Review Article

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# Ticagrelor: A Reversible P2Y12 Inhibitor in Preventionof Thrombotic Events

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## ABSTRACT

Antiplatelet drugs play a crucial role in patients of coronary artery diseases, cerebrovascular diseases, and maintaining the patency of revascularised arteries and stents after coronary angioplasty. Ticagrelor is a new, reversible inhibitor of P2Y12, a purinergic adenosine di phosphate receptor present on the surface of platelets. Ticagrelor is more potent, directly acting as it does not require conversion to active metabolite, therefore it has rapid onset and offset of action. It has greater and more predictable anti platelet action with lesser -individual variation as compared to Thinopyridine group (Clopidogrel, Ticlopidine, and Prasugrel). Clopidogrel like drugs are prodrugs and irreversible inhibitor of P2Y12 receptor. Ticagrelor is used in prevention of thrombotic events in acute coronary syndrome and stroke. It decreases mortality and major ischemic events. It has adverse effects in the form of dyspnea and risk of major and minor bleeding.

## INTRODUCTION

Antiplatelet drugs play a crucial role in prophylaxis of thromboembolic disorders. These drugs are beneficial in patients of coronary artery diseases, cerebrovascular diseases like transient ischaemic attacks, and prevention of stroke. They reduce formation of microthrombi and maintain patency of revascularised arteries and stents after coronary angioplasty. Antiplatelet and anticoagulant drugs are used in case of prosthetic heart valve and arteriovenous shunts. Anticoagulants are routinely used in prevention and treatment of venous thrombosis, pulmonary embolism, and peripheral vascular diseases while antiplatelet drugs are used prophylactically in arterial thrombosis.[1]

Presently available antiplatelet drugs of different classes[2] are shown in table 1. American College of Cardiology/ American Heart Association (ACC/AHA) update 2016 recommends dual therapy with low dose Aspirin plus P2Y12 inhibitor in patients with coronary artery disease. This article focuses on directly acting reversible P2Y12 receptor antagonists Ticagrelor and Cangrelor which belongs to chemical group cyclopentyl-triazolo-pyrimidine.[3]

### Mechanism of action of Ticagrelor

After vascular injury, within fraction of seconds the exposed collagen activates release of adenosine diphosphate (ADP) which acts on P2Y1 and P2Y12 type of purinergic receptors on the surface platelets leading to aggregation and adhesion. P2Y12 is a G-protein coupled

**Table 1: Presently available antiplatelet drugs**

| Drug class | Name of drugs |
|---|---|
| Phosphodiesterase inhibitors | Dipyridamole, Cilostazole |
| Thromboxane A2 synthesis inhibitor | Low dose Aspirin |
| Adenosine di phosphate (ADP) antagonist | Clopidogrel, Ticlopidine, Prasugrel,Ticagrelor |
| Glycoprotein IIb/IIIa antagonists | Abciximab, Tirofiban, Eptifibatide |
| Protease activated receptor 1 (PAR-1) inhibitor of thrombin receptors on platelets | Voraproxar |

receptor (GPCR) which mediates ADP induced platelet aggregation by inhibiting adenylyl cyclase and decreasing cyclic AMP.[1] Ticagrelor blocks platelet aggregation by inhibiting binding of ADP to P2Y12 receptors in a non-competitive manner as shown in figure 1. It also inhibits non-platelet P2Y12 receptors on vascular smooth muscles, where they cause vasoconstriction and increase myocardial per-fusion. Ticagrelor is unique among other antiplatelet drugs due to its pleiotropic effects like cardio-protection, restoration of myocardium after ischaemic events, promotion of release of anticoagulatory factors, and anti-inflammatory effect.[4]

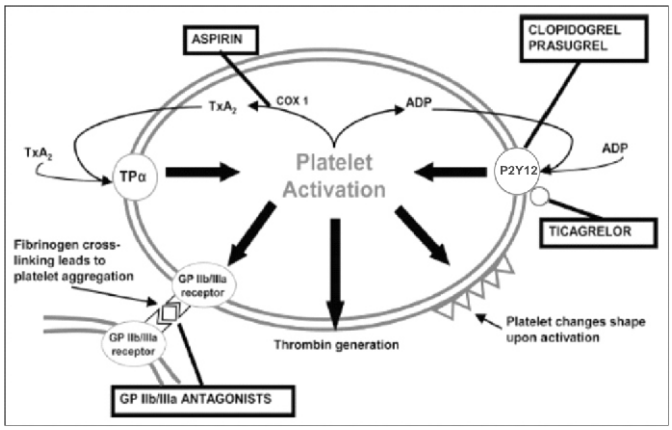


**Figure 1: Mechanism of action of antiplatelet drugs.**

**Pharmacokinetics of Ticagrelor**

Ticagrelor is orally effective while Cangrelor is an intravenous ADP antagonist. Ticagrelor is rapidly absorbed from the gut after oral administration and reaches peak plasma concentration in around 1.5 hours.[5] It has plasma half-life of 12 hours, given twice daily. Its bioavailability is around 36%. It does not need metabolic activation resulting in fastest onset of action and quicker offset, which might work better for patients with genetic variants regarding the enzyme CYP2C19, thus leading to less inter-individual variations. It is mainly metabolized to active metabolite via cytochrome enzymes.[2] Ticagrelor and its active metabolites show plasma protein binding greater than 99.7%, and they are mainly excreted via bile and faeces.[5-7]

Dose regimen: It is available as 90 mg tablet given as single 180 mg oral loading dose followed by a twice-daily 90 mg maintenance dose along with maintenance dose of 75-100 mg aspirin. No dosage adjustment is needed in hepatic and renal impairment.[7-8]

**Clinical trials on efficacy and safety of Ticagrelor**

The efficacy and safety of Ticagrelor verses Clopidogrel have been evaluated by the PLATO (Platelet Inhibition and Patient Outcomes) trial performed in 18,624 patients with either non-ST elevation or ST-elevation ACS; Ticagrelor compared with Clopidrogrel alongwith Aspirin consistently reduced the rate of ishchemic events and mortality. Major bleeding rate was similar between both the groups, but Ticagrelor was associated with an increase in non-CABG major bleeding (4.8 vs. 3.8%; HR 1.28; 95% CI = 1.051.56).[9-10]

In a randomized multicentre open label clinical trial by Zhao Q et al[11] conducted from July 2014 to Jan 2017, the effects of Ticagrelor plus aspirin, Ticagrelor (90 mg twice daily) alone or Aspirin (100 mg once daily) alone on saphenous vein graft patency one year after elective coronary artery bypass grafting (CABG) were compared in 500 patients. Saphenous vein graft patency rates 1-year post CABG with Ticagrelor plus Aspirin showed statistically significant result (88.7%) as compared to other two groups with Ticagrelor alone (82.8%) and with Aspirin alone (76.5%).There was no statistically significant difference in incidence of cardiovascular death, nonfatal MI, nonfatal stroke, and atrial fibrillation within seven days of post CABG among the three groups. Five major bleeding episodes occurred during one year of follow up (3 with Ticagrelor + Aspirin and two with Ticagrelor alone).

The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor compared to Placebo on a Background of Aspirin Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54)**:** The study was done in 21162 patients at 1161 sites in 31 countries. Eligible patients (50 years or older, diabetes mellitus, a second prior spontaneous myocardial infarction, multivessel coronary artery disease, or chronic renal dysfunction) were randomly assigned in a 1:1:1 ratio and given Ticagrelor 90mg/60mg twice daily/placebo for 33 months. The patients with a myocardial infarction who had attack more than one year previously, Ticagrelor showed significant reduction in the risk of cardiovascular death, myocardial infarction, or stroke but the risk of major bleeding was increased.[12]

In a randomised, multicentric clinical trial published in JAMA cardiology, short-term safety of Ticagrelor was compared with Clopidogrel among patients with ST-

elevation myocardial infarction pretreated with fibrinolytic therapy at 152 sites from 10 countries enrolling 3799 patients. The result of the study showed that the rates of fatal (0.16% v/s 0.11%) and intracranial bleeding (0.42% v/s 0.37%) were similar between the Ticagrelor and Clopidogrel groups, respectively. Minor and minimal bleeding were more common with Ticagrelor than with Clopidogrel, delayed administration of Ticagrelor after fibrinolytic therapy was non inferior to Clopidogrel for TIMI major bleeding at 30 days.[13]

Another randomised open-label superiority trial published in Lancet in 2018 was done at 130 sites in 18 countries among 15,968 patients undergoing percutaneous coronary intervention with a stent for stable coronary artery disease or acute coronary syndromes. The patients were randomly assigned into two groups (1:1). One group was given 75-100 mg Aspirin daily plus 90 mg Ticagrelor twice daily for one month, followed by 23 months of Ticagrelor monotherapy. The other group was given standard dual antiplatelet therapy with 75-100 mg Aspirin daily plus either 75 mg Clopidogrel daily (for patients with stable coronary artery disease) or 90 mg Ticagrelor twice daily (for patients with acute coronary syndromes) for 12 months, followed by Aspirin monotherapy for 12 months. The study concludes that Ticagrelor in combination with aspirin for one month followed by Ticagrelor alone for 23 months was not superior to 12 months of standard dual antiplatelet therapy followed by 12 months of Aspirin alone in the prevention of all-cause mortality or new Q-wave myocardial infarction two years after percutaneous coronary intervention.[14]

**Advantages of Ticagrelor over Clopidogrel**

1. Ticagrelor and Cangrelor are more potent, are not prodrugs and act as direct reversible inhibitors of P2Y12 receptors, therefore have rapid onset and offset of action. Thus they have greater and more predictable antiplatelet action.[1]
2. Ticagrelor is a reversible inhibitor of platelet aggregation, while Clopidrogel binds covalently to ADP binding site and renders the receptor permanently inactivate.
3. Ticagrelor also prevents re-stenosis by inhibiting P2Y12 receptor-induced inflammation. In comparison, these effects are not seen with Clopidogrel like drugs, as they cannot penetrate vascular wall due to their physicochemical properties.
4. Ticagrelor has no/fewer drug interactions, whereas Clopidogrel has frequent interaction with drugs like Omeprazole, Fluconazole, and Ticlopidine which inhibit the enzyme CYP2C19, hence lead to reduced clinical effects.
5. Ticagrelor does not require metabolic activation unlike Clopidogrel.[15] Due to genetic polymorphism Clopidogrel leads to increased risk of cardiovascular events as in these individuals active metabolite will not be formed. FDA has recommended CYP219 genotyping before prescribing Clopidogrel to find poor metabolisers.[2]

**Safety profile of Ticagrelor**

As it is a new drug, large safety data of Ticagrelor after post marketing surveillance is awaited. In PLATO clinical trial, the most common adverse events were dyspnea and bradycardia. It is believed that this effect may be due to increase concentration of adenosine.[9]

Clinical trial by Zhao Q et al showed major bleeding in the form of intracranial bleeding as adverse effects which did not led to discontinuation of treatment. Minor bleedings from upper and lower gastrointestinal tract, ear, nose, urinary tract, and dermal have been reported. Ticagrelor was reported to have ventricular pauses in the first week of treatment but difference did not persist by 30 days. Other adverse effects reported with Ticagrelor were headache, nausea, dyspepsia, insomnia, dizziness, syncope, and hypo-tension. Hypersensitivity is rare adverse effect.[11] Risk in pregnancy is not ruled out (category C drug). Strong inducers of CYP3A4 like Rifampicin and antiepileptic medications including Carbamazepine, Phenobarbital, and Phenytoin may potentiate metabolism of Ticagrelor and reduces its efficacy.[15]

**Therapeutic uses and current status of Ticagrelor**

Ticagrelor is used along with low dose Aspirin to prevent heart attack and stroke in patients with unstable angina/ heart surgeries like stent placement and CABG. Food and Drug Administration (FDA) approved it in year 2011 while it was approved by Drug Controller General India (DCGI) for marketing in year 2012. Cangrelor is intravenous preparation approved by FDA in 2015 as an adjuvant inpercutaneous intervention (PCI).

## CONCLUSION

Ticagrelor is latest, reversible P2Y12 inhbitor, with rapid onset of action as it does not require metabolic activation.

It is orally effective, with minimum drug interactions. Ticagrelor holds promise as an antiplatelet drug preventing thrombotic events in patients of acute coronary syndrome and stroke. However, Ticagrelor has important adverse effect in the form of bleeding. American College of Cardiology/American Heart Association update 2016 (ACC/AHA) now recommends that all patients at high risk of acute coronary syndrome should be given prophylactic Ticagrelor in addition to low dose Aspirin as a dual antiplatelet therapy.

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