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Review Article

# Antiplatelet therapies and the role of antiplatelet resistance in acute coronary syndrome

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ABSTRACT

Acute coronary syndrome is the number one killer in the industrialized world and, as such, continues to be one of the most well-studied disease states in all of medicine. Advancements in antiplatelet therapies for use in patients undergoing percutaneous coronary intervention have improved outcomes dramatically. However, a proportion of patients on long-term antiplatelet therapy continue to have cardiovascular events. Resistance to antiplatelet drugs may explain some of these events and this topic has become one of major interest and rapid evolution. This review describes the pathogenesis of acute coronary syndromes, outlines the evidence behind the use of the available antiplatelet agents, and examines the current data surrounding antiplatelet resistance.



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## Introduction

Acute coronary syndrome (ACS), the leading cause of death in the industrialized world, occurs as a result of thrombus formation within the lumen of a coronary artery. The pathophysiology of ACS involves chronic inflammation within the wall of the artery. Formation of a lipid core and infiltration of inflammatory cells results in plaque formation. Any disruption of the endothelium in the form of rupture or fissuring of the plaque leads to exposure of underlying collagen, von Willebrand factor (vWF), lipids and smooth muscle allowing initiation of platelet adhesion, activation, and aggregation [1]. Intact vascular endothelium normally produces inhibitors of platelet aggregation such as nitric oxide (NO) and prostacyclin (PGI2) [2]. When the endothelium is disrupted, its ability to produce these substances is impaired and, therefore, the milieu for platelet aggregation is enhanced.

Platelet adhesion to the vessel wall requires a synergistic interaction between multiple platelet receptors. The platelet GP1bα receptor, which is part of the GP1b-IX-V receptor complex, binds to the A1 domain of the exposed vWF in the subendothelial matrix [3]. vWF is released from activated or injured endothelial cells. The newly released high molecular weight vWF molecules are reduced in size by action of the proteolytic enzyme ADAMTS13 within the A2 domain of vWF. Additionally, full activation of vWF requires transformation of vWF from its compact form to an extended form thought to result from the mechanical shear of blood flow. The A3 domain of the

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extended vWF binds subendothelial collagen so that platelet adhesion can occur through the vWF A1-A3 binding mechanism. These initial bonds are unstable, but result in signal-transduction which, in turn, leads to further activation of the intergrin receptors, $\alpha_2\beta_1$ and $\alpha_{2b}\beta_3$ . These receptors stabilize platelet adhesion through tight collagen binding [4].

Thrombus growth and formation subsequently depends on platelet-platelet interaction. The bound platelets degranulate, releasing agonists such as adenosine diphosphate (ADP), thromboxane A2, growth factors and serotonin. This process requires multiple steps including mobilization of intracellular calcium stores, activation of intracellular kinases, and release of arachidonic acid from platelet membrane phospholipids [1]. The degranulation leads to recruitment of additional platelets, aggregation and, ultimately, thrombin generation [1]. With platelet activation the integrin IIb/IIIa receptor on the platelets changes molecular conformation allowing it to activate and bind the adhesive proteins, fibrinogen and vWF. A fibrinogen bridge is formed when two activated platelets each bind to the same fibrinogen molecule. Since GPIIb/IIIa is the most abundant receptor on the platelet surface, multiple fibrinogen bridges are formed by each platelet, resulting in a network of fibrinogen bridges [5]. vWF is thought to be the preferred $\alpha_{2b}\beta_3$ ligand in the presence of high mechanical shear stress.

Activated platelets provide a surface on which coagulation factors can assemble and initiate the clotting cascade leading to thrombin production. Thrombin, in turn, is a potent platelet activator leading to the recruitment of additional platelets which provide more surface area for the clotting cascade. This reciprocal relationship between thrombin formation and platelet activation eventually leads to a dense clot consisting of platelets and fibrin [5].

In the treatment of patients undergoing percutaneous coronary intervention (PCI), medical therapies are used which are aimed at blocking this complex pathway at various levels. Despite the advancements made over the past decade, post-PCI thrombosis continues to occur in a small proportion of patients, even among those who are compliant with their medications. The available proven anti-platelet therapies for patients undergoing PCI will be discussed in this article and, importantly, the limitations and caveats to these medications will be outlined.

## Aspirin

Aspirin (acetylsalicylic acid) has been a cornerstone of antiplatelet therapy in primary and secondary prevention of cardiovascular events for the past 4 decades. It irreversibly acetylates the cyclooxygenase (COX-1) enzyme at serine 530 which, in turn prevents the production of thromboxane A2 from arachidonic acid [6]. The first case report demonstrating its effect on platelet function was published in 1967 [7]. Since then, aspirin has been one of most extensively studied antiplatelet therapies. The first randomized trial showing a mortality benefit with aspirin was the Veterans Affairs (VA) trial, published in 1983, in which 1266 men with unstable angina were randomized to twelve weeks of treatment with 324 mg of aspirin daily versus placebo. This trial showed a 51% reduction in the risk of the primary endpoints of myocardial infarction (MI) or death among those patients taking aspirin [8]. The Canadian Multicenter Trial, published in 1985, was the next study to demonstrate benefit of aspirin in unstable angina. Five hundred fifty five patients with unstable angina were randomized to aspirin 325 mg four times daily, sulfinpyrazole 200 mg four times daily, a combination of the two, or placebo. Patients remained on treatment for up to two years with a mean of 18 months. By intention to treat analysis, it was evident that aspirin provided a 30% reduction in risk of nonfatal MI or death [9]. This study was followed by the Montreal Heart Study in 1988 which again demonstrated a survival benefit with aspirin, but in patients receiving only one week of treatment [10]. The Research on Instability Coronary Artery Disease (RISC) Study in 1990 included patients with non-ST elevation ACS who were treated with 75 mg per day of aspirin versus five days of heparin infusion versus placebo. This study showed a 12% absolute risk reduction for acute MI or death at 90 days in patients treated with aspirin. This benefit persisted after one year of therapy [11]. The Antithrombotic Trialists' Collaboration meta-analysis published in 2002 included 287 studies involving 135,000 patients and assessed the effects of antiplatelet therapy in patients who are at high risk for vascular events. Aspirin was the most widely studied drug and reduced the risk of any serious vascular event by approximately 25%. A daily dose of 75-150 mg was found to be as effective in preventing vascular outcomes as higher doses [12].

With the advent of percutaneous coronary intervention (PCI), more recent studies have been done in order to demonstrate benefit of aspirin in post-PCI patients. The only randomized trial that has evaluated the efficacy of long-term aspirin therapy in patients who have undergone PCI was published in 1995. In this trial, 752 patients who had undergone successful percutaneous transluminal coronary angioplasty (PTCA) were randomized to aspirin 325 mg daily, sulotroban (a selective thromboxane A2 receptor antagonist) 800 mg four times daily or placebo started 6 hours pre-intervention and continued for 6 months post-intervention. While neither treatment had a significant effect on restenosis rates, both aspirin and sulotroban resulted in a significant reduction in rates of myocardial infarction at 6 months (5.7% in the placebo group vs. 1.8% in the sulotroban group vs. 1.2% in the aspirin group) [13].

Despite the extensive evidence for the use of aspirin in patients with ACS, the optimal dose remains unknown. To date, there are no randomized trials comparing high and low dose aspirin regimens following ACS. In a subgroup analysis based on the CURE data, Peters et al showed that the benefits of aspirin exist at all doses between 75 mg and 325 mg daily. The risk of major bleeding was higher in those patients receiving 100 mg or more per day regardless of whether they were randomized to clopidogrel or placebo. Thus, the authors concluded that the optimal aspirin dose in ACS patients may be between 75 and 100 mg daily [14]. The CURRENT-OASIS 7 trial is a phase III study that will be the first randomized trial comparing high dose (300-325 mg) and low dose (75-100 mg) aspirin therapy in patients with ST and non-ST elevation ACS. The primary outcome will be a composite of cardiovascular death, MI or stroke at 30 days. The secondary outcome will evaluate the safety of the aspirin doses with regards to major bleeding at 30 days [15].

## Thienopyridines

When ADP is released from activated platelets, it binds to the P2Y12 and P2Y1 receptors (G protein-coupled receptors) of circulating platelets initiating platelet aggregation and amplifying platelet response to other agonists [16]. The currently available ADP receptor antagonists irreversibly bind to the platelet P2Y12 receptor, thereby blocking the effects of ADP. Ticlodipine and clopidogrel are the only ADP receptor antagonists that are available currently on the market. Thienopyridines are a class of drugs that irreversibly bind to P2Y12 and inhibit platelet activation by preventing activation by ADP. Thienopyridine are a class of prodrugs that require activation in the liver by cytochrome 3A4. The activated component of the prodrug then irreversibly binds to P2Y12 and inhibits platelet activation by preventing activation by ADP [17]. Ticlodipine was the first available drug of this class and has been studied in post-PCI patients. The earliest study was published in 1996 and showed no difference in the rate of stent thrombosis in patients receiving ticlodipine plus aspirin compared to patient receiving aspirin alone. However, the patients in the ticlodipine arm of the study only received five days of aspirin therapy after PCI [18]. During the following two years, four additional studies were conducted, each of which concluded that a combination of aspirin plus ticlodipine is superior to aspirin plus anticoagulation in