Original Article

Stent Thrombosis Treated With Ticagrelor

Stent Thrombosis in Patients Treated with Ticagrelor in Acute Coronary Syndrome (ACS) Among Pakistani Population

Faisal Ahmed, Rubina Khan, Gul Naz, Chander Parkash, Muhammad Nawaz Khan and Ali Nasir

ABSTRACT

Objective: To observe the stent thrombosis with Ticagrelor and to assess the frequency of main cardiovascular (CV) events (CV death, MI and Stroke) in patients treated with Ticagrelor after PCI (Stenting) during 24 weeks.

Study Design: Observational study

Place and Duration of Study: This study was conducted at the department of Cardiology, Liaquat National Hospital, Karachi from March, 2020 to September, 2020.

Materials and Methods: A total of 320 patients between the age of 18-75 year, presenting with acute coronary syndrome were included for this study. Demographic variables like age and gender were recorded. BMI, clinical features and history of previous diseases were also noted. Ticagrelor (Anplag®)90 mgbd was prescribed to the patients and was followed for 6 months for the occurrence of stent thrombosis, major cardiovascular events and adverse effects of Ticagrelor.

Results: The outcomes of present study showed that there were total 4(1.2%) cases of stent thrombosis.The result in the present study also showed that overall there were 12(3.75%) deaths due to all causes of mortality. The most common adverse effect after taking Ticagrelor within 24-weeks was nausea found in 37(11.6%) and the least common side effect was bleeding in 4 (1.3%) cases. The other side effects including dyspnea and dizziness were also observed in 29(9.1%) and 32(10%) cases respectively.

Conclusion: This study concludes that stent thrombosis is uncommon in a patient who receives anti-platelet therapy with Ticagrelor (Anplag®) 90 mg bd. A major prospective of Ticagrelor is the extra ordinary reduction in death among acute coronary syndrome patients.

Key Words: Stent thrombosis**,** Ticagrelor, Acute Coronary Syndromes

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INTRODUCTION

Acute Coronary Syndrome (ACS) has developed as a valuable operational term that can be defined as a group of conditions compatible with acute myocardial ischemia and/or infarction that are developed due to an immediate decline in coronary blood flow[1].

Globally, the frequency and occurrence of cardiovascular diseases vary depending upon several factors that are socioeconomic status, health care systems, etc. Among cardiovascular diseases, ACS is one of the major reasons of morbidity and mortality[2].

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Recent guiding principles recommend that the patients, who present with ACS, particularly ST segment elevation myocardial infarction (STEMI), must undergo primary percutaneous coronary intervention (PCI) in emergency in order to overcome both mortality and morbidity[3]. Primary PCI has its own complications like other interventional procedures and stent thrombosis is the most important one in which stented vessel becomes occluded completely.

Stent thrombosis is described as an occlusion of a coronary stent by a thrombus. It is associated with stent placement in percutaneous coronary intervention (PCI). High rates of morbidity and mortality occurs due to stent thrombosis, frequently leading to events of cardiac death or nonfatal myocardial infarction (MI)[4,5].

The aim of this study was to access the stent thrombosis with Ticagrelor in terms of, acute (<24 hours), sub-acute (24 hours–30 days) and late (>30 days up to 24 weeks) thrombosis and also to evaluate the incidence of major cardiovascular (CV) events (CV death, MI and Stroke) and adverse effects in patients pretreated with Ticagrelor after PCI (Stenting) during 24 weeks.

MATERIALS AND METHODS

This observational study by using non-probability convenient sampling technique was carried out at Liaquat National Hospital, Karachi. The ethical approval for the study was taken from Institutional Research and Ethical Committee (Ref:0510-2020-LNH-ERC). Duration of the study was 6 months from 15-03-20 to 15-09-20.

In this study, 320 patients presenting with ACS between the ages of 18-75 years, evidence of CAD, a previous history of MI, or previous revascularization with successful percutaneous coronary intervention with a stent after taking Ticagrelor (Anplag®, Pharm Evo Pvt Ltd, Karachi, Pakistan) 90 mg bd were enrolled for this study. Patients were followed for 6 months for the occurrence of stent thrombosis, major cardiovascular events and adverse effects of Ticagrelor. Exclusion criteria for this study were hypersensitivity to any component of Ticagrelor or contraindication for Ticagrelor, congestive heart failure, age ≥ 75 or < 18, pregnancy and breast feeding, limited life expectancy, bad prognosis due to another co-existing disease e.g. malignancy, liver failure or greater than 50 % mortality in next 6 months and having acardiogenic shock. Demographic variables like age and gender were recorded. BMI, clinical features and history of previous diseases were also noted.

The Academic Research Consortium (ARC) guiding principle were published in 2008, described the classifications of stent thrombosis [6]. These classifications were based on the type of underlying placement of stent and timing after initial placement of stent viz; acute, sub-acute and late. Early stent thrombosis can be acute or subacute: If thrombosis occurs within 24 hours of initial placement termed as acute. Sub-acute thrombosis occurs between 24 hours to 30 days after initial placement of stent. Furthermore, late stent thrombosis occurs between 30 days till 24th week of initial placement of stent[7].

Stent thrombosis can be classified into definite, probable, and possible stent thrombosis. Possible stent thrombosis, regarded as with unexplained reason of death in 30 days or later after stent placement. Probable stent thrombosis, regarded as mysterious death within 30 days of stent placement. Definite stent thrombosis in which angiography confirms the presence of stent thrombosis (within the existing stent or within 5 mm proximal or distal to the stent). Ticagrelor, which is classified as the anti-platelet medication, was given to patients with dosage of 90 mg bd.

Data was analyzed by using IBM-SPSS version 23.0. Counts with percentages given for baseline characteristics of studied samples, mean with standard deviation reported for quantitative measurements of samples. Outcomes on stent thrombosis, its risk factors, and major cardiovascular events were also reported with their count and percentages. Descriptive on adverse effects after taking Ticagrelor within 24-week, and compliance of medication were also reported in the tables. Pie diagram was given for graphical presentation of stent thrombosis**.**

RESULTS

Total 320 patients were included in the study after following the inclusion criteria. Table-1 shows the baseline characteristics of the patients. The mean age of samples was 58.41±10.43 years, mean systolic blood pressure was 125.5±17.66mmHg, mean diastolic blood pressure was 75.42±11.05 mmHg.

Table-II shows the co-morbids and clinical features of the patients, 233(72.8%) found with complain of chest pain, or discomfort, which may involve pressure, tightness or fullness, 202(63.1%) found with complain of discomfort in one or both arms, the jaw, neck, back or stomach, 136(42.5%) found with complain of shortness of breath, 19(5.9%) found with feelings of dizziness or lightheaded, 32(10%) found with Nausea, and 31(9.7%) with sweating. There were 224(70%)patients found with hypertension, 165(51.6%) with diabetes, 97(30.3%) with family history of IHD ,116(36.3%) with hyperlipidemia, 197(61.6%) with obesity and 16(5%) with chronic renal failure.

Table No.1: Baseline Characteristics of the patients (n= 320)

Variables		Mean±SD n(%)
Age Group	<50 years	54(16.9%)
	51 - 60 years	135(42.2%)
	61 - 70 years	94(29.4%)
	>70 Years	37(11.6%)
Gender	Male	218(68.1%)
	Female	102(31.9%)
Smoking	Yes	49(15.3%)
	No	271(84.7%)
Age (years)		58.41±10.43
Systolic (mmHg)		125.59±17.66
Diastolic (mmHg)		75.42±11.05
Weight (Kg)		70.28±11.062
Height (m^2)		1.67±0.11
BMI (kg/m^2)		25.61±4.83
Heart rate (b/min)		78.50±11.91

Table 3 reported the frequency of major cardiovascular events in patients treated with Ticagrelor after PCI (stenting) during 24-weeks, incidence of MI was observed in6(1.9%), and stroke was found in 3(0.9%). In the present study, overall there were 12(3.75%) deaths due to all causes of mortality. Out of them, 3(0.9%) were due to stent thrombosis and 9(2.8%) were due to unknown etiology. The adverse effects after taking Ticagrelor within 24-weekswere 4(1.3%)with bleeding, 29(9.1%) with dyspnea, 32(10%) with dizziness, and 37(11.6%) patients with nausea.

Figure I shows the frequency of stent thrombosis. There were total 4 cases of stent thrombosis, with only one case, (0.3%) of acute stent thrombosis classified into definite category, 2 (0.6%) cases of sub-acute stent thrombosis classified into probable category, and 1 (0.3%) case of late stent thrombosis classified into probable category.

Table No.2: Co-morbidities and Clinical features of patients (n=320)

Variable		N	%
Clinical features	Chest pain or discomfort, which may involve pressure, tightness or fullness	233	72.8
	Pain or discomfort in one or both arms, the jaw, neck, back or stomach	202	63.1
	Shortness of breath	136	42.5
	Feeling dizzy or lightheaded	19	5.9
	Nausea	32	10.0
	Sweating	31	9.7
Co morbidities	Hypertension	224	70.0
	Diabetes	165	51.6
	Family history of ihd	97	30.3
	Hyperlipidemia	116	36.3
	Obesity	197	61.6
	Chronic renal failure	16	5.0

Table No.3: Frequency of Major Cardiovascular (CV) Events and adverse effects in Patients treated with Ticagrelor after PCI (Stenting) during 24 Weeks

Variable		N	%
Adverse events	Mi	6	1.9
	Stroke	3	0.9
Adverse effects	Bleeding	4	1.3
	Dyspnea	29	9.1
	Dizziness	32	10.0
	Nausea	37	11.6
Outcomes	Total deaths	12	3.8

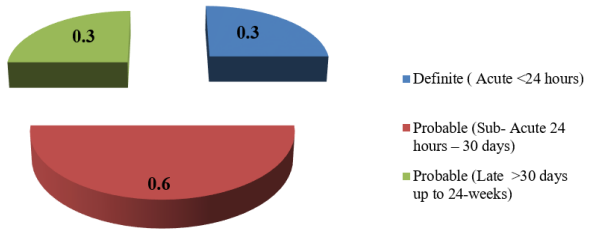

Figure No.I: Frequency of stent thrombosis in patients (n=320)

DISCUSSION

Primary Percutaneous Coronary Intervention (PPCI) is a successful procedure for patients who are suffering from ACS. It decreases the chances of myocardial injury because the infarcted arteries are perfused without any delay. Hence, it reduces the mortality rate and results in better quality of life. A patient of ACS gets advantage from a good pre-treatment before PPCI. The typical analysis is that pre-treated with Ticagrelor can decrease the chances of thrombus formationin ACS patients undergoing PPCI, so resulting in considerably decreased all-cause mortality (8-11).

In our study, the frequency of major adverse events such as MI was 1.9%in patients with coronary artery syndrome. In a research by KimWJ et al. (12) the frequency of major adverse effects was 2% in patients with ischemic heart disease that were vascularized with eluting stents. In another study by Jensen LO et al. (13) the rate of incidence of major adverse events was 10.3% inpatients pretreated with eluting stents. These findings were inconsistent with our result due to the pretreated with Ticagrelor that shows overall3.75% deaths. Myocardial infarction occurred at rate of 1.9% in our observation. In study byJ ensen LO et al. the frequency of myocardial infarction inpatients with ischemic heart disease already treated with eluting stents was 1.9%. In another research by Kalesan B etal. (14) in which patients with acute coronary syndrome vascularized with eluting stents were studied, the frequency of myocardial infarction was 2.1%. In our study 3.75%patients showed CV death, 1.9% shows MI and 0.6% suffered from stroke. Repetition of ischemic condition at follow up is an important incident that needs revascularization of targeted lesion and vessels. In study by KimWJ et al.(12) recurrence of ischemia after revascularization with eluting stents needs to target vesselfor revascularization was 0.7%. In similar study by Jensen LOet al.(13) recurrence of ischemia needing targeted vessel revascularization was 3.1%.

Stent thrombosis is an important reason of morbidity and mortality in patients vascularized with drug eluting stents. In study by KimWJ et al. the rate of occurrence of stent thrombosis including acute, sub-acute and late stent thrombosis was0.7%. In another study Park D Wet al. (15) the frequency of stent thrombosis in patients revascularized with eluting stents was 0.7%. In another study in which patients with acute coronary syndrome were observed, it was 3.8%. In our study it was 1.2% pretreated with Ticagrelor which is almost similar to first two studies.

In another study that has reported the rate of early stent thrombosis (acute or sub-acute) after primary PCI was found to be 5.8%, of which 0.5% was acute and 5.3% were sub-acute (16). But our study showed that the rate of early stent thrombosis (acute or sub-acute) after primary PCI was found to be 0.9%, of which 0.3% was acute and 0.6% was sub-acute and in late stent thrombosis it was 0.3% which was relatively low.

In our study, dyspnea and nausea were more common adverse effects following treatment with Ticagrelor in 9.1% and 11.6% respectively. But occasionally, discontinuation of therapy decreases the persistent

adverse effects. Most observed cases of dyspnea were mild-to-moderate, occurred previously and lasted for few days with Ticagrelor therapy. However, most of the dyspnea-related cases in the study resolved after discontinuation of therapy shows that Ticagrelor-related dyspnea does not causes chronic pulmonary changes.

Finally, our study demonstrated that in 320 patients admitted for ACS, treated with Ticagrelor for 24 weeks resulted in fewer deaths. Moreover, it had proved that treatment with Ticagrelor helps in preventing CV death, MI or stroke[17].

When the effectiveness of Ticagrelor therapy was checked across geographic regions, it had proved that the greater benefits may be achieved with Ticagrelor therapy among various categories of ACS patients. The Ticagrelor benefits remained considerably important as the reduction in the frequency of bleeding was observed in Ticagrelor-treated patients (18).

In fact, different studies proved that clopidogrel, which is a pro-drug with a short-lived active metabolite, had a low potency and a slow onset of action in its biological effects. These limitations were responsible for the adverse effects of ischemic events that is stent thrombosis (19). Hence, Ticagrelor is a faster and more potent $P2Y_{12}$ inhibitor that showed an important clinical benefit in comparison with other drugs like clopidogrel in ACS because there is no need of hepatic biotransformation in order to become active. It is therefore, suggested as a first-line agent in ACS and it can be used safely in high-risk PCI patients with stable angina.

However, the study might not be immune from observer and selection bias. Further studies with larger sample size and probability sampling technique might be helpful to generalize the results in larger population.

CONCLUSION

Our study has predicted that the stent thrombosis is a major complication that is connected with stent placement in percutaneous coronary intervention, which can be reduced if pretreated with Ticagrelor (Anplag®). Ticagrelor is an effective adjunctive pharmacotherapy in both early invasive as well as long-term management of a broad spectrum of Acute Coronary Syndrome patients by reducing the cases of all-cause mortality, stent thrombosis and myocardial infarction without a considerable difference in bleeding events in comparison with other anti-platelet therapy.

Author's Contribution:

Concept & Design of Study:	Faisal Ahmed
Drafting:	Rubina Khan, Gul Naz
Data Analysis:	Chander Parkash, Muhammad Nawaz Khan and Ali Nasir
Revisiting Critically:	Faisal Ahmed, Rubina Khan
Final Approval of version:	Faisal Ahmed

Conflict of Interest: The study has no conflict of interest to declare by any author.

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