ASSESSMENT OF ADHERENCE WITH TICAGRELOR IN ACUTE CORONARY SYNDROME PATIENTS IN TERTIARY CARE HOSPITAL

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Submitted by

SUGANTHI S

REGISTRATION No. 261740615

Under the guidance of

DR. C.SANKAR M.PHARM., PH.D

Department of Pharmacy Practice

KMCH COLLEGE OF PHARMACY
KOVAI ESTATE, KALAPPATTI ROAD
COIMBATORE - 641048

NOVEMBER 2019

PROF. DR. A. RAJASEKARAN, M. PHARM, PH. D,

Principal,

KMCH College of Pharmacy,

Kovai Estate, Kalappatti Road,

Coimbatore - 641048

CERTIFICATE

This is to certify that the dissertation work entitled **"ASSESSMENT OF ADHERENCE WITH TICAGRELOR IN ACUTE CORONARY SYNDROME PATIENTS IN TERTIARY CARE HOSPITAL"** was carried out by **SUGANTHI S (Reg No.261740615).** The work mentioned in the dissertation was carried out at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, Tamil Nadu, under the guidance of **DR. C.SANKAR M.PHARM., PH.D.,** for the partial fulfilment for the Degree of Master of Pharmacy during the academic year 2018-2019.

Date: **Prof. DR. A. RAJASEKARAN, M.Pharm., Ph.D.,**

Place: Coimbatore **PRINCIPAL**

DR. C.SANKAR M.PHARM., PH.D
Professor
KMCH College of Pharmacy,
Kovai Estate, Kalapatti Road,
Coimbatore - 641048

CERTIFICATE

This is to certify that the research work entitled **"ASSESSMENT OF ADHERENCE WITH TICAGRELOR IN ACUTE CORONARY SYNDROME PATIENTS IN TERTIARY CARE HOSPITAL"** was carried out by **SUGANTHI S (Reg No.261740615).** The work mentioned in the dissertation was carried out at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, Tamil Nadu, under my supervision and guidance for the partial fulfilment for the Degree of Master of Pharmacy during the academic year 2018-2019.

Date**:** **Prof. DR. C.SANKAR M.Pharm., Ph.D.,**

Place: Coimbatore

Dr. SURESH KUMAR, MBBS.,MD (General Medicine).,DM (Cardiology) ,

Department of Cardiology

Kovai Medical Center and Hospital

Coimbatore - 641014

CERTIFICATE

This is to certify that the research work entitled **ASSESSMENT OF ADHERENCE WITH TICAGRELOR IN ACUTE CORONARY SYNDROME PATIENTS IN TERTIARY CARE HOSPITAL."** The work mentioned in the dissertation was carried out at the Department of Cardiology, Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, under my supervision and guidance for the partial fulfilment for the Degree of Master of Pharmacy during the academic year 2018-2019.

Date: **Dr. SURESH KUMAR, MBBS.,MD**

Place: Coimbatore **(General Medicine).,DM (Cardiology)**

DECLARATION

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I hereby declare that the dissertation work entitled **"ASSESSMENT OF ADHERENCE WITH TICAGRELOR IN ACUTE CORONARY SYNDROME PATIENTS IN TERTIARY CARE HOSPITAL"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmacy Practice** was carried out under the guidance of **Prof. DR. C.Sankar M.Pharm., Ph.D.,** at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, Tamil Nadu during the academic year 2018-2019.

This research work either in part or full does not constitute any of other thesis / dissertation.

Date: **Suganthi S (Reg. No 261740615)**

Place: Coimbatore

EVALUATION CERTIFICATE

This is to certify that the research work entitled **"ASSESSMENT OF ADHERENCE WITH TICAGRELOR IN ACUTE CORONARY SYNDROME PATIENTS IN TERTIARY CARE HOSPITAL**" submitted by **SUGANTHI S (Reg No.261740615)** to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in the partial fulfilment for the Degree of **Master of Pharmacy** at the Department of Pharmacy Practice a bonafide work carried out by the candidate at KMCH College of Pharmacy, Coimbatore, Tamil Nadu during the academic year 2018-2019 and the same was evaluated.

Examination Centre: KMCH College of Pharmacy, Coimbatore

Date:

Internal Examiner **External Examiner**

Convener of Examination

Dedication

To my Beloved Parents,

Teachers

&

Friends

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S.SUGANTHI

ABBREVIATIONS

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ACS	Acute Coronary Syndrome
ACE	Angiotensin Converting Enzyme
ADP	Adenosine Diphosphate
ARB	Angiotensin Receptor Blocker
CAD	Coronary Artery Disease
CABG	Coronary Artery Bypass Surgery
CVS	Cardio Vascular System
CYP3A	Cytochrome P3A
DAPT	Dual Anti Platelet Therapy
ECG	Electro Cardio Gram
ETD	Early Ticagrelor Discontinuation
GP	General Physician
MI	Myocardial Infarction
MVD	Multi Vessel Disease
NSTEMI	Non ST Elevation Myocardial Infarction
STEMI	ST Elevation Myocardial Infarction
TIMI	Thrombolysis in Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PLATO	PLATelet inhibition and patient Outcomes
$P2Y_{12}$	Purinergic Receptor

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INTRODUCTION

1.INTRODUCTION

Cardiovascular diseases are currently the leading cause of death in industrialized countries and are expected to become so in emerging countries by 2020.[1] the clinical presentations of CAD include silent ischemia, stable angina pectoris, unstable angina, myocardial infarction (MI), heart failure, and sudden death. Distinguishing patients with acute coronary syndromes (ACS) within the very large proportion with suspected cardiac pain are a diagnostic challenge, especially in individuals without clear symptoms or electrocardiographic features. Despite modern treatment, the rates of death, MI, and readmission of patients with ACS remain high.[2]

1.1 ACUTE CORONARY SYNDROME

An Acute Coronary Syndrome (ACS) is an umbrella term for conditions caused by sudden blockage of the blood supply to the heart. The term acute coronary syndrome refers to a range of acute myocardial ischemic states. It encompasses

- Unstable angina,
- Non-ST segment elevation myocardial infarction (ST segment elevation is absent),
- ST segment elevation infarction (persistent ST segment elevation usually present) [3].

Acute coronary syndromes (ACS) are the leading cause of mortality and one of the main reasons for hospital admissions in the developed nations. Improvement of outcomes in patients with ACS is therefore a major health care task. Platelets play a central role in atherothrombosis, the main pathologic substrate in ACS.[4] Several platelet membrane receptors bind with extracellular factors in response to platelet activation, resulting in platelet adhesion and aggregation. Sufficient platelet inhibition is crucial to prevent formation of thrombus and related ischemic events[5]. Registry data consistently show that NSTE-ACS is more frequent than STE-ACS. The annual incidence is ~3 per 1000 inhabitants, but varies between countries[6]. Long-term follow-up showed that death rates were higher among patients with NSTE-ACS than with STE-ACS, with a two-fold difference at 4 years.[7]

1.2 PATHOGENESIS

The process central to the initiation of an acute coronary syndrome is disruption of an atheromatous plaque. Fissuring or rupture of these plaques and consequent exposure of core constituents such as lipid, smooth muscle, and foam cells leads to the local generation of

thrombin and deposition of fibrin. This in turn promotes platelet aggregation and adhesion and the formation of intracoronary thrombus.[8]

1.3 DIAGNOSIS

ACS is suspected when a person presents with symptoms, particularly chest pain, and especially when they also have known risk factors like high blood pressure, being overweight or a family history.[9] Symptoms patients with ACS may experience include:

- Pain such as pressure, squeezing, or a burning sensation across the chest, possibly radiating to the neck, jaw or either arm
- Heart palpitations
- Sweating
- Nausea
- Dyspnoea (difficulty breathing)
- Dizziness or fainting

Rapid and accurate diagnosis is critical because myocardial infarction (MI) requires immediate intervention and prognosis improves significantly with rapid treatment[9]. However, this is not always easy because symptoms vary greatly. On top of that, there are many other causes of chest pain that are not ACS. In fact, as many as 8 out of 10 patients who come to emergency departments with ACS-like symptoms turn out not to have ACS.[10,11]

1.4 MANAGEMENT

The immediate goals of treatment for acute coronary syndrome are:

- Relieve pain and distress
- Improve blood flow
- Restore heart function as quickly and as best as possible

Long-term treatment goals are to improve overall heart function, manage risk factors and lower the risk of a heart attack. A combination of drugs and surgical procedures may be used to meet these goals.

Medications: Depending on the diagnosis, medications for emergency or ongoing care (or both) may include the following:

- **Thrombolytic** (clot busters) help dissolve a blood clot that's blocking an artery.
- **Nitroglycerin** improves blood flow by temporarily widening blood vessels.
- **Antiplatelet drugs** help prevent blood clots from forming and include aspirin, Clopidogrel (Plavix), Prasugrel (Effient) and others.
- **Beta blocker helps relax the heart muscle and slows** the heart rate. They decrease the demand on the heart and lower blood pressure. Examples include metoprolol (Lopressor, Toprol-XL) and nadolol (Corgard).
- **Angiotensin-converting enzyme (ACE) inhibitors** widen blood vessels and improve blood flow, allowing the heart to work better. They include lisinopril (Prinivil, Zestril), benazepril (Lotensin) and others.
- **Angiotensin receptor blockers (ARBs)** help control blood pressure and include irbesartan (Avapro), losartan (Cozaar) and several others.
- **Statins** lower the amount of cholesterol moving in the blood and may stabilize plaque deposits, making them less likely to rupture. Statins include atorvastatin (Lipitor), simvastatin (Zocor, Flolipid) and several others.

Surgery and other procedure.

Angioplasty and stenting. In this procedure, your doctor inserts a long, tiny tube (catheter) into the blocked or narrowed part of your artery. A wire with a deflated balloon is passed through the catheter to the narrowed area. The balloon is then inflated, opening the artery by compressing the plaque deposits against your artery walls. A mesh tube (stent) is usually left in the artery to help keep the artery open.

Coronary bypass surgery. With this procedure, a surgeon takes a piece of blood vessel (graft) from another part of your body and creates a new route for blood that goes around (bypasses) a blocked coronary artery.[12]

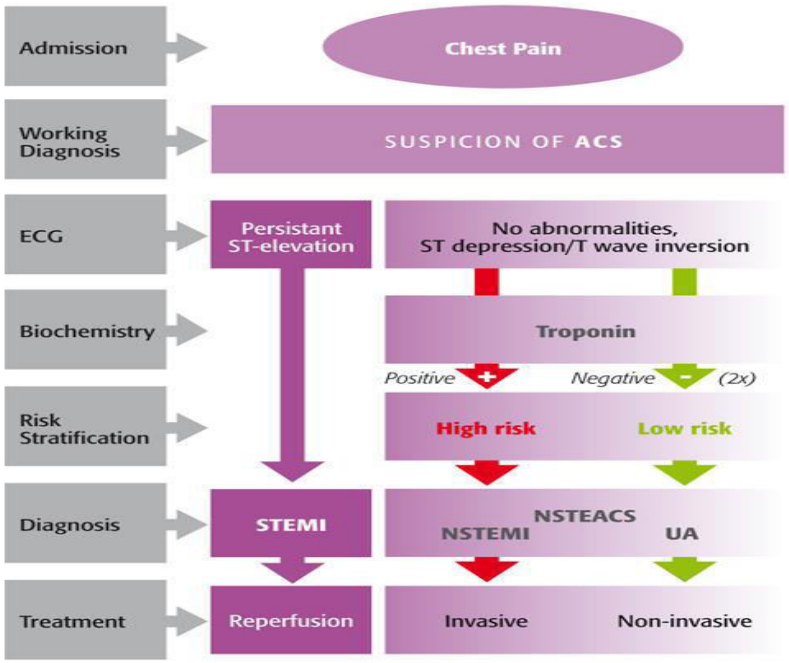

Figure 1. Approach to diagnosis and risk stratification of ACS.[13]

1.5 MEDICATION ADHRENCE

Medication adherence usually refers to whether patients take their medications as prescribed (eg, twice daily), as well as whether they continue to take a prescribed medication. Adherence has been defined as the "active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result. Medication adherence is a growing concern to clinicians, healthcare systems, and other stakeholders (eg, payers) because of mounting evidence that nonadherence is prevalent and associated with adverse outcomes and higher costs of care. Medication nonadherence is likely to grow as the US population ages and as patients take more medications to treat chronic conditions.[14]

1.6. TICAGRELOR:

1.6.1 INDICATION: to reduce the rate of CV DEATH mi and stroke in ACS patients. For at least 12 months following ACS, it is superior to Clopidogrel.

DOSING: 180 Mg- loading dose , administer 90mg twice daily during first year after ACS event. Administer 60mg twice daily. Use brilliant with a daily dose of Aspirin of 75-100mg.

1.6.2 WARNING: **Bleeding Risk**

- BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding
- Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage
- Do not start BRILINTA in patients undergoing urgent coronary artery bypass graft surgery
- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events

Aspirin Dose And Brilinta Effectiveness

Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided.

1.6.3 CONTRAINDICATIONS

- BRILINTA is contraindicated in patients with a history of intracranial hemorrhage or active pathological bleeding such as peptic ulcer or intracranial hemorrhage. BRILINTA is also contraindicated in patients with hypersensitivity (eg, angioedema) to Ticagrelor or any component of the product

1.6.4 ADVERSE REACTIONS

- The most common adverse reactions associated with the use of BRILINTA included bleeding and dyspnea: In PLATO, for BRILINTA vs. Clopidogrel, non-CABG PLATO-defined major bleeding (3.9% vs. 3.3%) and dyspnea (14% vs. 8%); in PEGASUS, BRILINTA vs. aspirin alone, TIMI Total Major bleeding (1.7% vs. 0.8%) and dyspnea (14% vs. 6%)

1.6.5 DRUG INTERACTIONS

- Avoid use with strong CYP3A inhibitors and strong CYP3A inducers. BRILINTA is metabolized by CYP3A4/5. Strong inhibitors substantially increase Ticagrelor exposure and so increase the risk of adverse events. Strong inducers substantially reduce Ticagrelor exposure and so decrease the efficacy of Ticagrelor

- As with other oral $P2Y_{12}$ inhibitors, co-administration of opioid agonists delays and reduces the absorption of Ticagrelor. Consider use of a parenteral anti-platelet in ACS patients requiring co-administration
- Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse events
- Monitor digoxin levels with initiation of, or change in, BRILINTA therapy.[15]

Ticagrelor is an oral antiplatelet agent that binds reversibly to the P2Y12 receptor without the requirement for metabolic activation. The Food and Drug Administration and the European Medicines Agency approved Ticagrelor in 2011 and 2010, respectively, for the treatment of patients with an acute coronary syndrome (ACS).[16] Ticagrelor is an orally active drug that binds reversibly to P2Y12 with a stronger and more rapid antiplatelet effect than Clopidogrel. As Ticagrelor is compared with Clopidogrel, Ticagrelor was associated with a 16% relative risk reduction with regard to the primary end point – a composite of death from CV cause, MI and stroke – but no significant increase in the overall risk of major bleeding.[17] As a result, the risk for premature drug discontinuation was 9% to 19.0% higher among Ticagrelor-treated patients compared with Clopidogrel in phase III trials procedures.[18]

Over the last few decades, percutaneous coronary intervention(PCI) has been one of the fastest growing therapeutic interventions for patients with narrowed coronary arteries due to coronary artery disease. Transitioning from hospital to home is particularly challenging for patients. After short hospital stays, patients need to adjust their lifestyle at home, incorporate into their daily routine new medications, and acquire an expanded care team. This is an aspect of post discharge care that has scarcely been investigated, even though it affects a large patient population. Several studies have reported poor medication adherence in patients with coronary artery disease.[19]

Typical medications prescribed after a percutaneous coronary intervention, such as beta-blockers, statins, and angiotensin-converting enzyme-inhibitors, have long-term prognostic effects (such as reduced mortality and reduced risk of reinfarction), whereas dual antiplatelet therapy, comprising acetylsalicylic acid and adenosine diphosphate receptor inhibitors (e.g., Clopidogrel or Ticagrelor), have an immediate effect on prognosis (such as reduced risk of stent thrombosis, and acute myocardial infarction).

Failure to adhere to the prescribed medication regimen is associated with poor clinical outcomes, higher readmission rates, increased healthcare costs, and increased morbidity and mortality. Indeed, poor adherence to dual antiplatelet therapy in particular may lead to immediate stent thrombosis within days or weeks, with a 15-45% mortality rate.[20]

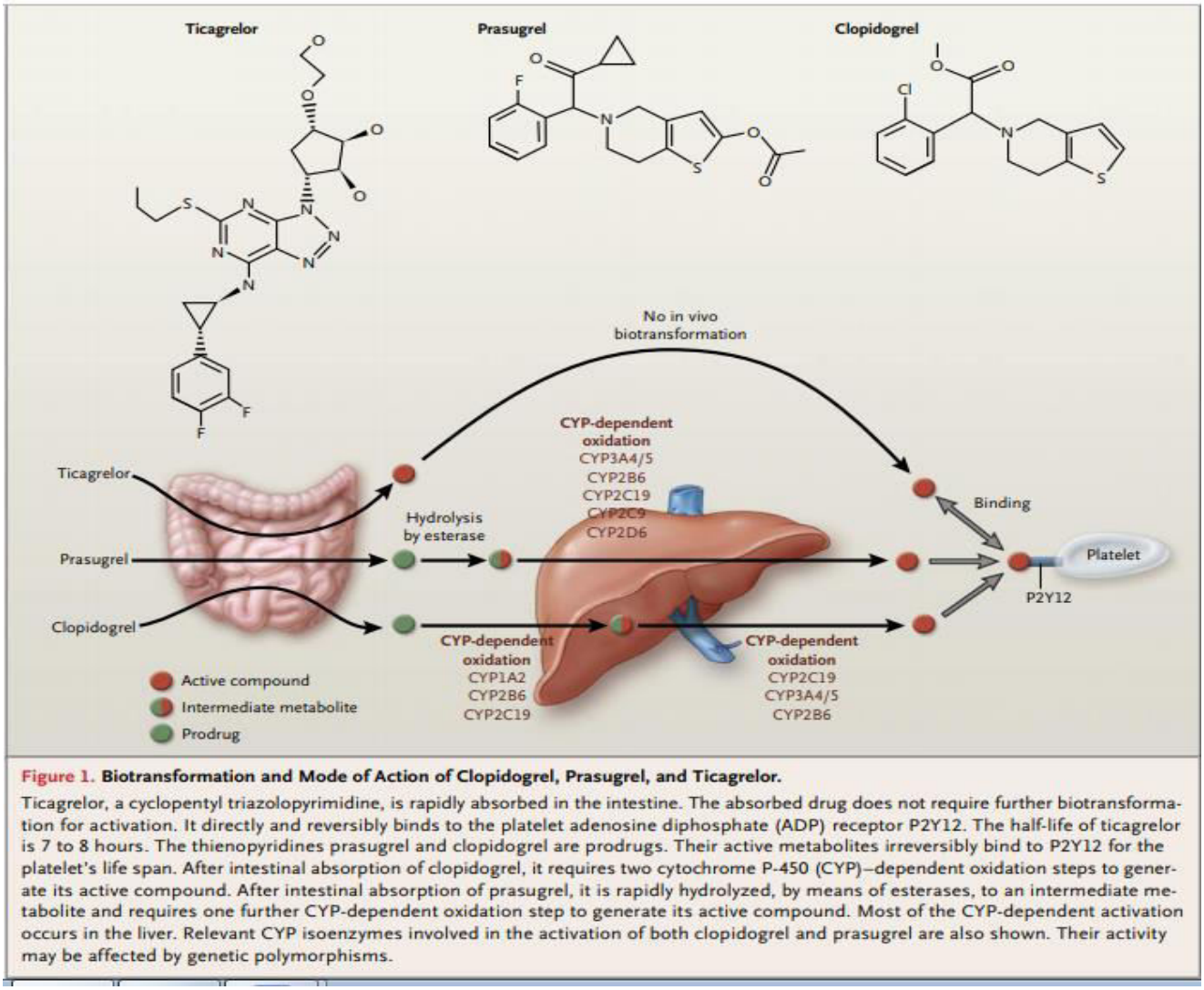

Figure 1. **Biotransformation and Mode of Action of Clopidogrel, Prasugrel, and Ticagrelor.**
Ticagrelor, a cyclopentyl triazolopyrimidine, is rapidly absorbed in the intestine. The absorbed drug does not require further biotransformation for activation. It directly and reversibly binds to the platelet adenosine diphosphate (ADP) receptor P2Y12. The half-life of ticagrelor is 7 to 8 hours. The thienopyridines prasugrel and clopidogrel are prodrugs. Their active metabolites irreversibly bind to P2Y12 for the platelet's life span. After intestinal absorption of clopidogrel, it requires two cytochrome P-450 (CYP)–dependent oxidation steps to generate its active compound. After intestinal absorption of prasugrel, it is rapidly hydrolyzed, by means of esterases, to an intermediate metabolite and requires one further CYP-dependent oxidation step to generate its active compound. Most of the CYP-dependent activation occurs in the liver. Relevant CYP isoenzymes involved in the activation of both clopidogrel and prasugrel are also shown. Their activity may be affected by genetic polymorphisms.

Figure 2. Biotransformation and mode of action of Clopidogrel, Prasugrel, and Ticagrelor.[17]

NEED OF THE STUDY

The Acute coronary syndrome patients switching over from Ticagrelor to other antiplatelet drug. This study focuses on assessing the compliance with Ticagrelor in Acute coronary syndrome patients and identifying the reason behind the discontinuation of Ticagrelor.

Ticagrelor is a new P2Y12-receptor antagonist which overcomes most of the limitations of Clopidogrel with a faster onset of action and a more intense and consistent platelet reactivity (PR) inhibition

Table 1.Comparison of limitation of antiplatelet drugs

CHARECTERISTICS	**CLOPIDOGREL**	**PRASUGREL**	**TICAGRELOR**
DRUG CLASS	Thienopyridine	Thienopyridine	**Cylopentyltriazolopyridine**
Mechanism of action	Irreversible inhibition of ADP receptor subtype P2Y12	Irreversible inhibition of ADP receptor subtype P2Y12	**Reversible inhibition of ADP receptor Subtype P2Y12.**
PRODRUG	Yes (Requires hepatic conversion to active form)	Yes (Requires hepatic conversion to active form)	**NO**
Dosage forms	75, 300mg tablets	5 ,10 mg tablets	**90 mg tablets**
Daily maintenance dose	75mg	10 mg	**90mg tablets**
Metabolism	Hepatic (CYP2C19)	Hepatic (primarily CYP3A4 and CYP2B6)	**Hepatic (CYP3A4)**
HALF LIFE	~6 hours (Clopidogrel); ~ 30 min (active	~7 hours (active metabolite; range =2-15 hours)	**~7 hours (Ticagrelor) ~ 9 hours (active metabolite)**

	metabolite)		
Onset of action	2 hrs steady state reached in 5 days	Within 30 mins steady state reached in 3 days	**Within 30 mins steady state reached in 1.5hrs**

REVIEW OF LITERATURE

2. REVIEW OF LITERATURES

Choongki Kim *et al.,* (2019)[40] conducted a study on a One-year clinical outcomes of Ticagrelor compared with Clopidogrel after percutaneous coronary intervention in patients with acute myocardial infarction, in a total of 20,270 patients, Ticagrelor showed a significant effect on reduction of all-caused death. Stroke was also reduced. Bleeding was not increased, there were nearly 30% of patients who switched from Ticagrelor to different P2Y12 inhibitors. Switching P2Y12 inhibitors was associated with clinical adverse events including MI, stroke and bleeding Ticagrelor was associated with lower incidence of all-cause mortality. Stroke risk was also reduced in patients with a prescription for Ticagrelor without an increase in bleeding risk.

Zeymer *et al*, (2018)[21] conducted a study on Adherence to dual antiplatelet therapy with Ticagrelor and they evaluated the 12-month course of patients with acute coronary syndromes (ACS) treated with percutaneous coronary intervention (PCI) and Ticagrelor during the acute phase, they conducted study on 614 patients 133 patients discontinued Ticagrelor prematurely: 9 patients before discharge and 124 at a mean 131 days after PCI. Side effects such as dyspnoea or bradycardias and bleeding leading to a premature discontinuation of Ticagrelor, 50% of patients there was no replacement with another platelet inhibitor, while in 28.2% it was replaced by Clopidogrel. And they concluded that in this real life experience of Ticagrelor in patients with ACS 22% of patients discontinued Ticagrelor early. Side effects were the cause for discontinuation in only 3 %, while age > 75 years, prior stroke, atrial fibrillation, CABG and bleeding during follow-up were associated with premature discontinuation.

Zanchin. T *et al*, (2018)[19] conducted a study on frequency, reasons, and impact of Premature Ticagrelor Discontinuation in Patients Undergoing Coronary Revascularization in Routine Clinical Practice Results from the Bern Percutaneous Coronary Intervention Registry. Out [of 1278 patients with Ticagrelor, premature treatment cessation occurred in 212 patients. De-escalation to Clopidogrel was the most frequent scenario followed by premature discontinuation and change to Prasugrel. Reasons for Ticagrelor cessation included adverse effects, bleeding (41%), dyspnoea (29%), and gastrointestinal symptoms (18%) and they concluded that Premature Ticagrelor cessation was not associated with an increased risk of cardiac death, myocardial infarction, or stroke Premature Ticagrelor cessation in routine clinical practice

occurred in 1 of 6 patients and was primarily related to adverse effects among which bleeding and dyspnoea were the most frequent. Although premature Ticagrelor cessation was not associated with adverse cardiovascular outcomes, this finding requires careful interpretation in view of the modest sample size.

Sameer Bansilal *et al.,* (2018)[44] conducted a study on Ticagrelor for Secondary Prevention of Atherothrombotic Events in Patients With Multivessel Coronary Disease in 12,558 patients, they compared with patients without MVD, those with MVD were at higher risk for MACE and for coronary events. In patients with MVD, Ticagrelor reduced the risk of MACE and coronary events, including a 36% reduction in coronary death. In this subgroup, Ticagrelor increased the risk of TIMI major bleeding, but not ICH or fatal bleeds, and they concluded that Patients with prior MI and MVD are at increased risk of MACE and coronary events, and experience substantial relative and absolute risk reductions in both outcomes with long-term Ticagrelor treatment relative to those without MVD. Ticagrelor increases the risk of TIMI major bleeding, but not ICH or fatal bleeding. For patients with prior MI and MVD, Ticagrelor is an effective option for long-term antiplatelet therapy.

Viveka Kumar *et al.,* (2018)[30] conducted a study on Clinical safety profile of Ticagrelor compared to Clopidogrel in 1208 patients they assessed retrospectively 604 patients received Ticagrelor and similarly 604 patient received Clopidogrel. No significant differences in the rates of major life threatening bleeding. There was increase in minor bleeding rate with Ticagrelor compared to Clopidogrel and they concluded that patients undergoing PCI treated with Ticagrelor showed similar safety profile compared to Clopidogrel but with increase in minor bleeding rate.

Konark Malhotra et al., (2018)[33] reviewed on Ticagrelor for stroke prevention in patients with vascular risk factors identified 13 RCTs, comprising 64,360 patients. In comparison to control group, Ticagrelor reduced the risk of IS combined ischemic and hemorrhagic strokes and composite stroke/MI/CVD Ticagrelor was not associated with increased risk of mortality or major bleeding events and they concluded that Ticagrelor seems to be a beneficial option for

primary and secondary stroke prevention in patients with vascular risk factors. Further RCTs are needed to evaluate the role of Ticagrelor in secondary stroke prevention

Pascal Vranckx et al., (2018)[39] conducted a study on Ticagrelor plus aspirin for 1 month, followed by Ticagrelor monotherapy for 23 months vs. aspirin plus Clopidogrel or Ticagrelor for 12 months after implementation of drug-eluting stent between 2013 and 2015 , 15968 participants were randomly assigned 7980 to the experimental group and 7988 to the control group. At 2 years 304 participants in the experimental group had died or had a non-fatal centrally adjudicated new Q-wave myocardial infarction, compared with 349 participants in control group and they concluded that Ticagrelor in combination with aspirin for 1 month followed by Ticagrelor alone for 23 months was not superior to 12 months of standard dual antiplatelet therapy followed by 12 months of aspirin alone in the prevention of all-cause mortality or new q wave myocardial infarction 2 years after percutaneous coronary intervention

Kamal shemisa *et.al.,* (2017)[37] conducted a study on Ticagrelor Adherence after Drug Eluting Stent Placement at a large Academic medical center between Jan 2012- Jun 2016, they collected 1 year fill data and measured the Ticagrelor adherence. And they concluded that in the urban safety net cohort, overall adherence to Ticagrelor was poor. Despite commonly reported Ticagrelor side effects like dyspnoea, they found patient level effects for non- adherence was more influential than drug effects.

Elizabeth A *et al.,* (2017)[38] reviewed a study of long term Ticagrelor in patients with prior myocardial infarction on Cost effectiveness with the objective to evaluate the cost effectiveness of Ticagrelor + low dose ASA in patients with in the prior 3 years. They performed a prospective economic sub study alongside the PEGASUS-TIMI 54. Hospitalization cost were similar for Ticagrelor and placebo after inclusion of daily Ticagrelor 60mg cost $10.52, and they concluded that the patients with a history of > 1 year previously, long term treatment with Ticagrelor 60mg+ low-dose ASA yields a cost effectiveness ratio suggesting intermediate value based on current guidelines. Ticagrelor appears to provide higher value for patients in several recognized high-risk subgroup. In patients with prior heart attack using Ticagrelor compared to placebo on a background of aspirin

Nina Johnston *et al.,* (2016)[34] they conducted a systematic review on causes of non-adherence to P2Y12 inhibitors in acute coronary syndromes and response to intervention, overview of the studies they reviewed Fifteen studies from seven countries met the inclusion criteria. 10–24 the majority of studies reviewed adherence to Clopidogrel, one to Prasugrel, one to Ticagrelor and the remaining to either thienopyridines or P2Y12 inhibitors. The studies included a total sample size of 21 954 patients, with a mean sample size of 1464 patients, with a mean of 75% men per study. An overview of these studies is provided in and they concluded after the systematic review that a number of factors are associated with OAP nonadherence, and encouragingly, there is some evidence of the effectiveness of intervention to modify treatment adherence in patients with ACS/CAD. Future evaluations ensuring a better cohesion between the factors studied as associated with non-adherence and those targeted by intervention would further increase understanding and lead to improved results.

Marc P. Bonaca *et al.,* (2016)[35] conducted a study on Long-term Tolerability of Ticagrelor for the Secondary Prevention of Major Adverse Cardiovascular Events with an objective of to investigate the reasons and timing of discontinuation of treatment with Ticagrelor among stable patients prior myocardial infarction. Over 33 months, 32% of 90 mg Ticagrelor, 29% of 60 mg Ticagrelor, and 21% of patients receiving Placebo. Discontinuation of treatment due to an adverse event occurred in 19%, 16%, and 9% of patients. Adverse events leading to discontinuation of treatment were bleeding and dyspnoea, they concluded that this early discontinuation of treatment was primarily driven by nonserious adverse events, including mild to moderate dyspnoea and nonmajor bleeding, illustrating the practical importance of such events.

Anders Sahlen *et al.,* (2016)[36] conducted a study on outcomes in patients treated with Ticagrelor or Clopidogrel after acute myocardial infarction: experiences from SWEDEHEART registry. They performed prospective study in 45073 ACS patients discharged with Ticagrelor (n=11954) or Clopidogrel (n=33119) between 2010 and 2013. The primary outcome was a composite of all-cause death, re-admission with myocardial infarction (MI) or stroke, secondary outcomes as the individual components of the primary outcome, and re-admission with bleeding. And they

concluded with Ticagrelor vs. Clopidogrel post-ACS was associated with a lower risk of death, MI, or stroke, as well as death alone. Risk

Baris Gencer *et al.,* (2015)[22] conducted a study on Reasons for discontinuation of recommended therapies according to the patients after acute coronary syndromes, Among 3014 patients were discharged with aspirin, 2983 with statin, 2464 with beta-blocker, 2738 with ACE inhibitors/ARB and 2597 with P2Y12 inhibitors if treated with coronary stent. At the one-year follow-up. Most patients reported having discontinued their medication based on their physicians' decision, while side effect, perception that medication was unnecessary and medication costs were uncommon reported reasons (<2%) according to the patients. And they concluded that Discontinuation of recommended therapies after ACS differs according the class of medication with the lowest percentages for aspirin. According to patients, most stopped their cardiovascular medication based on their physician's decision, while spontaneous discontinuation was infrequent.

Marc P. Bonaca *et al.,* (2015)[23] conducted a study on Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. They assigned 21,162 patients who had a myocardial infarction 1 to 3 years earlier to Ticagrelor at a dose of 90 mg twice daily, Ticagrelor at a dose of 60 mg twice daily, or placebo, along with low-dose aspirin, and resulted as bleeding were higher with Ticagrelor and with the rates of intracranial hemorrhage or fatal bleeding in the three groups were and they concluded that in patients with a myocardial infarction more than 1 year previously, treatment with Ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased the risk of major bleeding.

Kamal Shemisa *et al.*,(2015)[24] conducted a study on Premature Discontinuation of Ticagrelor among Patients who underwent PCI for ACS in a Large Urban Safety Net Hospital and they concluded that in this diverse patient population within a large healthcare system, adherence to Ticagrelor is poor in the year following PCI for ACS. While Ticagrelor adherence was lower than statin adherence, this difference was modest and suggests overall non-adherence primarily reflects patient level differences rather than Ticagrelor-specific reasons for non-adherence.

Lucenteforte *et al.*, (2015)[28] conducted a study on Ticagrelor-related dyspnoea in patients with acute coronary syndrome between 2012 and 2014, enrolled 1174 consecutive patients treated with Ticagrelor, among 1073 patients, 75.5% were males with a mean age of 55 years A total of 261 patients had respiratory disorders. A high number of these events could be Ticagrelor related dyspnoea. They concluded that could be useful to identify the optimal strategy to manage Ticagrelor-related dyspnoea and its possible consequent replacement therapy.

Guido Parodi *et al.*, (2015)[29] reviewed about Dyspnoea management in acute coronary syndrome patients treated with Ticagrelor and they concluded that ACS patients reporting dyspnoea have a high-risk profile and should be managed with the most effective treatment strategies, balancing side effects and therapeutic advantages of each single drug is needed and thus only in the case of persistent and intolerable Ticagrelor related dyspnoea should drug discontinuation be considered.

Anders Sahlen *et al.,* (2015)[31] conducted a study on Contemporary use of Ticagrelor in patients with acute coronary syndrome and they studied the use of Ticagrelor in patients admitted for ACS in Sweden between 1 January 2012 and 31 December 2013 they concluded that Ticagrelor is preferentially being used in patients at lower risk. A minority of patients are recommended Ticagrelor during, 12 months.

Payal Kohli *et al.,* (2013)[41] suggested that reduction in First and recurrent cardiovascular events with Ticagrelor compared with Clopidogrel in the PLATO study 18,624 patients presenting with ACS randomly received Ticagrelor (N=9333) or Clopidogrel (N=9291). Patients randomized to Ticagrelor had 1057 total primary endpoint events vs. 1225 for patients on Clopidogrel. Recurrent PLATO major or TIMI major non-CABG Bleeding events were infrequent and not different between the two therapies, and they concluded that treatment with Ticagrelor compared with Clopidogrel resulted in a reduction in total events, including first and subsequent recurrent cardiovascular events, when compared to Clopidogrel. These types of analyses demonstrate an even greater absolute benefit of Ticagrelor over Clopidogrel than previously reported.

Christian Weimar *et al.,* (2013)[42] conducted the study on Discontinuation of Antiplatelet Study Medication and Risk of Recurrent Stroke and Cardiovascular Events The recurrent stroke and cardiovascular event rates following discontinuation of aspirin plus extended-release dipyridamole (ASA + ERDP) or Clopidogrel were compared to the event rates in the on-treatment populations. Totally 7,212 treated with ASP+ERDP patients, the stroke incidence rate for the on-treatment group was 729 strokes with an average exposure of 17,048 person-years was 729 strokes with an average exposure of 17,048 person-years and Clopidogrel was permanently discontinued in 2,176 patients, and they concluded that Given the important cardiovascular risk associated with discontinuation of antiplatelet medication in secondary stroke prevention, physicians and patients should be aware of the hazards of not adhering or not complying with antiplatelet medication. Preoperative or preprocedural discontinuation (with or without bridging) should be advocated only when the risk and severity of bleeding clearly outweigh that of cardiovascular events. And they concluded that given the important cardiovascular risk associated with discontinuation of antiplatelet medication in secondary stroke prevention, physicians and patients should be aware of the hazards of not adhering or not complying with antiplatelet medication. Preoperative or preprocedural discontinuation should be advocated only when the risk and severity of bleeding clearly outweigh that of cardiovascular events.

Ann Wittfeldt *et al*.,(2013)[43] studied about Ticagrelor Enhances Adenosine-Induced Coronary Vasodilatory Responses in Humans with an objective was to determine if Ticagrelor augments adenosine-induced coronary blood flow and the sensation of dyspnoea in human subjects. 40 healthy male subjects were randomized to receive a single dose of Ticagrelor (180 mg) or placebo in a crossover fashion There was a significant correlation between Ticagrelor plasma concentrations and increases in the area under the curve (p 0.001). In both treatment groups, the adenosine-induced increase in CBFV was significantly attenuated by theophylline, with no significant differences between subjects receiving Ticagrelor or placebo (p 0.39). Furthermore, Ticagrelor significantly enhanced the sensation of dyspnoea during adenosine infusion, and the effects were diminished by theophylline and they concluded that there was a significant correlation between Ticagrelor plasma concentrations and increases in the area under the curve (p 0.001). In both treatment groups, the adenosine-induced increase in CBFV was significantly

attenuated by theophylline, with no significant differences between subjects receiving Ticagrelor or placebo (p 0.39). Furthermore, Ticagrelor significantly enhanced the sensation of dyspnoea during adenosine infusion, and the effects were diminished by theophylline.

Robert F. Storey *et al*., (2011)[26] conducted a study on Characterization of dyspnoea in PLATO study patients treated with Ticagrelor or Clopidogrel and its association with clinical outcomes. 18,624 patients were randomized to receive either Clopidogrel or Ticagrelor. The occurrence of reported dyspnoea adverse events (AEs) was analysed in the 18,421 patients who received at least one dose of study medication in relation to demographic characteristics, clinical outcomes and other associations of patients with and without dyspnoea. A total of 1339 Ticagrelor treated patients and 798 Clopidogrel-treated patients had a dyspnoea AE following randomization, with respectively 39 and 24 classified as severe in intensity and they concluded that Ticagrelor-related dyspnoea is usually mild or moderate in intensity and does not appear to be associated with differences concerning any efficacy or safety outcomes with Ticagrelor compared with Clopidogrel therapy in ACS patients.

Paul A *et al*., (2010)[25] conducted a study on Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies. Patients with stable coronary artery disease on aspirin therapy received a 300-mg Clopidogrel load; nonresponders were identified by light transmittance aggregometry. In a 2-way crossover design, nonresponders (n_41) and responders (n_57) randomly received Clopidogrel (600 mg/75 mg once daily) or Ticagrelor (180 mg/90 mg twice daily) for 14 days during period and they concluded that Ticagrelor therapy overcomes nonresponsiveness to Clopidogrel, and its antiplatelet effect is the same in responders and nonresponders. Nearly all Clopidogrel nonresponders and responders treated with Ticagrelor will have platelet reactivity below the cut points associated with ischemic risk.

Robert F. Storey *et al.*, (2010)[27] conducted a study on Incidence of Dyspnoea and Assessment of Cardiac and Pulmonary Function in Patients With Stable Coronary Artery Disease Receiving Ticagrelor, Clopidogrel, or Placebo in the ONSET/OFFSET. They prospectively assessed the 123 stable aspirin-treated CAD patients randomly received Ticagrelor, Clopidogrel, or placebo

for 6 weeks in a double-blind, double-dummy design. Dyspnoea was reported by 38.6%, 9.3%, and 8.3% of patients in the Ticagrelor, Clopidogrel, and placebo groups, respectively.

Lars Wallentin *et al.,* (2009)[32] conducted a study on Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes compared Ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) and Clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in 18,624 patients, In patients who have an acute coronary syndrome with or without ST-segment elevation, treatment with Ticagrelor as compared with Clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non- procedure-related bleeding.

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AIM & OBJECTIVES

3. AIM AND OBJECTIVES

AIM:

To evaluate the adherence with Ticagrelor in Acute Coronary Syndrome patients (ACS).

OBJECTIVES:

- To assess the adherence of Ticagrelor in patients with ACS.
- To investigate the drug therapy problems, reasons and timing of discontinuation of treatment with Ticagrelor.
- To find out whether Ticagrelor discontinuation is associated with adverse cardiovascular outcomes.

METHODOLOGY

4.METHODOLOGY

Study type: This is a Prospective and Retrospective observational Study

Study site: The study was conducted at a Department of Cardiology Kovai Medical Center and Hospital (KMCH), Coimbatore.

Sample size calcutation:

- Confidence level = 95% z score = 1.96
- Confidence interval (e)= 0.05
- Standard deviation (p)= 0.5
- Population size (N)= 400
- n= sample size

Formula $$n = \frac{\frac{Z^2 P\,(1-P)}{e^2}}{1+\left[\frac{Z^2\,P\,(1-P)}{e^2\,N}\right]}$$

Sample size (n) = **196**

Study period: The study was carried out for a period of 6 months

Inclusion criteria:

- Patient discharged from hospital with a diagnosis of ACS
- Patient discharged on Ticagrelor therapy

Exclusion criteria:

- Patient who are all prescribed with prasugrel or clopidogrel

OUTCOME OF THE STUDY:

- Incidence of major adverse cardiac events,
- Incidence major Adverse Effects
- Incidence of drug discontinuation.

PROJECT PROTOCOL

The institutional research and ethics committee approved the study and issued the letter of permission to conduct the study (EC/AP/721/06/2019). In this study the medication adherence was assessed and also assessed whether they were discontinuing the drug or adherent with the drug as per the guidelines. Here the patients are enrolled according to the inclusion criteria. The demographic details of the patients are collected and seeing the patient chart whether patient is on Ticagrelor therapy or with other antiplatelet therapy. If the patients are on therapy assess the adherence. If the patients are on other antiplatelet drug. Then assess the reason for the discontinuation. If adhered then it was assessed the with validated questionnaire Morisky green Levine scale. If the patients discontinued the cardiovascular drug, identify reason for discontinuation of the drugs. Then identifying the clinical events which occurred due to the discontinuation of Ticagrelor.

RESULTS

5. RESULTS

TABLE 2.DISTRIBUTION OF PATIENTS BASED ON DEMOGRAPHIC DATA

CHARACTERISTICS		NO. OF PATIENTS (N=213)	PERCENTAGE (%)
MALE		170	79.8
FEMALE		43	20.2
>20-30		2	.9
>30-40		10	4.7
>40-50		44	20.7
>50-60		65	30.5
>60-70		65	30.5
>70-80		18	8.5
>80		9	4.2
SMOKER	Yes	100	46.9
	No	113	53.1
ALCOHOLIC	Yes	50	23.5
	No	163	76.5
VEG		111	52.1
NON-VEG		102	47.9

Figure 3.Gender Wise Distribution among Study Population (N=213)

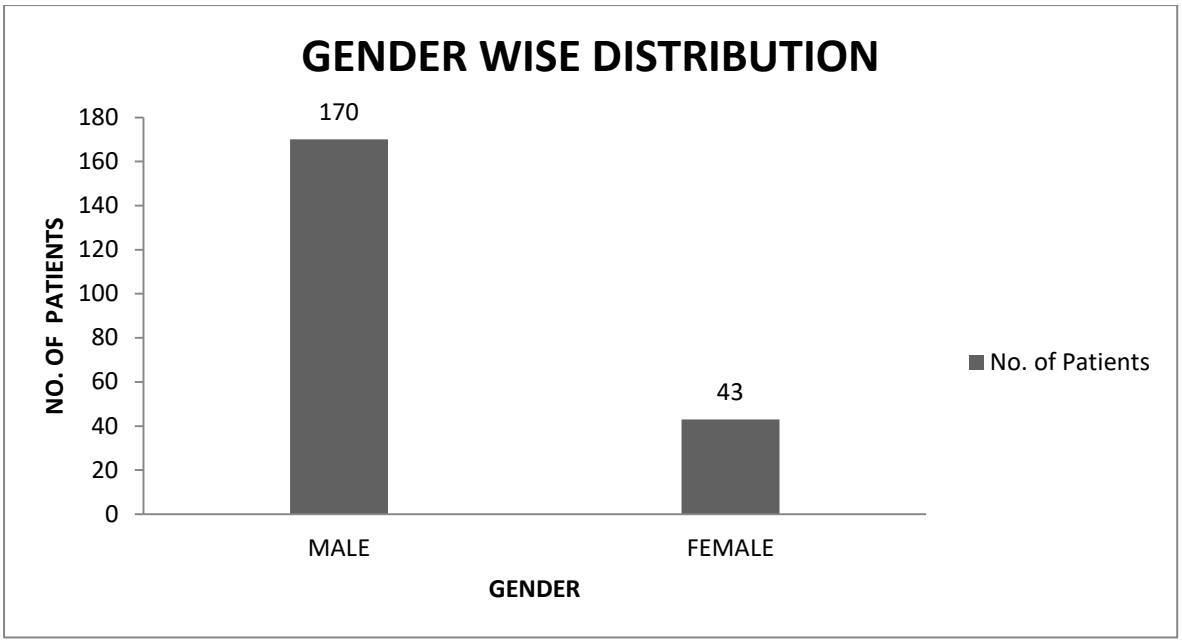


Figure 4.Age wise distribution among study population (N=213)

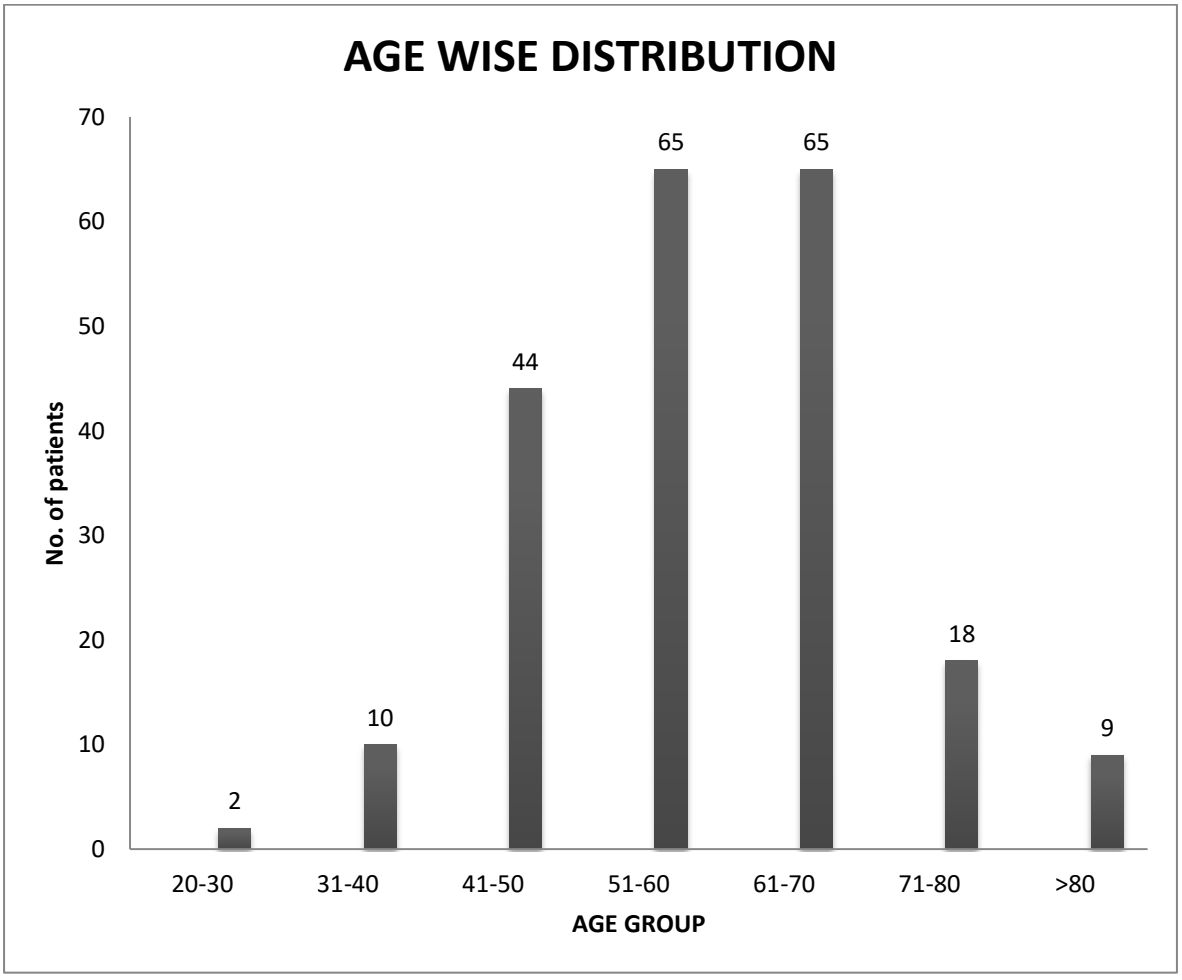


Figure 5.Social Habits among Study Population (N=213)

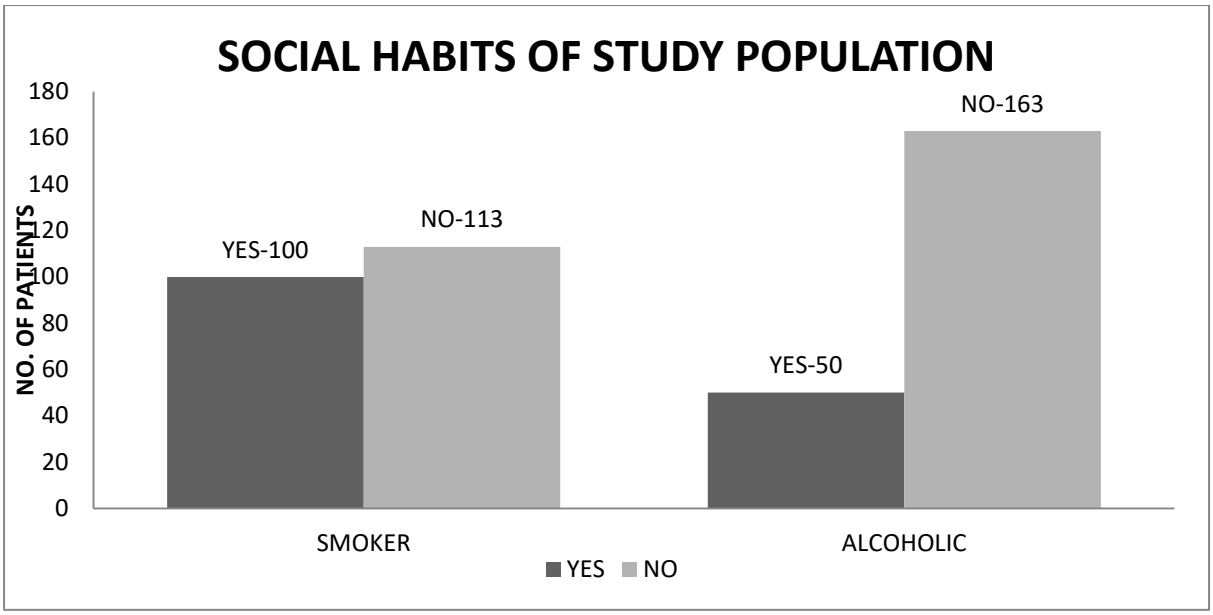


Table 3.Disease wise Distribution among study population (N=213)

DIAGNOSIS	NO. OF PATIENTS (N=213)	PERCENTAGE (%)
STEMI	147	69.0
NSTEMI	24	11.3
Stable angina	8	3.8
Unstable angina	28	13.1
CAD	6	2.8

Figure 6.Diagnosis of the Study population.(N=213)

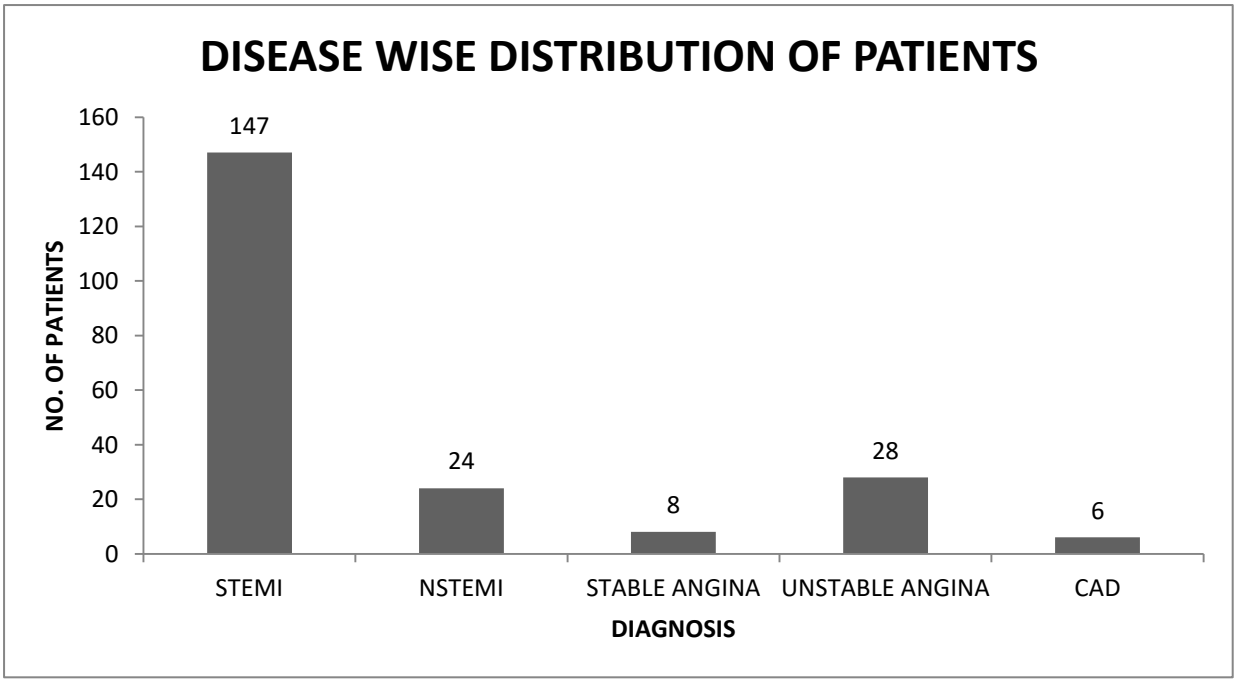


Table 4.Angiographic findings among study population (N=213)

ANGIOGRAPHIC FINDINGS	NO. OF PATIENTS (N=213)	PERCENTAGE (%)
Single vessel disease	68	31.9
Double vessel disease	111	52.1
Triple vessel disease	34	16.0

Figure 7. Angiographic findings among study population

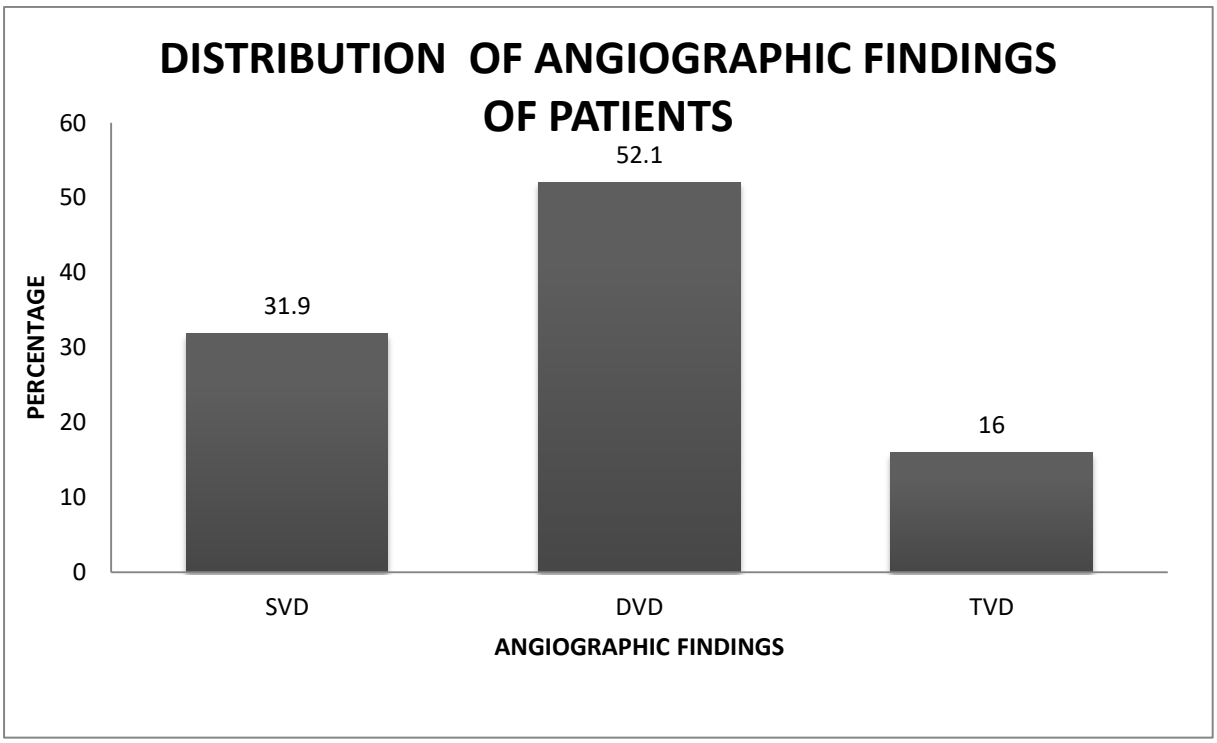


Table 5.Comorbidities among Study Population (N=213)

Comorbidities	No. Of patients (N=213)	Percentage (%)
Diabetes mellitus	61	28.6
Prior myocardial infraction	5	2.3
Atrial fibrillation	6	2.8
COPD	6	2.8
Angina	2	0.9
Dyslipidemia	12	5.6
Hypertension	31	14.6
DM+HTN	20	9.4
Hypothyroidism	5	2.3
No comorbidities	65	30.5

Figure 8. Comorbidities among Study Population (N=213)

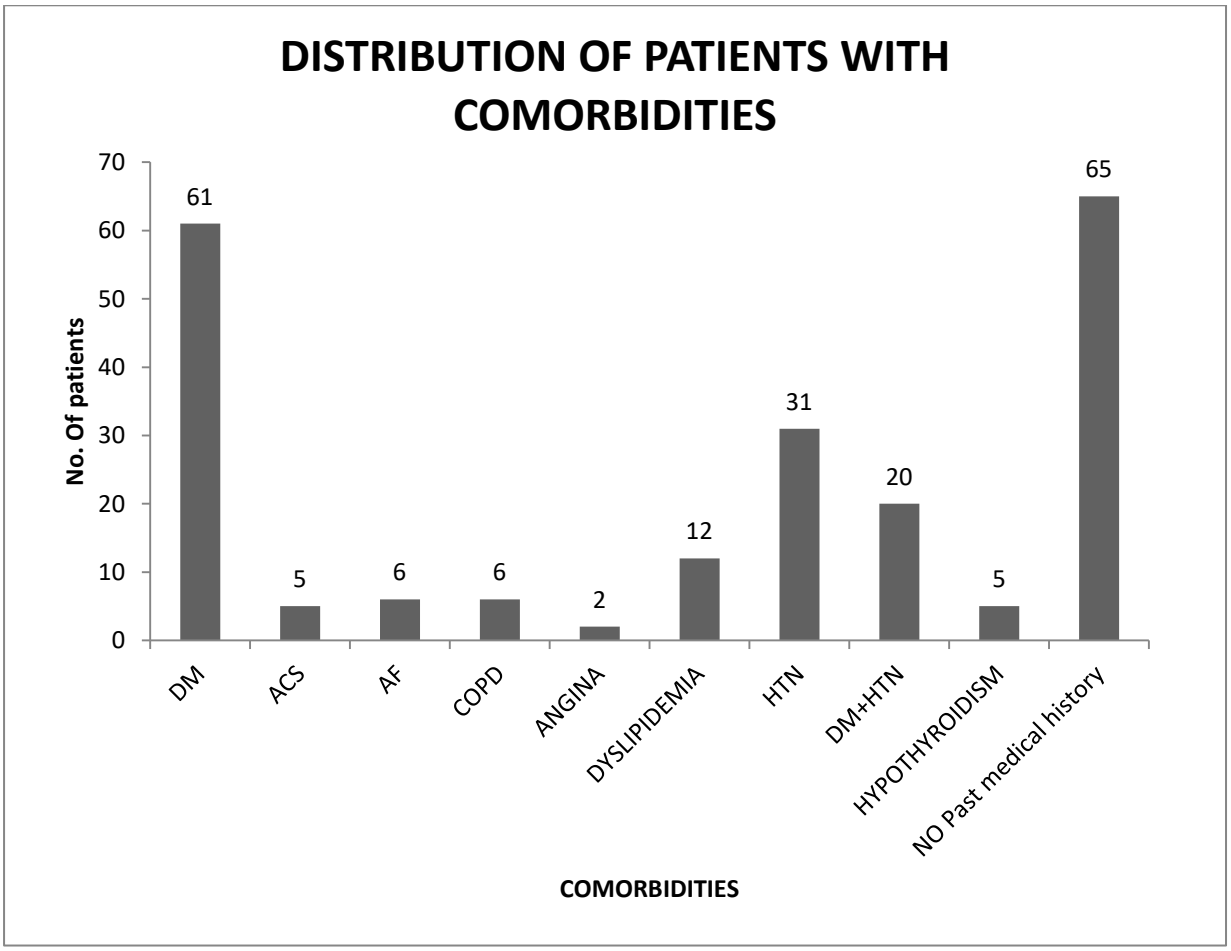


Table 6.Adherence And Nonadherence Of patients towards Ticagrelor after discharge Among Study Population

TICAGRELOR	NO. OF PATIENTS (N=213)	PERCENTAGE (%)
ADHERENCE	44	20.7
NON-ADHERENCE	169	79.3

Figure 9.Distribution of Patients with Discontinuation of Ticagrelor and not discontinuation of ticagrelor

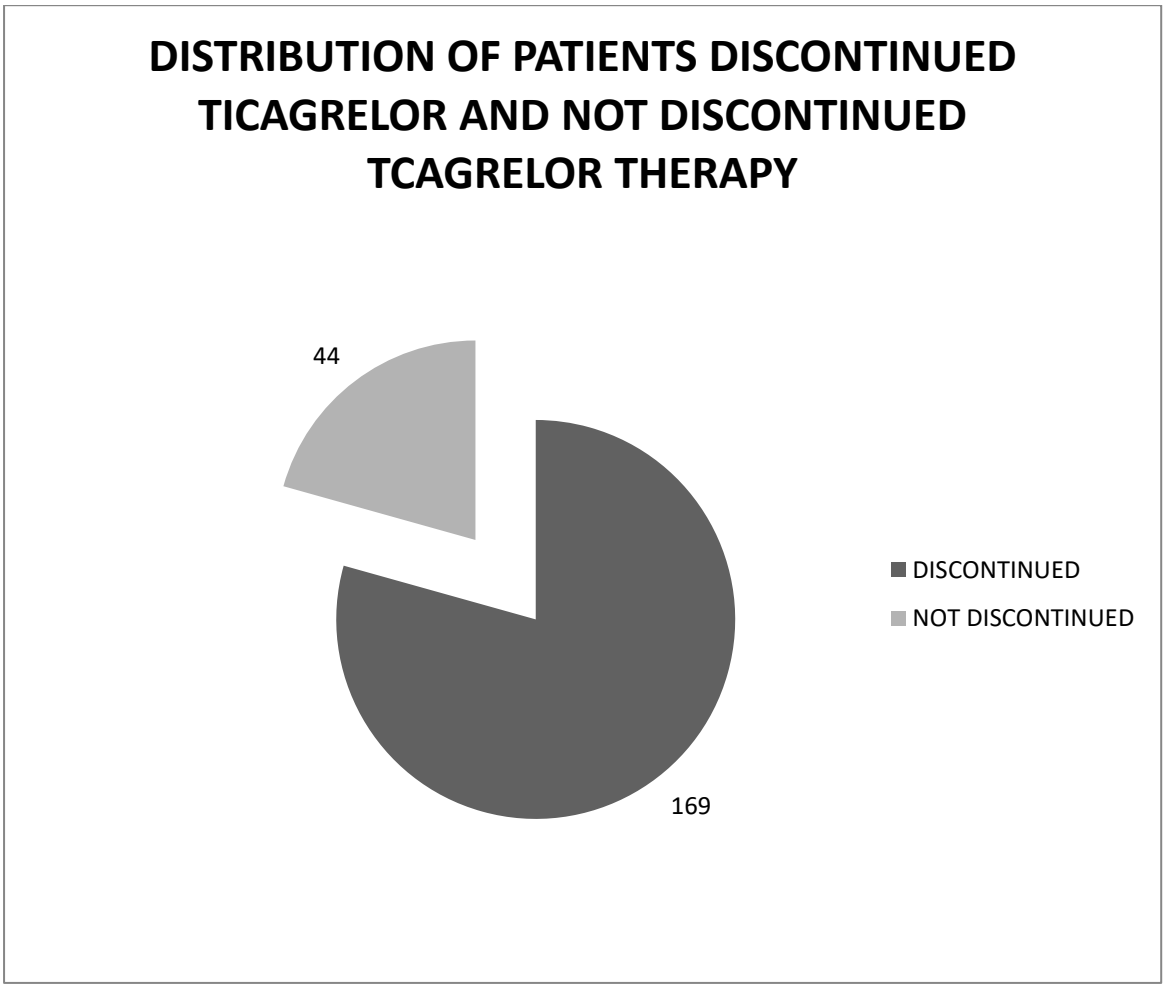


Table 7.Distribution of Patients Adherence with Ticagrelor

INTERPRETATION	NO. OF PATIENTS	PERCENTAGE
Low	3	6.8
Medium	25	56.8
High	5	11.3
Not responded	11	25

Figure 10.Distribution of patients Adherence with Ticagrelor (n=44)

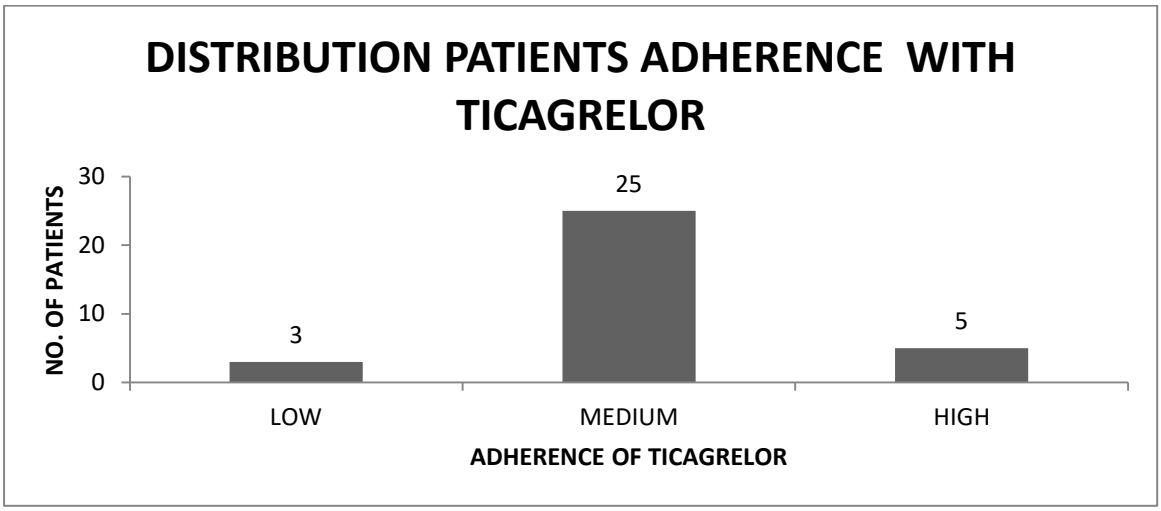


Table 8. Discontinuation of Ticagrelor Therapy Among Study Population (In Months)

DURATION IN MONTHS	NO. OF PATIENTS (N=213)	PERCENTAGE (%)
1st month	5	2.3
2nd month	22	10.3
3rd month	36	16.9
4th month	20	9.3
5th month	20	9.3
6th month	17	7.9
7th month	13	6.10
8th month	5	2.3
9th month	8	3.75
10th month	15	7
11th month	8	3.75
12th month	35	16.43
>12 months	9	4.2

Figure 11. Discontinuation of Ticagrelor Therapy Among Study Population (In months)

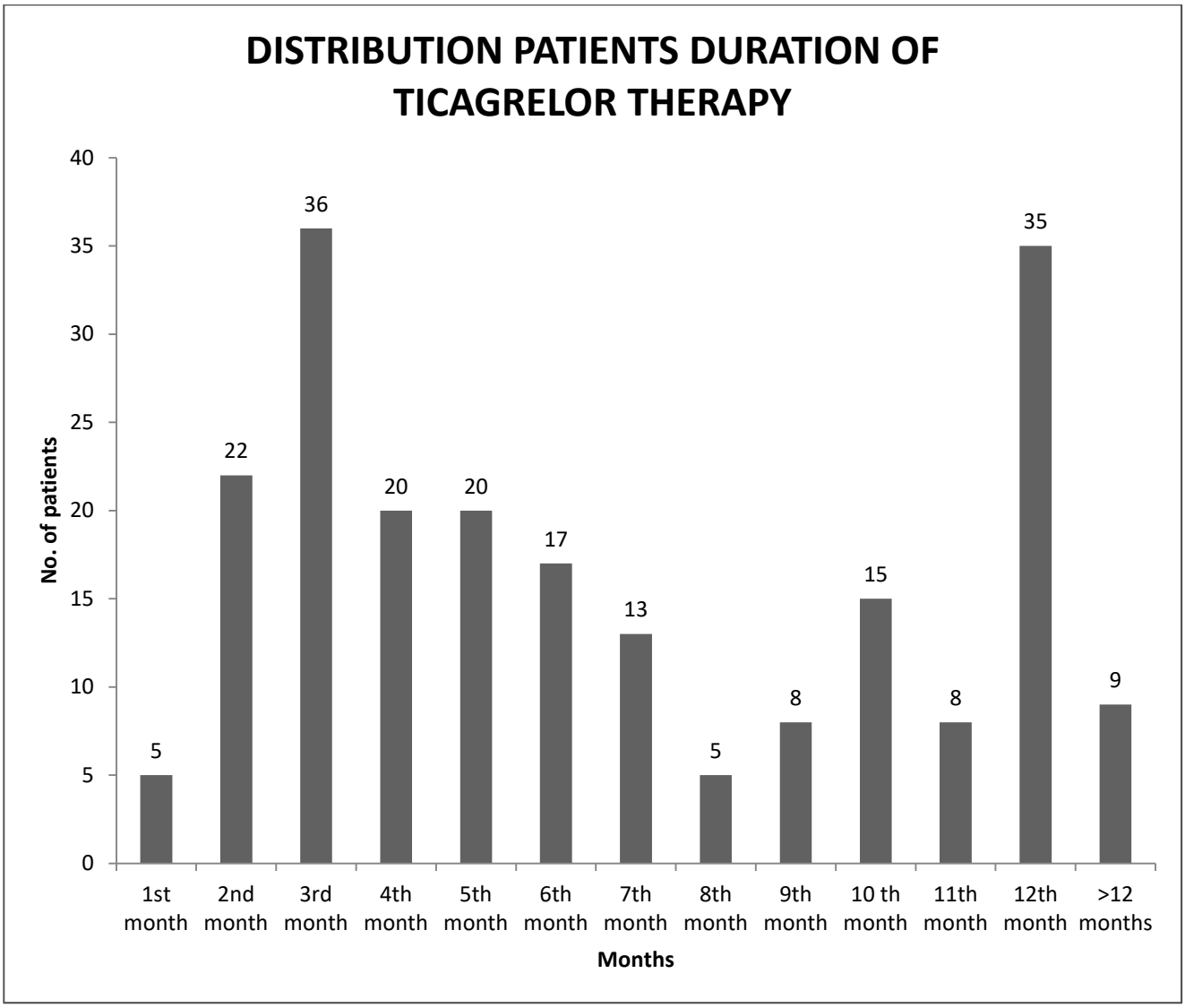


Table 9. Reason for discontinuation of Ticagrelor among study population

Reasons	No. Of patients (n=169)	Percentage (%)
Bleeding	**43**	**20.18**
Dyspnoea	**42**	**19.7**
Bleeding +dyspnoea	**13**	**6.1**
Bradycardia	**10**	**4.6**
Financial problem	**30**	**14**
Gp preference	**11**	**5.1**
Hypotension	**2**	**0.9**
Oral anticoagulants	**10**	**4.6**
Others	**8**	**3.75**

Figure 12. Reason for discontinuation of Ticagrelor among study population

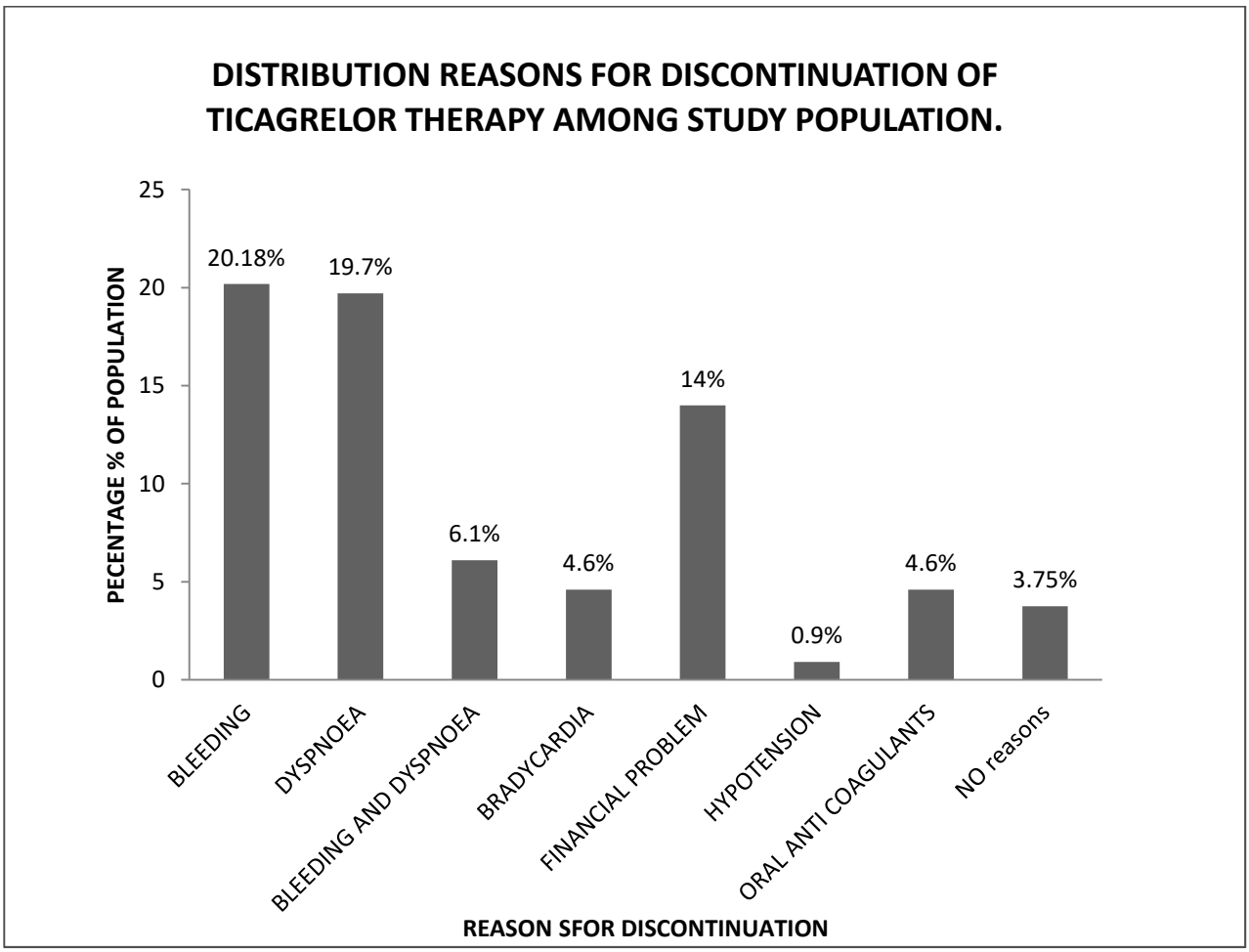


Table 10. Antithrombotic therapy used as replacement after Discontinuation of Ticagrelor after discharge among study population (n=169)

Ticagrelor treatment replaced with	No. of population (n=169)	Percentage
Clopidogrel	93	55.0
Prasugrel	66	39
Oral anticoagulant	10	5.9

Figure 13.Percentage of Patients Replaced with other Antithrombotic Therapy.

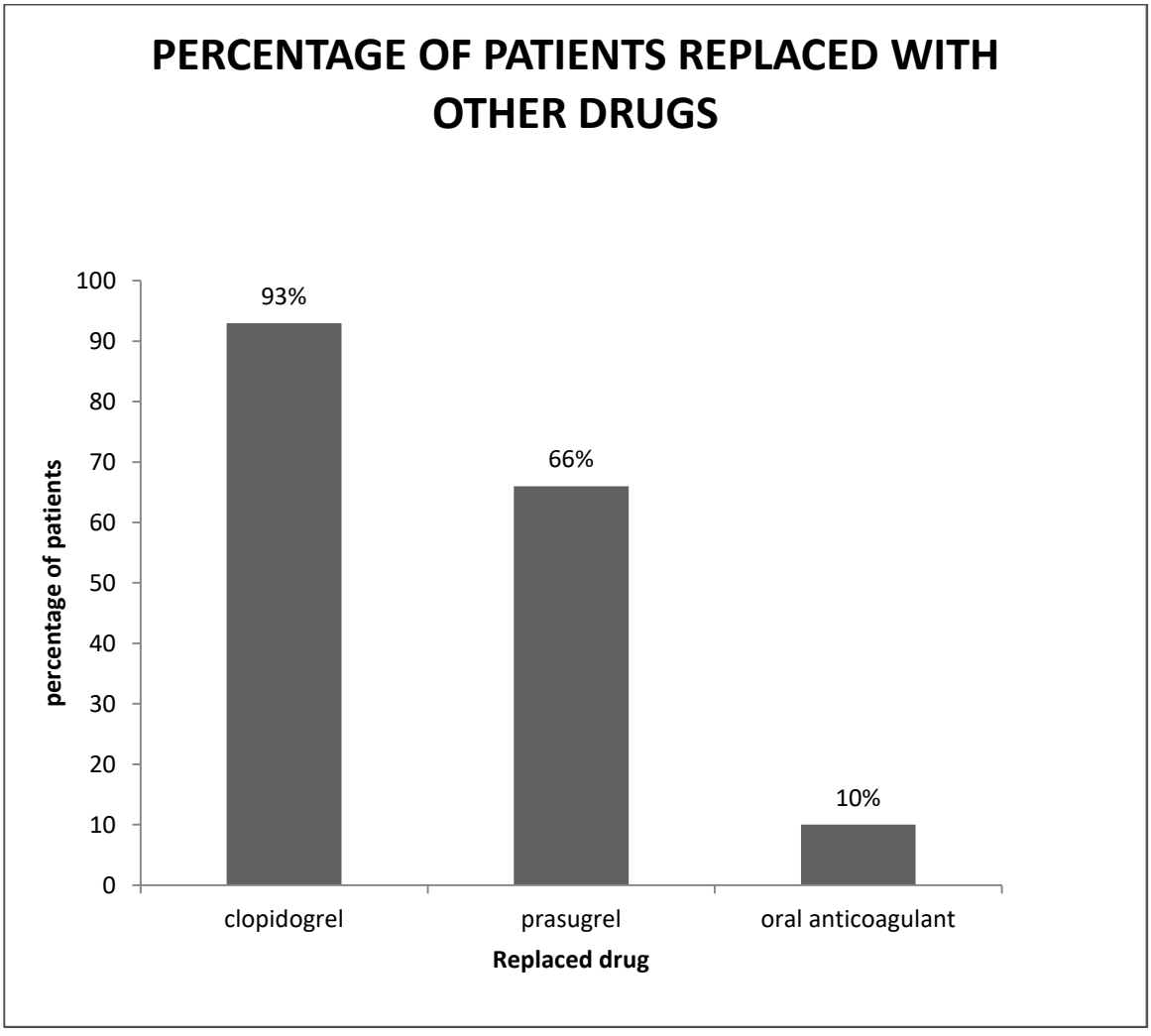


Table 11. Distribution of Patients with Clinical Event and without Clinical Event after one year among Study Population

CHARECTERISTICS	NO. OF PATIENTS (N=213)	PERCENTAGE OF PATIENTS
With clinical events	52	24.4
Without clinical event	161	75.5

Figure 14.Distribution of Percentage of study Population With And Without Clinical Events

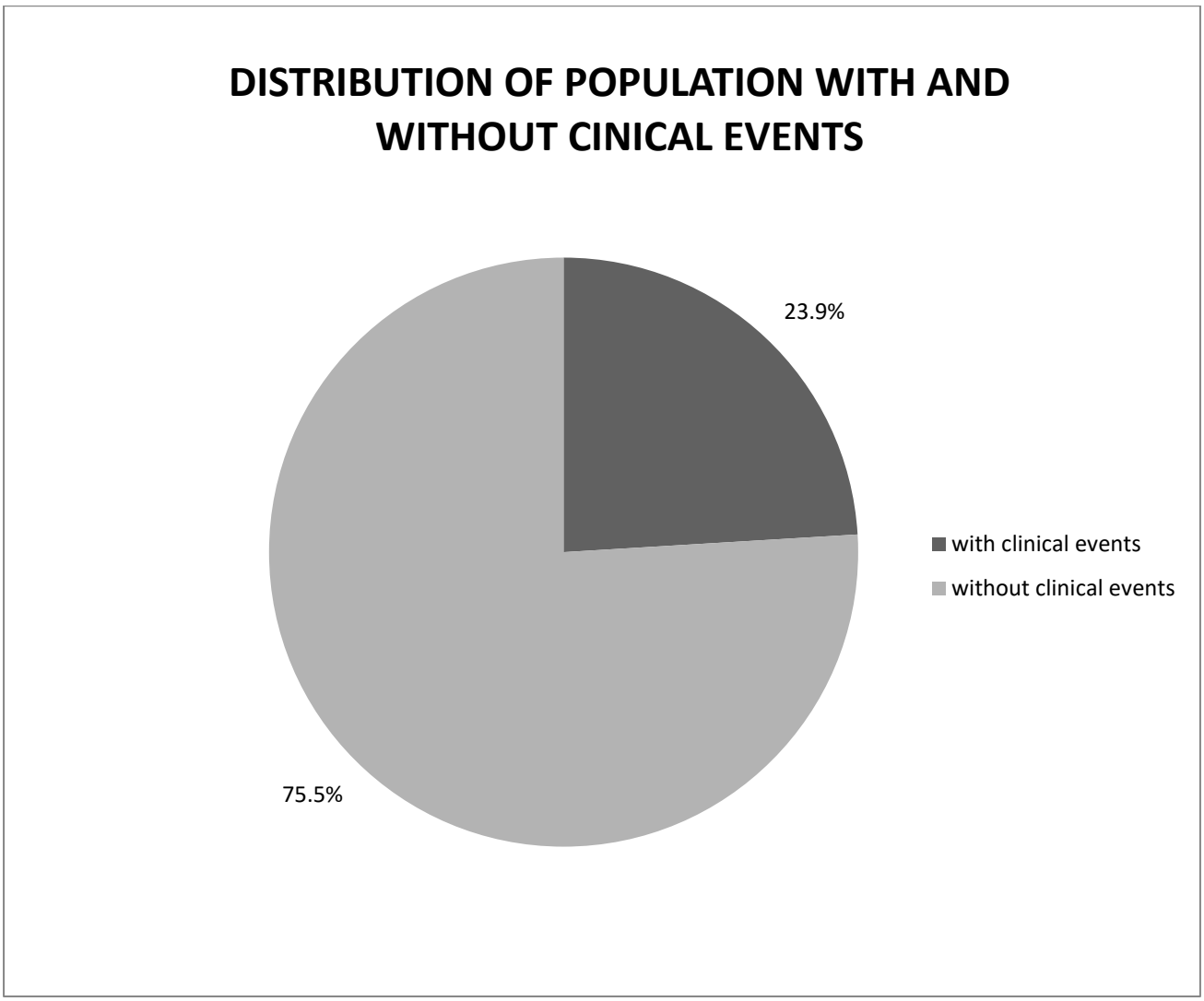
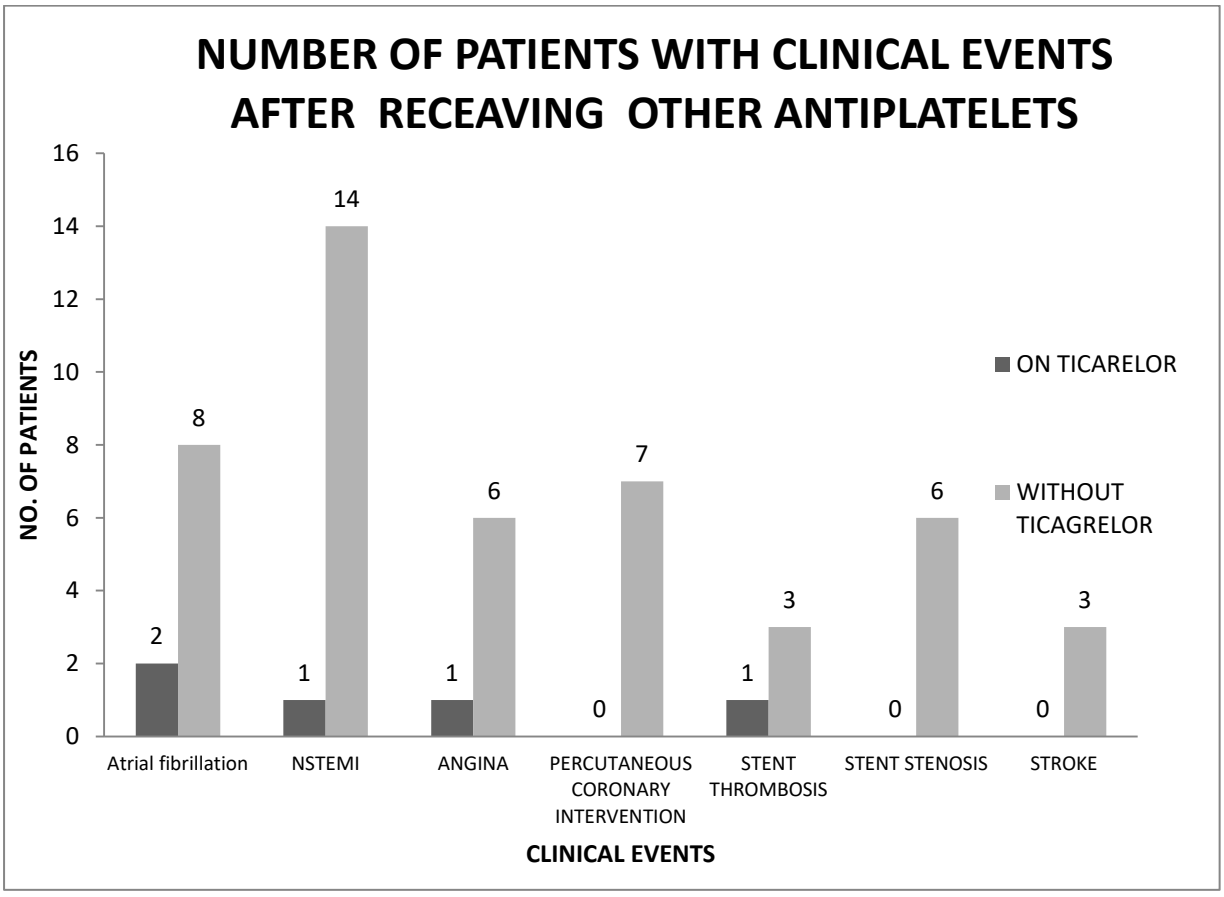


Table 12.Clinical Events between Discontinued Group And Not Discontinued Group

CHARECTERISTICS	NOT DISCONTINUED (ON TICAGRELOR)	DISCONTINUED GROUP (ON REPLACEMENT)
Atrial fibrillation	2 (4.54%)	8(4.73%)
NSTEMI	1(2.27%)	14(8.28%)
ANGINA	1(2.27%)	6(3.55%)
PCI	0	7(4.14%)
STENT THROMBOSIS	0	3(1.77%)
STENT STENOSIS	1(2.27%)	6(3.55%)
STROKE	0	3(1.77%)
TOTAL	**5(11.36)**	**47 (27.8)**

Figure 15.Clinical Events between Ticagrelor Discontinued group and not Discontinued group



5. RESULTS

A total of 213 patients were included in the study. In that 170 (79.8%) patients were male and 43 (20.2%) were female shown in Fig 2. In this study 2 (0.9%) patients were in the age group of 20-30, 10 (4.7%) were in the age group 31-40, 44 (20.7%) were in the age group of 41-50, 65 (30.5%) were in the age group of 51-60, 65 (30.5%) were in the age group of 61-70, 18 (8.5%) were in the age group of 71-80, 9 (4.2%) were above the age of 80 shown in Fig 3, Table 2

In consideration of social habits, 100 (46.9%) patients were smokers and 113 (53.1%) were non smokers. 50 (23.5%) were alcoholics and 163 (76.5%) were non-alcoholic shown in Fig 5. In the patients included for the study 111 (52.1%) were in vegetarian diet and 102 (47.9%) were in non vegetarian diet shown in Table 2

Out of 213 patients, 147 (69.0%) patients were diagnosed with STEMI, 24 (11.3%) were diagnosed with NSTEMI, 8 (3.8%) were diagnosed with stable angina, 28 (13.1%) were diagnosed with unstable angina and 6 (2.8%) were diagnosed with CAD shown in Fig 6, Table 3. While considering the angiographic findings, 68 (31.9%) was single vessel disease, 111 (52.1%) was double vessel disease, 34 (16.0%) were triple vessel disease, shown in Fig 7, Table 4.

In the patients included for the study, 148 patients were with co morbid condition. In that 61 (28.6%) were with diabetes mellitus, 5 (2.3%) patients were with prior myocardial infarction, 6 (2.8%) were with atrial fibrillation, 6 (2.8%) patients were with COPD, 2 (0.9%) patients were with angina, 12 (5.6%) patients were with dyslipidemia, 31 (14.6%) patients were with hypertension, 20 (9.4%) were with diabetes mellitus and hypertension, 5 (2.3%) patients were with hypothyroidism. Out of 213, 65 (30.5%) patients did not have any co morbid condition, sown in Fig 8, Table 5.

Assessment of adherence of the patients towards Ticagrelor after discharged from among 213 study population 44 (20.7%) patients were adhere to Ticagrelor and 169 (79.3%) patients were non adhere to Ticagrelor shown in Table 6, Fig 9. The adherence of 44 patients were assessed using Morisky green Levine scale in that 3 (6.8 %) patients were low adhere to the Ticagrelor, 20(56.8%) were medium adherence and 5 (11.36%) patients were high adherence to Ticagrelor and 16(25%) patients were not responded shown in Fig 10, Table 7.

Duration of Ticagrelor therapy was noted in which the patients how many months they were in adherence to the Ticagrelor, It means that the patients discontinued the Ticagrelor. In that for 5 patients Ticagrelor therapy was stopped on 1st month. For 22 patients the Ticagrelor therapy was stopped on 3rd month. For 36 patients the Ticagrelor therapy was stopped on 3rd month of therapy duration. For 20 patients Ticagrelor was stopped on 4th month. For 20 patients Ticagrelor therapy was stopped on 5th months. For 17 patients Ticagrelor therapy was stopped on 6th months, for 13 patients Ticagrelor therapy was stopped on 7th month. For 5 patients the Ticagrelor therapy was stopped on 8th month. For 8 patients the Ticagrelor therapy was stopped on 9th month. For 15 patients the Ticagrelor therapy was stopped on 10th month. For 8 patients the Ticagrelor therapy was stopped on 11th month. 35 patients were continued Ticagrelor therapy for 12 months. 9 patients were discontinued Ticagrelor therapy or more than 12 months shown in Fig.11, Table 8.

The patients after discontinuation of Ticagrelor they were switching over from Ticagrelor to other anti platelets and they were reported the reasons for discontinuation of Ticagrelor to the physician. There are bleeding in 43 (20.18%) patients,, dyspnoea in 42 (19.7%) patients, bleeding along with dyspnoea was in 13 (6.10%) patients, bradycardia in 10 (4.6%) patients, Financial problem in 30 (14%) patients, General physician preference in 11(5.1%) patients, Hypotension was the reason in 2 (0.9%) patients, prescription of oral anticoagulants in 10 (4.6%) patients and 8 (3.75%) patients had no reasons. And remaining 44 of them not changed their therapy shown in Fig 12, Table 9.

After the discontinuation of Ticagrelor among 169 study population they were prescribed with other anti platelets as a replacement. In 93 (55%) patients Ticagrelor was replaced with Clopidogrel, in 66 (39%) patients Ticagrelor was replaced with Prasugrel and in 10 (6%) patients prescribed with oral anticoagulants shown in Table 10, Fig 13.

Due to discontinuation of Ticagrelor within 1 year, among 213 patients 52 (23.9%) patients had several clinical events within in one year due to replacement of Ticagrelor, and 161 (75.5%) not had any clinical event shown in Table 11, Fig 14.

Clinical events between discontinued patients and not discontinued patients were compared. In patients on Ticagrelor 2 (4.54%) patient had atrial fibrillation, 1 (2.27%) patient had NSTEMI, 1 (2.27%) patient had Angina, and 1 (2.27%) patient had Stent stenosis. In patients changed to other drugs, 8 (4.73%) patients had atrial fibrillation, 14 (8.28%) patients had NSTEMI, 6(3.55%) patients had angina, 7 (4.14%) patients Undergone PCI , 3(1.77%)

patients had Stent thrombosis 6(3.55%) patients had stent stenosis and 3(1.77%) patients had stroke shown in Table 12, Fig 15.

DISCUSSION

6. DISCUSSION

In this study we present the data that shows the adherence of patients to Ticagrelor and also the reasons for discontinuation of Ticagrelor. This study also provides the details of clinical event which occurred due to the discontinuation of Ticagrelor within one year. In this study the adherence was checked in the patients who continued Ticagrelor for one year by using Morisky scale.

In our study out of 213 patients included, 170 were male and 43 were female. Considering the distribution of age group of patients included in the study the age group of 51-60 and 61-70 were more than other age groups.

The comorbid condition of the included patients in this study was identified. In that, diabetes mellitus (28.6%) was reported as the common comorbid condition followed (14.6%) patients were with hypertension. Similarly in a study conducted by **Sahlen et.al.,** diabetes (51.2%) was the most common comorbid condition followed by hypertension (47%)[31].

In our study, 69.0% patients were diagnosed with STEMI, 11.3% were diagnosed with NSTEMI. It shows that STEMI was more and Ticagrelor was prescribed more in STEMI. Similarly, a study conducted by **Husted et al.,** showed that STEMI(42.9%) was more common than NSTEMI (37.5%) and unstable angina (16.6%)[26].

Our study reported that about 79.3% patients discontinued the Ticagrelor and 20.7% patients were adhered to Ticagrelor upto 1 year. Similarly a study conducted by **Dehghani P et al.,** showed that only 21% of patients were considered highly adherent and one third of the patients were considered poorly adherent.[46]

The reasons for discontinuation of Ticagrelor were found out in our study and bleeding (20.18%) was reported as common reason followed by Dyspnoea (19.7%). Similarly in a study conducted by **Bergmeijer et al.,** shows the reason for discontinuation of Ticagrelor as, bleeding (11.6%), dyspnoea (3.7%) and bleeding was the common reason for discontinuation[46]. But a study conducted by **Marc P Bonaca et al**., reported that premature discontinuation of Ticagrelor is due to adverse reaction of Ticagrelor mainly dyspnoea (18.2%).[35]

In our study duration of Ticagrelor therapy was observed, in which 36 (16.9%) patients was discontinued within 3 months followed by 35 (16.4%) of them were taken up to

one year. Similarly in a study conducted by **Anders et al**., says that Ticagrelor was discontinued within 6 months was 45% and 25% of them were discontinue within 12 months and 30% of patients were patients were taken upto one year[31]**.** And also the another study conducted by **Sahlen et al**., says that the 37.7 % of patients discontinued Ticagrelor within 3 months and 24.8% of patients were taken upto one year.[36]

In our study discontinuation of Ticagrelor was reported as 79.3% of patients. After the discontinuation of Ticagrelor they were prescribed with other anti platelets as a replacement. In 93 (55%) patients Ticagrelor was replaced with clopidogrel, in 66 (39%) patients were replaced with prasugrel and in 10 (6%) patients prescribed with oral anticoagulants. Similarly the study conducted by **Martin et al.,** reported that Ticagrelor was replaced with Clopidogrel (28.2 %), Prasugrel (7.3 %), Oral anticoagulation (8.1%). It also shows that Ticagrelor was replaced mostly with clopidogrel.[21]

The high Ticagrelor discontinuation rate is relevant to clinical practice, because early discontinuation might increase the risk for atherothrombotic events. For instance, cessation of the P2Y12 inhibitor within 1 year after PCI (Percutaneous Coronary Intervention) is the most important predictor for the occurrence of stent thrombosis. Clinical events between discontinued patients and not discontinued patients were compared. In 5 patients had got clinical events and 52 patients had changed to other drugs.

Clinical events between discontinued patients and not discontinued patients were compared. In patients on Ticagrelor 2 (4.54%) patient had atrial fibrillation, 1 (2.27%) patient had NSTEMI, 1 (2.27%) patient had Angina, and 1 (2.27%) patient had Stent stenosis. In patients changed to other drugs, 8 (4.73%) patients had atrial fibrillation, 14 (8.28%) patients had NSTEMI, 6(3.55%) patients had angina, 7 (4.14%) patients Undergone PCI , 3(1.77%) patients had Stent thrombosis 6(3.55%) patients had stent stenosis and 3(1.77%) patients had stroke. Similarly a study conducted by the **Zeymer et al** in their study they reported that patients who discontinued Ticagrelor had occurred with Myocardial infarction in 3.5 % patients, Stroke had occurred in 1.7 % patients, Coronary angiography in 17.5 % patients, Percutaneous coronary intervention done in 8.0 % patients, Coronary artery bypass graft surgery done in 5.3 % patients, Cardiac pacemaker implantation done in 1.8 % patients and Bleeding occurred in 10.4%. In patients on Ticagrelor, stroke occurred in 0.4%, coronary angiography done in 15.5% patients, Percutaneous coronary intervention done in 12.0% patients, Coronary artery bypass graft surgery done in 0.4%patients, and Cardiac pacemaker

implantation done in 0.4% patients[21]. The clinical events were high in patients who discontinued Ticagrelor, Similarly in our study the clinical events were higher in patients discontinued Ticagrelor. However, in the PARIS study, only "disruption" of antiplatelet therapy defined as cessation of dual antiplatelet therapy because of bleeding or noncompliance was significantly associated with an increase in a combined thrombotic endpoint.[47]

The benefits of Ticagrelor compared to clopidogrel in PLATO trial was seen in patients who had an acute coronary syndrome with or without ST elevation. But in this real world study more than 40% of patients were stable angina patients undergoing elective PCI. Thus this may be assuring that even in patients with lesser risk profile Ticagrelor may be a safe option and could be considered in high-risk patients to achieve reliable P2Y12 inhibition.[30]

CONCLUSION

7. CONCLUSION

In our study adherence to Ticagrelor was poor in the 1 year follow up of Acute Coronary Syndrome patients. Premature discontinuation of Ticagrelor in routine clinical practice occurred in patients and was primarily related to adverse effects. The reasons for discontinuation of Ticagrelor were found to be ADRs issues in 43 patients (bleeding) 42 patients (dyspnoea) and 13 patients (bleeding and dyspnoea). Other issues like financial problem leaded to discontinuation in 30 patients. 44 patients strictly adhered to therapy. Because of discontinuation within 1 year 52 patients had clinical untoward events. Medication therapy discontinuation after MI is common and occurs early after discharge. Patients who discontinue taking Ticagrelor are at increased mortality risk. So this study suggested that adherence of medication strictly to be followed to avoid untoward complication of therapy in Acute coronary syndrome.

LIMITATIONS

- Due to short duration the limited number of patients are included
- Medication adherence of Ticagrelor was identified and not for the clopidogrel and prasugrel, because the Ticagrelor was majorly prescribing for ACS patients during discharge.
- The patients was died due to complications may be due to discontinued the Ticagrelor and those Patients was not included in this study
- This results describe a "real-world" scenario, although do not allow to draw any conclusion regarding hard clinical endpoints and also this results represent a single-center experience.

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ANNEXURES

DATA COLLECTION FORM

PATIENT INFORMATION		CONSULTANT:
NAME :	AGE/GENDER:	WARD/ BED NO :
IP/OP NO:	WEIGHT:	DATE OF ADMISSION :
HEIGHT:	BMI:	DATE OF DISCHARGE :

PATIENT COMPLAINTS	
H/O PRESENT ILLNESS	
DIAGNOSIS	
LAB INVESTIGATION	
ECG	

PAST MEDICAL HISTORY	PAST MEDICATION HISTORY/ ALLERGIES

MARRIED	YES	NO	*SMOKER*	YES	NO
OCCUPATION			*ALCOHOLIC*	YES	NO
EDUCATIONAL STATUS			*LIFE STYLE*		
ANGIOGRAPHIC FINDINGS	IF YES-				
PROCEDURE					

CURRENT MEDICATION

MEDICINES (BRAND AND GENERIC NAME)	*DOSE*	*ROUTE*	*FREQUENCY*	*M*	*A*	*N*	*QUANTITY/ DURATION*

DISCHARGE MEDICATION;

MEDICINES WITH BRAND AND GENERIC NAME	*DOSE*	*ROA*	*FREQUENCY*	*M*	*A*	*N*	*DURATION*

DIET	*VEG*	*NON VEG*	*EGGTERIAN*

IF PREMATURE DISCONTINUATION OF TICAGRELOR	**YES**		**NO** (check adherence & other reasons)
REPLACEMENT	WHEN		
	TO WHICH DRUG		
OTHER REASON FOR DISCONTINUATION AND REPLACEMENT (ADR,COST,OTHER)	**ADR**	**OTHERS**	
	Bleeding ☐ ***Dyspnoea*** ☐ ***Headache*** ☐ ***Bradycardia*** ☐ ***Hypotension*** ☐ ***Muscular side effect*** ☐ ***Rash*** ☐ ***Gastrointestional prob*** ☐ ***Other side effect***		

IF ANY COMPLICATIONS (If They Are Discontinued) ( )	
IF ANY COMPLICATIONS (If They Are Not Discontinued) ( )	

ASSESSMENT OF ADHERENCE WITH TICAGRELOR IN ACUTE CORONARY SYNDROME PATIENTS IN TERTIARY CARE HOSPITAL

MEDICATION ADHERENCE SCALE

Patient Name: **No.:**
Gender: **Date:**
Age: **MRN:**

Questions	Yes	No	Score
Do you ever forget to take your medicine?	1	0	
Are you careless at times about taking your medicine?	1	0	
When you feel better do you sometimes stop taking your medicine?	1	0	
Sometimes if you feel worse when you take the medicine, do you stop taking it?	1	0	
Total score			

Yes item	Interpretation
3 or 4	**Low adherence**
1 or 2	**Medium adherence**
0	**High adherence**

Adopted from Morisky DE, Green LW and Levine DM. Concurrent and Predictive Validity of a Self-reported Measure of Medication Adherence. Medical Care 1986;24(1):67-74.