

## INCIDENCE OF ANTIPLATELET DRUG RESISTANCE AND TRIPLE ANTIPLATELET THERAPY IN ACUTE CORONARY SYNDROME

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### ABSTRACT

Dual antiplatelet therapy with aspirin and clopidogrel is the standard of care in acute coronary syndromes. Clopidogrel is having significant variability in on treatment platelet reactivity. Sometimes patients exhibit normal platelet aggregation in dual antiplatelet therapy. This resistance to drug comes due to drug unable to hit its pharmacological target or to alterations of the target. And novel P2Y<sub>12</sub> receptor antagonist comes at with increased side effects and cost. Therefore, alternative or additional antiplatelet therapies are needed. Cilostazole having vasodilatory and antiplatelet action through inhibition of phosphodiesterase 3 and subsequent elevation of intracellular cAMP levels. It was found that, cilostazol shown to significant improve high on treatment platelet reactivity in patient receiving both aspirin and clopidogrel in patient undergoing percutaneous coronary intervention. Triple antiplatelet therapy was associated with high platelet inhibition, reduced major cardio vascular events, target lesion revascularization and target vessel revascularization with low risk for a haemorrhagic event. Triple antiplatelet therapy might be safely applied in patients with high risk of stent thrombosis or restenosis.

**Keywords:** Cilostazol, antiplatelet therapy, acute coronary syndrome, stent thrombosis.

### INTRODUCTION

Coronary artery disease is a health care issue of epidemic proportions, and has a profound impact on resource utilization. A quiescent atherosclerotic lesion may follow the course of progressive luminal encroachment, or succumb to an acute thrombotic event. Reduced de novo collagen synthesis and increased extracellular matrix metabolism contribute to weakening of the fibrous cap. Platelet aggregation is a crucial component of this process.<sup>1</sup> Inhibition of platelet aggregation is a major therapeutic goal for patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI) to prevent adverse cardiovascular events, such as acute myocardial infarction, stent thrombosis, or cardiovascular death.<sup>2-4</sup> Endothelial disruption and platelet recruitment, activation, and aggregation are fundamental to the pathogenesis of arterial thrombosis.<sup>5</sup>

Drugs that inhibit platelet function are widely used to decrease the risk of occlusive arterial events in patients with atherosclerosis.<sup>6</sup> Antiplatelet drugs are beneficial in the treatment of coronary artery disease (CAD), ischemic stroke, and peripheral arterial disease.<sup>7</sup> Despite advances in the management of symptomatic atherosclerotic disease, thromboembolic complications still occur at sites of plaque instability.<sup>5</sup>

There are 3 families of antiplatelet agents with proven efficacy: (i) Cyclo-oxygenase-1 (COX-1) inhibitors, such as aspirin; (ii) adenosine 5-diphosphate (ADP) receptor antagonists, such as thienopyridine compounds ticlopidine and clopidogrel; and (iii) glycoprotein IIb/IIIa antagonists such as abciximab, eptifibatid and tirofiban. All these antiplatelet drugs are used during coronary interventions and in the medical management of acute coronary syndromes, while aspirin and thienopyridine

only are used in long-term prevention of cardiovascular and cerebrovascular events.<sup>6</sup>

### ANTIPLATELET THERAPY

Antiplatelet therapy with aspirin (ASA) 75-325 mg/day offers protection against myocardial infarction (MI), stroke, and death. The mechanism of aspirin's antiplatelet action was first described in 1971 by British pharmacologist John Vane. In platelets, ASA irreversibly inhibits the enzyme cyclooxygenase-1 (COX-1), which in turn inhibits production of thromboxane A<sub>2</sub>, a facilitator of platelet aggregation. (Figure. 1) Significant benefit is evident among patients with acute coronary syndromes, such as unstable angina or acute MI, patients undergoing percutaneous coronary and peripheral intervention, and those with chronic ischemic vascular disease, or cerebrovascular disease. With regard to safety, efficacy, and cost effectiveness, ASA has demonstrated the best risk-benefit ratio of any available therapy for acute MI. Clopidogrel and ticlopidine are both thienopyridine agents with similar therapeutic effects, although clopidogrel has a better safety and side effect profile. Clopidogrel is a prodrug that undergoes activation by the cytochrome P450 3A4 system to become an irreversible inhibitor of the platelet P2Y<sub>12</sub> receptor by blocking the binding of adenosine 5'-diphosphate (ADP). Blocking ADP leads to direct inhibition of the binding of fibrinogen to the glycoprotein IIb/IIIa complex, thereby inhibiting platelet aggregation. Clopidogrel has demonstrated significant benefit across a wide spectrum of coronary artery disease clinical scenarios including ST elevation myocardial infarction (STEMI), non-STEMI, and routine percutaneous coronary intervention (PCI). Ticlopidine, as mentioned, is similarly effective but associated with frequent side effects including rash and gastrointestinal upset, as well as the rare but potentially life-threatening occurrence of neutropenia. Still, it remains an alternative when clopidogrel therapy is not tolerated. Parenteral glycoprotein (GP) IIb/IIIa antagonists inhibit the final common pathway of platelet aggregation, the crossbridging of platelets secondary to fibrinogen binding to the activated GP IIb/IIIa receptor, resulting in near complete inhibition of platelet aggregation.<sup>8</sup>

There is a well documented variability between patients (and normal volunteers) with regard to laboratory test responses to antiplatelet drugs.<sup>9-18</sup> Evidence from small clinical studies suggest that decreased response, or 'resistance', to antiplatelet drugs

is associated with subsequent major adverse clinical events (MACE).<sup>9-14,16,18-20</sup>

Up to one third of the patients exhibit normal platelet aggregation in spite of dual antiplatelet therapy with aspirin and clopidogrel. This phenomenon is often referred to as non-responsiveness or, more commonly antiplatelet drug resistance.<sup>21,22</sup> The term 'resistance' to a drug should be used when a drug is unable to hit its pharmacological target, because of inability to reach it (as a consequence of reduced bioavailability, in vivo inactivation, or negative interaction with other substances) or to alterations of the target.<sup>23</sup>

The reason for non-responsiveness to antiplatelet treatment may vary and are not fully understood. Compliance to treatment, bioavailability, enzyme activities, and generic polymorphisms may play a role.<sup>21</sup> Antiplatelet therapy resistance is common, with approximately half of all patients having resistance to either aspirin, clopidogrel, or both. It also confers an increased risk of adverse outcomes associated with acute coronary syndromes and percutaneous coronary interventions. However, the definition is complicated by the absence of standardized methods for the platelet function assessment and the use of multiple assays and agonists. The occurrence of an ischemic clinical event while on antiplatelet therapy, although reflective of treatment failure, does not necessarily indicate that resistance is present.<sup>8</sup> There are two methods of platelet aggregation testing. The first, light transmission platelet aggregometry (LTA), has been the gold standard of platelet function analysis for decades. However, this technology is tedious, time consuming, and not available in all hospitals. Furthermore, results of LTA are not immediately available, and thus cannot be used to guide acute therapies in the catheterization laboratory setting. The second, point-of-care platelet function assays, have become available more recently and are analogous to an activated clotting time (ACT) in that results are immediately available to guide therapy.<sup>8</sup>

Light transmission aggregometry and point-of-care platelet function assays typically express results as percent aggregation. The assessment of platelet function after administration of platelet inhibitors may be expressed as residual platelet aggregation, or as level of platelet inhibition, which is the inverse of residual platelet aggregation. The most widely accepted definition of ASA resistance is  $\geq 70\%$  residual platelet aggregation with 10  $\mu\text{mol}$  ADP stimulation or  $\geq$

20% residual platelet aggregation with 0.5 mg/ml arachidonic acid stimulation.<sup>24</sup>

Optimal management of patients with platelet resistance has not yet been established. Standardized methods of platelet function testing and interpretation, as well as integration of point-of-service testing, may assist in adjusting antiplatelet therapy to improve outcomes in patients with platelet resistance. Likewise, newer pharmacologic agents may demonstrate better efficacy and a lower incidence of resistance compared to the current standard of care of aspirin and clopidogrel.<sup>8</sup>

### **ASPIRIN RESISTANCE: INCIDENCE AND OUTCOMES**

The incidence of aspirin resistance varies from 5-60% of patients with cardiovascular disease depending upon the definition and assay used, as well as the population studied<sup>24</sup>. The etiology of aspirin resistance is poorly understood and likely involves a combination of clinical, cellular, and genetic factors (Figure 2)<sup>25</sup>. Ischemic stroke patients with aspirin resistance have an increased risk of future cardiovascular events, including stroke, MI, or vascular death<sup>26</sup>. In a study of 151 patients undergoing non-urgent PCI, the incidence of aspirin resistance was 19.2%. Despite pretreatment with clopidogrel, those patients who were aspirin-resistant had a significantly higher rate of CK-MB and troponin I elevation post-procedure than those who were aspirin-sensitive (51.7% vs. 24.6%,  $p=0.006$ )<sup>27</sup>. Interestingly, there was a significantly higher incidence of women in the aspirin-resistant group (44.8%) compared with the aspirin-sensitive group (19.7%) ( $p=0.007$ ).

### **CLOPIDOGREL RESISTANCE: INCIDENCE AND OUTCOMES**

The prevalence of clopidogrel resistance varies from 4-30% of patients with coronary artery disease (CAD) depending upon the clinical scenario, test assay, and clopidogrel dose<sup>28,29,30</sup>. A number of extrinsic and intrinsic factors have been hypothesized as operative in the etiology of clopidogrel resistance (Figure 3)<sup>30</sup>. Among patients undergoing PCI, those with high pretreatment platelet reactivity are the most likely to demonstrate post-treatment resistance to clopidogrel<sup>28</sup>. The early risk of PCI is related to the level of platelet aggregation during the procedure. Time from clopidogrel loading has a strong effect on the change in platelet aggregation, but even patients on chronic clopidogrel therapy who exhibit high ADP-induced platelet aggregation are at increased risk for post-procedural

ischemic events<sup>31</sup>. Clopidogrel resistance has been associated with adverse outcomes in a variety of clinical scenarios. Up to 25% of STEMI patients undergoing primary PCI are resistant to clopidogrel and have an increased risk of adverse cardiovascular events including stent thrombosis<sup>32</sup>.

Large clinical trials have shown that dual antiplatelet therapy (aspirin plus clopidogrel) reduce risk of recurrent cardiovascular events in patients with coronary artery disease. Dual antiplatelet therapy is the standard care in patients with acute coronary syndromes.<sup>33-37</sup>

There is no compelling evidence to support the superiority of clopidogrel to ASA monotherapy in optimizing graft patency following CABG. The mechanisms of action of thienopyridines and ASA differ, allowing for a cumulative anti-aggregative effect. ASA irreversibly suppresses cyclooxygenase-1 activity thereby reducing thromboxane A2 production, whereas clopidogrel acts on the P2Y12 adenosine diphosphate (ADP) receptor to inhibit ADP-mediated platelet aggregation. While dual antiplatelet therapy offers a reduction in atherosclerotic events in patients undergoing percutaneous coronary interventions, this benefit has not been reliably reproduced in other clinical settings. Issue of dual antiplatelet therapy in patients undergoing coronary artery surgery who have been found to be aspirin resistance or clopidogrel resistance. In the event that the addition of clopidogrel proves to be beneficial in this subject of surgical patients.<sup>38</sup>

Stent thrombosis (ST) is associated with considerable morbidity and mortality. An impaired response to antiplatelet therapy might be related to an increased risk for stent thrombosis. Study evaluated the relation between ST and platelet aggregation (PA). The principal finding was a significantly higher aggregation level in patients with ST compared with control patients and volunteers. The addition of clopidogrel to ASA did not overcome this difference but reduced the aggregation level in all groups to a similar extent. The incidence of ASA resistance was consistently higher in patients with ST compared with control patients and volunteers. Previous studies identified ASA resistance as a strong predictor for cardiovascular events during follow-up. Another important finding of the study was the inability of clopidogrel to overcome the impaired response to ASA in ST patients because the level of ADP-induced aggregation remained higher in this group. The phenomenon of resistance to ASA the combination of ASA and clopidogrel may play an important role in pathophysiology of ST.

Aspirin but not clopidogrel resistant appears to be associated with ST.<sup>39</sup>

Wide variability has been reported in response to aspirin and clopidogrel. There are limited data on the simultaneous responses to both drugs. There are limited data regarding the simultaneous responses to both aspirin and clopidogrel. Aim of study was to evaluate prospectively response to clopidogrel among aspirin-resistant versus aspirin-sensitive patients, and to characterize factors that affect responses to either drug in patients undergoing elective PCI. During this study they identified a unique group of dual antiplatelet resistance patients who do not achieve adequate antiplatelet effect either from aspirin or clopidogrel. The relatively high incidence of CK-MB elevation after PCI in these patients suggests that they may be at high risk for thrombotic complications. Although this study is limited by small number of patients so this finding should be confirmed in a larger scale study. The lower response to clopidogrel is very important in aspirin resistance patients because clopidogrel is given as alternative therapy for aspirin resistance patients. There data may not be sufficient and that other platelet inhibitors acting on additional targets other than cyclooxygenase-1 and P2Y12 should be developed and investigated.<sup>40</sup>

Although standard doses of aspirin can reduce the incidence rate of thromboembolic events, effect is partial and does not inhibit the effect of physiologic agonists such as ADP, directly. Long term prophylactic treatment with the ADP receptor antagonist ticlopidine hydrochloride or clopidogrel bisulphate has shown a small but significant benefit over aspirin alone, with no increase in bleeding. In the more acute setting of intracoronary intervention, a combination of aspirin and thienopyridine reduced thrombotic events without an increased incidence of bleeding, either after surgery or systemically, compared with nonconventional antithrombotic regimens. Therapeutically active doses of both ticlopidine and clopidogrel have shown to prolong BT in humans but there have been relatively few studies of the combined therapy of clopidogrel with aspirin on bleeding risk in humans. The combination of aspirin and ticlopidine or clopidogrel has shown additive effects on ex vivo platelet function and in animal models of acute and subacute thrombosis with only a modest increase in BT. There has been only one study reported of combination antiplatelet therapy in open surgery, with no systemic assessment of bleeding. Data suggest that combining clopidogrel with aspirin for major cardiovascular or general surgical procedures

may carry a significantly increased risk of bleeding. The recent CURE study has shown a significant benefit for the simultaneous administration of both drugs in the prevention of acute coronary syndromes. Patients undergoing vascular intervention with dual therapy should carefully about increased bleeding.<sup>41</sup>

Cilostazole is a potent oral antiplatelet agent with a rapid onset of action that selectively inhibits phosphodiesterase III, a mechanism different from adenosine diphosphate (ADP) receptor antagonists. Previous study suggested that Cilostazol has similar antiplatelet effect as ticlopidine or clopidogrel. Adding Cilostazol to aspirin and clopidogrel regimen was shown to provide additional suppression of the expression of p-selectin, a marker of platelet activation, in 76.6% of study population, suggesting synergistic or additive antiplatelet effects. On basis of this they evaluated the safety and efficacy of triple antiplatelet therapy of aspirin, clopidogrel (or ticlopidine), and Cilostazol compared with dual antiplatelet therapy with aspirin and clopidogrel (or ticlopidine) in patients undergoing successful coronary artery stenting. After study they found that compared to dual antiplatelet therapy, triple antiplatelet therapy seemed to be more effective in preventing thrombotic complications after stenting without an increased risk of side effects. Triple antiplatelet therapy might be safely applied in patients or lesions with a high risk of stent thrombosis.<sup>42</sup>

Cilostazol has been shown to significantly improve high on treatment platelet reactivity in patients receiving both aspirin and clopidogrel and has antiproliferative effects, thus reducing the risk of restenosis after coronary stent implantation. Cilostazol in addition to aspirin and clopidogrel versus DPAT in patients undergoing percutaneous coronary intervention showed that triple antiplatelet therapy (TPAT) was associated with a significantly greater platelet inhibition, reduced major adverse cardiovascular events, target lesion revascularization, and target vessel revascularization with no increased risk for a haemorrhagic event.<sup>43</sup>

Uncertainties still remain in terms of what kinds of patients benefit most from Cilostazol-based triple antiplatelet therapy (TAT) after coronary stenting. Meta-analysis of all relevant randomized controlled trials (RCTs) to investigate the effect of TAT versus dual antiplatelet therapy (DAT) in terms of major adverse cardiovascular events (MACEs) in patients undergoing coronary stenting, they concluded that addition of Cilostazol is an effective and relatively safe strategy in

preventing MACEs after coronary stenting, especially for patients at high risk of restenosis or clinical events.<sup>44</sup>

Outcomes of patients undergoing percutaneous coronary intervention (PCI) with drug eluting stents (DES) and bare metal stents (BMS) have not been evaluated separately for specific dual and triple antiplatelet agent use. This meta-analysis want to determine whether triple antiplatelet therapy (combination of clopidogrel, aspirin and Cilostazol) has any advantage in efficacy compared with standard dual antiplatelet therapy (aspirin and clopidogrel) in patients undergoing PCI. And they concluded that Cilostazol appears to be effective in reducing the rates of ISR without any significant benefit for MACE/MACCE (MAJOR ADVERSE CARDIAC AND/OR CEREBROVASCULAR EVENTS).<sup>45</sup>

Whether triple antiplatelet therapy is superior or similar to dual antiplatelet therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention in the era of drug-eluting stents remains unclear so Kang-Yin Chen and his colleague studied on that and concluded that antiplatelet treatment with aspirin, clopidogrel and Cilostazol not only had a good safety profile but also improved midterm clinical outcomes in acute STEMI patients who underwent primary PCI in the era of DES. Also conclude that female patients, old patients and diabetic patients seemed to get more benefits from the triple antiplatelet therapy. These study results give rational for the use of triple antiplatelet therapy in these patients. Limitations of the registry study, a randomized trial designed to compare triple and dual antiplatelet therapy in these patients is needed.<sup>46</sup>

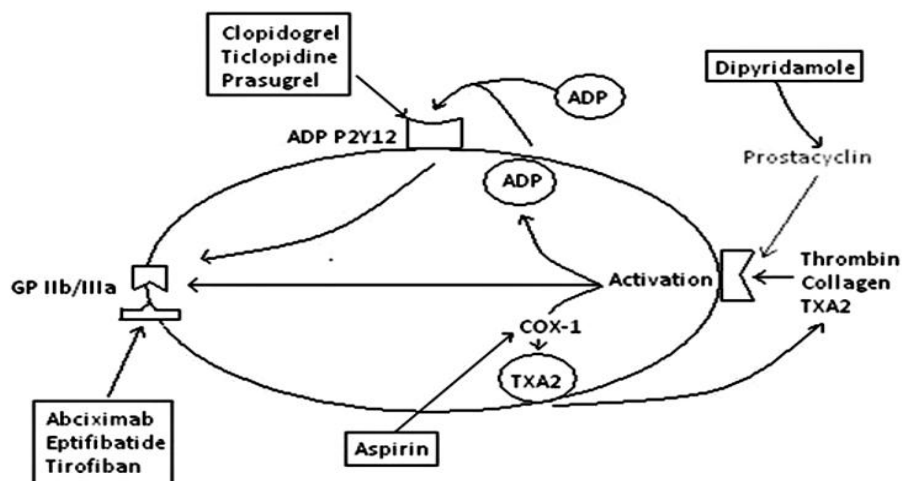


Fig. 1: Mechanism of antiplatelet agents

CLINICAL FACTORS	
•	Non-absorption
•	Interaction with NSAIDS
•	Acute coronary syndrome
•	Congestive heart failure
•	Hyperglycemia
•	Catecholamine surge
CELLULAR FACTORS	
•	Insufficient suppression of COX-1
•	Over-expression of COX-2 mRNA
•	Erythrocyte induced platelet activation
•	Increased norepinephrine
•	Generation of 8-iso-PGF 2 $\alpha$
•	Resolvins
GENETIC FACTORS	
•	COX-1
•	GP IIb/IIIa receptor polymorphism
•	Collagen receptor polymorphism
•	vWF receptor polymorphism
•	P2Y1 single nucleotide polymorphism

Fig. 2: Factors contributing to Aspirin resistance

ExtrinsicFactors

- |  |
|--|
| <ul style="list-style-type: none"> <li>• Dose</li> <li>• Drug-Drug Interactions (i.e. Lipitor)</li> <li>• CYP3A4 Activity</li> <li>• Variable Pro-Drug absorption</li> <li>• Variable active metabolite clearance</li> </ul> <p><b>Intrinsic Factors</b></p> <ul style="list-style-type: none"> <li>• P2Y12 receptor variability in numbers or affinity for drug</li> <li>• Increased intrinsic ADP levels</li> <li>• Up-regulation of other platelet activation pathways</li> </ul> |
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**Fig. 3: Potential mechanism of Clopidogrel Resistance**

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