Impact of Antiplatelet Therapy in Heart Disease

Giulia Renda · Raffaele de Caterina
Institute of Cardiology and Center of Excellence on Aging, ‘G. d’Annunzio’ University, Chieti, Italy

Abstract
Because platelet activation plays an important pathophysiological role in acute coronary syndromes, antiplatelet agents are a mainstay of cardiovascular therapy, both in high-risk primary prevention and in secondary prevention. This is usually done with aspirin in all such cases, and adding a P2Y₁₂ inhibitor in secondary prevention usually for 1 year after an acute coronary syndrome, especially after stent implantation. P2Y₁₂ inhibitors include ticlopidine (now rarely used), clopidogrel, prasugrel, and ticagrelor. In the setting of high-risk acute coronary syndromes treated with percutaneous coronary interventions, the addition of a glycoprotein IIb/IIIa antagonist, especially abciximab, is contemplated. Conversely, the role of antiplatelet therapy in preventing stroke after atrial fibrillation has been recently downgraded in most risk classes, in favor of anticoagulants. This chapter provides a general overview of the use of antiplatelet agents in heart disease.

Acute Coronary Syndromes

Acute coronary syndromes (ACS) are life-threatening manifestations of atherosclerosis, usually precipitated by acute thrombosis induced by a ruptured or eroded atherosclerotic plaque, with or without concomitant vasoconstriction, and causing a sudden and critical reduction in coronary blood flow and myocardial perfusion. Morphological and biochemical features characterize ‘vulnerable’ or ‘unstable’ plaques before the actual complication – rupture or erosion – occurs: a large lipid core, a low abundance of smooth muscle cells and collagen, a high concentration of inflammatory cells (including macrophages and T lymphocytes), and a thin fibrous cap separating the lipid core from the lumen. Plaque size, when it causes severe lumen reduction (very severe stenosis), also appears to confer features of instability. In addition to intrinsic plaque features, the circumferential wall stress, plaque location, and impact of blood flow on the luminal plaque surface contribute to plaque vulnerability [1]. Multiple sites of plaque rupture with or without intraluminal thrombosis, elevated levels of systemic markers of inflammation and thrombosis, and the activation of coagulation system characterize ‘vulnerable patients’, i.e. patients at high risk of ischemic events [2, 3].
The impact of antiplatelet therapy in ACS is related to the crucial role of platelets in the pathogenesis of arterial thrombosis. Endothelial dysfunction and/or a physical interruption in the integrity and continuity of the arterial endothelial layer trigger a series of molecular reaction aimed at vessel repair. The first step is the formation of a hemostatic plug through the combined action of vasoconstriction, platelet adhesion, and fibrin formation at the place of injury. When injury is severe enough, the exposure of sufficient amounts of deep intimal components, including collagen and tissue factor [4], activates both platelets and the coagulation cascade. Thrombin generated by coagulation itself becomes a powerful platelet agonist and a critical enzyme in early thrombus formation, cleaving fibrinopeptides from fibrinogen to yield soluble and then cross-linked fibrin. Moreover, platelet activation through different agonists triggers intracellular signaling initiating contractile processes that induce platelet shape change and the secretion of granule content, and at the same time induce the expression of platelet membrane receptors, such as platelet glycoprotein (GP)IIb/IIIa, promoting platelet-platelet interaction and intensifying platelet aggregation. The local release of several substances from the injured vessel wall (e.g. collagen and thrombin) and from activated platelets [including epinephrine, serotonin, adenosine diphosphate (ADP), and thromboxane A₂, synthesized from arachidonic acid sequentially by cyclooxygenase and thromboxane synthetase] contributes to vasoconstriction, platelet activation, and thrombus formation [5] (fig. 1).
Bleeding and the Use of Antiplatelet Agents in the Management of Acute Coronary Syndromes and Atrial Fibrillation

John P. Vavalle • Sunil V. Rao
The Duke Clinical Research Institute, Durham, N.C., USA

Abstract
Antiplatelet therapy serves an important role in the management of acute coronary syndromes and in reducing the risk of thrombotic complications from atrial fibrillation. There has been rapid development of newer and more potent antiplatelet therapies over the last several years that have further reduced ischemic complications, but with a trade-off of increased bleeding risk. Bleeding complications associated with antiplatelet and anticoagulant therapies are associated with significantly increased risk of adverse outcomes, including death. Understanding the risk of bleeding associated with antiplatelet agents is critical to developing strategies to mitigate this risk.

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Central to the treatment of acute coronary syndromes (ACS) and atrial fibrillation are anticoagulant and antiplatelet therapies. Over the last several decades, a better understanding of the pathogenesis of coronary heart disease and atrial fibrillation has led to refinements in antithrombotic strategies and clinical outcomes. However, as ischemic complications have continued to improve, a greater emphasis has been placed on the importance of bleeding complications and their relationship to increased morbidity and mortality.

Several studies have shown that bleeding of any severity is associated with adverse outcomes and that there is a stepwise increase in mortality as bleeding severity increases [1]. It is not clear if these relationships are causal, particularly for less severe bleeding events; however, both randomized trials and observational studies have demonstrated an association between strategies that decrease bleeding risk and reduced mortality [2–4].

Bleeding complications in the setting of antiplatelet therapy can occur acutely [e.g. with the use of parenteral antiplatelet agents such as glycoprotein (GP)IIb/IIIa inhibitors] or chronically, as with long-term oral dual antiplatelet therapy. This chapter will
review the incidence of bleeding during acute and chronic therapy with antiplatelet agents, describe the risks associated with bleeding, and outline strategies to reduce bleeding risk.

Definitions of Bleeding Used in Trials and Registries

Several different definitions and scales used to define and qualify bleeding events have been developed and are currently being used. The lack of consistency among these definitions is one of the challenges in quantifying the bleeding risk in patients treated with antithrombotic therapies. Moreover, the definition of bleeding used can have an impact on its association with subsequent outcomes [5]. An analysis of thirteen large clinical trials evaluating antithrombotic drugs in patients with ACS or undergoing percutaneous coronary intervention (PCI) found that many different bleeding definitions were used among these trials and that reported bleeding rates within a trial can vary markedly depending on the definition selected [6]. This can hinder the ability to determine the relative safety of one antiplatelet agent over another outside of direct comparisons in randomized trials.

Clinical Trial Bleeding Definitions

In many ACS clinical trials over the past two decades, two commonly used definitions to classify bleeding severity have been the Thrombolysis In Myocardial Infarction (TIMI) and the Global Use of Strategies to Open Occluded Arteries (GUSTO) bleeding definitions [7, 8]. While the TIMI scale is based on laboratory evaluation with severity determined by the drop in hemoglobin or hematocrit, the GUSTO scale is based on clinical events that determine the severity of bleeding. Trials have also combined elements of these two definitions and/or added additional data elements to create entirely new definitions. Examples of trial-specific definitions created specifically for that trial are listed in table 1 and include such large studies as the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy), CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events), REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events II), PLATO (Study of Platelet Inhibition and Patient Outcomes), and STEEPLE (Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients) trials [9–13].

Based on how bleeding events are defined and classified, the rates and severity of bleeding can vary widely when different definitions are applied, even within the same clinical trial. An example of this is in the REPLACE-2 trial. This study compared unfractionated heparin with planned GPIIb/IIIa inhibitor versus bivalirudin with provisional GPIIb/IIIa in patients undergoing urgent or elective PCI. Using the TIMI definitions, there were no differences in TIMI major bleeding between the two groups (0.9 vs. 0.6%, p = 0.30). When the REPLACE-2 definitions are applied, a significant difference in bleeding is noted with less major bleeding in the bivalirudin
<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>Agents studied</th>
<th>Bleeding definition</th>
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</table>
| CURE         | Non-ST elevation ACS | Clopidogrel vs. placebo in addition to aspirin | Major bleeding: substantially disabling bleeding, intraocular bleeding leading to loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood  
Life-threatening bleed: fatal bleed, led to a reduction in the hemoglobin level of at least 5 g/dl, hypotension requiring the use of intravenous inotropic agents, necessitated a surgical intervention, symptomatic intracranial hemorrhage, or necessitated the transfusion of 4 or more units of blood  
Minor bleeding: other hemorrhages that led to the interruption of the study medication |
| REPLACE-2    | PCI-elective       | Bivalirudin + provisional GPIIb/IIIa inhibitors vs. heparin + planned GPIIb/IIIa inhibitors | Major bleeding: intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting in a decrease in hemoglobin >3 g/dl; any decrease in hemoglobin >4 g/dl, transfusion of ≥ 2 units of PRBC or whole blood  
Minor bleeding: clinically overt bleeding not meeting criteria for major bleeding |
| STEEPLE      | PCI-elective       | UFH vs. enoxaparin 0.5 mg/kg vs. enoxaparin 0.75 mg/kg | Major bleeding: fatal bleeding, retroperitoneal, intracranial or intraocular bleeding, bleeding that leads to hemodynamic compromise requiring specific treatment, bleeding requiring surgical or endoscopic intervention, clinically overt bleeding requiring ≥1 unit of PRBC or a hemoglobin drop >3 g/dl  
Minor bleeding: gross hematuria, prolonged epistaxis, gastrointestinal hemorrhage, hemoptysis, subconjunctival hemorrhage, hematoma >5 cm or causing hospitalization, overt bleeding with 2–3 g/dl drop in hemoglobin, bleed requiring protamine |
| ACUITY       | PCI-Non ST ACS     | UFH/LMWH + GPIIb/IIIa inhibitor vs. bivalirudin + GPIIb/IIIa inhibitor vs. bivalirudin | Major bleeding: intracranial or intraocular bleed, access site hemorrhage requiring intervention, ≥5 cm diameter hematoma, drop in hemoglobin ≥4 g/dl without a source, drop in hemoglobin ≥3 g/dl with a source, reoperation for bleeding, use of any bleed products |
| PLATO        | ACS with or without ST elevation | Ticagrelor vs. clopidogrel | Major life-threatening bleeding: fatal, intracranial, or intrapericardial with cardiac tamponade bleed, bleeding leading to hypovolemic shock, severe hypotension requiring pressors or surgery, a drop in hemoglobin of ≥5.0 g/dl, transfusion of ≥4 units PRBC  
Major bleeding: bleeding that led to clinically significant disability, bleeding with a drop in the hemoglobin level of 3.0–5.0 g/dl, or bleeding requiring transfusion of 2–3 units PRBC  
Minor bleeding: any bleeding requiring medical intervention but not meeting the criteria for major bleeding |

PRBC = Packed red blood cells; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; GPIIb/IIIa = glycoprotein IIb/IIIa; ACS = acute coronary syndrome.
Antiplatelet Therapy in Stroke Prevention

Stavros Apostolakis\(^a\) · Francisco Marín\(^b\) · Gregory Y.H. Lip\(^a\)

\(^a\)Haemostasis Thrombosis and Vascular Biology Unit, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; \(^b\)Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain

Abstract

Ischemic stroke is a major cause of death and disability worldwide. Determination of the underlying stroke mechanism is critical for the optimization of treatment. The role of antiplatelet therapy in primary and secondary stroke prevention is of major significance. Antiplatelet agents predominantly in use are aspirin, clopidogrel, and combination regimens. Novel antiplatelet agents either in use or in advance clinical development seek an indication in the management of stroke patients; yet data are limited. The present review focuses on the optimization of antithrombotic therapy in the field of primary and secondary prevention of stroke, based on data obtained from randomized controlled trials and systemic reviews of the literature.

Stroke is a leading cause of death and disability. The World Health Organization estimates that 5.7 million people die from stroke every year [1, 2]. Efforts to prevent recurrences in stroke survivors are critically important and a major concern for healthcare professionals worldwide. Approximately 80% of strokes are caused by focal cerebral ischemia due to arterial occlusion; 20% are caused by intracerebral hemorrhages [3, 4]. Thirty-day mortality among people 45–65 years of age with ischemic stroke is estimated to be 8–12%. The overall risk of a recurrence in stroke survivors is 7.7% at 1 year, increasing to 18.3% in 5 years [5, 6]. Recurrent stroke risk after transient ischemic attack (TIA) or ischemic stroke ranges from 5 to 20% annually [5, 6]. The highest risk is within the first few days following the initial event [5–7].

Antithrombotic therapy is the cornerstone of secondary prevention of ischemic stroke. Nevertheless, unlike acute coronary syndromes, which consistently occur due to plaque destabilization and local thrombosis, ischemic stroke is a heterogeneous condition requiring individualized treatment strategies. A methodical diagnostic approach should be applied in all patients with stroke in order for further management...
to rely on evidence-based treatment options. Additionally, there are patients who will benefit from antithrombotic therapy as a means of primary prevention of ischemic stroke. Atrial fibrillation (AF) is the most common underlying condition associated with an increased risk for embolic stroke [8]. Patients with nonrheumatic AF that present with TIA or stroke have an overall risk of recurrent stroke of 12% in the first year and 5% per annum afterwards [9].

In the present chapter we attempt to provide current insight into the use of antithrombotic drugs for primary and secondary stroke prevention. While acute antithrombotic management of stroke and non-antithrombotic strategies for stroke prevention are crucial for improving the outcome in stroke survivors, they are outside the scope of this overview.

**Antiplatelet Therapy for Primary Prevention of Stroke**

**Aspirin**

The aim of primary prevention is to reduce the risk of stroke in asymptomatic people. Six large randomized trials have evaluated the benefits of aspirin for the primary prevention of cardiovascular (CV) events [10–15]. A meta-analysis including these studies reported that aspirin reduced coronary events and CV events, but not stroke, CV mortality, and all-cause mortality [16]. In women, aspirin reduced stroke and ischemic stroke [17]. In a separate study of 39,876 healthy women aged 45 years or older, aspirin reduced stroke and ischemic stroke, and caused a non-significant increase in hemorrhagic stroke, over 10 years. Aspirin did not reduce the risk of fatal or nonfatal myocardial infarction (MI) or CV death [18]. The largest collaborative meta-analysis assessing the impact of low-dose aspirin on the risk of CV events in low-average-risk subjects included 95,000 individuals followed for 660,000 patient years. The Antithrombotic Trialists reported that in the primary prevention setting, aspirin allocation yielded a 12% proportional reduction in serious vascular events, mainly due to a reduction of about a fifth in nonfatal MI. The net effect on stroke was not significant. Vascular mortality did not differ significantly, but aspirin was associated with an increase in major gastrointestinal and extracranial bleeding [19].

There is conflicting evidence regarding the use of antiplatelet therapy in subpopulations with predisposing factors, but no evidence of overt cardiovascular disease (CVD). A randomized study and a systematic review of randomized studies comparing antithrombotic agents with placebo in patients with elevated blood pressure and no prior CVD showed that aspirin did not reduce stroke or total CV events [17, 20]. Another issue of scientific debate is the efficacy of antiplatelet therapy for primary prevention of CV events in diabetics. Despite some inconsistencies, aspirin is recommended by major medical societies for the primary prevention of CV events in people with diabetes. Nevertheless, a meta-analysis of six randomized trials (10,117
participants) evaluated the benefits and harms of low-dose aspirin in people with diabetes and no CVD. When aspirin was compared with placebo there was no statistically significant reduction in the risk of major CV events, CV mortality, or all-cause mortality. Significant heterogeneity was found in the analysis for MI and stroke. Aspirin significantly reduced the risk of MI in men but not in women. Evidence relating to harm was inconsistent. The investigators concluded that a clear benefit of aspirin in the primary prevention of major CV events in people with diabetes remains unproven [21].

**Clopidogrel**
The data currently available on the use of other antiplatelet agents in primary prevention in low-risk subjects is limited. In the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, the combination of aspirin and clopidogrel was less effective than aspirin alone in the subgroup of patients with multiple vascular risk factors but no ischemic event [22]. The most important data on antiplatelet therapies for primary prevention of stroke are summarized in table 1.

**Table 1. Antiplatelets in primary prevention of stroke**

<table>
<thead>
<tr>
<th>Antiplatelet</th>
<th>Population</th>
<th>Conclusion</th>
<th>Major data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>General</td>
<td>Aspirin is of uncertain net value as the reduction in CV events needs to be weighed against any increase in major bleeds</td>
<td>Antithrombotic Trialists Collaboration [19]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin did not significantly decrease the incidences of stroke or CV mortality</td>
<td>Bartolucci et al. [16]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin reduced the risk of ischemic stroke in women and MI in men</td>
<td>Berger et al. [17]</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>Aspirin lowered the risk of stroke without affecting the risk of MI or death from CV causes</td>
<td>Ridker et al. [18]</td>
</tr>
<tr>
<td></td>
<td>Hypertensive</td>
<td>Aspirin significantly reduced major CV events with the greatest benefit seen in MI There was no effect on the incidence of stroke</td>
<td>Hansson et al. [13]</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>A clear benefit of aspirin in the primary prevention of major CV events in people with diabetes remains unproven</td>
<td>De Berardis et al. [21]</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>General</td>
<td>Clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of MI, stroke, or death from CV causes</td>
<td>Bhatt et al. [22]</td>
</tr>
</tbody>
</table>