Therapeutic experience of ticagrelor in Indian patients with acute coronary syndrome: A non-interventional, prospective, and observational study

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Abstract

Objective: This observational study was designed to understand the usage pattern of ticagrelor in real-life clinical practice among a large number of acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or medical management (MM). The study also recorded clinical events, i.e., bleeding, dyspnea, and cardiovascular (CV) events, reported by the investigator during the follow-up period.

Methods: The ACS patients aged ≥18 years hospitalized for ACS and were prescribed ticagrelor upon discharge or ≥1 month and patients who underwent PCI, CABG, or MM for ACS were enrolled. The subjects were followed up for a period of up to 12 months. The data were collected on a case report form.

Result: The study recruited 2997 subjects from 49 sites in India. Approximately half of the ACS subjects had ST segment elevation myocardial infarction (48.9%), and PCI was used as management in 92.4% subjects. The mean (±SD) duration of use of ticagrelor was 314 (±110.2) days over a period of 12 months.

Of 136 subjects (4.5%) who experienced any clinical events, CV deaths were reported in 20 (0.7%), myocardial infarction in 19 (0.6) subjects and ischemic stroke in 23 (0.8%) subjects, and severe dyspnea was reported in 68 (2.2%) subjects. Out of 33 bleeding cases, 25 (0.8%) subjects had thrombolysis in myocardial infarction (TIMI) minimal, seven (0.2%) had TIMI minor, and one TIMI major. Platelet inhibition and patient outcomes (PLATO) major was reported in two subjects and CABG bleed in one subject.

The incidence of PLATO defined major and minimal bleeding were lower in subjects undergoing fibrinolysis than overall population.

Conclusion: Ticagrelor has been used across ACS types and in different management strategies in real-world settings in India. The incidence of clinical events was lower as compared with data in literature.

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1. Introduction

Acute coronary syndrome (ACS), a complication of coronary artery disease (CAD), is one of the leading causes of mortality across the globe. ACS is a group of diseases comprising ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). Together, CAD and ACS account for around seven million deaths every year worldwide. In India, cardiac diseases affect approximately 45 million patients, of whom more than 30 million have CAD. In India, cardiovascular (CV) risk factors associated with ACS are on upsurge making it a major public health problem.

The most commonly prescribed medications in ACS patients include aspirin (162–325 mg), morphine, nitroglycerine, β-blockers, angiotensin-converting enzyme inhibitors, P2Y12 inhibitors, and statins. The most commonly used thienopyridine in ACS patients is clopidogrel. However, the drug causes irreversible
platelets inhibition and also has limitation that it requires hepatic conversion to an active metabolite and thus has delayed action. The drug also has interpatient variation in conversion rate because of pharmacogenomics differences. These factors necessitate the need for a new antiplatelet agent which does not have these limitations.

Ticagrelor, a reversible and direct-acting oral antagonist of cyclopentyl triazolopyrimidines class provides faster P2Y12 inhibition than available alternatives. Ticagrelor binds reversibly and noncompetitively to the P2Y12 receptor. Ticagrelor 90 mg bid has demonstrated good efficacy and an acceptable tolerability profile among patients with ACS in randomized controlled trials.7,8

Ticagrelor has been used in India since 20129{, #99}{cdsco.nic.in/writereaddata/New%20Drug%20Update%202012.docs, #98}. However, retrospective analysis of available data has not been possible because of poor infrastructure and lack of electronic case recording formats in Indian hospitals. As such, this study was designed to understand the usage pattern of ticagrelor in real life clinical practice in a sample of 3000 ACS patients undergoing percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or medical management (MM) in India.

1. Aims and objectives

The primary objective of the study was to understand the usage pattern of ticagrelor in ACS patients undergoing PCI, CABG, or MM in a clinical practice setting in India.

Other objectives included observing the usage of ticagrelor in patients preloaded with clopidogrel, recording clinical events (bleeding, dyspnea, and CV events) reported by the investigator during the follow-up period and observing the usage of ticagrelor in patients who received fibrinolytic therapy for current ACS event to record the various risk factors and reasons of discontinuation of ticagrelor therapy.

1.2. Patients and methods

This noninterventional, prospective, observational, and multicenter study enrolled ACS patients of either gender aged ≥18 years who were hospitalized for ACS and had been prescribed ticagrelor upon discharge or ≤1 month and patient underwent PCI, CABG, or MM for ACS. The subjects were assessed for the proportion of enrolled patients with different types of ACS, namely STEMI, NSTEMI, and UA. The diagnosis of STEMI was based on the criteria of chest discomfort, with ST-segment elevation, presumed left bundle branch block (LBBB), and elevated creatine kinase-muscle/brain (CK-MB) and troponin; NSTEMI is chest discomfort, lack of persistent ST elevation, lack of presumed LBBB and elevated cardiac enzymes, and UA are symptoms of angina at rest or on minimal exercise and transient ST-T changes.

Patients with medical history of intracranial hemorrhage, the presence of serious co-morbidities, who were not fit to receive ticagrelor, and the pregnant women were excluded from the study. Patients were followed up for a period of up to 12 months (according to the label). Because this was an observational study, the therapy was not prescribed for the purpose of inclusion of the patients in this study. The patients were included in the study who were being prescribed ticagrelor according to the prescribing information as part of routine patient care. The study objectives and methodology had been published earlier.10

The study was planned to enroll a total of 3000 ACS patients. The duration of participation was 12 months with visits at 1, 3, 6, and 12 months; if subjects were not able to come to the site, the telephonic visit was conducted. Once the subjects met eligibility criteria and signed the informed consent, they were enrolled in the study. The data were collected on a case report form. Subject data about demographic characteristics, disease characteristics, medical history, vital signs, physical examination, laboratory investigations, angiography findings, and management of ACS were recorded at baseline. Data regarding clinical events (bleeding, dyspnea, and CV events), ticagrelor discontinuation, and ongoing current treatment were captured at all follow-up visits.

The study was performed in accordance with ethical principles that were consistent with the Declaration of Helsinki, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use—Good Clinical Practice and the applicable legislation on noninterventional studies after obtaining written informed consent from the subjects.

1.2.1. Statistical analysis

Statistical analysis wherever specified was performed using SAS, version 9.4, (SAS Institute, Cary, NC). This article summarizes the findings of an observational study and presents primary and secondary endpoint data from the analysis. Categorical variables were summarized with the frequency and percentage of patients in each category. Continuous variables were summarized descriptively with the number of patients, mean, standard deviation, minimum, median, and maximum values.

2. Results

2.1. Patient demographics and baseline characteristics

A total of 3001 subjects were enrolled in the study. Four subjects in the study were not on ticagrelor and were excluded from the analysis population. All the analysis for the study were performed on 2997 subjects. The subject disposition of 2997 subjects who fulfilled the eligibility criteria is presented in Table 1. Majority of (77%) subjects completed the study. The mean (SD) age of study population was 57.8 (10.1) years with a mean (SD) weight of 69.6 (11.3) kg. A clear predominance of males (80.1%) was documented in the study population (Table 2).

The history of hypertension was reported in 54.6% of patients followed by diabetes mellitus (45.2%), dyslipidemia (9.2%), and renal impairment (1.2%). Few of the patients also had a history of transient ischemic attack (0.2%) and nonhemorrhagic stroke (0.7%).

2.2. Primary analysis

Out of 2997 subjects, 48.9% had STEMI while NSTEMI were reported in 23% and UA 28.1%. The type of ACS and summary of management of ACS is presented in Tables 2 and 3 respectively. Single stent was used in 57.1% of subjects, whereas two stents were
Percentages are based on the total number of subjects enrolled.

N — Total number of subjects in the treatment group; n — number of subjects in the specific category; ACS — acute coronary syndrome; STEMI-ST — segment elevation myocardial infarction; NSTEMI-ST — non-ST segment elevation myocardial infarction; UA — unstable angina; CV — cardiovascular.

used in 30.1% subjects. There were 85% of subjects in whom drug eluting stent was used. The subjects with one coronary stenosis or occlusion were more than one third (41.4%) followed by two vessels (34.0%) and three coronary stenosis or occlusion (21.9%). The subjects with history of coronary stenosis or occlusion had 90–100% culprit coronary stenosis or occlusion in 73.2% subjects, and 41.2% subjects had 70–89% nonculprit vessels with single blockade.

2.3. Secondary analysis

2.3.1. To record various risk factors and their association with ACS and usage of ticagrelor

The duration of treatment with ticagrelor (in days) was calculated for 2993 subjects. The mean (SD) duration was 314 (110.2) days over 12 months. The uninterrupted use of ticagrelor was documented in 2437 (81%) subjects participated in the study (Table 3).

The majority of diabetic subjects had STEMI (641 out of 1354) in the study followed by UA (388) and NSTEMI (325). The risk factor and their association with ACS is presented in Table 2.

2.3.2. Details of clinical events incidence rate: bleeding, dyspnea, and CV events

There were 136 (4.5%) subjects who experienced any clinical event. There were 20 (0.7%) subjects who had CV deaths, five reported myocardial infarction (MI), and five ischemic stroke (IS). Bleeding and dyspnea were reported in 32 and 71 subjects, respectively. Two subjects experienced an event of bleeding with PLATO-major severity grade (Table 4).

The analysis of events of bleeding in subjects taking concurrent medication compared with overall population was performed. There were 21 subjects who experienced the event of bleeding while on concurrent medications. However, when compared the incidence with overall population experiencing the same event, it was not statistically significant (p 0.109) (Table 7).

Table 2
Details of demographics, intervention used, risk factors, and their association with ACS.

|Parameters| Patients (N = 2997) |
|---|---|
|Age in years Mean (SD)| 57.8 (10.9) |
|Gender n (%)| |
|Male| 2402 (80.1) |
|Female| 595 (19.9) |
|Weight in kg* Mean (SD)| 69.6 (11.3) |
|Type of ACS n (%)| |
|STEMI| 1466 (48.9) |
|NSTEMI| 689 (23.0) |
|UA| 842 (28.1) |
|Intervention used for patient n (%)| |
|PCI| 2769 (92.4%) |
|CABG| 102 (3.4%) |
|MM| 126 (4.2%) |

Risk Factors and their association with ACS

Table 3
Summary of ACS management by type and usage pattern of ticagrelor in ACS patients.

|Parameters| STEMI (N = 1456) | NSTEMI (N = 689) | UA (N = 842) |
|---|---|---|---|
|ACS management, n (%)| | | |
|Percutaneous coronary intervention| 1363 (93.0) | 622 (90.3) | 784 (93.1) |
|Coronary artery bypass graft| 36 (2.5) | 32 (4.6) | 34 (4.0) |
|Medical management| 67 (4.6) | 35 (5.1) | 24 (2.9) |
|Whether stent was used n (%)| | | |
|Yes| 2801 (93.5) | | |
|No| 91 (3.0) | | |
|NA| 105 (3.5) | | |
|Number of stents used n (%)| | | |
|1| 1711 (57.1) | | |
|2| 843 (28.1) | | |
|3| 191 (6.4) | | |
|4| 45 (1.5) | | |
|>4| 11 (0.4) | | |
|Stent type| | | |
|BMS| 169 (5.6) | | |
|DES| 2547 (85.0) | | |
|BVS| 115 (3.8) | | |
|Missing| 195 (6.5) | | |
|Duration of treatment with ticagrelor (in days)| | | |
|Mean (SD) n = 2993| 314.1 (110.2) | | |
|Median| 366.0 | | |
|Min, Max| (1.0, 414.0) | | |
|Ticagrelor interrupted/discontinued, n (%)| | | |
|Ticagrelor not interrupted| 2437 (81.3) | | |
|Ticagrelor interrupted| 13 (0.4) | | |
|Ticagrelor discontinued| 547 (18.3) | | |
|Reason for interruption/discontinued, n (%)| | | |
|Bleeding| 19 (0.6) | | |
|CV events| 17 (0.6) | | |
|Dyspnea| 27 (0.9) | | |
|Nonavailability| 7 (0.2) | | |
|Nonavailability| 397 (13.2) | | |
|Subject unwillingness| 88 (2.9) | | |

STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST segment elevation myocardial infarction; UA — unstable angina; CV — cardiovascular. N — Total number of subjects in the treatment group; n — number of subjects in the specific category; NA — not available; SD — standard deviation. BMS — bare metal stent; DES — drug eluting stent; BVS — bioresorbable vascular scaffold; ACS — acute coronary syndrome.
coronary syndrome. Two subjects had multiple events. 

Table 4
Details of clinical events incidence rate: bleeding, dyspnea, and CV events.

| Clinical events | Ticagrelor (N = 2997) |
|-----------------|-----------------------|
| Yes             | 136 (4.5)             |
| No              | 2861 (95.5)           |
| MI              | 19 (0.6)              |
| IS              | 23 (0.8)              |
| CV death        | 20 (0.7)              |
| Missing         | 76 (2.5)              |

Incidence of stent thrombosis, n (%) No 126 (4.2) Possible 4 (0.1) Probable 4 (0.1) Definite 4 (0.1)

Table 5
Details of thrombolytic given for current episode for ACS management and clopidogrel received previously for ACS management.

| Thrombolytic given for current episode, n (%) | Ticagrelor (N = 2997) |
|-----------------------------------------------|-----------------------|
| Yes                                           | 338 (11.3)            |
| No                                            | 2659 (88.7)           |
| Fibrinolytic used, n (%)                      |                       |
| Streptokinase                                 | 189 (55.9)            |
| Urokinase                                      | 3 (0.9)               |
| Tenecteplase                                   | 75 (22.2)             |
| Alteplase                                      | 3 (0.9)               |
| Others                                        | 68 (20.1)             |

Patient received Clopidogrel previously, n (%) Yes 1067 (35.6) No 1930 (64.4)

Table 6
Summary of concomitant medication (all enrolled subjects).

| Concomitant medication | Ticagrelor (N = 2997) |
|------------------------|-----------------------|
| Aspirin                | 2972 (99.2)           |
| Unfractionated heparin | 1236 (41.2)           |
| Low molecular weight heparin (LMWH) | 601 (20.1)          |
| Fondaparinux           | 197 (6.6)             |
| GP 2b/3a inhibitors—Tirofiban | 171 (5.7)          |
| GP 2b/3a inhibitors—Abciximab | 82 (2.7)             |
| GP 2b/3a inhibitors—Eptifibatide | 56 (1.9)           |
| Bivalirudin            | 12 (0.4)              |

Table 7
Incidence of bleeding events and concomitant medications.

| Category | Ticagrelor (N = 2997) | p valueb |
|----------|-----------------------|----------|
| Bleeding in overall population | 32 (1.1) | 0.1092 |
| Bleeding in patients with concurrent medications | 21 (0.7) |
| Unfractionated heparin | 20 (69.2) |
| Low molecular weight heparin | 8 (38.1) |
| Fondaparinux | 0 (0.0)        |
| GP 2b/3a inhibitors—Tirofiban | 6 (28.6) |
| GP 2b/3a inhibitors—Abciximab | 3 (14.3) |
| GP 2b/3a inhibitors—Eptifibatide | 0 (0.0) |
| Bleeding in patients without concurrent medications | 11 (0.4) |

Percentages in the bleeding main categories are based on the “all enrolled” patients. Percentages in the medication subcategories are based on the total number of patients in the “bleeding in patients with concurrent medications” row.

2.3.3. Details of thrombolytic given for current episode for ACS management and duration of ticagrelor load

Overall, 338 (11.3%) subjects received thrombolytic treatment for their current episode, and over half of those patients (55.9%) received streptokinase as fibrinolytic therapy (Table 5). The time between fibrinolysis and ticagrelor loading in a large proportion of patients (69.5%) was ≥24 h, and nearly half of them (48.8%) were administered with ticagrelor in Cath lab after angiography. The subjects who were received clopidogrel before ticagrelor at the baseline were 35.6%. Streptokinase was the most common fibrinolytic used followed by tenecteplase. Incidence of any clinical event was numerically similar in fibrinolyzed subgroup compared with overall population with numerical increase in the incidence of myocardial infarction (MI). Incidence of PLATO defined major and minimal bleeding were lower in patients undergoing fibrinolysis than overall population (Table 5 and Fig. 1).

2.3.4. Details of ticagrelor discontinuation and reason

Ticagrelor was interrupted in 13 (0.4%) subjects, whereas 81% of subjects continued it with no interruption. Nonaffordability of the drug was the reason for interruption and discontinuation in 397 (13.2%) subjects (Table 3).

2.3.5. Background/concomitant medication

Almost the entire study population (99.2%) received concomitant medication. The most prescribed medication included aspirin as acute coronary syndrome.
(99.2%) followed by unfractionated heparin (41.2%) and low molecular weight heparin (20.1%) (Table 6).

3. Discussion

CV diseases are major causes of morbidity and mortality in the Indian subcontinent, causing more than 25% of deaths. It has been predicted that these diseases will increase rapidly in India, and this country will represent more than half the cases of heart disease in the world within the next 15 years.11 ACS remains a vital health issue worldwide. ACS needs close patient monitoring and attention as it imposes significant restrictions on the patient’s quality of life. Its pathogenesis is attributable to many etiologies including physical inactivity, smoking, elevated low-density lipoprotein, hypertension, and genetic factors.12

The present study was a large observational study conducted in tertiary care hospitals across India with 2997 subjects. The results suggested that in >90% of patients with STEMI or NSTEMI or UA underwent PCI as an intervention in the management of ACS, PCI can restore the flow of blood into the myocardium in >90% of patients if performed by a skilled provider at a proficient PCI facility.13,14 A tertiary care hospital in Delhi completed a registry study in STEMI patients from Feb 2013 to May 2015. Out of a total of 371 enrolled patients, 96.4% of patients underwent successful primary PCI.15 The majority of the patients in the TREASURE study population used a drug-eluting stent. A single stent was used in more than half study population. However, a maximum of ≥4 stents were used in around 02% of patients.

The evaluation of risk factors for ACS such as smoking, diabetes mellitus, and renal impairment performed in the study. The researchers found that smoking is a common risk factor in patients with <40 years. A retrospective analysis of PLATO study on Asian population demonstrated that patients with a history of smoking were between 38% and 41%.16 However, the overall patient population with a history of smoking was significantly lower in the present study. The enrolled patients who presented a history of diabetes mellitus constituted >40% population in all categories, i.e., STEMI, NSTEMI, and UA. However, the studies reported a lower percentage of the diabetic population with ACS.13–17

There was a low incidence of clinical events (4.5%) reported in the study which included 20 (0.7%) of CV deaths and 19 (0.6) of MI and 23 (0.8) of IS. SWEDHEART registry conducted in Sweden with 45,000 subjects, published the composite of all-cause death, readmission with MI, or stroke with ticagrelor vs. clopidogrel as 11.7 vs. 22.3% [adjusted hazard ratio (HR) 0.85; 95% confidence interval: 0.78–0.93] at 24 months.18 In an another multicenter, double-blind, and randomized controlled trial of ticagrelor vs. clopidogrel for the prevention of CV events in 18,624 patients, the incidence of CV deaths with clopidogrel were reported to be 4.0%.7

A small fraction of the study population experienced clinical events of bleeding during the study duration as compared with results published in previous studies. The PLATO study demonstrated 11.6% of cases of major bleeding with ticagrelor, while in the present study, two subjects experienced PLATO major bleeding.7 The percentage of the population with TIMI-minimal bleeding was also less than one percent, and single patient reported TIMI-major event. The researchers demonstrated that fibrinolytic therapy contributed to TIMI events.19 The incidence of PLATO defined major and minimal bleeding were lower in patients undergoing fibrinolysis than overall population in TREASURE study. Streptokinase (6%) was the most commonly prescribed fibrinolytic among all. A multicenter, randomized, and double-blind trial conducted in 18,624 patients from October 2006 through July 2008. The interventions studied were of ticagrelor and clopidogrel. In our study, the bleeding events were significantly lesser than reported in the PLATO study. The event of dyspnea occurred in 68 (2%) patients with ticagrelor. The reason for discontinuation of ticagrelor among 27 (0.9%) patients was dyspnea. The event of dyspnea was reported significantly less in the present study as compared with the abovementioned study (13.8%). More than 60% of subjects with the reported event of bleeding, prescribed concomitant medication such as unfractioned heparin, GP 2b/3a inhibitors, and low molecular weight heparin. The concomitant medications could have an association with the risks of bleeding. Though the incidence of bleeding reported in the present study was lower than the literature.16

Antiplatelet therapy is of high importance in ACS patients. The majority of the population using ticagrelor continued with the drug in an uninterrupted fashion. The reason for discontinuation of ticagrelor in 13.2% of patients was reported to be nonaffordability of the drug. Whereas, only a small fraction of patients switched/discontinued the treatment because of CV events, dyspnea, or nonavailability. The proportion of patients restarting ticagrelor intake after discontinuation or switching was reported to be low. Almost the entire study population was found to be taking concomitant medications.

The limitations of the study were that majority of sites from where data has been collected are tertiary care hospitals, and management of the CV events with PCI, CABG, and MM may not represent the true incidence. Also, the study design wherein there were subjects who were followed up at 30 days may have contributed for underrepresentation of CV events. Also, another limitation of study was that evaluation of use of morphine and its effects on activity of ticagrelore was not performed.
4. Conclusion

Ticagrelor has been used across ACS types and in different management strategies in real world settings in India. Majority of the patients who had STEMI and underwent PCI were prescribed ticagrelor. Moreover, the most commonly used stent was drug eluting stent. The major reason for discontinuation of drug was nonaffordability of treatment.

Conflicts of interest

All authors have none to declare.

Disclosures

Ethics

All necessary ethical approvals were taken for conducting of this study.

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Author contribution

All authors have contributed in the concept, data analysis, execution, interpretation, statistics and manuscript preparation.

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