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ACUTE CORONARY SYNDROME

# Novel Antiplatelet Agent Ticagrelor in the Management of Acute Coronary Syndrome

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*Current clinical guidelines recommend dual antiplatelet agents namely aspirin and clopidogrel for the treatment of patients suffering from acute coronary syndrome (ACS). But the efficacy of clopidogrel is variable as it is a pro-drug, which has to be metabolized to become an active drug thus exhibiting variable platelet inhibition, increases risk of bleeding, stent thrombosis, and ischemia. To overcome this limitation, prasugrel was developed with increased antiplatelet activity thereby reducing the risk of myocardial ischemia and stent thrombosis. This action of prasugrel was associated with an increased risk of major bleeding. Finally, a novel reversible and direct-acting oral adenosine diphosphate (ADP) receptor antagonist, ticagrelor was developed that showed consistent and increased P2Y12 inhibition with similar incidence of bleeding but greater reduction in cardiac events compared to clopidogrel. The focus of this article is to review ticagrelor as a new class of P2Y12 inhibitor.* (J Interven Cardiol 2011;24:199–207)

## Introduction

Antiplatelet drugs are the backbone in the management of acute coronary syndrome (ACS). Aspirin has been used as an antiplatelet agent for a long time and when thienopyridines, a new class of drugs, were introduced, it was found that addition of these agents along with aspirin improved secondary prevention in ACS. At the present time clopidogrel, a thienopyridine, is the key drug of choice, which has been used in combination with aspirin for the treatment of ACS. However, there have been various drawbacks in the uses of clopidogrel as a pro-drug. Clopidogrel has to be metabolized in the liver and intestines in order to be activated.[1] Ticlopidine, another thienopyridine has fallen out of favor after discovery of clopidogrel due to its major risk for causing neutropenia. Prasugrel, a third-generation thienopyridine, was recently approved for use in the United States and Europe in 2009. Prasugrel has distinct advantage over clopidogrel due to faster onset of platelet inhibition and stronger antiplatelet activity. In a recently published multicenter randomized trial (TRITON-TIMI38), prasugrel was more effective in reducing cardiac events in comparison to clopidogrel at the cost of higher bleeding risk.[2] The main limitations of these drugs are long half-life and the need for pro-drug activation by the liver into the active metabolites. Furthermore, stent thrombosis continues to occur despite treatment with these P2Y12 receptor inhibitors in combination with aspirin due to platelet resistant in some patients. For these reasons, there has been an intensive research for developing a novel antiplatelet agent, which does not require liver activation and has shorter half-life. Ticagrelor (cyclopentyl triazolopyrimidine, previously known as AZD6140, Brilinta®), an oral antiplatelet medication that is a reversible inhibitor of the P2Y12 receptor, was developed with shorter half-life and without a need for liver activation compared with thienopyridines, such as ticlopidine, clopidogrel, and prasugrel (Fig. 1). Ticagrelor

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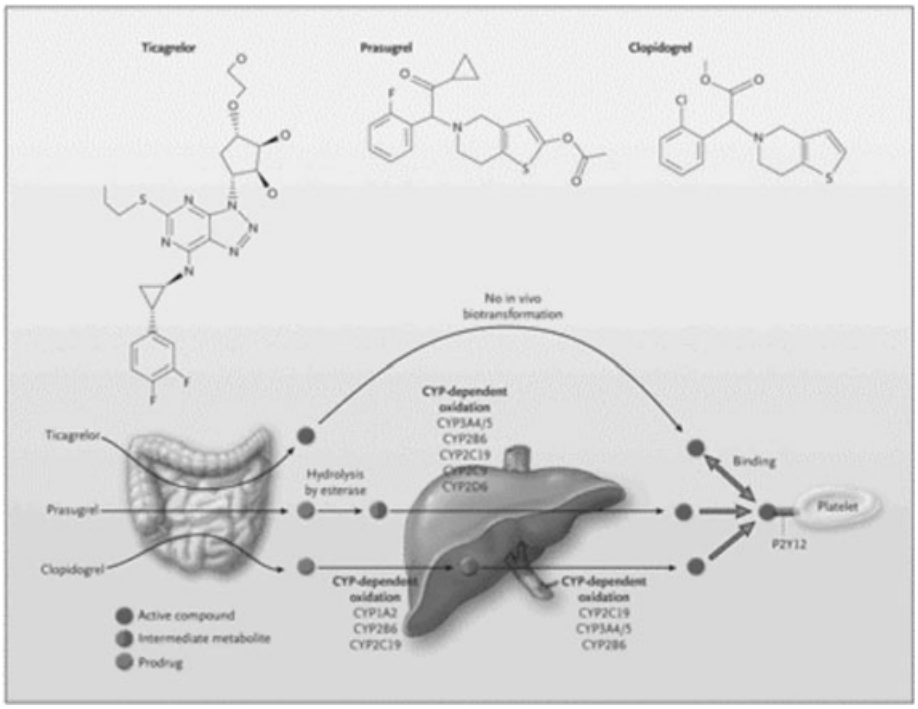


**Figure 1.** Biotransformation and mode of action of clopidogrel, prasugrel, and ticagrelor. Ticagrelor, a cyclopentyl triazolopyrimidine, is rapidly absorbed in the intestine. The absorbed drug does not require further biotransformation for activation. It directly and reversibly binds to the platelet adenosine diphosphate (ADP) receptor P2Y12. The half-life of ticagrelor is 7–8 hours. The thienopyridines prasugrel and clopidogrel are pro-drugs. Their active metabolites irreversibly bind to P2Y12 for the platelet's life span. After intestinal absorption of clopidogrel, it requires two cytochrome P-450 (CYP)-dependent oxidation steps to generate its active compound. After intestinal absorption of prasugrel, it is rapidly hydrolyzed, by means of esterases, to an intermediate metabolite and requires one further CYP-dependent oxidation step to generate its active compound. Most of the CYP-dependent activation occurs in the liver. Relevant CYP isoenzymes involved in the activation of both clopidogrel and prasugrel are also shown. Their activity may be affected by genetic polymorphisms. (Reproduced with permission from Schomig A. N Engl J Med 2009;0:NEJMe0906549v1–1).

compared with clopidogrel has been recently studied in a large randomized trial (PLATelet inhibition and patient Outcomes [PLATO] trial), demonstrating a significant reduction in the death rate from vascular causes, myocardial infarction (MI), or stroke without increasing major bleeding. In this article, we discuss the role of platelet in homeostasis and the effect of ticagrelor on platelets in detail.

## What is the Role of Platelets in Primary Hemostasis?

Primary homeostasis is caused by three factors: vascular contraction, platelet adhesion, and activation of coagulation factors leading to thrombus formation. The normal endothelium prevents thrombus formation by providing a physical barrier and by secretion of substances that inhibit platelets, including nitric oxide and prostaglandin $I_2$ (prostacyclin). Following injury to the vessel wall, the early incident is vasoconstriction, which is a temporary, locally induced phenomenon. Vasoconstriction not only limits extravascular blood loss, but also slows local blood flow, enhancing the adherence of platelets to exposed subendothelial surfaces triggering the activation of coagulation process. Therefore, the formation of the primary platelet plug involves platelet adhesion followed by platelet activation then aggregation to form a platelet plug.

**Platelet Adhesion.** The first incident in hemostasis is the adhesion of platelets to exposed subendothelium. Damaged endothelial surface exposed to platelets triggers platelet adhesion and activation as an important first step of hemostasis in the area of damaged

blood vessels. Adhesion process requires von Willebrand factor (vWf) binding to glycoproteins on the surface of platelets. In general, vWf serves as a bridge to help platelets to adhere fibrinogen, which also helps adhesion of platelets to the subendothelium (by attaching to a platelet receptor—the integrin, glycoprotein Ia/IIa).

**Platelet Activation.** Platelets circulating vessels with an intact, healthy endothelium remain in their original, inactivated state. This mechanism is supported by the absence of activating factors and also the release of prostacyclin (prostaglandin I2) by the healthy endothelium. However, when there is a damage in the cells, the adhesion of platelets to the vessel wall activates them, causing the platelets to change in shape, consequently activate the collagen receptors on their surface (an integrin receptor called glycoprotein IIb/IIIa), and undergo the release reaction (release alpha and dense granule constituents). In addition, upon activation, thromboxane $A_2$ ($TXA_2$) and platelet-activating factor (PAF) are synthesized by platelets and thromboxane is released, which is a potent platelet aggregating agonist and vasoconstrictor.

**Platelet Aggregation.** $TXA_2$, ADP (adenosine diphosphate), PAF, collagen, thrombin, and serotonin are platelet agonists, causing the activation of additional platelets, which bind to the adhered platelets. This activation is enhanced by the production of thrombin, which is an important platelet agonist through the coagulation cascade. Platelet aggregation is mediated mainly by fibrinogen, which binds to glycoprotein IIb/IIIa on adjacent platelets. The platelet aggregation controls the formation of the primary platelet clot, which is stabilized by the formation of fibrin.

**Coagulation Cascade and Platelet Activation (Secondary Hemostasis).** Platelets also play an important role in secondary hemostasis (coagulation cascade) due to its phospholipid surface and receptors for the binding of coagulation factors. Coagulation is not a simple process and involves a complex set of protease reactions involving different proteins that are normally present in plasma in the inactivation state. Once activation of clotting process starts, these proteins interact in sequential order. The final outcome of all these reactions is to convert fibrinogen, a soluble protein, to insoluble strands of fibrin.[3] Together with platelets, the fibrin strands form a stable blood clot. The major role of thrombin is to convert fibrinogen to fibrin, which is essential for the formation of hemostatic clot, which binds to aggregate platelet to form final step of hemostasis.

## Why Do We Need a New Antiplatelet Agent?

Platelets play a major role in atherosclerosis. Atherosclerotic plaques have shown the presence of chemokines and several growth factors derived from platelets.[4–7] Similar studies suggest that increased atherogenic risk factors have an association with activation of platelets.[8–13] The hypothesis for ACS is the rupture of atherosclerotic fibrous cap and the exposure of the extracellular matrix, which initiates thrombus formation, which in turn stimulates and recruits more platelets.[14–16] As the platelets play a key role in atherosclerosis, there have been multiple antiplatelet drugs developed for secondary prevention of coronary artery disease. Despite treatment with aspirin, clopidogrel and heparin in patients with ACS, thrombus formation can occur triggering myocardial ischemia or infarction.[17,18] There have been various reasons for this failure. One of the main reasons is thought to be clopidogrel resistance. Furthermore, clopidogrel is a pro-drug that needs to be activated before it can exert its antiplatelet effect. Many drugs that act on the same pathway as the clopidogrel interfere with its antiplatelet action, thus may increase the risk of thrombus formation and myocardial ischemia.[19–21] As compared with clopidogrel, prasugrel, another thienopyridine pro-drug, has a more consistent and pronounced inhibitory effect on platelets,[19,20] resulting in a lower risk of MI and stent thrombosis, but is associated with a higher risk of major bleeding in patients with ACS who are undergoing percutaneous coronary intervention (PCI).[2] Direct-acting $P2Y_{12}$ inhibitors (cangrelor and ticagrelor) introduce a conformational change of the $P2Y_{12}$ receptor, which results in concentration-dependent reversible inhibition of the receptor. Table 1 shows the comparison of properties of various antiplatelet agents.

## What is the Difference between Antiplatelets and Anticoagulants?

Anticoagulants are drugs that are administered to prevent the blood from thrombosis or prevent existing thrombus from getting larger. They can prevent the formation of thrombus in veins or arteries. Thrombus

**Table 1.** Comparison of Main Properties of Antiplatelet Agents

| | Ticagrelor | Prasugrel | Clopidogrel | Aspirin |
|---|---|---|---|---|
| Basic information | New class of orally active nonthienopyridine antiplatelet agents, the cyclopentyl triazolopyrimidines | 3rd generation thienopyridine | 2nd generation thienopyridine | Aspirin has an antiplatelet effect by inhibiting the production of thromboxane, which binds platelet molecules together |
| Mechanism of action | Reversible inhibitor of the adenosine diphosphate (ADP) P2Y12 receptor | Irreversible inhibitor of the adenosine diphosphate (ADP) P2Y12 receptor | Irreversible inhibitor of the adenosine diphosphate (ADP) P2Y12 receptor | Suppress the production of prostaglandins and thromboxanes, owing to its irreversible inactivation of the cyclooxygenase (COX) enzyme |
| Active substance drug/metabolite | Both drug and its metabolite are active | Drug is inactive and needs to be metabolized to active metabolites | Drug is inactive and needs to be metabolized to active metabolites | Acetylsalicylic acid |
| Time to achieve maximum platelet inhibition or maximum plasma concentration | After loading dose 180 mg the maximum plasma concentrations and maximum platelet inhibition are reached in 1–3 hours | After loading dose 60 mg, the maximum 60–70% platelet inhibition is usually achieved 2–4 hours, maximum plasma concentrations of active metabolite is reached within 0.5 hours | After loading dose 600 mg, the maximum plasma concentration is achieved in 1 hour and maximum platelet inhibition is within 2–3 hours | Plasma concentration is dose dependent, can continue to rise for up to 24 hours after ingestion when overdose |
| The mean elimination half-life | The mean elimination half-life is 6–13 hours (dose independent) | The mean elimination half-life of active metabolite is 3.7 hours | After a single of 75 mg dose half-life is approximately 6 hours. The elimination half-life of the inactive acid metabolite is 8 hours after single and repeated dose | Elimination half-life of about 2–4.5 hours. When higher doses of salicylate are ingested (more than 4 g), the half-life becomes much longer (15–30 hours) |
| Absorption | Rapidly absorbed | Rapidly absorbed | Rapidly absorbed | Acetylsalicylic acid is poorly soluble in the acidic conditions of the stomach, which can delay absorption of high doses for 8–24 hours |
| Elimination | No specific data have been found. | Approximately 70% of prasugrel metabolites eliminated by kidney | Approximately 40% of a 75 mg dose is excreted in urine and 35–60% is excreted in feces | Salicylates are excreted mainly by the kidneys as salicyluric acid (75%), free salicylic acid (10%), salicylic phenol (10%) and acyl (5%) glucuronides, and gentisic acid ( $< 1\%$) |

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formation can obstruct blood flow and cause MI, stroke, or thrombo-embolic disease. Anticoagulants and antiplatelet agents are drugs that reduce the risk of thrombus formation in vascular system. The main difference between them is the mechanism of action. Antiplatelet agents like aspirin decrease platelet aggregation and thrombus formation. They are mostly used for prevention of thrombus formation in the arterial system. Anticoagulant drugs such as warfarin prevent thrombus formation by inhibiting many coagulation factors. However, warfarin requires close dose monitoring and is associated with higher bleeding risk

in comparison to antiplatelet drugs. In general anticoagulants, including indirect (heparins) and direct (bivalirudin) thrombin inhibitors, do not target platelet signaling pathways or cell surface inhibitors, which are important in the pathogenesis of stent thrombosis.

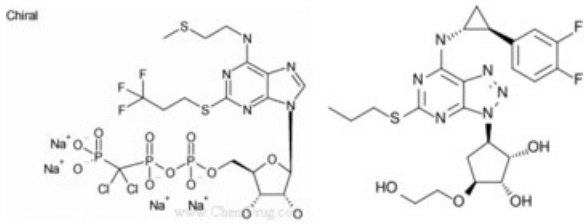
## Pharmacokinectics and Pharmacodynamics of Ticagrelor

Ticagrelor is the first reversible oral P2Y12 receptor antagonist.[22] Ticagrelor does not involve metabolic activation to inhibit the P2Y12 receptor as thienopyridines do, because it is not a pro-drug. Furthermore, ticagrelor has valuable pharmacokinetics and pharmacodynamics, including rapid peaking of plasma levels within approximately 1.5–3 hours and rapid onset of antiplatelet effects approximately within 2 hours.[22] In addition, the Ticagrelor has a half-life of 7–8 hours, and its antiplatelet effect is about 48 hours after the last dose.[23] This reversibility might be beneficial for surgical procedures.[24] On the other hand, in relation to possible poor compliance that could be a disadvantage.[25] However, study has shown that 24 hours after a maintenance dose of 90 mg, the mean percentage platelet aggregation was higher than that with 75 mg clopidogrel.[22]

## How Does Ticagrelor Work?

Ticagrelor is the first oral antiplatelet therapy to accomplish a significant reduction in cardiovascular mortality in ACS patients versus clopidogrel. The important thing is there has been no increase in major bleeding compare with clopidogrel. Clopidogrel is a thienopyridine that will bind to the ADP receptor through its active metabolites to impair the ADP-mediated activation of the glycoprotein GPIIb/IIIa complex.[1] There is no direct interference occurring with the GPIIb/IIIa receptor. As the glycoprotein GPIIb/IIIa complex is the major receptor for fibrinogen, its impaired activation prevents fibrinogen binding to platelets and inhibits platelet aggregation.[26] Common antiplatelets such as clopidogrel or prasugrel are thienopyridines that act directly on the P2Y12 receptor, but ticagrelor is a non-thienopyridine with a rapid onset of action of approximately 2 hours. Being a reversible antagonist, it also has a rapid offset of action of approximately 12 hours.

**Structure:** Ticagrelor is (1S,2S,3R,5S)-3-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol with the chemical formula of $C_{23}H_{28}F_2N_6O_4S$.




Ticagrelor is an analogue of ATP (adenosine triphosphate) and a member of the new cyclopentyl triazolopyrimidine class of agents that act to direct-acting inhibitor of the ADP receptor P2Y12 and block ADP-induced platelet aggregation.[27]

Structure activity relationship has revealed that placing substituents in the two position of adenine ring of ATP has increased the activity of the molecule toward binding with the receptor. In addition, studies have shown that replacing the phosphate groups of ATP with beta and gamma methylene group has increased the stability of the molecule. Ticagrelor binds to the P2Y12 receptor on a different site than ADP-binding site or binding site of thienopyridines. Therefore, there is no competition between ticagrelor and clopidogrel or other thienopyridines. Ticagrelor inhibits the receptor conformational changes, consequently locking the receptor in an inactive state and inhibiting ADP signaling.[28] Ticagrelor binds to P2Y12 through hydrogen bonding unlike thienopyridines that bind covalently to P2Y12. Therefore, the inhibition of platelet aggregation depends on the concentration of the drug that binds to the receptors. The half-life of the ticagrelor is only 7–8 hours so as soon as the active drug is not present, the P2Y12 receptor will be free of drug, which is around the half-life time of the drug.

The P2Y12 has three active sites: intracellular domains, extracellular domains, and transmembrane region. It has been shown that the ATP-binding sites of P2Y12 may be the same as the ADP-binding site. ADP has two binding sites, one hydrogen bond between hydroxyl hydrogen of P1 and amide oxygen of Gly 140 the other one between hydroxyl hydrogen of P with amide hydrogen of Lys 142.[29] The binding of ticagrelor would be similar to ADP binding with P2Y12.

The main difference between binding of ADP or ATP and thienopyridines with P2Y12 is that ATP or ADP analogous is the only forming hydrogen bond and there is no S-S covalent bond formation as in thienopyridines. The main reason for reversibility of the ticagrelor binding to ADP might be due to the formation of hydrogen bond rather than covalent bond to ADP receptor. Hydrogen bonding is usually stronger than normal dipole forces between molecules but it is not nearly as strong as normal covalent bonds within a molecule (it is only about 1/10 as strong). A normal covalent bond has a bond length of 0.96 Å, while the hydrogen bond length is 1.97 Å. In proteins typical hydrogen bond length ranges from 2.7 to 3.1 Å, which is relatively weak force, with hydrogen bond strength of around 1–5 kcal/mol. However, multiple hydrogen bonds can be formed between an enzyme's binding sites and ligand so that the increasing effect of these hydrogen bonds reveal a considerable stabilizing force for the enzyme-ligand binding.

Ticagrelor is forming hydrogen bonds with the ADP receptor in three different sites of binding. This could be the main reason for ticagrelor to be a reversible antiplatelet since hydrogen bonding is a weaker bonding than covalent bonding.

## What are the Adverse Effects of Ticagrelor?

In the PLATO trial, dyspnea was associated with the treatment with ticagrelor, which was not related to any changes in cardiopulmonary status. There were also reportedly more ventricular pauses in the acute phase, with transient elevations in levels of creatinine and uric acid. The mechanism for the above findings are not yet explained; one of the plausible suggested reasons is that the molecular structure of ticagrelor are almost identical to those of adenosine, which can then be degraded to uric acid. Adenosine can induce dyspnea by bronchoconstriction[30] causes depression of the atrio-ventricular node,[31] and causes deterioration in renal function by arteriolar constriction.[32] Treatment with ticagrelor showed an increased trend for risk of hemorrhagic stroke compared with clopidogrel. In a recent PLATO substudy, analyzed data on 13,408 patients found that patients received ticagrelor (180–270 mg loading dose followed by 90 mg twice daily) or clopidogrel (300–600 mg loading dose followed by 75 mg daily) for 6–12 months. Ticagrelor was associated with a significant reduction in the cardiovascular risk for death, MI, or stent thrombosis than clopidogrel, without increasing the risk for bleeding in patients presenting with ACS.[33]

## Randomized Trials Comparing ADP Receptor Antagonists

DISPERSE 2 was the first randomized, double-blinded, double-dummy, phase IIb trial assessing safety, tolerability, and initial efficacy of different doses of ticagrelor (plus aspirin) versus clopidogrel (plus aspirin) in patients with non-ST-elevation MI. Ticagrelor was found to be associated with a lower rate of composed end-point of cardiovascular death, MI, and stroke (1.9% vs. 3.8%), which was not statistically significant due to small number of patients enrolled with similar rates of major bleeding (6.3% vs. 8.7% in the clopidogrel arm).[34]

This led to a large phase III randomized trial comparing clopidogrel to ticagrelor (Inhibition and Patient Outcomes PLATO trial).[35] There are also two other major randomized controlled trials conducted to study the effect of ADP receptor antagonist in addition to aspirin. The first one was the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial.[36] The second one was the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI 38).[2] All previous trials have shown that as the antiplatelet effect increases, there is an increased risk of bleeding.[2,36] But the PLATO trial demonstrated that ticagrelor tenders a mortality benefit over clopidogrel without increase in risk of bleeding (Table 2). Furthermore, PLATO sample size (n = 18,624) was nearly 25% larger than that of TRITON–TIMI 38 (n = 13,608) and ticagrelor has a significant absolute risk reduction (Hazard ratio = 0.78 and confidence interval = 0.69–0.89) when compared to clopidogrel.[2,35] Coronary artery bypass graft–(CABG)-associated risk of bleeding cohort shows a slight advantage of ticagrelor over clopidogrel compared with prasugrel. There is also a trend toward increase in lung, breast, and colorectal cancers in prasugrel,[37] whereas in PLATO there was a lower rate of cancer in ticagrelor (1.4%) than clopidogrel (1.7%).[35] Based on the indirect and direct comparisons, ticagrelor appears to be superior to thienopyridines.

**Table 2.** Three Randomized Trials of Adenosine Diphosphate Receptor Antagonists in Acute Coronary Syndromes

| | PLATO | TRITON- TIMI 38 | CURE |
|---|---|---|---|
| Number of patients | 18,624 | 13,608 | 12,562 |
| Drugs tested | Ticagrelor versus Clopidogrel | Prasugrel versus Clopidogrel | Placebo versus Clopidogrel |
| End-point – death from cardiovascular cause | 3.4% versus 4.3%, P = 0·02 | 2.1% versus 2.4% P = 0.31 | 5.5% versus 5.1%, P = ns |
| Major bleeding | 11.5% versus 11.6%, P = 0.88 | 2.4% versus 1.8%, P = 0.03 | 2.7% versus 3.7%, P = 0.001 |

Prasugrel has shown to have higher bleeding risk in comparison to clopidogrel. Noncoronary bypass graft–related bleeding was 2.4 in the prasugrel arm in comparison to 1.8 in the clopidogrel group in TIMI 38 trial. Life-threatening bleeding was also significantly higher in the prasugrel arm (1.4 vs. 0.9, P = 0.01). In addition, fatal bleeding in the prasugrel arm was significant as well (0.4 vs. 0.1, P = 0.002). Higher bleeding risk offset the reduction in ischemic even found in the prasugrel arm leading to no significant differences in total mortality (in prasugrel arm 3.0 vs. 3.2 in clopidogrel cohort, P = 0.64).

In subgroup analysis, the higher bleeding risk occurred in patients over age of 75, those weighing less than 60 kg, and in patients with a history of previous stroke or transient ischemic attack (TIA). Therefore, prasugrel was deemed to be contraindicated in patients with prior stroke or TIA and has to be used with caution in patients with age of over 75 or weight of less than 60 kg. For this reason, a lower maintaining dose of 5 mg is recommended in the patients with higher bleeding risk.

Ticagrelor has to be taken twice daily due to its half-life. This could be a problem in patients who are not compliant in taking their medications. That could lead to a theoretical higher risk of stent thrombosis. However, in the PLATO trial using a large number of patients ticagrelor use was associated with low stent thrombosis rate both within 30 days and at 1 year with the assumption that some patients may have not been compliant in taking their medication.

Recently, an indirect comparative meta-analysis of prasugrel and ticagrelor in patients presenting with ACSs was published.[38] Authors performed comparative analysis of prasugrel and ticagrelor in patients presenting with ACS using three randomized trials with a total of 32,893 patients: the DISPERSE-2 and the PLATO studies—both comparing ticagrelor versus clopidogrel and the TRITON-TIMI 38 study—comparing prasugrel and clopidogrel. This analysis suggested that head-to-head comparison of prasugrel to ticagrelor showed no significant differences in the risk of the main composite end-point of death, MI, or stroke but the risk of definite or probable stent thrombosis was significantly lower in prasugrel arm (OR = 0.6, CI: 0.43–0.93, P = 0.02) at the expense of a higher major bleeding risk (OR = 1.43, CI: 1.10–1.85, P = 0.007). It is important to notice that this meta-analysis performed an indirect comparison of prasugrel with ticagrelor that cannot be adjusted for differences in the trial design and population studied limiting their interpretation. A direct comparison of prasugrel with ticagrelor in a randomized placebo controlled trial is needed for further clarification.

The reason for major differences in the bleeding risk for the same drug in different trials is related to the study design and definition of major bleeding. For example, in regards to the absolute bleeding risk in different trials involving clopidogrel, clopidogrel related major bleeding was 11.2% in PLATO study but only 1.7% in TRITON trial. This appears to be related to different definitions used for major bleeding in these trials. In PLATO trial, major bleeding was defined according to TIMI definition, which was using a cutoff for hemoglobin of at least 15 g/L without the documentation of excessive bleeding after CABG with severe bleeding defined according to the Global Use of Strategies To Open, occluded coronary arteries (GUSTO). In contrast, in TRITON trial major bleeding was defined as fatal or life-threatening bleeding, intracranial hemorrhage or a decrease in hemoglobin of at least 5 g, which is more robust definition of major bleeding leading to a lower total major bleeding rate in this trial in comparison to PLATO trial. Similarly, different trials have different definitions for efficacy explaining major differences in the efficacy rates for the same drug, For example, in PLATO study, primary end-point was defined as the composite of death from vascular causes, MI, or stroke. In contrast, in the TRITON trial primary efficacy end-point was defined as

a composite rate of death from cardiovascular causes, nonfatal MI, or nonfatal stroke during the follow-up period. As one can see nonfatal events were added to the primary end-point in the TRITON study but not in the PLATO trial leading to the higher total primary end-point event rates for clopidogrel in the TRITON study (12.1%) in comparison to the PLATO trial (10.7%). Therefore, it is important to notice the differences in the design and definition of end-points in different trials when comparing one study to others.

## Conclusion

The superior antiplatelet action of ticagrelor has been shown in PLATO trial. However, we will need to identify possible side-effects post marketing. Due to increased availability of various antiplatelet agents, it would be possible to individualize treatment options. For example, ticagrelor can be used in patients where CABG is a possible procedure such as in patients with previously known coronary anatomy not amenable for PCI or patients with extensive cardiovascular risk factors, such as diabetes and peripheral vascular disease. Editorial accompanying PLATO trial has suggested in patients on clopidogrel or prasugrel who need elective surgery, it is reasonable to switch them to ticagrelor 5–7 days before surgery.[39] Due to higher bleeding risk, the use of prasugrel should be avoided in patients with cerebrovascular disease.[40]

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