

Review Article

Aspirin Resistance and Newer Combatants against It

F Ahammad¹, Shamsunnahar²

Abstract :

Aspirin is the widely used cheap antiplatelet agent globally. Since marketing it was unbeaten for use in coronary diseases and ischemic stroke patients. Unfortunately for the last two decades the term "Aspirin resistance" (AR) has been evolved due to its failure to protect the aspirin users against major cardiovascular events. Although the PIA1/A2 polymorphism in the GPIIIa platelet receptor along with other factors have been identified as responsible for this resistance, the term has not yet been defined. There is no consensus about ideal platelet function test. So it is more appropriate to say "treatment failure" to aspirin therapy rather using the term AR. Although Clopidogrel is being used alone or in combination with aspirin to overcome AR, platelet receptor (p2y12) inhibitors both Prasugrel and Ticagrelor are more potent than Clopidogrel in Acute Coronary Syndrome (ACS). Worldwide Prasugrel and Ticagrelor have been included in different guidelines to use in ACS.

Key words : Resistance, Polymorphism, Platelet receptor inhibitors.

Introduction :

Aspirin is the most commonly used antiplatelet drug and for more than 100 years. It represents a cornerstone in the primary and secondary prevention of cardiovascular diseases most notably myocardial infarction and stroke. The US Preventive Services Task Force and the American Heart Association recommended aspirin use for all men and women whose 10-years risks are > 6% and 10% or more respectively. They also expect that in all these patient categories, including secondary prevention, acute MI and acute occlusive stroke, as well as primary prevention, increased and appropriate use of aspirin will prevent large numbers of premature deaths and myocardial infarctions (MIs)¹. But based upon various platelet function tests and the fact that patients experience vascular events despite taking aspirin, it is now established that a significant fraction of aspirin treated patients (upto 57%) is resistant to the antiplatelet effects of the drug²⁻⁴. Diabetic patients including a significant portion of metabolic syndrome patients have a high rate of chance to develop such a resistance and this is proved by a high rate of entry of new platelets into the circulation of diabetic patients^{5,6}.

Although the term "aspirin resistance" was created almost two decades ago, it is still not defined. Platelet function tests are not standardized, providing conflicting information and cut-off values are arbitrarily set. Interest comparison reveals low agreement. Even point of care tests have been introduced before appropriate validation. The mechanism/s for aspirin resistance has not yet been fully established, but it is almost certainly due to a combination of clinical, biological, and genetic properties affecting platelet function. There are no criteria for distinguishing true resistance from treatment failure, and there is no consensus on whether the definition of aspirin resistance should be based on clinical outcomes, laboratory evidence, or both^{2,7}.

In this update, we will discuss about mechanisms or factors responsible for aspirin resistance and the role of other antiplatelet drugs notably adenosine diphosphate (ADP) receptor inhibitors clopidogrel, prasugrel and Ticagrelor to overcome this problem.

Classification of antiplatelet drugs:

- * Irreversible cyclooxygenase inhibitors
 - * Aspirin
- * Adenosine diphosphate (ADP) receptor inhibitors
 - * Clopidogrel
 - * Prasugrel
 - * Ticagrelor
 - * Ticlopidine

1. Dr. Faruk Ahammad. MBBS, FCPS (Medicine), Associate Professor, Department of Medicine, FMC, Faridpur.

2. Dr. Shamsunnahar, MBBS, FCPS (Radiotherapy), Assistant Professor, Department of Oncology, BSMMU, Dhaka.

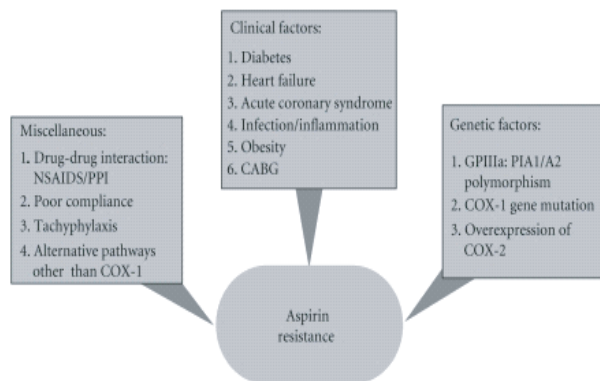
Address of correspondence :

Dr. Faruk Ahammad. MBBS, FCPS (Medicine), Associate Professor, Department of Medicine, FMC, Faridpur. Mobile No: +88-01817011894. Email: farukahammad26@yahoo.com

- * Phosphodiesterase inhibitors
 - * Cilostazol
- * Glycoprotein IIB/IIIA inhibitors (intravenous use only)
 - * Abciximab
 - * Eptifibatid
 - * Tirofiban
- * Adenosine reuptake inhibitors
 - * Dipyridamole
- * Thromboxane inhibitors
 - * Thromboxane synthase inhibitors
 - * Thromboxane receptor antagonists
 - * Terutroban

Proposed factors for aspirin resistance:

The possible mechanisms of AR are multifactorial. Following picture has shown the factors which may play role to develop AR -



Among the mentioned factors, genetic factors are important as these factors are nonmodifiable. At least 50 polymorphisms in 11 genes are found. The PIA1/A2 polymorphism in the GPIIIa platelet receptor is the most frequently observed polymorphism⁸. A potential role of -765G/C polymorphism (rs20417) in COX-2 gene also has been found with AR in ischemic stroke patients⁹. The role of nucleated cells (endothelium, monocytes) and hypercholesterolemia are also to be claimed to develop AR¹⁰. Statins uses improve aspirin response. No association is found between aspirin response and age, body mass index, education, smoking status, family history of cardiovascular disease, aspirin dose and duration of aspirin use and not related to parameters such as HbA1c and low-density lipoprotein (LDL), comorbidities including dyslipidaemia, and hypertension, and concurrent use of other medications such as beta blockers, angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers¹¹.

Laboratory tests for aspirin resistance :

Platelet functions are assessed clinically and by laboratory tests. The laboratory tests are Optical platelet aggregometry or method of Born using platelet-rich plasma (PRP) which is traditionally used to assay platelet activity. But 'Verify Now' and 'IMPACT' two simple tests can be considered as point-of-care tests to assay AR. There are very much reported variability in these tests due to the large and diverse biomarker and platelet function tests to define aspirin resistance. Aspirin achieves its primary antithrombotic effects

through the inactivation of cyclooxygenase 1 (COX-1), a key enzyme in platelet arachidonate metabolism and the formation of thromboxane A₂, a potent activator of platelets. Measurement of thromboxane A₂ to be suggested as the most direct measurement of aspirin resistance but unfortunately, this is not yet defined as a consensus point of view^{12,13}. Using urinary 11-Dehydrothromboxane B2 also may be a surrogate marker for antiplatelet efficacy¹⁴.

Clopidogrel :

Clopidogrel is an effective antiplatelet drug mostly used in combination with aspirin or as a single drug in aspirin intolerant patients. It has become an essential component of therapy in patients with ACS, because it significantly improves the outcomes but has at least three drawbacks: delayed onset of action, large interindividual variability in platelet response, and irreversibility of its inhibitory effect on platelets. The two-step activation process, involving a series of cytochrome P-450 (CYP) isoenzymes, is susceptible to the interference of genetic polymorphisms and drug-drug interactions¹⁵. Clopidogrel irreversibly binds to the P2Y₁₂ receptor hence its antiplatelet effect is prolonged. So it is undesirable when emergency surgery like coronary artery by-pass grafting (CABG) is needed¹⁶.

Prasugrel :

Prasugrel also irreversibly binds to P2Y₁₂ receptors. In contrast to Clopidogrel's two-step CYP-dependent activation, Prasugrel has a more efficient and simpler metabolism, which requires only one reaction by the liver enzymes to yield its active metabolite. As a result its onset of action is more rapid than Clopidogrel¹⁷. Prasugrel also cause platelet aggregation more consistently and to a greater extent than do standard and higher doses of clopidogrel in healthy volunteers and in patients with coronary artery disease, including those undergoing percutaneous coronary intervention (PCI)¹⁸. From a head-to-head comparison with clopidogrel, prasugrel is superior in reductions of clinical events like unstable angina (UA)/non-ST elevation myocardial infarction (NSTEMI)¹⁹. In diabetics, prasugrel exhibited a marked benefit over clopidogrel. On July 10, 2009, the US Food and Drug Administration (FDA) approved the use of prasugrel for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI²⁰. As compared with clopidogrel, prasugrel shows lower variability in platelet response and no measurable vulnerability to genetic variation in CYP isoenzymes¹⁵. So there is less chance of person to person variability of its response. However, the efficacy of prasugrel is offset by a higher risk of bleeding than Clopidogrel specially in CABG-related cases and patients aged ≥ 75 years, those weighing < 60 kg and those with a history of stroke or transient ischemic attack (TIA). A lower dose of prasugrel in patients aged ≥ 75 years and those weighing < 60 kg may help to minimize the bleeding risk¹⁸.

Ticagrelor :

This was approved by FDA on July 20, 2011 and has been included in 2011 American Heart Association (AHA)/American College of Cardiology (ACC) recommendations for use in ACS²¹. Ticagrelor is an orally active drug that binds reversibly to P2Y₁₂ receptors. The bindings are stronger and onset of action is more rapid than clopidogrel. In stroke patients, it is not so beneficial. Patients of acute coronary syndrome with or without ST-segment elevation, ticagrelor as compared with clopidogrel significantly reduces 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^{22,15}. Ticagrelor therapy may also be preferred in patients whose coronary anatomy is unknown and for whom CABG procedure is deemed probable. Dyspnea may occur after its use in few cases. So it is not advised in patients with chronic pulmonary diseases. Patients with hyperuricemia, moderate to severe renal failure, bradyarrhythmias unprotected by pacemaker and history of syncope also discouraged for Ticagrelor. Simvastatin, digoxin, rifampicin, ketoconazole, grapefruit juice interact with it and maintenance dose of aspirin above 100 mg reduces the effectiveness of Ticagrelor.

Discussion :

Aspirin-related compounds are among the oldest known medicinal substances, with stone tablets documenting the use of willow leaf (a source of salicylic acid) dating back to the Sumerian period²³. Controversy surrounding the use of aspirin can be traced back to the Greek empire, when Hippocrates was a proponent of willow bark for pain, whereas Dioscorides preferred coriander²⁴. We will never know whether Dioscorides was merely resistant to the beneficial properties of aspirin because thousands of years later we are still trying to understand and define the individual variability seen with its use. Because a significant fraction of aspirin treated patients showing resistance to the drug²⁻⁴. Although there is well-known variability in regards to platelet function tests and biomarker testing and a controversy persists to say aspirin resistance or aspirin failure there is no doubt that a significant number of coronary events are occurring in patients with regular use of aspirin. In this situation, over the past decade or more, newer antiplatelet agents have come to the forefront as adjuncts to or substitutes for aspirin in many clinical situations. However, the role of individual antiplatelet agents relative to each other is still evolving.

Clopidogrel is the first platelet receptor (p2y₁₂) inhibitors. It alone reduces (5.8% to 5.3%), the combined risk of major cardiovascular (CV) events, ischemic stroke, MI, and vascular death compared with aspirin alone and led to less gastrointestinal (GI) bleeding (2.7% to 2.0%) and is recommended as an

alternative agent for patients with CV disease unable to take aspirin due to allergy, bronchospasm or chance of major GI bleeding²⁵. Combination of Clopidogrel and aspirin is highly statistically significant in secondary prevention but not in primary prevention. In this cases chance of bleeding was more than Clopidogrel alones. In the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) trial with 7599 patients with stroke or TIA were randomly assigned to the combination of clopidogrel (75mg daily) plus aspirin (75mg daily) versus clopidogrel (75mg daily) alone. Follow-up upto 18 months showed that Aspirin plus Clopidogrel treatment did not reduce the risk of major vascular events compared with Clopidogrel alone and the combination was associated with a significant increase in life-threatening bleeding, mainly intracranial and gastrointestinal. This observation may be defend by the logic that, in the MATCH trial the patients who also had some additional "high-risk" feature, like prior MI, prior stroke, diabetes, angina, or symptomatic peripheral artery disease (PAD) were also included in the study. The non-defendable drawbacks of Clopidogrel are that it binds with receptors irreversibly, so action is long lasting and is of concern when patients need non-deferrable surgery such as urgent CABG. Moreover due to it's complicated metabolic activation, onset of action is delayed and more chance of drug-drug interaction. Lastly Clopidogrel resistance has been found as aspirin resistance although definition and mechanism(s) of this therapeutic failure are poorly understood²⁶.

Prasugrel action is also prolong and persistent due to its irreversible binding to p2y₁₂ receptors but due to its simple metabolic activation onset of action is more rapid than Clopidogrel. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) study of 13,608 patients with ACS (moderate-to-high risk) with scheduled PCI compared prasugrel against clopidogrel, both in combination with aspirin, and found that, as a more potent anti-platelet agent, prasugrel reduced the combined rate of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. Prasugrel reduced major CV events from 12.1% to 9.9% compared with Clopidogrel but increased major bleeding from 1.8% to 2.4% and fatal bleeding from 0.1% to 0.4%. Prasugrel can't be given in patients with age 75 years or more and previous history of stroke or TIA. It is used cautiously in patients with weight less than 60 kg or with renal impairment. Moreover, in the Targeted platelet Inhibition to clarify the Optimal strategy to medically manage Acute Coronary Syndromes (TRILOGY ACS) study, patients of UA and NSTEMI who are medically managed without revascularization, prasugrel has failed to show a reduction in major cardiovascular events compared with Clopidogrel.

In patients of acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor as compared with Clopidogrel significantly reduced the rate of death from vascular causes. The results of the

PLATElet inhibition and patient Outcome (PLATO)²⁷ trial showed the reduced primary endpoint of vascular death, MI, or stroke from 11.7% to 9.8% with Ticagrelor compared with Clopidogrel, with no significant difference in major bleeding (11.6% versus 11.2%) but with an increased risk of non-CABG related major bleeding (3.8% to 4.5%). In both the Clopidogrel in Unstable Angina to Prevent Recurrent Events (*CURE*) trial and TRINTON-TIMI 38 trial stronger platelet inhibition was associated with an increased risk of bleeding, whereas in PLATO the risk of major bleeding was not increased with Ticagrelor. Genetic variations in CYP isoenzymes do not appear to affect metabolism of Ticagrelor. So drug-drug interaction is not possible and onset of action is not delayed as Clopidogrel. It binds reversibly to P2Y₁₂ receptors, so after it's withdrawal emergency surgical procedure is easier than Clopidogrel or Prasugrel. Ticagrelor has been included in 2011 AHA/ACC recommendations for use in ACS²¹. Patients whose coronary anatomy is unknown and for whom a CABG procedure is deemed probable Ticagrelor therapy may be preferred¹⁵. But still it is not widely available.

Conclusion :

As the term "aspirin resistance" is still not defined and platelet function tests are not standardized it may be more appropriate to say "treatment failure" to aspirin therapy rather using the term "aspirin resistance". Obesity, diabetes mellitus, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, infection or inflammation along with genetic factors are thought to be responsible for AR. Platelet receptor(p2y₁₂) inhibitors are more effective than aspirin in preventing CV events. Prasugrel and Ticagrelor both are more potent than old golden standard Clopidogrel for patients with ACS. Regarding CABG related bleeding, Ticagrelor is safer than Prasugrel. Both Prasugrel and Ticagrelor have been rapidly adopted for the treatment of ACS in the past 2 years in the guidelines of different societies and associations worldwide. Nevertheless, the choice for one of the new compounds should be based on the patient's individual bleeding risk, cost benefit, availability in the local market and guideline recommendations.

References :

- Hennekens CH. Update on aspirin in the treatment and prevention of cardiovascular disease. *Am J Manag Care*. 2002; 8 (22):691-700.
- Berent R, Sinzinger H. "Aspirin - resistance"? A few critical considerations on definition, terminology, diagnosis, clinical value, natural course of atherosclerotic disease, and therapeutic consequences. *Vasa*. 2011; 40 (6):429-38.
- Sharma V, Kaul S, Al-Hazzani A, Prabha TS, Rao PP, Dadheech S, et al. Association of C3435T multi drug resistance gene-1 polymorphism with aspirin resistance in ischemic stroke and its subtypes. *J Neurol Sci*. 2012; 315 (1-2):72-6.
- Cañivano PL, García YC. Resistance to aspirin: prevalence, mechanisms of action and association with thromboembolic events: A narrative review. *Farm Hosp*. 2010; 34 (1):32-43.
- DiMinno MN, Lupoli R, Palmieri NM, Russolillo A, Buonauro A, Di Minno G et al. Aspirin Resistance, Platelet Turnover, and Diabetic Angiopathy: A 2011 Update. *Thromb Res*. 2012; 129 (3): 341-4.
- Cagirci G, Ozdemir O, Geyik B, Cay S, Ozturk S, Aras D, et al. The prevalence of aspirin resistance in patients with metabolic syndrome. *Turk Kardiyol Dem Ars*. 2009; 37 (7):461-6.
- Cheng X, Chen WH, Simon DI. Aspirin resistance or variable response or both? *Am J Cardiol*. 2006; 98 (10A):11-17.
- Timothy G, Albert F, Pankaj S. Pharmacogenetics of aspirin resistance: a comprehensive systematic review. *Br J Clin Pharmacol*. 2008; 66 (2):222-32.
- Sharma V, Kaul S, Al-Hazzani A, Alshatwi AA, Jyothy A, Munshi A, et al. Association of COX-2 rs20417 with aspirin resistance. *J Thromb Thrombolysis*. 2013; 35 (1):95-9.
- Szczeklik A, Musial J, Undas A. Reasons for Resistance to Aspirin in Cardiovascular Disease. *Circulation*. 2002; 106:181-82.
- Al-Azzam SI, Alzoubi KH, Khabour O, Alowidi A. The prevalence and factors associated with aspirin resistance in patients premedicated with aspirin. *Acta Cardiol*. 2012; 67 (4):445-8.
- Michelson AD, Cattaneo M, Eikelboom JW, Gurbel P, Kottke-Marchant K, Kunicki TJ, et al. Aspirin resistance: position paper of the Working Group on Aspirin Resistance. *J Thromb Haemost*. 2005; 3:1309-11.
- Cattaneo M. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. *Arterioscler Thromb Vasc Biol*. 2004; 24: 1980-87.
- Wai-Hong Chen, Xi Cheng, Pui-Yin Lee, William Ng, Jeanette Yat-Yin Kwok, Hung-Fat Tse, et al. Aspirin Resistance in Indian patients with coronary disease and cardiovascular events. *The American Journal of Medicine*. 2007; 55 (7):252-56.
- Albert Schömig, MD. Ticagrelor - Is There Need for a New Player in the Antiplatelet-Therapy Field? *N Engl J Med*. 2009; 361:1108-11.
- Nawarskas JJ, Clark SM. Ticagrelor: a novel reversible oral antiplatelet agent. *Cardiol Rev*. 2011; 19 (2):95-100.
- Snoep JD, Hovens MM, Eikenboom JC. Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis. *Am Heart J* 2007; 154:221-31
- Wiviott SD, Braunwald E, McCabe CH. "Prasugrel versus clopidogrel in patients with acute coronary syndromes". *N Engl J Med*. 2007; 357 (20):2001-15.
- R. Scott Wright, Jeffrey L. Anderson, Cynthia D. Adams, Charles R. Bridges. ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline). *J Am Coll Cardiol*. 2011; 7 (19):1920-59.
- Baker WL, White CM. Role of Prasugrel, a Novel P2Y₁₂ Receptor Antagonist, in the Management of Acute Coronary Syndromes. *American Journal of Cardiovascular Drugs*. 2009; 9 (4):213-29.
- Levine GN, Bates ER, Blankenship JC, Cercek B, Bailey SR, Bittl JA, et al. ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011; 124:e574-e651.
- Lars W, Richard CB, Andrzej B, Christopher PC, Håkan E, Claes H, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2009; 361 (11):1045-57.
- Jones R. Nonsteroidal anti-inflammatory drug prescribing: past, present, and future. *Am J Med*. 2001; 110 (1A): 4-7.
- Jack DB. One hundred years of aspirin. *Lancet*. 1997; 350 (9075):437-39.
- Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; 352 (12):1179-89.
- Güray Y, Güray U, Korkmaz S. Clopidogrel resistance. *Anadolu Kardiyol Derg*. 2009; 9 (3):231-7.
- Wallentin L, Becker RC, Budaj A, Richard C, Cannon CP, Emanuelsson H, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361 (11): 1045-57.