A Report on Comparative Safety and Efficacy of Ticagrelor in the Management of Acute Coronary Syndrome (ACS)

Dr. Mohammad Younus Mohiuddin – Portfolio Management

Introduction

Novel antiplatelet drugs, including Ticagrelor, are being successively introduced into the therapy of atherothrombotic conditions due to their superiority over a standard combination of Clopidogrel with Aspirin in patients with acute coronary syndromes (ACS)[1].

Blood coagulation is a series of complex chemical chain reactions characterized by initiation, propagation, and termination phases of thrombin generation, and anticoagulants are chemical compounds or proteins that prevent blood from clotting by binding to coagulation factors and preventing them from binding to phospholipid membranes[2]. The coagulation cascade is initiated by two pathways, known as the intrinsic pathway and extrinsic pathway. The intrinsic pathway is initiated by substances within the damaged blood vessel, whereas the extrinsic pathway is activated when blood is exposed to tissue factors from the surface of extravascular cells[3]. Coagulation factors join both the intrinsic and extrinsic pathways of coagulation, in which factors I, II, V, VIII, X are important components[4]. The common process of the intrinsic and extrinsic coagulation pathways is to activate the resulting prothrombin (FII) to form thrombin (IIa), which subsequently catalyzes fibrinogen (FI) to fibrin monomers (FIa). FIIa not only converts FI into FIa but also enhances its own generation through the activation of the cofactors FV, FVIII, and FXI in the so-called feedback loop[5]. Studies show that the FXa activation of FV is of paramount importance in initiating the coagulation system[6]. Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (FIB) were associated with coagulation, which is frequently used to examine thrombotic diseases[7].

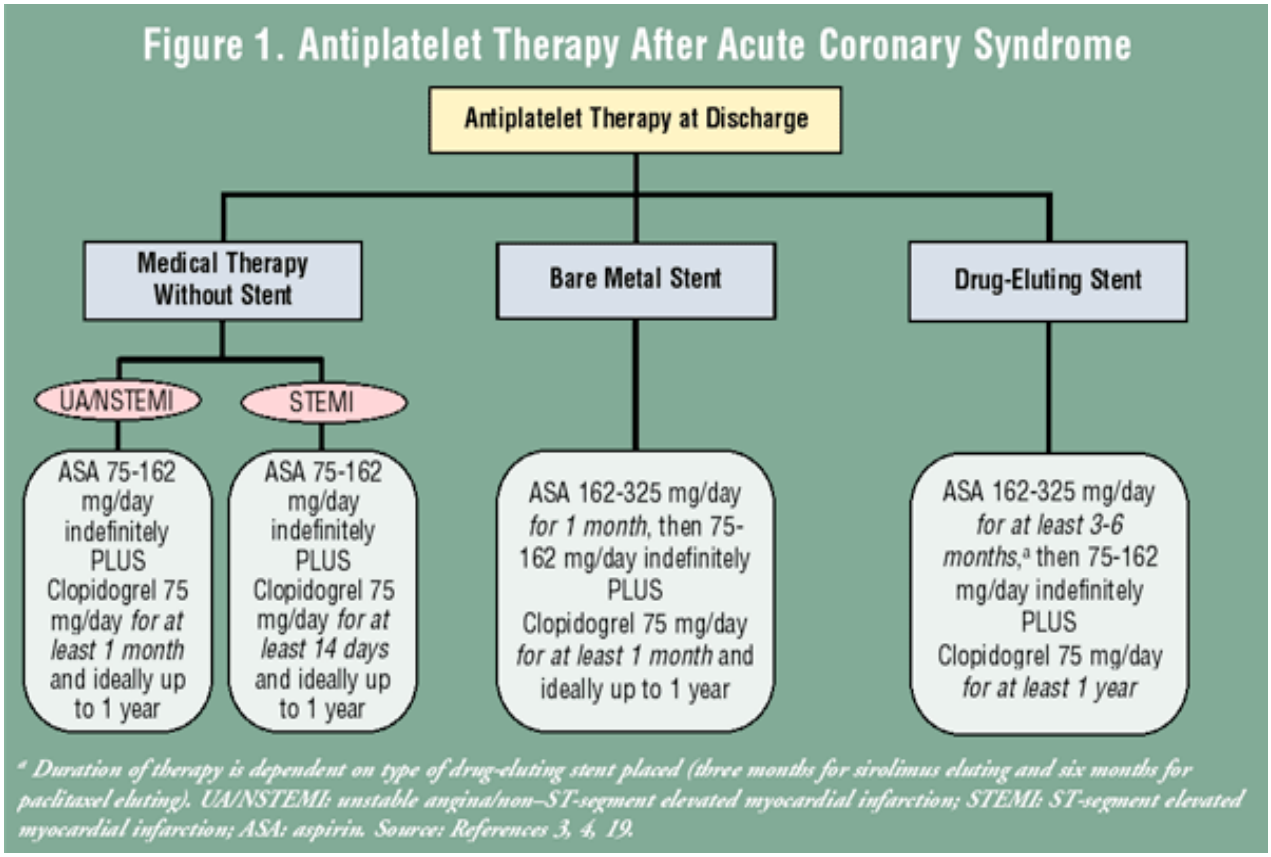
Predominantly used agents in antiplatelet therapy are Clopidogrel and Aspirin. Clopidogrel is a prodrug, which is activated in two steps, first by CYP2C19, CYP1A2 and CYP2B6, then by CYP2C19, CYP2C9, CYP2B6 and CYP3A.The active metabolite then specifically and irreversibly inhibits the $P2Y_{12}$ subtype of ADP receptor, which

is important in activation of platelets and eventual cross-linking by the protein fibrin[8].Platelet inhibition can be demonstrated two hours after a single dose of oral Clopidogrel, but the onset of action is slow, so a loading dose of either 600 or 300 mg is administered when a rapid effect is needed[9].

Low-dose aspirin causes irreversible inactivation of the cyclooxygenase enzyme and prevents the formation of prostaglandin and thromboxane A_2 in platelets, producing an inhibitory effect on platelet aggregation during the lifetime of the affected platelet (8–9 days). This antithrombotic property makes aspirin useful for reducing the incidence of heart attacks in people who have had a heart attack, unstable angina, ischemic stroke or transient ischemic attack[10]. 40 mg of aspirin a day is able to inhibit a large proportion of maximum thromboxane A_2 release provoked acutely, with the prostaglandin I2 synthesis being little affected; however, higher doses of aspirin (75mg and 150mg) are required to attain further inhibition[11].

Activation of platelets on a ruptured or eroded atherosclerotic plaque is a key event in atherothrombosis, including acute coronary syndromes (ACS) and acute ischemic stroke (AIS)[12]. Beyond thrombus formation, activated platelets trigger and disseminate vascular inflammation by exposure and release of pro-inflammatory molecules, thereby contributing to the progression of atherosclerosis. Platelet P2Y12 receptors for adenosine diphosphate (ADP) are essential for platelet activation[13]. For this reason, dual antiplatelet therapy (DAPT) comprising acetylsalicylic acid (ASA) and antagonists of the P2Y12 receptor is widely used to prevent recurrent ischemic events in patients with ACS[14,15]. Among the P2Y12 antagonists, Clopidogrel has been the standard treatment since its approval by the US Food and Drug Administration in 1997. Findings from recent large-scale clinical trials demonstrated that platelet inhibition with a novel and more potent P2Y12 receptor antagonist, Ticagrelor, and Prasugrel reduced the rate of ischemic events compared to Clopidogrel[16, 17].

Ticagrelor (developed by AstraZeneca), approved by USFDA in 2011, is a P2Y12 receptor antagonist, is unique among antiplatelet drugs, and Ticagrelor inhibits the platelet P2Y12 receptor in a reversible manner[1].



Pharmacokinetic data[18-21]

Innovator	AstraZeneca
Regulatory Approval	USFDA – 2011, CDSCO - 2012
Patent Information (Orange Book/Newport)	Initial Product Patent expiring in Sept, 2021 (Orange Book), Jul, 2021 (Newport)
Pregnancy Category	C
Dose & Dosage form	Tablet – 60mg, 90mg - BID
ROA	Oral
Approved Indications	Indicated to reduce the rate of cardiovascular death, Myocardial Infarction, and Stroke in patients with Acute Coronary Syndrome (ACS) or a history of Myocardial Infarction (MI) also reduces the risk of Stent Thrombosis
Indications under trial	Phase III Stroke; Vaso-occlusive crisis Phase II/III Coronary Artery Disease (CAD) Phase II Abdominal Aortic Aneurysm; Community-Acquired

	Pneumonia
Bioavailability	36%
Time to peak	1.5 hours
Protein binding	>99%
Metabolism	CYP3A4
Elimination T½	7 hours
Excretion	Feces, Urine
Contraindications	Contraindicated in patients with a history of intracranial hemorrhage, active pathological bleeding, hypersensitivity to Ticagrelor

Comparison of Safety[18]

Adverse events	Ticagrelor	Clopidogrel	Aspirin
Fatal/life-threatening bleeding	3.9%	3.3%	-
Fatal Bleeding	0.2%	0.2%	0.2%
Intracranial Hemorrhage	0.3%	0.2%	0.3%
Dyspnea	13.8%	7.8%	5.5%
Dizziness	4.5%	3.9%	4.1%
Nausea	4.3%	3.8%	2.5%

Parameter	Ticagrelor[18]	Clopidogrel[22]	Aspirin[23]
Warnings & Precautions	Black Box warning for having Bleeding risk and Maintenance dose of Aspirin greater than 100mg reduces the effectiveness of Ticagrelor. No dosage adjustment is recommended in patients with any degree of renal impairment or mild hepatic impairment. Dyspnea was reported more frequently than with control	Black Box Warning issued for Diminished antiplatelet effect in patients with two loss-of-function alleles of the cyp2c19 gene. Increased risk of bleeding. No dosage adjustment is necessary in patients with hepatic impairment.	Increased risk of bleeding especially GI associated. Avoid usage in patients with severe hepatic and severe renal impairment.

	agents in clinical trials. Dyspnea resulting from Ticagrelor is self-limiting. Severe Hepatic Impairment: Likely increase in exposure to Ticagrelor	Not extensively studied in patients with severe and moderate renal impairment	

Comparison of Efficacy[18, 22]

Outcome	Ticagrelor	Clopidogrel	Clopidogrel + Aspirin
Primary outcome: Composite of CV death, MI or Stroke	9.8%	11.7%	9.3%
Reduction in the Primary outcome: Cardiovascular death, MI, Stroke	90.2%	88.3%	90.7%
CV death	2.9%	4.0%	-
Non-fatal MI	5.8%	6.9%	-
Non-fatal Stroke	1.4%	1.1%	-

CV – Cardiovascular, MI – Myocardial Infarction

Conclusions

- Ticagrelor (developed by AstraZeneca), approved by USFDA in 2011, is a P2Y12 receptor antagonist like Clopidogrel, it is superior to Clopidogrel in terms of inhibition of platelet aggregation.
- Because Ticagrelor inhibits the platelet P2Y12 receptor in a reversible manner; it is required to be taken twice a day, unlike Clopidogrel which is to be taken once a day. This might affect the patient compliance of Ticagrelor.
- Ticagrelor is superior to Clopidogrel in terms of Efficacy and reduction of cardiovascular death. It is also claimed to be more efficient in reducing risk of stent thrombosis after having a stent placed post Acute Coronary Syndrome (ACS). Hence most of the cardiologists prefer Ticagrelor at least for three months to one year post an ACS event.

- Safety wise, both Ticagrelor and Clopidogrel carry black box warning, as Ticagrelor is more potent than Clopidogrel, theoretically it must possess more bleeding tendency but surprisingly the reported bleeding events were almost similar with both the drugs. Other adverse effects such as dyspnea, dizziness and nausea were reported more in Ticagrelor group.
- Further, Ticagrelor is a safer choice in patients with concomitant renal impairment; in contrast Clopidogrel is safer in patients with hepatic impairment.
- At last, it can be concluded that Ticagrelor exhibited a more favorable safety vs. efficacy profile over Clopidogrel.

References

1. Kubisa MJ, Jezewski MP, Gasecka A, Siller-Matula JM, Postuła M. Ticagrelor - toward more efficient platelet inhibition and beyond. Ther Clin Risk Manag. 2018 Jan 17;14:129-140. doi: 10.2147/TCRM.S152369. PMID: 29398917; PMCID: PMC5775739.
2. Jin N.Z., Gopinath S.C.B. Potential blood clotting factors and anticoagulants. Biomed. Pharmacother. 2016;84:356–365. doi: 10.1016/j.biopha.2016.09.057.
3. Ryu R., Jung U.J., Kim H.J., Lee W., Bae J.S., Park YB., Choi M.S. Anticoagulant and antiplatelet activities of artemisiaprincepspampanini and its bioactive components. Prev. Nutr. Food Sci. 2013;18:181–187. doi: 10.3746/pnf.2013.18.3.181.
4. Butenas S., Mann K.G. Blood coagulation. Biochemistry. 2002;67:3–12.
5. Prevention T.S. The italian guidelines for stroke prevention. Neurol. Sci. 2000;21:5–12.
6. Schuijt T.J., Bakhtiari K., Daffre S., Deponte K., Wielders S.J., Marquart J.A., Hovius J.W., van der Poll T., Fikrig E., Bunce M.W., et al. Factor Xa activation of factor V is of paramount importance in initiating the coagulation system: Lessons from a tick salivary protein. Circulation. 2013;128:254–266. doi: 10.1161/CIRCULATIONAHA.113.003191.
7. Qiu H., Zhang L., Zhu M., Zhang M., Chen J., Feng L., Jia X., Jacob J.A. Capture of anti-coagulant active ingredients from Moutan Cortex by platelet immobilized chromatography and evaluation of anticoagulant activity in rats. Biomed. Pharmacother. 2017;95:235–244. doi: 10.1016/j.biopha.2017.08.051.

8. John J, Koshy SK (2012). "Current Oral Antiplatelets: Focus Update on Prasugrel". Journal of American Board of Family Medicine. 25 (3): 343–349. doi:10.3122/jabfm.2012.03.100270. PMID 22570398.
9. Cattaneo M (March 2012). "Response variability to clopidogrel: is tailored treatment, based on laboratory testing, the right solution?". Journal of Thrombosis and Haemostasis. 10 (3): 327–36. doi:10.1111/j.1538-7836.2011.04602.x. PMID 22221409.
10. "Aspirin in heart attack and stroke prevention". American Heart Association. Archived from the original on 31 March 2008. Retrieved 8 May 2008.
11. Tohgi H, Konno S, Tamura K, Kimura B, Kawano K (October 1992). "Effects of low-to-high doses of aspirin on platelet aggregability and metabolites of thromboxane A2 and prostacyclin". Stroke. 23 (10): 1400–3. doi:10.1161/01.STR.23.10.1400. PMID 1412574.
12. Linden MD, Jackson DE. Platelets: pleiotropic roles in atherogenesis and atherothrombosis. Int J Biochem Cell Biol. 2010;42:1762–1766.
13. Hechler B, Gachet C. Purinergic receptors in thrombosis and inflammation. Arterioscler Thromb Vasc Biol. 2015;35:2307–2315.
14. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Eur Heart J. 2014;35:2541–2619.
15. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC) Eur Heart J. 2016;37:267–315.
16. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–1057.
17. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001–2015.
18. HIGHLIGHTS OF PRESCRIBING INFORMATION. FDA. BRILINTA (ticagrelor). PRESCRIBING INFORMATION. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf.

19. Adis Insight. Available online: https://adisinsight.springer.com/drugs/800013258.
20. Drugs@CDSCO. Available online: https://cdscoonline.gov.in/CDSCO/Drugs.
21. USFDA. ORANGE BOOK. Available online: https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=022433&Appl_type=N.
22. Label (PDF)-FDA. PLAVIX (Clopidogrel bisulphate). HIGHLIGHTS OF PRESCRIBING INFORMATION. Available online:https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020839s062s064lbl.pdf.
23. Label (PDF)-FDA. DURLAZA (aspirin). HIGHLIGHTS OF PRESCRIBING INFORMATION. Available online:https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/200671s000lbl.pdf.