Pulmonary Function Tests in Patients on Ticagrelor and Clopidogrel: A Comparative Study

Authors

Abhinav Chhabra1, Prashant Udgire2
1 Resident, DM Cardiology, 2 Associate Professor
Department of Cardiology, MGM Medical College & Hospital, Aurangabad, Maharashtra
*Corresponding Author
Abhinav Chhabra
Resident, DM Cardiology, Department of Cardiology, MGM Medical College & Hospital, Aurangabad, Maharashtra (431003), India

Abstract

Introduction: Acute coronary syndrome (ACS) can be defined as any group of clinical symptoms consistent with acute myocardial ischemia. This may include unstable angina (UA), non—ST-segment elevation and ST-segment elevation myocardial infarction. Antiplatelet therapy is an essential part of management of patients with acute coronary syndrome and may consist of aspirin (irreversibly inhibiting cyclooxygenase 1), clopidogrel (P2Y12 adenosine diphosphate receptor blocker), newer P2Y12 ADP Inhibitors (Prasugrel & Ticagrelor) and GP IIb/IIIa Inhibitors. There are studies which have reported that there is increased risk of dyspnea in patients of acute coronary syndrome who have been on Ticagrelor (The Platelet Inhibition and Patient Outcomes (PLATO) trial) due to which Ticagrelor was being avoided in patients who had history of COPD. We conducted this comparative study to compare effects of Ticagrelor and clopidogrel on pulmonary functions of patients with CAD.

Materials and Methods: This was a comparative study which a total 120 patients with acute coronary syndrome were enrolled depending upon a predefined inclusion and exclusion criteria. The study was conducted in the department of medicine in a tertiary care medical college. A detailed clinical history was taken and through clinical examination was done in all the cases. Demographic details were noted in all the cases. Out of these total 120 patients 60 patients each were randomized to ticagrelor (90 mg twice daily) (Group A) and clopidogrel (75 mg once daily) (Group B). After a continuous therapy of 1-month pulmonary function tests (Pulse oximetry (SpO2), spirometry FEV1, FVC, FEF25-75) were repeated. Pulmonary function tests in Group A and Group B were compared. For statistical purposes P value less than 0.05 was taken as statistically significant.

Results: Out of 120 patients there were 80 (66.67%) males and 40 (33.33%) females with a M:F ratio of 1:0.5. The gender difference in both the groups was statistically not significant (P>0.05). The mean age of the patients in group A and group B was found to be 61.56 +/- 3.98 and 62.41 +/- 3.40 respectively. Hypertension, dyslipidemia and diabetes mellitus were the most common co-morbid conditions in patients with CAD. Mean FEV1 values, FEV1/FVC ratio, FEF25-75 % and SPO2 levels were found to be comparable in both the groups with no statistically significant difference.

Conclusion: Ticagrelor does not appear to be any adverse effect on pulmonary function tests as compared to clopidogrel in patients with CAD and hence appears to be preferable as compared to clopidogrel due to considerable reduction in cardiovascular death, myocardial infarction and stroke.

Keywords: Coronary Artery Disease, Ticagrelor, Clopidogrel, Pulmonary Function Test.
Introduction
Acute coronary syndrome (ACS) can be defined as any group of clinical symptoms consistent with acute myocardial ischemia. This may include unstable angina (UA), non—ST-segment elevation and ST-segment elevation myocardial infarction. Management of acute coronary syndrome may consist of antiplatelet therapy, angiography and further interventions depending upon the findings of angiography. Antiplatelet therapy is an essential part of management of patients with acute coronary syndrome and may consist of aspirin (irreversibly inhibiting cyclooxygenase 1), clopidogrel (P2Y12 adenosine diphosphate receptor blocker), newer P2Y12 ADP Inhibitors (Prasugrel & Ticagrelor) and GP IIb/IIIa Inhibitors. Choosing antiplatelet therapy for a particular patient is a crucial decision for treating cardiologist keeping in mind patient profile, presence of co-morbidities such as diabetes, hypertension and chronic obstructive pulmonary disease.

Its common for patients who have been diagnosed with acute coronary syndrome to have other co-morbidities such as diabetes, hypertension and chronic obstructive pulmonary disease. Moreover, patients with COPD are at an increased risk of acute coronary syndrome because of risk factors which are common for COPD as well as acute coronary syndrome such as smoking, increasing age and obesity. Shared risk factors are not the only cause of increased risk of acute coronary syndrome in patients with COPD but also there are studies which have showed that the COPD is an independent risk factor for adverse cardiac events such as acute coronary syndrome, unstable angina and even sudden cardiac arrests have been reported in patients with COPD. Moreover, even in properly treated patients with acute coronary syndrome presence of COPD is found to be an independent risk factor for recurrent ischemic events and mortality.

Given the high chances of COPD in patients with acute coronary syndrome effect of therapy on lung function becomes one of the important considerations while selecting antiplatelet therapy. Many randomized controlled trials have reported that newer P2Y12 ADP Inhibitors (Prasugrel & Ticagrelor) have a better safety profile, superior efficacy and overall reduced mortality rates as compared to clopidogrel (P2Y12 adenosine diphosphate receptor blocker) in patients with acute coronary syndrome. Moreover, Ticagrelor is found to have better safety profile in patients with various co-morbidities including diabetes, hypertension and Renal Failure. There are studies which have reported that there is increased risk of dyspnea in patients of acute coronary syndrome who have been on Ticagrelor (The Platelet Inhibition and Patient Outcomes (PLATO) trial) due to which Ticagrelor was being avoided in patients who had history of COPD. However, some other studies have supported the use of Ticagrelor in patients with acute coronary syndrome and concomitant COPD since Ticagrelor reduces the prevalence of inflammatory reactions and stabilize functions of endothelium thereby substantially decreasing risk of ischemic events without increase in overall risk of major bleeding events.

Since there were conflicting reports about suitability of Ticagrelor in patients with acute coronary syndrome and concomitant chronic obstructive airway disease and incidence of dyspnea we decided to undertake this comparative study of pulmonary function tests in patients with acute coronary syndrome treated by Ticagrelor and Clopidogrel.

Materials and Methods
This was a prospective comparative study in which a total 120 patients with acute coronary syndrome were enrolled depending upon a predefined inclusion and exclusion criteria. The study was conducted in the department of medicine in a tertiary care medical college. Institutional ethical committee approved the study and an informed written consent was obtained from all the patients enrolled in this study. A detailed clinical history was taken and through
clinical examination was done in all the cases. Demographic details were noted in all the cases. Age, gender, presence of co-morbidities and body mass index of all the patients were noted. Tobacco use, smoking or any other habit was noted. History of any significant pulmonary pathology in past was asked for and noted. History of kochs or kochs contact was also noted. Complete blood count, lipid profile, liver function and renal function tests were done in all the cases. Pulmonary function tests (Pulse oximetry (SpO2), spirometry FEV1, FVC, FEF25-75), lung volumes (TLC, FRC, RV)) were also done before beginning of the antiplatelet therapy. The study included a total of 120 patients after excluding the patients who had any factor related to exclusion criteria. Out of these total 120 patients 60 patients each were randomized to ticagrelor (90 mg twice daily) (Group A) and clopidogrel (75 mg once daily) (Group B). After a continuous therapy of 1-month pulmonary function tests (Pulse oximetry (SpO2), spirometry FEV1, FVC, FEF25-75) were repeated. Pulmonary function tests in Group A and Group B were compared. The statistical analysis was done using SSPE 21.0 software and for statistical purposes P value less than 0.05 was taken as statistically significant. Microsoft office was used for preparation of charts and graphs.

Results
This was a prospective comparative study of 120 patients admitted with acute coronary syndrome. Out of these total 120 patients 60 patients each were randomized to ticagrelor (90 mg twice daily) (Group A) and clopidogrel (75 mg once daily) (Group B). In group A there were 39 (65%) males and 21 (35%) females whereas in group B there were 41 (68.33%) males and 19 (31.67%) females. Overall out of 120 patients there were 80 (66.67%) males and 40 (33.33%) females with a M:F ratio of 1:0.5. The gender difference in both the groups was statistically not significant (P>0.05)

Table 1: Gender Distribution in the studied cases

| Gender Distribution | Group A | Group B |
|---------------------|---------|---------|
| Males               | 39      | 41      |
| Females             | 21      | 19      |
| Total               | 60      | 60      |
| P > 0.05 (Not Significant) | | |

The analysis of age groups of the patients showed that in both the groups most of the patients were between the age group of 61-65 years (51.67% (Group A) and 58.33% (Group B)) followed by 66-70 years (20% (Group A) and 21.67% (Group B)) and 55-60 years (18.33% (Group A) and 15.00% (Group B)). Only 9 (7.5%) patients were below the age of 55 years. The mean age of the patients in group A and group B was found to be 61.56 +/- 3.98 and 62.41 +/- 3.40 respectively. Mean age of the patients in both the groups was found to be comparable and there was no statistically significant difference in mean ages of both the groups (P>0.05).

Table 2: Age groups of the studied cases

| Age Groups of the cases | Group A | Group B |
|-------------------------|---------|---------|
| < 55 years              | 6       | 3       |
| 55-60 years             | 11      | 9       |
| 61-65 years             | 31      | 35      |
| 66-70 years             | 12      | 13      |
| Total                   | 60      | 60      |
| Mean Age                | 61.56 +/- 3.98 | 62.41 +/- 3.40 |
| P =0.210 (Not Significant) | | |
The analysis of body mass index of the studied cases showed that in group A majority of the patients (55%) were overweight (BMI = 25 but < 30) whereas 15 (25%) were obese (BMI =/> 30). 12 (30%) patients were having normal BMI (< 25). In group B normal BMI, overweight and obesity was seen in 9 (15%), 12 (20%) and 39 (65%) patients respectively.

![BMI Of Studied Cases](image1)

**Figure 1:** BMI of the studied cases

The analysis of patients on the basis of presence of co-morbid conditions showed that in group A out of 60 patients 40 (66.67%) patients had hypertension. Other co-morbid conditions included dyslipidemia 36 (60.00%), diabetes mellitus 22(36.67%), chronic renal diseases 5(8.33%) and peripheral artery disease 3(5.00%). In group B hypertension, dyslipidemia, diabetes mellitus, chronic renal disease and peripheral artery disease was present in 35 (58.33%), 32 (53.33%), 24 (40.00%), 4 (6.67%) and 2 (3.33%) patients respectively.

![Co-Morbid Conditions](image2)

**Figure 2:** Co-Morbid Conditions in the studied cases

Patients either received ticagrelor (90 mg twice daily) (Group A) or clopidogrel (75 mg once daily) (Group B). Before beginning of therapy pulmonary function tests were done and after 30 days’ continuous therapy pulmonary function tests were repeated. Comparison of pulmonary functions in both the groups was done. The analysis of forced expiratory volume in 1 second (FEV1) was done in both the cases. The mean FEV1 in group A and B was found to be 2.69 +/- 0.68 and 2.63 +/- 0.56 respectively. Mean FEV1 values were found to be comparable in both the groups and there was no statistically significant difference in FEV1 of both the groups.

**Table 3:** Mean FEV1 in studied cases.

|          | Mean FEV1 (Liters) | Std Deviation |
|----------|--------------------|---------------|
| Group A  | 2.69               | 0.68          |
| Group B  | 2.63               | 0.56          |

*P = 0.598 (Not Significant)*

The analysis of FEV1/FVC ratio showed that it was 71 +/- 5.6 % and 72 +/- 4.8% in group A and group B respectively. The FEV1/FVC ratio were found to be comparable in both the groups and there was no statistically significant difference (P=0.29)

**Table 4:** Mean FEV1/FVC ratio (%) in studied cases.

|          | Mean FEV1/FVC ratio (%) | Std Deviation |
|----------|-------------------------|---------------|
| Group A  | 71                      | 5.6           |
| Group B  | 72                      | 4.8           |

*P > 0.29 (Not Significant)*

FEF25-75 % of the patients in both the groups was analyzed. It was found that the mean FEF25-75 % in group A and group B was 75.26 +/- 3.92 and group was 75.35 +/- 5.33 respectively. The mean FEF25-75 % of both the groups were found to be comparable and there was no statistically significant difference in the mean FEF25-75 % of both the groups (P=0.91).
The analysis of SpO2% of the patients in both the groups showed that mean SpO2 in group A was 97.49 +/- 0.75 whereas mean SpO2 in group B was found to be 97.27 +/- 0.86. The mean SpO2 levels in group A and Group B were found to be comparable and there was no statistically significant difference in mean SpO2 of both the groups (P=0.13).

**Figure 3: FEF25-75 % in studied cases**

**Figure 4: SpO2 % in studied cases**

**Discussion**

This was a prospective comparative study of pulmonary function tests in patients with acute coronary syndrome treated by Ticagrelor (Group A) and Clopidogrel (Group B). In our study there were 80 (66.67%) males and 40 (33.33%) females with a M:F ratio of 1:0.5. The male preponderance in patients of coronary artery disease is well-known. Jamee A et al in a cross-sectional study based on 155 cardiac patients found that Myocardial infarction in male compared with female was 2 times higher. Estrogen in females is found to have a cardioprotective role. It further delays the manifestation of atherosclerotic disease in women. Similarly, Folsam AR examined a population-based sample (n = 13,446 free of baseline CHD). The purpose of the study was to determine the association of coronary heart...
disease (CHD) incidence with diabetes, fasting serum glucose, and insulin in middle-aged men and women. Over a follow up period of 4-7 years, 209 men and 96 women developed CHD\textsuperscript{12}. Various other authors such as McCarter RV et al\textsuperscript{13} and Wang C et al\textsuperscript{14} have reported male preponderance in incidence of coronary artery disease.

The mean age of the patients in group A and group B was found to be 61.56 +/- 3.98 and 62.41 +/- 3.40 respectively. The overall mean age of the patients was found to be 61.98 years. Though the risk of coronary artery disease increases after the age of 45 years in men and 55 years in women usually the patients present in 6\textsuperscript{th} decade. Banasiak W et al conducted a cross sectional study to gather comprehensive information regarding individuals with CAD treated by specialists as well as by general practitioners on an outpatient basis. The data of 2593 patients with CAD was collected and analyzed. The authors found that the mean age of patients with CAD was 65.0 +/- 9.8 years\textsuperscript{15}. Hypertension, dyslipidemia, family history of CAD, diabetes mellitus and active smoking were the common risk factors in studied cases. Similar studies by Soubassi LP et al\textsuperscript{16} and Brochu M et al\textsuperscript{17} found mean age of patients with CAD to be 67 +/- 13 years and 60.0 +/- 13.3 years respectively.

Antiplatelet therapy is one of the cornerstones of therapy for CAD. Various options available for antiplatelet therapy include drugs such as aspirin (irreversibly inhibiting cyclooxygenase 1), clopidogrel (P2Y12 adenosine diphosphate receptor blocker), newer P2Y12 ADP Inhibitors (Prasugrel & Ticagrelor) and GP IIb/IIIa Inhibitors. One of the largest trials studying the efficacy of ticagrelor in patients of CAD the Platelet inhibition and patient Outcomes (PLATO) trial found that there is considerable reduction in cardiovascular death, myocardial infarction and stroke in these patients with similar rates of major bleeding compared with clopidogrel. One of the drawbacks of prescribing ticagrelor in these patients was reported to be increased incidence of dyspnea in patients who had been given ticagrelor. These findings have discouraged many cardiologists from prescribing ticagrelor in patients with CAD particularly if they had any history of respiratory morbidity such as asthma. Subsequently many studies have compared clopidogrel and ticagrelor with respect to pulmonary function tests in an attempt to find out whether ticagrelor adversely affect pulmonary function test as compared to clopidogrel. Robert F. Storey et al conducted a sub-study to assess whether ticagrelor affects pulmonary function in ACS patients? In this study Pulse oximetry (SpO2), spirometry (FEV1, FVC, FEF25-75; pre and 20 min post inhaled beta agonist), lung volumes (TLC, FRC, RV) and diffusion capacity (DLCOSB) were performed after receiving study medication (ticagrelor 90 mg bid (n=101) or clopidogrel 75 mg qd (n=98)) for 30-40d. The study found that at the end of treatment (mean 211d) and after discontinuation of medication (mean 32d post last dose), there was no evidence of change in pulmonary function in either group\textsuperscript{18}. On the basis of these findings the authors concluded that Ticagrelor in ACS patients is not associated with any detectable detrimental effect on pulmonary function compared to clopidogrel. Similar findings were also reported by the studies conducted by Butler K et al\textsuperscript{19} and Andell P et al\textsuperscript{20}.

**Conclusion**

Ticagrelor is associated with a considerable reduction in cardiovascular death, myocardial infarction and stroke in patients with coronary artery diseases. PLATO trial reported that there was an increased incidence of dyspnea in patients who had been given ticagrelor. These findings have discouraged use of ticagrelor in CAD patients. Our study found that ticagrelor does not affect pulmonary functions and hence can be considered a better option as compared to clopidogrel in patients with CAD.

**Conflict of interest:** None
References

1. Kumar A, Cannon CP. Acute coronary syndromes: diagnosis and management, part I. Mayo Clin Proc. 2009;84(10):917–938.
2. Chaturvedula S, Diver D, Vashist A. Antiplatelet Therapy in Coronary Artery Disease: A Daunting Dilemma. J Clin Med. 2018 Apr 9;7(4). pii: E74.
3. Falk JA, Kadiev S, Criner GJ, Scharf SM, Minai OA, Diaz P. Cardiac disease in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008;5(4):543–548.
4. Boschetto P, Beghé B, Fabbri LM, Ceconi C. Link between chronic obstructive pulmonary disease and coronary artery disease: implication for clinical practice. Respirology. 2012 Apr;17(3):422-31.
5. Cazzola M, Calzetta L, Matera MG, Muscoli S, Rogliani P, Romeo F. Chronic obstructive pulmonary disease and coronary disease: COPD-CoRi, a simple and effective algorithm for predicting the risk of coronary artery disease in COPD patients. Respir Med. 2015 Aug;109(8):1019-25.
6. Lee CW. Dual antiplatelet therapy for coronary artery disease. Circ J. 2015; 79(2):255-62.
7. Gurbel PA, Myat A, Kubica J, Tantry US. State of the art: Oral antiplatelet therapy. JRSM Cardiovasc Dis. 2016;5:2048004016652514. Published 2016 Jun 1.
8. James S, Budaj A, Aylward P, Buck KK, Cannon CP, Cornel JH, Harrington RA, Horro J, Katus H, Keltai M, Lewis BS, Parikh K, Storey RF, Szummer K, Wojdyla D, Wallentin L. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation. 2010 Sep 14;122(11):1056-67.
9. James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, Skene A, Steg PG, Storey RF, Harrington R, Becker R, Wallentin L. Comparison of Ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J. 2009 Apr;157(4):599-605.
10. Nicolau JC, Baracioli LM, Giugliano RP. Ticagrelor for the prevention of ischemic events in patients with prior myocardial infarction and peripheral artery disease. Expert Opin Pharmacother. 2018 Jun;19(9):1013-1019.
11. Jamee A, Abed Y, Jalambo MO. Gender difference and characteristics attributed to coronary artery disease in Gaza-Palestine. Glob J Health Sci. 2013;5(5):51–56. Published 2013 May 26.
12. Folsom AR, Arnett DK, Hutchinson RG, Liao F, Clegg LX, Cooper LS. Physical activity and incidence of coronary heart disease in middle-aged women and men. Med Sci Sports Exerc. 1997 Jul;29(7):901-9.
13. McCarter RV, McKay GJ, Quinn NB, Chakravarthy U, MacGillivray TJ, Robertson G,Pellegrini E, Trucco E, Williams MC, Peto T, Dhillon B, van Beek EJ, Newby DE,Kee F, Young IS, Hogg RE. Evaluation of coronary artery disease as a risk factor for reticular pseudodrusen. Br J Ophthalmol. 2018 Apr;102(4):483-489.
14. Wang C, Zhao P, Luo P, Liu W, Wang H, Zhao Q. Prevalence and risk factors of coronary artery disease in patients with chronic viral hepatitis. Postgrad Med.2015;127(8):786-90.
15. Banasiak W, Pociupany R, Wilkins A, Ponikowski P. Characteristics of patients
with coronary artery disease managed on an outpatient basis in the population of Poland. Results of the multicentre RECENT trial. Kardiol Pol. 2007 Feb;65(2):132-40; discussion 141-2.

16. Soubassi LP, Papadakis ED, Theodoropoulos IK, Poulos GD, Chaniotis D, Tsapakidis IP, Zerefos SN, Douli M, Chiras TCh, Kouvelis A, Daglas GK, Soubassi SP, Valis DN, Zerefos NS. Incidence and risk factors of coronary artery disease in patients on chronic hemodialysis. Int J Artif Organs. 2007 Mar;30(3):253-7.

17. Brochu M, Poehlman ET, Savage P, Ross S, Ades PA. Coronary risk profiles in men with coronary artery disease: effects of body composition, fat distribution, age and fitness. Coron Artery Dis. 2000 Mar;11(2):137-44.

18. Storey RF, Becker RC, Harrington RA, Husted S, James SK, Cools F, Steg PG, Khurmi NS, Emanuelsson H, Lim ST, Cannon CP, Katus HA, Wallentin L. Pulmonary function in patients with acute coronary syndrome treated with ticagrelor or clopidogrel (from the Platelet Inhibition and Patient Outcomes [PLATO] pulmonary function substudy). Am J Cardiol. 2011 Dec 1;108(11):1542-6.

19. Butler K, Maya J, Teng R. Effect of ticagrelor on pulmonary function in healthy elderly volunteers and asthma or chronic obstructive pulmonary disease patients. Curr Med Res Opin. 2013 May;29(5):569-77.

20. Andell P, James SK, Cannon CP, et al. Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes and Chronic Obstructive Pulmonary Disease: An Analysis From the Platelet Inhibition and Patient Outcomes (PLATO) Trial. J Am Heart Assoc. 2015;4(10):e002490. Published 2015 Oct 9.