



## A CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF TICAGRELOR IN BANGLADESHI PATIENTS WITH ACUTE CORONARY SYNDROME (ACS) UNDERGOING PERCUTANEOUS CORONARY INTERVENTION (PCI) [GLORIOUS TRIAL]

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### ABSTRACT

**Background:** In several clinical trials, Ticagrelor was superior to Clopidogrel in reducing cardiovascular events among patients with Acute Coronary Syndrome (ACS). We evaluated the safety and efficacy of Ticagrelor in Bangladeshi ACS patients undergoing Percutaneous Coronary Intervention (PCI).

**Methods:** Applying the inclusion and exclusion criteria, patients were allocated to Ticagrelor group or Clopidogrel group. After the procedure, the patients were followed up for 12 months. The primary endpoint of efficacy (death, myocardial infarction [MI] and stroke), and safety (bleeding, and dyspnea) were evaluated and compared between the two groups.

**Results:** 163 patients with ACS were recruited and 93 patients were assigned to Ticagrelor group and 70 patients to Clopidogrel group. The primary endpoint occurred in fewer patients in Ticagrelor group than in Clopidogrel group (10% in Clopidogrel and 3.2% in Ticagrelor group;  $p=0.13$ ). There was significant increase in the incidence of bleeding and dyspnea in Ticagrelor group (minor bleeding occurred in 1.4% of patients in Clopidogrel and 5.4% of patients in Ticagrelor group, and dyspnea occurred in 1.4% of patients in the Clopidogrel group and 12.9% of patients in Ticagrelor group;  $p=0.009$ ).

**Conclusion:** Ticagrelor numerically reduced the risk of death in ACS patients undergoing PCI, but the incidence of minor bleeding and dyspnea were significantly more with Ticagrelor compared to Clopidogrel in Bangladeshi patients.

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### INTRODUCTION

Acute coronary syndrome (ACS) refers to a group of clinical conditions which share some common steps in pathogenesis such as rupture of coronary atheromatous plaque, platelet aggregation and thrombosis. Thus, anti-platelet therapy is one of the mainstays in the treatment for ACS.

Second-generation thienopyridines (Clopidogrel and Prasugrel) are widely used antiplatelet therapy. Clopidogrel is converted to its active metabolites which irreversibly inhibit the platelet P2Y<sub>12</sub> adenosine diphosphate receptor<sup>1,2</sup>. So, its onset of action is relatively slow<sup>3</sup>. Furthermore, 30% of patients show drug resistance to Clopidogrel, which can induce a high risk of reinfarction and stent thrombosis<sup>4</sup>. Prasugrel is another antiplatelet with the same mechanism of action as Clopidogrel. Its onset of action is shorter<sup>5</sup>. Furthermore, compared with Clopidogrel, it has greater efficacy and lower variability. However, it increases the risk of bleeding<sup>6-8</sup>. Given the limitations of these two widely used drugs,

additional studies are required in developing efficient new P2Y<sub>12</sub> receptor antagonists. Ticagrelor (AZD6140) is the first reversibly binding oral P2Y<sub>12</sub> receptor antagonist that blocks ADP-induced platelet aggregation<sup>9</sup>. Unlike the thienopyridines, Ticagrelor is not a prodrug and shows rapid onset and offset of action<sup>10</sup>. Furthermore, Ticagrelor has a stronger and less variable effect than Clopidogrel because its direct action does not require catabolite activation<sup>11</sup>.

Among the Non Communicable Diseases (NCDs), Cardiovascular Disease (CVD) is probably the most important cause of mortality and morbidity in Bangladesh. In 2014, NCDs represented 59% of the total deaths; CVD was the single-most important contributor and was responsible for 17% of the deaths<sup>12</sup>. According to the Health Bulletin 2015<sup>13</sup>, CVD and stroke together was the topmost cause of death in Upazila, District and Medical College Hospitals. Recently percutaneous coronary intervention (PCI) has evolved as one of the gold standard in the management of patients with ACS in Bangladesh. Clopidogrel has been used as an adjunctive antiplatelet for PCI in Bangladesh for long. Recently, Ticagrelor has been introduced in Bangladesh. Several clinical studies have shown that Ticagrelor is superior to Clopidogrel

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in reducing myocardial infarction, cardiovascular death and stroke<sup>14</sup>. It may also have reduced incidence of bleeding events compared with Prasugrel<sup>15, 16</sup>. **However**, no such study has yet been done in Bangladesh. As the socio demographic factors, ethnicity and physical factors of patients in Bangladesh are different from the patients of other ethnic origin, we decided to do a clinical trial on this topic in a cardiac center where PCI in ACS patients is done regularly. The results of the study will definitely help us in choosing the best anti platelet for ACS patients undergoing PCI.

## MATERIALS AND METHOD

### Objective

**General:** To assess the efficacy (reduction of death, vascular events) and safety (especially bleeding and dyspnea) of Ticagrelor (AZD6140) compared to Clopidogrel, in Bangladeshi patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI).

**Specific:** To measure and compare the incidence of the following events in both groups

- Any major or minor bleeding event.
- Other side effects e.g., dyspnea, bradycardia.
- Any event from the composite of death from any causes, Myocardial Infarction (MI) and stroke.

## METHODOLOGY

Applying the inclusion and exclusion criteria, 163 consecutive Bangladeshi patients attending AFC Health Fortis Heart Institute with ACS who were planned to undergo PCI between the timeframe of 1<sup>st</sup> June, 2018 to 31<sup>st</sup> May, 2019 were enrolled in a single center, prospective clinical trial.

### Inclusion criteria

- Bangladeshi patients with Acute Coronary Syndrome (ACS)
- Patients undergoing Percutaneous Coronary Intervention (PCI)
- Patients who are given Tablet Ticagrelor (GLORINTA of AFC Pharmaceutical) 180 mg loading followed by 90mg twice daily maintenance dose, or tablet Clopidogrel 300-600 mg loading followed by 75mg daily maintenance dose.
- Patients who are given tablet Aspirin 300mg loading followed by 75mg daily maintenance dose.

### Exclusion criteria

- Patients with a history of intracranial hemorrhage or active pathological bleeding such as peptic ulcer or intracranial hemorrhage.
- Patients with hypersensitivity (e.g., angioedema) to Ticagrelor or Clopidogrel or any component of these products
- Patients taking strong CYP3A inhibitors and strong CYP3A inducers.
- Patients having contraindications to Aspirin
- Patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardia-related syncope and not protected with a pacemaker).
- Patients requiring urgent Coronary Artery Bypass Graft (CABG) surgery

- Patients having acute complication of PCI.

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of our institution (Reference- AFC Health/CUM/2018/0963). The sample size was calculated at 5% level of significance and 80% power using data from PLATO trial.<sup>17</sup> These patients were non randomly allocated to Ticagrelor group [ Tablet Ticagrelor 180 mg loading followed by 90mg twice daily maintenance dose for 12 months ] or Clopidogrel group [ Tablet Clopidogrel 600mg loading followed by 75mg daily maintenance dose for 12 months]. Aspirin was given to all patients according to guideline<sup>18, 19</sup>. There was no blinding. The PCI procedure and post-procedure treatment followed the standard guidelines of European society of cardiology and American College of Cardiology for ACS patients<sup>18, 19</sup>. Study visits were scheduled at 1 month, 3 months, 6 months and 12 months after hospital admission for the recording of first event. Data were collected using a structured questionnaire containing the key variables of interest.

The primary endpoint of efficacy were death, myocardial infarction [MI] and stroke, and safety endpoints were bleeding, and dyspnea. The endpoints were defined by standard operational definitions<sup>20-24</sup> and comparison were made between the two groups. Myocardial infarction was defined according to universal definition<sup>21</sup>. Death included cardiovascular death, non-cardiovascular death and death of undetermined cause<sup>22</sup>. Stroke was defined as disability due to vascular brain injury<sup>23</sup>. Stent thrombosis was defined by the Academic Research Consortium criteria<sup>24</sup>. Major bleeding was defined by fatal or intracranial bleeding, or clinical signs of hemorrhage with decrease in hemoglobin of  $\geq 5$  g/dl, or a fall in hematocrit of 15%<sup>20,21</sup>. Minor Bleeding is the bleeding which is clinically apparent with 3-5 g/dl decrease in hemoglobin<sup>20, 21</sup>.

The Cox proportional hazards model was used to analyze the endpoints. The proportional hazards assumption was assessed with a model of time to event with allocated treatment. All analyses were made by intention to treat, and were done with SAS (version 9.2). A p value of 0.05 was regarded as significant for the overall treatment differences.

## RESULT

163 patients with ACS were recruited for this trial and 93 patients were assigned to Ticagrelor group and 70 patients to Clopidogrel group. The baseline characteristics (age, gender, BMI) of both groups were well balanced. Although there was significant difference in the index diagnosis during hospitalization [ STEMI in 80% of patients in Clopidogrel group and 88% in Ticagrelor group; Non STEMI in 18.6% in Clopidogrel and 5.4% in Ticagrelor group; Unstable Angina in 1.4% in Clopidogrel and 6.5% in Ticagrelor group; p= 0.01], there was no significant variation in the distribution of patients with heart failure and cardiogenic shock, angiographic characteristics, use of anticoagulants during procedure and intake of other guideline-directed medical therapy after procedure- between the two groups. The primary endpoint occurred in fewer patients in Ticagrelor group than in Clopidogrel group (10% in Clopidogrel and 3.2% in Ticagrelor group; p= 0.13). Stent Thrombosis with Myocardial infarction Occurred in 2 patients (2.9%) in Clopidogrel Group. Death from all causes occurred in 5 patients (7.1%) in Clopidogrel and in 3 patients (3.2%) in Ticagrelor group. Overall, patients

with double vessel disease had higher mortality than those with single vessel disease and those with triple vessel disease had higher mortality than patients with double vessel disease. Moreover the patients with heart Failure had higher mortality than those without heart failure.

Logistic Regression shows Ticagrelor reduced the risk of death by 57% compared to Clopidogrel (Odds Ratio = 0.43; p = 0.26). There was significant increase in the incidence of bleeding and dyspnea in Ticagrelor group (minor bleeding occurred in 1.4% of patients in Clopidogrel and 5.4% of patients in Ticagrelor group, and dyspnea occurred in 1.4% of patients in the Clopidogrel group and 12.9% of patients in Ticagrelor group; p= 0.009). There was no incidence of major bleeding in any of the groups. Discontinuation of study drug because of dyspnea occurred in 2 (2.1 %) patients in the Ticagrelor group.

**Table 1** Baseline characteristics of the patients

Variables	Clopidogrel	Ticagrelor	p
Age (years)	57.37±11.79	56.32±9.87	0.54
Follow up days	343.07±80.38	347.33±62.38	0.70
<b>Gender</b>			
Male	58 (82.9)	81 (87.1)	0.45
Female	12 (17.1)	12 (12.9)	
<b>BMI</b>			
Normal	50 (71.4)	66 (71.0)	0.31
Overweight	20 (28.6)	24 (25.8)	
Obese	0	3 (3.2)	

Table 1 shows the baseline characteristics did not differ among the two groups of patients. We can see that the patients were almost homogeneous in terms of age and follow up days, though Ticagrelor group had a higher follow up days indicating its superiority over Clopidogrel. There was no difference in gender, BMI between the two groups of patients.

**Table 2** Clinical characteristics and diagnosis of patients

Variables	Clopidogrel	Ticagrelor	Total	p
<b>Diagnosis</b>				
STEMI	56 (80.0)	82 (88.2)	138 (84.7)	
Non STEMI	13 (18.6)	5 (5.4)	18 (11.0)	0.01
Unstable Angina	1 (1.4)	6 (6.5)	7 (4.3)	
Total	70	93	163	
<b>PCI type</b>				
Primary	52 (74.3)	61 (65.6)	113 (69.3)	
Phar. invasive	0	5 (5.4)	5 (3.1)	0.02
Rescue PCI	5 (7.1)	17 (18.3)	22 (13.5)	
Early invasive	13 (18.6)	10 (10.8)	23 (14.1)	
Total	70	93	163	
<b>Heart failure</b>				
No	60 (85.7)	83 (89.2)	143 (87.7)	
Yes	10 (14.3)	10 (10.8)	20 (12.3)	0.50
Total	70	93	163	
<b>Cardiogenic shock</b>				
No	67 (95.7)	89 (95.7)	156 (95.7)	0.97
Yes	3 (4.3)	4 (4.3)	7 (4.3)	
Total	70	93	163	

Table 2 shows a significant difference was found between the diagnosis and intervention type. STEMI was more in Ticagrelor group, non STEMI was more in Clopidogrel group while Unstable angina was more in Ticagrelor group compared to its counterpart (p=0.01). Therefore, the type of intervention was significantly different among the two groups. There was no significant difference in the incidence of Heart Failure and cardiogenic shock between the two groups.

**Table 3** Angiographic and Percutaneous Coronary Intervention (PCI) characteristics of the patients

Variables	Clopidogrel	Ticagrelor	Total	p
<b>Coronary angiogram</b>				
Single vessel	28 (40.0)	40 (43.0)	68 (41.7)	
Double vessels	25 (35.7)	35 (37.6)	60 (36.8)	0.75
Triple vessels	17 (24.3)	18 (19.4)	35 (21.5)	
Total	70	93	163	
<b>Stent number</b>				
Single	47 (67.1)	66 (71.0)	113 (69.3)	
Double	20 (28.6)	20 (21.5)	40 (24.5)	0.65
Triple	2 (2.9)	4 (4.3)	6 (3.7)	
No	1 (1.4)	3 (3.2)	4 (2.5)	
Total	70	93	163	

Table 3 shows there was no significant difference in the diagnosis of coronary angiogram between the two groups. Also, there was no significant difference in the number of stents used among the two groups.

**Table 4** Primary efficacy endpoints in both groups

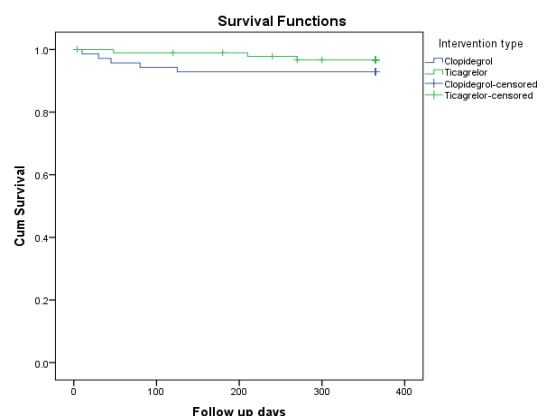
Efficacy endpoint	Clopidogrel	Ticagrelor	Total	p
No event	63 (90.0)	90 (96.8)	153 (93.9)	
Stent thrombosis	2 (2.9)	0	2 (1.2)	0.13
Death	5 (7.1)	3 (3.2)	8 (4.9)	
Total	70	93	163	

Table 4 shows stent Thrombosis with Myocardial infarction Occurred in 2 patients (2.9%) in Clopidogrel Group. Death from all causes occurred in 5 patients (7.1%) in Clopidogrel and in 3 patients (3.2%) in Ticagrelor group.

**Table 5** Primary safety endpoints in both groups

Safety endpoint	Clopidogrel	Ticagrelor	Total	p
No problem	68 (97.1)	76 (81.7)	142 (87.1)	
Minor Bleeding	1 (1.4)	5 (5.4)	6 (3.7)	0.009
Dyspnea	1 (1.4)	12 (12.9)	15 (9.2)	
Total	70	93	163	

Table 5 reveals the occurrence of minor bleeding and dyspnea were significantly higher in Ticagrelor group than Clopidogrel group (5.4% vs. 1.4% for Bleeding and 12.9% vs. 1.4% for Dyspnea; p = 0.009). There was no incidence of major bleeding in any of the groups. Discontinuation of study drug because of dyspnea occurred in 2 (2.1 %) patients in the Ticagrelor group.



**Figure 1** Kaplan-Meier estimates of survival during 360 days in patients given Ticagrelor versus Clopidogrel. Overall, the patients with Ticagrelor group had higher survival rate than those in Clopidogrel group.

## DISCUSSION

GLORIOUS trial showed that treatment with Ticagrelor as compared to Clopidogrel reduced the rate of death in patients with acute coronary syndrome (7.1% in Clopidogrel vs. 3.2% in Ticagrelor group). This beneficial effect occurred without any increase in major bleeding. Previous trials have shown benefits of Clopidogrel in Acute Coronary Syndrome<sup>25, 26, 27, 28</sup>. Thus, Ticagrelor will expand on the previously demonstrated benefits of Clopidogrel in ACS. The reduction in mortality with Ticagrelor in this trial was not statistically significant. This may be due to small sample size that we worked with. Even the absence of randomization may have played a role for this non significance.

The increased reduction of coronary thrombotic events (i.e., stent thrombosis in 2.9% patients in Clopidogrel vs. 0% in Ticagrelor group) through more effective P2Y<sub>12</sub> inhibition with Ticagrelor is consistent with similar effects of Prasugrel in the TRITON-TIMI 38 trial<sup>8</sup> and of Ticagrelor in the PLATO trial<sup>17</sup>.

Compared with Clopidogrel, treatment with Ticagrelor was associated with an absolute reduction of 3.9 % and a relative reduction of 57% in the rate of death from any cause at 1 year. This survival benefit from more effective platelet inhibition with Ticagrelor is consistent with reductions in the mortality rate obtained by platelet inhibition with Ticagrelor in patients with ACS<sup>17</sup>, with aspirin in patients who had ACS<sup>29, 30</sup> and with Clopidogrel in patients who had STEMI<sup>31</sup>. In contrast, other trials on ACS have not shown significant reductions in mortality rate with Clopidogrel<sup>25</sup>, Prasugrel<sup>32</sup> or glycoprotein IIb/IIIa inhibitors<sup>33</sup>. The increased survival rate with Ticagrelor might be due to the decrease in the risk of thrombotic events without an increase in the risk of major bleeding, as seen with other antithrombotic treatments in patients with ACS<sup>10, 34, 35</sup>.

Since P2Y<sub>12</sub> inhibition with Ticagrelor is reversible, the antiplatelet effect decreases more rapidly than with thienopyridines which are irreversible P2Y<sub>12</sub> inhibitors. Therefore, less procedure related bleeding is expected. The more intense platelet inhibition with Ticagrelor was not associated with an increase in the rate of any major bleeding in GLORIOUS trial. As with Prasugrel<sup>10</sup>, which is a more potent platelet inhibitor than Clopidogrel but is irreversible, there was more minor bleeding with Ticagrelor than with Clopidogrel (5.4% patients in Ticagrelor vs. 1.4% patients in Clopidogrel group). Dyspnea occurred more frequently with Ticagrelor (12.9%) than with Clopidogrel (1.4%). Most of the dyspnea episodes lasted less than a week. Discontinuation of study drug because of dyspnea occurred in 2 (2.1 %) patients in the Ticagrelor group. The occurrence of minor bleeding and dyspnea in this trial was consistent with those found in the PLATO trial<sup>17</sup>. No incidence of major bleeding was reported in any of the groups. The difference of socio demographic factors, ethnicity, genetic and physical factors of patients in Bangladesh from the patients of other ethnic origin might explain the absence of any major bleeding in our study.

## CONCLUSION

In patients with ACS in Bangladesh, treatment with Ticagrelor as compared with Clopidogrel reduced the rate of death, MI without an increase in the rate of major bleeding but with an

increase in the rate of minor bleeding. This is the first clinical trial in Bangladesh to evaluate the effects of Ticagrelor. The results of the study will help us in choosing the best anti platelet for ACS patients undergoing PCI and will open the scope of future larger trials of this first reversible P2Y<sub>12</sub> receptor antagonist.

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