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ANTIPLATELET THERAPY AND RESISTANCE: A MINI REVIEW

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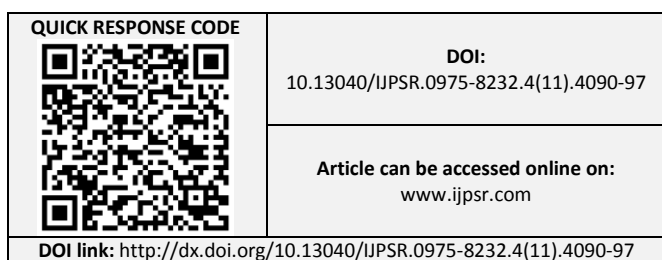
ABSTRACT: Arterial thrombus formation are due to mainly platelet activation and aggregation which are considered to be central to pathological changes occurring in the vessel leading to the various complications and mortality. Antiplatelet drugs are used to prevent and help in the reversal of platelet aggregation in arterial thrombosis which was the major culprit in the pathology of myocardial infarction and ischaemic stroke. The most widely used antiplatelet agent namely Aspirin inhibits platelet cyclo-oxygenase which helps in conversion of arachidonic acid to platelet agonist thromboxane A₂ but does not prevent platelet activation occurring via various signalling pathways that are independent of thromboxane A₂ release. So apart from aspirin, a number of other compounds have been developed to overcome the deficiency by aspirin. Another major concern regarding the antiplatelet therapy was the resistance by these drugs in preventing the troublesome complications. Bleeding is the most dreadful complication of most of the antiplatelet drugs. In general, in clinical practice, antiplatelet therapy is instituted in patients whose thrombotic risk clearly overweighs their use of risk of bleeding manifestations. The development of newer antiplatelet drugs based on the understanding of their pharmacological mechanisms helps in the prevention of cardiovascular mortality with the least side effects.

INTRODUCTION: Platelets are the vital components of a proper normal homeostasis and important key participants in atherothrombosis.

The platelets, by virtue of their capacity to adhere to injured endothelial cells of the blood vessels, and to accumulate at sites of injury causes the formation of atherothrombosis¹.

Role of Platelets in Arterial Thrombosis²: In normal persons with healthy vasculature, the circulating platelets are maintained in an inactive state by the endothelial synthesis of nitric oxide (NO) and the prostacyclin. Also the CD39 expression in the endothelial surface, a membrane associated ectoadenosine diphosphatase (ADPase) helps in the degradation of ADP released from activated platelets.

All these mechanisms were impaired when the vessel wall is damaged and the subendothelial matrix is exposed causing the opposite of the protective mechanisms. The adherence of the platelets to exposed collagen occurs via $\alpha_2\beta_1$ and glycoprotein (GP) V1 and to the von Willebrand



factor (vWF) via GPIIb/IIIa and GPIIb/IIIa (α IIb β 3) receptors that are expressed constitutively on the platelet surface. Thromboxane A₂ and ADP were synthesized and released by the adherent platelets. This causes the cyclical activation of ambient platelets and recruits them to the site of vascular injury.

The activation of the extrinsic pathway of coagulation occurred due to the disruption of the vessel wall which exposes tissue factor expressing cells to the blood. The binding of the clotting factors by the activated platelets potentiate the coagulation pathways and also supports the assembly of activation complexes that enhance

thrombin generation. This thrombin in addition to converting fibrinogen to fibrin, it also serves as a potent platelet agonist and recruits more circulating platelets at the site of vascular injury.

Activated platelet expresses the most abundant GPIIb/IIIa receptor on the platelet surface which undergoes a conformational change that enables the platelets to bind to the fibrinogen and to vWF at a very shear conditions (**Figure 1**). Platelet aggregates were formed by the fibrinogen or vWF molecules which bridge adjacent platelets together. Platelet/fibrin mesh were formed by the fibrin weaved with these platelet aggregates.

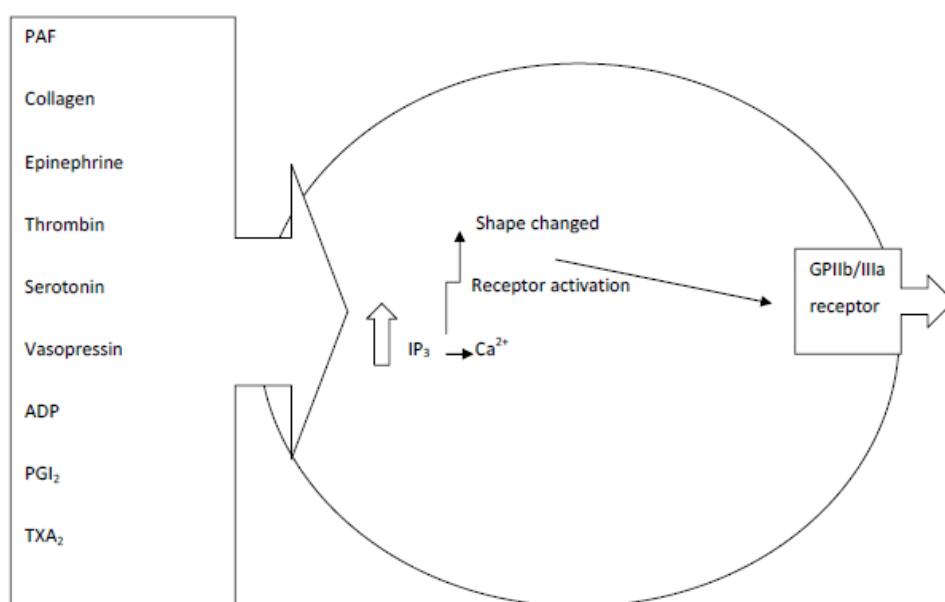


FIGURE 1: ACTIVATION OF PLATELETS

Classification of antiplatelet drugs:

- **Irreversible cyclooxygenase (COX) inhibitors:** Aspirin
- **Adenosine diphosphate (ADP) receptor inhibitors:** Clopidogrel, Prasugrel, Ticagrelor, Ticlopidine,
- **Phosphodiesterase inhibitors:** Cilostazol
- **Glycoprotein IIB/IIIA inhibitors (intravenous use only):** Abciximab, Eptifibatide, Tirofiban
- **Adenosine reuptake inhibitors:** Dipyridamole

- **Thromboxane inhibitors:**
- **Thromboxane synthase inhibitors:**
- **Thromboxane receptor antagonists:** Terutroban

Aspirin³: Aspirin is the leading therapeutic drug for the prevention of thromboembolic complications from atherosclerotic disease.

- **Pharmacokinetics:** Aspirin is rapidly absorbed from the upper gastrointestinal (GI) tract after oral administration with peak occurring at a time ranging of 30 to 40 minutes after ingestion. At a dose of > 300 mg in majority of patients there was no additional effect on

platelet activity. Use of enteric-coated formulations may considerably delay the time to peak effect.

- **Pharmacodynamics:** The effect of aspirin on platelet function is to permanently inactivate a key platelet enzyme (cyclooxygenase [COX]). This effect can only be reversed by generation of new platelets thus permitting once-daily dosing. COX exists in 2 isoforms (COX-1 and COX-2) and catalyzes the first step in prostanoid synthesis mainly the conversion of arachidonic acid to prostaglandin PGH₂. PGH₂ is metabolised to bioactive prostanoids including PGI and thromboxane A₂ and PGI₂.

As a result Arachidonic acid do not gain access to catalytic site of COX enzyme, TXA₂ gets generated by platelets mediated by the enzyme COX being a very sensitive process due to inhibition of enzyme by aspirin. PGI₂ gets generated by the vascular endothelium, largely mediated by COX-2, being a less sensitive process to inhibition by aspirin as a result; low dose of aspirin has limited effects on vascular function dependent on PGI₂, whereas aspirin is sufficient to suppress the production of TXA₂ in a period of 1 week with a daily dose of 30 mg.

- **Adverse Effects:** Increased risk of bleeding complications is found to be the major adverse effect with a very favourable risk benefits ratio.

The most common site of bleeding is GI tract, which can be prevented by using PPI which are gastro protective drugs.

- **Drug Interactions:** Administration of Ibuprofen, naproxen which is non-selective reversible inhibitors of COX1 decreases the efficacy of aspirin.
- **Resistance in Aspirin response and High on Treatment Platelet Reactivity (HPR):** Aspirin resistance is defined as the inability of aspirin to reduce platelet production of thromboxane A₂ and thereby platelet activation and aggregation. Resistance in aspirin response leads to increased risk of cardiovascular events. The various methods by which Aspirin resistance was detected by laboratory tests of platelet thromboxane A₂ production or platelet function. Inadequate dose, drug interactions, pharmacogenetic variation of COX-1 and other genes involved in thromboxane biosynthesis, alternative up regulation of non-platelet sources of thromboxane biosynthesis and increased platelet turnover were all possible cause of aspirin resistance (**Figure 2**). The strategy which tried to overcome Aspirin resistance could be by treating the causes and reduced by minimising thromboxane production and activity and blocking other alternative pathways of platelet activation.

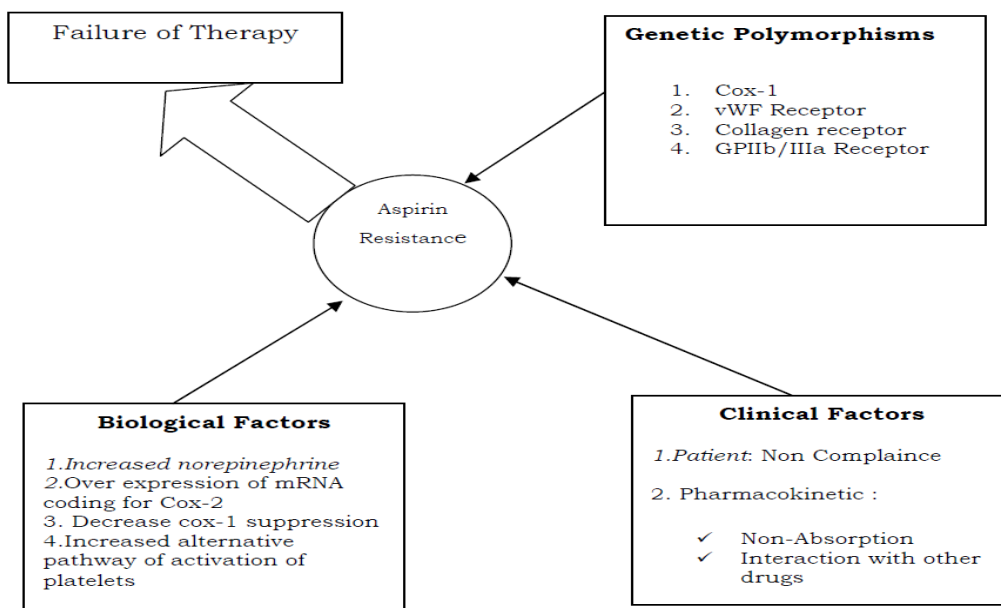


FIGURE 2: POSSIBLE FACTORS FOR ASPIRIN RESISTANCE

P2Y12 Receptor Blocking Drugs:

The Thienopyridines:

Clopidogrel ⁴:

- **Efficacy:** Clopidogrel is found to be slightly more effective than aspirin in the vascular event prevention. It was introduced as a safer drug than ticlopidine, its precursor.
- Based on the cost and side effect it is considered as the primary drug in preventing cardiovascular events for those patients who are allergic and intolerant to aspirin or it can be combined with aspirin for enhanced protection.
- **Pharmacokinetics:** It is a prodrug. After oral administration it is moderately absorbed variably with 50 % bio-availability. Inactive carboxylic acid metabolite is produced by hydrolysis of clopidogrel by esterases. In liver a short lived active metabolite are produced in 2 steps process by CYP3A4 / 3A5 also contributed by CYP2B6 / 1A2 / 2C9 / 2C19. This gives a clear picture about the inter-patient variability and it may involve a genetic component. The platelet response to clopidogrel was found to be diminished in those who are identified with variants of CYP2C19 genotype. Within 1 to 2 hours peak concentration of parent drug, carboxylic acid metabolite and its active metabolite are attained and for doses of about 600 mg there is little increased efficacy because of limited drug absorption.

In those patients of renal or hepatic compromise dose adjustment is not needed.

With the administration of about 75 mg for 3 to 7 days the inhibition of platelet aggregation reaches about 40% to 60%, but with administration of initial loading dose this duration can still be reduced.

- **Pharmacodynamics:** The active metabolite of clopidogrel forms disulphide bridges with extracellular cysteine residues cys 17 and cys 270 by binding of active metabolite to platelet P2Y12 receptor to irreversibly inhibit ADP induced platelet aggregation.

- **Adverse Effects:** Increased risk of bleeding is the major side effect upon administration. But relatively there were fewer GI symptoms compared with aspirin. Increased incidence of diarrhoea and rash is also accounted on administration. Rarely thrombotic thrombocytopenic purpura develops.
- **Drug interactions:** Since the metabolism of clopidogrel involves hepatic enzymes CYP3A4 / 3A5 to produce active metabolite, there is significant drug interaction leading to therapeutic failure.

About 40 % to 80% of cytochromes responsible for metabolism of drug in human is brought about CYP3A, 3A4 allele predominately metabolises clopidogrel however 50% of hepatic CYP3A activity is contributed by 3A5. 3A5 function polymorphism may influence the antiplatelet effect of clopidogrel. The drugs which are CYP3A substrates inhibit the production of active metabolite of clopidogrel and leading to thrombosis.

Randomized Clinical Trials shows that PPI reduces the antiplatelet effect of clopidogrel and was found combination of PPI and clopidogrel may lead to increased mortality in large observational study. Similar to aspirin it also exhibits resistance and HPR.

Prasugrel ⁵: Prasugrel is one of the many newer drugs which have been introduced for preventing thrombosis after PCI. It also acts at P2Y12 receptor.

- **Efficacy:** As an anti-thrombotic drug the efficacy of prasugrel was established by randomized clinical trials.
- Initial Studies showed that prasugrel produced greater anti-platelet effect than clopidogrel and found to be associated with fewer major cardiac events (MI, Recurrent ischemia and clinical target vessel thrombosis). In follow up Phase III study patient who were undergoing PCI and receiving aspirin were randomized to receive either initial loading dose of 60 mg prasugrel and then daily 10 mg or loading dose of 300 mg clopidogrel and daily 75 mg, following for about 6 to 15 months.

Significant reduction in death from cardiovascular causes non-fatal MI or non-fatal stroke

- **Pharmacokinetics:** Prasugrel is a pro-drug and its anti-platelet activity is exhibited by its active metabolite. The conversion involves the single Cyt P450 depended step and is more rapid than clopidogrel. Thus increased clinical effects are produced by increased levels of active metabolite. Genetic variation in CYP2C19 and CYP2C9 only affect prasugrel metabolism to a least extent and also the drug interactions involving CYP3A4 leading to less variation in active metabolite.
- At 0.5 hours peak concentration of metabolite are attained. Dose finding studies revealed maximum effect with a safety profile with initial loading dose of 40 to 60 mg and daily dose of 15 mg produces dose dependent anti-platelet activity and also sustained response.
- **Pharmacodynamics:** Like other thienopyridine derivates, the active metabolite binds irreversibly with P2Y12 receptor forming disulphide bridges between extracellular cysteine residues at Cys17 and Cys270 and thus preventing platelet activation. The resistance in clopidogrel usage due to involvement of CYP2C19*2 loss of function allele was not demonstrated in the usage of prasugrel which further increases the efficacy of the drug in treating as anti-thrombotic
- **Adverse Effect:** Bleeding is found to be the major adverse effect upon the administration of prasugrel, which is more potent platelet function inhibitor than clopidogrel.
- **Drug Interactions:** Involvement of Cytochrome P450 system in a metabolism indicates the possibilities of interactions with the drugs metabolized by the same system of enzyme. But enzyme kinetic studies disprove this fact. Only fewer nonresponders and better clinical response was found in diabetic patient with the use of prasugrel than clopidogrel. Due to reduction in the amount of active metabolite to interact with platelets because of alteration in P2Y12 receptors leading to poor response to clopidogrel.

Elinogrel ⁶: Elinogrel belonging to sulfonylurea, is a directly acting reversible inhibitor of P2Y12 receptor which can be administrated both orally and I.V

- **Efficacy:** During phase I study, with in 20 min of administration it was able to inhibit platelet aggregation induced by ADP; inhibition of platelet aggregation depends on the dose; synergism when introduced along with aspirin; and with I.V. elinogrel additional inhibition of platelet aggregation in early rapid reversal of platelet thrombosis before PCI to optimize reperfusion in acute myocardial infarction.
- **Pharmacokinetics and pharmacodynamics:** About 56% and 48% of total dose was excreted in urine and faeces respectively after oral administration of about 50 mg. The circulating compound was unchanged elinogrel and the parent was excreted in urine and faeces. The major metabolite was formed after demethylation. It has a half-life of 12 hours which was excreted by hepatic and renal routes with limited metabolism. After 6 hours of administration peak concentration was obtained and was eliminated by around 24 hours. Based on plasma concentration the pharmacodynamics effect was observed, at 4-6 hrs. The antiplatelet effect showed peak levels and by 24 hours it returned to the basal levels. Elinogrel does not demonstrate resistance which was seen with aspirin and clopidogrel.
- **Adverse effects:** Single dose of elinogrel was well tolerated with no significant adverse events in Phase I clinical trials, whereas incidence of bleeding and serious adverse events occurred in Phase II trial. As it is a sulfonylurea derivative, patient who has history of adverse reactions to sulfonylurea drug might have increased risk of developing allergic type of reactions.

ADP Receptor Antagonists:

Cangrelor ⁷: Cangrelor is ADP receptor antagonists. It plays a significant role in managing patients with atherosclerotic disease in the perioperative period due to its short acting nature, I.V., reversible inhibitor of platelet function.

- **Efficacy:** In small studies, patients with ACS, unstable angina or non Q-wave MI Cangrelor was an effective antithrombotic drug
- **Pharmacokinetics:** When administered I.V cangrelor has rapid onset of action and clearance with half-life of 9 minutes.
- When the drug is discontinued platelet function returns rapidly. There is no active metabolism is by dephosphorylation. Drug is metabolised in plasma and so dose adjustments is not needed in patients with liver and renal compromise.
- **Pharmacodynamics:** Cangrelor brings greater inhibition of platelet aggregation than clopidogrel by acting as a reversible inhibitor of P2Y12 receptor on surface of platelet.
- **Adverse effects:** Cangrelor was well tolerated in early clinical trials. In phase III trials, increased bleeding was associated with cangrelor administration.
- **Drug interactions:** In combined therapy along with clopidogrel, Cangrelor inhibits antiplatelet activity of clopidogrel. This effect was not seen when clopidogrel was administered after cangrelor which is due to inhibition of binding of active metabolite of clopidogrel to the P2Y12 receptor on the platelet surface.

Cyclopentyltriazolopyrimidines:

Ticagrelor⁸: Ticogrelor is one of the Cyclopentyltriazolopyrimidines classes of drugs undergoing clinical trials which are an orally active reversible P2Y12 receptor antagonist.

- **Efficacy:** With dose ranging 50-200 mg twice daily it inhibits rapidly and highly effective platelet aggregation.
- **Pharmacokinetics:** Ticagrelor does not require metabolic activation for clinical effect. In healthy people after oral administration the peak effect was found to be at 2 to 4 hours showing linear kinetic. The half-life is about 7 hours. There was a linear and dose related increase in ticagrelor and its metabolite upon twice daily administration to patient with coronary artery disease.

- **Pharmacodynamics:** Ticagrelor binds reversibly to P2Y12 receptor and nearly completely inhibits platelet aggregation induced by ADP. Compared to clopidogrel it has faster onset and offset of platelet inhibition. At doses ranging from 50 to 200 mg twice daily it rapidly and effectively inhibit platelet aggregation.
- **Adverse Effect:** Bleeding is the most common adverse effect. In PLATO trial, dyspnoea occurred in a large proportion of patients which required discontinuation of therapy.

Phosphodiesterase Inhibitors:

Dipyridamole⁹: Dipyridamole, a pyrimido pyrimidine derivative as vasodilator and antiplatelet properties

- **Efficacy:** Recent guidelines in patient with non cardioembolic TIA or stroke for the prevention of cerebral ischemic events includes aspirin and extended release dipyridamole as an acceptable choice.
- **Pharmacokinetics:** Oral doses of dipyridamole are variably absorbed but the bio availability has improved with modified release formulation. The drug is subjected to enterohepatic circulation after getting metabolised to a glucuronide conjugated product and excreted in bile, having a terminal half-life of about 19 hours with modified release formulation making twice daily dosage possible.
- **Pharmacodynamics:** The mechanism of action is by inhibition of phosphodiesterases which helps in increasing cAMP, increasing the adenosine concentration at the platelet vascular interface by uptake blockade of adenosine or helps in the release of prostacyclin from the endothelium. The limiting factor for its use as an antiplatelet drug is that, at high doses the drug causes vasodilation which in turn causes reflex tachycardia causing myocardial ischaemia. It produces sustained platelet inhibition via a broad range of mechanism compared with aspirin, clopidogrel, and dipyrimidole.

- **Adverse Effects:** Bleeding is associated with the usage. Headache is the most common adverse effect of chronic administration. It is one of the drugs for cardiac diagnostic testing (Stress ECG)
- **Drug Interactions:** There is increased risk of bleeding when administered with aspirin

Cilostazol¹⁰: Cilostazol, a Phosphodiesterases 3 inhibitor has vasodilator and antiplatelet aggregation properties.

- **Efficacy:** Cilostazol is effective in patients of peripheral vascular disease and for patients with moderate to severe intermittent claudication. It is helpful in prevention stent thrombosis and restenosis. With triple therapy an enhanced antiplatelet effect has been demonstrated but its use was limited because of its side effect with cilostazol.
- **Pharmacokinetics:** When cilostazol is orally administered the absorption is largely variable. CYP3A4 / 5 primarily metabolize the drug to inactive metabolite with a lesser contribution from CYP2C19. It is extensively protein bound and half-life is approximately 10 hours. In patient with renal failure cilostazol clearance was increased whereas in patient with liver failure it was decreased, but no dosage adjustments were necessary.
- **Pharmacodynamics:** Compared to ticlopidine and aspirin cilostazol is a more potent inhibitor of aggregation of platelet. It increases cAMP with resultant decrease in platelet aggregation and vasodilation by inhibiting Phosphodiesterases an intra-cellular enzyme.
- **Adverse Effects:** Most common side effect is headache which could be a reason for some patients to discontinue the therapy.
- **Drug Interactions:** Cilostazol is metabolized by CYP3A4 and CYP2C19 and therefore may involve in drug interaction with those drugs which require these system of enzymes for their metabolism. Omeprazole (CYP2C19 inhibitor) and Erythromycin (a CYP3A4 inhibitor) inhibits cilostazol metabolism.

As a result plasma concentration of cilostazol and its active metabolite decreases. Non clinical significant reduction in plasma levels of cilostazol has been reported when administered with lovastatin. Increased level of lovastatin was reported but does not require dosage adjustment. When administered along with aspirin no clinically significant interaction was reported.

GPIIb/IIIa Receptor Antagonists¹¹: In patients with acute coronary syndromes, parenteral GPIIb/IIIa Receptor Antagonists have been used. This class of drugs comprises abciximab, tirofiban and eptifibatide.

- **Mechanism of Action:** GPIIb/IIIa belonging to integrin family of adhesion receptors with about 80,000 copies per platelet is present on the surface of the platelets and megakaryocytes. The conformational activation of receptor occurs, when the platelet becomes activated by inside outside signal transduction pathway. GP IIb/IIIa binds with adhesive molecule namely fibrinogen and vWF when it becomes activated. Once bound, the adhesive molecule bridges other adjacent platelets causing aggregation.

Abciximab: Abciximab, an antagonist to the activated form of GPIIb/IIIa is a humanized murine monoclonal antibody. Abciximab blocks the binding of adhesive molecules by binding to activated receptor with a very high affinity. The presence of this drug on the surface of the platelets for upto 2 weeks could be detected as it has long half-life and indicated for PCI. It does not have renal clearance and don't require any dose modification. Unlike Abciximab, synthetic small molecules such as eptifibatide and tirofiban have renal clearance and very short half-life and it is used in case of PCI and unstable angina.

- **Side Effects:** Administration of GPIIb/IIIa antagonist produces most serious complication such as bleeding, thrombocytopenia. Thrombocytopenia is immune mediated and is caused by auto antibodies against new antigens on GPIIb/IIIa receptors that are exposed upon binding of an antagonist.

Thromboxane inhibitors^{12, 13}: **Terutroban**: In Phase III clinical trial, PERFORM (Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history of ischemic stroke or Transient Ischemic attack) for secondary prevention of acute thrombotic complications terutroban has been tested. But unluckily the study was stopped prematurely because the efficacy of terutroban against aspirin could not be determined.

- **Method of action:** Terutroban, an antagonist of the thromboxane receptor blocks platelet aggregation and vasoconstriction induced by thromboxane.

Ifetroban is a potent and selectively antagonises the thromboxane receptors.

CONCLUSION: Ischaemic heart disease (IHD) is the biggest killer worldwide and main reason for the condition is the platelet aggregation and therefore any treatment that improves its outcome will help in saving millions of lives. Much attention has focused on inhibiting the central platelet aggregation in order to prevent thrombotic occlusion in very recent years. Aspirin the oldest of the antiplatelet drugs remains the cornerstone of therapy even with its adverse effects on gastric mucosa.

Clopidogrel is beneficial in prevention as well as medical and interventional therapy of acute coronary syndromes (ACS). But resistance with the use of aspirin and clopidogrel were the main concern for the cardiologist worldwide. So, various lab parameters and preventive measures were focused in reducing resistance. One main approach was the pharmacogenetic approach and treatment according to their genetic profile.

Dipyridamole has not been proven as an effective agent in cardiovascular disease although it was showing some benefit in cerebrovascular disease.

The other focus could be made on platelets interaction with leucocytes and the intervention against this will prevent further aggregation apart from platelet-platelet interaction. Newer antiplatelet therapy was on emergence and the results were convincing.

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REFERENCES:

1. Davi G, Patrono C: Platelet activation and atherothrombosis. *New England Journal of Medicine*, 2007; 357:2482–2494.
2. Collier BS: Blockade of platelet GPIIb/IIIa Receptors as an Antithrombotic Strategy. *Circulation*, 1995; 92:2373–2380.
3. Perneby C, Wallen NH, Rooney C, Fitzqerald D, Hjemdahl P: Dose- and time-dependent antiplatelet effects of aspirin. *Thrombosis Haemostasis*, 2006; 95(4):652–658.
4. Taubert D, Kastrati A, Harlfinger S, Gorchakova O, Lazar A, von Beckerath N et.al: Pharmacokinetics of clopidogrel after administration of a high loading dose. *Thrombosis Haemostasis*, 2004; 92: 311–316
5. Jakubowski JA, Winters KJ, Naganuma H, Wallentin L: Prasugrel: a novel thienopyridine antiplatelet agent—a review of preclinical and clinical studies and the mechanistic basis for its distinct antiplatelet profile. *Cardiovascular Drug Review*, 2007; 25:357–374
6. Oestreich JH: Elinogrel, a reversible P2Y12 receptor antagonist for the treatment of acute coronary syndrome and prevention of secondary thrombotic events. *Current Opinion in Investigational Drugs*, 2010; 11:340–348
7. Bhatt DL, Lincoff AM, Gibson CM, Stone GW, McNulty S, Montalescot G, Kleiman NS et.al: Intravenous platelet blockade with Cangrelor during PCI. *New England Journal of Medicine*, 2009; 361:2330–2341
8. Schomig A: Ticagrelor: is there need for a new player in the antiplatelet-therapy field? *New England Journal of Medicine*, 2009; 361:1108–1111
9. FitzGerald GA: Dipyridamole. *New England Journal of Medicine*, 1987; 316:1247–1257
10. Robless P, Mikhailidis DP, Stansby GP: Cilostazol for peripheral arterial disease. *Cochrane Database Systematic Review*, 2008; (1):CD003748.
11. Schneider DJ: Antiplatelet therapy: glycoprotein IIb-IIIa antagonists. *British Journal of Clinical Pharmacology*, 2011; 72(4):672–682.
12. Sorbera LA, Serradell N, Bolos J, Bayes M: Terutroban sodium. *Drugs of the Future*, 2006; 31(10):867–873.
13. Dockens RC, Santone KS, Mitroka JG, Morrison RA, Jemal M, Greene DS, et al: Disposition of radiolabeled ifetroban in rats, dogs, monkeys, and humans. *Drug Metabolism and Disposition*, 2000; 28 (8):973–980.

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