Hygeia.J.D.Med. October 2015 –March 2016 ISSN 2229 3590
Hygeia:: journal for drugs and medicines
October 2015
Open Access www.hygeiajournal.com
Research article section: Clinical Pharmacy
A Half Yearly Scientific, International, Open Access Journal for Drugs and Medicines
DOI:10.15254/H.J.D.Med.7.2015.148 Review Article

NEWER ANTIPLATELET AGENTS IN CARDIOVASCULAR DISEASE

Siji MP, K. Krishna Kumar, K. Jayapraksah, L. Panayappan*

Department of pharmacy practice, St James College of Pharmaceutical Sciences, Chalakudy, Kerala
St James Hospital Trust Pharmaceutical Research Centre, Chalakudy, Kerala

Keywords: Platelet aggregation inhibitors, blood platelets

Correspondence
L.Panayappan
Department of pharmacy practice,
St James College of Pharmaceutical Sciences,
Chalakudy, Kerala

Received: 24 July 2015,
Revised: 20 August 2015,
Accepted: 25 August 2015,
Available online: 8 October 2015

ABSTRACT

Plan: *Antiplatelet drugs are the corner stone in the treatment of cardiovascular disease. They remain the main stay in preventing aberrant platelet activation in pathophysiological conditions like myocardial infarction, ischemia and stroke.*
Preface: *According to consensus guidelines, early revascularization and intensive antiplatelet therapy are key to reducing the complication that arises from myocardial ischemia and the recurrence of cardiovascular events. The different anti-platelets are aspirin, clopidogrel, ticagrelor, elinogrel, ticlopidine. Effective antagonism of the $P2Y_{12}$ platelet receptor is central to the treatment of acute coronary syndrome. Limitations in safety, efficacy and tolerability have precluded many of the antiplatelet inhibitors from use in patients. Unforeseen incidences of increased bleeding risk and recurrent arterial thrombosis observed in patients have hampered the development of superior next generation antiplatelet therapies.*
Outcome: *The effective antiplatelet therapy is important for the acute and secondary prevention of cardiovascular disease. The newer antiplatelet agents will reduce the limitation of the current therapy.*

1. INTRODUCTION

Platelets are essential for primary haemostasis and repair of the endothelium. But they also play a key role in the development of thrombus and acute coronary syndromes. Acute coronary syndrome refers to a range of acute myocardial ischemic states which include unstable angina, non ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI). It remains a significant global problem with very high mortality and morbidity. The majority of the drugs in development have focused on targeting either surface receptor of enzymes in the platelet for protecting the unwanted clot formation.

Corresponding author email: stjamesdruginfo@gmail.com

Hygeia journal for drugs and medicines, 2229 3590
Rid: K-7122-2015

But in the antiplatelet therapy, the main target was cyclooxygenase-1 by aspirin. While newer approaches have been developed mainly, the combination regimen of aspirin and clopidogrel is the standard treatment for the prevention of the platelet activation, thrombosis, and stroke[1].Given the expanding number of antiplatelet agents available clinicians have to make difficult decisions about the choices, dosage, combination and timing of these agents. Selecting the right drug at the right time, for the right patients with a careful assessment of the risk of bleeding and adverse events is crucial[2].

2. Activation of platelets

Blood platelets are formed from megakaryocytes in bone marrow. They are the smallest corpuscular component in the circulating blood with a diameter of 2-3 micrometre in the resting stage. Platelet count in the peripheral blood is normally between 150000 and 450000 per microliter of blood. Their average physiological lifespan in the peripheral blood stream is about 7 days with a daily renewal rate of about 20% of the total platelet count. Platelet activation is a series of cascading responses which allow blood platelet to react to an injury in the vessel wall in ordered to achieve adequate haemostasis[1]. The initial event in thrombus formation is the adherence of platelet to the disrupted surface of the plaque via the glycoprotein (GP) 1b receptor and Vonwillebrand factor. Adherent platelets become activated and degranulate, resulting in the release of substrates like serotonin, ADP, thromboxane A_2, platelet factor-4, P-selection, VWF, plasminogen activator inhibitor-1, and fibrinogen[2]. The mediators initiate the platelet response and they will form haemostatic plug. This results in further reduction of blood flow through local vasoconstriction in addition to the developing thrombus[3].

2.1. Guidelines for the management of ACS

The management of patients with ACS is extremely complex given the choices available not just about pharmacotherapy but also about coronary interventional procedures. Internationally recognized guidelines such as ACC/AHA, ESC, NICE is highly recommended in order to simplify decision making, achieve optimal outcome and avoid serious bleeding complication[4, 5].

2.2. Choice of antiplatelet therapy

It depends on the

- Patient characteristics(age, body weight)
- Risk factors profile (Presence of diabetes, renal insufficiency, previous stroke/ TIA)
- TIMI/GRACE risk stratification of ACS
- Choice of early invasive versus conservative management.
- Choice of coronary interventional procedures (coronary angioplasty versus CABG)
- Choice of intracoronary stents (drug eluting versus bare metal stents)
- Choice of thrombolysis versus primary PCI in patients with ST elevation MI[6]

2.3. Table 1. Antiplatelet medications

Mechanism of action	*Antiplatelet agents*
Cox1/TXA_2 inhibitor	Aspirin
ADP/$P2Y_{12}$ Blockers	Ticlopidine,clopidogrel,prasugrel,ticagrelor
GPIIb/IIIa inhibitors	Abciximab,Eptifibatide,Tirofiban
PAR-1 antagonist	Under development

2.3.1. Cox1/ Thromboxane A2 inhibitor

Aspirin acts promptly to irreversibly inactivated cyclooxygenase activity and inhibit the conversion of arachidonic acid to prostaglandin H_2 (PG H_2) and formation of thromboxane, which is a potent induces of platelet aggregation and vasoconstriction. Aspirin has been demonstrated to be effective across the entire range of ACS. A meta-analysis of a subgroup of patients with NSTE-ACS in the antithrombotic trialists collaboration, a 46% reduction in vascular events were observed with aspirin[7].

2.3.2. ADP/P_2Y_{12} receptor antagonist

The P_2Y_{12} receptors are G protein couple (GPCR) purinergic receptors belonging to the P_2 family. Two receptors, P2Y1 and P2Y12, are present in the platelet. P2Y1 is a Gq coupled GPCR, while P2Y12 is coupled to Gα 12. Activation of P2Y1 signals phospholipase β, leading to DAG formation, calcium mobilization, and eventually PKC and CalDAG-GEF activation[6]. In contrast, P2Y12 activation inhibits adenylyl cyclase, activates phosphoinositide 3-kinase[7], the small GTPase Rap 1[8], and activation of α II b β 3[8].

2.3.3. Clopidogrel

Clopidogrel is an oral prodrug requiring metabolism by the hepatic cytochrome P450 enzyme system to generate active metabolite. The use of clopidogrel in addition to aspirin (dual antiplatelet therapy) became standard form of treatment in the management of NSTE-ACS and STEMI. Specifically there undergoing PCI[9].Over the last few years, clopidogrel resistance is emerging on a clinical entity with potentially serious consequences like stent thrombosis. The mechanism of resistance remains in completely defined, but there may be clinical, cellular, metabolic and genetic factor that influence therapeutic failure with clopidogrel[10].

2.3.4. Prasugrel

It is a newer ADP receptor blocker and has been shown to be more effective than Clopidogrel in a recent TRITON TIME 38 trial comparing Prasugrel with Clopidogrel in ACS[11]. An excess of major bleeding was seen in patients over 75 years, there less than 60kg in weight and these with previous TIA/ stroke and hence Prasugrel is not indicated in those subgroups of patients. Prasugrel is also a prodrug requiring hepatic cytochrome-dependent metabolism for activity; but unlike Clopidogrel, it requires a single rather than a multiple-step process for activation, giving it a more predictable efficacy in platelet inhibition.

NICE guidelines in the UK recommended use of prasugrel (in place of clopidogrel) in patients undergoing primary PCI for STEMI, as well as NSTE-ACS patients with stent thrombosis during clopidogrel treatment or with diabetes mellitus[11, 12].

2.3.5. Ticagrelor

It is the latest ADP-P2Y12 receptor antagonist and the first member of a new class of cyclopentyl-triazolo-pyrimidine analogue. Ticagrelor exerts its action via binding to the P2Y12 receptor at a site distinct from the ADP binding site, thus making it an allosteric inhibitor. As a consequence of P2Y12 inhibition, ATP is converted to cyclic monophosphate, vasodialator-stimulate phosphor protein is dephosphorylator, and activation of P13-K is inhibited. The PLOTO trial compare ticagrelor with clopidogrel in which the primary composite endpoints, stroke, MI, Cardiovascular death and stent thrombosis and were reduced in patients with ACS. The benefit of ticagrelor appears to be attenuated in patients with lowering body weight and not taking lipid lowering drugs[13, 14].

2.3.6. Elinogrel

It is a direct acting reversible P2Y12 receptor inhibitor that is currently undergoing clinical investigation (INNOVATE-PCI) for efficacy and safety in patients undergoing PCI. Preclinical data show that intravenous or orally administered elinogrel is superior to Clopidogrel and has minimal effect on bleeding times. A single dose of elinogrel has been shown to overcome high platelet reactivity in patients undergoing PCI who were known responsive to Clopidogrel. This drug is still in clinical development for safety and efficacy assessment in patients, show promise as a next generation P2Y12 antagonist[15].

2.3.7. Cangrelor

It is an intravenous known theinopyridine and reversible P2Y12 inhibitor. Like Prasugrel and ticagrelor, Cangrelor showed a more rapid onset of action and greater degree of platelet inhibition than Clopidogrel. Recent evaluation of the inhibitor in the CHAMPION-PCI and CHAMPION- PLATFORM trials were stopped early due to its lack of apparent difference in the primary end point of death, MI or ischemia-driven revascularization 48hrs after PCI. Also the rate of major bleeding in patients undergoing PCI was higher with Cangrelor compared with Clopidogrel in both studies[16].

2.3.8. Glycoprotein IIb /IIIa receptor inhibitors

These are the most potent inhibitor of platelet activity as they selectively and comprehensively block the receptor necessary for the final common pathway of platelet aggregation. Because GPIIb/IIIa inhibitor does not block thromboxane A2 production from the activated platelets, concomitant use of aspirin may still enhance their anti-thrombotic activity. There are 3 agents currently available in this class: Abciximab, Eptifibatide, and tyrofiban. These are very powerful antiplatelet agents and are used intravenously during acute management of high risk patients with NSTE-ACS or STEMI planned for an early invasive strategy. ACC/AHA as well as ESC guidelines, recommended use of GPIIb/IIIa inhibitors within the 1st 25hrs of presentation who have elevated troponins, ST segment depression or diabetes mainly as an adjunct to PCI procedures[17, 18].

2.3.9. PAR1 antagonists

Thrombin is rapidly generated at the sites of vascular injury and, in addition to cleaving fibrinogen, it is a very effective platelet activator. Thrombin induces pro coagulant activity on the platelet surface, which supports additional thrombin generation. Platelet responses to thrombin are largely mediated through G-protein-coupled protease-activated receptors (PARs) that convert an extracellular proteolytic cleavage event into a transmembrane signal PAR1 antagonist are currently being developed for the prevention and treatment of atherothrombosis[19, 20].

3. CONCLUSION

An effective antiplatelet therapy is importance for secondary prevention in patients with acute coronary syndrome. Newer agents have been developed to overcome the shortcomings of clopidogrel as a P2Y12 antagonist and the pivotal trials to date have shown that prasugrel and ticagrelor in particular improve outcome. Further, while aspirin continues to be the first line of pharmacological intervention in antiplatelet therapy, the risk of bleeding is significantly exacerbated by its irreversible action coupled to the additional regimen of dual therapy often employed to minimize thrombotic events.

REFERENCES

1. Sathyamurthy, I, Jayanthi, K .Dual antiplatelet therapy in acute coronary syndromes and coronary artery interventions *J Assoc Physicians India*. **2014**; 62(7): p596-601.
2. Theroux, P., Fuster, V. Acute coronary syndromes. Unstable angina and non-Q wave myocardial infarction.*Circulation* **1998**; 97: p1195-1206.
3. Spinler, SA., Hilleman, DE ., Cheng, JW., Howard, PA ., Mauro, VF., Lopez, LM., Munger, MA., Gardner, SF., Nappi, JM. New recommendations from the 1999 American College of Cardiology/American Heart Association acute myocardial infarction guidelines. *Ann Pharmacother.* **2001**; 35(5): p589-617.
4. Rapezzi, C., Biagini, E., Branzi, A. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: the task force for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes of the European Society of Cardiology. *Eur Heart J.* **2008**; 29(2):p277-278.
5. Coady, E. Managing patients with non-ST-segment elevation acute coronary syndrome. *Nurs Stand.* **2006**; 20(37): p49-56.
6. Showkathali, R., Natarajan, A. Antiplatelet and Antithrombin Strategies in Acute Coronary Syndrome: State-Of-The-Art Review. *Curr Cardiol Rev*. **2012**; 8(3): p239–249.
7. Brown, C., Joshi, B., Faraday, N., Shah, A., Yuh, D., Jeffrey, J., Charles, W., Hogue, R. Emergency Cardiac Surgery in Patients with Acute Coronary Syndromes: A Review of the Evidence and Perioperative Implications of Medical and Mechanical Therapeutics. *AnesthAnalg.* **2011**; 112(4): p777–799.
8. Dominick, J., Capodanno, AD., Goto, S. Platelet thrombin receptor antagonism and atherothrombosis. *Eur Heart J.* **2010**; 31(1): p17–28.
9. Nicholas, B., Norgard, R., Abu-Fade, M. Comparison of prasugrel and clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Vasc Health Risk Manag*. **2009**; 5: p873–882.
10. Lindholm, D., Varenhorst, C., Cannon, CP ., Harrington, RA., Himmelmann, A., Maya, J., Husted, S., Steg, PG., Cornel JH., Storey RF., Stevens, SR., Wallentin, L., James SK. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. *Eur Heart J.* **2014**; 35(31): p2083–2093.

11. Marchini, J., Morrow, D., Resnic, F., Manica, A., Kirshenbaum, J., Cannon, C., Croce, K. An Algorithm for use of Prasugrel (Effient) in Patients Undergoing Cardiac Catheterization and Percutaneous Coronary Intervention. *Crit Pathw Cardiol*. **2010**; 9(4): p192–198.
12. Sabina, A., Murphy., Elliott, M., Antman, H., Wiviott, SD., Weerakkody, G., Morocutti, G., Huber, K., Lopez-Sendon, J., McCabe, CH., Braunwald, E. Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial. *Eur Heart J*. **2008**; 29(20): p2473–2479.
13. Sinha, N. Ticagrelor: molecular discovery to clinical evidence. Ticagrelor: a novel antiplatelet agent. *Indian Heart J*. **2012**; 64(5): p497–502.
14. Abergel, E., Nikolsky, E. Ticagrelor: An investigational oral antiplatelet treatment for reduction of major adverse cardiac events in patients with acute coronary syndrome. *Vasc Health Risk Manag.* **2010**; 6: p963–977.
15. Oprea, AD., Wanda, M. $P2Y_{12}$ Receptor Inhibitors in Acute Coronary Syndromes: What Is New on the Horizon.*Cardiol Res Pract.* **2013**; 2013: 195456.
16. Xiang, B., Zhang, G., Ren, H., Sunkara, M., Morris, AJ, Gartner, TK., Smyth, SS., Zhenyu, L. The $P2Y_{12}$ Antagonists, 2MeSAMP and Cangrelor, Inhibit Platelet Activation through $P2Y_{12}$/Gi-Dependent Mechanism. *PLoS One.* **2012**; 7(12):p51037.
17. Bauer, T., Mollmann, H., Weidinger, F., Zeymer, U., Seabra-Gome, R., Eberli, F., Serruys, P., Vahanian, A., Silber, S., Wijns, W., Hochadel, M., Nef, HM, Hamm, CW., Marco, J., Gitt AK. Use of platelet glycoprotein IIb/IIIa inhibitors in diabetics undergoing PCI for non-ST-segment elevation acute coronary syndromes: impact of clinical status and procedural characteristics. *Clin Res Cardiol.* **2010**; 99(6): p375–383.
18. Berny-Lang, MA, Jakubowski, JA, Sugidachi, A., Barnard, MR., Michelson, AD., Frelinger, AL. $P2Y_{12}$ Receptor Blockade Augments Glycoprotein IIb-IIIa Antagonist Inhibition of Platelet Activation, Aggregation and Procoagulant Activity. *J Am Heart Assoc.* **2013**; 2(3): e000026.
19. Zhang, P., Gruber, A., Kasuda, S., Kimmelstiel, C., Callaghan, KO., Cox DH., Bohm, A., Baleja, JD., Covic, L., Kuliopulos, A. Suppression of Arterial Thrombosis without Affecting Hemostatic Parameters with A Cell-Penetrating PAR1 Pepducin. *Circulation.* **2012**; 126(1): p83–91.
20. Duvernay, M., Young, S., Gailani, D., Schoenecker, J., Hamm, H. Protease-Activated Receptor (PAR) 1 and PAR4 Differentially Regulate Factor V Expression from Human Platelets. *Mol Pharmacol.* **2013**; 83(4): p781-792.

Siji MP, K. Krishna Kumar, K. Jayapraksah, L. Panayappan. Newer Antiplatelet Agents in Cardiovascular Disease. *Hygeia.J.D.Med* **2015**; 7(2):28-33. Available from http://www.hygeiajournal.com / Article ID-Hygeia.J.D.Med/148/15.
DOI: 10.15254/H.J.D.Med.7.2015.148.