

## Dyspnea in Post Percutaneous Transluminal Coronary Angioplasty (PTCA) Patients on Dual Antiplatelets in a Tertiary Care Hospital in South India

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### Abstract

**Background:** For post Percutaneous Transluminal Coronary Angioplasty for Acute Coronary Syndromes, Dual Antiplatelet Therapy with Aspirin and a P2Y<sub>12</sub> receptor inhibitor like Ticagrelor or Clopidogrel is required minimum for a period of 12 months. There are few studies which have shown the incidence of dyspnea in patients receiving antiplatelet therapy.

**Methods:** In this retrospective, single centre, cohort study, patients who underwent PTCA and were on dual antiplatelets were randomly selected from the clopidogrel and ticagrelor group between July 2013 and June 2014. Patient's relevant data were collected from electronic medical records and cross checked with manually maintained medical records wherever necessary. The study endpoint was incidence of dyspnoea within a follow up period of 9 months.

**Results:** Among the 100 patients started on dual antiplatelet therapy with aspirin and ticagrelor, dyspnea occurred in 10% patients. Ticagrelor was substituted with clopidogrel in 60% cases. In 100 patients on clopidogrel, dyspnea occurred in 5% of patients, but clopidogrel was continued in all cases. Onset of dyspnea in patients on Ticagrelor occurred in 50% of patients in the first month of follow up, 10% cases at 3 months, 30% cases at 6 months and 10% cases at 9 months. But in clopidogrel group dyspnea occurred in 40% cases at 6 months follow up and 60% cases at 9 months. The p value on comparison of dyspnoea among the two groups was found to be 0.283, which was not statistically significant probably due to less sample population.

**Conclusion:** Risk for dyspnoea induced by Ticagrelor was found to be higher than with Clopidogrel in the same ethnic groups when used as dual antiplatelet along with Aspirin. So it may not be a class effect or due to P2Y<sub>12</sub> receptor inhibitory action alone.

### Introduction

A huge population worldwide undergo Percutaneous Transluminal Coronary Angioplasty (PTCA) every year for the treatment of Acute Coronary Syndrome (ACS). These patients require Dual Antiplatelet Therapy (DAPT) with a P<sub>2</sub>Y<sub>12</sub> receptor inhibitor like ticagrelor or clopidogrel in combination with aspirin (a cyclooxygenase inhibitor) for 1 year after PTCA. Antiplatelet drugs are those drugs which prevents the blood platelets from sticking together and forming a blood clot. DAPT is important for preventing stent thrombosis and also the recurrence of ACS events [1-3].

Aspirin is an irreversible inhibitor of Cyclooxygenase 1 and 2 (COX-1 and 2) enzymes by acetylation resulting in reduced formation of prostaglandin precursors thereby inhibiting platelet dependent prostaglandin derivative thromboxane A<sub>2</sub> formation and thus platelet aggregation [4]. Clopidogrel, a thienopyridine irreversibly inhibits the binding of ADP to its receptor on platelets which prevents the activation of GP IIb/IIIa receptor complex and thereby inhibits platelet aggregation [5]. Ticagrelor, a Cyclopentyltriazolopyrimidine (CPTP) antiplatelet, was approved by FDA in July 2011 for the treatment of patients with ACS [6,7]. It non competitively and reversibly binds to the ADP P<sub>2</sub>Y<sub>12</sub> receptor on the platelet surface and prevents the ADP mediated activation of GP IIb/IIIa receptor complex and reduces platelet aggregation [8]. There are mainly three main advantages of ticagrelor over traditionally used antiplatelets like clopidogrel and prasugrel. It includes (i) Ticagrelor does not require metabolic activation as it is not a prodrug, (ii) It binds reversibly to platelet P<sub>2</sub>Y<sub>12</sub> receptor and (iii) it binds to a different receptor site than clopidogrel and prasugrel [9-12].

According to PLATO (Platelet Inhibition and Patient Outcomes) trial dyspnoea and ventricular pauses are the most frequent adverse reactions associated with ticagrelor [13]. Many studies shown that ticagrelor induced dyspnea is not related to previous history of Congestive Heart Failure (CHF), Chronic Obstructive Pulmonary Disease (COPD), asthma or any other causes of dyspnea [14-16]. In PLATO pulmonary function substudy it was concluded that ticagrelor had no effect on pulmonary function in patients with ACS [17].

There are many hypotheses supporting dyspnoea related to ticagrelor. Ticagrelor inhibits the reuptake of adenosine by inhibition of a sodium independent equilibrative nucleoside transporter mainly ENT 1 and it also induces release of Adenosine Triphosphate (ATP) from human RBCs in a dose dependent fashion thus increasing adenosine levels. Increased adenosine levels can cause dyspnoea by activation of vagal-C fibres. This combined effect of ticagrelor on both adenosine reuptake and ATP release results in induction of dyspnoea

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[18]. Another hypothesis is that ticagrelor induced dyspnoea is mediated by inhibition of P<sub>2</sub>Y<sub>12</sub> receptors. P<sub>2</sub>Y<sub>12</sub> receptors are expressed in neuronal tissues to inhibit neuronal signalling. So, by inhibition of P<sub>2</sub>Y<sub>12</sub> receptor, there will be increase in neuronal signalling and thereby dyspnoea sensation [15,19,20].

## Methods

It was a retrospective single-centre cohort study. The patients who underwent PTCA between July 2013 and June 2014 and on treatment with dual antiplatelets consisting of aspirin (75 mg once daily) and ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily) were selected for the study. Patients were strictly selected from Indian population approaching the study centre, a tertiary care teaching hospital. 100 patients each were randomly selected from the clopidogrel and ticagrelor group using SPSS software version 17.0. Patients who did not have complete medical data availability were excluded from the study. The patient's data including demographic details and pertinent laboratory values were obtained from the automated data base, medical records of the patients as well as direct telephonic interview of the patient and/or care giver wherever necessary. 9 months follow up was carried out and the endpoint of the study was occurrence of dyspnea. Chi square test was used to determine the statistical significance of the study.

## Results

During our study period, 100 patients within the age range of 59.69 ± 10.7 years were started on dual antiplatelet therapy with ticagrelor and aspirin and 100 patients with age range of 62.38 ± 10.1 years were started on clopidogrel and aspirin. In the ticagrelor group, 12% were female, 60% had systemic hypertension, 63% had diabetes mellitus, 73% had dyslipidemia, 6% had bronchial asthma or Chronic Obstructive Pulmonary Disease (COPD) as comorbidity 16% had a social history of smoking. In the clopidogrel group, 17% were female, 60% had systemic hypertension, 53% had diabetes mellitus, 77% had dyslipidemia, 10% had bronchial asthma or Chronic Obstructive Pulmonary Disease (COPD) as comorbidity 23% had a social history of smoking (Table 1). There was regular follow up conducted for these patients at 1 month, 3 months, 6 months and 9 months.

Ticagrelor related dyspnoea occurred in 10% patients. Clinical examination was unrevealing and BNP was normal in patients who developed dyspnoea on ticagrelor. Ticagrelor was stopped in about 60% cases among these patients and were started on clopidogrel, following which their condition improved (Figure 1). In the remaining 40% cases, dyspnoea improved with time in patients who did not have a history of COPD or asthma and dyspnoea improved on treatment with Salmeterol and fluticasone MDI who had a history of COPD or asthma and so ticagrelor was continued throughout the study period. Among the 10 patients with dyspnoea, 2 patients had history of COPD, 1 patient had history of bronchial asthma and 3 patients had social history of smoking. When we analyzed the time of onset of dyspnoea we found that 50% of patients had complaints of dyspnoea at 1 month follow up, 10% patients at 3 months follow up, 30% patients at 6 months follow up and 10% patients at 9 months follow up (Figure 2). Among patients who developed dyspnoea, 4 patients were below mean age and 6 were above mean age.

Dyspnea occurred in 5% of patients on treatment with clopidogrel, but the study drug was not discontinued for any patients (Figure 1). Among the patients with dyspnoea, 1 patient had social history of

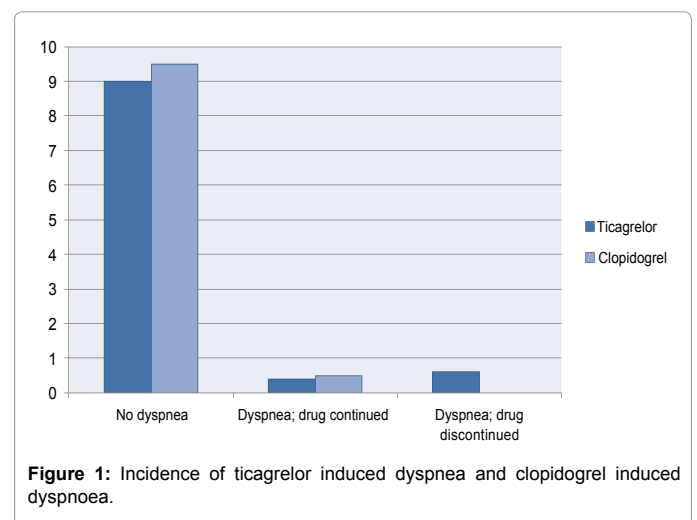
smoking. When we analyzed the time of onset of dyspnea we found that 40% patients at 6 months follow up and 60% patients at 9 months follow up (Figure 2). Among patients who developed dyspnoea, 3 patients were below mean age and 2 were above mean age.

The p value on comparison of dyspnoea among the two groups was found to be 0.283, which was not statistically significant probably due to less sample population.

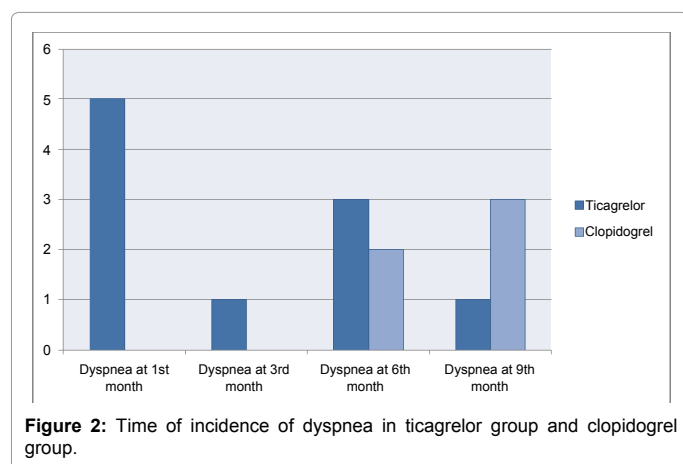
There were 84 patients with Drug Eluting Stents (DES), 3 patients with Bare Metal Stents (BMS), 2 patients with Plain Old Balloon Angioplasty (POBA), 1 patient with combination of DES and BMS and 10 patients with combination of DES and POBA in the ticagrelor group. There were 92 patients with Drug Eluting Stents (DES), 2 patients with Bare Metal Stents (BMS), 1 patient with Plain Old Balloon Angioplasty (POBA), 5 patients with combination of DES and POBA in the clopidogrel group (Table 1).

Characteristic	Number of patients	
	Ticagrelor gp (n=100)	Clopidogrel gp (n=100)
Mean age	59.69 ± 10.7 years	62.38 ± 10.1 years
Female sex	12 (12%)	17 (17%)
Alcohol use	9 (9%)	19 (19%)
<b>Comorbidities</b>		
Systemic hypertension	60 (60%)	60 (60%)
Diabetes mellitus	63 (63%)	53 (53%)
Dyslipidemia	73 (73%)	77 (77%)
<b>Risk factors for dyspnea</b>		
Smoker	16 (16%)	23 (23%)
Bronchial asthma	3 (3%)	4 (4%)
COPD	3 (3%)	6 (6%)
<b>Stent specifications</b>		
DES	84	92
BMS	3	2
POBA	2	1
DES and BMS	1	0
DES and POBA	10	5
<b>Concomitant medications administered</b>		
Nitrates	38 (38%)	40 (40%)
Beta blockers	94 (94%)	96 (96%)
ACE inhibitors	11 (11%)	8 (8%)
ARB	27 (27%)	30 (30%)
Calcium Channel blocker	11 (11%)	8 (8%)
Statins	100 (100%)	100 (100%)

**Table 1:** Demographic and baseline characteristics of patients in the study group.



**Figure 1:** Incidence of ticagrelor induced dyspnea and clopidogrel induced dyspnoea.



## Discussion

Several studies have reported the occurrence of dyspnea on treatment with ticagrelor in Acute Coronary Syndrome (ACS) patients. In the PLATO trial, 13.8% patients developed dyspnea on treatment with ticagrelor but only 0.9% patients had to discontinue the drug [13]. In a study conducted in North Indian population in two institutions GGS Medical College, Faridkot and Fortis Escorts Heart Institute and Research Centre, New Delhi by Sandhu et al., 18.7% patients developed dyspnea on treatment with ticagrelor where 12% patients had to discontinue the drug [20]. In a study by Storey et al., in multiple centres across U.S. and U.K., 24.6% patients developed dyspnea on treatment with ticagrelor but only 5.2% patients had to discontinue the drug [16]. In a study by Gaubert et al. in France, 55.6% patients developed dyspnea on treatment with ticagrelor where 16.7% had to discontinue the drug [21]. In our study 10% patients developed dyspnea on treatment with ticagrelor but only 6% of patients discontinued the drug. Among them (n=10) 50% of patients developed dyspnea within first month of therapy. Dyspnea developed in 5% of patients treated with clopidogrel, but no patients underwent discontinuation of the study drug.

Some studies are in process which is designed to identify the exact mechanism of dyspnea induced by ticagrelor. Several other studies evaluate dyspnea management using caffeine and other xanthine derivatives that are adenosine inhibitors considering the adenosine related hypothesis in development of dyspnea. According to some data available currently, discontinuation of ticagrelor is considered only if dyspnea is intolerable or persistent whereas the drug is continued if dyspnea is mild and tolerable. The same treatment approach is followed in this study, also bronchodilator MDI treatment was provided for patients already with a history of COPD or bronchial asthma [16,17].

There was a 6% absolute increase in the incidence of dyspnea in ticagrelor group compared to clopidogrel group according to PLATO trial but in a study by Storey et al., there was a 20.9% absolute increase in dyspnea incidence in ticagrelor group compared to clopidogrel group [13,16]. A study by Serebruany et al., concluded that the reversible antiplatelet agents (ticagrelor, elinogrel and cangrelor) causes excess dyspnea compared to irreversible antiplatelet agents (clopidogrel/placebo). After intravenous administration of Cangrelor, the risk of dyspnea development was much smaller (<2%) compared to other reversible antiplatelet agents like ticagrelor or elinogrel [22]. In our study there was a 5% increased incidence of dyspnea in Ticagrelor

group compared to clopidogrel group.

Prevention of Cardiovascular Events in Patients with Prior Heart Attack using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial evaluated two doses of Ticagrelor 90 mg and 60 mg twice daily in patients who received low dose aspirin. Results shown that dyspnea was more frequent with 90 mg twice daily ticagrelor (18.93%) than 60 mg twice daily ticagrelor (15.84%). Rates of discontinuation of drug due to dyspnea were 6.5% in 90 mg group and 4.55% in 60 mg group. Hence ticagrelor induced dyspnea is dose related [23]. But in our study all patients received ticagrelor 90 mg only.

There are documents suggesting that ticagrelor does not cause dyspnea by inducing any changes in pulmonary or cardiac function in patients with Stable CAD or ACS. In our study history was collected from all patients who developed dyspnea on treatment with ticagrelor to assess whether patients had dyspnea or history of any other respiratory illness like COPD, bronchial asthma [16].

The study could not give a statistically significant result as the sample population was less. The study has to be conducted in a larger population to get a statistically significant result.

## Conclusion

The risk for Dyspnea induced by ticagrelor was found to be higher than with clopidogrel and prasugrel in the same ethnic groups when used as dual antiplatelet drug along with aspirin. So it may not be due to P2Y12 receptor inhibitory action alone or a class effect. As it was a retrospective study and same dosage schedule was followed for all patients further studies are required to find out whether dosage de-escalation reduces incidence of dyspnea in this ethnic group.

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