

A PROSPECTIVE, OBSERVATIONAL STUDY OF ADVERSE EFFECTS AND CLINICAL OUTCOMES OF TICAGRELOR

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Abstract: Even after the advancement in treatment of Acute Coronary Syndrome, it remains life-threatening. The standard therapy for treatment of ACS is dual antiplatelet therapy which includes combination of P2Y₁₂ receptor antagonist along with aspirin. Ticagrelor is a drug which is a P2Y₁₂ receptor antagonist belonging to the class cyclopentyltriazolopyrimidines. The study was conducted in AIG Hospitals, Gachibowli for a period of 6 months. A total of 85 patients of different age groups were considered. Out of 85 patients, 70 (82%) were found to be males and 15 (18%) were found to be females. The patients with age group ranging from 46-60 years which is late middle aged in both males and females were suffering from ACS. It has been shown that 35 males among 70 and 6 females among 15 were in the age group of 46-60 years to whom ticagrelor was prescribed after the stent was placed. Among 85 patients only 21.1% patients showed obesity. Among 85 patients 54 patients had hypertension, 45 patients had diabetes mellitus. Around 11% ,7% , and 3.5% patients showed dyspnea, bleeding and bradycardia respectively, these adverse effects were assessed using Naranjo's casualty assessment scale. Drug discontinuation was also seen in 6 patients because of the adverse effects. Around 6% patients were re-hospitalized while on the drug Ticagrelor. From this study, it was concluded that maximum number of patients suffering from ACS are males, in the age group of 46-60 yrs. NSTEMI contributes maximum number of cases among the total cases. ADR's were seen in 17 patients which were related with increased concentration of endogenous adenosine. Though the drug was discontinued in 3 patients because of severe dyspnea. Bleeding was reported in very few cases out of which 1 patient showed severe epistaxis and 2 patients showed severe brown spots; as a result, the drug was discontinued. Maximum number of ADR's were seen in male patients and patients with co-morbidities. Re-hospitalization was seen in 5 patients during our study.

Keywords: cyclopentyltriazolopyrimidines, acute coronary syndrome, antiplatelet, Naranjo's casualty assessment scale, NSTEMI.

INTRODUCTION:

To prevent reinfarction and stent thrombosis in Acute Coronary Syndrome (ACS) and Coronary Artery Disease (CAD) a novel anti-platelet called Ticagrelor is usually prescribed. The term Acute coronary syndrome (ACS) refers to a variety of conditions in which myocardial ischemia or infarction develops as a result of severe blockage of blood flow to any part of the heart. The most common cause of severe obstruction is coronary artery thrombosis caused by rupture or erosion of atheromatous plaque¹. An imbalance between myocardial metabolic demands and blood supply, due to the reduction in blood flow to the heart leads to myocardial ischemia, which is the hallmark of ACS^{2,3}. ACS can be categorized into three types based on ischemic state, cardiac marker levels(e.g., troponin), location of occlusion, elevation of ST- segment on the electrocardiogram(ECG) into unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI).

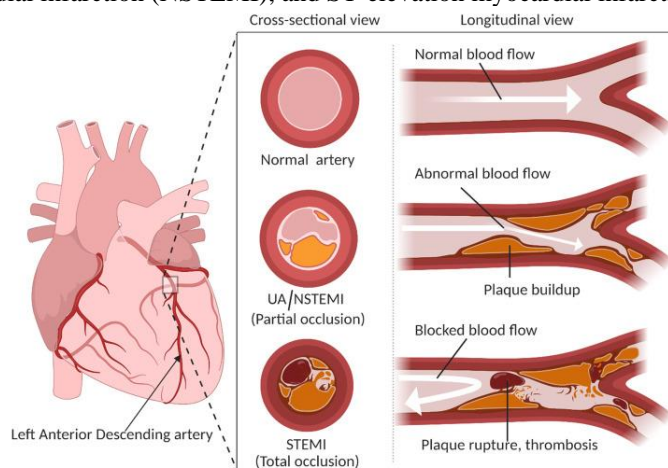


FIG:1.1 Classification Of Acute Coronary Syndrome

Classification of acute coronary syndromes. Acute coronary syndromes is classified into unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). STEMI is caused when the coronary blood flow is completely obstructed because of the complete coronary artery occlusion due to thrombus formation. Whereas, NSTEMI or UA is caused due to partial occlusion of artery (blood flow is not entirely restricted).

TICAGRELOR

INDICATIONS:⁴

In patients with acute coronary syndrome (ACS) or a history of myocardial infarction, ticagrelor is used to lower the risk of cardiovascular mortality, myocardial infarction, and stroke (MI). At least for the first 12 months after ACS

CONTRAINDICATION:⁴

- History of intra-cranial hemorrhage
- Active bleeding
- Hypersensitivity to drug or its products

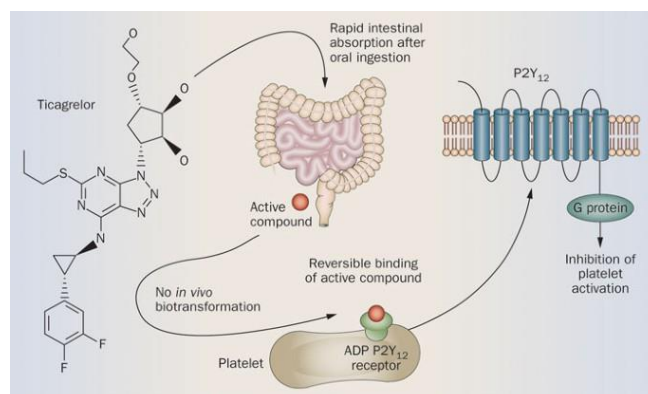
DOSAGE FORMS AND STRENGTHS⁴

Ticagrelor 90 mg is available as a round, biconvex, yellow, film-coated tablet with a "90" above a "T" on one side and a "90" above a "T" on the other.

Ticagrelor 60 mg is available as a round, biconvex, pink, film-coated tablet with "60" above "T" on one side and "60" above "T" on the other.

MECHANISM OF ACTION:

Ticagrelor is directly-acting P2Y₁₂-receptor antagonist which is administered orally^{5,6} It acts by binding reversibly and noncompetitively to the P2Y₁₂ receptor at a site distinct from that of the endogenous agonist adenosine diphosphate (ADP), based on the in vitro studies.⁵



PHARMACOKINETICS:

Ticagrelor has dose proportionate pharmacokinetics that are similar in healthy volunteers and patients.

I Absorption.

ticagrelor can be taken orally with or without food. The drug's mean absolute bioavailability is around 36%, with a median time to maximum plasma concentration (t_{max}) of 1.5 hours (range, 1–4 hours).⁷

II Distribution.

Ticagrelor's steady-state distribution volume is 88 L. Ticagrelor and its active metabolite are highly bound to human plasma proteins (more than 99 percent).⁷

III Metabolism.

Ticagrelor is metabolised largely by the cytochrome P450 (CYP) isoenzyme CYP3A4. The primary active metabolite is formed as a result of this. Ticagrelor and its active metabolite are both weak substrates and inhibitors of P-glycoprotein.⁷

IV Excretion.

Hepatic elimination is the primary route of ticagrelor elimination, whereas biliary excretion is most likely the primary route of elimination for the principal metabolite. Ticagrelor has a half-life of approximately 7 hours. The active metabolite has a 9-hour half-life on average.⁷

Ticagrelor's Pharmacokinetic and Pharmacodynamic Parameters at Day 14 of the DISPERSE Trial^{4,8,9}

END POINT	TICAGRELOR
Metabolic activation required	NO
Reversibility of binding to ADP receptor	REVERSIBLE
t _{1/2}	7.7-13.1h
40–50 % IPA	30 min
Maximum IPA	2 h
Duration of IPA	3-5 days

adenosine 5'-diphosphate -ADP, inhibition of platelet aggregation- IPA,
elimination half-life - $t_{1/2}$

Table: 1.1 Pharmacokinetics and pharmacodynamics of Ticagrelor

ADVERSE DRUG EVENTS:¹⁰

- nosebleeds, bruises, or bleeding that takes longer to stop – bleeding more easily than usual
- unexpected shortness of breath when resting – this might happen in the first few weeks of using ticagrelor and is typically moderate
- joint pain and edoema – these can be symptoms of gout (this is because ticagrelor can lead to high levels of uric acid in your blood)
- headaches
- dizziness
- feeling sick or indigestion
- diarrhoea
- constipation
- mild rash

Drug-Drug Interactions:¹¹

Basis for Interaction	Interacting medication examples	Suggestions for people who are taking ticagrelor.
CYP3A4	Strong CYP3A4 inhibitors: ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, telithromycin Potent CYP3A4 inducers: rifampin, dexamethasone, phenytoin, carbamazepine, phenobarbital	Potent CYP3A4 inhibitors are contraindicated Potent CYP3A4 inducers should be avoided Simvastatin or lovastatin doses greater than 40 mg/day should not be taken together (ticagrelor increases serum concentrations of these drugs)
P-glycoprotein	Digoxin (P-glycoprotein substrate)	Monitor digoxin levels when initiating ticagrelor
Clinical effectiveness	Aspirin	Avoid maintenance doses of aspirin > 100 mg/day

Table: 1.2 drug-drug interactions of Ticagrelor

OBJECTIVES:

- To evaluate the adverse effects of ticagrelor in patients with ACS
- To evaluate the potential risk of interaction of ticagrelor with various drugs
- Termination of ticagrelor therapy.
- Incidence of rehospitalization with ticagrelor

METHODOLOGY:

The study was conducted in AIG Hospitals, Gachibowli for a period of 6 months. It is well recognized specialized multi-specialty hospital. A total of 85 patients of different age groups were considered. Informed consent was obtained from all the subject's. subjects enrolled in the study were from In-patient and Out-patient department. This study appraises the adverse effects and clinical outcomes related to ticagrelor. The adverse effects were assessed using Naranjo's casualty assessment scale.

RESEARCH PARTICIPANTS:

A total of 85 patients comprising of 70 males and 15 females were considered and the disease condition was evaluated after obtaining the informed consent forms from the patients. Patient details including demographic details, details of angioplasty, co-morbidities, vitals, laboratory investigations, medication chart, contact details and other relevant information was collected from case reports. The obtained data and test results were re-examined and entered in the data collection forms and further results obtained were tabulated. The subject's and there caretakers were counselled which helped them improve quality of life

RESULTS:**BASED ON GENDER:**

Out of 85 patients around 82% patients were male and around 18 % patients were female

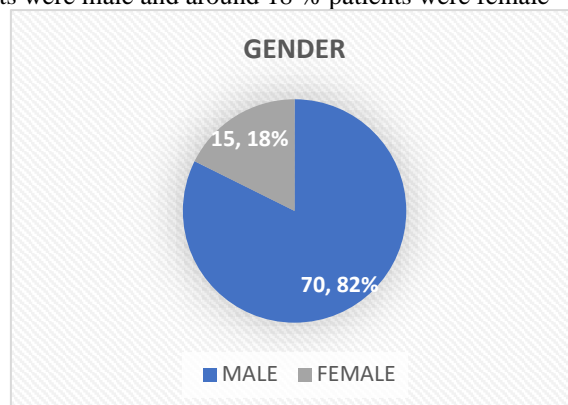


Fig:6.1.1 distribution of patients based on gender

BASED ON AGE:

Among 85 patients around 48%(41) patients between the age group of 46-60 years were prescribed with the drug ticagrelor where as 34%,16 %, and 1 % patient between the age groups of 61-75, 31-45, and 76-90 years were prescribed with ticagrelor respectively.

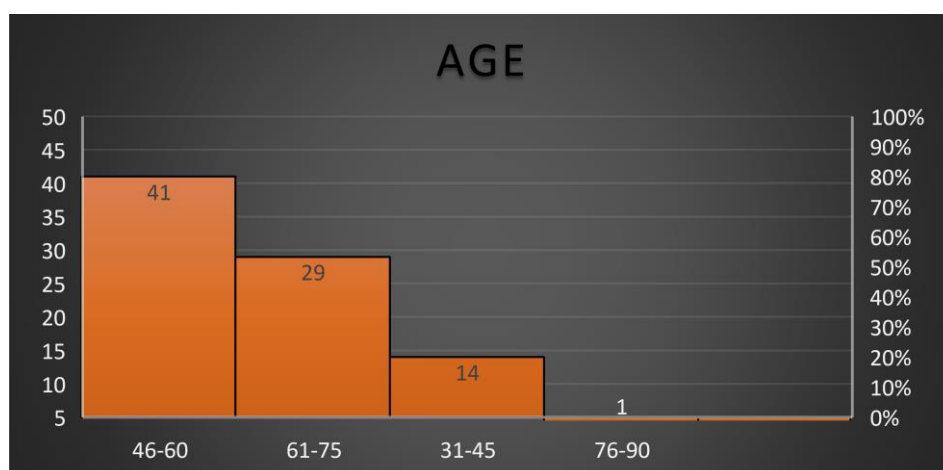


Table 6.2 distribution of patients based on Age

BASED ON ADDICTION

Out of 85 patients 26% patients were addicted to smoking, 23 % patients were addicted to alcohol, and 1% patient was addicted to tobacco chewing (other), whereas 50 % patients had no addictions.

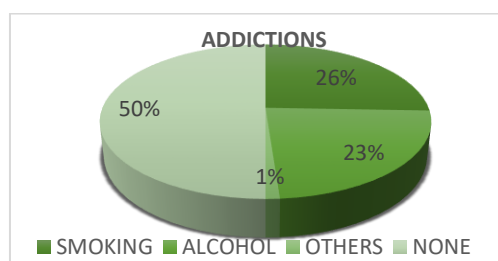


Fig 6.4 distribution of patients based on Addiction

BASED ON DIAGNOSIS

Out of 85 patients who were on ticagrelor 66 %(56) were diagnosed with Non ST elevated myocardial infraction (NSTEMI), 18%(15) were diagnosed with ST elevated myocardial infraction, 16%(14) were diagnosed with unstable angina.

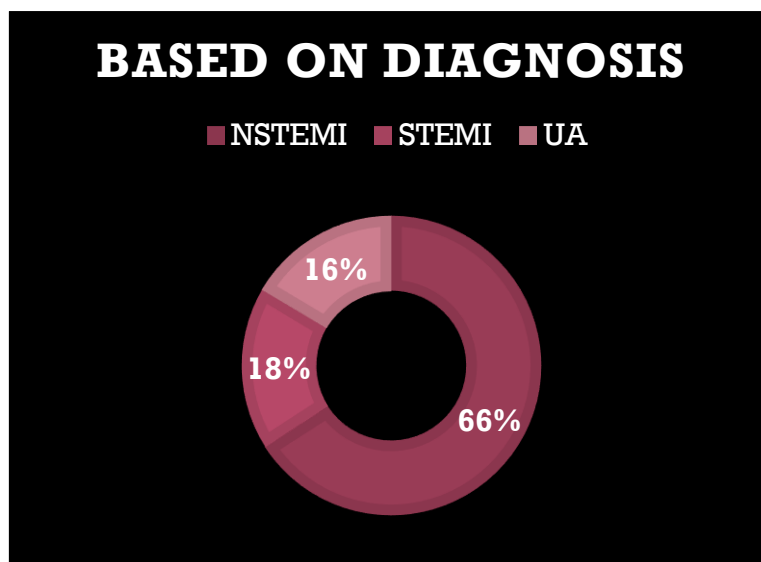


Fig 6.5 distribution of patients based on Diagnosis

BASED ON NO.OF DISEASED VESSELS INVOLVED

Out of 85 patients who were on ticagrelor, 51%(43) were diagnosed with single vessel disease (SVD), 28%(24) were diagnosed with double vessel disease (DVD), and 21%(18) were diagnosed with triple vessel disease (TVD)

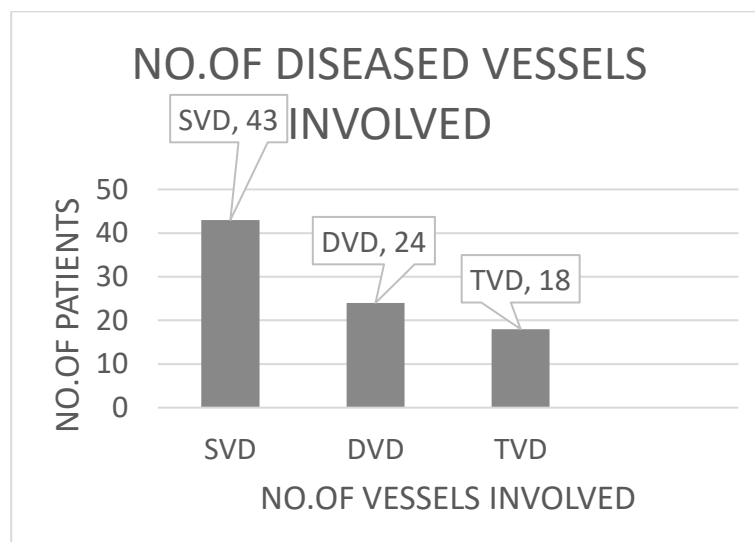


Fig 6.6 distribution of patients based on No. of vessels involved

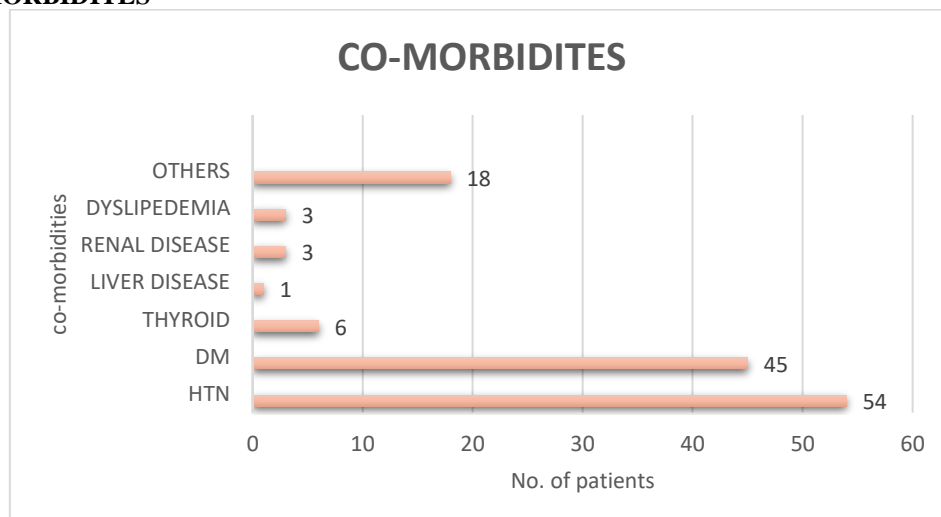
BASED ON CO-MORBIDITIES

Fig 6.7 distribution of patients based on Co-morbidities

Out of 85 patients majority of patients prescribed with ticagrelor had a co-morbidity of Hypertension, and Diabetes Mellitus

BASED ON LEFT VENTRICULAR EJECTION FRACTION (LVEF)

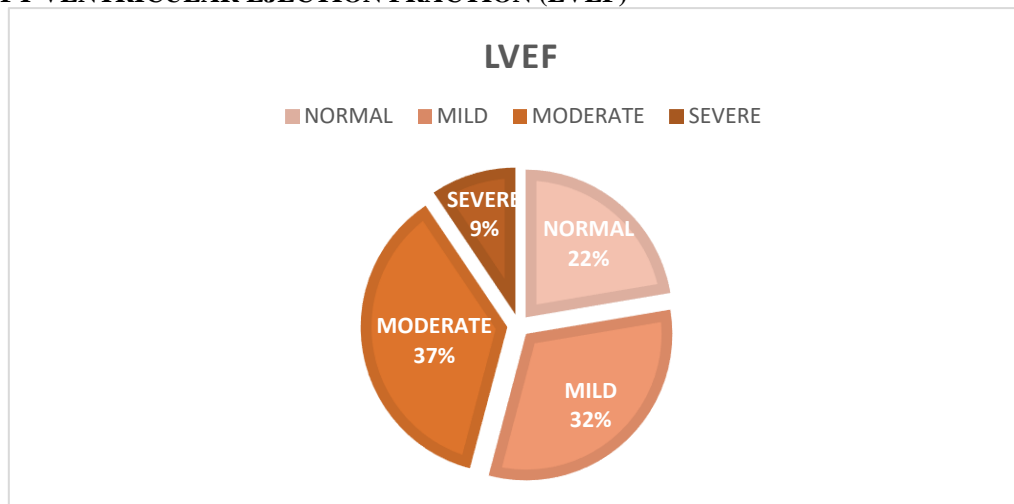


Fig 6.8 distribution of patients based on LVEF

Out of 85 patients who were on Ticagrelor 37 % (31) patients showed moderate LVEF, whereas 32% (27) patients showed mild LVEF, 9% (8) patients showed severe LVEF and 22% (19) patients had normal LVEF.

AVERAGE NO.OF DRUGS PER PATIENT

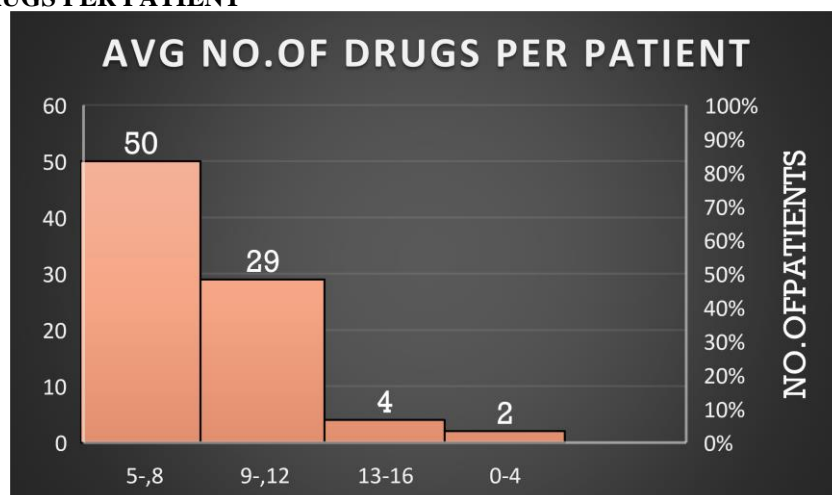


Fig 6.9 Average no. of drugs per patient

BASED ON ADR'S

Out of 85 patients 7 % patients showed the side effect of bleeding which was categorized according to the PLATO's definition of bleeding, 4 % patient showed bradycardia, and 9 % patient showed SOB(dyspnea). Whereas 80 % of patients had no side effects.

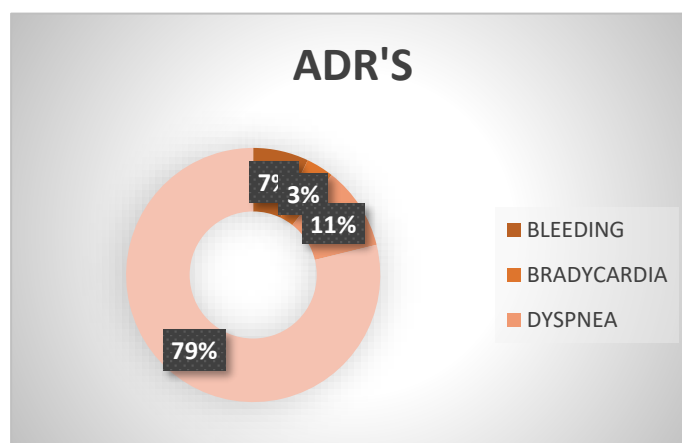


Fig 6.10 distribution of patients based on ADR'S

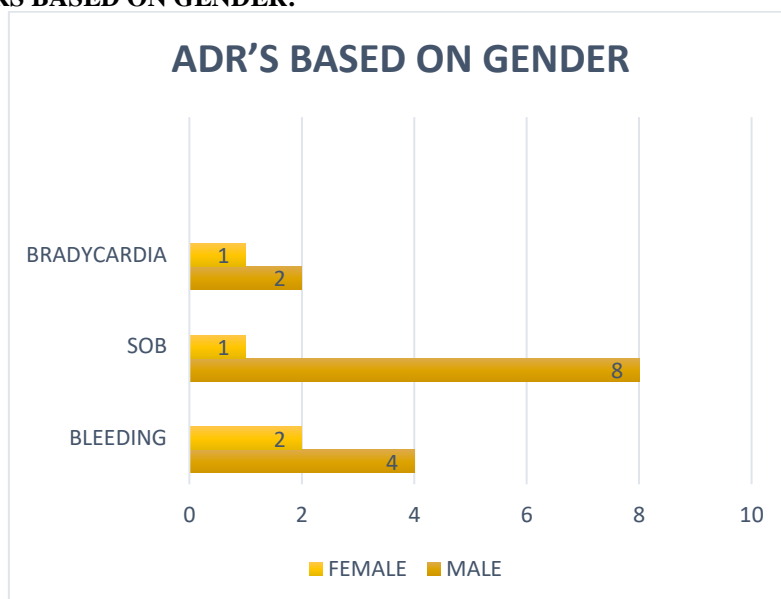
DISTRIBUTION OF ADR'S BASED ON GENDER:

Fig 6.11 distribution of ADR'S based on Gender

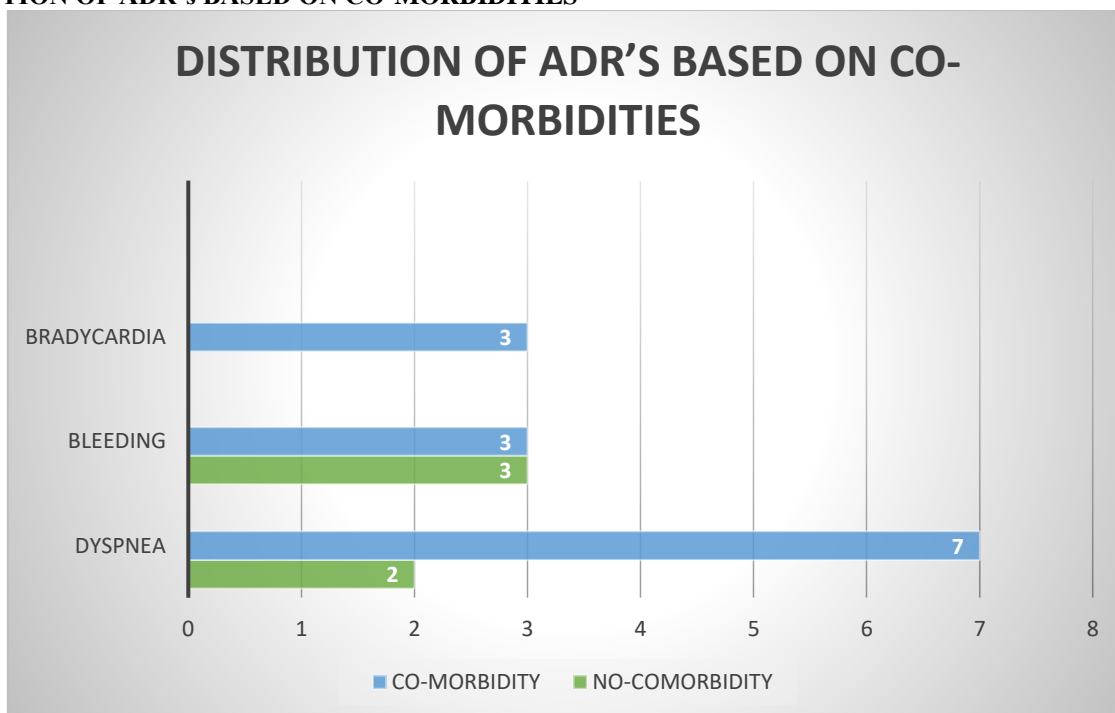
DISTRIBUTION OF ADR'S BASED ON CO-MORBIDITIES

Fig 6.12 distribution of ADR'S based on Co-Morbidities

Based on the co-morbidities it was found that out of 18 patients 9 patients developed dyspnea out of which 7 patients had co-morbidity such as HTN, and DM, whereas 2 patients had no co-morbidity. 6 patients showed bleeding out of which 3 patients had co-morbidity HTN, and DM where as 3 patients had no co-morbidity. 3 patients showed bradycardia and they had co-morbidity.

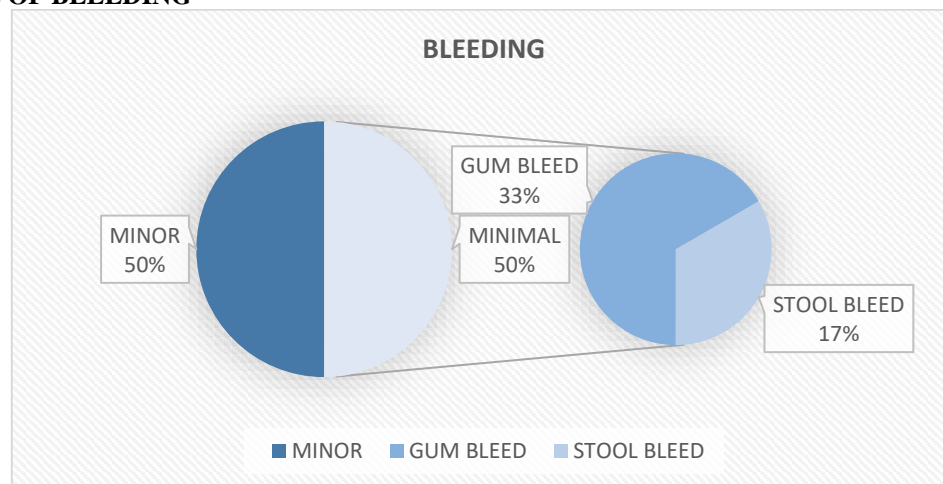
BASED ON TYPE OF BLEEDING

Fig:6.13 distribution of patients based on type of bleeding

According to the PLATO'S definition of bleeding events out of 85 patients 3 patients showed minor bleeding which resulted in the discontinuation of drug and 3 patients showed minimal bleeding in the form of gum bleed and stool bleed.

ADR ASSESMENT:

Out of 85 patients who were on Ticagrelor 17 patients showed the adverse effect in the form of Dyspnea, Bleeding, and Bradycardia. The adverse effects were assessed using Naranjo scale it was found to be a possible reaction.

Type of adverse reaction	No. of patients	Causality
Bleeding	6	Possible
Dyspnea	9	Possible
Bradycardia	3	Possible

Table 6.15 ADR assessment

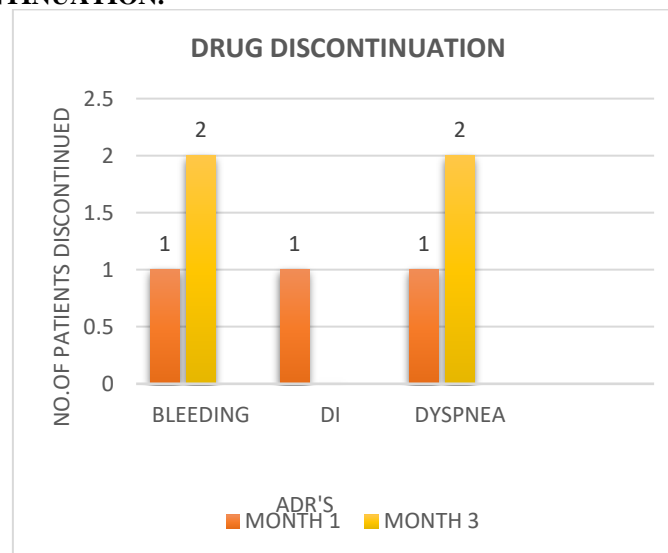
BASED ON DRUG DISCONTINUATION.

Fig 6.16 distribution of patients based on Drug discontinuation

Out of 85 patients 7 patients discontinued the drug because of bleeding, dyspnea and possible drug-drug interaction.

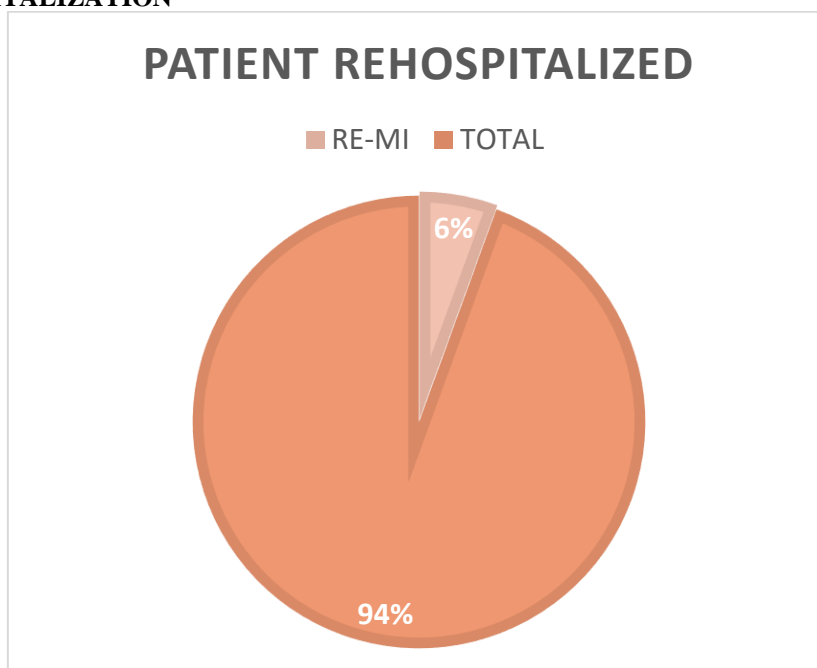
BASED ON RE-HOSPITALIZATION

Fig 6.17 distribution of patients based on Re-hospitalization

Out of 85 patients around 6% patients showed rehospitalization with RE-MI while on ticagrelor.

DRUG INTERACTION ASSESMENT

A 59 yrs female patient with co-morbidities diabetes mellitus, hypertension, bronchial asthma, and chronic kidney disease showed a possible drug interaction with statins after two months of therapy based on the laboratory reports and patient complaints the interaction was assessed using Drug Interaction Probability Scale (DIPS), the interaction was found to be "Possible"

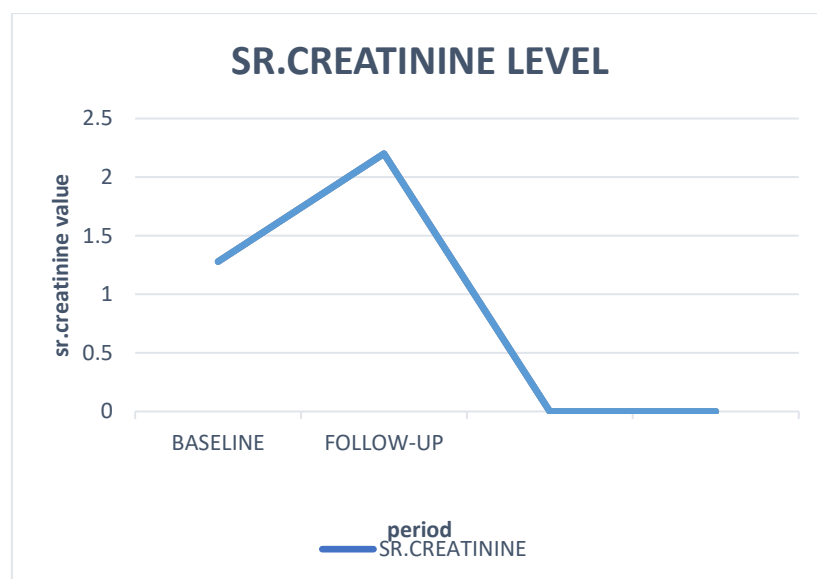


Fig 6.18 Sr. Creatinine levels

CONCLUSION

We conducted a prospective observational study on adverse effects and clinical outcomes of ticagrelor in patients with ACS for a period of 6 months. We conducted our study by taking sample size of 85 patients out of which 82% were male and 18% were female. According to age wise distribution, patients in the range of 46-60 were more in number suffering with ACS. Many patients also had comorbid conditions like hypertension, diabetes mellitus, hypothyroidism, and others.

The patients are diagnosed as STEMI, NSTEMI, and UA based on ECG, TMT troponin I. More patients were diagnosed with NSTEMI and many patients were having single vessel disease. These patients were treated with anti-platelet drugs before and after PTCA were performed.

Ticagrelor is reasonably safe. Though in our study it has shown few ADR's, which were associated with increased concentration of endogenous adenosine (dyspnea, bradycardia). The ADR's are usually mild to moderate and subside gradually while being upon therapy. Though the drug was discontinued in 3 patients because of severe dyspnea. Bleeding was reported in very few cases out

of which 1 patient showed severe epistaxis and 2 patients showed severe brown spots; as a result, the drug was discontinued. Maximum number of ADR's were seen in male patients and patients with co-morbidities. Re-hospitalization was seen in 5 patients during our study.

Hence, further studies are required on larger sample sizes so that the prescriber can identify patients who are at higher risk of developing adverse effects and possible drug interactions and can make informed decisions while prescribing the drug.

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