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Role of Antiplatelet Therapies in Preventing Atherothrombosis

Mohamed Z Khalil*

Consultant Cardiologist, Saudi British Hospital, Riyadh, Saudi Arabia

Abstract

Platelets exhibit a major role in development and progression of atherothrombosis. The normal function of platelets is to secure hemostasis at sites of vascular injuries. Abnormal endovascular structure may result in excessive platelet function with consequence of progressive or acute reduction in vascular lumen and cessation of blood flow. Despite succeeding in averting bleeding, total occlusion of a vessel leads to inevitable ischemia with eventual cell death upon lack of blood supply clinically manifesting as myocardial infarction in coronary vessels, cerebral infarction (stroke) in cerebral vessels, or peripheral gangrene in peripheral arterial disease. Antiplatelets long have been used to halt the process of atherothrombosis preventing further tissue damage at the expense of bleeding as well as other side effects. In this review, the role of antiplatelets in primary and secondary prevention of thrombotic events is explored in light of evidence based clinical practice.

Keywords: Antiplatelets; Atherothrombosis; Myocardial infarction; Stroke; Acute coronary syndrome

Introduction

Acute coronary syndromes (ACS) are increasing in incidence throughout the world with clear heavy burden on humanity. The progressive and pervasive nature of ACS affecting younger and more commonly older men as well as women, sparing only young children has activated scientific research for proper understanding the magnitude of the problem.

In contrast to ACS, stroke in the young is unusual and most probably a manifestation of structural abnormality, nonetheless, older individuals with transient ischemic attack (TIA) and stroke show evidence of pathophysiology similar to ACS with common denominator being atherothrombosis in the vast majority of cases.

Generally, atherothrombotic manifestation of ischemia relies on the presence or absence of collateral circulation. Lack of such collaterals, at the cellular level, means only one outcome and that is death of cells fed by the occluded vessel. Documentation of reversing pre-infarction tissue is evident in coronary vessels and to a lesser extent in cerebral as well as peripheral circulations [1-4]. It is imperative to understand the nature of atherothrombotic development in order to initiate timely treatments.

Atherothrombosis is a simple term refers to thrombus formation on top of atherosclerotic plaque disruption of diseased arterial lumen. Fascinatingly, platelets are activated in response to disrupted atheromatous plaque in an attempt of mending the vessel wall, however, in the presence of atherosclerosis; thrombus formation narrows the lumen resulting in ischemia that may extend to total vessel occlusion. Moreover, studies have demonstrated that softer atherosclerotic plaques are more vulnerable to atherothrombosis, irrespective to the luminal diameter prior to platelet activation [5-9]. Vulnerable plaque is characterized by similar cholesterol deposition and inflammatory cellular infiltrates but thinner cap that is more likely to disrupt compared to non-vulnerable plaque [10-20]. Additionally, vulnerable plaques are asymptomatic as the luminal effects of these lesions are less likely to cause ischemia, hence interventional stabilization is not recommended.

The role of antiplatelet therapies, shown in clinical trials, is well established in the management of atherothrombosis [21-28]. Reduction of atherothrombotic events is clearly gained at the expense of bleeding from administration of antiplatelets, particularly in patients with platelet dysfunction such as patients with chronic kidney disease [29]. The balance between platelet inhibition and evading bleeding remains to be a difficult task to physicians administering antiplatelet therapies. Furthermore, combination of antiplatelet therapies is another concern increasing the risk for bleeding while achieving modest platelet inhibition as well as modest reduction of thrombotic events [30-35].

Platelets are discoid un-nucleated cells (thrombocytes), produced from the bone marrow to circulate in the blood stream for a lifespan of 10 days. Obviously, decrease in platelet count is accompanied by reduction in platelet function that manifests clinically at low critical count. It is important to emphasize that platelet dysfunction may be present despite normal platelet count. Moreover, the concept of selective inhibition of certain platelet function whereas other functions of platelets are intact has ignited an era of scientific research targeting development of antiplatelet agents that are selective in performance.

Thrombocytopenia is a term used to describe reduction in the number of platelets, nonetheless, platelet function may remain intact in the presence of thrombocytopenia till reaching critical alarming number beyond which bleeding is inevitable. The reserve function of platelets is what maintains platelet function despite reduction in platelet count. That is why we don't have universal cutoff number for platelets count that work correctly for all patients suffering from thrombocytopenia.

It has been shown that platelets are not that simple in their response towards endovascular injuries harboring many receptors upon activation thrombus formation ensue [36-39]. The function of platelets may be altered either by reduction in platelet count or decreased function in the setting of normal platelet count in several disorders including renal disease, hepatic disease, hematological malignancies, infectious diseases, disseminated intravascular coagulopathy, pancreatitis, immune-mediated thrombocytopenia, and certain medications.

Platelet Function

Understanding of platelet function is mandatory prior to discussing

***Corresponding author:** Mohamed Z Khalil, Consultant Cardiologist, Saudi British Hospital, P. O. Box 285627, Riyadh, 11323, Saudi Arabia, Tel: 966 550055587, Fax: 966 12693760, E-mail: mzkhalil@hotmail.com

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antiplatelet therapies, hence; the term "antiplatelet" needs to be refined in the near future, either to describe platelet receptor antagonists, or more specifically to represent inhibition of platelet function; namely: activation, degranulation (release), adhesion, or aggregation.

Activation of platelets in the blood flow is provoked by exposure of adhesive molecules, including collagen and von Willebrand Factor (vWF), at the site of vascular lumen injury. This step is integral in securing hemostasis by circulating platelets adjacent to luminal wall at the periphery of blood flow, and enforced by high sheer rates. Activation of platelet occurs through surface receptors for collagen, thromboxane A2, thrombin, and adenosine diphosphate (ADP). The exact size of platelet plug required to patch up the area of vascular injury in an attempt to prevent bleeding is governed by the release of natural platelet inhibitors namely prostaglandin I2 and nitric oxide from activated endothelial cells at the perimeter of vessel injury. Further control of later thrombus formation is mediated by activation of protein C; a natural anticoagulant inhibits thrombin formation by carving activated factors V and VIII, as well as the natural fibrinolysis.

Platelets contain several different types of storage granules to be released upon activation, a process often referred to as degranulation. Dense granules contain small non-protein molecules such as; ADP, adenosine triphosphate (ATP), serotonin and calcium, which are released to recruit other platelets. Alpha granules are more abundant and contain large adhesive polypeptides for instance vWF, protease inhibitors, platelet derived growth factors, and fibrinogen that provide essential aid to healing at the site of injury. The third type of platelet storage granules are lysosomes whose enzymes are released to act on platelets as well as vascular endothelial cells to eliminate the circulating platelet aggregate and to form stable covalent cross-links between proteins.

Adhesion is a crucial function of platelets at the site of vascular injury, which is activated in response to exposure to subendothelial matrix triggering interactions between glycoprotein (GP) Ib and vWF. Furthermore, exposed collagen type I, III, and VI are vessel wall components prompting platelet adhesion to impede bleeding. Other adhesive molecules corroborating in the process of platelet adhesion are integrin α2β1, GP VI, fibronectin, thrombospondin, and laminin.

Thrombus propagation is dependent on the formation of platelet aggregation. Platelets bind soluble adhesive proteins and form a reactive surface for continuing platelet aggregation. Recruitment of additional platelets for aggregation is mediated by platelet agonists such as thromboxane A2 (TA2), platelet activating factor (PAF), ADP and serotonin, which bind recruited platelets to the adhered platelets. Additionally, platelet agonists signal morphological changes in the shape of platelets resulting in long membrane projections, which allow the platelets to interact with one another to form aggregates. GPIIb/IIIa is an integrin receptor present at high density on platelets and is considered the main adhesion molecule involved in platelet aggregation. The final common pathway of platelet aggregation is induced by fibrinogen acting as a bridge between two GPIIb/IIIa molecules on the membranes of adjacent platelets under lower shear rates, while aggregation induced by high shear conditions is induced by vWF substituting for fibrinogen. Moreover, activated platelets not only recruit additional platelets to the growing plug formed at the site of vascular injury, but also play a principal role in secondary hemostasis by providing a valuable catalytic surface for activation of the coagulation cascade.

Site of Action of Antiplatelet Therapies

Aspirin: Aspirin (acetylsalicylic acid) irreversibly inhibits cyclo-oxygenase-1 (COX-1) enzyme and blocks the production of TA2 from arachidonic acid of platelets. The detailed mechanism of action is summarized to acetylation of the platelet COX-1 at the functionally important amino acid serine529 preventing access of arachidonic acid to the catalytic site of the enzyme at tyrosine385 and results in an irreversible inhibition of platelet-dependent TA2 formation.

There are several limitations of the antiplatelet efficacy of Aspirin; first: platelet activation caused by other factors, such as shear stress and ADP, remains unchanged and might result in aspirin resistance. Secondly: inhibition of COX-1 by aspirin will also reduce the amount of precursors for vascular prostacyclin synthesis. Third: in the presence of aspirin that blocks COX-1, platelets utilize COX-2 pathway to synthesize TA2.

The beneficial efficacy of aspirin for primary prevention of vascular thrombosis is counterbalanced by hazards of excess bleeding, which has resulted in critically selecting subjects at increased risk of thrombosis for prevention after considerable evaluation for the existing risk of bleeding [40,41]. Conversely, the benefits of aspirin for secondary prevention clearly outweigh the risks of bleeding, thus aspirin continues to be fundamental of antithrombotic therapy as secondary prevention in coronary, cerebral as well as peripheral vascular thrombotic events. Moreover, it has been shown that aspirin therapy for secondary prevention reduces both fatal and nonfatal coronary events, while only nonfatal thrombotic events were prevented by aspirin in the primary prevention of ischemic heart disease [42].

Thienopyridines: The action of thienopyridines is mediated through prevention of ADP-induced platelet activation and aggregation by irreversibly inhibiting the platelet ADP receptor P2Y12. Indirectly acting thienopyridines (ticlopidine, clopidogrel, and prasugrel) are prodrugs that need to be converted by hepatic cytochrome P-450 (CYP) to active metabolites, which covalently and irreversibly bind to the P2Y12 receptor. The antiplatelet activities of the indirectly acting thienopyridines are delayed as a consequence of the need for metabolism of the prodrug. Furthermore, there are considerable inter-individual discrepancies in the degree of metabolism of the prodrug leading to unpredictability in platelet inhibition.

Direct P2Y12 inhibitors: The recent additions of antiplatelet therapies are direct and reversible P2Y12 antagonists (cangrelor, ticagrelor, and elinogrel), which have rapid onset and offset of platelet inhibition in contrast to thienopyridines. Blocking the P2Y12 receptor causes inhibition of stimulated adenylyl cyclase, ADP, TA2, and the proteinase-activated receptor-1 (PAR1) selective peptide agonist [43-47]. Furthermore, blockade of the P2Y12 receptor has been shown to decrease platelet aggregation under shear conditions as well as subsequent thrombus formation [48-50].

Glycoprotein (GP) IIb/IIIa inhibitors: The final common pathway of platelet aggregation is operational through Platelet membrane GPIIb/IIIa receptors that allow binding of fibrinogen and vWF at multiple sites present on each platelet, resulting in aggregation. Gp IIb/IIIa receptor antagonists (abciximab, tirofiban, eptifibatide) inhibit fibrinogen from effectively cross-linking platelets preventing aggregation and thrombus probagation. The benefit of this mechanism of action is that inhibition of platelet aggregation occurs independently of the specific platelet activating agonist without inhibition of initial platelet adherence to injured vascular surface. Moreover, GP IIb/IIIa blockade has the ability to induce dethrombosis via dissolution of platelet-rich clot by disrupting fibrinogen-platelet interaction [51-61].

PAR-1/thrombin receptor antagonists (TRAs): The ideal

antiplatelet therapy is one that is easily administered, available in oral format, promotes platelet activation contributing to thrombosis but not essential for hemostasis. Currently, novel oral antiplatelet agents targeting the PAR-1 pathway may provide more comprehensive platelet inhibition without increased bleeding risk. Inhibition of PAR-1 represents a reasonable advance to development of novel antiplatelet agents [62-71]. Two oral PAR-1 inhibitors are currently in clinical research with promising efficacy but noticeable bleeding risk indicative of further requirement for patients' selection; vorapaxar is undergoing evaluation in large phase 3 trials, whereas Atopaxar is currently being evaluated in phase 2 trials [72-75].

Antiplatelet therapies in clinical practice: Atherosclerosis is a continuum of multiple risk factors affecting the structure and function of blood vessels throughout the body over long duration. The clinical manifestations of atherothrombosis is obviously evident by either chronic narrowing of the vascular lumen giving rise to reduced blood supply to certain tissues, or mare dramatically abrupt and acute occlusion of a feeding vessel with consequent catastrophic cellular death if left untreated. Coronary artery disease (CAD), cerebro-vascular disease, and peripheral artery disease (PAD) are of major importance due to the ability of reversing a devastating clinical event upon timely intervention. Therefore, the role of antiplatelet therapies is to halt the natural thrombotic function of platelets at sites of atherothrombotic pathological events.

Coronary atherothrombosis: Non ST segment elevation myocardial infarction (NSTEMI), as well as unstable angina (UA), is the outcome of incomplete occlusion of a particular coronary artery, with evident chance for intervention to reverse the pathology. Patients with NSTEMI are identified on vectorcardiography (ECG) by the absence of ST segment elevation and further ECG evaluation do not show Q waves, in contrast to patients with ST elevation and eventually develop Q waves on ECG, while patients without elevated biomarker values are designated with a diagnosis of unstable angina [76]. Early studies on antiplatelet therapy, were conducted mainly to study the efficacy of aspirin in short-term as well as long-term treatment for patients with CAD, have shown it to be effective in both primary i.e. in patients without previous coronary events but are at increased risk for developing CAD, as well as secondary prevention, and therefore rendered as standard of care in clinical practice [77-94]. Nonetheless, another antiplatelet has to be added to aspirin in the treatment of patients with NSTEMI/UA, from the thienopyridines or more recently from the P2Y12 inhibitors, for initial and maintenance treatment as well as GPIIa/IIIb for the acute phase therapy [95-104].

The concept of dual antiplatelet therapy has been the standard of care to patients with acute coronary events, particularly for those who underwent percutanous coronary intervention (PCI) and following coronary stenting [105-109]. Dual antiplatelet therapy (DAPT) is a term used to describe additional antiplatelet therapy to aspirin. The pathophysiologic motivation for DAPT is prompted by the presence of two different pharmacodynamic mechanisms. The duration of DAPT remains to be determined according to patient's requirements, nonetheless, recent analysis revealed no clinical benefit of prolonged dual antiplatelet therapy for duration of 2 years compared to 6 months, in patients with CAD and treated with PCI, irrespective of the type of stent used, and resulted in increased risk of bleeding [110]. Moreover, it has been demonstrated that preoperative use of dual antiplatelet therapy is associated with an increased risk of infection, blood transfusion, and mortality after coronary artery bypass grafting (CABG) surgery [111].

The use of P2Y12 receptor inhibitors in the setting of ACS as well as PCI is associated with faster onset of action, greater potency and reversibility of platelet inhibition compared to clopidogrel [112]. Clinical studies have shown evident reduction of rates of vascular death and myocardial infarction (MI) comparing ticagrelor to clopidogrel in patients with ACS at the expense of increased bleeding [113-123]. Additionally, shorter period of drug discontinuation before CABG surgery was required in ticagrelor-treated patients compared to clopidogrel-treated patients to limit the severity of post-surgical bleeding [124-126]. Furthermore, prasugrel was significantly more effective than clopidogrel in reducing ischemic events and stent thrombosis of different types [127-128]. Current guidelines reflect the superiority of newer P2Y12 inhibitors (ticagrelor, prasugrel) as both agents are recommended in STEMI patients replacing clopidogrel [129-131]. The administration of ticagrelor is recommended in patients with NSTEMI/UA, regardless of invasive or non-invasive treatment strategy is opted [132, 133].

In patients with ACS, the use of GP IIb/IIIa inhibitors is associated with beneficial reduction of death and MI, and this benefit has been demonstrated among patients with STEMI as well as high risk patients with NSTEMI/UA. The beneficial use of these agents as part of triple-antiplatelet therapy may not outweigh the risk, particularly, in patients with a concern for increased risk of bleeding. An early invasive strategy using GP IIb/IIIa inhibitor significantly reduced the incidence of major cardiac events in patients with unstable angina who demonstrated elevated levels of cardiac markers as well as patients with NSTEMI [134]. Antiplatelet therapy with the GP IIb/IIIa inhibitor abciximab in patients with STEMI treated with PCI, improved outcome and reduced major adverse coronary events (MACE). The INFUSE-AMI trial demonstrated reduction in infarct size of intracoronary administration of abciximab compared to thrombectomy in patients treated with PCI for large anterior STEMI [135]. Efficacy of small-molecule GP IIb/IIIa inhibitors (tirofiban, eptifibatide) has been demonstrated in high-risk patients with NSTEMI/UA treated with early invasive strategy, while safety concerns, particularly, increased bleeding as well as transfusions rates, lashed out their use in low risk NSTEMI/UA patients [136].

Cerebral atherothrombosis: Secondary prevention of recurrent cerebral Atherothrombosis (TIA, Stroke) using aspirin as initial antiplatelet therapy remains the cornerstone of treatment in patients without indication for anticoagulation [137,138]. Overall, prevention for non cardio-embolic cerebral Atherothrombosis is attained by administration of single antiplatelet agent and mostly, this is done using aspirin, unless in patients who are intolerant to aspirin, alternative use of clopidogrel, or to lesser extent, ticlopidine has been used [139,140]. It is important to emphasize that primary prevention of cerebral atherothrombosis using aspirin is recommended only in selected patients after establishing a clear cause for treatment that outweigh the risk of bleeding [141].

Aspirin has been shown to result in approximately a quarter risk reduction for recurrent nonfatal stroke compared to placebo [142]. The dose of aspirin has been debated in clinical trials for long time, ultimately, evidence has documented lower doses, between 50 and 325 mg for prevention of recurrent non-cardioembolic TIA or stroke, as efficacious as higher doses but with less bleeding risk, predominantly gastrointestinal bleeding [143,144].

Primary as well as secondary prevention of cerebral atherothrombosis research clinical trials were largely unsuccessful in confirming superiority of clopidogrel over aspirin, nonetheless, for patients intolerant to aspirin use, clopidogrel may be used as a reasonable alternative [145]. Moreover, combination of clopidogrel

with aspirin for stroke prevention, have been shown to result in more bleeding without marked benefit to balance the risk, over using either aspirin or clopidogrel antiplatelet monotherapy [146].

For secondary prevention of non-cardioembolic stroke, aspirin in combination with extended-release dipyridamole antiplatelet therapy has been shown to be more effective than aspirin alone [147]. Fascinatingly, the combination of aspirin and extended-release dipyridamole was twice as effective for stroke prevention as either drug alone, with rates of bleeding of not exceeding those of aspirin monotherapy [148-152]. Triflusal is a derivative of salicylic acid that inhibits platelet-dependent TA2 formation by blocking COX while preserving vascular prostacyclin, which provides safety of less bleeding compared to aspirin particularly in secondary prevention [153]. Moreover, for secondary prevention of stroke, cilostazol; another antiplatelet agent has been shown to provide similar efficacy to aspirin with potentially less bleeding events [154].

Appropriate choices for therapy in patients with non-cardioembolic stroke or TIA may consist of either aspirin as monotherapy, the combination of aspirin and extended-release dipyridamole, or clopidogrel alone. Furthermore, the combination of clopidogrel with aspirin for stroke secondary prevention is inappropriate compared to monotherapy due to increased bleeding risk without significant benefit.

Peripheral atherothrombosis: Peripheral artery disease (PAD) is a clinical manifestation of reduced arterial blood supply to the extremities (upper and lower limbs) secondary to pathological mechanisms similar to CAD as well as cerebral atherothrombosis. Patients with PAD present a spectrum of disease severity that may be asymptomatic or symptomatic with intermittent claudication and peripheral gangrene comparable to NSTEMI and STEMI or TIA and stroke in CAD or cerebro-vascular disease respectively. It has been found that combination antithrombotic therapy with an antiplatelet agent and an oral anticoagulant was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications [155]. Antiplatelet monotherapy primarily by aspirin or by clopidogrel in aspirin intolerant patients is beneficial for patients with asymptomatic PAD, while combination therapy of aspirin and clopidogrel is reserved for patients with symptomatic PAD.

Summary

The effect of aging on vascular patency is magnified by adopting unhealthy lifestyle resulting in atherothrombosis presenting as ACS, MI, TIA, or stroke either alone or in combination. Platelets play pivotal role in the pathology of progressing atherothrombosis, hence, antiplatelet therapy is recommended. The choice of antiplatelet therapy for treatment decisions is largely related to patient's clinical variables. Bleeding is a major side effect of antiplatelet treatment that often can be prevented by appropriate therapeutics initiation as well as patient's monitoring. The faultless antiplatelet agent is still to be developed hopefully in the near future guided by more biochemical dissection of platelet functions and pharmaceutical progress.

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