

**THINK BEYOND ASPIRIN**

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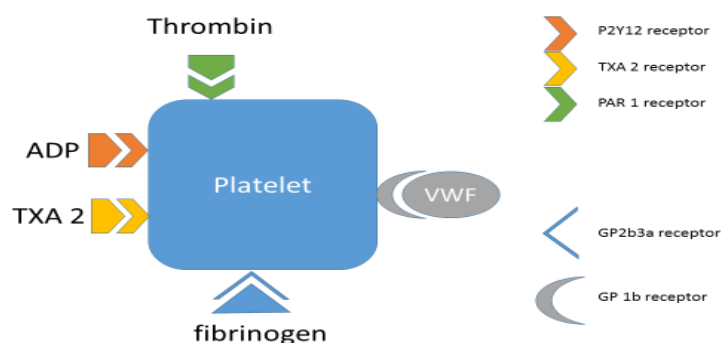
**INTRODUCTION**

Cardiovascular diseases like acute coronary syndrome, ischemic stroke and coronary artery disease (CAD) are a few among the leading causes of death in the world.<sup>[1]</sup> The etiology for these manifestations is multiple but ultimately leads to clot formation because of platelet activation.<sup>[2]</sup>

Antiplatelet drugs are currently the mainstay treatment for the above clinical manifestations of cardiovascular diseases which includes aspirin and P2Y<sub>12</sub> antagonists like Prasugrel, Clopidogrel etc. Aspirin irreversibly inhibits COX-1 and reduces TXA<sub>2</sub> synthesis thereby inhibiting platelet aggregation. P2Y<sub>12</sub> inhibitors inhibit ADP mediated platelet adhesion and aggregation.<sup>[2]</sup>

However, despite use of dual antiplatelet drugs, recurrent thrombotic complications continue to occur. This is probably due to multiple mechanisms leading to platelet activation that are unaffected by the above-mentioned drugs. In addition, there have been reports of emergence of resistance to both Aspirin and Clopidogrel thereby reducing its effectiveness.<sup>[3]</sup>

## CURRENT TARGETS



The figure shows various targets on the platelet cell surface. Actions of ADP, TXA2 and thrombin on P2y12, TXA2 and PAR1 receptors respectively lead to platelet activation. Platelet adhesion takes place when vWF binds to gp1b receptor and aggregation takes place when fibrinogen binds to gp2b3a receptor. Tirofiban, Abciximab and Eptifibatide inhibits platelet aggregation by gp2b3a inhibition.<sup>[7]</sup>

## NOVEL TARGET

PAR (Protease activated receptors) are a group of G protein coupled receptors. To date, 4 types of PAR's have been recognized namely 1, 2, 3 and 4. PAR 1, 3 and 4 are activated by thrombin and PAR 2 is activated by trypsin. PAR 1 has fast and robust activation. PAR 2 is widely distributed. PAR 3 is least understood of the receptors and are absent in primates. PAR 4 is a slowly activated receptor which is activated at high thrombin concentrations.<sup>[3, 4]</sup>

## CLINICAL TRIALS

TRACER (thrombin receptor antagonism for clinical event reduction in ACS)

It was a trial designed to compare placebo vs Vorapaxar with efficacy as the primary end point showed no improved efficacy but a significant increase in bleeding. Thus the trial was prematurely terminated.

TRA 2P TIMI 50 trial

This trial confirmed the efficacy of the drug. But at 2 years post enrolment an increase of intracranial bleeding in cases with history of stroke in the Vorapaxar group was observed thereby stopping of the drug in all patients with stroke in the past, in addition to those who developed new stroke during the trial was recommended. Whereas in patients with no history of stroke continuation of Vorapaxar was advised.

**VORAPAXAR**

It is a synthetic tricyclic 3-phenylpyridine, an analogue of Himbacine which is a natural product.<sup>[3]</sup>

It is a Thrombin receptor antagonist which Inhibits platelet activation by inhibition of PAR-1. Major route of excretion is faeces. It has a half-life of 159 to 311 hours.<sup>[5]</sup> It is given at a dose of 2.08 mg once daily orally in addition to aspirin and/ or clopidogrel.<sup>[6]</sup>

Adverse effects are usually mild in severity like headache, upper respiratory infection, and fatigue. These are dose independent.<sup>[5]</sup> Like other antiplatelet agents, Vorapaxar can cause bleeding which can be serious.<sup>[6]</sup>

Vorapaxar is contraindicated in patients with history of transient ischemic attack, intracranial haemorrhage and stroke. It is also contraindicated in patients with active pathological bleeding like in case of peptic ulcers. It is not recommended in severe liver impairment due to increased risk of bleeding. In case of over dosage no antidotes are available.<sup>[6]</sup>

Vorapaxar is metabolized mainly by the CYP3A4 enzyme. Drugs like ketoconazole which are potent inhibitors of CYP3A4 may increase plasma concentrations of Vorapaxar and drugs like Rifampicin which are potent inducers may decrease the plasma concentrations of Vorapaxar.<sup>[6]</sup>

In case of pregnancy, it is a class 2 drug.<sup>[6]</sup>

**CONCLUSION**

In spite of two potent class of antiplatelet in aspirin and P2Y<sub>12</sub> antagonists, recurrence of ischemic event is a major problem in managing post MI patients. PAR1 receptor is an alternate target to inhibit platelet activation and Vorapaxar is a good addition to the arsenal for secondary prophylaxis of ischemia.

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