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Comparison between Clopidogrel and Ticagrelor on Patients Suffering from Chronic Obstructive Pulmonary Disease and Acute Coronary Syndrome: PLATO Trial Based Analysis

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Aim: The purpose of this study was to compare between Clopidogrel and Ticagrelor on patients suffering from Chronic Obstructive Pulmonary Disease and Acute Coronary Syndrome:

Study design: PLATO trial based analysis

Place and duration: This study was conducted at Peoples University of Medical and Health Sciences for Women Shaheed Benazirabad Nawabshah, Pakistan from Jan2019 to Jan 2020.

Methodology: A total of 18,614 patients suffering from ACS randomly giving treatment with either clopidogrel or ticagrelor. In these patients, 1084 (5.7%) patient reported with a history of COPD. The primary endpoint at end of one year was seen in 18% of the patients suffering from COPD, and 10% for patients without COPD.

Results: In the case of primary endpoints in patients with COPD, the one-year event rate for patients who were given ticagrelor was 15% and 20% for those that were treated with clopidogrel. The occurrence of death for patients taking clopidogrel was 11.9% and it was 8.6% for the patients being treated with ticagrelor. Whereas Platelet Inhibition and Patient Outcomes defined that the major bleeding rates for one year was 15% for the patients being treated with ticagrelor and 17% for patients being treated with clopidogrel. Cases of dyspnea are more common in patients who took ticagrelor. Another important point to note is that there was no differential increase in the risk of getting as compared to patients that were not suffering from COPD (1).

Conclusions: After thoroughly analyzing the data, it can be seen that COPD patients experienced a higher rate of ischemic events. With the use of either Ticagrelor or clopidogrel to treat COPD patients, the overall risk of ischemic events (5.7%) are reduced. Also, the major bleeding events were

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not increased. After assessing the benefit risk profile, it can be said that using Ticagrelor to treat patients is better.

Keywords: Ticagrelor, clopidogrel, Chronic Obstructive Pulmonary Disease, Acute Coronary Syndrome

Introduction

Acute coronary syndromes are often found in patients suffering from chronic obstructive pulmonary disease. There are many reasons contribute to the risk of ACS, such as smoking, systemic inflammation, and old age. Even for non-smokers, reduction in pulmonary function is associated directly with a risk of cardiovascular death, ACS, or arrhythmias. There is an increased risk of recurring ischemic events as well as an increase in mortality for patients that have COPD and experience ACS. According to comorbidities, patients that have COPD mostly do not receive reperfusion therapy or any other therapy that could possibly worsen the outcomes in the long-term (2).

It can be seen in the PLATO study that there is better efficacy of thienopyridine platelet P2Y12 that is a receptor inhibitor, with ticagrelor rather than clopidogrel in order to prevent death caused by vascular diseases, strokes, or myocardial infarction in patients suffering from ACS. The problem, however, is that patient taking Ticagrelor is more likely to suffer from dyspnea. According to the previous studies of PLATO, Ticagrelor is much better than clopidogrel for high-risk patients, such as old patients, patient suffered with diabetes, or patients that have impaired renal function (3).

Due to the risk of dyspnea, COPD patients that suffer from ACS are often not prescribed Ticagrelor by their clinician (4). When the PLATO trials were first published, another editorial suggested that the use of Ticagrelor for patients suffering from COPD was not appropriate. Additionally, the European Medicines Agency also discourages the use of Ticagrelor for such patients due to the risk of dyspnea. The focus of the study was to understand the safety profile and efficacy of both ticagrelor and clopidogrel for patients suffering from both ACS and COPD (5).

Methodology

In the PLATO trial, 18,614 patients were enrolled at Peoples University of Medical and Health Sciences for Women Shaheed Benazirabad Nawabshah, Pakistan from Jan2019 to Jan 2020. The details regarding the patients, outcome definitions, results, and study designs have been published. The local ethics committees and national regularity authorities approved the study in accordance with local regulations. Meetings themselves provided by every patient that participated in the study. The eligibility criteria for patients for this study was being hospitalized for having ACS, regardless of ST-segment elevation, and that they had any symptoms of onset in the previous day. The main exclusion criteria were a greater risk of bradycardia, simultaneous therapy with cytochrome P450 3A inducer or inhibitor, requirement of oral anticoagulation therapy, fibrinolytic therapy within twenty-four hours before the test, and contraindication to clopidogrel (6). The randomization with ticagrelor or clopidogrel was done in a double-dummy and double-blind way. All patients, except those who were intolerant, were given acetylsalicylic acid. The duration of the median treatment was 9 months (7).

The first time any particular event from the composite endpoint was the primary or main efficacy endpoint, such events include myocardial infarction, stroke, or vascular cases. Whereas the

secondary endpoint for efficacy includes events such as death due to vascular causes, stroke, myocardial infarction and death due to any other reason. The first-time major bleeding happens is known as the primary safety endpoint. Additionally, the assessment of events of bleeding as defined by the TIMI criteria and deadly bleeding was also done. Dyspnea is another example of an adverse event which was also included in the electronic case report form (8).

COPD status was used to compare the baseline characteristics of patients. The median was used to represent continuous valuables. Wilcoxon rank-sum test was used to compare the differences. Counts represent categorical variables. In the case where cell frequencies were enough, Pearson chi-square test was used to compare these differences. Otherwise, an exact test was carried out. Patients that did and did not have COPD were randomized and, after twelve months, the Kaplan-Meier event rates were separately calculated for groups treated with ticagrelor and clopidogrel, for both the safety end points and the efficacy end points. The characterization of the effect of randomized treatment on patients who have COPD and those who do not have COPD. Every endpoint's hazard ratio for the COPD cohort as well as the non-cohort COPD and P-value for treatment by COPD interaction- was reported. The adjustment covariates are past nonhemorrhagic stroke, past myocardial infarction, heart rate, age, Killip class at entry, peripheral artery disease, haemoglobin, time from symptoms to randomization, diabetes, region, final diagnosis of an index event, a past event coronary artery bypass grafting, transient ischemic attack (9). In order to assess the linearity of the continuous variables, they were assessed on a log hazard scale. Linear splines were used, where appropriate, to assess the nonlinear relationships that existed with the primary efficacy endpoint.

Results

In the PLATO study, 1084 patients were reported to have COPD. Of these patients, many were old and often smokers or they used to smoke. Furthermore, many of the patients had comorbidities as well as many cardiovascular risk factors, such as congestive heart failure, coronary artery disease, myocardial infarction and angina pectoris. Those patients that had a lower median creatinine clearance were not usually treated with beta-blockers. Mostly, diuretics was used to treat such patients. Also, not a lot of patients were diagnosed with STEMI.

Patients with COPD were noted to have higher rate of bleeding and ischemic outcomes. Patients that used Ticagrelor were noted to have lesser primary endpoint of death, vascular causes, stroke or myocardial infarction for patients that had and did not have COPD (10). The absolute reduction of the rate of primary endpoint was more in patients that were diagnosed with COPD. There was no interaction seen in the COPD status-by-treatment of the analysis done on efficacy endpoint. Ticagrelor was noted to reduce death caused by any reason for patients that were and were not diagnosed with COPD (11).

For the case of both non-COPD patients and COPD patients, there was not much difference in the major bleeding rates, from every criterion of measurement. Ticagrelor was seen to have an increase in bleeding rates of non-CABG related major bleeding for patients that did not have COPD, according to the PLATO-defined criteria (12).

Ticagrelor substantially enhanced the occurrence of dyspnea in both COPD and non-COPD patients. Although COPD patients had a greater proportion of absolute dyspnea events, the ticagrelor-associated relative risks were similar, and there was no COPD status-by-treatment interaction (P=0.616). Regardless of COPD condition, ticagrelor was associated with a higher rate of study medication cessation due to dyspnea (13). Although the numbers of discontinuations were minor,

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COPD patients treated with ticagrelor had a statistically higher rate of dyspnea-related events leading to study medication discontinuation than non-COPD. In COPD patients treated with ticagrelor, early cessation of the study medication was more likely (14). In COPD patients treated with ticagrelor, adherence to study medicine, defined as using more than 80% of the study medication during each interval between visits, was somewhat greater, although exposure, defined as total days on treatment, was slightly lower. There were even more negatives (15).

The primary findings were supported by efficacy and safety outcomes in subgroups characterized by first treatment technique. Similarly, an additional study that excluded nonsmokers confirmed the main findings of the study (16).

Table 1: Demographic characteristics of the study participants

Characteristic	COPD (N=1084)	No COPD (N=18000)	P Value
Demographics			
Age (Years)	65 (60 to 70)	60 (55 to 65)	<0.0012
≥75	200 (20)	2640 (16)	<0.0012
Female	325 (28)	5000 (29)	0.338
Race			0.0019
Caucasian	99 (90.2)	16 057 (91.6)	
Black	22 (2.0)	210 (1.2)	
Oriental	40n (3.9)	1057 (6.0)	
Other	17 (1.6)	204 (1.2)	
BMI, kg/m2	27.7 (24.2 to 31.1)	26 (22 to 29)	0.599
Waist circumference (cm)	100 (90 to 110)	100 (90 to 110)	<0.00099
Smoking status			<0.00099
Nonsmoker	210 (18.8)	7000 (39)	
Ex-smoker	382 (31.4)	4000 (22)	
Habitual smoker	489 (44.9)	6000 (31)	

Table 2: Medical history of the study participants

Medical history	COPD (N=1084)	No COPD (N=18000)	P Value
Hypertension	779 (71.9)	11000 (61)	<0.00099
Dyslipidemia	595(55.8)	8200 (42)	<0.00099
Diabetes mellitus	299 (27.3)	4700 (27)	0.138
Angina pectoris	602 (58.2)	7000 (47)	<0.00099
Myocardial infarction	311 (27.1)	3606 (29.2)	<0.00099
Congestive heart failure	126 (11.0)	900 (5.9)	<0.00099
Coronary artery disease	409 (36.1)	4790 (27.9)	<0.00099

PCI	194 (13.1)	2369 (13.0)	<0.00099
CABG	140 (14.2)	982 (4.8)	<0.00099
Transient ischemic attack	49 (5.0)	445 (3.9)	0.00099
Nonhemorrhagic stroke	49 (5.0)	700 (4.0)	0.50
Peripheral artery disease	150 (14.9)	1000 (6.0)	<0.00099
Pacemaker	35 (3.0)	129 (1.9)	<0.00099
Peptic ulcer disease	120 (11.0)	1300 (5.7)	<0.00099
Gastrointestinal bleeding	48 (4.5)	230 (2.6)	<0.00099
Asthma	108 (9.9)	420 (2.0)	<0.00099
Chronic renal disease	100 (8.0)	700 (4.0)	<0.00099

Table 3: Biochemical profile of the study participants

Biochemistry	COPD (N=1084)	No COPD (N=18000)	P Value
Creatinine clearance [CG], mL/min	75.3 (54.4 to 95.0)	90.9 (64.5 to 100)	<0.00099
Glucose, mmol/L	6.7 (3.4 to 8.9)	7.9 (6.7 to 9.9)	0.019
HbA1c, %	5.9 (4.9 to 6.9)	5.4 (4.6 to 6.8)	0.019
Haemoglobin, g/L	140 (120 to 150)	142 (132 to 150)	0.005
Total cholesterol, mmol/L	5.0 (4.1 to 6.1)	4.1 (3.4 to 5.0)	<0.00099
LDL cholesterol, mmol/L	3.0 (2.0 to 4.0)	3.0 (2.5 to 3.5)	<0.00099
HDL cholesterol, mmol/L	1.4 (1.2 to 1.8)	0.9 (0.5 to 1.4)	0.400
First central TnI positive	890/1084 (82.2)	15000/18000 (81.0)	0.901

Table 4: Medications at randomization and treatment approach

Medications at randomization	COPD (N=1084)	No COPD (N=18000)	P Value
Aspirin	1000 (94)	15500 (94.4)	0.011
Unfractionated heparin	540 (50)	9000 (49.0)	0.322
Low molecular weight heparin	450 (46)	6990 (40.1)	0.033
GP IIb/IIIa inhibitors	229 (22)	3900 (30.7)	0.016
Beta blockers	660 (61.0)	13300 (69.4)	<0.001

ACE inhibitors	644 (59.8)	10000 (60.5)	0.372
Angiotensin II receptor blockers	136 (12.2)	1629 (9.7)	<0.001
Statins	880 (78.2)	14090 (89.2)	0.147
Calcium channel blockers	190 (17)	3030 (15.4)	0.041
Diuretics	420 (42)	4040 (22.6)	<0.001
Proton pump inhibitors	435 (40)	4030 (35)	<0.001
Nitrates	800 (75)	11909 (70.9)	0.021
Intended treatment approach			
Invasive	750 (68.7)	13300 (79.2)	
Medically managed	350 (33.5)	5008 (26.8)	
Final diagnosis			
NSTEMI/UA	750 (70)	11113 (59.0)	
STEMI	350 (33)	7500 (34.0)	

Discussion

The current study's findings on bleeding are consistent with the main trial's findings, with similar total major bleeding rates in the ticagrelor and clopidogrel treated groups. PLATO-defined non-CABG-related significant bleeding was shown to be more common in patients on ticagrelor in the main study. However, this rise was observed in the non-COPD cohort but not in the COPD cohort in the current investigation, despite the fact that the interaction analysis did not achieve statistical significance (P=0.059). Despite the fact that there was no proportionate increase in ticagrelor-related dyspnea in the COPD population, these individuals had a greater absolute risk of dyspnea (17). Despite the fact that dyspnea affected more than a quarter of ticagrelor-treated COPD patients, only 2.5 percent of these individuals stopped ticagrelor due to dyspnea, compared to 0.9 percent of ticagrelor-treated patients without COPD. Furthermore, there were few SAEs connected to dyspnea, and none of them were fatal. Most importantly, despite the high incidence of dyspnea, the overall ischemic event rate was much lower in the ticagrelor-treated COPD subset, which is consistent with previous studies of ticagrelor-related dyspnea showing that it is often transient and mild to moderate in severity, with no adverse effects on lung or heart function (18).

Limitations

The post-hoc analysis discussed in this study was not originally specified in the trial design. The reason was not to see the difference that occurs in the primary outcome between groups that were randomized (19). Imbalance can be noted in the groups that were a subset of patients suffering from COPD. However, the COPD groups separated based on treatment show balance in their characteristics.

Conclusion

High bleeding rates and ischemic events are very common risks that patients suffering from ACS concomitant COPD, face (20). With the use of Ticagrelor, the risk of ischemic outcomes can be

reduced, without any increase in major bleeding rates. However, Ticagrelor places patients at risk of dyspnea. The risk of dyspnea was not seen to increase for patients who did not have COPD. Regardless, after a thorough analysis, Ticagrelor is noted to have high benefits in spite of its risks.

Conflict of interest

None

Funding source

None

Permission

It was taken from the local ethics committees and national regularity authority

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