

Review



## TICAGRELOR, A NOVEL DRUG CHOICE TO ANTIPLATELET THERAPY IN ACUTE CORONARY SYNDROME

Pasupati Rajoria, Yang Ke Ping, Yang Jiawei, Yang Hua

Cardiology Department, Jingzhou Central Hospital, Affiliated to Yangtze University, Medical College, Jingzhou 434023, Hubei Province, P.R. China.

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### ABSTRACT:

The main drug for the treatment of acute coronary syndrome (ACS) is Aspirin but dual antiplatelet therapy decreases the risk of stent thrombosis and cardiovascular events in the long run. Thienopyridine like clopidogrel has been used for more than a decade for those patients undergoing percutaneous coronary intervention (PCI) and has been the drug of choice for the treatment of ACS. Clopidogrel has a modest and variable platelet inhibition as well as slow and variable metabolism. This further leads to inefficient conversion of clopidogrel to its active form resulting in a reduced pharmacodynamic response which confers an increased risk of recurrent cardiovascular events. Due to these drawbacks or limitations of clopidogrel there has been a long debate as to which antiplatelet agent should be added to aspirin for the same. Ticagrelor is a novel P2Y<sub>12</sub> receptor antagonist which, is recently approved by US Food and Drugs Administration (FDA) and unlike clopidogrel has reversibly and noncompetitively binds the P2Y<sub>12</sub> subtype of ADP receptors on the platelet surface, which prevents ADP-mediated activation of the GIIb/IIIa receptor complex, thereby reducing platelet aggregation. Bleeding is the most common side effect with ticagrelor, although dyspnea, ventricular pauses, and elevations in serum creatinine and uric acid are also associated with ticagrelor therapy.

**Objectives:** This review focuses on Ticagrelor, as a latest novel antiplatelet agent, its uses in the treatment of ACS, its adverse effects, the different research and trials conducted on it and comparison studies with clopidogrel a thienopyridine which is widely used today

**Methods and Materials:** A literature search was done by using various World Wide Web, search engines like Google and PubMed. Some important selected articles were analyzed on antiplatelet therapy for the treatment of Acute Coronary Syndrome and a comparison study was done to conclude as to which one was best keeping in mind the various adverse effects of the antiplatelet agents.

**Results:** After analyzing all the selected articles, it can be concluded that the use of the latest approved new novel antiplatelet agent "Ticagrelor" can be used as an antiplatelet agent for the treatment of Acute Coronary Syndrome.

**Conclusion:** In patients who have an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding.

**KEYWORDS:** Ticagrelor, P2Y<sub>12</sub> receptor antagonist, Clopidogrel, Antiplatelet agents, Acute coronary syndrome, Prasugrel

**Corresponding Author:** Pasupati Rajoria,

E-mail: [pashupati577@gmail.com](mailto:pashupati577@gmail.com)

Mobile Number: 0086-15090774849

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**INTRODUCTION:**

Acute coronary syndromes (ACS) are the leading cause of mortality and one of the main reasons for hospital admissions in the developed nations. [1] Improvement of outcomes in patients with ACS is therefore a major health care task. ACS is caused by myocardial underperfusion, as a result of the rupture or erosion of an atherosclerotic plaque within a blood vessel. The damage caused to the vessel wall results in the activation of blood platelets through a number of pathways, including adenosine diphosphate (ADP)-mediated platelet activation, where ADP binds the P2Y<sub>12</sub> receptor. Platelet activation leads to aggregation, and therefore thrombus formation. [2]

Current treatment guidelines for ACS from the American College of Cardiology, American Heart Association and European Society of Cardiology recommend the use of antiplatelet agents as important medications for reducing the risk of subsequent thrombotic events following an initial event. [3,4,5,6,7],

Aspirin and thienopyridines have been demonstrated to be of clinical benefit in patients with ACS, and are currently recommended with a Class I level of evidence by the guidelines issued by the American Heart Association, American College of Cardiology, and European Society of Cardiology. [3,7,8]

Over the last few years, new antiplatelet agents have become available, and this review article describes the latest treatment approaches for ACS, and addresses the key clinical questions surrounding the use of ticagrelor, the most recently approved antiplatelet agent for the treatment of ACS on the basis of previously published trials and research studies.

**Treating Acute Coronary Syndrome:** Until recently, most patients with ACS received aspirin plus a thienopyridine. Thienopyridines are a class of compounds that bind the platelet P2Y<sub>12</sub> receptor irreversibly, thereby inhibiting ADP-activation.

The most frequently used thienopyridine is clopidogrel (approved in the US for the treatment of ACS in 2002), but prasugrel is another option in this chemical class (approved in 2009 for patients with ACS who are to be managed with percutaneous coronary intervention [PCI]). [6,9] Both are prodrugs, which means that they require metabolic activation before they can have a therapeutic benefit.[10].

**Dual antiplatelet therapy for ACS:** Several antiplatelet agents with different modes of action are available. [11,12,13] ASA inhibits platelet activation by irreversibly acetylating cyclooxygenase-1, thereby inhibiting synthesis of the platelet activator thromboxane A<sub>2</sub>. Clopidogrel, a thienopyridine, irreversibly inhibits the action of another platelet activator, adenosine diphosphate, by antagonizing its P2Y<sub>12</sub> platelet receptor. The newer antiplatelet agent, prasugrel, also a thienopyridine, irreversibly inhibits the P2Y<sub>12</sub> receptor whereas ticagrelor, a nonthienopyridine, is a reversible P2Y<sub>12</sub> receptor antagonist. Dual antiplatelet therapy (DAPT) with ASA/clopidogrel, and more recently ASA/prasugrel or ASA/ticagrelor, simultaneously inhibits these 2 routes to platelet activation, producing an additive effect to improve thromboprophylaxis.

Rigorously developed clinical practice guidelines are available from the European Cardiology Society and the American Society of Cardiology. We will now focus our analysis on the treatment of ACS according to the Guidelines with suggested roles of prasugrel and ticagrelor which are an alternative to Clopidogrel widely used today.

1. American College of Cardiology/American Heart Association (ACC/AHA) Guidelines: The ACC/AHA created a widely used version of North American based ACS guidelines. Guidelines for STEMI (written in 2004 [14],

updated in 2007 [14] and again in 2009 [15]) and for NSTEMI/UA (2007 [16], updated 2011 [17], 2012 [18], and 2014) are in existence. The initial 2004 guidelines for STEMI recommended initial treatment with ASA as an antiplatelet agent. Additional antiplatelet agents were not recommended in the emergency department. Once diagnostic angiography had been performed, clopidogrel was recommended to be started for patients scheduled to undergo PCI. In subsequent updates to this document, the role of antiplatelet agents was modified; one primary change focused on the use of thienopyridine antiplatelet agents. The 2009 update recommended the use of clopidogrel as soon as possible in patients that may receive primary or non-primary PCI (class one recommendation, level of evidence C) or prasugrel as soon as possible for patients that will be receiving primary PCI (class one recommendation, level of evidence B). The guidelines do not address the role of ticagrelor. The current ACC/AHA NSTEMI guidelines were very recently published in September 2014 and prasugrel and ticagrelor play a large role in the management of ACS. Dual antiplatelet therapy is now recommended (class one recommendation, level of evidence B) with ASA and one of clopidogrel, or ticagrelor in both short- and long-term management of ACS. It is important to note that the guideline writing group did not recommend one P2Y<sub>12</sub> receptor inhibitor over another.

2. European Cardiology Society (ESC) Guidelines: The European Cardiology Society produces clinical practice guidelines to help guide medical practitioners in the treatment of ACS. Similar to the ACC/AHA, they have separate documents for NSTEMI/ACS (2011) [7] and for STEMI/Acute Myocardial Infarction (2012) [19]. ECS STEMI guidelines recommend dual antiplatelet therapy with ASA (class 1 recommendation, grade B evidence) and an ADP receptor antagonist (class 1 grade

A) as early as possible for patients with planned PCI. The key difference in the ECS guidelines when compared to the ACC/AHA guidelines is that prasugrel and ticagrelor are suggested as the preferred ADP receptor antagonists (class 1 grade B) and suggest clopidogrel only when prasugrel and ticagrelor are contraindicated or unavailable. The ECS also suggests dual antiplatelet therapy to be started as soon as possible in NSTEMI patients (class 1 grade A). Similar to their STEMI recommendations, the ECS suggests prasugrel or ticagrelor (both class 1 grade B) as the ADP receptor antagonists of choice and again suggests clopidogrel only when prasugrel and ticagrelor are contraindicated or unavailable (class one grade A). Additionally, the ECS guidelines suggest a 600mg loading dose of clopidogrel for patients scheduled for invasive management when this medication is chosen as the ADP receptor antagonist (class 1 grade B).

#### **MATERIALS AND METHODS:**

A literature search was done by using various World Wide Web, search engines like Google and PubMed. Some important selected articles were analyzed on antiplatelet therapy for the treatment of Acute Coronary Syndrome and a comparison study was done to conclude as to which one was best keeping in mind the various limitations of the old and the latest novel antiplatelet agents.

#### **RESULT AND DISCUSSIONS:**

**Limitations of Thienopyridines:** Clopidogrel as an antiplatelet agent has several principal limitations.

**The first limitation** is related to the metabolism of clopidogrel, which is a prodrug requiring two-step activation involving several hepatic cytochrome P isoenzymes to convert to the active metabolite. This results in a delayed onset of action (6–8 hours after a 300 mg loading dose) and potentially increases the risk of ischemic events especially in the scenario of

urgent coronary intervention. Doubling of the loading dose from 300 mg to 600 mg with a subsequent increase in the maintenance dose from 75 mg to 150 mg for seven days, in the recently reported randomized trial Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT OASIS-7) trial in an ACS population had no significant effect on the primary endpoint of cardiovascular death, MI, or stroke at 30 days (4.2% in patients on the high dose versus 4.4% in patients on the standard dose; hazard ratio [HR] 0.95, 95% confidence interval [CI]: 0.84–1.07).[20] However, among patients managed with PCI within 24 hours (approximately two thirds of the study patients), high-dose clopidogrel yielded a significant 15% reduction in the composite of cardiovascular, death, MI, or stroke (3.9% versus 4.5%, HR 0.85, 95% CI:0.74–0.99) that was driven mainly by significantly lower rates of MI in the high-dose clopidogrel group (2.0% versus 2.6%,HR 0.78, 95% CI: 0.64–0.95). There was also a significant 42% reduction in the risk of the key secondary endpoint of definite stent thrombosis in the high-dose clopidogrel group (0.7% versus 1.2%, HR 0.58, 95% CI: 0.42–0.79). However, reduction in the rates of ischemic endpoints was offset by higher rates of major bleeding with the higher clopidogrel dose both in the entire study population (2.5% versus 2.0%; HR 1.25, 95% CI: 1.05–1.47) and in the PCI population (1.6% versus 1.1%; HR 1.44, 95% CI: 1.11–1.86).[20]

**The second limitation** of clopidogrel is related to its irreversible binding to P2Y<sub>12</sub> receptors, leading to a gradual recovery of platelet function after drug withdrawal. This places patients who need urgent surgical revascularization at increased risk of bleeding within 5–7 days after cessation of clopidogrel.

In the CURE study, among patients undergoing coronary artery bypass grafting (CABG), bleeding tended to be more common if CABG was performed within five days of clopidogrel administration (8.5% with clopidogrel versus 5.7% with placebo,  $P$  0.07), compared with longer than five days (4.4% versus 5.3%,  $P$  0.53).[21] Furthermore, in a prospective study of 224 consecutive patients undergoing non-emergent first-time CABG, patients with versus without preoperative clopidogrel exposure within seven days had greater 24-hour mean chest tube output (1224 mL versus 840 mL,  $P$  0.001), were less frequently extubated within eight hours (54.2% versus 75.8%,  $P$  0.002), required more frequent transfusions of packed red blood cells (2.51 units versus 1.74 units,  $P$  0.04), platelets (0.86 units versus 0.24 units,  $P$  0.001), and fresh frozen plasma (0.68 units versus 0.24 units,  $P$  0.02), and had significantly higher rates of reoperation for bleeding (6.8% versus 0.6%,  $P$  0.018).[22]

**The third limitation** of clopidogrel is the broad interindividual variability in levels of platelet inhibition achieved with clopidogrel as an antiplatelet agent. Clopidogrel results in only 30% to 40% mean inhibition of platelet aggregation response to ADP, with up to one third of patients having inadequate platelet inactivation (“nonresponders”). [23] This has particular significance given that clopidogrel resistance correlates with higher rates of ischemic events. [24] Within the last few years, bleeding is gaining recognition as the most common complication in patients with ACS. [25]

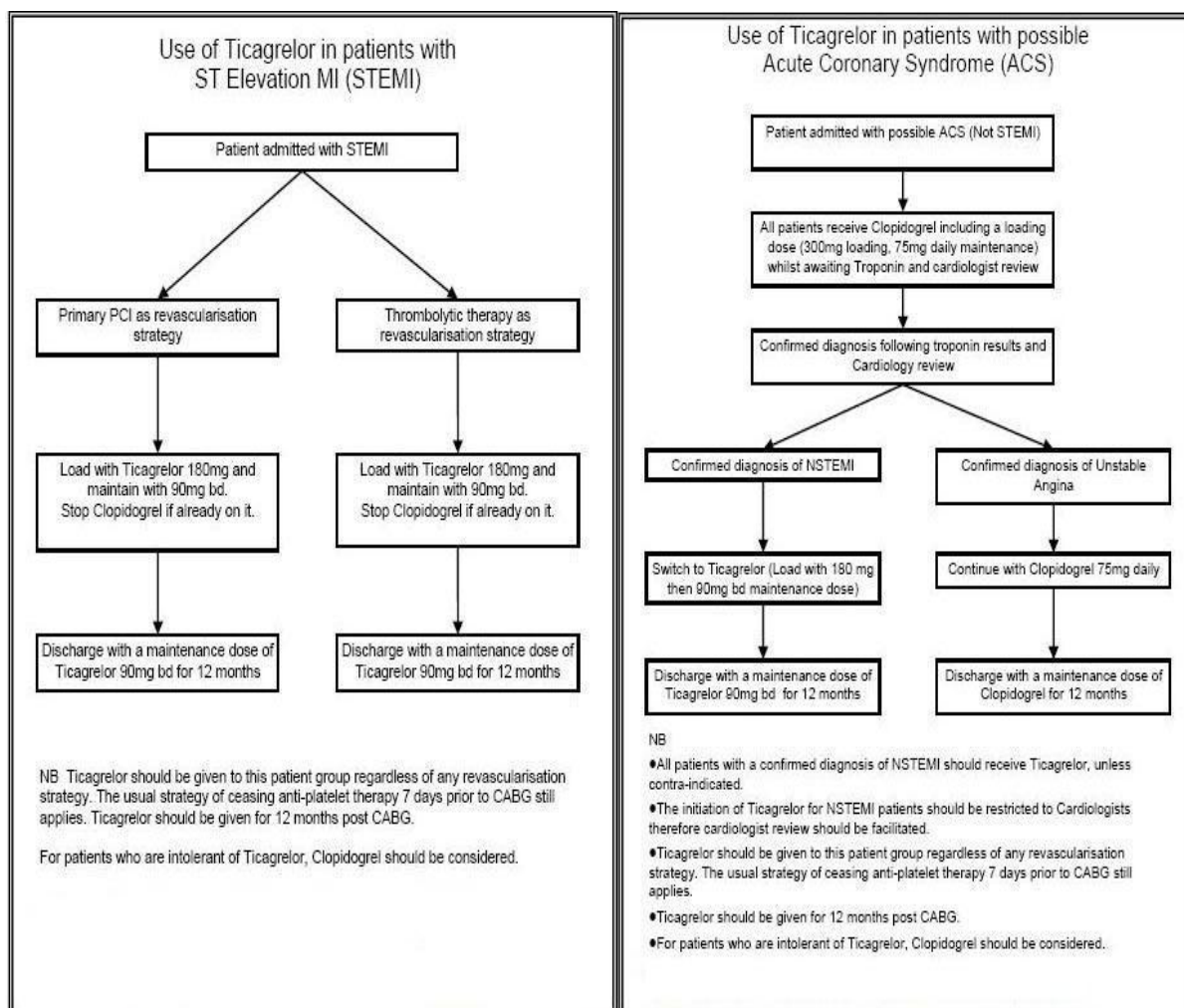
Because hemorrhagic events confer an unfavorable prognosis in patients with ACS, [26,27,28] bleeding and ways of preventing it assume particular importance. Increased risk of hemorrhagic events is the main disadvantage of prasugrel as compared with clopidogrel. In the randomized, double-blind TRITON-TIMI 38

trial, treatment with prasugrel was associated with an increased rate of non-CABG-related major TIMI bleeding (2.4% versus 1.8%,  $P$  0.03), including life-threatening bleeding (1.4% versus 0.9%,  $P$  0.01) and fatal bleeding (0.45% versus 0.15%,  $P$  0.002).[29] Besides, CABG-related major TIMI bleeding occurred more frequently with prasugrel (13.4% versus 3.2%,  $P$  , 0.001), including two cases of fatal bleeding in the prasugrel group versus none in the clopidogrel group. These data prompted the Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee to recommend avoiding using prasugrel close to surgical procedures. The relative risk of bleeding with prasugrel was higher in patients weighing less than 65 kg (HR 1.73, 95% CI: 1.07–2.79,  $P$  0.05) and patients 75 years of age or older (HR 1.35, 95% CI: 0.97–1.88,  $P$  0.078). The rates of hemorrhagic stroke were also remarkably higher in patients with a history of prior stroke or transient ischemic attack treated with prasugrel than with clopidogrel (6.5% versus 1.2%,  $P$  0.002).[29] Given the above mentioned limitations of the second and third-generation thienopyridines, there is an obvious clinical need to improve on the benefits observed with clopidogrel and prasugrel. The ever continuing development of pharmacotherapy for ACS is directed towards creating an antiplatelet agent that will overcome the limitations of the currently available thienopyridines, have a better safety profile, and have at least equivalent efficacy compared with the thienopyridines.

**Ticagrelor: A new novel antiplatelet agent:**

Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor

P2Y<sub>12</sub> that has a more rapid onset and more pronounced platelet inhibition than clopidogrel. Ticagrelor is a potent antiplatelet agent licensed for use in combination with aspirin to reduce the risk of further cardiovascular events in patients presenting with acute coronary syndrome (ACS). Ticagrelor in combination with low-dose aspirin for up to 12 months as a treatment option in adults with acute coronary syndromes (ACS) is recommended. [Flowchart A and B] That is, people: (a) with ST-segment-elevation myocardial infarction (STEMI) is defined as ST elevation or new left bundle branch block on electrocardiogram that cardiologists intend to treat with primary percutaneous coronary intervention (PCI) or (b) with non-ST-segment-elevation myocardial infarction (NSTEMI) or (c) admitted to hospital with unstable angina is defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus ONE of the characteristics (1) age 60 years or older, (2) previous MI or CABG , (3) coronary artery disease with stenosis of 50% or more in at least two vessels, (4) previous ischaemic stroke or TIA, (5) carotid stenosis of at least 50%, or cerebral revascularization, (6) diabetes mellitus, (7) peripheral arterial disease, (8) chronic renal dysfunction, defined as a creatinine clearance of less than 60 ml/ min. [30]. Therefore, ticagrelor should be considered for patients with: (a) A new STEMI treated with primary PCI or thrombolytic therapy. (b) A confirmed diagnosis of NSTEMI irrespective of any revascularization, strategy. [31] Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist. [Flowchart A and B] [32]



**Flowchart A.** Dr. Mather, et al. [32]

**Flowchart B** Dr. Mather, et al. [32]

**Adverse Effects of Ticagrelor:** Non-bleeding side effects were only seldom observed in all clinical trials. Interestingly, dyspnea was quite frequent. In ONSET/OFFSET trial dyspnoic phenomena attributed to the drug occurred in 25%, 4%, and 0% of patients in the ticagrelor, clopidogrel, and placebo groups, respectively (ticagrelor versus clopidogrel  $p=0.01$ ). Three patients in the ticagrelor group stopped the study drug due to dyspnea. In the DISPERSE trial nonspecific symptoms, such as headache, were common. Nausea, dyspepsia, and hypotension seemed more common among ticagrelor recipients as was dyspnea. Of those who reported dyspnea, 27% of the patients had resolution of this symptom within 24 h, 25% had resolution of the dyspnea after 24 h and 48%

experienced persistent symptoms during treatment (>15 days). As expected, PLATO trial confirmed this observation. Dyspnea was more common in the ticagrelor group than in the clopidogrel group (13.8% vs 7.8%). An immune-mediated mechanism has been proposed to explain this adverse reaction. Although this suggestion has been contradicted, it seems that the immune conflict between the hostile platelet receptors subjected to the reversible blockade by the antiplatelet agent may lead to mild episodes of thrombotic thrombocytopenic purpura and consequent fluid retention contributing to dyspnea. Furthermore, as an ATP modified molecule, AZD 6140 can be metabolized to adenosine and cause bradycardia or trigger dyspnea especially in cases of airway

hyper-reactivity. [33] In the same study, there was also a higher incidence of ventricular pauses in the ticagrelor group in the first week, but not at day 30. Pauses were rarely associated with symptoms and the two treatment groups were not significantly different in terms of the incidence of syncope or the pacemaker implantation rate. Ticagrelor intake was associated with a mild increase in creatinine and uric acid levels. [33, 34]

### **Ticagrelor Comparison Studies with Clopidogrel:**

**1. The Platelet Inhibition and Patient Outcomes (PLATO) trial** of ticagrelor enrolled 18,624 patients with ACS, with or without ST-segment elevation. [35] In the acute phase (within a median of 5 hours of hospitalization), the patients were randomized to receive initial loading doses of 180 mg ticagrelor or 300 mg clopidogrel plus ASA, followed by daily doses of 90 mg ticagrelor or 75 mg clopidogrel plus ASA. At 12 months, the primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92;  $P < 0.001$ ). Predefined hierarchical testing of secondary end points showed significant differences in the rates of other composite end points, as well as myocardial infarction alone (5.8% in the ticagrelor group vs. 6.9% in the clopidogrel group,  $P = 0.005$ ) and death from vascular causes (4.0% vs. 5.1%,  $P = 0.001$ ) but not stroke alone (1.5% vs. 1.3%,  $P = 0.22$ ). The rate of death from any cause was also reduced with ticagrelor (4.5%, vs. 5.9% with clopidogrel;  $P < 0.001$ ). No significant difference in the rates of major bleeding was found between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively;  $P = 0.43$ ), but ticagrelor was associated with a higher rate of major

bleeding not related to coronary-artery bypass grafting (4.5% vs. 3.8%,  $P = 0.03$ ), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types. [36] A substudy of the PLATelet inhibition and patient Outcomes (PLATO) trial (ie, PLATO PLATELET) showed ticagrelor to have greater and more consistent platelet inhibition than clopidogrel and did not increase the risk of bleeding. [37] The two cohorts that were evaluated in this substudy were 69 patients who had received either clopidogrel (300–600 mg loading dose followed by 75 mg per day) or ticagrelor (180 mg loading dose followed by 90 mg twice a day) for at least 28 days and 24 patients who had not received the study medication and have not received clopidogrel treatment within the previous 14 days. The three methods that were used to study platelet aggregation were light transmittance aggregometry (LTA), the Verify Now P2Y12 assay, and vasodilator-stimulated phosphoprotein. In all three studies of platelet aggregation, ticagrelor showed more suppression of platelets than clopidogrel in both peak and trough plasma concentrations. Loading doses of ticagrelor showed more platelet inhibition at one hour compared with clopidogrel. Ticagrelor is not a prodrug and does not have to be metabolically activated to have an antiplatelet effect, while clopidogrel is a prodrug which needs to be activated before eliciting a pharmacologic effect. The bioactivation of clopidogrel occurs in two sequential steps in the liver, with one pathway going through the CYP system, particularly CYP2C19. Once clopidogrel is activated by this enzyme, the active metabolite can inhibit platelets. This bioactivation of clopidogrel takes time and is evident even with loading doses of clopidogrel. A loading dose of clopidogrel significantly shortens the time to achieve maximal IPA; without a loading dose, it takes approximately 5 days to reach maximal IPA with clopidogrel 75 mg once daily. [38]

With 300 mg and 600 mg loading doses of clopidogrel, it takes about 4–8 hours to reach the final extent of platelet aggregation inhibition (i.e., IPA observed at the end of the platelet aggregation response), which is about 30% and 45%–50%, respectively, for the 300 mg and 600 mg doses of clopidogrel. [39,40]. This is in comparison with ticagrelor in which the final IPA of 80%–90% is reached approximately 2–4 hours after a 180 mg loading dose. [39,40]

**2. The Dose confirmation Study assessing antiPlatelet Effects of AZD6140 versus clopidogRel in non-ST-segment Elevation myocardial infarction (DISPERSE)** evaluated the pharmacodynamics, pharmacokinetics, safety, and tolerability of various dosages of ticagrelor (AZD6140) versus clopidogrel in patients receiving aspirin therapy.[41] This was a randomized, double-blind, parallel-group study conducted in patients with known atherosclerotic disease. The dosages of ticagrelor were 50 mg twice daily (n .41), 100 mg twice daily (n .39), 200 mg twice daily (n .37), or 400 mg once daily (n .46) and the dose of clopidogrel was 75 mg once daily (n .37). Treatments were given for 28 days and all patients received aspirin 75–100 mg once daily. Platelet aggregation was analyzed via optical aggregometry of platelet-rich plasma taken from blood samples of the patients at times 0 (predose), 2, 4, 8, and 12 hours(post-dose) on days 1, 14, and 28 and post-dose at 24 hours on days 14 and 28. The IPA was measured using 20 MADP as the agonist. The safety of the trial medication was assessed by reports of adverse events, including bleeding. The results showed ticagrelor at dosages of 100 mg twice daily, 200 mg twice daily, and 400 mg once daily inhibited ADP-induced platelet aggregation to a greater extent compared with either clopidogrel or ticagrelor 50 mg twice daily. The three higher dosages of ticagrelor did not differ from each other in terms of mean IPA. With this increase in IPA, there was also an increase in bleeding with

ticagrelor compared with clopidogrel. Most of the bleeding events were considered to be mild to moderate in severity. There was one major bleed in the ticagrelor group (400 mg once daily) that was gastrointestinal in nature. There was also an increased incidence of dyspnea in the ticagrelor group compared with the clopidogrel group which appeared to be dose-dependent, occurring with greatest severity in the patients receiving 400 mg once daily. The severity of dyspnea varied from mild to moderate, with a total of 29 reported instances of dyspnea, 21 of which were considered mild and eight were considered to be moderate.

**3. The ONSET/OFFSET** study was a randomized, multicenter, double-blind trial to evaluate the time to onset and offset of antiplatelet effects of ticagrelor 90 mg given twice daily compared with placebo and clopidogrel 75 mg once daily. [39] This study included patients with stable coronary artery disease who were receiving low-dose (75–100 mg per day) aspirin therapy. Patients were divided into one of three groups, i.e, ticagrelor (n .57), clopidogrel (n .54), or placebo (n .12). The ticagrelor and clopidogrel groups received loading doses (180 mg and 600 mg, respectively) before receiving the maintenance dosages. Fifty patients in each of the treatment arms were necessary for a 91% power to detect mean differences in IPA of 15% or more in the two treatment groups. Platelet function was determined by the use of three tests, i.e, LTA, the VerifyNow P2Y12 assay, and vasodilator-stimulated phosphoprotein-P. The primary outcome for onset was IPA (20 mol/L ADP) at 2 hours post initial dose, and offset was assessed by the slope of the IPA between 4 and 72 hours after the final study dose. The primary outcome was much greater in the ticagrelor group compared with the clopidogrel group (88% versus 38%,  $P$  , 0.0001). There was no difference in IPA in the ticagrelor group at 2



hours and 8 hours post loading dose, while IPA was greater in the clopidogrel group at 8 hours compared with 2 hours post loading dose ( $P$  .0.02). The maximum IPA was much higher in the ticagrelor group (93%) when compared with the clopidogrel group (58%) after the loading dose ( $P$  value not reported). The time to reach maximum IPA was faster in the ticagrelor group (2.0 hours) compared with the clopidogrel group (7.8 hours;  $P$  value not reported). Ticagrelor also had a faster offset of antiplatelet action compared with clopidogrel. The primary outcome for offset was higher in the ticagrelor group than in the clopidogrel group ( $P$  , 0.0001). A sub analysis of the ONSET/OFFSET data focused on the offset of antiplatelet action of both ticagrelor and clopidogrel with a high antiplatelet drug response. [42] Platelet activity was evaluated in this study in a similar fashion to the other studies discussed in this section. All three tests, LTA, VerifyNow, and vasodilator-stimulated phosphoprotein-P, showed significant differences in platelet function for ticagrelor compared with clopidogrel at 48 hours after the last dose was given. The IPA at 48 hours for clopidogrel was

approximately 60% compared with less than 40% for ticagrelor ( $P$  , 0.01). There was good recovery of platelet function by 72 hours in patients treated with ticagrelor, with IPAs of about 20% in patients with high platelet reactivity and about 10% in patients without high platelet reactivity. This is in comparison with values of about 45% and 20%, respectively, for clopidogrel. The IPA for ticagrelor after 2 days (36%) was similar to the IPA for clopidogrel after 5 days (33%) from the last treatment dose. Since it is recommended that clopidogrel be withheld 5 days prior to surgery, [42] these data can be useful for gauging how long a clinician should withhold ticagrelor before an invasive procedure. While the prescribing information for ticagrelor recommends discontinuation of ticagrelor 5 days prior to surgery, [43] one can argue for a shorter window of about 3 days based on the ONSET/OFFSET data. Therefore, Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y12 that has a more rapid onset and more pronounced platelet inhibition than clopidogrel. [44]

**Table 1: Comparison of Antiplatelet P2Y12 Inhibitors Clopidogrel vs Ticagrelor [40,45,46,47]**

	<b>Parameter</b>	<b>Clopidogrel</b>	<b>Ticagrelor</b>
1.	<b>Class</b>	2 <sup>nd</sup> generation thienopyridine	The first of a new class of orally active non-thienopyridine antiplatelet agents: cyclopentyltriazolopyrimidines
2.	<b>Metabolism Required</b>	Yes; 2 step P450 activation	Hepatic (CYP34A)
3.	<b>Mechanism of action</b>	Irreversible inhibitor of the adenosine diphosphate (ADP) P2Y12 receptor	Reversible inhibitor of the adenosine diphosphate (ADP) P2Y12 receptor
4.	<b>Prodrug</b>	Yes- Drug is inactive and needs to be metabolized to active metabolites.	No- Both drug and its metabolite are active.

5.	<b>Doses-</b>	Loading- 300-600mg Maintainance- 75mg daily	Loading- 180mg Maintainance- 90mg twice daily
6.	<b>Onset of action (IPA)</b>	300–600mg loading dose detected within 2 hours	180mg loading dose ~ 41% within 30 minutes
7.	<b>Maximum IPA</b>	30%–60%	85%–95%
8.	<b>Time to maximal IPA</b>	6-8 hours after loading dose	2-4 hours after loading dose
9.	<b>Half-life elimination of active metabolite</b>	After a single of 75 mg dose half-life is approximately 6 h.	~9 hours
10.	<b>Excretion</b>	Renal (50%), biliary (46%)	Biliary
11.	<b>Significant adverse effects</b>	None	Increased minor/major bleeding
2.	<b>Contraindications</b>	Hypersensitivity, active bleeding, significant liver impairment, and cholestatic jaundice	Hypersensitivity, active bleeding, history of intracranial hemorrhage, hepatic impairment, concomitant use of strong CYP3A4 inhibitors.
3.	<b>Resistance to Antiplatelet Effect?</b>	Yes	No

Ticagrelor is a novel non-thienopyridine inhibitor of the P2Y<sub>12</sub> ADP platelet receptor, which binds reversibly to its ligand allowing platelets to almost fully regain their activity within 3 days after therapy discontinuation. It also achieves rapid onset of action due to its rapid absorption and pharmacokinetics and is a powerful antiplatelet agent, more potent than the well-established thienopyridine clopidogrel. Initial studies as well as the large phase III PLATO trial have shown that ticagrelor use in acute coronary syndromes is associated with better outcomes with respect to all cause mortality, cardiovascular death and myocardial infarction, without a concomitant increase in major bleeding complications with the exception of intracranial hemorrhage which was more frequent although the absolute numbers were small. The relatively rapid cessation of ticagrelor's action after its withdrawal would make it suitable in cases where an open-heart surgery is anticipated.

However, by-pass surgery related bleeding showed only a trend towards reduction with ticagrelor compared to clopidogrel, which did not reach statistical significance. Moreover, extrapolation of the results from PLATO trial to other indications for clopidogrel monotherapy, such as stroke, or peripheral arterial disease, is premature. Ticagrelor's usefulness in patients undergoing elective stenting is also undetermined so far and finally, concomitant use of fibrinolytic agents is another issue that needs to be addressed particularly in view of the associated increase in intracranial bleeding and taking into account that patients undergoing fibrinolysis were excluded from PLATO. [46].

#### CONCLUSION:

The different trials and studies like CURRENT OASIS-7, CURE, TRITON-TIMI 38, bring light of the low efficacy and drawbacks of the presently used antiplatelet agents like

Clopidogrel and Prasugrel which further lead to the need of a new novel antiplatelet agent in the treatment of ACS. The various studies like PLATO, DISPERSE, ONSET/OFFSET carried out on the new novel antiplatelet agent "Ticagrelor", have proved its efficacy over the old ones. Ticagrelor has been recently included in the current ACC/AHA NSTEMI guidelines which has been published in September 2014 stating Ticagrelor as a antiplatelet agent for the Dual Antiplatelet Therapy which further proves it plays a large role in the management of ACS but further upcoming studies should provide us more insight view of the drug in specific subgroups of patients especially the dealing with its adverse effects. In patients who have an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding. Therefore, Ticagrelor is a very propitious new antiplatelet drug with impressive efficacy and reasonable safety.

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**ABBREVIATIONS:**

ACS- acute coronary syndrome

IPA- inhibition of platelet aggregation

ASA- acetylsalicylic acid (aspirin)

DAPT - Dual antiplatelet therapy

TIMI- Thrombolysis in Myocardial Infarction

CABG- coronary artery bypass graft

LTA- light transmittance aggregometry

HR- hazard ratio

ADP- adenosine diphosphate

PCI- percutaneous coronary intervention

FDA- Food and Drugs Administration

STEMI- ST-elevation myocardial infarction

NSTEMI- non ST-elevation myocardial infarction

PLATO - PLATelet inhibition and patient Outcomes

CI - confidence interval

UA- unstable angina

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