OPINE-IT: Oral AntiPlatelets Usage Pattern IN AcutE Coronary Syndrome: Exploring The Indian Ticagrelor Experience

Abstract

Background: Dual anti-platelet therapy (DAPT) includes aspirin and a P2Y12-receptor antagonist, is the cornerstone of treatment for patients with acute coronary syndrome (ACS). Real-world data on the perception and belief on the use of oral anti-platelets (OAP) for the management of ACS can provide vital information about any existent gaps between clinical practice and evidence based medicine and can help effectively address the ways to improve patient care management.

Aims and objectives: The purpose was to record the responses from the real-world practice amongst Indian cardiologists on the uses of OAPs to manage ACS.

Materials and methods: The present survey was a prospective observational survey on a set of 16 questions, of which response was collected from 192 clinicians [Cardiologists (majorly), cardio-vascular thoracic surgeons and physicians].

Results: A high prevalence of ACS was noted by the clinician each month. The majority of the patients reached the emergency room (ER) of a hospital between 2-4 hours (57.2%) after the onset of symptoms. ST-segment elevation myocardial infarction (STEMI) accounted for 42.4% of all patients. The major factors deciding the choice of OAP amongst clinicians were faster onset of action of the drug (84.2%), followed by lesser bleeding risk (47.3%). Overall, ticagrelor was the most preferred P2Y12 antagonist (92%) in this real-world practice survey; the perceived reasons being primarily due to its faster onset and offset of action (85.2%). The high cost was the major factor for not considering ticagrelor (63%). The majority of the participants found ticagrelor treatment (65%) to be safe, as per lesser bleeding experience in clinical practice.

Conclusion: In this pan-India survey, ticagrelor was found to be the drug of choice among Indian Cardiologists due to multiple benefits for ACS management in real-world practice.

Keywords: a real-world survey, acute coronary syndrome, cardiologist, dual anti-platelet therapy, ticagrelor

Introduction

Cardiovascular disease (CVD) is one of the most common non-communicable disease which leads to more than 17 million deaths globally every year and out of that India accounts for 20% death, especially in young population. According to Global Burden of Disease study state age-standardized CVD death rate of 272 per 100000 population in India which is much

higher than that of global average of 235 and Coronary Artery Disease (CAD) is major contributor for death related to CVD [1]

The burden of ACS in India is higher in comparison to the rest of the world. The CREATE registry reported 20,468 ACS patients from 89 centers from 10 regions and 50 cities in India and observed that amongst Indian ACS patients, the rates of ST-elevation myocardial infarction (STEMI) were higher (61%) as compared to developed countries. [2]

Dual anti-platelet therapy (DAPT) is the cornerstone of treatment for patients with ACS. DAPT with a P2Y12 inhibitor and aspirin is the standard anti-thrombotic therapy in patients with ACS and those undergoing percutaneous coronary intervention (PCI).

Clopidogrel, ticagrelor or prasugrel form the preferred component of DAPT with aspirin in the management of ACS. Clopidogrel and prasugrel are irreversible inhibitors of the P2Y12 receptor.[3] Ticagrelor is an oral, reversible, direct-acting, P2Y12 inhibitor that provides faster and more consistent P2Y12 inhibition than clopidogrel.[4] Ticagrelor offers several advantages over clopidogrel as the preferred component of DAPT.

To the best of our knowledge, there is no data available, till date, on the real-world use of these three P2Y12 inhibitors. Real-world surveys can provide crucial information about the cardiologists' perceptions and beliefs, regarding the use of DAPT. Through the present survey, we recorded the cardiologists' responses to the preference of oral anti-platelet (OAP) as a component of DAPT for the management of ACS, and have attempted to gain an insight into this important issue.

Materials and methods

OPINE-IT was a prospective and observational survey that included 192 participants [*majority were cardiologists (n=188)*, 2 were cardiothoracic and vascular surgeons (CVTS), and 2 were physicians]. Responses from all the participants were recorded in end of 2019 year on the usage of OAPs in the management of ACS.

A set of 16 questions with multiple choice answers was presented to each participant, and individual responses were recorded.

Table 1: The list of questions is as follows;

Question number	Question
1	How many patients with ACS do you treat per month (an approximate number)?
2	What is the average time that an Indian patient presents to the emergency room after the onset of symptoms of ACS?
3	In your practice, what proportion of ACS patients present with the different ACS subtypes?
4	What proportion of STEMI patients are treated with fibrinolysis in your centre?
5	Based on which criteria, would you like to select an OAP agent for an ACS

	patient?
6	Which P2Y12 antagonist (along with aspirin) is preferred in patients with ACS immediately after its onset?
7	Which are the beneficial features of ticagrelor compared to clopidogrel, which makes it preferable for use as a part of DAPT in ACS?
8	What proportion of ACS patients is treated with ticagrelor as a part of DAPT in your clinical practice?
9	What could be the reasons for not considering ticagrelor as the preferred OAP in ACS patients?
10	What is the average duration of ticagrelor therapy in ACS patients in your practice?
11	What are the possible reasons for shifting patients from ticagrelor to other oral antiplatelets?
12	What proportion of your post-ACS patients receive ticagrelor 60 mg BD after the 1st year of the event?
13	What is the most important reason for not using 60 mg ticagrelor in post-MI patients after one year of the event?
14	What proportions of STEMI patients who are treated with fibrinolysis receive ticagrelor?
15	How many of your patients, who were on ticagrelor treatment, had any adverse event due to ticagrelor?
16	Kindly specify the type of adverse event you have experienced most with ticagrelor in your ACS patients.

All the responses to above mentioned 16 questions were recorded in an excel sheet. Data analysis was performed using IBM SPSS ver. 20 software. The frequency distribution of each response was documented. All the data are expressed as number and percentage. No further statistical test was performed.

Results

The majority (76.5%) of the participants responded that they treated 20-60 ACS patients each month, whereas 12% affirmed treating less than 20 ACS patients each month (the overall range being 20-300 per month).

In response to Question 2; the majority of cardiologists believed that Indian patients presented to the emergency room between 2-4 hours (57.2%) and 30.1% felt that patients presented within 1-2 hours after the onset of symptoms. Sixteen (8.2%) cardiologists responded that patients reached the emergency room after 4 hours.

In response to Question 3; the majority believed that the most common subtype of ACS was STEMI (42.4%), followed by non-ST segment elevation myocardial infarction (NSTEMI) (32.4%) and Unstable Angina (26.4%).

The majority of the cardiologists believed that less than 10% of the STEMI patients were treated with fibrinolysis at their centre. However, 18.7% and 11.4% perceived this percentage to be between 10-20% and 20-40%. (Fig 1)

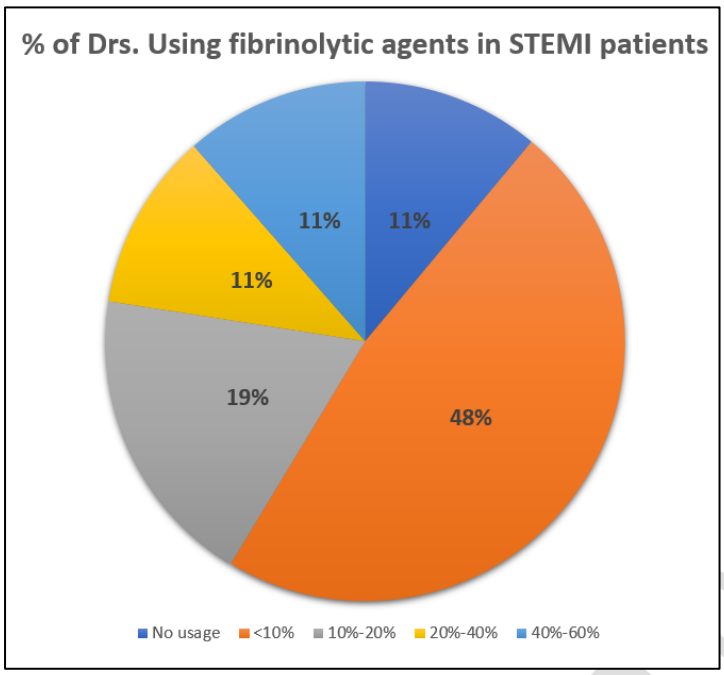
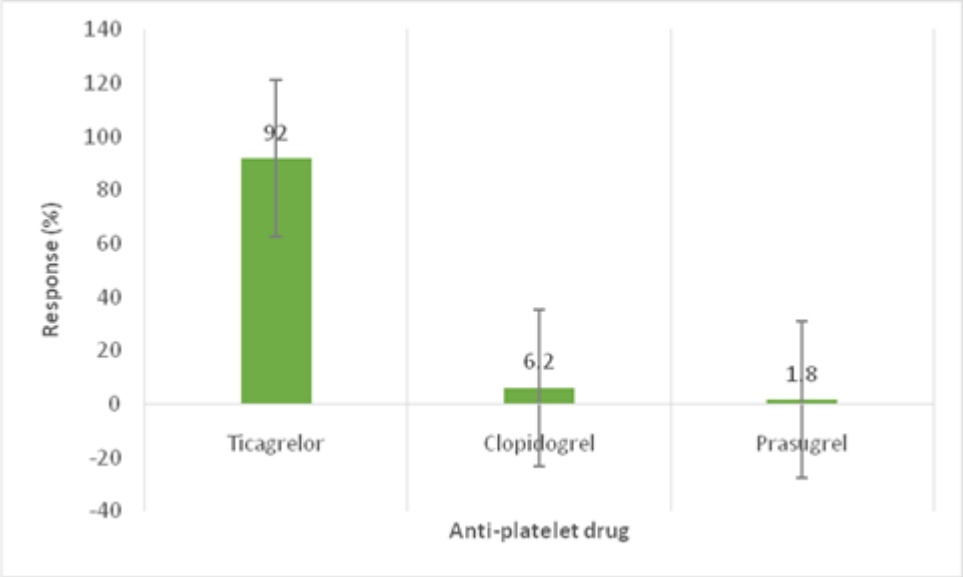


Figure 1: Perceived use of fibrinolytic agents in STEMI patients

For the majority of the cardiologists, selection of OAP agent for managing ACS patients was based on faster onset of action of the drug (84.2%) followed by lesser bleeding risk (47.3%), the advantage of being used for a longer duration period [more than 12 months, (32.24%)] and lack of drug-drug interactions with other agents like statins, beta-blockers, fibrinolytics administered in the emergency room (29.12%).

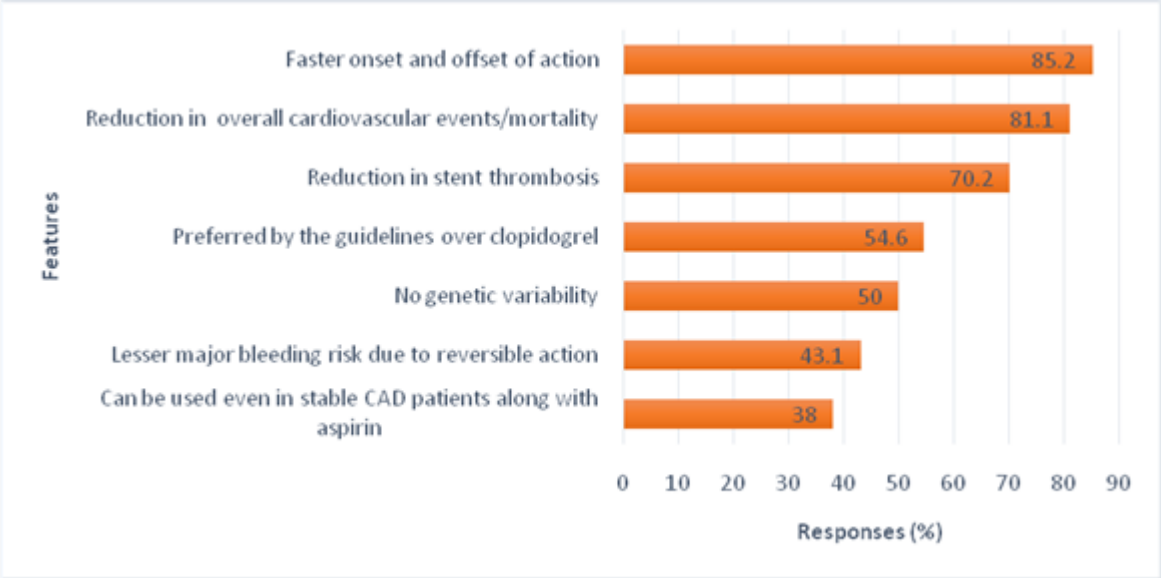
Ticagrelor was the most preferred P2Y12 antagonist (along with aspirin) by 177 (92%) participants in ACS immediately after its onset. Clopidogrel [12 (6.2%)] and prasugrel [3 (1.8%)] were the least preferred in the management of ACS compared to ticagrelor. (Fig. 2)

Figure 2: Showing the preference of anti-platelet drug among the study participants



In response to Question 7; majority of the cardiologists believed that ticagrelor has a faster onset and offset of action [164 (85.2%)] and this was related to definite evidence-based reduction in overall cardiovascular events/mortality [156 (81.1%)] with ticagrelor compared to clopidogrel. (Fig. 3)

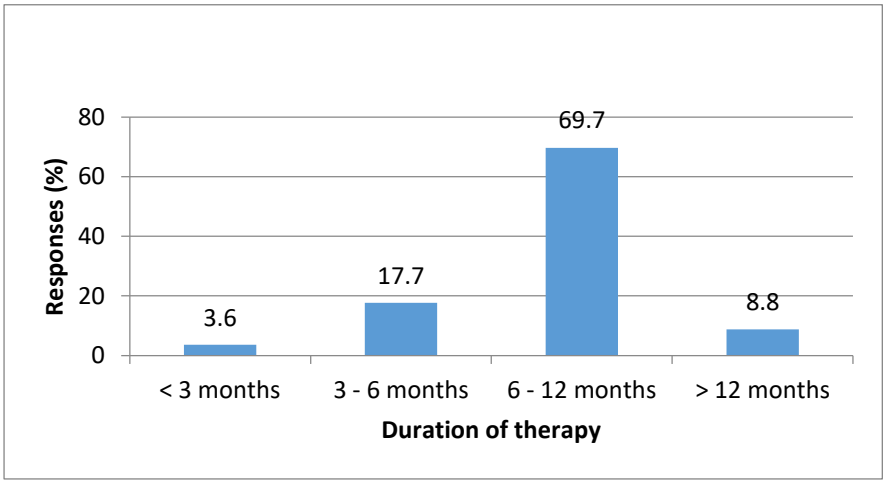
Figure 3: Reasons for preference of ticagrelor compared to clopidogrel



The most common reason for not considering ticagrelor as the preferred OAP in ACS patients was the high cost of the drug (63%) followed by risk of bleeding (19.2%). Three cardiologists (1.6%) did not perceive any clinical benefits of ticagrelor over other P2Y12 inhibitors, whereas 10% fear dyspnoea as the drug's side effects.

The majority of the participants consider the average duration of ticagrelor therapy in ACS patients for 6 to 12 months (69.7%), followed by 3-6 months (17.7%). Other 3.6% and 8.8% of participants used ticagrelor for fewer than three months and more than 12 months, respectively. (Fig. 4)

Figure 4: Considering the average duration of ticagrelor therapy in ACS



The high cost (59.2%) followed by an increased incidence of dyspnea (41.6%) and bleeding (14.6%) were the most common reasons for shifting patients from ticagrelor to other oral antiplatelets in the present survey.

The majority (47.3%) of the participants considered the use of ticagrelor 60 mg twice daily after the 1st year of the ACS in less than 10% of the patients. Other 24.4% and 16.1% of participants believed ticagrelor 60 mg twice daily after the 1st year of the ACS in 10-20% and 20-40% patients.

The most common reason for not considering 60 mg ticagrelor in post-MI patients after one year of the event was high cost [80 (41.6%)] followed by minimal clinical benefits [56 (29.1%)] and increased risk of bleeding [43 (22.4%)]. Other reasons were compliance and non-availability of 60 mg dose.

The majority of the participants were not readily treating STEMI patients with fibrinolysis receive ticagrelor. 36.4% responded that in <10% of the STEMI patients treated with fibrinolysis receive ticagrelor, while 46% used ticagrelor in less than 50% of STEMI patients treated with fibrinolysis.

In response to Question 16; majority (65%) responded that only <10% of the ACS patients have any type of adverse event due to ticagrelor. In the real-world practice, the most common type of adverse event experienced by the patients using ticagrelor ACS is dyspnoea (54%), followed by mild bleeding, ventricular pauses, and fatigue/hyperuricemia. (Table 2)

Table 2: Most common adverse events with ticagrelor

Common Adverse events with ticagrelor	Response (%)
Dyspnoea	54
Mild bleeding	19.8
Ventricular pauses	2.6
Fatigue/hyperuricemia	2

Discussion

The present survey was performed to record the responses from real-world users, mainly cardiologists, of P2Y12 inhibitors to manage ACS. To the best of our knowledge, this is the first of its kind, analysing cardiologists' views.

The present survey has highlighted and confirmed the previously reported higher incidence of ACS in India, where most participants affirmed providing consultation to 20-60 ACS patients every month. This is an alarming trend and mandates the importance of quick and evidence-based interventions to reduce these rising trends.

In present study, it was observed that more than half Indian ACS patients reached to the ER of a hospital within 2-4 hours after the onset of ACS symptoms, while ~30% of the patients presented between 1-2 hours of the event. However, a study from North-Eastern India highlighted the greater delay in seeking treatment among ACS patients.[5] This difference could be due to differences in population sampled in the two studies, resulting in better hospital reach in the current study and also increased awareness amongst patients to seek early medical help. In agreement, a cross-sectional multi-centre study reported that the median duration between chest pain onset and ER arrival was 2 hours.[6]

In response to the question for the different ACS subtype, the majority were treating STEMI, followed by NSTEMI patients. Unstable Angina was the third most common ACS which was being treated by the cardiologist. Reports from North-Eastern India reported a greater percentage of STEMI patients than NSTEMI, which is in line with the present nationwide survey.[5] Similarly, a higher incidence of STEMI was reported by the ERICO Study.[7] The incidence of ACS in young Indians is on the rise and is of particular concern. Contrary to Indian data, a lower incidence is reported in the western population (2-5% compared to Asian Indians, 11-16%). A study from England, including Myocardial Infarction (MI) patients, found ten times more risk of developing MI in young Indians than the white population.[8]

Faster onset and offset of action is the crucial component in the management of ACS to halt the next event's occurrence and prevent the chances of adverse events such as bleeding. The onset of action of ticagrelor is faster than clopidogrel.[9] The faster onset and offset of action is one of the crucial benefits of ticagrelor; the same was revealed in the present survey. The majority of the cardiologists believe that ticagrelor has a faster onset and offset of action. The faster onset may be because ticagrelor is not a prodrug and does not require metabolic activation for anti-platelet activity.[10]

Another reason for considering ticagrelor by most cardiologists was the clinical benefits observed in overall cardiovascular events/mortality with ticagrelor compared to clopidogrel in real-world practice In another real-world study by Choe *et al.* including 9684 ACS patients who underwent PCI, ticagrelor was found to improve clinical outcomes than clopidogrel,[11] Supporting the present survey findings. Clinical improvement in ACS patients using ticagrelor is revealed in a large international PLATO trial (Platelet Inhibition and Patient Outcomes), where ticagrelor was found to be superior to clopidogrel.[12] The findings of

PLATO trial are also in agreement where at 12 months, the primary combined endpoint occurred in 9.8% of patients treated with ticagrelor versus 11.7% of patients treated with clopidogrel (hazard ratio [HR] 0.84, confidence interval [CI] 95% 0.77-0.92; p<0.001).[12]

In previous studies, a low incidence (0.5-2%) of stent thrombosis was observed, but it has a significant clinical impact due to a high risk of myocardial infarction and death.[13] Mortality due to stent thrombosis has been reported to be as high as 45%. [14] In the present survey, most cardiologists believe that ticagrelor leads to a reduction in stent thrombosis, which seems to be one of the most significant advantages from the cardiologist's perspective. Findings of a recent study by Park *et al.* agree with the present survey results where definite stent thrombosis was low with ticagrelor use. [15]

The recommendations by associations or medical bodies of any country have a significant impact on practicing physicians. European Society of Cardiology (ESC) and ACC/AHA also recommends that ticagrelor be preferred over clopidogrel as a P2Y12 antagonist in ACS patients with or without PCI.[16] The same was revealed in the present survey where cardiologists were aware of recommendations on the use of ticagrelor over clopidogrel to manage ACS.

Other beneficial features of ticagrelor compared to clopidogrel highlighted in the current survey were that ticagrelor has lesser major bleeding risk due to reversible action and belief that it can be used even in stable CAD patients along with aspirin. PLATO trial is in line with the present survey where the trial found that ticagrelor was superior in reducing the rate of death from vascular causes, myocardial infarction (MI), or stroke, without an increase in the rates of major bleeding in patients who had ACS, with or without ST elevation. [12]

Half of the cardiologists in the present survey believe that ticagrelor has no genetic variability and due to that it is the preferred drug as part of DAPT. In contrast, clopidogrel has been reported to have issues related to variability in anti-platelet response, pharmacogenomic influences, and drug interactions.[17, 18, 19]

The ACC/AHA guidelines highlighted ticagrelor's superiority in NSTEMI patients when used for more than 12 months as DAPT. The ESC guidelines also recommend administration of a $P2Y_{12}$ receptor inhibitor in addition to ASA for the 12 months following the index event, unless there are contraindications such as excessive bleeding risk.[20] The findings of the current survey are in line with these guidelines, where 12 months or more than 12 months of therapy were believed to be more effective by participants.

The cost of therapy is a significant factor deciding the use of any drug in developing countries, including India. Despite the recommendations of the guidelines and clinical benefits, patients are either shifted to other oral anti-platelet (OAP) or prescribed less costly drugs. In line with that in the present survey, cardiologists also believed that high-cost ticagrelor is the most common reason for not considering the preferred OAP in ACS patients. This was also highlighted in the SWEDEHEART registry, where the cost of ticagrelor was the major issue leading to increasing uses of clopidogrel. [21]A similar report was presented by Dobesh *et al.* [3]

In a recent retrospective cohort study analysis of ACS patients who underwent PCI (a large US and Korean database), it was demonstrated that net adverse clinical events (NACE) encompassing recurrent MI, revascularization, ischemic or hemorrhagic stroke, and GI bleeding—were not significantly different between the ticagrelor and clopidogrel groups at 1 year. This study also however concluded that unmeasured confounders could not be completely excluded, and therefore more real world clinical evidence based studies were required for providing more understanding on selection of antiplatelet agents in ACS management.[22]

The aim of the current pan-India survey was to precisely attempt to answer some of these questions and this real-world experience is a strength of the present survey; however, in such surveys, lack of randomization and personal biases and opinion play a confounding role and also represent a limitation. More such data needs to be generated to provide further insights into factors that drive the choice of DAPT, an integral component of therapy of all ACS patients.

Conclusion

ACS is highly prevalent in India, of which patients with STEMI are high in number despite early presentation in the hospital. Out of three P2Y12-receptor antagonists discussed in this survey, ticagrelor was the drug of choice among cardiologists due to multiple benefits for managing ACS in the real-world practice. Cost is the crucial factor for shifting or non-uses of ticagrelor among the cardiologists. OPINE-IT has provided real-world data and has answered many unanswered questions. It found that DAPT, including ticagrelor, is the most commonly used anti-platelet agent for ACS management due to its quick onset and offset effect resulting in faster and more platelet inhibition than clopidogrel. It also provides a significant reduction in mortality from vascular causes, myocardial infarction, and stroke as per already published literature. Class I recommendation by the guidelines also support the use of ticagrelor for the management of ACS. The major advantages of using ticagrelor are reduction in stent thrombosis and lesser major bleeding risk. The average duration of ticagrelor therapy in ACS patients should be for 6 to 12 months. However, the drug's high cost and fear of bleeding and dyspnoea limit its use in real-world practice. Time tested OAP like ticagrelor, which was once patent-protected, is now available at a low and affordable cost for Indian ACS patients.

List of abbreviations

ACS; acute coronary syndrome, OAP; oral anti-platelet agent, DAPT;dual antiplatelet therapy, ER; emergency room, STEMI; ST-segment elevation myocardial infarction, CVD; cardiovascular disease, PCI; percutaneous coronary intervention, NSTEMI; non-ST segment elevation myocardial infarction

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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