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Original Research Article

Prasugrel versus ticagrelor in patients with acute coronary syndrome treated with percutaneous coronary intervention

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ABSTRACT

Background: No association studies for the efficacy and safety of ticagrelor vs. prasugrel have been published in India. Aim of the study was to compare the safety and efficacy of Prasugrel versus Ticagrelor in patients with acute coronary syndrome treated with percutaneous coronary intervention.
Methods: This retrospective study was designed to compare the efficacy and safety of prasugrel and ticagrelor in acute coronary syndromes (ACS) with percutaneous coronary intervention (PCI). A total of 480 patients were studied who had been prescribed either prasugrel or ticagrelor during PCI. Primary end-point was defined as death, re-infarction, urgent target vessel revascularization, serious bleeding requiring transfusion.
Results: Primary endpoint was different between the groups receiving prasugrel and ticagrelor (1.2% and 4.0%, respectively; OR (95% CI) 0.38 (0.098; 1.43); P=0.065). Difference was found in the need for urgent target vessel revascularization which was significantly lower in the prasugrel group. Rest of the parameters were almost similar with no significant difference.
Conclusions: This study comparing prasugrel and ticagrelor shows that Prasugrel is more effective than Ticagrelor in lowering ischemic events in the acute coronary syndromes treated with PCI strategy, especially incidence of stent thrombosis. These observations need further analysis and follow-up.

Keywords: Acute Coronary Syndrome, Prasugrel, Percutaneous coronary intervention, Ticagrelor

INTRODUCTION

Percutaneous coronary intervention (PCI) is therapy of choice in patients with acute coronary syndrome (ACS).[1] Both aspirin and clopidogrel have established their role as anti-platelets in ACS. But clopidogrel has some limitations and so the need for newer anti-platelets.

Ticagrelor and prasugrel are newer anti-platelets which have been shown to be more effective than clopidogrel. Latest guidelines recommend the use of prasugrelor ticagrelorover clopidogrel and do not give any preference among the two.[2] Only in patients with prior stroke or TIA prasugrel is contraindicated. There are only two trials namely TRITON and PLATO to support the use of these drugs over clopidogrel in Acute coronary syndrome.[3,4]

And there is only one head to head trial comparing prasugrel and ticagrelor (PRAGUE 18 Trial) which showed no difference between the two.[5] But there is no Indian data for the use of these two drugs. The need for a comparison of the newer anti-platelets in India motivated

us to perform this study, which is a single centre retrospective observational study designed to compare the efficacy and safety of prasugrel and ticagrelor in ACS patients treated with PCI.

METHODS

This is a single centre retrospective observational study in ACS patients admitted to ICCU of Ram Manohar Lohia Institute of Medical Sciences, Lucknow. Data was collected from the ACS patients who underwent PCI between May 2015 to February 2017 and who were taking either prasugrel or ticagrelor.

Study patients

Patients with Acute Coronary Syndrome (STEMI and high-risk NSTEMI) treated with PCI strategy was enrolled in the study. The study inclusion criteria were the following: Patients with ACS who had undergone PCI with at least one intracoronary stent and were either taking Prasugrel or Ticagrelor. A diagnosis of ACS was determined based on the clinical presentation, ECG findings of ST changes and positive troponin levels. Because this was a retrospective observational study there were no exclusion criteria's and indications and contraindications had already been catered to while prescribing the relevant drugs to these patients. Only those patients were excluded who not give consented to be part of the trial.

Study design and treatment

The patients with ACS who had been admitted to our ICCU from May 2015 to February 2017 and underwent PCI were enrolled in the study. They had been prescribed either prasugrel or ticagrelor therapy. The dosing scheme for patients on prasugrel was a 60mg loading dose and 10mg once daily as a maintenance dose. Patients given ticagrelor received a loading dose of 180mg, and 90mg twice daily as a maintenance dose. Patients used the study medication for 12 months. Most of these patients also received 75mg of aspirin.

Patient contact and follow-up up data at 30 days and 1 year from the index event were included in this study.

Study endpoints

The primary composite endpoint consisted of all-cause death, urgent revascularisation, re-infarction, stroke, serious bleeding. The key secondary efficacy endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, stent-thrombosis or stroke during the follow-up period.

Statistical analysis

Statistical significance of differences among the groups of patients was tested using the Fisher exact or chi-square test. Odds ratios were used to measure the effect of prasugrel vs. ticagrelor with respect to the endpoints. All the analysis was carried out by using SPSS 21.0 version (Chicago, Inc., USA).

RESULTS

Study population

Patients with ACS admitted to the ICCU of RMLIMS from May 2015 to February 2017 who underwent PCI on newer anti-platelet drugs were enrolled in the study. The baseline characteristics of the patient set were balanced between the study groups. At least one intracoronary stent (Drug eluting stent) was implanted in all the patients. Information on vital status during the 30-day and 1-year follow-up period was available for all the patients.

Study endpoints

Primary endpoint was different between the groups receiving prasugrel and ticagrelor (1.2% and 4.0%, respectively; OR (95% CI) 0.38 (0.098; 1.43); P=0.065) (Table 2). Difference was found in the need for urgent target vessel revascularization which was significantly lower in the prasugrel group. Rest of the parameters were almost similar with no significant difference. The occurrence of key secondary endpoints 1 year after randomization, composed of cardiovascular death, non-fatal myocardial infarction, or stroke, stent thrombosis also exhibited difference in favour of Prasurgrel (2% and 5%, respectively; OR (95% CI) 0.42 (0.145-1.2); P=0.084) (Table 2).

There was significantly higher risk of stent thrombosis in the ticagrelor arm compared to the prasugrel group. And this was the reason for difference in the secondary endpoints. Rest of the endpoints like death, stroke and non-fatal MI were similar in both the groups. Serious bleeding requiring transfusion was a component of the net primary endpoint. No significant difference was found between patients on prasugrel and ticagrelor according to TIMI bleeding events (Table 3).

Absolute and relative frequencies for categorical variables; statistical significance of differences between patient groups were tested using the chi-square test or Fisher exact test (categories with low frequencies). The odds ratio estimate was based on logistic regression.

DISCUSSION

PLATO and TRITON studies discussed the effectiveness of ticagrelor and prasugrel in myocardial infarction-compared to clopidogrel which has inherent limitations.[4-7]

And these two studies form the basis for the preference of prasugrel and ticagrelor in ACS patients over clopidogrel. But there is limited data comparing the two drugs and

guidelines do not recommend which of the two should be used in different clinical scenario. Authors know from extrapolation that prasugrel has some advantage over ticagrelor in STEMI and diabetic patients. Similarly, prasugrel should be avoided in patients with prior history of stroke or TIA.

There has been only one large study comparing the two, namely PRAGUE 18 trial which depicted no significant difference between the two drugs at 30 days follow up. The observed occurrence of major efficacy and safety outcomes in the multicenter randomized PRAGUE 18 study comparing prasugrel and ticagrelor, were similar, but with broad confidence intervals around the estimates due to small number of subjects.

A randomized study in patients with STEMI undergoing primary PCI has shown that of the new P2Y12 inhibitors, neither was superior to the other in laboratory antiplatelet efficacy.[8]

Table 1: Baseline characteristics of study patients (N = 480).

Characteristics	Prasugrel (N=240)	Ticagrelor (N=240)	P value
Drug-eluting stent	312	307	
Stent graft	0 (0.0%)	1 (0.2%)	0.317
Post-procedural TIMI flow (N=1 220)[1]			
0	2 (1.0%)	2 (1.0%)	1.000
1	1 (0.5%)	1 (0.5%)	
2	8 (4.0%)	8 (4.1%)	
3	229 (94.5%)	229 (94.5%)	
Discharge			
Aspirin	240 (100%)	240 (100%)	
Beta-Blockers	231 (97%)	230 (96.5%)	0.815
ACE Inhibitors/ARB	230 (96.5%)	230 (96.5%)	1.000
Statins	240 (100%)	240 (100%)	1.000
Proton Pump Inhibitors	240 (100%)	240 (100%)	1.000
Characteristic: Men	182 (77%)	178 (73.7%)	0.673
Age (years)	61.8 (42.7; 78.7)	61.8 (44.6; 79.8)	
Admission			
ECG			0.751
STEMI	180 (75%)	179 (74.5%)	
NSTEMI	60 (25%)	61 (25.5%)	
Killip classification			
I	190 (80%)	182 (75%)	0.656
II	21 (8%)	28 (11%)	
III	19 (8%)	22 (8%)	
IV	10 (4%)	08 (4%)	
History			
Hypertension	180 (75%)	174 (73%)	0.534
Current smoker	96 (40%)	94 (40%)	0.852
Diabetes	50 (20.0%)	64 (23%)	0.133
Previous MI	8 (4%)	13 (6%)	0.265
Previous PCI	4 (2.5%)	7 (3.6%)	0.360
Chronic heart failure	2 (0.9%)	2 (1.0%)	1.000
Chronic kidney disease	8 (4%)	8 (4%)	1.000
Radial access	232 (97%)	230 (96.5%)	0.820

Absolute and relative frequencies for categorical variables; median with the 5^{th}-95^{th} percentile for continuous variables not available for patients without PCI[1]. The body-mass index (BMI) = weight in kilograms divided by the square of the height in meters.
NSTEMI denotes non-ST-elevation myocardial infarction (MI), STEMI ST-elevation MI, BBB: bundle brunch block, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, PTCA: percutaneous transluminal coronary angioplasty, TIMI: thrombolysis in myocardial infarction, ACE: Inhibitors angiotens inconverting-enzyme inhibitors, ARB: angiotensin-receptor blocker

Table 2: End points.

Endpoint	Prasugrel	Ticagrelor	Odds ratio (95% CI)	P value
Day 30				
Primary endpoint: Death from any cause, re-infarction				
Urgent revascularization, stroke, serious bleeding requiring transfusion or prolonging hospital stay	3 (1.2%)	8 (4%)	0.38 (0.098-1.431)	0.653
Death from any cause	1 (0.4%)	3 (1.2%)	0.33 (0.034-3.227)	0.315
Re-infarction	0 (0%)	1 (0.4%)	–	0.317
Urgent revascularization	0(0%)	5 (2%)	–	0.025
Stroke: Serious bleeding requiring transfusion or	1 (0.4%)	1 (0.4%)	1.00 (0.062-16.080)	1.000
Prolonging hospital stay	0(0%)	0(0%)	–	–
Day 365				
Key secondary endpoint				
Death from cardiovascular causes, non-fatal myocardial infarction or stroke	5 (2%)	12 (5%)	0.42 (0.145-1.201)	0.084
Death from cardiovascular causes	1 (0.04%)	4 (1.7%)	0.25 (0.028-2.253)	0.177
Non-fatal myocardial infarction	1 (0.4%)	5 (2%)	0.20 (0.023-1.725)	0.100
Stroke	1 (0.4%)	1 (0.4%)	1.00 (0.062-16.080)	1.000
Definite stent thrombosis	0 (0%)	5 (2%)	-	0.025
Death from any cause	2(1%)	3(1.2%)	0.67 (0.110-4.026)	0.653

Table 3: Bleeding within 30 days of study enrolment.

	Prasugrel	Ticagrelor	OR (95% CI) Prasugrel: Ticagrelor	P value
TIMI Minimal	4 (2%)	5 (2.3%)	0.80 (0.212-3.015)	0.736
TIMI Minor	1 (0.4%)	1 (0.4%)	1.00 (0.062-16.080)	1.000
TIMI Major	1 (0.4%)	1 (0.4%)	1.00 (0.062-16.080)	1.000

Absolute and relative frequencies for categorical variables. TIMI thrombolysis in myocardial infarction, BARC Bleeding Academic Research Consortium.

This study differed from PRAGUE-18 and other studies in depicting that Prasugrel is more effective than Ticagrelor in preventing Stent thrombosis, hence lesser need for urgent revascularisation in patients on Prasugrel. This is contrary to the findings of PRAGUE -18, though a major difference between the two studies is that in this study, patients had ACS (both STEMI and NSTEMI), while majority of the patients enrolled in PRAGUE-18 were STEMI patients.

And because STEMI patients have high thrombotic burden, probably any potent anti-thrombotic would suffice and therefore no difference between the efficacy of Prasugrel and Ticagrelor. Our patients were a mix of STEMI and NSTEMI and NSTEMI may not have the kind of thrombotic burden seen with STEMI and hence more efficacious anti-platelet would have lesser ischemic events in the follow-up period.[9]

The baseline characteristics of our study population were well-balanced between the compared groups (Table 1). Mortality was low in this study and this conformed to the accepted results from other studies.

Results of our study are consistent with the other studies of patients with ACS treated with PCI; and depicted better outcomes and prognosis due to the use of drug eluting stents, supported by the most efficient available dual antiplatelet therapy. We used radial access in majority of the patients which like other studies has shown benefit over femoral route.[10]

This study like the European registries shows that prasugrel, if prescribed in accordance to the recommendations does not have increased incidence of bleeding. The incidence of bleeding complications was low in both treatment arms and the difference in serious bleeding events was not statistically significant. As reported in many real-world registries we also noted increased incidence in complaint of dyspnoea in patients on ticagrelor and in this case it was about 12% which was similar to the real-world scenario.

This study has several limitations. It is a retrospective observational study. The study was underpowered in order to draw the final conclusion regarding a direct comparison of efficacy and safety of prasugrel and

ticagrelor. However, identified differences in the occurrence of primary endpoint between compared groups were low in absolute numbers except stent thrombosis which was less in the prasugrel arm compared to ticagrelor. A confounding factor here could be the number and type of stents used in the two groups and no sub- analysis was done for this.

The results of this study points to the fact that despite rampant use of the newer P2Y12 inhibitors (i.e., prasugrel and ticagrelor) very little data is available about the comparative efficacy of the two drugs. And their use is basically driven by the two large studies TRITON and PLATO which compared the drugs to clopidogrel, which has known limitation in form of clopidogrel resistance (more so in India), inter-patient variability and slow onset of action. And despite the presence of these newer P2Y12 agents in the market for last so many years no head to head studies have been published apart from PRAGUE 18 which was limited to STEMI patients. We therefore hope, despite limitations of the presented study, that the results of our study will contribute to clinical practice.

CONCLUSION

This retrospective analysis of prasugrel and ticagrelor in ACS patients, depicts that prasugrel is more effective than ticagrelor in preventing ischemic events in ACS treated with PCI. The observed difference between outcomes was lesser in the prasugrel arm compared to the ticagrelor group, mainly due to decreased incidence of stent thrombosis in the prasugrel group. A randomized study of a sufficient sample size would be required to properly ascertain the interesting findings found in this study and determine the germane indications for the two drugs.

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