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Review Article

TICAGRELOR: A NEW REVERSIBLE ORAL ANTIPLATELET AGENT

Ahmed Khaleel*, Singhal Rohit, Pathak Kashyap, Shah Anand, and Srivastava Ambrish
Department of Clinical Research, Torrent Research Centre, Torrent Pharmaceuticals Limited, Village Bhat, 382428 Dist. Gandhinagar, Gujarat, India

*Khaleel Ahmed Hafiz Abdul Karim**,** Scientist II**,** Department of Clinical Research, Torrent Research Centre, Torrent Pharmaceuticals Limited, Village Bhat, 382428 Dist. Gandhinagar, Gujarat, India
E-mail: pharmacrnd@gmail.com
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ABSTRACT
Presently, the choices for long-term anti-thrombotic therapy in patients with acute coronary syndrome (ACS) who are to undergo percutaneous coronary intervention (PCI) are the oral antiplatelet agents: aspirin, ticlopidine, clopidogrel and others.
The latter three agents are prodrugs that lead to irreversible blockade of adenosine diphosphate (ADP) receptor of platelets, are used in combination with aspirin in patients suffering from ACS. Although these agents are effective, still there is need for improvement with respect to better efficacy and tolerability. In this context, the largest and latest Phase III trial of ticagrelor (PLATelet inhibition and patient Outcomes (PLATO)) compared ticagrelor and clopidogrel in patients with or without ST segment elevation myocardial infarction STEMI in a total of 18,624 patients. Ticagrelor is proved to be a better option then the available treatment option as it is a reversible antagonist of the ADP receptor P_2Y_{12} that may be taken orally. In addition, it is observed that it significantly reduced the incidence of vascular events without significant increase in the rate of major bleeding.
Unlike other orally active antiplatelets, it does not require metabolic activation for its antiplatelet effects. The agent appears to have more rapid and consistent inhibitory effects on platelet function than does clopidogrel. It has the potential to overcome some of the limitations of clopidogrel due to its superior potency, rapid onset, reversibility and decreased interpatient variability.

KEY WORDS: Ticagrelor, reversible platelet inhibition, ADP, acute coronary syndrome, percutaneous coronary intervention, antiplatelets, inhibition of platelet aggregation

INTRODUCTION

Cardiovascular diseases, especially acute coronary syndrome are the leading cause for mortality and morbidity and it is expected to be emerging in 2020. Though there are modern treatments available for Acute Coronary syndrome (ACS) incidences of death, myocardial infarction (MI) and re-hospitalization remains high. According to the report of global burden of cardiovascular diseases, 5.2 millions and 9.1 millions deaths occurred in developed and developing countries respectively. Likewise, out of 9.4 millions deaths in India 2.5 millions deaths are because of cardiovascular diseases which correspond to 25% approximately. The projected increase of such events is expected to rise in 2020 by 111% in India which is much higher than 77% of China, 106% of other Asian countries and 15% of economically developed countries.[1, 2]
When an atherosclerotic plaque ruptures or erodes, it leads to coronary occlusion. The collagen gets exposed and interacts with variety of receptors followed by platelets activation and adhesion through various intracellular signaling. Thromboxane A_2 and ADP are the local mediators which are produced in response to platelet adhesion. Glycoprotein (GP) IIb/IIIa is the receptor which is expressed on the platelets. This receptor is responsible for binding of fibrin and thrombin resulting in platelet aggregation as well as thrombus formation. This pathophysiological process leads to ACS either in form of unstable

angina (UA), non ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI). According to pathophysiology of myocardial infarction and stroke; peripheral occlusion are being precipitated by thrombosis in which platelets play the main role. However, pathophysiological as well as pathological functions of platelets are overlapping therefore; its risk and benefits are difficult to be distinguished. Numerous antiplatelet agents are being developed but only those agents which results in reduction of thrombosis outweighs the risk of bleeding can bring revolution in clinical practice and outcomes of cardiovascular medicines.[3, 4]

Antiplatelet agents with different mechanism of action are GP IIb/IIIa inhibitor, aspirin, and theinopyridine. Periprocedural thrombotic complications are being prevented by glycoprotein IIb/IIIa inhibitor. It inhibits GP IIb/IIIa receptor and prevents the process of platelet aggregation in final pathway. But because of its short duration of action and parenteral administration, it is not generally preferred for long duration. Aspirin is been used since many years for prevention of thrombotic events. Aspirin act by inhibiting cycloxygenase (COX) enzyme followed by blockade of thromboxane A_2 synthesis in platelets.[5] Though it is cost effective treatment, there are issues of limited efficacy, aspirin resistance and gastrointestinal adverse events; which led to development of new agent which can act by different mechanism. Oral anti platelet therapy with a P_2Y_{12} receptor inhibition is a cornerstone of antithrombotic treatment in patients with ACS with or without STEMI or undergoing PCI. Clopidogrel is an irreversible theinopyridine act by inhibiting ADP P_2Y_{12} on platelets. Clopidogrel has reduced cardiovascular outcomes significantly both alone and in combination with aspirin. This combination had become the standard therapy for ACS and in those who were undergone PCI [6.] Firstly the irreversible inhibition of platelets and the lifetime of platelets may complicate management of patient who require surgery and would therefore be at increased risk of bleeding. Secondly the clopidogrel requires hepatic conversion to an active metabolite resulting in delayed onset of effect, drug resistance, drug interaction, inter individual variability and poor response. Even bleeding is common problem making it non deferable for coronary artery bypass grafting (CABG).[8]

Ticagrelor

Ticagrelor is an orally active antiplatelet agent acting directly and reversibly at the P_2Y_{12} receptor. It belongs to cyclo-pentyl-triazolo-pyrimidines family and chemically it is [(1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl) cyclopropyl]amino} -5-(propylthio) -3*H*[1,2,3]- triazolo [4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane- 1,2-diol].[9]

Mechanism of action

Ticagrelor binds reversibly and directly to ADP P2Y12 receptors on platelets which changes the conformation of these receptors. Such binding inhibits platelet activation and eventual aggregation.

Figure 1

Pharmacodynamics

Ticagrelor have shown non-competitive antagonism on ADP P_2Y_{12} which is main target for inhibiting platelet aggregation. In radioligand binding studies ticagrelor binds to [33P] 2Mes-ADP competitively and do not displace [3HADP] which shows non competitive inhibition of ADP induced signaling. This shows that ticagrelor act as reversible P_2Y_{12} receptor inhibitor by different mechanism from other antiplatelets and thus, possesses greater affinity and potency towards ADP receptor. Therefore, this is evident to have better inhibition of platelets by ticagrelor than clopidogrel.[10]

Optical agrregometry has been used to assess the inhibition of ADP induced platelet aggregation through ticagrelor, in one of the dose escalation studies. At doses of 100-400 mg final extent aggregation is shown at 2 hours and peaked near 4 hours. The effect of inhibition of platelet aggregation decreases at 12-24 hours. This shows that ticagrelor has dose related ADP induced platelet inhibition.[11]

Single-nucleotide polymorph (SNP) is the gene which interferes with the clinical efficacy of clopidogrel. Therefore, in one study interference of same gene SNP in efficacy of ticagrelor has been determined. Different SNPs like P_2RY_{12}, P_2RY_1 and integrin, beta 3 (ITGB3) are been checked for any interference and it showed no effect on its efficacy. Its inter individual variability are been checked by observing IPA (inhibition of platelet aggregation) in stable atherosclerotic diseases (DISPERSE I) and Dose confirmation Study assessing anti Platelet Effect of ticagrelor versus clopidogrel in non-ST segment

Elevation myocardial infarction (DISPERSE II). A consistent response has been shown which proves it has less inter individual variability and less effect of diseases on its efficacy.[13]

Pharmacokinetics

Ticagrelor exhibits linear pharmacokinetics following first dose for dosages up to 100 mg twice daily and slightly exceeded dose proportionality at 200mg twice daily and 400mg once daily. Ticagrelor has one active metabolite which is one third of its concentration in blood and has relatively equal potency. Peak plasma levels of parent compound and metabolite reach within 1.5 and 3 hours respectively which are excreted in the feces primarily, and less than one 1% of either active compound in urine. The elimination half life and steady state are 6-12 hours and 2-3 days respectively. Age and gender does not affect the pharmacokinetic parameters.[12]

Drug interaction and adverse effects

As ticagrelor affect on platelet function, warfarin and NSAIDs may increase the risk of bleeding if concomitantly administered. Dyspnea, nausea, insomnia, diahorrea, hypertension, syncope and rash were common adverse effect of ticagrelor. Administration of ticagrelor also leads to elevation of serum creatinine and uric acid. These adverse events were observed in phase III trial of ticagrelor.[12]

Dosing and administration

About 50-60% inhibition of ADP induced maximal platelet aggregation within 2-4 hours by 180 mg ticagrelor and the effect remain consistent even with the maintenance dose of 90 mg. Accordingly 180 mg loading dose followed by 90 mg/day as maintenance dose is recommended.[12, 14]

Phase I study

In phase I, sequential, parallel group, placebo controlled, ascending dose study-the pharmacokinetics, pharmacodynamics, safety and tolerability of multiple doses of ticagrelor in healthy volunteers was evaluated. Based on these, optimal dosing regimen for other subsequent studies was developed.

All enrolled patients were divided into three groups in this study. Out of these 16 patients from group A, group B were randomized to receive different doses of ticagrelor (group A n=7 and group B n= 7) and placebo (n=2). Group A received 50, 100, 200, and 300 mg once or twice daily (n=7) for 16 days. Group B received ticagrelor 50, 100, 200, and 300 mg once daily (n=7) or ticagrelor 50, 100, 200, 300, 400, and 600 mg for total duration of 20 days. Group C received 300 mg followed by 75 mg for 14 days (n=14).

A single dose pharmacokinetic study showed increase in AUC_{0-t} and C_{max} in ticagrelor itself and its metabolite. The absorption of both parent and its metabolite (40%) was rapid. The T_{max} and elimination $T_{1/2}$ for the parent compound was 2 hour and 6.2-6.9 hours respectively whereas same for its metabolite was 2.5-4 hours and 6.4-9.4 hours respectively.

Same parameters were assessed for once daily and twice daily administration of ticagrelor to determine steady state pharmacokinetics. AUC_{0-t} and C_{max} of both once daily and twice daily administration was increased after few days. Ticagrelor shows linear pharmacokinetics. When mean C_{max} and AUC_{0-12h} for twice daily dosing and AUC_{0-24h} for once daily dosing was measured it showed that there was 2.37 and 2.32 fold increase in AUC_{0-t} in ticagrelor and 2.2 fold increase in C_{max} with increase in dose to its double of its previous value. T_{max} for once daily and twice daily administration of ticagrelor was 1.5-3.0 hours and 2-3 hours respectively and elimination $T_{1/2}$ of same was 7.7-13.1 and 6.7-9.1 hours respectively. Tmax and elimination $T_{1/2}$ of its metabolite for both once or twice daily administrations was 2-4 hours and 7.5-12.4 hours respectively.

The exposure of ticagrelor 200 mg has been increased with 25% in presence of food. There was rise in 20% in AUC_{0-t} and 17% in C_{max} in 200 mg with food whereas the same for twice daily with food was 31% and 11% respectively. However, it had no effect of food on exposure of metabolite and final extent IPA.

The effect of bleeding time indicates that the median baseline bleeding time was 165 s (range 128–263 s). Compared with baseline, median bleeding times was increased with ticagrelor by approximately 1.1- to 3.3-fold as compared with a 1.1- to 1.2-fold increase with placebo and a 1.5- to 1.9-fold increase with clopidogrel.

In this study myalgia and not dyspnea was the adverse effect in patient receiving ticagrelor. There was elevation of alanine amino transferase and aspartate aminotranferase from two to three times to its upper limit was seen in patient receiving ticagrelor, but it returned back to its normal values after few days.

Therefore no profound etiology was found for this event and considered to be the causal relationship between study drug and its plasma levels. There were no significant changes in parameters like electrocardiographs, laboratory values and vital signs.

In conclusion, the findings shows that the pharmacokinetics of ticagrelor are predictable, and are associated with consistent inhibition of platelet activity, to a greater extent than clopidogrel. The rapid onset of activity of ticagrelor coupled with a fast rate of platelet recovery may offer several advantages to patients with ACS.[15]

Disperse study

In DISPERSE study, pharmacokinetic, pharmacodynamic, safety and tolerability profile of ticagrelor has been explored in patients with atherosclerosis disease. DISPERSE and DISPERSE II were multicentre randomized clinical trials.

The DISPERSE trial was a dose ranging study comparing ticagrelor to clopidogrel in patients with stable atherosclerotic disease. 200 patients with stable atherosclerotic disease were randomized to ticagrelor 50 mg (n = 41), 100 mg (n = 39), 200 mg (n = 37) bid, 400 mg qd (n = 46), or to clopidogrel at the standard maintenance dose of 75 mg/day (n = 37) for 28 days. All drugs were taken with aspirin (75–100 mg/day). The main pharmacodynamic measure was inhibition of ADP induced platelet aggregation (20 μM ADP) measured by optical agrregometry, and the primary tolerability measure was the incidence of adverse events.

Platelet inhibition of three higher dose of ticagrelor was approximately 90-95% whereas same with low dose of ticagrelor and clopidogrel was 60%. This reveals that the higher dose of ticagrelor i.e. 100 mg and 200 mg twice daily and 400 mg once daily had rapid as well as greater inhibition as compared to low doses of ticagrelor and clopidogrel.

There were no serious adverse events reported during the study. Bleeding occurred with high doses of ticagrelor; however dyspnea occurred even with low dose which exacerbated with increase in doses. This lead to conclusion that ticagrelor at the dose of 100 mg twice daily and 200 mg twice daily shows greater platelet inhibition than low dose of ticagrelor and clopidogrel. In addition the dose up to 200mg twice daily is even safer and well tolerable than 400 mg twice daily dose.

In DISPERSE-II, 990 patients (984 in safety cohort) with non-ST-elevation ACS receiving aspirin and standard therapy for ACS were randomized to receive either ticagrelor 90 mg bid (n = 334), with a profile similar to ticagrelor 100 mg bid studied in DISPERSE, or 180 mg (n = 323) bid or to clopidogrel (n = 327) at a 300-mg loading dose followed by 75 mg/day for up to 12 weeks. Patients in the ticagrelor group were also randomized to a loading dose of 270 mg or no loading dose, and patients undergoing PCI within 48 h of randomization were allowed to receive an additional 300 mg of clopidogrel or matching placebo; patients already receiving clopidogrel at study entry received clopidogrel 75 mg, if randomized to the clopidogrel group. Across all treatment groups, 66% of patients underwent diagnostic coronary angiography, 43% had PCI, and 9% underwent CABG.[16, 17] The clinical end points were shown as follows (table I):

Though the cardiovascular events leading to mortality were similar but the incidences of MI were lesser numerically in the group receiving ticagrelor as compared to patients receiving clopidogrel, however, the results from this study lacks the significant power to assess the clinical events. Major and minor bleeding has been assessed which were more or less same in both groups i.e. 8.0% in 180 mg ticagrelor group and 8.1% in clopidogrel group. 48% of patient had persistent symptoms of dyspnea. Ventricular pause is also a prominent adverse effect in ticagrelor group. In conclusion, the adverse event profile of ticagrelor demonstrated comparable safety and tolerability than clopidogrel.

Onset and offset study

A multicentric, randomized, double blind, double dummy, parallel group study was designed to determine and compare the onset and offset of clopidogrel and ticagrelor. 123 patients on baseline aspirin therapy (75-100 mg) were randomized to receive either ticagrelor (180 mg loading, 90 mg maintenance) and clopidogrel (600 mg loading, 75 mg/ day) or placebo.

Loading dose of ticagrelor showed high IPA after 0.5 hours and significant IPA by loading and maintenance dose within 24 hours. The mean time to maximum IPA was 5.8 hours less and area under effect curve was higher than in clopidogrel group. Concerning offset effect, IPA was same at 24 hours

between the groups, but significantly decreased in ticagrelor group after 72-120 hours. This shows that ticagrelor achieve faster onset as well as offset in loading and maintenance dose (table II).[14]

Respond study

A randomized, double blind, double dummy and cross over investigation compared the antiplatelet response of clopidogrel and ticagrelor in patient with acute coronary syndrome. All the patients were on aspirin therapy receive clopidogrel. Among these patients 41 respond to therapy and 57 were non-responders to therapy. Among the responders 29 patients received clopidogrel and 28 patients received ticagrelor. After crossover, half of them continued the same treatment and others switched to other treatment. Among the nonresponders 20 patients received clopidogrel and 21 patients received ticagrelor and all responders switched to other therapy in period II. IPA of ticagrelor was always high at its loading as well as maintenance dose. IPA of patients who switched from clopidogrel to ticagrelor was same as that of ticagrelor in period I. The IPA of patient who switched from ticagrelor to clopidogrel was lower, as it was in period I clopidogrel group. Likewise, in responder cohort IPA was always high in patients who received ticagrelor than clopidogrel.[18]

Plato Study

According to a hypothesis ticagrelor can lowers the risk of recurrent thrombotic events along with this it is safe with clinically acceptable bleeding in wide population with ACS. Therefore, to test this hypothesis PLATO trial has been designed. Primary efficacy variables in this trial were deaths from vascular causes, MI and strokes and secondary variables were primary variables with invasive management or with recurrent cardiac ischemia, transient ischemic attack or occurrence of stent thrombosis or any cause of mortality. Similarly, safety and tolerability were also assessed in this trial.[16, 19, 20, 21]

Patients were randomized to receive ticagrelor at a loading dose of 180 mg followed by 90 mg bid or clopidogrel at a loading dose of either 300 mg, with provision for an additional 300 mg in patients undergoing PCI, followed by 75 mg qd for up to 12 months. Patients already receiving clopidogrel at study entry were allowed to receive a ticagrelor loading dose or matching placebo, followed by the daily regimen of either ticagrelor or clopidogrel. All patients were on a baseline aspirin (75–100 mg/day) therapy throughout the study as shown in table III.[25]

The incidences of deaths because of MI vascular causes were lower in ticagrelor than clopidogrel (9.8% vs 11.7% at 12 months). Additionally, incidence of deaths with respect to composite end points like recurrent cardiac ischemia, transient ischemic attack or other vascular events were also lower than clopidogrel (10.2% vs 12.3% P= 0.01), however, there were no significant decrease in incidences of stroke by both clopidogrel as well as ticagrelor group. There were no significant differences found in incidences of fatal or life threatening bleeding. The incidences of CABG related bleeding were less in ticagrelor (0.1 vs 0.3 p=0.03), nevertheless, non CABG bleeding was more in ticagrelor than clopidogrel group (0.3 vs 0.2 p=0.06). Dyspnea and ventricular pauses were other adverse events likely associated with the use of ticagrelor. An elevated creatinine and uric acid was also found in patients who were randomized to receive ticagrelor.

Though ticagrelor reduced cardiovascular outcomes according to PLATO trial, dyspnea was major adverse event. Therefore, a sub study was designed to determine the effects of ticagrelor on pulmonary function test. Out of all enrolled patient in PLATO trial 199 patients who received ticagrelor (n= 101) and clopidogrel 75 mg (n= 98) were enrolled in this study. All pulmonary function tests were assessed for patient receiving drugs for 30-40 days. Even after discontinuation these test were repeated at an interval of 10, 20 and 30 days.

Only 6 patients receiving ticagrelor experienced dyspnea as compared to 8 receiving clopidogrel. There was no difference in parameters at 31st day and there were no evidence of change in pulmonary function test at the end as well as after discontinuation. Therefore any detrimental effect on pulmonary function is not associated with ticagrelor.

DISCUSSION

The receptor binding studies suggests that clopidogrel gave indirect action on ADP P_2Y_{12} receptor whereas ticagrelor has direct action on ADP P_2Y_{12} receptor. Clopidogrel antagonizes the ADP P_2Y_{12} irreversibly whereas ticagrelor antagonizes the same reversibly[19]. Clopidogrel is inefficient as prodrug

because 85% of clopidogrel get hydrolyzed by esterase which leads to drug resistance or hyporesponsiveness or poor antiplatelet drug response, whereas, ticagrelor does not have such problem without affecting its antiplatelet activity[22]. Gene interference study concludes that clopidogrel requires CYP450 enzyme for activation and hence leads to many drug interaction and affected by SNP genes which leads to intersubject variability, whereas, ticagrelor does not require CYP450 for its activation, therefore, it does not have drug interaction as well as no interference by SNP genes and hence no intersubject variability[10]. Clopidogrel has delayed platelet inhibition which is due to slow onset of action that is 6-15 hours where as ticagrelor have faster onset of action that is 2-4 hours[23]. Clopidogrel is not having dose proportional response whereas ticagrelor is having dose proportional response[24, 25]. Clopidogrel itself is inactive and its metabolite is active, whereas, ticagrelor itself and its metabolite both are active[17]. The drug concentration in clopidogrel ticagrelor returns to its pretreatment level at 7 days and 2-3 days respectively. Therefore ticagrelor cause less CABG bleeding than clopidogrel. Hence during CABG drug should be withheld for 5 days in clopidogrel whereas 24-72 hours for ticagrelor[26].

CONCLUSION

The data from the clinical studies conducted reveals that ticagrelor could prove a better option for patients with ACS who would manage to undergo PCI as per its efficacy and safety profile; however, further data on safety can be scrutinized only after its use in clinical practice.

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Table 1: Clinical End Points

End points (%)	A Clopidogrel 75 mg daily (n= 327)	B Ticagrelor 90 mg twice daily (n=334)	P values B v/s A	C Ticagrelor 180 mg twice daily (n=329)	P values C v/s A
Through 4 weeks (%)					
All cause death	0.6	1.9	0.18	1.0	0.64
CV death	0.6	1.9	0.18	1.0	0.64
MI	3.5	2.2	0.34	1.0	0.047
Stroke	0.3	0.6	0.57	0.0	0.99
SRI	0.6	0.6	0.99	1.3	0.41
RI	1.6	3.2	0.21	1.6	0.98
Others	3.8	4.3	0.71	1.9	0.17
Through 12 weeks (%)					
All cause death	1.3	2.4	0.38	1.7	0.72
CV death	1.3	1.9	0.54	1.7	0.72
MI	5.6	3.8	0.41	2.5	0.06
Stroke	0.3	0.6	0.57	0.0	0.99
SRI	1.4	2.3	0.50	3.7	0.09
RI	3.0	4.9	0.29	3.4	0.78
Others	6.2	6.0	0.90	3.5	0.12

P values: level of significance, SRI: sever recurrent ischemia, RI: recurrent ischemia, MI: Myocardial infraction, CV: Cardio Vascular

TABLE II: IPA (20 µMOL/L ADP) AT 2 HOURS AFTER FIRST DOSE OF TICAGRELOR AND CLOPIDOGREL

	Ticagrelor		Clopidogrel		Placebo	
	IPA %	PA%	IPA %	PA%	IPA %	PA%
Final extent	88 ± 15	7 ± 9	38 ± 33	44 ± 24	< 0.0001	< 0.001
Maximum extent	65 ± 17	23 ± 10	25 ± 23	55 ± 18	< 0.0001	< 0.001

PA: platelet aggregation, IPA: inhibition of platelet aggregation, values are mean ± SD

Table III: Clinical End Points

End Points	Ticagrelor group (%)	Clopidogrel group (%)	P value
Primary End Point			
Death from vascular causes, MI or stroke	9.8	11.7	< 0.01
Secondary end points			
Death from any cause	10.2	12.3	< 0.01
Death form vascular cause	14.6	16.7	< 0.01
MI	5.8	6.9	0.05
Death from vascular causes	4.0	5.1	0.01
Stroke	1.5	1.3	0.22
Ischemic	1.1	1.1	0.74
Haemorhaggic	0.2	0.1	0.10
Unknown	0.1	0.02	0.04

P value: level of significance; MI: Myocardial infraction

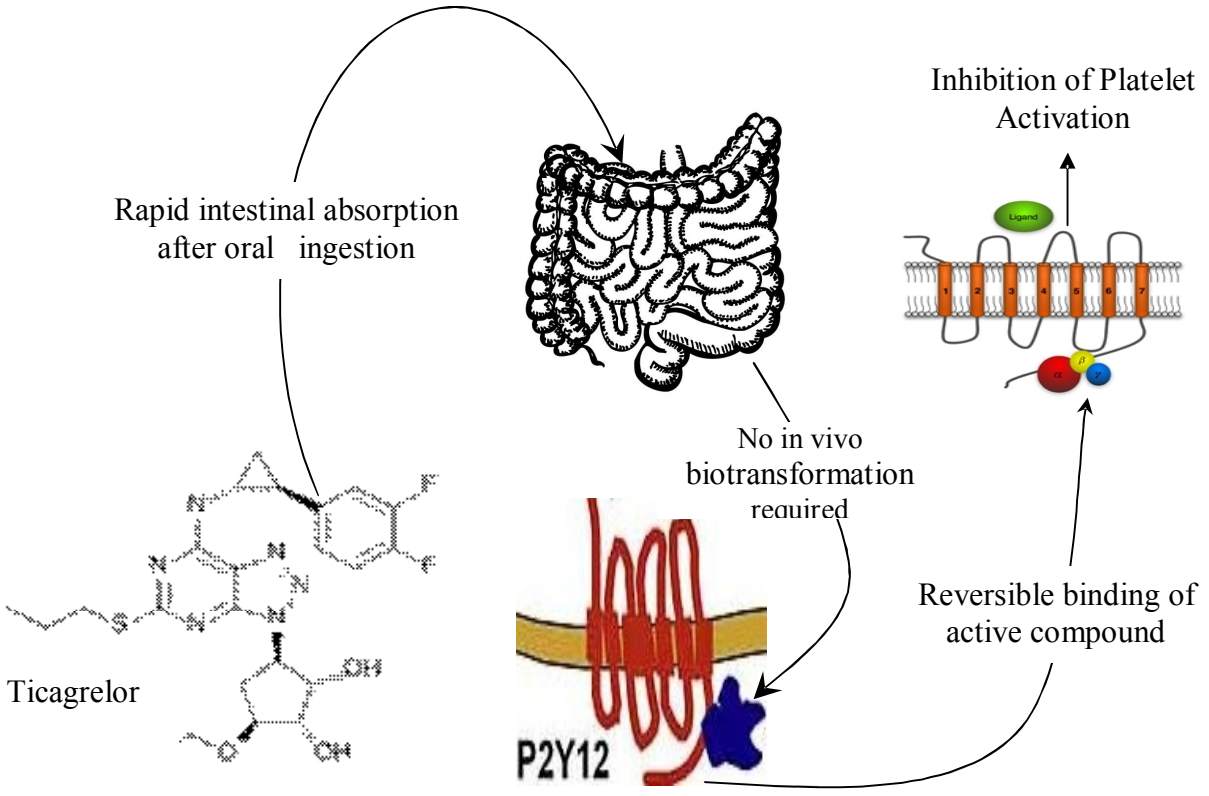

Figure I: Mechanism of action of Ticagrelor