Review Article

Ticagrelor Versus Clopidogrel in Acute Coronary Syndromes

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ABSTRACT

The thienopyridine clopidogrel, which irreversibly blocks the adenosine diphosphate (ADP) receptor P2Y12 on platelets, has become an essential component of therapy in patients with acute coronary syndromes, because it significantly improves the outcomes. However, clopidogrel has at least three drawbacks: delayed onset of action, large inter individual variability in platelet response, and irreversibility of its inhibitory effect on platelets. The U.S. Food and Drug Administration approved the Ticagrelor on July 20, 2011.Ticagrelor is an anti-platelet drug which is orally active and binds reversibly to P2Y12 receptor antagonist that blocks ADP-induced platelet aggregation. It was specifically designed to address the limitations of the available antiplatelet agents while maintaining comparable or better antiplatelet effects. It does not require metabolic activation and demonstrates greater platelet inhibition, a faster offset of action and comparable bleeding risk compared to clopidogrel. Theoretically, this property might be expected to result in less bleeding than with an irreversible compound that binds to the platelet for its lifespan. The Safety and efficacy of ticagrelor compared with clopidogrel in ACS patient has been recently evaluated by the PLATelet inhibition and patient Outcomes (PLATO) trial. The pivotal PLATO trial in patients with an acute coronary syndrome demonstrated improved cardiovascular outcomes, including a reduction in myocardial infarctions and vascular events using ticagrelor as compared to clopidogrel with comparable rates of major bleeds.

Keywords: Ticagrelor, Clopidogrel, Acute Coronary Syndrome, Pletelet Aggregation, ADP Receptor.

INTRODUCTION

The term acute coronary syndrome (ACS) is used to refer to a group of clinical symptoms associated with acute myocardial ischaemia[1]. It encompasses unstable angina, non-ST segment elevation myocardial infarction (ST segment elevation generally absent), and ST segment elevation myocardial infarction (persistent ST segment elevation usually present)[2].

Each year in the United States, approximately 1.36 million hospitalizations are required for ACS (listed either as a primary or a secondary discharge diagnosis), of which 0.81 million are for myocardial infarction (MI) and the remainder are for UA. Roughly two-thirds of patients with MI have NSTEMI; the rest have STEMI[3].

In patients who have acute coronary syndromes with or without ST-segment elevation, current clinical practice guidelines recommend dual antiplatelet treatment with aspirin and clopidogrel[4,7]. The efficacy of clopidogrel is hampered by the slow and variable transformation of the prodrug to the active metabolite, modest and variable platelet inhibition, [8,9] an increased risk of bleeding[10,11] and an increased risk of stent thrombosis and myocardial infarction in patients with a poor response[12].

Ticagrelor, a reversible and direct-acting oral antagonist of the adenosine diphosphate receptor P2Y12, provides faster, greater, and more consistent P2Y12 inhibition than clopidogrel[13,14]. The U.S. Food and Drug Administration approved the Ticagrelor on July 20, 2011. It was specifically designed to address the limitations of the available antiplatelet agents while maintaining comparable or better antiplatelet effects[15].

Biotransformation and Mechanism of action of Clopidogrel and Ticagrelor[16]

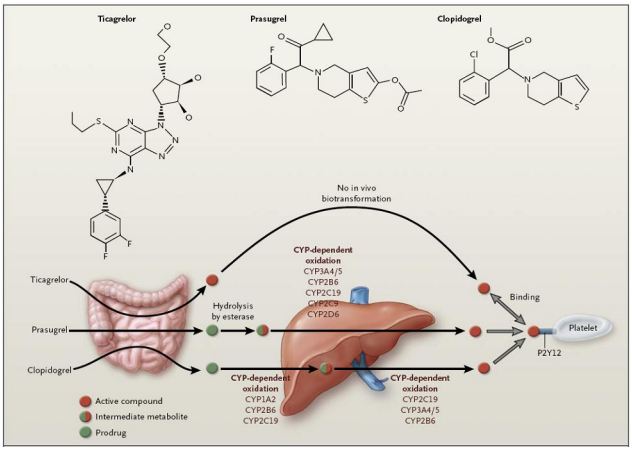


Fig. 1: Biotransformation and Mechanism of action of Clopidogrel and Ticagrelor

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 to 8 hours[16]. Reversible inhibition with ticagrelor may allow for more rapid surgical intervention after discontinuation, suggesting greater flexibility in treatment of ACS[17]. The irreversible binding of the thienopyridines results in slow offset of effect, with a gradual recovery of platelet function after drug withdrawal based on the generation of fresh platelets[18]. To avoid an increased risk for serious bleeding, an interval of 5 to 7 days off clopidogrel in patients undergoing coronary artery bypass grafting (CABG) is recommended[19,20]. Thus, the development of P2Y12 receptor antagonists that are reversible and that exhibit a better balance between efficacy and safety is desirable.

Clopidogrel is a prodrug that requires 2-step metabolism for conversion to its active metabolite, which irreversibly binds the platelet adenosine diphosphate (ADP) P2Y12 receptor[21,22]. After intestinal absorption of clopidogrel, it requires two cytochrome P-450 (CYP)–dependent oxidation steps to generate its active compound.[16]Because of the metabolic activation, the onset of effect of clopidogrel is relatively slow; with steady-state platelet inhibition achieved 2 to 4 hours after a loading dose of 600 mg. Even during maintenance dosing, there is considerable interindividual variation in levels of inhibition of platelet aggregation (IPA) due to variable metabolic conversion to the active metabolite[16,23,24].

The thienopyridines prasugrel is also a prodrug. 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[16].

Irreversible binding of Ticagrelor to receptor[25]

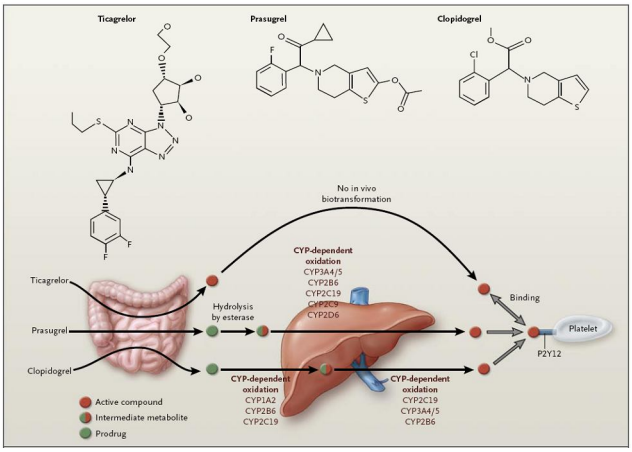
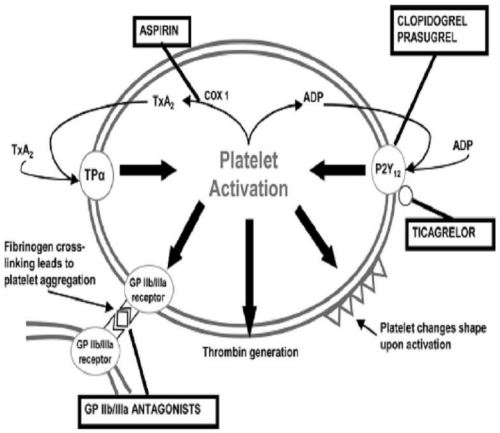


Fig. 2: Irreversible binding of Ticagrelor to receptor

Adenosine diphosphate (ADP) binds to the P2Y12 receptor and stimulates platelet activation, which ultimately leads to a conformational shape change of the platelet, thrombin generation and platelet aggregation. Clopidogrel and prasugrel directly and irreversibly block ADP through antagonism of the P2Y12 receptor for the life of the platelet. Ticagrelor binds at a separate P2Y12 sub-receptor that non-competitively blocks ADP activation through inactivating the receptor. Ticagrelor has reversible binding and leaves the receptor intact. Antiplatelet agents working at P2Y12 can be used simultaneously with aspirin due to separate and complementary mechanisms of action.

TxA2- thromboxane A2; GP- glycoprotein; COX- cyclooxygenase; TP- thromboxane A2 receptor[25].

Irreversible binding of Ticagrelor to receptor[26]



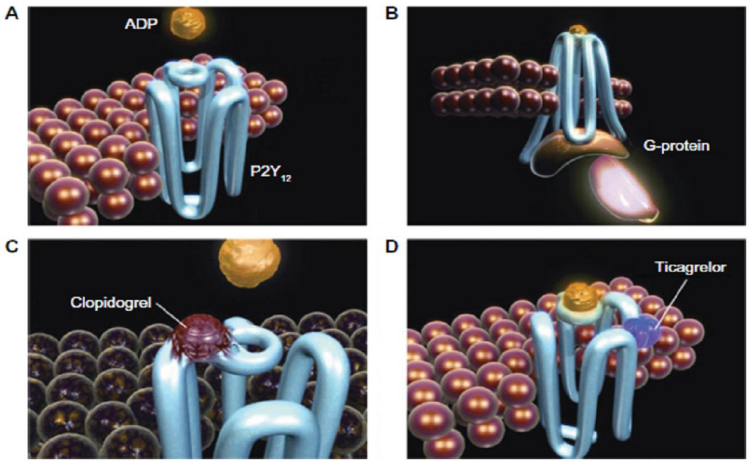


Fig. 3: Irreversible binding of Ticagrelor to receptor

A and **B**: ADP binds to the P2Y12 receptor, resulting in conformational change and G-protein activation.
C: Binding of the clopidogrel active metabolite to the P2Y12 receptor is irreversible, rendering the receptor nonfunctional for the life of the platelet.
D: Ticagrelor binds reversibly to P2Y12 at a site distinct from the ADP binding site and inhibits ADP signaling and receptor conformational change by "locking" the receptor in an inactive state; the receptor is functional after dissociation of the ticagrelor molecule. ADP can still bind at its binding site, and the degree of receptor inhibition (and inhibition of ADP-induced signaling) is dependant on the concentration of ticagrelor.

Abbreviation: ADP- adenosine diphosphate[26].

Table 1: Comparison of Antiplatelet P2Y12 Inhibitors

Parameter	Clopidogrel	Ticagrelor
Dose	300–600 mg loading dose, 75- mg maintenance dose once daily	180-mg loading dose, 90-mg BID maintenance dose
Binding	IRR	R
Metabolism Required for Effect?	Yes; 2 step P450 activation	No
Absorption	>50%	36%
Peak plasma levels	1 hour	1.5-3 hours
Plasma protein binding	98%	≥99%
Resistance to Antiplatelet Effect?	Yes	No
Maximum IPA	40%–60%	85%–95%
Time to maximum platelet inhibition	5–6 h	Within 2 h
Half-life (h)	8	7-8
Offset of Action	5–7 d	3–5 d
Excretion	Urine 50%; feces 46%	Bile ; feces

Comparison of Antiplatelet P2Y12 Inhibitors[27-35]
R indicates reversible; IRR, irreversible; IPA, inhibition of platelet aggregation.

Advantages of Ticagrelor (AZD 6140-an oral reversible P2Y12 antagonist) over Clopidogrel[36]
Direct acting:

- Not a prodrug, does not require metabolic activation
- Rapid onset of inhibitory effect on the P2Y12 receptor
- Greater inhibition of platelet aggregation than clopidogrel reversibly bound:
- Degree of inhibition reflects plasma concentration
- Faster offset of effect than clopidogrel
- Functional recovery of all circulating platelet.

Table 2: Risks Associated with Platelet Adenosine Diphosphate–Receptor Antagonists in Patients with Acute Coronary Syndromes, According to Trial

Event	CURE Trial (N = 12,562)			TRITON–TIMI 38 (N = 13,608)			PLATO (N = 18,624)		
	Clopidogrel Group	Placebo Group	Relative Risk with Clopidogrel (95% CI)	Prasugrel Group	Clopidogrel Group	Relative Risk with Prasugrel (95% CI)	Ticagrelor Group	Clopidogrel Group	Relative Risk with Ticagrelor (95% CI)
Death from any cause	5.7	6.2	0.93 (0.81—1.07)	3.0	3.2	0.95 (0.78–1.16)	4.5	5.9	0.78 (0.69–0.89)
Death from cardiovascular cause	5.1	5.5	0.93 (0.79–1.08)	2.1	2.4	0.89 (0.70–1.12)	4.0	5.1	0.79 (0.69–0.91)
Myocardial infarction†	5.2	6.7	0.77 (0.67–0.89)	7.3	9.5	0.76 (0.67–0.85)	5.8	6.9	0.84 (0.75–0.95)
Stroke†	1.2	1.4	0.86 (0.63–1.18)	1.0	1.0	1.02 (0.71–1.45)	1.5	1.3	1.17 (0.91–1.52)
Death from cardiovascular causes, myocardial infarction, or stroke†‡	9.3	11.4	0.80 (0.72–0.90)	9.9	12.1	0.81 (0.73–0.90)	9.8	11.7	0.84 (0.77–0.92)
Major bleeding	3.7	2.7	1.38 (1.13–1.67)	2.5	1.7	1.45 (1.15–1.83)	11.6	11.2	1.04 (0.95–1.13)

Risks Associated with Platelet Adenosine Diphosphate–Receptor Antagonists in Patients with Acute Coronary Syndromes, According to Trial.*[37,38,39]

* The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial [37] included patients who had acute coronary syndromes without ST-segment elevation; both PLATO (Study of Platelet Inhibition and Patient Outcomes)[39] and TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel– Thrombolysis in Myocardial Infarction 38)[38] included patients who had acute coronary syndromes with or without ST-segment elevation.

† TRITON–TIMI 38 counted only nonfatal myocardial infarction and nonfatal stroke.

‡ Death from cardiovascular causes, myocardial infarction, or stroke was the primary end point in all three studies.

PLATO is the third randomized trial evaluating novel antagonists of platelet ADP receptors in patients with acute coronary syndromes, following the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial and TRITON–TIMI 38 (Table 2).[37,38]

Study of Platelet Inhibition and Patient Outcomes (PLATO) is conducted to determine whether ticagrelor is superior to clopidogrel for the prevention of vascular events and death in a broad population of patients presenting with an acute coronary syndrome.[40]

Two striking differences among the outcomes of these three trials deserve special consideration (Table 2). First, in both the CURE trial and TRITON–TIMI 38, stronger platelet inhibition was associated with an increased risk of bleeding, whereas in PLATO, the risk of major bleeding was not increased with ticagrelor. As compared with clopidogrel, ticagrelor was associated with more frequent non–CABG-related bleeding, but it was safer than clopidogrel in patients undergoing CABG. This result highlights the important advantage of reversibility in the mechanism of action of ticagrelor[41].

Second, neither the CURE study nor TRITON–TIMI 38 showed a significant reduction in the mortality rate in association with stronger platelet inhibition. In PLATO, the rates of death from any cause were 4.5% with ticagrelor and 5.9% with clopidogrel, with a significant relative risk reduction (22%). This finding may simply reflect the play of chance, because the trial was not powered to detect differences in the mortality rate. However, since the mortality rate in patients treated with antiplatelet drugs is determined by the risks of both

ischemia and bleeding, ticagrelor may reduce the mortality rate by reducing the risk of death from ischemia without increasing the risk of death from bleeding. This hypothesis needs to be addressed in future investigations[41].

Third, new side effects, not seen with clopidogrel or prasugrel, were seen with the use of ticagrelor. These include dyspnea, bradyarrhythmia, and increased serum levels of uric acid and creatinine. Although they do not seem to have put patients at higher risk for death, these side effects may certainly have a negative effect on the quality of life. There was also a trend toward a higher risk of hemorrhagic stroke with ticagrelor than with clopidogrel, which becomes significant if cases of stroke classified as being of unknown origin are also counted as hemorrhagic strokes[41].

Conclusion:

Ticagrelor is a new oral antiplatelet drug for the patients who had an acute coronary syndrome with or without ST-segment elevation. It possesses many desirable characteristics in comparison with the thienopyridines clopidogrel in terms of rapid, predictable, and reversible antiplatelet effects and clinical efficacy superior to clopidogrel. Ticagrelor, as compared with clopidogrel, significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke, without an increase in the rate of overall major bleeding but with an increase in the rate of non–procedure-related bleeding. The main adverse effect seen with ticagrelor in clinical trials was Dyspnea. Additional benefits of ticagrelor are its efficacy in patients unresponsive to clopidogrel and lack of interaction with proton-pump inhibitors.

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