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Original Article

Clinical safety profile of ticagrelor compared to clopidogrel in 1208 patients: Real world evidence

Viveka Kumar [a], Vivek Kumar [a,*], Kajal Kumari [b], K.K. Talwar [a], Divya Prasad [c], Sunil Agarwal [a], M.S. Yadav [a], Hamed Bashir [a], Suman Jatain [a], S.K. Gupta [b]

[a] Department of Cardiology, Max Super Speciality Hospital, Saket, New Delhi, India
[b] Department of Pharmacology, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi, India
[c] Hamdard Institute of Medical Sciences and Research, New Delhi, India

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ABSTRACT

Introduction: Dual antiplatelet treatment is recommended by current clinical practice guidelines for patients undergoing PCI. The PLATO trial showed superiority of ticagrelor to clopidogrel in reducing the rate of death from vascular causes, myocardial infarction and stroke without increase in the rate of overall major bleeding in ACS patients. However, real world evidence in Indian patients is limited. The objective of this study is to compare safety profile of ticagrelor with clopidogrel in real world settings.
Methodology: In this single centered retrospective observational study, a total of 1208 serial patient records undergoing PCI (ACS and stable angina patients as well) treated with Ticagrelor or Clopidogrel were collected and analyzed to look into in hospital outcomes. We excluded the patient's data that were incomplete.
Results: In total of 1208 patients, 604 patients received ticagrelor and similarly 604 patient received clopidogrel. No significant differences in the rates of major life threatening bleeding and any major bleeding were observed between ticagrelor and clopidogrel group (0.2% (n = 1) vs. 0.7% (n = 4), p = 0.18 and 2.8% (n = 17) vs. 3% (n = 18), p = 0.86 respectively). There was increase in minor bleeding rate with ticagrelor compared to clopidogrel (21.4% & 13.6%, p = 0.00).
Conclusion: In the real world settings, patients undergoing PCI treated with ticagrelor showed similar safety profile compared to clopidogrel but with increase in minor bleeding rate. The observed results were in alignment with PLATO clinical trial.

1. Introduction

ACC/AHA guideline recommend dual antiplatelet treatment for the management of patients who have acute coronary syndromes with or without ST elevation.[1,2] Clopidogrel combined with aspirin has been used in patients with ACS to prevent thrombotic events.[3–5] The efficacy of clopidogrel is hampered by reduced generation of active metabolite as it is prodrug, which results in increased risk of myocardial infarction and stent thrombosis in poor responder.[6–8] Up to one third of patients have poor response due to inadequate levels of platelet inhibition.[9] Prasugrel, a third generation thienopyridine has more pronounced and consistent inhibitory effect on platelets resulting in lower risk of myocardial infarction and stent thrombosis in patients with acute coronary syndrome, who are undergoing percutaneous coronary intervention (PCI) but associated with increased risk of major bleeding.[10–12]

Ticagrelor is an oral, non-thienopyridine, direct and reversible antagonist of P2Y12 receptor. Ticagrelor provides consistent and greater platelet inhibition compared to clopidogrel with rapid onset and offset action.[13–15] In the platelet inhibition and patient outcome study (PLATO), ticagrelor showed better P2Y12 inhibition than clopidogrel, which resulted in significant reduction in CV death, myocardial infarction and stroke without increase in the overall rate of major bleeding.[16] However, real world evidence in Indian patients is limited. In this present study, we compared safety profile of ticagrelor with clopidogrel in real world patients (ACS and stable angina combined), who underwent PCI.

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* Corresponding author.
E-mail addresses: viveka.kumar@maxhealthcare.com (V. Kumar), drvivek@ymail.com (V. Kumar), kk.talwar@maxhealthcare.com (K.K. Talwar), sunil.agarwal@maxhealthcare.com (S. Agarwal).

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2. Materials and methods

2.1. Study population

The study population included all serial patients undergoing PCI with Ticagrelor or Clopidogrel for ACS or stable angina at Max super speciality hospital, Saket, New Delhi from January 2014 to October 2015. The exclusion criteria included all serial patients undergoing PCI with prasugrel or those with incomplete data.

2.2. Study design

This was a single centred retrospective observational cohort study, involved patients undergoing PCI treated with clopidogrel or ticagrelor. Based on their treatment profile, patients were divided into two groups. - Ticagrelor group and clopidogrel group. Data regarding patient profile, procedure details and in hospital course were accessed from central patient record system (CPRS).

The current study used PLATO bleeding classification.

(a) Major life threatening bleeding includes fatal bleeding, intracranial bleeding, decline in 5gm per decilitre or more in haemoglobin values, need for at least 4 units of red cells transfusion, intrapericardial bleeding with cardiac tamponade, severe hypotension or hypovolemic shock due to bleeding requiring surgery or pressors.
(b) Other major bleeding includes bleeding that caused clinically significant disability (e.g., permanent vision loss) or bleeding associated with decline in at least 3gm per decilitre and less than 5gm per decilitre in haemoglobin values, need 2–3 units of red cells transfusion.
(c) Minor bleeding includes bleeding, which required medical intervention but not met major bleeding criteria.

The primary endpoint was PLATO defined major bleeding; secondary endpoint included, cardiovascular death, stent thrombosis and stroke.

The study protocol was reviewed and approved by Institutional Ethics Committee.

2.3. Statistical analysis

2.3.1. Sample size calculation

In PLATO trial, the primary end point – a composite of death from vascular causes, stroke or myocardial infarction had occurred in 9.8% in patients on ticagrelor compared to 11.7% of those on clopidogrel. The present study aimed to detect difference of 5% with power 80% at level of significance 5%; sample size came to be 604 per group. Sampling was done backwards to include 604 cases in each group. Data analysis was done using independent t test for numeric variables and chi square test applied for categorical variables using the SPSS system 20.0 software. All statistical testing was two-sided and analysis was performed using a significance (alpha) level of 0.05.

3. Results

A total of 1208 patients who underwent PCI treated with either ticagrelor or clopidogrel were recruited into the study. Baseline characteristics except age, history of PCI and route of angioplasty were balanced in the study (Table 1). 21.7% and 22.7% were female and 56.1% 57.5% were ACS patients in ticagrelor and clopidogrel group respectively. Mean age of patients in ticagrelor group was less than in clopidogrel group (61.2 ± 10.4 vs. 62.5 ± 11.9, p = 0.05). History of previous percutaneous coronary intervention in ticagrelor group was less (12.4%) compared to clopidogrel group (18.2%) and significantly more number of patients underwent trans radial angioplasty in ticagrelor group than in clopidogrel group (22.5% vs. 14.7%, P < 0.001).

Table 1
Patient characteristics at baseline.

Characteristics	Ticagrelor (n=604)	Clopidogrel (n=604)	P-value
Age			
Mean	61.2 ± 10.4	62.5 ± 11.9	0.05
Gender			
Male	78.3% (473/604)	77.3% (467/604)	0.68
Female	21.7% (131/604)	22.7% (137/604)	0.68
BMI	27.1 ± 23.8	31.4 ± 24.0	0.30
CV risk factors			
1. Smoking	14.9% (90/604)	13.1% (79/604)	0.36
2. Hypertension	57% (344/604)	58% (351/604)	0.68
3. Diabetes	41.2% (249/604)	40.6% (245/604)	0.82
4. Alcoholic	1.7% (10/604)	3.1% (19/604)	0.09
History			
1. PCI	12.4% (75/604)	18.2% (110/604)	0.01
2. CABG	7.1% (43/604)	6.6% (40/604)	0.73
Coronary artery disease			
a. Stable	43.7% (264/604)	42.5% (257/604)	0.68
b. ACS	56.1% (339/604)	57.5%(347/604)	0.64
Route of angioplasty			
a. Femoral	77.5% (468/604)	85.3% (515/604)	0.001
b. Radial	22.5% (136/604)	14.7% (89/604)	0.001

Regarding the primary endpoint (Table 2) there was no significant difference in major life threatening and other major bleeding between ticagrelor and clopidogrel group (0.2% vs. 0.7%, p = 0.18 and 2.6% vs. 2.3%, p = 0.71 respectively). Overall major bleeding also did not differ between ticagrelor and clopidogrel group (2.8% vs. 3%, p = 0.86). However, there was increased minor bleeding rate with ticagrelor compared to clopidogrel (21.4% and 13.6%, p = 0.00). There was also no significant difference in the secondary endpoint (Table 3) consisting of cardiovascular death, Stent thrombosis and stroke (11 in ticagrelor vs. 10 in clopidogrel group, p = 0.83). Only 8 patients among 604 (1.33%) in ticagrelor group required discontinuation of ticagrelor because of dyspnoea.

4. Discussion

The present study showed similar rate of major life threatening bleeding and other major bleeding with ticagrelor compared to

Table 2
Primary endpoint: Comparison of bleeding safety profile between Ticagrelor and Clopidogrel.

Plato bleeding classificatin	Ticagrelor (n = 604)	Clopidogrel (n = 604)	P value
1. Major life –threatening bleed	1(0.2%)	4(0.7%)	0.18
Other Major bleed	16(2.6%)	14(2.3%)	0.71
Any Major bleed	17(2.8%)	18(3.0%)	0.86
2. Minor bleeding	129(21.4%)	82(13.6%)	0.00

Table 3
Secondary endpoint.

	Ticagrelor (n = 604)	Clopidogrel (n = 604)	P value
Death	10	10	1
Stent thrombosis	0	0	–
Stroke	1	0	0.32
Total	11	10	0.83

clopidogrel but there is increased rate of minor bleeding in ticagrelor group. Similar result was seen in PLATO trial which demonstrated superiority of ticagrelor compared to clopidogrel in reducing CV death, stroke and myocardial infraction without significant increase in major bleeding rate.[16] The benefits of ticagrelor compared to clopidogrel in PLATO trial was seen in patients who had an acute coronary syndrome with or without ST elevation.[16] But in this real world study more than 40% of patients were stable angina patients undergoing elective PCI. Thus this may be assuring that even in patients with lesser risk profile ticagrelor may be a safe option and could be considered in high-risk patients to achieve reliable P2Y12 inhibition. There were some significant differences in the baseline characteristics between the groups that may have contributed to this result. Significant number of patients in ticagrelor group was having lesser mean age and more patients on ticagrelor underwent PCI through trans radial route than femoral route (22.5% vs. 14.7%, P = 0.001). Both of these may be confounding factors for no significant increase in bleeding events in ticagrelor group. Considering other randomized trials on ticagrelor in which net clinical safety of ticagrelor persisted irrespective of the vascular access route, it is assumed that the access site is less likely to be a factor in our study. Regarding age factor, as shown in the landmark PLATO trial, there has been no evident age related increased bleeding events.

Another inference that may be drawn from the observation that the patients in ticagrelor group were relatively younger (61.2 ± 10.4 vs. 62.5 ± 11.9, p = 0.05), is the persistent apprehension for age related bleeding risk with newer potent P2Y12 inhibitors. In the TRITON TIMI 38 trial[12], prasugrel was associated with increased bleeding events in patients with 75 years of age or older and so prasugrel is contraindicated in this age group. But there was no significant association of age related increased bleeding with ticagrelor in PLATO trial.[16] Despite of this fact, in real world practice apprehension regarding newer potent antiplatelet drugs including ticagrelor may be still persisting.

The benefits with ticagrelor are consistent regardless whether patients receive appropriate treatment initiation with recommended high dose clopidogrel and whether management is invasive or non-invasive.[17–22] As a routine practice at our centre, clopidogrel treated ACS patients undergoing PCI receive 600 mg loading dose and for other patients if they are already taking clopidogrel, receive 300 mg loading or 600 mg if they are clopidogrel naïve. Although this study was an in hospital outcome study, still it carries merit as it shows that ticagrelor is safe in whole spectrum of Indian patients undergoing PCI in real world scenario. Average Indian has a lesser body weight and body surface area compared to European or American counterpart, and there was no dose ranging study done exclusively in Indian patients. There are still reservations regarding the safety and tolerability of new potent antiplatelet agents because of this fact, as it has been for high dose statins historically. Peri-procedural as well as post procedural major bleeding is a strong independent predictor of early and late major adverse cardiovascular events and mortality.[23–27] A physician is in a state of constant battle balancing the risk of bleeding and preventing thrombus-associated events. As a matter of fact the peri-procedure and the post procedure period is the most vulnerable period for both of these extreme events of bleeding and thrombosis. One at others cost is not an option. In this respect this study is important as the results are reassuring and we can expect that the long-term outcomes should also be in line with other randomized trials of ticagrelor.[17–22] Although rate of major bleeding with ticagrelor in PLATO trial was not lower than clopidogrel, there was no increase in rate of any major bleeding with more intense P2Y12 inhibition by ticagrelor. We observed similar rate of major life threatening bleeding and any major bleeding with some increase in minor bleeding in the current study. If we look into the profile of patients who suffered mortality in this study we find that 90% (9/10) in each group were having ACS and more than 50% were in cardiogenic shock, and majority were having high-risk profiles in form of CKD, DM and multivessel CAD. Interestingly in patients who died (Table 4), per-procedural events in form of slow flow, thrombosis, VT or hypotension were numerically more in clopidogrel group compared to ticagrelor group. We do not have PCI data regarding events of all the patients, so we cannot make a conclusion regarding ticagrelor's beneficial effect on per procedural events. Further study is needed to look into this, as it may seem logical that reliable and prompt P2Y12 inhibition should have positive impact on procedural outcomes. One patient in ticagrelor had suffered post procedural fatal ICH, this was a 69 year old male having history of carotid artery disease and stroke in past. Stroke was associated with increased bleeding events with prasugrel[12] but no such relation has been found with ticagrelor.[16] We do not have data on previous stroke in all of our patients, so we cannot comment on significance of the observed ICH event and its relation to stroke when treated with ticagrelor. Further real world data may be needed to ascertain this observation. In our study 1.33% patient required discontinuation of ticagrelor because of dyspnoea which is quite consistent with discontinuation rate of 0.9% in the landmark PLATO trial.[16]

Table 4
Profile of patients with mortality.

(Death)	Ticagrelor (n = 10)	Clopidogrel (n = 10)
Male	8	8
Mean age (yrs.)	66.3	64.7
ACS (STEMI)	9 (5)	9 (7)
Cardiogenic shock	5	6
Periprocedural events (Slow flow, thrombosis, VT, hypotension)	1	3
Major bleed (ICH)	5 (1)	2 (0)
DM	5	4
Previous PCI	2	0
CKD (creatinine ≥ 1.5 mg/dl)	6	5
TVD	6	3
Femoral access	10	10

There are limitations in this study, like it being a retrospective observational study and data was not randomized. Further it was an in hospital outcome study so long-term safety and clinical outcome could not be no commented upon. Age and route of access were potential confounding factors. But still this study holds merit, as it is perhaps one of the first studies evaluating ticagrelor with clopidogrel in real world Indian patients, who as a matter of fact have CAD at an earlier age and have tendency to have more severe disease, and also clopidogrel resistance is reported to be from 15.2% to 32%.[28–30]

In conclusion, similar clinical safety profile related to major life threatening bleeding and any major bleeding was observed in patients undergoing PCI for ACS or stable angina treated with ticagrelor compared to clopidogrel but with increase in minor bleeding. Observed similar rate of major bleeding with ticagrelor compared to clopidogrel (2.8% and 3%, respectively p = 0.86) in current study is in alignment with safety results of PLATO trial (11.6% and 11.2% respectively = 0.43).[16]

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