST-segment-elevation ACS practice guideline, a more fibrin-specific agent, such as Alteplase, Reteplase, or Tenecteplase, is preferred over a non-fibrin-specific agent, such as Streptokinase.

➢ Intracranial hemorrhage and major bleeding are the most serious side effects of fibrinolytic agents. The risk of intracranial hemorrhage is higher with fibrin-specific agents than with streptokinase. The dose of different Fibrinolytic agent is depicted in Table.No.2.

Table.2. Dose and Administration of Fibrinolytic agents

FIBRINOLYTIC AGENT	DOSE AND ADMINISTRATION
STREPTOKINASE	1.5 million units IV over 60 min
ALTEPLASE	15 mg IV bolus followed by 0.75 mg/kg IV over 30 min (max 50 mg) followed by 0.5 mg/kg (max 35 mg) over 60 min (max dose = 100 mg)
TENECTEPLASE	<60 kg = 30 mg IV bolus 60–69.9 kg = 35 mg IV bolus 70–79.9 kg = 40 mg IV bolus 80–89.9 kg = 45 mg IV bolus ≥90 kg = 50 mg IV bolus
RETEPLASE	10 nits IV × 2, 30 min apart

b) Percutaneous coronary intervention

The introduction of primary PCI (angioplasty and/or stent insertion without prior or concomitant fibrinolytic therapy) has demonstrated Superiority to fibrinolysis. PCIs encompass various invasive procedures to improve myocardial blood delivery by opening up the blood vessels. PCIs open stenosed coronary vessels and are less invasive than coronary bypass surgery, where the coronary vessels are replaced.

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A percutaneous (through the skin) transluminal (through the lumen of the blood vessels) coronary (into the heart) angioplasty (surgery or repair of the blood vessels) was first carried out on a conscious patient in 1977. Now over 2 million people a year undergo PCIs. The procedure is less invasive than coronary artery bypass graft surgery. PCI involves the passing of a catheter via the femoral or radial artery and aorta into the coronary vasculature under radio-contrast guidance. Inflation of a balloon at the end of the catheter in the area of the atheromatous plaques opens the lumen of the artery.[8, 9]

1.4.3 ANTITHROMBOTIC THERAPY

Current antiplatelet and anticoagulant therapies for acute coronary syndromes act on distinct sites in the pathways for platelet activation and coagulation. While these therapies are effective in reducing the morbidity and mortality associated with ACS, they are associated with a clinically significant increase in the risk of bleeding events. Novel therapies that minimize bleeding risk while providing protection against thrombotic events may improve outcomes in patients with ACS.[10] The different antithrombotic therapy and their dose was depicted in Table.3.

Table.3. Adjunctive Antithrombotic Therapy to Support Reperfusion with Primary PCI [11]

ANTIPLATELET THERAPY	RECOMMENDATIONS OF DOSE AND ADMINISTRATION
ASPIRIN	162- to 325-mg load before procedure 75-150 mg maintenance dose
P2Y$_{12}$ INHIBITORS CLOPIDOGREL PRASUGREL TICAGRELOR CANGRELOR	600 mg load orally and then 75 mg daily 60 mg load orally and then 10 mg daily 180 mg load orally and then 90 mg BD 30 μg/kg bolus and 4 μg/kg/min infusion
GP IIb/IIIa RECEPTOR ANTAGONISTS ABCIXIMAB EPTIFIBATIDE TIROFIBAN	0.25 mg/kg iv infusion, 0.125 mcg/kg/min 180 mcg/kg iv infusion, 2mcg/kg/min 25mcg/kg iv infusion, 0.15mcg/kg/min

ANTICOAGULANTS	RECOMMENDATIONS OF DOSE AND ADMINISTRATION
UFH (UNFRACTIONATED HEPARIN)	Bolus 60 U/kg (max 4000 U) iv, infusion 12 U/kg/h (maximum 1000 U) initially.
LMWH ENOXAPARIN	1mg/kg s.c. BD
INDIRECT THROMBIN INHIBITOR FONDAPARINUX	2.5 mg s.c. OD
DIRECT THROMBIN INHIBITOR BIVALIRUDIN	Bolus 0.75mg/kg iv infusion, 1.75mg/kg/h

Fig.2. Targets for antithrombotic drugs [11]

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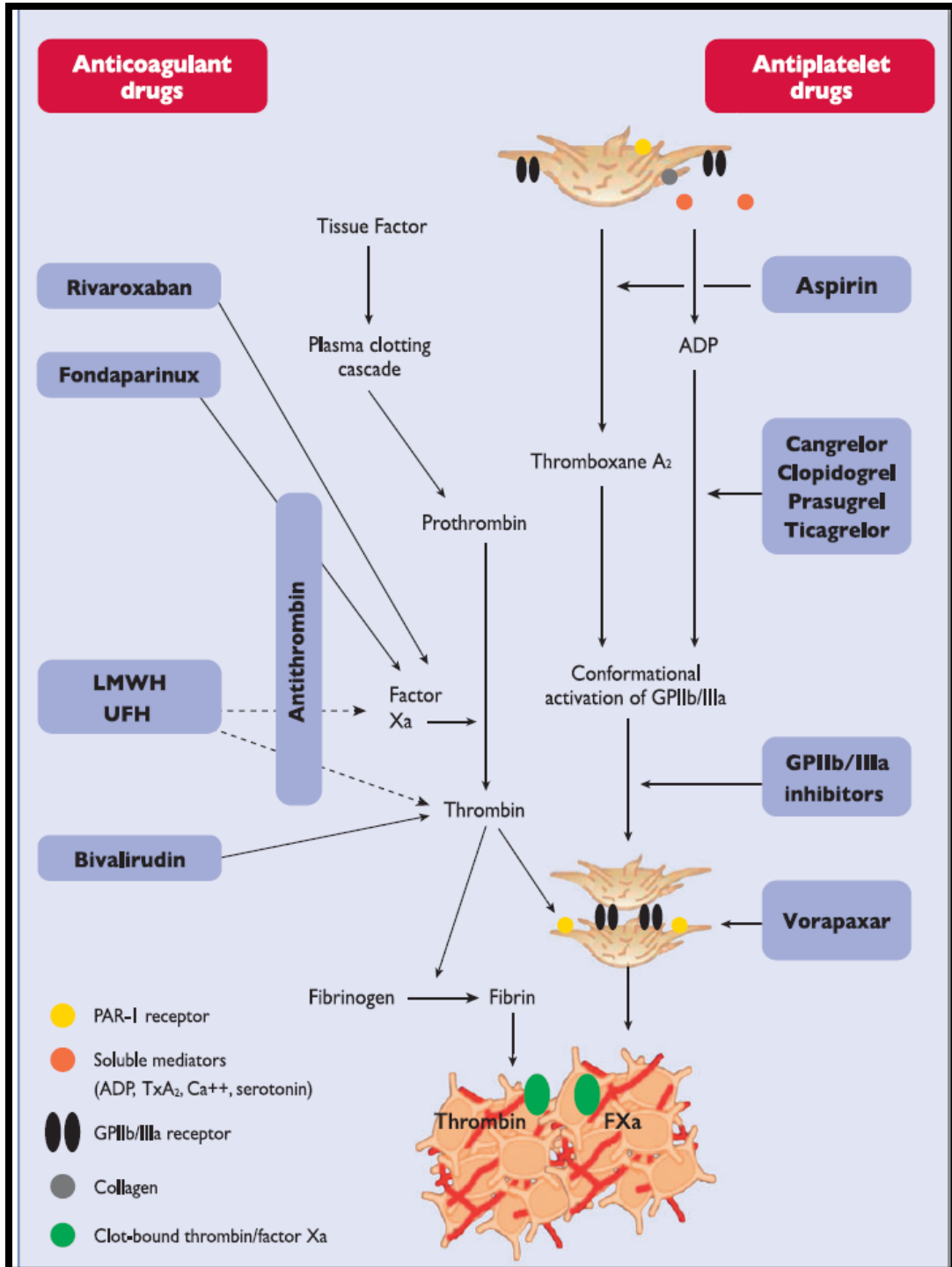
1.4.4 PREVENTION OF FURTHER INFARCTION OR DEATH (SECONDARY PROPHYLAXIS)

a) LIPID-LOWERING AGENTS

Early initiation (within 24 hours of presentation) of statin therapy is recommended in patients with an ACS or Acute Myocardial Infarction, if patients are already on statin therapy should continue the therapy.

b) BETA BLOCKERS

Early Beta blocker administration may help prevent arrhythmias and reduce reinfarction, but there is an increased incidence of cardiogenic shock. Current ACC/AHA guidelines recommend Beta blockers be initiated orally within the first 24 hrs after hospitalization.

Contraindications of Beta blockers

➢ Moderate to severe LV failure

➢ Pulmonary edema

➢ Bradycardia (<60 bpm)

➢ Hypotension (SBP<100mmHg)

➢ Signs of poor peripheral perfusion

➢ Reactive airway disease

c) ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ACE inhibitors and Angiotensin Receptor Blockers have been shown to reduce long-term risk of mortality in patients suffering an Acute Myocardial Infarction, but there is insufficient evidence to support the routine initiation of ACE inhibitors and ARBs in the prehospital or emergency department setting.

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d) CALCIUM CHANNEL BLOCKERS

Calcium channel blocking agents have not been shown to reduce mortality after acute MI and in certain patients with cardiovascular disease there are data to suggest that they are harmful. Beta blockers have been used much more broadly, have a much safer profile, and appear to be a more appropriate choice for patients presenting with myocardial infarction compared to calcium channel blockers.[12]

1.5 DRUG RELATED COMPLICATIONS IN ACUTE CORONARY SYNDROME

Dual antiplatelet therapy is currently the standard treatment for acute coronary syndrome patients. The use of anticoagulant therapy during primary percutaneous coronary intervention is a class 1 indication according to international guidelines.[13] The common adverse effects of antiplatelet therapy include upper gastrointestinal bleeding, ecchymosis, hematuria, epistaxis and ticagrelor- related dyspnea. Severe cases of purpura associated with antiplatelet or anticoagulant are characterized by purpura in non exposed parts of the body and the mucous membrane that rapidly lead to skin necrosis and signs of inflammation. The most common adverse effect associated with antiplatelet agents is bleeding, which commonly occurs in GI tract, nose, urinary tract, subcutaneous/dermal tissues or at puncture or surgical sites.[14]

1.6 BLEEDING RISK WITH ANTIPLATELETS AND ANTICOAGULANTS

Currently, the standard therapy for hospitalized patients with ACS includes antiplatelet agents such as including aspirin, P2Y12 inhibitors, glycoprotein IIb/IIIa inhibitor in combination with antithrombotic agents unfractionated heparin, low molecular weight heparin, direct thrombin inhibitors or anti-Xa agents). Balancing the risk of bleeding and thromboembolism is crucial in the management of acute coronary syndrome. Several studies demonstrate that the risk of bleeding rises with an increased number of antithrombotic agents. Major bleeding is a serious complication that is associated with increased morbidity and mortality particularly when it occurs after a stent procedure.

Current ACC/AHA guidelines recommend dual antiplatelet therapy in patients with an STEMI for at least 1 year for bare metal stent and drug eluting stent. In patient with Unstable angina or NSTEMI receiving a bare metal stent, Dual antiplatelet therapy should be given for at least 1 month and preferably for 1 year. In patients who receive an elective drug eluting stent, the current recommendations are for 1 year of dual antiplatelet therapy.[15]

1.7 RISK SCORES IN ACUTE CORONARY SYNDROMES

Risk scores are formula generated numbers used for quantitative risk assessment that rank-order individuals according to the likelihood of developing a specific outcome (or combination of outcomes) during a defined time interval. Risk scores are helpful tools for the assessment of risk in ACS patients. Risk scores allow accurate estimations of ischaemic and bleeding risk for individual patients.[16]

1.7.1 RISK SCORES FOR ISCHAEMIC RISK ASSESSMENT

Different scores are now available based on initial clinical history, ECG, and laboratory tests that enable early risk stratification on admission. The most popular ischaemic risk scoring systems in clinical practice have been the TIMI risk score, the GRACE risk scores, and, to a lesser extent, the PURSUIT risk score. The GRACE score is more advantageous as all its variables are objective data.

TIMI   :   Thrombolysis In Myocardial Infarction

GRACE   :   Global Registry of Acute Coronary Events

PURSUIT :   Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy.[16, 17]

The GRACE hospital discharge prediction model for 6-month mortality (GRACE score) was developed from a multinational registry involving all subsets of ACS including ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction, and unstable angina.[18]

The TIMI risk score, defined as the number (zero to seven) of positive individual variables, relates to a risk of adverse outcomes ranging from approximately 5% to 41% when applied retrospectively to patients studied in large NSTE ACS trials.[19]

1.7.2 RISK SCORE FOR BLEEDING RISK ASSESSMENT

Antithrombotic therapies after coronary intervention reduce ischemic events but invariably increase bleeding risk, which in turn may adversely affect short and long term outcomes. Hence, it is important to predict the bleeding risk in ACS patients in order to modify their treatment aiming to reduce their bleeding events and improve their outcome.

Many bleeding risk scores have been validated for the prediction of early and late bleeding events, and some have been tested on large cohorts with acute coronary syndrome, demonstrating reasonably good performance. Among them, the CRUSADE score has been validated in 17,857 patients with non–ST segment elevation myocardial infarction (MI), and its predictive capability was consistent in terms of hemorrhagic risks in patients taking ≥2 antithrombotic medications.[20]

I. CRUSADE RISK SCORE

The CRUSADE risk score comprises eight characteristics, including baseline patient characteristics (gender, history of diabetes, prior vascular disease), admission clinical variables (heart rate, systolic blood pressure, and signs of congestive heart failure), and admission laboratory values (haematocrit and calculated creatinine clearance).

A history of stroke and peripheral artery disease were considered as prior vascular disease according to the CRUSADE registry. These were collected based on information from medical records.[21] The eight predictors range and corresponding scores is depicted in Table. No: 4. Each of the variables was converted into points, the points were totaled for each patient, and each patient was placed in one of five major bleeding risk categories as shown below:

➢ Very low (≤20)
➢ low (21 to 30)
➢ moderate (31 to 40)
➢ high (41 to 50)
➢ very high (>50)

Only patients who had completed all of the CRUSADE variables were included in the analysis.[22]

Table.4. CRUSADE RISK SCORE – predictors and their scores

S.NO	PREDICTOR	RANGE	SCORE
1	BASELINE HEMATOCRIT (%)	<31 31-33.9 34-36.9 37-39.9 ≥40	9 7 3 2 0
2	CREATININE CLEARANCE (ml/min/1.73m^2)	>15-30 >30-60 >60-90 >90-120 >120	35 28 17 7 0
3	DIABETES MELLITUS	NO YES	0 6
4	SIGNS OF HEART FAILURE	NO YES	0 7
5	SYSTOLIC BLOOD PRESSURE	≤90 91-100 101-120 121-180 181-200 ≥201	10 8 5 1 3 5
6	HEART RATE	≤70 71-80 81-90 91-100 101-110 111-120 ≥121	0 1 3 6 8 10 11
7	PRIOR VASCULAR DISEASE	NO YES	0 6
8	FEMALE SEX	NO YES	0 8

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II. HAS-BLED SCORE

HAS-BLED risk score was initially used to access the risk of bleeding in patients with atrial fibrillation receiving anticoagulation therapy. Subsequently, clinical studies proved that it also has good discriminatory and predictive performance for stroke, thromboembolism, MI, and cardiovascular death in patients with AF. Recently, some studies have tried to extend its clinical usage in patients undergoing percutaneous coronary interventions irrespective of whether or not they have AF.

HAS-BLED stratified patients into 3 risk categories as shown below:

- Low risk (<2)
- Intermediate risk (2)
- High risk (>2).[23]

III. WILL-BLEED RISK SCORE

Bleeding after cardiac surgery is known to be associated with poor outcome, and increased morbidity and mortality due to the need for blood transfusion, hypoperfusion- related injuries to critical organs and the need for re-exploration. Cardiac surgery, especially coronary artery bypass grafting confers a huge challenge, as patients are treated with various antithrombotic drugs, which are known to increase perioperative risk. Hence identification of patients at high risk of bleeding would be of great importance in order to optimize management.

It includes few variables all easily available in clinical practice: antithrombotic therapy, gender, acute coronary syndrome, anaemia, renal impairment and critical preoperative state.[24]

1.8 SIGNIFICANCE OF BLEEDING RISK SCORES IN ACUTE CORONARY SYNDROME

The development of antiplatelet and antithrombotic therapies, in addition to invasive therapy has resulted in great improvements in the outcomes of patients with acute coronary syndrome but increases the risk of bleeding. The use of risk scores can identify patients at increased risk of bleeding and help choose medications for treating acute coronary syndrome. Among the bleeding risk scores developed, the CRUSADE bleeding score is the most widespread and it should be noted that these scores should not limit the use of medication, but help to individualize the treatment of acute coronary syndrome. The clinical implementation of this risk score can potentially facilitate clinical decision making for patient with acute coronary syndrome.

1.9 ROLE OF PHARMACIST IN ACUTE CORONARY SYNDROME

The pharmacist is vital to ensure the delivery of quick, effective and safe therapies in the treatment of acute coronary syndrome. Monitoring of each therapeutic agent for adequate dosing based on the specific patient parameters of age, weight, renal function and liver function will ensure the maximum effectiveness of a chosen regimen. Pharmacists are in a unique position to measure the quality of care writing and implementing pharmacotherapeutic guidelines and measuring the adherence to these guidelines.

Because many of the drugs used in acute coronary syndrome are associated with a risk of bleeding. Therefore the use of international guidelines recommended risk scores will help to identify patients at high risk. Dietary guidelines, exercise recommendations, counseling on the importance of compliance with prescribed regimens are also provided for patients with acute coronary syndrome at discharge and can be incorporated into standardized care protocols.[25, 26]

2. LITERATURE REVIEW

Zhao et al (2018)[27] performed a prospective observational study on evaluation of CRUSADE and ACUITY- HORIZONS scores for predicting long term out of hospital bleeding after percutaneous coronary interventions with drug eluting stents in patients receiving dual antiplatelet therapy. They had found that 2.5% of patients had major bleeding during a 2 year follow up. The calculated risk scores by CRUSADE and ACUITY-HORIZONS were significantly higher in the major bleeding group than non major bleeding groups. They concluded that the value of CRUSADE and ACUITY- HORIZONS scores did not differ significantly.

Sanchez-Martinez et al (2017)[28] conducted a study to assess the predictive ability of the CRUSADE risk score in patients with concomitant ACS and chronic kidney disease. It was found that Patients with kidney dysfunction had a higher CRUSADE bleeding risk score and compared to patients without kidney dysfunction.

Bang et al (2017)[29] conducted a study on CRUSADE score is superior to platelet function testing for prediction of bleeding in patients following coronary interventions. They compared the performance of the CRUSADE with platelet reactivity testing to predict major bleeding events in Korean patients with acute coronary syndrome. They concluded that major bleeding events are more common in real life than reported in clinical trials. CRUSADE score was superior to platelet reactivity testing for predicting short-term bleeding.

Cordero et al (2017)[30] conducted a study on additive value of the CRUSADE score to the GRACE score for mortality risk prediction in patients

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with acute coronary syndromes. It was found that the addition of the CRUSADE score to the GRACE score improved mortality risk estimation. They concluded that the CRUSADE score >50 identified patients with higher post-discharge mortality and higher hospital mortality. The CRUSADE score improved hospital and long-term mortality prediction in patients with GRACE score >140. Individual mortality risk estimation should integrate the CRUSADE and GRACE scores.

Antoniou et al (2017)[31] conducted a study on risk scoring to guide antiplatelet therapy post-percutaneous coronary intervention for acute coronary syndrome. Over the follow-up period, a significant reduction in major adverse cardiac event rates between the patients risk score stratified and control was seen. They concluded that using appropriate risk scoring to guide antiplatelet therapy after ACS is safe and can result in improved clinical outcomes.

Gibbs et al (2016)[32]determined association between the CRUSADE bleeding risk score, DAPT regimen and in-hospital bleeding. Patients were sub-grouped according to DAPT regimen: aspirin with Ticagrelor and aspirin with Clopidogrel or Prasugrel. In conclusion, Ticagrelor-based regimen showed lower bleeding risk.

Alam et al (2015)[33] performed a prospective study to evaluate drug utilization and the economic impact of anticoagulants for the treatment of unstable angina and myocardial infarction. It was found that the data of 487 UA/NSTEMI hospitalizations demonstrated that enoxaparin was found to be widely used anticoagulant and attributed by 70% of drug utilization comparative to 24.8% fondaparinux and 5.1 % dalteparin among private and government Hospitals in Karachi. They concluded that fondaparinux remain a choice of drug for the treatment of unstable angina/NSTEMI patients by reducing total drug cost.

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Singh et al (2015)[34] conducted a prospective, cross sectional study to evaluate the drug utilization pattern of anticoagulants, identify and assess drug interactions and adverse drug reactions with the use of anticoagulants in a tertiary care teaching hospital. It was found that Heparin was mainly used for prophylaxis. Enoxaparin and acenocoumarol were other commonly used drugs. Acenocoumarol and warfarin were the drugs prescribed at discharge. 35 drug interactions were identified and out of this, 16 interactions were severe in intensity. 6 adverse drug reactions were also observed during this study. They concluded that the pharmacotherapy with anticoagulant drugs should be cost effective and with minimum risks involved.

Taha et al (2015)[35] performed a meta-analysis to evaluate the accuracy of different bleeding risk scores for ACS patients. This study has identified Nine studies and 13 759 patients. CRUSADE, ACUITY, ACTION and GRACE were the scores externally validated. The rate of in-hospital major bleeding was 7.80%, 2.05% being related to access and 2.70% needing transfusions. They concluded that ACTION, CRUSADE and ACUITY perform similarly to predict risk of bleeding in ACS patients. The CRUSADE score is the only one externally validated for NSTEMI, while accuracy of the scores increased with radial access.

Ariza-sole et al (2014)[36] performed a prospective observational study to assess the efficacy of bleeding risk scores in elderly patients with acute coronary syndromes. Older patients had higher bleeding risk (CRUSADE, 42 vs 22) and a slightly higher incidence of major bleeding events (CRUSADE bleeding, 5.1% vs 3.8%). They concluded that the Current bleeding risk scores showed poorer predictive performance in elderly patients with acute coronary syndromes than in younger patients.

Abu-assi et al (2014)[37] conducted a review on bleeding risk stratification in an era of aggressive management of acute coronary syndrome. Hemorrhagic complications occur with a frequency of 1% to 10% during treatment for ACS. They performed an update about the ACS bleeding risk scores most frequently used in daily clinical practice. This study suggests that CRUSADE score represents a useful objective clinical tool which could lead to improvements in ACS care. They concluded that using appropriate risk stratification allows properly select those patients at increased risk of bleeding, focusing on them the efforts to reduce bleeding complications.

Nahar et al (2013)[38] focused on deriving and validating a genetic bleeding risk score based on the genetic and non genetic factors associated with bleeding in patients on long term anticoagulant therapy. The genetic bleeding risk score was validated to perform better than non genetic bleeding risk score and the sensitivity also increased two-folds with genetic bleeding risk score as compared to clinical bleeding risk scores.

Ariza-sole et al (2013)[39] performed a prospective study on CRUSADE bleeding risk score validation for ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. It was found that the rates of in-hospital bleeding across the quintiles of risk groups were 0.4% (very low risk), 2.6% (low), 4.6% (moderate), 7.2% (high), and 13.4% (very high) (p<0.001). Patients with bleeding events had higher mortality during follow up. They concluded that STEMI patients had a significantly lower bleeding risk as compared to CRUSADE NSTEMI population. CRUSADE Bleeding Risk Score accurately predicted major in-hospital bleeding in this different clinical scenario, including patients with radial artery approach.

Ariza-sole et al (2013)[40] conducted a study on is it possible to separate ischemic and bleeding risk in patients with non-ST segment elevation acute coronary syndromes. It was found that the incidence of major CRUSADE bleeding was 27/558 (4.8%). 19 patients (3.4%) died during hospitalization. The incidence of death or reinfarction at 30 days was 26/558 (4.99%). A close linear relationship was observed between ischemic and bleeding risk scores. They concluded that the score that best predicted bleeding complications was the GRACE score (designed for predicting ischemic events). Likewise, the score that best predicted ischemic events was the ACTION score, which was designed for predicting haemorrhagic complications.

Nicolau et al (2013)[41] conducted a study on the bleeding risk score as a mortality predictor in patients with acute coronary syndrome. They calculated the ACUITY/HORIZONS bleeding risk score prospectively and retrospectively. In conclusion, the bleeding risk score is a very useful and highly reliable predictor of in-hospital mortality in a wide range of patients with acute coronary syndrome, especially in those with NSTEMI or Unstable angina.

Abu-assi et al (2012)[42] conducted a study on comparing the predictive validity of three contemporary bleeding risk scores in acute coronary syndrome at Spain. They calculated the ACTION, CRUSADE, and Mehran et al (2010) bleeding risk score and evaluated their performance for predicting major bleeding events and thrombolysis in myocardial infarction bleeding episodes, in patients with either NSTEMI or STEMI. They concluded that the CRUSADE score was found to be the most accurate quantitative tool for NSTEACS and STEMI patients undergoing coronary arteriography.

Amador et al (2011)[43] conducted a study on comparison of ischemic and bleeding risk scores in non-ST elevation acute coronary syndromes. There were

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36 major bleeding events, 34 recurrent ischemic events and 10 deaths. GRACE and CRUSADE risk scores demonstrated a better performance than TIMI risk score for predicting in-hospital death. They concluded that both ischemic and bleeding risk scores are able to predict in-hospital bleeding, ischemic and fatal events.

Erdem et al (2011)[44] conducted a review on assessing the bleeding risk in acute coronary syndromes. It was found that CRUSADE, ACUITY-HORIZONS and GRACE risk scores developed to predict bleeding risk among ACS patients. They concluded that patients at highest risk of bleeding are also at highest risk of ischaemic and thrombotic complications. The use of effective treatments with lower risks of bleeding may be the preferred choices and the use of gastrointestinal protection such as proton pump inhibitors may be helpful.

Kadakia et al (2010)[45] conducted a study to evaluate anticoagulant use patterns and bleeding risk in a contemporary population of patients with acute coronary syndrome at 360 US Hospitals. It was found that among STEMI patients, unfractionated heparin was most commonly used (66%), followed by bivalirudin (14%) and low molecular weight heparin (8%) in NSTEMI patients, unfractionated heparin was also the most commonly used anticoagulant (42%), followed by low molecular weight heparin (27%) and then bivalirudin (13%). More than 50% of patients with either STEMI or NSTEMI were in the 2 lowest (≤20 or 21 to 30) of the five CRUSADE bleeding risk groups. More NSTEMI patients (33.7%), compared with only 17.3% of STEMI patients, were in the highest 2 risk groups (41 to 50 or ≥50). They concluded that the risk of bleeding can be evaluated using a simple risk score in both NSTEMI and STEMI, and across anticoagulant strategies, providing important prognostic information for the clinician.

Abu-assi et al (2010)[46] conducted a study to evaluate the performance CRUSADE bleeding score in patients with Non–ST-Segment elevation acute myocardial infarction. It was found that a total of 657 patients (84%) were treated with ≥2 antithrombotic, of whom 609 (92.7%) underwent cardiac catheterization. The overall incidence of major bleeding was 9.5%. This incidence increased with the risk category: very low (1.5%), low (4.3%), moderate (7.8%), high (11.8%) and very high (28.9%). it showed little capacity to discriminate bleeding risk in patients treated with ≥2 antithrombotics who did not undergo cardiac catheterization. They concluded that the CRUSADE risk score was generally validated and found to be useful in a Spanish cohort of patients treated with or without ≥2 antithrombotics and in those treated with or without ≥2 antithrombotics who underwent cardiac catheterization.

Mehran et al (2010)[47] conducted a study to develop a practical risk score to predict the risk and implications of major bleeding in acute coronary syndromes. They concluded that a simple risk score based on 6 baseline measures plus anticoagulation regimen identifies patients at increased risk for non coronary artery bypass grafting related bleeding and subsequent 1-year mortality, for whom appropriate treatment strategies can be implemented.

Subherwal et al (2009)[48] conducted a study on baseline risk of major bleeding in Non-ST-Segment elevation myocardial infarction using the CRUSADE bleeding score. Major bleeding was significantly associated with lower baseline hematocrit and lower creatinine clearance. They concluded that the CRUSADE bleeding score quantifies risk for in-hospital major bleeding across all post admission treatments, which enhances baseline risk assessment for NSTEMI care.

Xavier et al (2008)[49] described the treatment and outcomes of acute coronary syndromes in India. It was found that more patients with STEMI than those with NSTEMI were given anti-platelets, ACE inhibitors or ARBs and PCI. The 30-day outcomes for patients with STEMI were death, reinfarction and stroke. Outcomes for Unstable angina or NSTEMI were better than STEMI. Patients in India have a higher rate of STEMI than do patients in the developed countries.

Nikolsky et al (2007)[50] performed a study on development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach. It was found that the risk of major bleeding varied from 1.0% in patients without risk factors to 5.4% in high-risk patients. They concluded that a simple risk score of baseline clinical and procedural variables is useful to predict the incidence of major peri-procedural bleeding after contemporary percutaneous coronary intervention using the femoral approach.

Cohen (2005)[51] conducted a review on predictors of bleeding risk and long-term mortality in patients with acute coronary syndromes. The aim of this review was to collate the published evidence on independent predictors of bleeding and late mortality in acute coronary syndrome patients, to compare the two sets of risk factors, and to investigate whether bleeding is reported as a predictor of late mortality. They concluded that the available evidence suggests that any impact of bleeding on mortality in ACS patients appears to be confined to the short term, and long-term outcomes do not reflect the impact of in-hospital bleeding.

3. SCOPE OF THE STUDY

Coronary artery disease is the leading cause of mortality and morbidity in the world. Acute coronary syndrome includes unstable angina, Non-ST-Segment elevation myocardial infarction and ST-Segment elevation myocardial infarction, are the commonest causes of mortality in patients with CAD. The prevalence of CAD and the incidence of ACS also are very high among Indians.[52]

Recurrent ischemic events after an acute coronary syndrome remain common. The combined use of antithrombotic agents, antiplatelet agents and invasive coronary procedures reduces the risk of ischemic events but also increases the risk of bleeding. Not only the bleeding result in an immediate treat, but it also associated with an increased coronary artery mortality and reinfarction, both in the short and long term adverse outcomes. From the previous studies, major bleeding is associated with a 60% increased risk of in-hospital death and fivefold increase in one year mortality and reinfarction. These findings have brought a paradigm change to risk stratification that takes into account not only ischemic risk, but also bleeding risk in the selection of an optimal management strategy supported by clinical practice guidelines. Strategies to reduce bleeding include:

➢ Assessment of bleeding risk in each individual
➢ Recognizing early signs of bleeding
➢ Using gastro protective agents to reduce gastrointestinal bleeding
➢ Appropriate dosing of antithrombotic therapy and minimizing the duration of antithrombotics
➢ Use of drugs with proven reduced risk of bleeding

For the assessment of bleeding risk, various patient-based scoring algorithms have been validated for risk stratification in patients referred for cardiovascular interventions. The CRUSADE risk score can be used to calculate the risk of major bleeding for an individual patient. Cardiovascular risk scores are recommended and should be used for the diagnosis and treatment of individuals presenting with both NSTEMI and STEMI, as well as for the stratification of all ACS survivors in a long-term follow up.[53, 54, 55, 56, 57]

Clinical pharmacists play an essential role in ensuring beneficial outcomes for acute coronary syndrome patients by recommending and monitoring therapies as outlined in practice guidelines. Therapeutic guidelines recommended of using established risk scores to improve the patient outcomes and decreasing the readmission rates to the hospital. To determine an acute coronary syndrome patient's level of risk, clinical pharmacist play a key role in calculating bleeding and ischemic risk scores using several patient parameters. These prediction scores may help physicians stratify patients into categories of increasing risk of bleeding so as to evaluate the individual risk/benefit ratio of antithrombotic therapy, either prior to starting or during treatment and choose appropriate strategies to reduce bleeding risk.[58]

4. OBJECTIVES OF THE STUDY

The proposed study entitled "Study on anticoagulant utilization evaluation and risk score assessment for predicting bleeding among patients with acute coronary syndrome" includes the following objectives.

- ➢ To evaluate anticoagulant use patterns
- ➢ To assess the prognostic value of CRUSADE (Can Rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) score in predicting risk of major bleeding among patients with acute coronary syndromes (ACS).
- ➢ To monitor the ADR associated with drugs prescribed in ACS.
- ➢ To study the drug interactions in the prescriptions.

5. PLAN OF THE STUDY

The proposed study entitled "Study on anticoagulant utilization evaluation and risk score assessment for predicting bleeding among patients with acute coronary syndrome" was planned and carries out for duration of 10 months and the various phases of the study were given below:

Phase 1 :- (Nov-2017 to Jan-2018)

- Literature survey to identify the scope of the work.
- Designing of:
  - Data entry format
  - Patient information and consent form
  - Inclusion and exclusion criteria for data collection.
- Submission of protocol and obtaining consent from hospital authority

Phase 2 : - (Feb-2018 to Jun-2018)

- Data collection through designed standard data entry format during ward rounds.
- Anticoagulant utilization evaluation and risk score assessment.
- Literature survey (continued)
- Data analysis.

Phase 3:- (July-2018 to Aug-2018)

- Literature survey (continued)
- Application of statistical tool on the obtained data.
- Preparation and submission of report.

6. METHODOLOGY

STUDY SITE

The proposed study was conducted at a private tertiary care hospital located at Coimbatore. It is a 1000 bedded multi-specialty institution where top-flight consultants and expertly trained staff offer advanced treatments and procedures ranging from advanced neurosurgery to chemotherapy to stem cell transplantation to organ transplants and so on. New 230-bed super-specialty block has a high staff-patient ratio ensuring that individual attention is at its maximum. The various specialties includes Neurosurgery, Cardiology, Diabetology and Endocrinology, Neurology, Orthopedics, General surgery, Psychiatry, Pediatrics, Maxillofacial surgery, Dentistry, Anesthesiology, Interventional radiology, Psychotherapy, Emergency care, Neonatology, ENT, IN Vitro Fertilisation, Dermatology, Gastroenterology, Cardiovascular and Thoracic surgery, Nephrology and Urology, Pulmonology, Plastic surgery, Oncology, Clinical laboratory, Liver transplant unit, Physiotherapy, Haematology, Rheumatology and clinical Immunology, Pain Management.

DEPARTMENT SELECTED FOR STUDY

The study was conducted in the department of Cardiology General Medicine. The reason for the selection of this department was that the preliminary ward rounds had revealed a better scope for the study in the department of Cardiology and General Medicine. The prevalence of Cardiovascular diseases were found to be more and the department of pharmacy practice provides service to the above department and a good co-operation from medical team added up as a reason for selecting the department for conducting the present study. The study was conducted with expert guidance of the physicians, Clinical Pharmacy Professionals and other health care professionals from the study department.

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CONSENT FROM HOSPITAL AUTHORITIES

The protocol of the study which included the study background, objectives, methodology and probable outcomes was prepared and submitted to the Institutional Ethical Committee of the study hospital. The approval from the committee was procured through the letter (**SRH/EC.12-11/2017-18 dated on 28th December 2017**) and the same was given in **Annexure No.1** for reference. The author was permitted to utilize the hospital facilities to make a follow up of the cases, in the selected departments. All the health care professionals of the study site were well informed through Dean's official circular.

LITERATURE SURVEY

The purpose of a literature survey is to gain an understanding of the existing research and debates to a particular topic or area of the study, and to present that knowledge in the form of a written report. An extensive literature survey was carried out regarding the study entitled "STUDY ON ANTICOAGULANT UTILIZATION EVALUATION AND RISK SCORE ASSESSMENT FOR PREDICTING BLEEDING AMONG PATIENTS WITH ACUTE CORONARY SYNDROME". The literatures supporting the study were gathered from various sources includes:

- ➢ Secondary sources
  - International Journal of Cardiology
  - European Society of Cardiology
  - Clinical Cardiology
  - European Heart Journal
  - Journal of American Heart Association
  - Journal of the American College of Cardiology
  - Interventional Cardiology

- Journal of Thrombosis Research

- World Journal of Cardiology

- Indian Journal of Pharmacy Practice

- Journal of Pharmacy and Pharmaceutical services

- Journal of Cardiorenal medicines

- Chinese Medical Journal

- Journal of Thrombosis and Homeostasis

- Journal of Cardiology

- Journal of Heart, Lung and Circulation

- Indian Heart Journal

- Journal of Academic Emergency Medicines

- Journal of Global burden of Cardiovascular diseases

- The Lancet

- Micromedex

➢ Tertiary sources

- Dipiro JT, Robert L.Talbert, Gary C. Yees, Barbara G.Wells, L.Michael Posey LM. Pharmacotherapy-A Pathophysiologic Approach Sixth edition; 2008. p. 291-319.

- Harrison TR. Harrison's principles of internal medicine sixteenth edition; 2005. P.1434-1459.

- Walker Roger, Cate Whittlesea. Clinical pharmacy and therapeutics fifth edition; 2012. p. 312-332.

STUDY DESIGN

A prospective observational study

STUDY DURATION

10 months

SAMPLE SIZE

122 patients

PATIENT SELECTION

➢ **Inclusion criteria:** All inpatients

❖ of age $\geq$ 18, of either sex,

❖ having baseline characteristics of CRUSADE risk score

❖ Who have been diagnosed to have ST Segment Elevated Myocardial Infarction and Unstable Angina/ Non ST Segment Elevated Myocardial Infarction,

❖ For STEMI and NSTEMI:-Ischemic symptoms at rest lasting $\geq$10 min, ECG changes associated with STEMI and positive Cardiac markers associated with NSTEMI,

❖ For Unstable angina: defined as ischemic chest pain lasting more than 30 minutes with no evidence of ST-elevation,

❖ Willing to participate.

➢ **Exclusion criteria:** Patients who are,

❖ critically ill patients,

❖ with insufficient data in their records,

❖ Not willing to participate.

PATIENT INFORMATION FORM

A patient information form has been prepared to inform the patients and care givers of patients about the purpose, necessity of the study assuring them that the confidentiality will be strictly maintained and this is for only the betterment of patient's health. The format includes the details like Department address, name and signature of the investigator and supervisor, date, place and details of the study. The model of the patient information form was given in the **Annexure No: 2** for reference.

PATIENT CONSENT FORM

A patient consent form has also been prepared to obtain written consent from all the patient or bystander and will be included in the study. They will be informed about the study using patient consent form. The format contains details like address, date, place, provision for signature of the patient or bystander, investigator and supervisor. The same was given in the **Annexure No: 3** for reference.

DATA ENTRY FORMAT

A separate data entry form was designed for collecting the data related to patients including patient details like name, age, gender, height, weight, BMI, IP. No., date of admission, date of discharge, vital signs (BP, pulse, heart rate), reason for admission, past medical history, past medication history, social history and allergies. Provision was also given in the format for entry of clinical laboratory data (blood counts, liver function test, renal function, electrolytes, and urine examination), diagnosis, drug chart, anticoagulant utilization pattern and drug interaction chart and any interventions. The data entry format also provides for recording bleeding risk category using CRUSADE risk score. The model of a patient data entry form was given in the **Annexure No.: 4** for reference.

MATERIAL AND METHODS

Each patient's medical record was reviewed. All demographic and clinical characteristics were obtained and recorded on admission. Data were collected during a regular ward round participation in the department of Cardiology and General medicine. Patients who had satisfied the inclusion criteria were included in the study. All of the patients signed informed consent for data collection and use. Appropriate permission to conduct the study was obtained from the Hospital authorities.

Anticoagulant utilization evaluation

The obtained data during the ward rounds were thoroughly analyzed to evaluate the utilization of different Anticoagulants and their costs in the General and Cardiology ward. The collected data were also screened to check the drug interactions using the Micromedex drug data base.

Risk score calculation

The CRUSADE risk score calculated for each patient using prognostic variables. The CRUSADE risk score comprises eight characteristics, including baseline patient characteristics (gender, history of diabetes, prior vascular disease), admission clinical variables (heart rate, systolic blood pressure, and signs of congestive heart failure), and admission laboratory values (haematocrit and calculated creatinine clearance). Creatinine clearance was estimated with the help of Cockroft-Gault formula. These were collected based on information from medical records. The laboratory results (creatinine, haemoglobin, haematocrit, and platelet count) were also collected. A history of stroke and peripheral artery disease were considered as prior vascular disease according to the CRUSADE

registry.

Each of the variables was converted into points, the points were totaled for each patient, and each patient was placed in one of five major bleeding risk categories:

- ➢ Very low (≤20)
- ➢ Low (21to30)
- ➢ Moderate (31to40)
- ➢ High (41to50)
- ➢ Very high (>50)

Only patients who had completed all of the CRUSADE variables were included in the analysis

7. RESULTS

The work entitled "Study on anticoagulant utilization evaluation and risk score assessment for predicting bleeding among patients with acute coronary syndrome" was carried out in the department of General medicine and cardiology at a 1000 bedded multispecialty hospital. A total number of 122 patients with acute coronary syndrome have participated in the study as per the inclusion criteria. Data were collected, analyzed and the results are furnished below:

GENDER DISTRIBUTION

Among the 122 patients enrolled 98 (80%) were males and 24 (20%) were females (Table.No.5, Fig.3). The study results showed that the incidence of ACS was more common in males compared to females.

Table.No.5: Gender distribution

S.NO	GENDER	NO OF PATIENTS (n=122)	PERCENTAGE (%)
1	Female	98	80
2	Male	24	20

Fig. 3: Gender distribution

GENDER DISTRIBUTION (n=122)

■ Male ■ Female

20%

80%
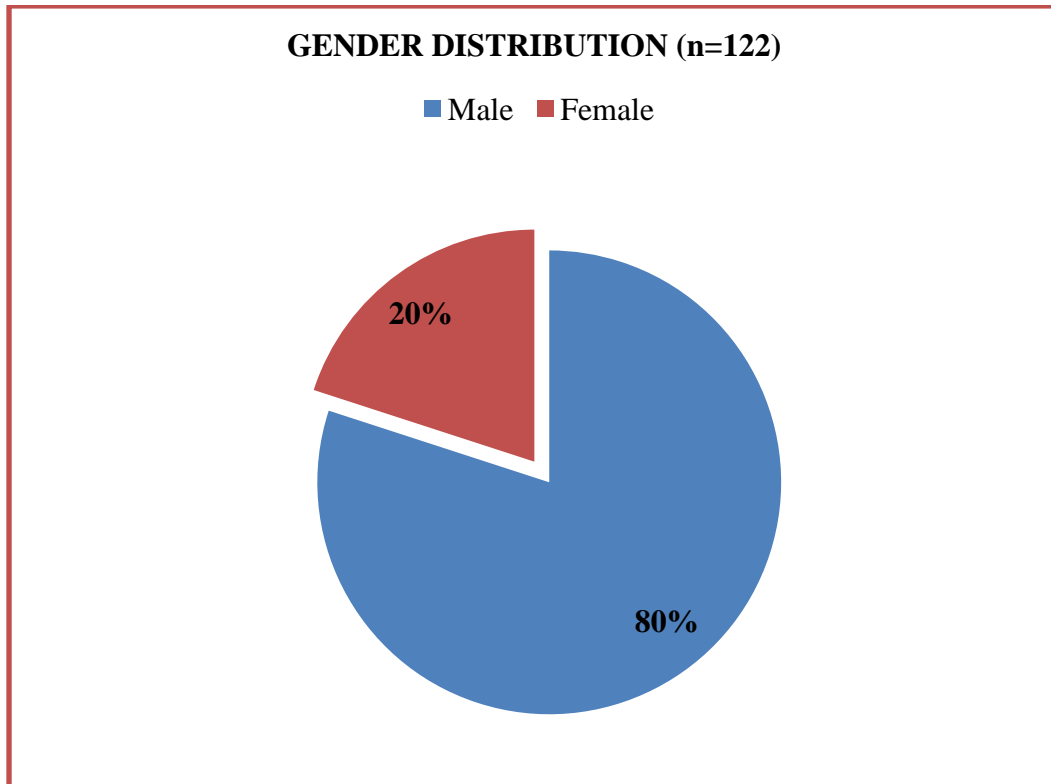
AGE CATEGORISATION

The patients were divided into four groups based on their age group as per WHO guidelines (Table.No.6, Fig.4). The mean age of the overall study population was **55.63± 10.02**. The most predominant group was middle adulthood (34-59) which accounts for about 74(60.65%) of the overall study population, out of this 67 patients were males and 7 patients were females followed by Later adulthood (60-75) which accounts for 43(35.24%), Very old age (>75) which accounts for 3(2.45%) and Early adulthood (24-34) which accounts for 2(1.63%).

Table.No.6: Age categorization

S.NO	AGE	MALE	FEMALE	NO OF PATIENTS (n=122)	PERCENT AGE (%)
1	EARLY ADULTHOOD (24-33)	2	0	2	1.63
2	MIDDLE ADULTHOOD (34-59)	67	7	74	60.65
3	LATER ADULTHOOD (60-74)	28	15	43	35.24
4	VERY OLD AGE (>75)	1	2	3	2.45

Fig.4: Age categorization
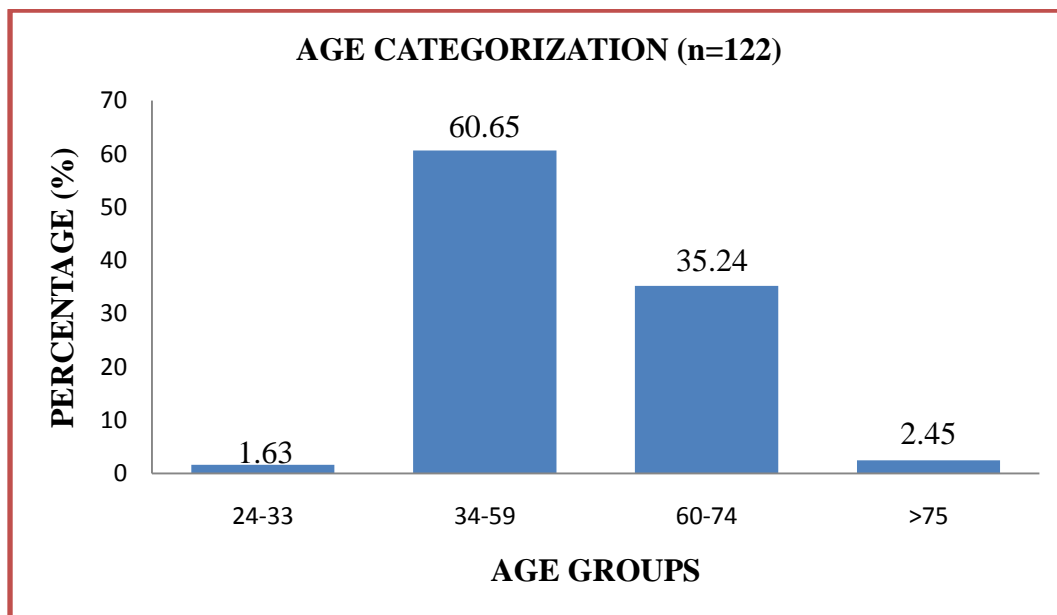
CATEGORIZATION OF ACUTE CORONARY SYNDROME PATIENTS

The patients in the study population were categorized into STEMI, NSTEMI, UA and STEMI+UA (Table.No.7, Fig.5). The categorization reveals 103(84.42%) patients were ST elevated myocardial infarction and they were most prevalent followed by patients with unstable angina 8(6.55%), 6(4.91%) patients with STEMI + UA and 5(4.09%) patients with NSTEMI.

Table.no.7: Categorization of ACS

S.NO	CATEGORY OF ACS	NO OF PATIENTS (n=122)	OVERALL PERCENTAGE %
1	STEMI	103	84.42
2	UA	8	6.55
3	STEMI+UA	6	4.91
4	NSTEMI	5	4.09

Fig.5: Categorization of ACS
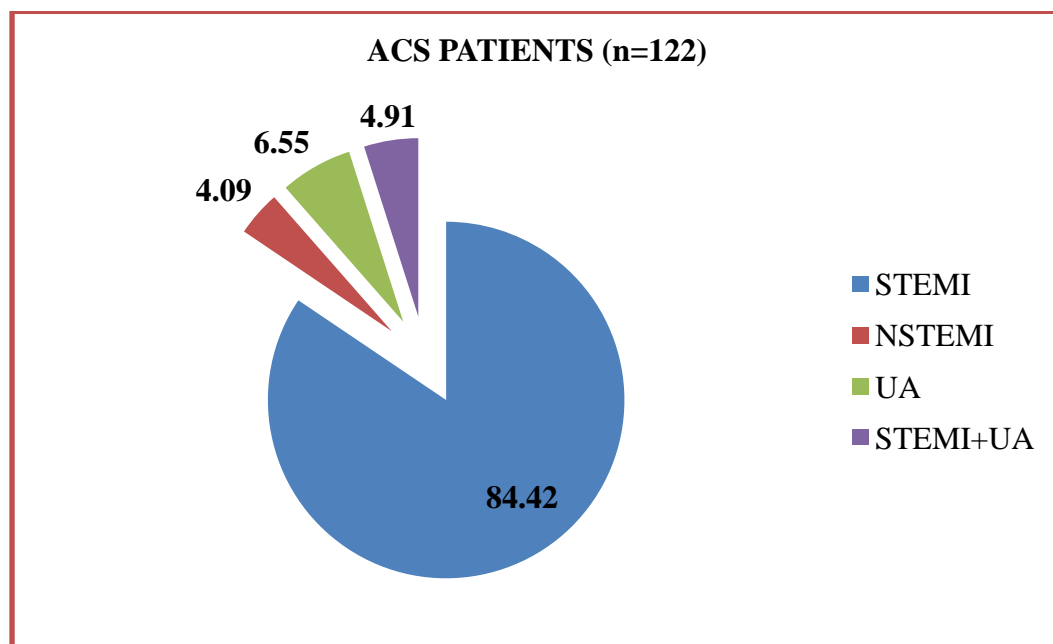
NUMBER OF VESSELS AFFECTED

The study population was categorized based on the number of vessels affected (Table.No.8, Fig.6). It was found that patients with single vessel disease 59(48.3%) was more prevalent followed by double vessel disease 44(36.06%) and triple vessel disease 19(15.57%).

Table.no.8: Number of vessels affected

S.NO	NO.OF VESSELS AFFECTED	NO OF PATIENTS AFFECTED (n=122)	OVERALL PERCENTAGE (%)
1	Single vessel disease	59	48.3
2	Double vessel disease	44	36.06
3	Triple vessel disease	19	15.57

Fig.6
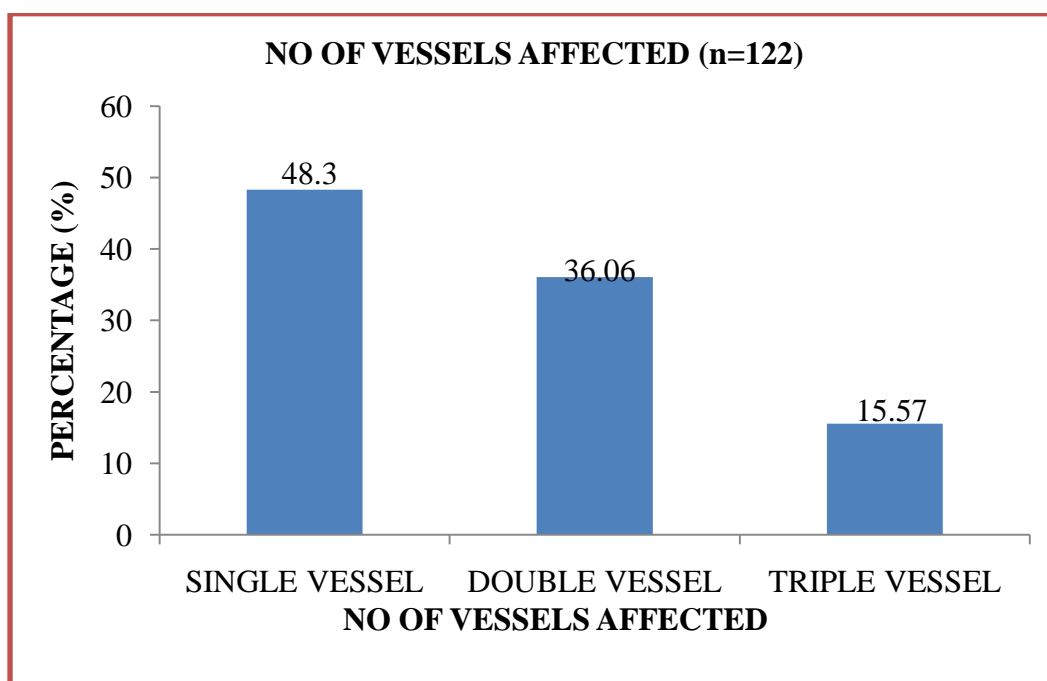
CONCOMITANT DISEASES

Various co-morbid conditions like hypertension, diabetes mellitus, hypothyroidism etc were seen among the study population and many of these were found to be risk factors of coronary artery disease. It was observed that 30(32.96%) of the study population suffered from diabetes mellitus followed by 25(27.47%) suffered from both diabetes and hypertension, 21(23.07%) suffered from hypertension, 5(5.49%) suffered from chronic kidney disease and hypothyroidism, 3(3.29%) suffered from stroke and 2(2.19%) suffered from congestive heart failure (Table.No.9, Fig.7).

Table.No.9: Concomitant diseases

S.NO	CONCOMITANT DISEASES	NO OF PATIENTS (n=91)	OVERALL PERCENTAGE (%)
1	Diabetes Mellitus	30	32.96
2	Diabetes and Hypertension	25	27.47
3	Hypertension	21	23.07
4	Chronic Kidney diseases	5	5.49
5	Hypothyroidism	5	5.49
6	Stroke	3	3.29
7	Congestive Heart failure	2	2.19

Fig.7: Concomitant diseases

CONCOMITANT DISEASES (n=91)

Figure: Bar chart showing percentage of concomitant diseases. DM: 32.96, DM, SHT: 27.47, SHT: 23.07, CKD: 5.49, HYPOTHYROIDISM: 5.49, STROKE: 3.29, CHF: 2.19. Y-axis: PERCENTAGE (%). X-axis: CONCOMITANT DISEASES.
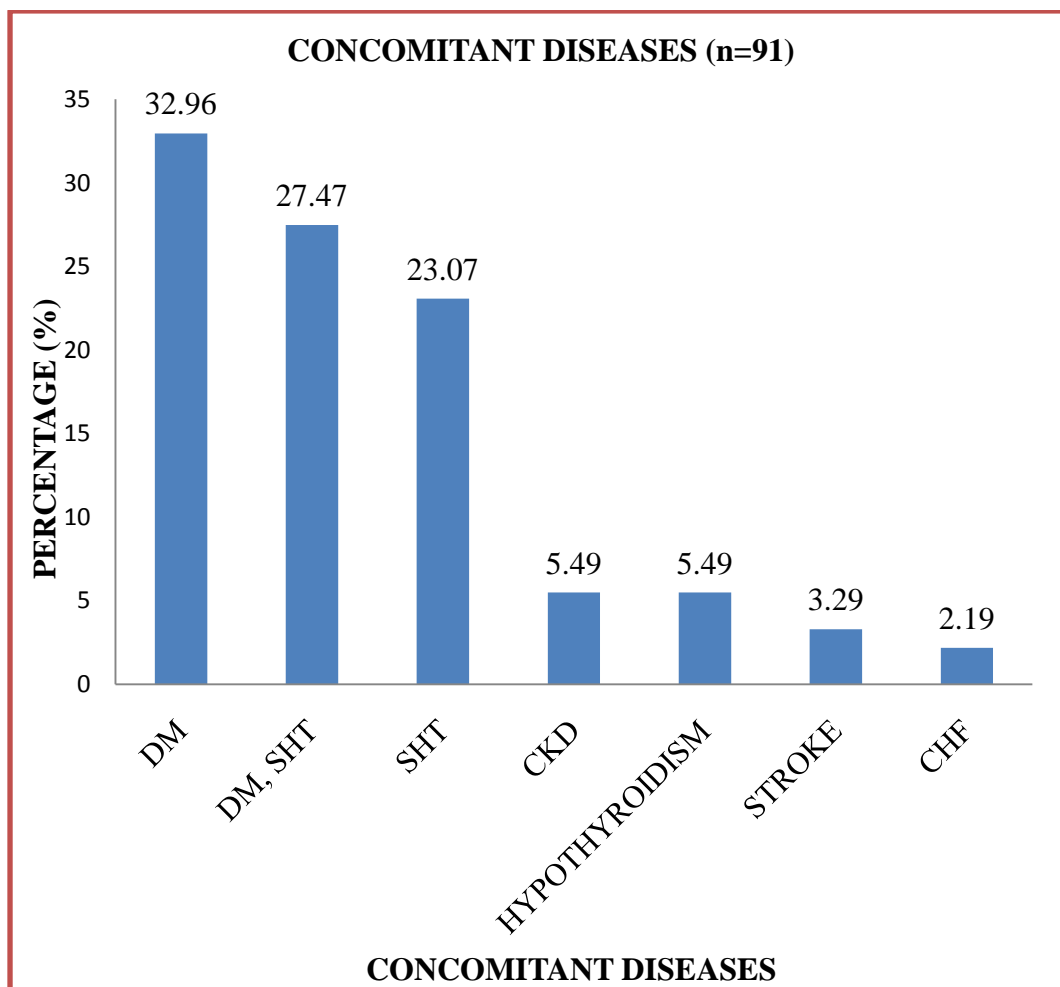
RISK FACTORS OF ACUTE CORONARY SYNDROME

The risk factors of ACS were analyzed among the study population. It was found that the only non modifiable risk factor was found to be males 98(80%). Other important modifiable risk factors was found to be diabetes mellitus 30(24.59%) followed by both diabetes and hypertension 25(20.49%), Hypertension 21((17.21%), smoking and alcoholic 14(11.47%), smoking 8(6.55%), alcoholic 7(5.73%) and obesity 6(4.91%) (Table.No.10, Fig.8).

Table.No.10: Risk factors of ACS

S.NO	RISK FACTORS	NO OF PATIENTS (n=122)	PERCENTAGE (%)
1	Type 2 diabetes	30	24.59
2	Diabetes and hypertension	25	20.49
3	Hypertension	21	17.21
4	Smoking and alcoholic	14	11.47
5	Smoking	8	6.55
6	Alcoholic	7	5.73
7	obesity	6	4.91

Fig.8: Risk factors of ACS

RISK FACTORS OF ACS (n=122)
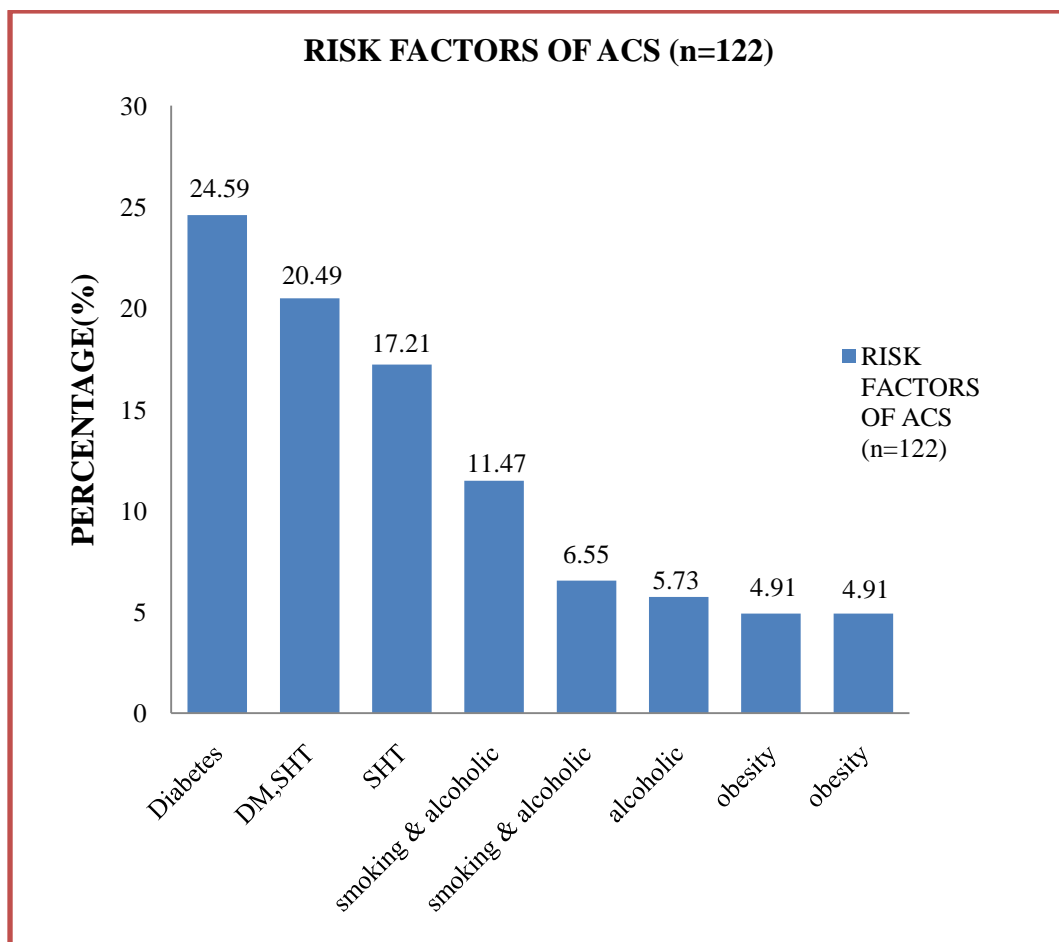
NUMBER OF DRUGS PRESCRIBED PER PATIENT

The total number of drugs prescribed to the study population was found to be 1254. The mean number of drugs prescribed per patient was found to be **11.5±4.18**. It was observed that minimum of 5 drugs and maximum of 18 drugs were prescribed per patient (Table.No.11, Fig.9).

Table.No.11: Number of Drugs prescribed per patient

S.NO	NO OF DRUGS PRESCRIBED	NO OF PATIENTS (n=122)	PERCENTAGE (%)
1	5	3	0.02
2	6	7	5.73
3	7	8	6.55
4	8	15	12.29
5	9	17	13.93
6	10	16	13.11
7	11	18	14.75
8	12	11	9.01
9	13	10	8.19
10	14	7	5.73
11	15	3	2.45
12	16	5	4.09
13	17	1	0.81
14	18	1	0.81

Fig.9: No of drugs prescribed per patient
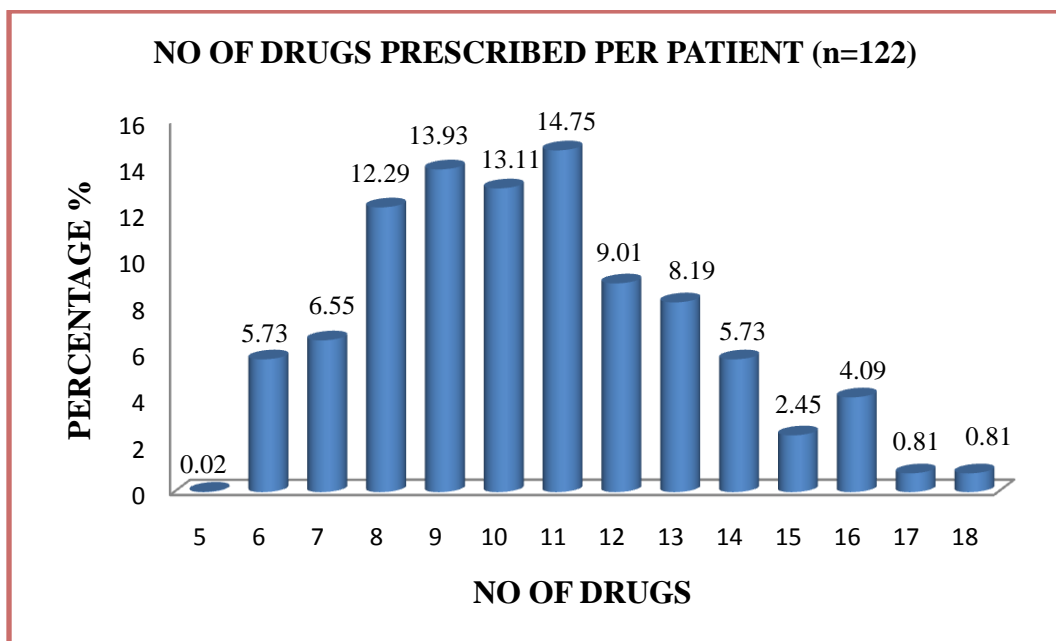
THERAPEUTIC CATEGORY OF DRUGS PRESCRIBED

The drugs prescribed to the study population were analyzed and the analysis revealed that majority of the study population has received antiplatelets 242(19.29%) followed by anti-ulcerative agents 135(10.76%), anticoagulants 118(9.40%), hypolipidemic agents 114(9.09%), anti-anginal 104(8.29%), anti-hypertensives 76(6.06%), diuretics 68(5.42%) and Hypoglcemic agents 58(4.62%) (Table.No.12, Fig.10).

Table.No.12: Therapeutic category of drugs prescribed

S.NO	CATEGORY	TOTAL NO OF DRUGS (n=1254)	PERCENTAGE (%)
1	ANTIPLATELETS	242	19.29
2	ANTI-ULCERATIVE AGENTS	135	10.76
3	ANTICOAGULANTS	118	9.40
4	HYPOLIPIDEMIC AGENTS	114	9.09
5	ANTI-ANGINAL	104	8.29
6	ANTI-HYPERTENSIVES	76	6.06
7	DIURETICS	68	5.42
8	HYPOGLYCEMIC AGENTS	58	4.62
9	NSAIDs ANDANALGESICS	48	3.82
10	ANTI-EMETICS	44	3.50
11	STEROIDS	43	3.42
12	ANTIHISTAMINES	43	3.42
13	ANTIBIOTICS	34	2.71
14	VASOPRESSORS	24	1.91
15	LAXATIVES	14	1.11
16	SEDATIVES-HYPNOTICS	12	0.95
17	ANTI-CHOLINERGICS	11	0.87
18	ANTI-ASTHMATICS	10	0.79
21	THROMBOLYTICS	5	0.39
27	OTHERS	51	4.06

Fig.10

DRUGS PRESCRIBED PER PATIENT (n=1254)

Drug	Percentage
ANTIPLATELETS	19.29
ANTIULCERATIVES	10.76
ANTICOAGULANTS	9.4
HYPOLIPIDEMICS	9.09
ANTIANGINAL	8.29
ANTI-HYPERTENSIVES	6.06
DIURETICS	5.42
HYPOGLYCEMICS	4.62
NSAID AND...	3.82
ANTI-EMETICS	3.5
STEROIDS	3.42
ANTIHISTAMINES	3.42
ANTIBIOTICS	2.71
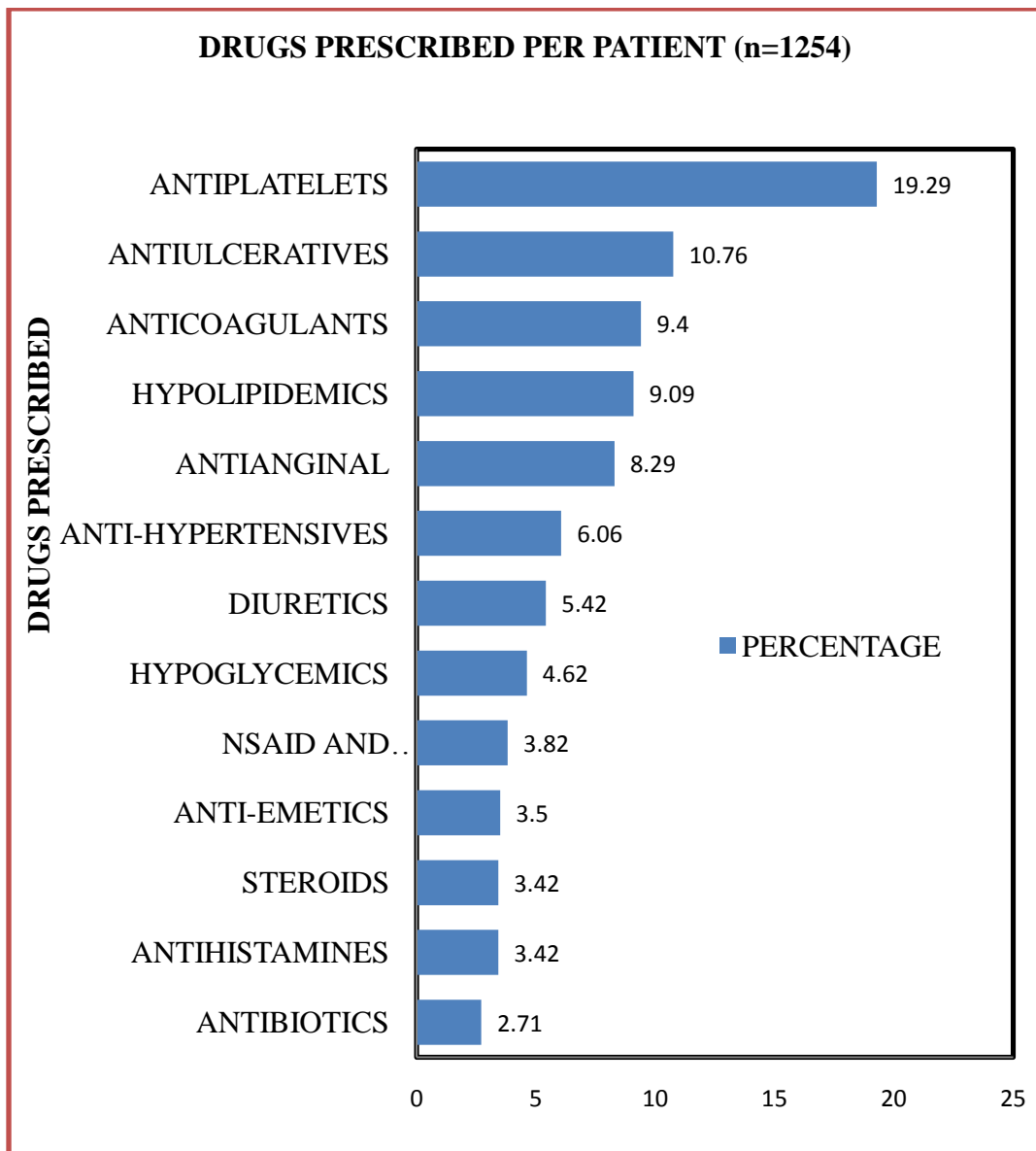
DETAILS OF THERAPEUTIC CATEGORY OF DRUGS PRESCRIBED

Table.N0.13

ANTI-PLATELETS

The analysis of details of antiplatelet drugs prescribed revealed that majority of the study population has received aspirin 114(47.50%) followed by clopidogrel 98(39.25%), ticagrelor 21(8.67%), tirofiban 8(3.30%) and prasugrel 1(0.41%).

S.NO	NAME OF THE DRUG	NO OF PATIENTS (n=242)	PERCENTAGE (%)
1	Aspirin	114	47.10
2	Clopidogrel	98	39.25
3	Ticagrelor	21	8.67
4	Tirofiban	8	3.30
5	Prasugrel	1	0.41

HYPOLIPIDEMIC AGENTS

The analysis of details of hypolipidemic agents prescribed revealed that the majority of study population has received atorvastatin 112(98.24%) followed by rosuvastatin 2(1.75%).

S.NO	NAME OF THE DRUG	NO OF PATIENTS (n=114)	PERCENTAGE (%)
1	Atorvastatin	112	98.24
2	Rosuvastatin	2	1.75

ANTI-ANGINAL AGENTS

The analysis of details of the anti-anginal agents prescribed revealed that most commonly prescribed were trimetazidine 39(37.5%) followed by isosorbide mononitrate 22(21.15%), nitroglycerin 17(16.34%), ivabradine 15(14.42%), ranolazine 7(6.73%) and isosorbide dinitrate 4(3.84%).

S.NO	NAME OF THE DRUG	NO OF PATIENTS (n=104)	PERCENTAGE (%)
6	Trimetazidine	39	37.5
2	Isosorbide mononitrate	22	21.15
5	Nitroglycerin	17	16.34
1	Ivabradine	15	14.42
4	Ranolazine	7	6.73
3	Isosorbide dinitrate	4	3.84

ANTI-HYPERTENSIVES

The analysis of the details of the anti-hypertensives prescribed revealed that the most commonly prescribed anti-hypertensives were carvedilol 18(23.68%), metoprolol 15(19.73%), nebivolol 11(14.47%). Amlodipine and ramipril was found to be used in 10(13.15%) of the patients. Telmisartan was found to be used in 6(7.89%) of the patients.

S.NO	NAME OF THE DRUG	NO OF PATIENTS (n=76)	PERCENTAGE (%)
1	Carvedilol	18	23.68
2	Metoprolol	15	19.73
3	Nebivolol	11	14.47
4	Amlodipine	10	13.15
5	Ramipril	10	13.15
6	Telmisartan	6	7.89
7	others	6	7.89

DIURETICS

The analysis of the details of the diuretics prescribed revealed that most commonly prescribed were furosemide 33(48.52%) followed by spironolactone 25(36.76%), torsemide 8(11.76%). Eplerenone and metolozone was found to be used in 1(1.47%) of the patients.

S.NO	NAME OF THE DRUG	NO OF PATIENTS (n=68)	PERCENTAGE (%)
1	Furosemide	33	48.52
2	Spironolactone	25	36.76
3	Torsemide	8	11.76
4	Eplerenone	1	1.47
5	Metolozone	1	1.47

THROMBOLYTICS

The analysis of the details of thrombolytics prescribed revealed that most commonly prescribed were streptokinase 3(60%) followed by nattokinase 2(40%).

S.NO	NAME OF THE DRUG	NO OF PATIENTS (n=5)	PERCENTAGE (%)
1	Streptokinase	3	60
2	Nattokinase	2	40

HYPOGLYCEMIC AGENTS

The analysis of the details of hypoglycemic agents prescribed revealed that majority of the study population has received insulin 38(65.51%) followed by metformin 10(17.24%), gliclazide 4(6.89%) and glimepiride 3(5.17%).

S.NO	NAME OF THE DRUG	NO OF PATIENTS (n=58)	PERCENTAGE (%)
1	Insulin	38	65.51
2	Metformin	10	17.24
3	Gliclazide	4	6.89
4	Glimepiride	3	5.17
5	others	3	5.17

DRUG-DRUG INTERACTIONS

The medication charts of the study population were analyzed for any drug-drug interactions using Micromedex software. It was observed that total number of drug interactions was found to be 721. The severity of drug interactions was categorized into minor, moderate and major (Table.No.14, Fig.11). Major interactions were among the highest 439(60.88%) followed by moderate 237(32.87%) and minor 45(6.24%).

SEVERITY OF DRUG-DRUG INTERACTIONS

Table.No.14: Severity of drug-drug interactions

S.NO	SEVERITY OF DRUG INTERACTION	NO OF DRUG INTERACTIONS (n=721)	OVERALL PERCENTAGE (%)
1	MAJOR	439	60.88
2	MODERATE	237	32.87
03	MINOR	45	6.24

Fig.11: Severity of drug interactions

SEVERITY OF DRUG INTERACTIONS (n=721)
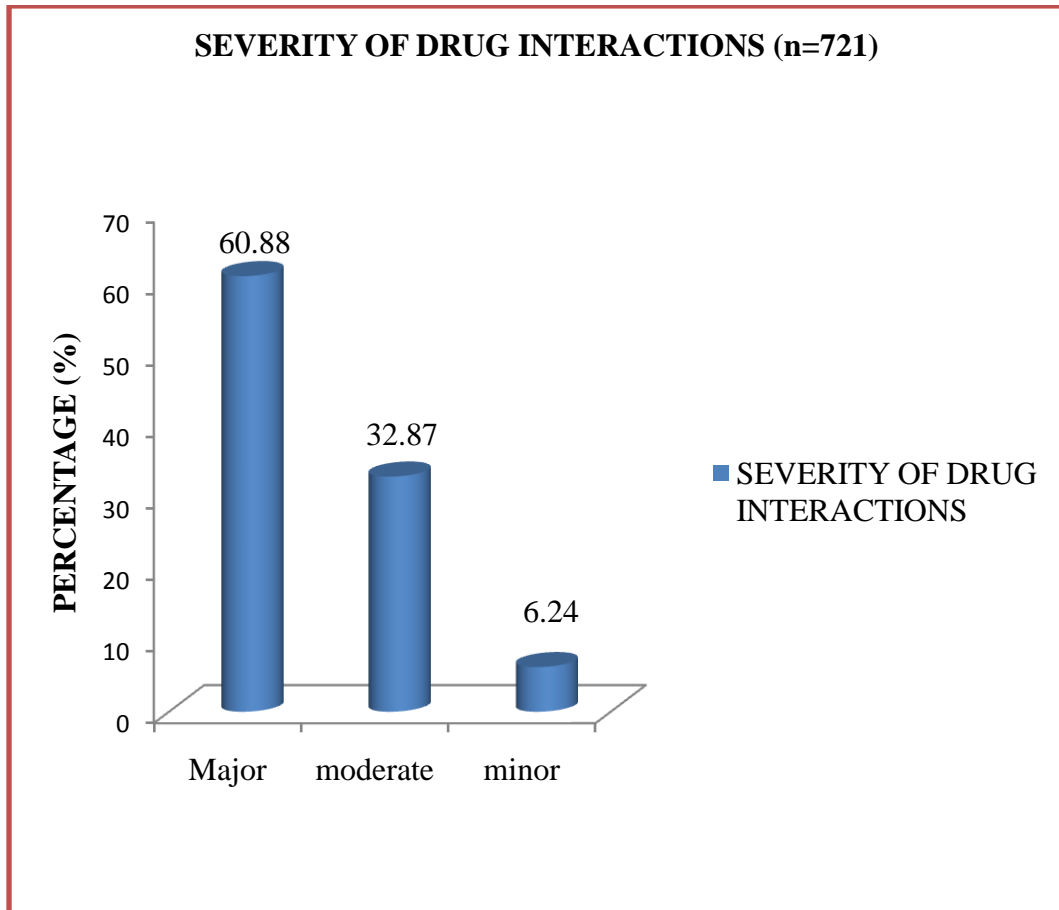
MAJOR DRUG INTERACTIONS

Table.No.15: List of Major drug interactions

DRUG 1	DRUG2	NO. OF INTERACTIONS (n=439)	EFFECTS	INFERENCE
Aspirin	Clopidogrel	89	Increased risk of bleeding	Monitoring of blood counts
	Heparin	104	Increased risk of bleeding	Evaluate any signs and symptoms of blood loss
	Furosemide	25	nephrotoxicity	Assure diuretic efficacy
	Spironolactone	24	nephrotoxicity	Assure diuretic efficacy
	Ticagrelor	20	Increased risk of bleeding	Monitored for signs of active bleeding
	Tirofiban	7	Increased risk of bleeding	Monitored for signs of active bleeding
	Metformin	11	Increased risk of hypoglycemia	Monitor blood sugar
	Torsemide	5	nephrotoxicity	Assure diuretic efficacy
	Prasugrel	1	Increased risk of bleeding	Monitored for signs of active bleeding
	Enoxaparin	1	Increased risk of bleeding	Monitored for signs of active bleeding
	Piroxicam	1	Increased risk of bleeding	Giving aspirin 2 hours earlier
	Glimepiride	2	Increased risk of hypoglycemia	Monitor blood sugar
	Aceclofenac	1	Increased risk of bleeding	Giving aspirin 2 hours earlier
	Indomethacin	3	Increased risk of bleeding	Giving aspirin 2 hours earlier
	Digoxin	1	Prolonged half life of digoxin	Monitoring of serum digoxin levels

DRUG 1	DRUG 2	NO.	EFFECTS	INFERENCE
Clopidogrel	Heparin	90	Increased risk of bleeding	Monitored for signs of active bleeding
	Amlodipine	7	Decreased antiplatelet effects	Addition of cilastazol
	Enoxaparin	2	Increased risk of bleeding	Monitored for signs of active bleeding
	Piroxicam	1	Increased risk of bleeding	Monitored for signs of active bleeding
	Ticagrelor	1	Increased risk of bleeding	Monitored for signs of active bleeding
	Rabeprazole	1	Reduced antiplatelet activity	Rabeprazole-4 hrs after lunch clopidogrel-after breakfast
	Diltiazem	1	Reduced antiplatelet activity	Monitoring of blood counts
	Indomethacin	2	Increased risk of bleeding	Monitored for signs of active bleeding
	Aceclofenac	1	Increased risk of bleeding	Monitored for signs of active bleeding
Heparin	Tirofiban	7	Increased risk of bleeding	Monitored for signs of active bleeding
	Enoxaparin	2	Increased risk of bleeding	Monitored for signs of active bleeding
	Streptokinase	2	Increased risk of bleeding	Monitored for signs of active bleeding
	Aceclofenac	1	Increased risk of bleeding	Monitored for signs of active bleeding
	Prasugrel	1	Increased risk of bleeding	Monitored for signs of active bleeding
	Piroxicam	1	Increased risk of bleeding	Monitored for signs of active bleeding
	Indomethacin	2	Increased risk of bleeding	Monitored for signs of active bleeding

DRUG 1	DRUG 2	NO.	EFFECTS	INFERENCE
Tirofiban	Ticagrelor	4	Increased risk of bleeding	Monitored for signs of active bleeding
Rifampicin	Isoniazid	1	hepatotoxicity	Monitor liver function
	Ticagrelor	1	Decreased ticagrelor activity	Should be avoided
Ondansetron	Tramadol	2	Risk of serotonin syndrome	Closely observe patient
	Ivabradine	3	QT prolongation	Use caution
Diltiazem	Atorvastatin	1	Increased risk rhbdomyolysis	Monitor patient for any signs
	Nebivolol	1	Increased risk of hypotension	Monitor BP
Digoxin	Spironolactone	1	Increased spironolactone exposure	15% to 30% reduce dose of digoxin
	Atorvastatin	1	Increased digoxin concentration	15% to 30% reduce dose of digoxin
	Ranolazine	1	Increased digoxin concentration	Reduce digoxin dose by 30% to 50%
Alprazolam	Fentanyl	1	Increased risk of CNS depression	Adjust dosage
Metolozone	Torsemide	1	Risk of electrolyte and fluid balance	Monitor fluids and electrolytes
Amlodipine	Domperidone	1	QT prolongation	Administer Lower dose of domperidone
Ivabradine	Clarithromycin	1	QT prolongation	contraindicated
Atorvastatin	Clarithromycin	1	Increased risk of rhabdomyolysis	Prefer Pravastatin or fluvastatin
Ranitidine	Tramadol	1	Increased tramadol exposure- respiratory depression	Reducing the dose

ANTICOAGULANT UTILIZATION EVALUATION

Drug utilization helps to recognize variability in drug use and to support interventions that improve patient outcomes. Anticoagulants are blood thinners, usually prescribed to prevent blockage of coronary arteries. In this study it was aimed to perform drug utilization evaluation in order to determine appropriate use of anticoagulants.

ANTI-COAGULANTS PRESCRIBED FOR ACUTE CORONARY SYNDROME PATIENTS

Unfractionated heparin was found to be most extensively prescribed anticoagulants among the study population 114(96.61%) followed by Low molecular weight heparin (Enoxaparin 4(3.38%)) (Table.No.16, Fig.12).

Table.No.16: Anticoagulants prescribed

S.NO	NAME OF THE DRUG	NO OF PATIENTS (n=118)	PERCENTAGE (%)
1	Unfractionated heparin	114	96.61
2	Low molecular weight heparin (Enoxaparin)	4	3.38

Fig.12: Anticoagulants prescribed
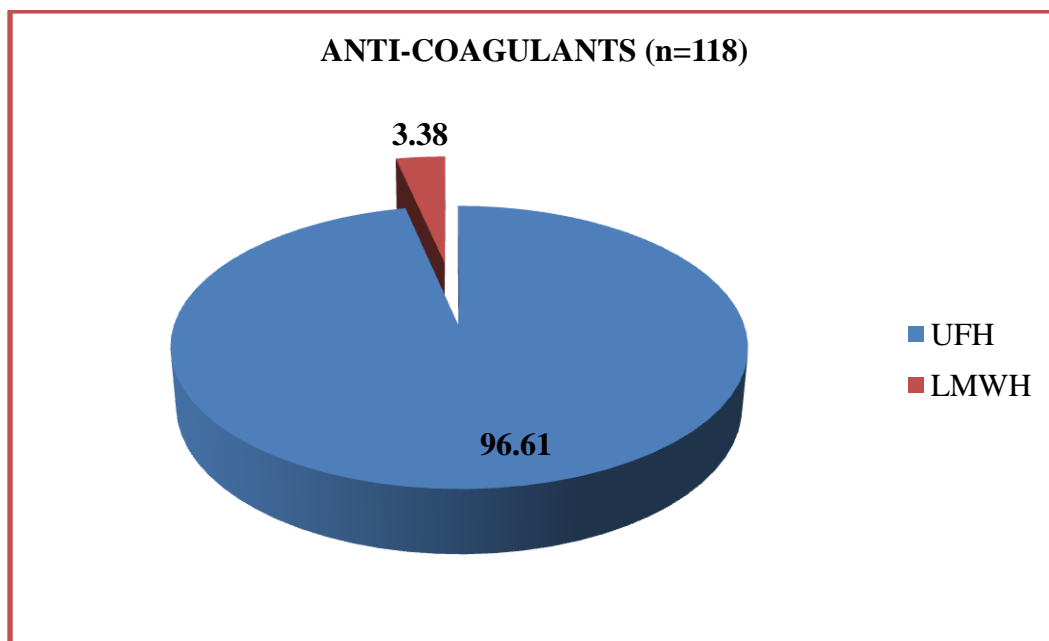
BLEEDING RISK SCORE ANALYSIS

The accurate assessment of bleeding risk is to maximize benefits and to minimize risk of such complications. It was aimed to calculate CRUSADE bleeding risk score among the study population.

CALCULATION OF BLEEDING RISK SCORE

The CRUSADE bleeding risk score was calculated for each individual and was categorized into Very low, Low, Moderate, High and Very high based on CRUSADE bleeding risk score (Table.No.17, Fig.13). The study results revealed that 45(36.88%) of the study populations were in the very low bleeding risk category (≥20), 33(27.04%) of the study populations were in the low bleeding risk category (21-30), 12(9.83%) were in the moderate bleeding risk category (31-40), 25(20.49%) were in the high bleeding risk (41-50) and 7(5.73%) were in the very

high bleeding risk score (>50). It was found that more number of patients were in the very low bleeding risk category (≥20).

CRUSADE BLEEDING RISK SCORE CATEGORY

Table.No.17: CRUSADE bleeding risk score category

S.NO	CRUSADE RISK CATEGORY	RISK SCORE RANGE	NO OF PATIENTS (n=122)	OVERALL PERCENTAGE %
1	Very low	≥20	45	36.88
2	Low	21-30	33	27.04
3	Moderate	31-40	12	9.83
4	High	41-50	25	20.49
5	Very high	>50	7	5.73

Fig.13: CRUSADE bleeding risk score category
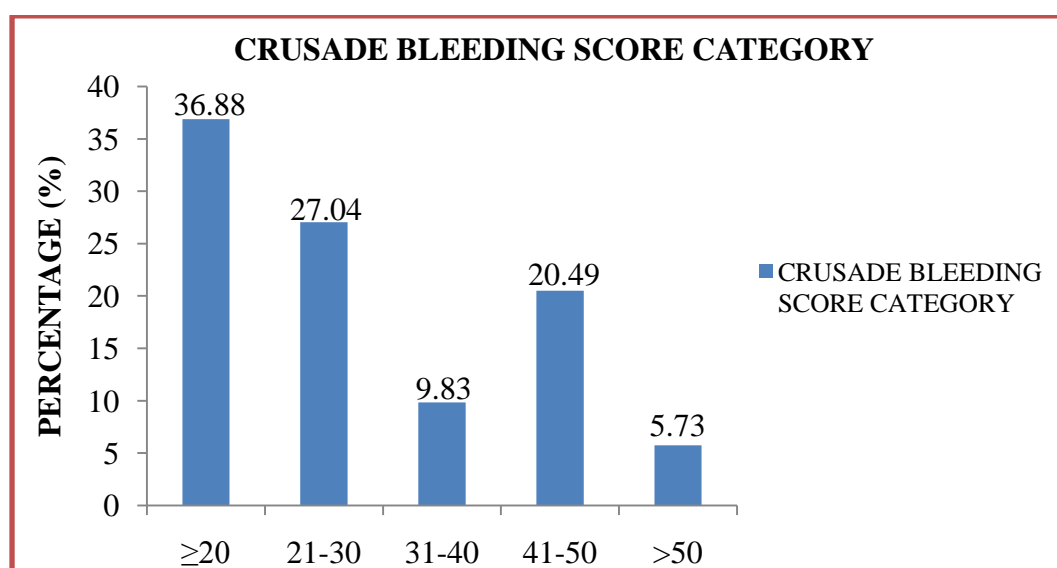
RISK FACTORS FOR BLEEDING IN ACS

The study populations were analyzed for any bleeding risk factors. It was found that most commonly found bleeding risk factors were Age (≥65yrs) 27(22.13%) followed by Diabetes 26(21.31%), Gender (Female) 24(19.67%), Weight (BMI≥25) 24(19.67%), Diabetes and hypertension 22(18.03), Renal insufficiency (CrCl≤60ml/min) 19(15.57%), hypertension 19(15.57%) and anemia 18(14.75%) (Table.No.18, Fig.14).

Table.No.18: Bleeding risk factors

S.NO	NON MODIFIABLE RISK FACTORS	NO OF PATIENTS (n=122)	OVERALL PERCENTAGE%
1	Age (≥65yrs)	27	22.13
2	Diabetes	26	21.31
3	Gender (Female)	24	19.67
4	Weight (BMI≥25)	24	19.67
5	Diabetes and Hypertention	22	18.03
6	Renal insufficiency (CrCl≤60ml/min)	19	15.57
7	Hypertention	19	15.57
8	Anemia (Male<13g/dl, Female<12g/dl)	18	14.75

Fig.14: Risk factors for bleeding

RISK FACTORS FOR BLEEDING IN ACS (n=122)
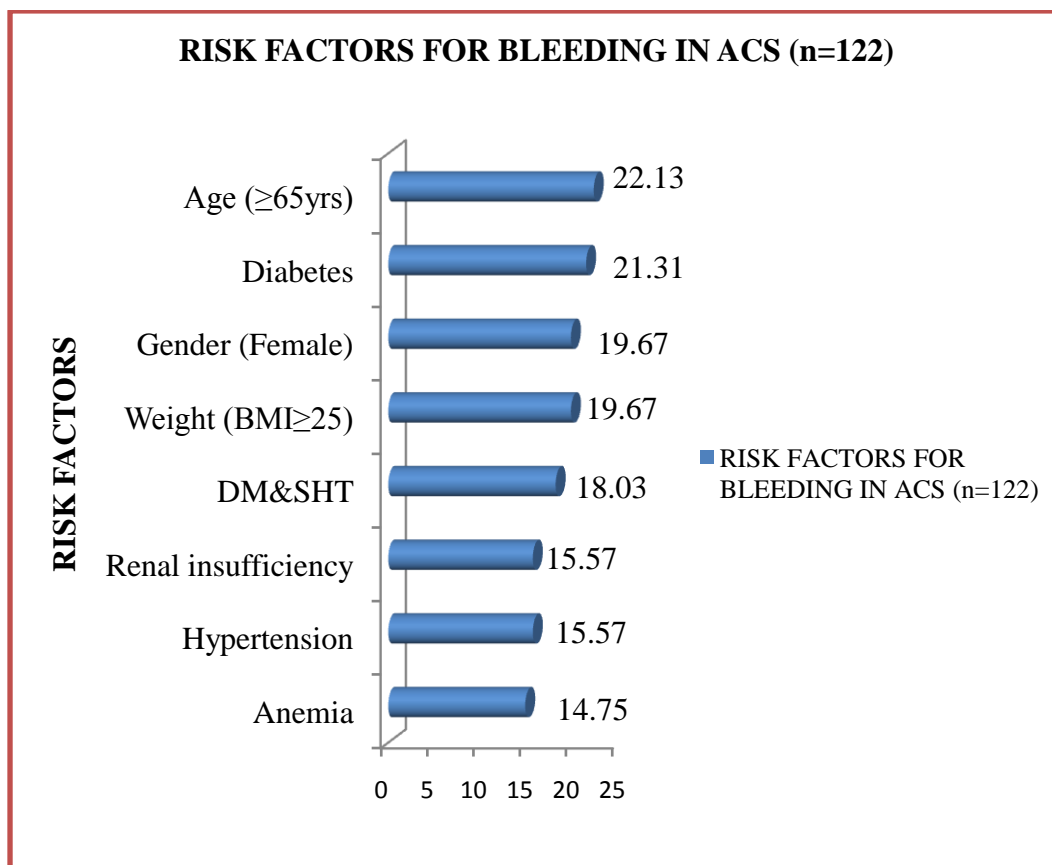
NUMBER OF RISK FACTORS FOR BLEEDING PER PATIENT

The study population was divided into subgroups based on the number of patients with and without bleeding risk factors (Table.No.19, Fig.15). Among the 122 patients, 25(20.49%) patients had no bleeding risk factor and 97(79.50%) patients without bleeding risk factors. Among the 97(79.50%) patients, more number of patients 41(33.60%) were having atleast one bleeding risk factor, 33(27.04%) patients were having 2 bleeding risk factors,

12(9.83%) patients were having 3 bleeding risk factors, 6(4.91%) patients were having 4 bleeding risk factors and 5(4.09%) patients were having 5 risk factors (Table.No.20, Fig.16).

Table.No.19: Categorization of patients based on risk factors

S.NO	NO. OF PATIENTS WITH BLEEDING RISK FACTORS (n=122) (%)	NO. OF PATIENTS WITHOUT BLEEDING RISK FACTORS (%)
1	97(79.50%)	25(20.49%)

Fig.15: Categorization of patients based on risk factors

BLEEDING RISK FACTORS (n=122)

20.49
79.5

- PATIENTS WITH BLEEDING RISK FACTORS
- PATIENTS WITHOUT RISK FACTORS
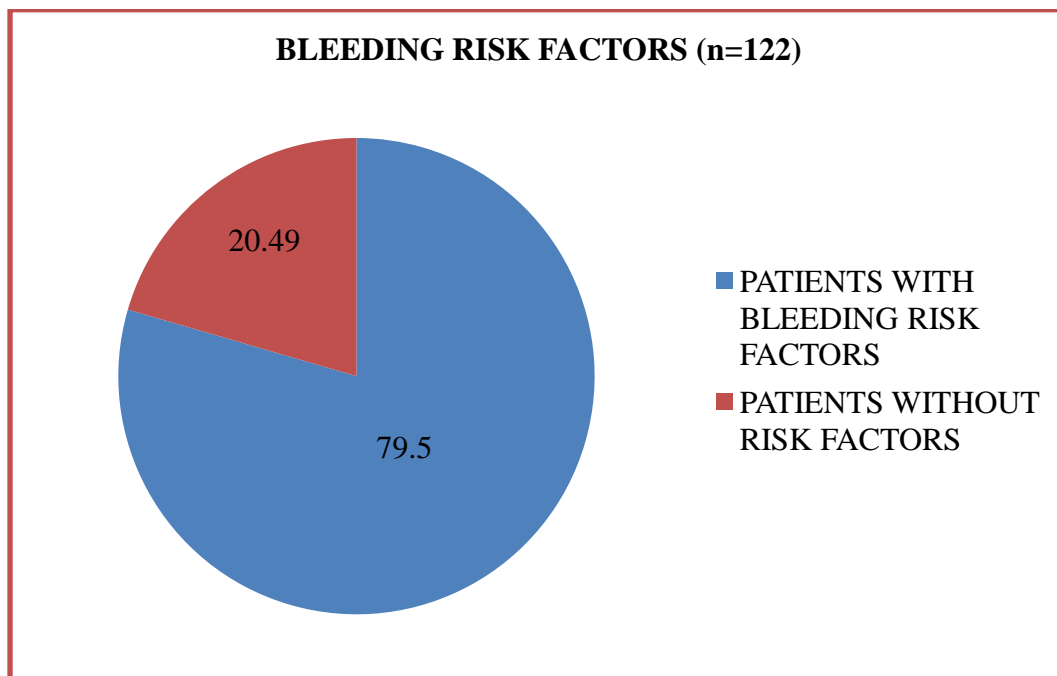
Table.No.20: Number of risk factors for bleeding per patient

S.NO	NO OF RISK FACTORS	NO OF PATIENTS (n=97)	OVERALL PERCENTAGE (%)
1	1	41	42.26
2	2	33	34.02
3	3	12	12.37
4	4	6	6.18
5	5	5	5.15

Fig.16: Number of risk factors for bleeding per patient

NO OF RISK FACTORS PER PATIENT (n=97)
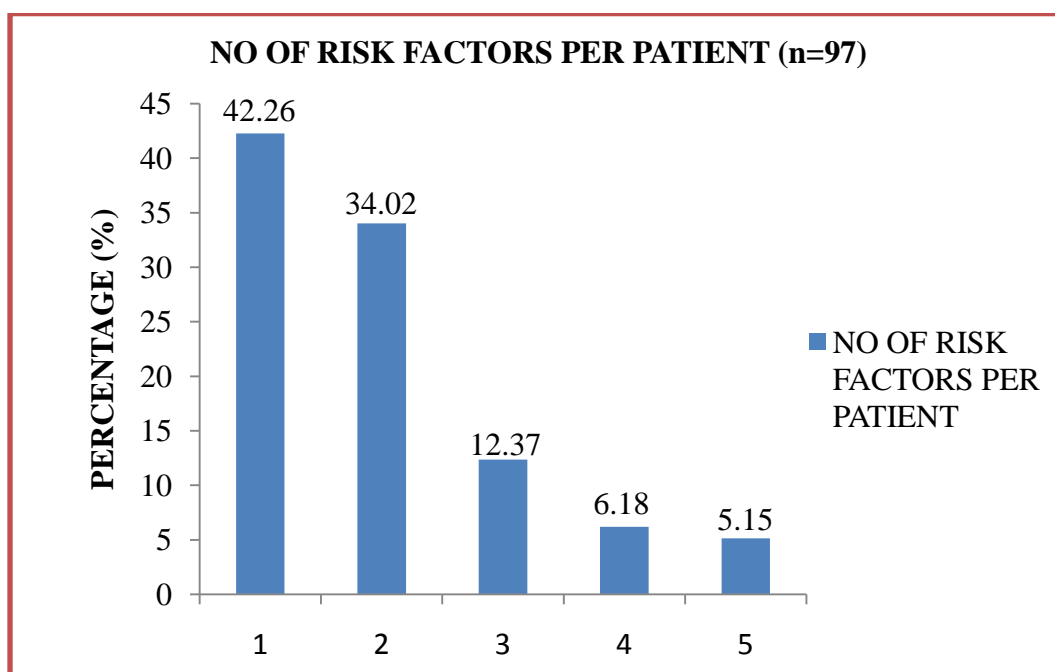
NO OF RISK FACTORS IN EACH BLEEDING RISK CATEGORY

The number of risk factors in each bleeding risk category was analyzed for individual patient (Table.No.21). The study results showed that patients in very high risk of bleeding had more number of risk factors and patients with very low bleeding risk category has less number of risk factors.

Table.No.21: Number of risk factors in each bleeding risk category

S.NO	RISK CATEGORY (Based on CRUSADE)	NO OF RISK FACTORS FOUND (n=122)					
		0	1	2	3	4	5
1	Very low (n=45)	14	20	8	-	-	-
2	Low (n=33)	6	16	8	1	2	-
3	Moderate (n=25)	2	3	13	4	1	-
4	High (n=12)	2	2	2	6	-	2
5	Very high (n=7)	1	-	2	1	3	3

CRUSADE SCORE GROUPS AND BLEEDING EVENTS

Among the study populations, the overall incidence of bleeding rates was found to be 8(6.55%). The study population was categorized into groups with no bleeding events and bleeding events based on CRUSADE risk score (Table.No.22). 101(98.05%) patients in the CRUSADE risk category ≤40 and 13(68.42%) patients in the CRUSADE risk category >40 were not having any bleeding events. The bleeding rate was more in the CRUSADE risk category (>40) which accounts for 6(31.57%) as compared to CRUSADE risk category (<40) which accounts for 2(1.94%).

Table.No.22: CRUSADE score groups and bleeding events

S.NO	CRUSADE BLEEDING RISK CATEGORY	NO OF PATIENTS WITHOUT BLEEDING EVENTS (%) (n=114)	NO OF PATIENTS WITH BLEEDING EVENTS (%) (n=8)
1	CRUSADE ≤40	101(88.5%)	2(25%)
2	CRUSADE >40	13(11.4%)	6(75%)

Fig.17: CRUSADE score groups and bleeding events
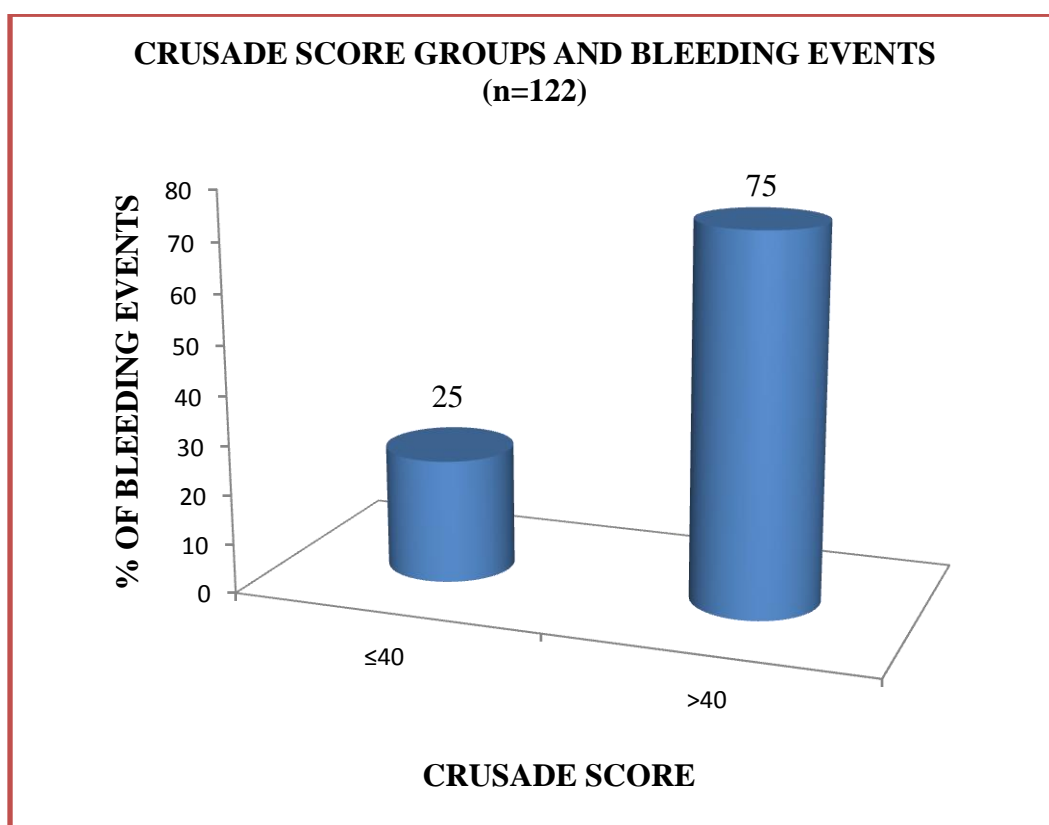
ACS CATEGORY AND BLEEDING EVENTS

The study population was divided into groups with no bleeding events and bleeding events based on acute coronary syndrome category (Table.No.23). 96(93.20%) patients with STEMI, 7(87.5%) with UA, 6(100%)It was found that the bleeding rate was more in patients with ST elevated myocardial infarction 7 (6.79%) followed by Unstable angina 1(12.5%).

Table.No.23: ACS category and bleeding events

S.NO	ACS CATEGORY (n=122)	NO OF PATIENTS WITHOUT BLEEDING EVENTS (%) (n=114)	NO OF PATIENTS WITH BLEEDING EVENTS (%) (n=8)
1	STEMI	96(84.21)	7(87.5)
2	UA	7(6.14)	1(12.5)
3	UA+STEMI	6(5.26)	0(0)
4	NSTEMI	5(4.38)	0(0)

Fig.18: ACS category and bleeding events
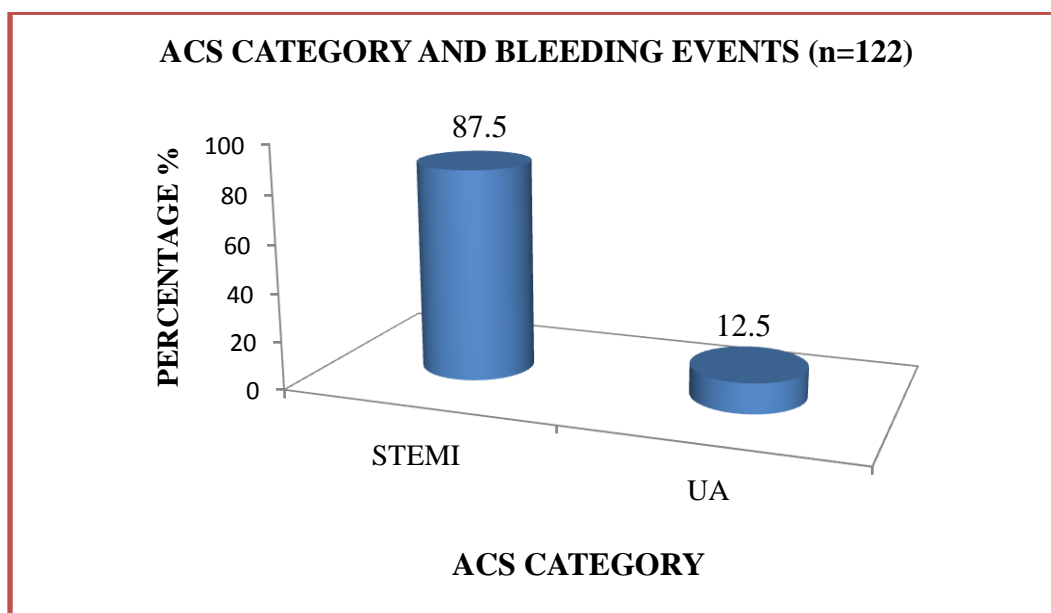
8. DISCUSSION

The work entitled "Study on anticoagulant utilization evaluation and risk score assessment for predicting bleeding among patients with acute coronary syndrome" was conducted in the department of General Medicine and Cardiology at a 1000 bedded multispecialty hospital which has got state of art facilities. The study was undertaken to know the anticoagulant utilization pattern and also to predict bleeding risk in the study subjects with acute coronary syndrome with the help of a widely accepted CRUSADE risk score. A pilot scale study was conducted in the study site to find out the scope of this research. After ensuring the potential of the study, the study protocol was prepared and submitted to the Institutional ethical committee and the approval was obtained to carry out this research study in the study site.

A total of 122 patients were enrolled during the study period as per the inclusion criteria. The analysis of the study conducted for a period of 10 months from November 2017 to August 2018 revealed that there were 98 (80%) male patients and 24 (20%) female patients. Our study results correlates to a similar study conducted by **Seong et al**[59] (2016) reported that coronary artery disease is more prevalent in the men than women.

The age categorizations of the study population revealed that maximum number of patient 74(60.65%) are in the age group of middle adulthood (34-59 years). Our study results correlates with a previous study carried out by **Egred M et al**[60] (2013) reported that acute myocardial infarction generally more occurs in patients older than 45 because of smoking, obesity and lack of physical activity.

The present study revealed that majority of patients was diagnosed with STEMI (84.42%). A study conducted by **Bacci M. R et al**[61] (2015) reported that

the most prevalent type of ACS was STEMI which correlates with the present study.

A study conducted by **Gupta S et al**[62] (2017) concluded that commonest non modifiable risk factor was male sex 23(77%) in young adults and hypertension, diabetes etc are other modifiable risk factors. The analysis of risk factors for ACS in the study population also revealed that the most common non modifiable risk factor was found to be males 98(80%). Other common modifiable risk factors were found to be diabetes 30(24.59%), hypertension 21(17.21%) and smoking 8(6.55%).

According to **Burke L A et al**[63] (2017) revealed that Diabetes mellitus was one of the most prominent co morbid condition found in ACS patients. This result was found to be consistent with the present study i.e. major comorbid condition suffered by the study population was diabetes mellitus 30(32.96%).

The analysis of the drugs prescribed to the study population was done inorder to describe drug utilization pattern. The most commonly prescribed drug category was found to be antiplatelet agents 242(19.29%) followed by antiulceratives 135(10.68%), anticoagulants 118(9.40%), hypolipidemics 114(9.09%) and antianginal drugs 104(8.29%). Our study results correlates with a previous study conducted by **Rakesh et al**[64] (2016) reported that the major prescriptions include antiplatelet agents followed by antianginal drugs.

Majority of the present study population were prescribed with dual antiplatelet therapy. A similar study conducted by **Patti G et al**[65] (2017) revealed that current guidelines recommend the use of dual antiplatelet therapy (aspirin plus a p2Y12 inhibitor). This reveals the antiplatelet therapy given at the study site was appropriate as per the guidelines recommended.

Unfractionated heparin 114(96.61%) was found to be most extensively prescribed anticoagulant among the study population followed by Enoxaparin 4(3.38%). This is comparable with the previous study conducted by **Kadakia M. B et al** [45] (2010) which reports that unfractionated heparin (66%) was the most commonly used anticoagulant. A study conducted by **Perez J. L et al** [66] (2012) suggests that Enoxaparin is an economically attractive alternative compared with UFH. Eventhough the studies suggest the benefit of enoxaparin still the UFH widely used in clinical settings.

Bleeding is the most important complication from acute coronary syndrome treatment, especially in patients who are currently on multiple antithrombotic therapies. **AD Mohamed et al** [22] (2016) concluded that CRUSADE bleeding score is a good predictor for major bleeding with acute coronary syndrome and it is applicable in both STEMI and UA/STEMI as well as both men and women. **Abu A et al** [42] (2012) compared 3 different bleeding risk scores and concluded that greatest accuracy obtained with the use of CRUSADE bleeding risk score. So the bleeding analysis among the study population was done using CRUSADE risk score.

The CRUSADE bleeding risk score was calculated for each individual and was categorized into very low, low, moderate, high and very high bleeding risk category. The present study reports that more of the patients were in the very low bleeding risk score 45(36.88%) and fewer patients were in the very high bleeding risk score 7(5.73%). A study conducted by **Kadakia et al** [45] (2010) revealed that more patients were in the very low bleeding risk score. A study conducted by **Abu A et al** [46] (2014) reported that patients at high and very high bleeding risk category are also at increased risk bleeding and appropriate bleeding reducing strategies should be implemented in patients with high bleeding risk category.

The study population was categorized based on bleeding risk factors. It was found that most prevalent bleeding risk factor was Age (≥65yrs). Our study results was found to be consistent with a previous study conducted by **Manokian S V et al [57]** (2007) showed that patients with major bleeding were older (≥65yrs).

In the present study, it was found that majority of patients were having more than one risk factor, which intensify monitoring of these patients. A study conducted by **Alhassan M et al [67]** (2017) concluded that high prevalence of risk factors will increases the cardiovascular mortality in ACS patients thus an intensive monitoring is required.

The present study revealed that the overall incidence of bleeding events was found to be 8(6.55%) among the study population. A study conducted by **Voss WB et al [68]**(2016) reported that incidence of bleeding rate was found to be 10.4%.

Our study results revealed that high numbers of bleeding risk factors were found in the patients with very high bleeding risk category. This study results correlates with a previous study conducted by **Jinatongthai p et al[21]** (2014) conducted a study revealed that there is an increased risk of bleeding with high number of risk factors in the higher CRUSADE bleeding risk categories.

In the present study, it was found that the more number of bleeding rates were in the CRUSADE risk >40 (75%) as compared to CRUSADE risk <40 2(25%). This study results was consistent with a previous study conducted by **Subherwal et al[48]** (2009) reported that bleeding rates was more in the high risk category and bleeding increases the mortality rate. A study conducted by **Misumida N et al [69]**(2017) concluded that asian patients with STEMI had increased incidence of bleeding events. Similarly our study also reveals 87.5% patients with bleeding were belongs to STEMI group.

Patients with myocardial infarction are indicated for the combined use of anticoagulants and antiplatelet agents which reduces the ischemic risk due to stent implantation but increases the risk of bleeding. Inorder to prevent bleeding events, continuous monitoring of patients and assessment of bleeding risk score can be done. Clinical pharmacist plays a key role in monitoring of bleeding and assessment of bleeding risk scores. Calculation of bleeding risk scores and assessment of individual bleeding risks enable the health care professionals to focus more on the patients with higher bleeding risk category, which inturn prevents the morbidity and mortality due to bleeding events. So the present study strongly recommends for continuous assessment on bleeding risk for individual patient and drug utilization evaluation for updating treatment guidelines for ACS patients.

9. SUMMARY

The study entitled "Study on anticoagulant utilization evaluation and risk score assessment for predicting bleeding among patients with acute coronary syndrome" was carried out in the General medicine and Cardiology ward for a period of 10 months as per the inclusion criteria after obtaining consent from the Hospital authorities. This study was carried out to predict the bleeding risk of an individual subjects with acute coronary syndrome using CRUSADE bleeding risk score. The results obtained from the study population are summarized as follows:

- The study population consisted of 122 patients with acute coronary syndrome as per the inclusion criteria.

- In this study, it was observed that incidence of ACS was more common in males 98(80%) than female 24(20%) population.

- The mean age of the overall study population was found to be 55.63±10.02 and the most predominant age group was middle adulthood 74(60.65%) followed by Later adulthood 43(35.24).

- The incidence of ST elevated myocardial infarction 103(84.42%) was higher as compared to Non ST elevated myocardial infarction 5(4.09%)/ Unstable angina 8(6.55%) among the study population.

- Patients with single vessel disease 59(48.3%) was more common than double vessel disease 44(36.06%) and triple vessel disease 19(15.57%).

- The risk factors of ACS in each individual were identified and it was found that most common non modifiable risk factor was males 98(80%). Other risk factors includes diabetes 30(24.59%), both diabetes and hypertension 25(20.49%), Hypertension 21((17.21%), smoking and alcoholic 14(11.47%), smoking 8(6.55%), alcoholic 7(5.73%) and obesity 6(4.91%)

- Analysis of co morbidities among the study population revealed that Diabetes mellitus 30(32.9%) and Hypertension 21(23.07%) was the most prominent.

- The most commonly prescribed drug classes were antiplatelets 242(19.29%) followed by anti-ulceratives 135(10.76%) and anticoagulants 118(9.40%)

- The analysis of drug-drug interactions prevailing in the prescription of study population had revealed that 439(60.88%) of drug interactions were in the major category, 237(32.87%) were in the moderate category and 45(6.24%) were in the minor category. The total number of drug-drug interactions was found to be 721. Most commonly found drug interaction were heparin with aspirin (104) which increases the risk of bleeding followed by clopidogrel with aspirin.

- Among the STEMI and NSTEMI, Unfractionated heparin 114(96.61%) was the most commonly prescribed followed by Enoxaparin 4(3.38%).

- The CRUSADE bleeding risk score were calculated for each subject. More patients 45(36.88%) in the study populations were in the very low bleeding risk category followed by low bleeding risk category 33(27.04%).

- The analysis of the bleeding risk factors revealed that Age ($\geq$65yrs), Diabetes mellitus, gender (females) and weight (BMI $\geq$25) was most commonly found among the study population.

- Higher numbers of risk factors (5) were found in the very high bleeding risk category.

- The overall bleeding rates were found to be 8(6.55%) and the bleeding rates was more in the CRUSADE risk category (>40) and also more in the STEMI population as compared to NSTEMI population.

Study on anticoagulant utilization evaluation and risk score assessment for predicting bleeding among patients with acute coronary syndrome

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10. CONCLUSION

Risk assessment is important for the fine calculation of the prognosis of individual patients, which is an important issue for therapeutic decision making. Several trials have shown that antithrombotic drugs and coronary invasive procedures can reduce the number of ischemic events in acute coronary syndrome patients, but these treatments usually increase the risk of bleeding. Risk of bleeding can be evaluated using a simple risk score (i.e. CRUSADE bleeding risk score) in both STEMI and NSTEMI and across anticoagulant strategies, providing important prognostic information for the Clinician.

In the present study, the study populations were divided into five groups based on CRUSADE bleeding risk score. Based on CRUSADE scores, there was significant number of patients were at higher risk for bleeding. The patients with higher risk of bleeding require continuous monitoring and patient education inorder to prevent the morbidities and mortalities. The drug utilization pattern of anticoagulants reveals the more use of UFH at the study site. According to research studies there are many anticoagulants with lesser bleeding risk are available. The utilization of safer anticoagulants will ensure the lesser events of bleeding. The number of bleeding events observed in the study was low, which shows the continuous monitoring and prevention of bleeding is ensured at the study site.

The clinical pharmacist can involve in the assessment of bleeding risk and appropriateness of the therapy. The continuous studies are required for the disease like ACS which is found to be more prevalent among the Indians. There are many factors which can influence the therapy for ACS, thus a proper assessment may result in effective and safer therapy in ACS.

11. FUTURE OUTLOOK

The present study covers the clinical utility of widely available, guideline-recommended bleeding risk scores (CRUSADE bleeding risk score). Risk stratification with the help of appropriate risk scores is a clinical need pivotal for everyday clinical decision making. The future of this research study can focus on various bleeding reducing strategies as follows:

➢ Personalized, tailored patient therapy based on risk scores
➢ Prospective randomized trials (whether novel anticoagulants can be combined with anti-platelets will reduce bleeding risks) is suggested.

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Social Scientist

SRH/EC.12-11/2017-18   28th December 2017

ETHICAL CLEARANCE CERTIFICATE

Project Title:" Study On Anticoagulant Utilization Evaluation And Risk Score Assessment For Predicting Bleeding Among Patients With Acute Coronary Syndrome".

Researcher: MS.APARNA.N
M.Pharmacy II year
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Coimbatore – 641 044

The following members of the ethics committee were present at the meeting held on 23.12.2017 at 11.00am at New Auditorium, Sri Ramakrishna Hospital Campus, Coimbatore.

SI NO	Members Name	Qualification	Designation	Address	Affiliation To the Institution Yes/NO
1.	Dr.P.Murali	M.Sc.,Ph.D., D.Sc	Scientist Mg. Director & CEO	Mg.Director & CEO Evolve Biotech Pvt.Ltd., 401 – 405, 4th floor Ticel Bio park Ltd, Taramani, Chennai - 13	No
2.	Dr.P.Sukumaran	MS., M.Ch., FIACS	Scientific / EC Member Secretary Dean	Dean Sri Ramakrishna Hospital, 395, Sarojini Naidu Road, Sidhapudur, Coimbatore	Yes
3.	Dr.R.Lalitha	DGO.,(OG)	Clinician	Sr Consultant Gynecologist & HOD Sri Ramakrishna Hospital, 395, Sarojini naidu Road, Sidhapudur, Coimbatore.	Yes
4.	Dr.M.Rangasamy	B.E., M.Sc., Ph.D.,	Lay Person	Former Professor Government College of Technology, Coimbatore.	No

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5.	Dr S Rajagopal	M.Ch.	Clinician	Sr. Consultant Neuro Surgeon, Sri Ramakrishna Hospital, 395, Sarojini naidu Road, Sidhapudur, Coimbatore	Yes
6.	Dr N Paramasivan	MBBS ,MD	Basic Medical Scientist	Prof of pharmacology and HOD Sri Ramakrishna Dental College and Hospital, Coimbatore	Yes
7.	Mrs Mythili Padmanabhan	M.Sc., (Physiology)	Social Scientist	Corresponded Vriksha 5/14, 2nd street, G G Avenue Coimbatore	No

This is to certify that the research work entitled **"Study On Anticoagulant Utilization Evaluation And Risk Score Assessment For Predicting Bleeding Among Patients With Acute Coronary Syndrome"**, placed before the Institutional Ethical Committee has been approved as there is no objection to do this research work.

This ethics committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report.

The Ethics Committee wishes her well in her research.

Yours Truly,

Member Secretary,
Institutional Human Ethics Committee,

Dr. P. SUKUMARAN, M.S.,M.Ch.,FIACS.,
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SNR
SONS TRUST

PATIENT CONSENT FORM

Project Title: "STUDY ON ANTICOAGULANT UTILIZATION EVALUATION AND RISK SCORE ASSESSMENT FOR PREDICTING BLEEDING AMONG PATIENTS WITH ACUTE MYOCARDIAL INFARCTION."

I _____ *Alagoji Gowri* _____

have been made understood the necessity of the work entitled " **Study on anticoagulant utilization evaluation and risk score assessment for predicting bleeding among patients with acute myocardial infarction"** that is being carried out by **Ms. Aparna.N** in College of Pharmacy, SRIPMS, Coimbatore. I voluntarily here by agree by giving my consent to participate in this study and provide the necessary co-operation for the same.

Place: Coimbatore

Signature of the Patient/bystander:

Date: 9|3|18

Name of the Patient: *Alagoji Gowri*

Name of the By-stander:

Signature of the Supervisor

Signature of the Investigator

Dr. V. Shivashankar, M.Pharm, Ph.D.,
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PATIENT INFORMATION FORM

Project Title: "STUDY ON ANTICOAGULANT UTILIZATION EVALUATION AND RISK SCORE ASSESSMENT FOR PREDICTING BLEEDING AMONG PATIENTS WITH ACUTE MYOCARDIAL INFARCTION."

I, **Ms. Aparna.N**, second year M.Pharm., (Pharmacy practice) student of College of Pharmacy, SRIPMS, Coimbatore which is attached to Sri Ramakrishna Hospital Coimbatore, pursuing a dissertation work, entitled **"Study on anticoagulant utilization evaluation and risk score assessment for predicting bleeding among patients with acute myocardial infarction"** which has to be submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai for partial fulfillment for the award of degree of Doctor of Pharmacy. The details about the patient and the treatment are required by the investigator for carrying out the dissertation. It is here by assured that the details collected are only for the purpose of research and it will helpful to the patient and care giver. It is also assured that the information obtained from the patient will be maintained confidentially. We hope you will provide us the necessary co-operation for the above mentioned work by providing a written consent.

Thanking you

Signature of the Supervisor

Dr. V. Shivashankar, M.Pharm, Ph.D.,
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Signature of the Investigator

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College Of Pharmacy, SRIPMS
Coimbatore – 641 044

DEPARTMENT OF PHARMACY PRACTICE
College of Pharmacy, SRIPMS, Coimbatore
M. PHARM PROJECT

Case No:

PROPOSED TITLE: STUDY ON ANTICOAGULANT UTILIZATION EVALUATION AND RISK SCORE ASSESSMENT FOR PREDICTING BLEEDING AMONG PATIENTS WITH ACUTE CORONARY SYNDROME

PATIENT PROFILE FORM

Dr. Manoharan

PATIENT DETAILS

Name	Age	Sex.	Wt.	Ht.	BMI	IP No.	Dept.	DOA	DOD
Mr. Sureshkumar	33 yrs	M	05			201807 047	Cardio	9/3/18	12/3/18

REASON FOR ADMISSION c/o chest pain one month

PAST MEDICAL HISTORY k/c/o nil

PAST MEDICATION HISTORY

SOCIAL HISTORY ✓ | Known allergies: nil

Smoker : Y / N ✓ Alcoholic : Y/N ✓ | Marital status : Married
Tobacco in any form : Y / N ✓ None :

LABORATORY INVESTIGATIONS

Date	D_1	D_2	D_3	D_4					Blood sugar (mg %)			
Temp.	N	N	N	N					F.B.S (60-90)			
BP	130/70	140/80	120/80	110/70					P.P.S(80-150)			
Pulse	84	92	90	88					R.B.S(90-110)	94		

BLOOD COUNTS

Hemoglobin (g/dl) M:12-16 F: 11-14	TLC (Cells/cumm) (5000-10000)	ESR (mm/hr.) (M<10:F<20)	Differential Leukocyte Count (%)	
15.6	8590.		Polymorphs (40-60)	63.8
			Lymphocytes (20-30)	25.5
Platelets(1-3 lakhs)	Clotting Time(3-5 min)	Bleeding Time (1-3 min)	Basophils (0-1)	0.7
2.34			Eosinophils (1-4)	2.3
			Monocytes (1-2)	7.9

Hct - 46.3 Troponin T - <0.010 Cholesterol - 93

LIVER FUNCTION TEST / RENAL FUNCTION TESTS

Total bilirubin (<1mg %)	P.T. Time (14 Sec)	aPTT (25-35s)	INR (0.8-1.2)	ALP (86-306U/L)	SGPT (7-56U/L)	SGOT (5-40U/L)	Urea (mg%)(15-45)	18
							Uric acid (mg%) F-2-5, F-2-7	6.4
0.6			0.8	68	49	26	Sr Creatinine (mg %) (0.6-1.4)	0.9

ELECTROLYTES (m.Eq/l) / URINE EXAMINATION

ELECTROLYTES (m.Eq/l)				URINE EXAMINATION	
Sodium (130-150)	146			Colour	Sugar
Potassium (3.5-5.8)	3.9			Bile Salts	WBC
Chloride (98-100)	107			Bile Pigment	RBC
Bicarbonate(22-36)	9.6			Albumin	Casts

C/S : Y/S | No. of organisms isolated : ☐
Organism Isolated : | Sensitive to :

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Physical examination

Pt   conscious
       Oriented
       Afebrile

o/e :-   P̄ Ī C̄ C̄ Ī Ē

Systemic examination

CVS :- S₁S₂ +

PR - 74/min

P/A - soft

CNS :- No Neurological deficit.

Discharge medication

1).   T. CLOPILET-A   150mg 1-0-1

2)   T. TONACT   40mg 0-0-1

3).   T. PLANEP-T 25/10mg 1-0-0

4)   T. WABRID   7.5mg 0-0-1

5)   T. RANTAC   150mg 1-0-1

6)   T. RANOZEX 500mg 1-0-1

7)   T. SENA sof   0-0-1

Case No:

STEMI

Other Investigations :

Chest x ray :- Normal

echo :- EF- 40 %

ecu - SR, Normal PR, AWMI.

SVD

DIAGNOSIS :

IHD - AWMI (not lysed. due to late presentation)
PTCA with stenting to LAD (10|3|18).

DRUGS PRESCRIBED

S.No	Drugs T. Name	G.Name	Dose	9/3	10/3	11/3	12/3							
01	T. CLOPILET	CLOPIDOGREL	1-0-1 75mg	✓	✓	✓	✓							
02	T. ECOSPRIN	ASPIRIN	1-0-0 150mg		✓	✓	✓							
03	INJ. HEPARIN	HEPARIN	6000U	5000 ✓	✓									
04	INJ. ATROPINE	ATROPINE		—	✓									
05	INJ. DOBUTAMINE	DOBUTAMINE	2.5mg/s	—	✓									
06	T. ATORVA	ATORVASTATIN	40mg	✓	✓	✓	✓							
07	T. ALDACTONE	SPIRONOLACTONE	0-0-1 50mg	✓	✓	✓	✓							
08	T. ULTRACET	ACETAMINOPHEN	1-1-0 1-0-1	—	✓	✓	✓							
09	SYP. LACTIHEP	TRAMADOL 37.5mg	325mg 0-0.3ml	—	✓	✓	✓							
10		LACTITOL	66.67mg											
11		MONOHYDRATE	200ml											
12														
13														
14														
15														

ANTICOAGULANT UTILIZATION EVALUATION

S N O	ANTICOAGULANT GIVEN GENERIC NAME	BRAND NAME	DOSE GIVEN	FREQUENCY	COST/ UNIT (RS.)	ALTERNATE BRAND	COST/ UNIT (RS.)	COST DIFFERENCE
1.	INJ. HEPARIN	BEPARIN	6000U	Q6H	Rs. 82.88	CAPRIN	Rs. 96.30	Rs. 13.42
						OR HEPAREN	OR Rs. 70	Rs. 12.88

Other Investigations :

chest x ray :- Normal

echo :- EF- 40%

SVD

ECG - SR, Normal PR, AWMI.

DIAGNOSIS :

IHD - AWMI (not lysed. due to late presentation)

PTCA with stenting to LAD (10/3/18).

DRUGS PRESCRIBED

S.No	Drugs		Dose	DATE OF TREATMENT										
.	T. Name	G.Name		9/3	10/3	11/3	12/3							
01	T. CLOPILET	CLOPIDOGREL	1-0-1 75mg	✓	✓	✓	✓							
02	T. ECOSPRIN	ASPIRIN	1-0-0 150mg		✓	✓	✓							
03	INJ. HEPARIN	HEPARIN	6000U	5000 ✓	✓									
04	INJ. ATROPINE	ATROPINE		—	✓									
05	INJ. DOBUTAMINE	DOBUTAMINE	2.5min	—	✓									
06	T. ATORVA	ATORVASTATIN	40mg	✓	✓	✓	✓							
07	T. ALDACTONE	SPIRONOLACTONE	0-0-1 50mg	✓	✓	✓	✓							
08	T. ULTRACET	ACETAMINOPHEN	1-1-0 1-0-1	—	✓	✓	✓							
09	SYP. LACTIHEP	TRAMADOL 37.5mg	0-0-3ml	—	✓	✓	✓							
10		LACTITOL	66.67mg											
11		MONOHYDRATE	200ml											
12														
13														
14														
15														

ANTICOAGULANT UTILIZATION EVALUATION

S N O	ANTICOAGULANT GIVEN		DOSE GIVEN	FREQUENCY	COST/ UNIT (RS.)	ALTERNATE BRAND	COST/ UNIT (RS.)	COST DIFFERENCE
	GENERIC NAME	BRAND NAME						
1.	INJ. HEPARIN	BEPARIN	6000U	Q6H	Rs. 82.88	CAPRIN	Rs. 96.30	Rs. 13.42
						OR HEPAREN	OR Rs. 70	Rs. 12.88

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RISK SCORE ANALYSIS (CRUSADE RISK SCORE)

S.NO	PREDICTOR	REFERENCE RANGE	REFERENCE SCORE	OBSERVED RANGE	OBSERVED SCORE
1	BASELINE HEMATOCRIT	<31	9	46.3 %	0
		31-33.9	7		
		34-36.9	3		
		37-39.9	2		
2	CREATININE CLEARANCE	>15-30	35	103 ml /min m²	7
		>30-60	28		
		>60-90	17		
		>90-120	7		
		>120	0		
3	DIABETES MELLITUS	NO	0	No	0
		YES	6		
4	SIGNS OF HEART FAILURE	NO	0	No	0
		YES	7		
5	SYSTOLIC BLOOD PRESSURE	91-100	8	110	5
		101-120	5		
		121-180	1		
		181-200	3		
		≥201	5		
6	HEART RATE	71-80	1	88	3
		81-90	3		
		91-100	6		
		101-110	8		
		111-120	10		
		≥121	11		
7	PRIOR VASCULAR DISEASE	NO	0	No	0
		YES	6		
8	FEMALE SEX	NO	0	No	0
		YES	8		

TOTAL SCORE: 15

FIVE MAJOR BLEEDING RISK CATEGORIES:

- ✓ VERY LOW (≤ 20)
- o LOW (21-30)
- o MODERATE (31-40)
- o HIGH (41-50)
- o VERY HIGH (>50)

Very low bleeding risk (≤20)

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DRUG INTERACTIONS/ADVERSE DRUG REACTIONS

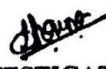| DRUG	EFFECTS	INFERENCE
– Aspirin + clopidogrel	Major	↑sed risk of bleeding
– Aspirin + Heparin	"	"
– Heparin + clopidogrel	"	"
– Aspirin + spironolactone	"	↓sed diuretic effectiveness.

ANY INTERVENTIONS MADE

DATE OF SUBMISSION: 13/3/18

SIGNATURE OF INVESTIGATOR:

SIGNATURE OF GUIDE:

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