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 it's failure to protect the aspirin users against major cardiovascular events. Although the PIAl/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 drug²⁴. Diabetic patients including a significant portion of metabolic syndrome patients have a high rate of chance to develope such a resistance and this is proved by a high rate of entry of new platelets into the circulation of diabetic patients⁵⁶. 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 both²⁷.

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
Aspirin Resistance and Newer Combatants against It

F Ahammad et al.

Among the mentioned factors, genetic factors are important as these factors are nonmodifiable. At least 50 polymorphisms in 11 genes are found. The PL/A1/A2 polymorphism in the GPIIIa platelet receptor is the most frequently observed polymorphism. A potential role of -765G/C polymorphism (rs20417) in COX-2 gene also has been found with AR in ischemic stroke patients. The role of nucleated cells (endothelium, monocytes) and hypercholesterolemia are also to be claimed to develop AR. Statins use improves 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 blockers.

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 -

![Proposed factors for aspirin resistance](image)

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 Clopidogrel. Prasugrel also cause platelet aggregation more consistently and to a greater extent than do standardand higher doses of clopidogrel in healthy volunteers and in patients with coronary artery disease, including those undergoing percutaneous coronary intervention (PCI). 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). 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 PCI. As compared with clopidogrel, prasugrel shows lower variability in platelet response and no measurable vulnerability to genetic variation in CYP isoenzymes. 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 specialty in CABG-related cases and patients aged ≥75 years, those weighing <60 kg and those with a history of stroke or transient ischemic attack. A lower dose of prasugrel in patients aged ≥75 years and those weighing <60 kg may help to minimize the bleeding risk.
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 ACS. 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. 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, bradycardrhythmias unprotected by pacemaker and history of syncope also discouraged for Ticagrelor. Simbastatin, digoxin, rifampicin, ketoconazol, 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 period. 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 coriander. 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 drug. 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 antplatelet agents have come to the forefront as adjuncts to or substitutes for aspirin in many clinical situations. However, the role of individual antplatelet agents relative to each other is still evolving.

Clopidogrel is the first platelet receptor (P2Y12) inhibitors. It alone reduces (5.8% to 3.3%), 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 bleeding. 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 alone. 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 upt to 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 understood.

Prasugrel action is also prolong and persistent due to its irreversible binding to p2y12 receptors but due to it's 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) 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 ACS. Patients whose coronary anatomy is unknown and for whom a CABB procedure is deemed probable Ticagrelor therapy may be preferred. 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: