British Journal of Anaesthesia **111** (S1): i3–i17 (2013)
doi:10.1093/bja/aet402

BJA

CARDIOVASCULAR

Perioperative management of antiplatelet therapy

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Editor's key points

- Antiplatelet medications are commonly used by high-risk patients presenting for invasive procedures.
- Both continuation and discontinuation of antiplatelet therapy can be associated with significant risks.
- A team-based approach to risk stratification is critical to optimizing the perioperative approach to antiplatelet therapy.

Summary. Worldwide, cardiovascular events represent the major cause of morbidity and mortality. A key role in the pathogenesis of these events is played by platelets. Interventional procedures, with placement of coronary and vascular stents, often represent the preferred therapeutic strategy. Antiplatelet medications are considered first-line therapy in preventing cardiovascular thrombotic events. A wide array of antiplatelet agents is available, each with different pharmacological properties. When patients on antiplatelet agents present for surgery, the perioperative team must design an optimal strategy to manage antiplatelet medications. Each patient is stratified according to risk of developing a cardiovascular thrombotic event and inherent risk of surgical bleeding. After risk stratification analysis, various therapeutic pathways include continuing or discontinuing all antiplatelet agents or maintaining one antiplatelet agent and discontinuing the other. This review focuses on the pharmacological and pharmacokinetic properties of both older and novel antiplatelet drugs, and reviews current literature and guidelines addressing options for perioperative antiplatelet management.

Keywords: antiplatelet agents; haemorrhage; perioperative period

Antiplatelet agents, used as monotherapy or in combination, have a major role in preventing and managing cardiac and vascular events.[1] These medications are of particular relevance, as coronary artery disease and stroke represent the top two causes of mortality worldwide, as reported by the World Health Organization in a report updated in 2013.[2] Furthermore, the same report shows an increase in mortality as a result of such events in this decade when compared with the previous one. Physicians are encountering patients who are older and sicker than previously, and anaesthesiologists frequently encounter patients on medications affecting platelet function in the perioperative period. Understanding the indications, pharmacokinetics and pharmacodynamics of these agents allows physicians to anticipate and address possible undesired effects of continuing or discontinuing antiplatelet agents within this time frame.[3]

Role of the activated platelet in coagulation

Atherothrombosis, a systemic disseminated process affecting the entire vascular tree, represents the underlying aetiology for both coronary and cerebral thrombotic events. However, the substrate for thrombus formation is atherosclerosis. Platelet activation represents the key step in the thrombotic process. The activated platelet plays not only an important role in the initiation and progression of atherosclerotic disease, but also has a quintessential role in the development of atherothrombosis, being implicated in endothelial, thrombotic, immune, and inflammatory responses.[4] Recent evidence suggests that platelets also have a new and previously unsuspected role in tissue repair and vascular remodelling.[5]

In their inactive state, platelets do not adhere to the endothelial wall or to each other. Endothelial activation leads to exposure of collagen to blood and von Willebrand factor. Platelet surface glycoprotein receptors [glycoprotein (GP) Ib–V–IXa, GP Ia/IIa and IV] interact with these components and promote platelet adherence to the vascular subendothelium and subsequent activation. The activated platelet undergoes conformational changes that result in degranulation of dense and alpha vesicles with the release of adenosine diphosphate (ADP), thromboxane A_2 (TxA_2), and thrombin. These platelet-activating substances lead to a conformational change in the GP IIb/IIIa receptor and its expression on the platelet membrane. Its surface expression leads to binding of other platelets through fibrinogen bridges. Subsequent to the release of platelet products (i.e. thrombin, platelet activating factor, ADP, TxA_2), neighbouring platelet activation and recruitment occurs, rapidly forming a platelet aggregate. This interacts with fibrin and thrombin and promotes thrombus formation.[6] Moreover, activation of ADP receptors severely blunts the antiaggregant and vasodilatory effects of nitric oxide and prostaglandin (PG) I2, to which inactive platelets are constantly exposed.[7]

The role of the platelet in the coagulation cascade was defined more recently. Thrombin is generated through activation of factor VII by phosphate released from the dense granules. Moreover, the activated platelet provides the necessary surface for activation of other clotting factors and further promotes thrombus formation. In the inactive state, phosphatidylserine is present on the inner layer of the platelet membrane. Subsequent platelet stimulation results in its exposure on the outer layer, thus interacting with the factor Va–Xa complex and ultimately leading to thrombin formation.[8]

Additionally, proinflammatory effects of platelets have received attention lately as critical steps in the initiation of atherosclerosis. Activated platelets release bioactive substances into the local microenvironment, which modify the adhesive and chemotactic properties of endothelial cells. Increased chemotaxis enables monocytes and other leucocytes to adhere and transmigrate through the endothelium to inflammatory sites.[9]

Owing to both the key role of platelets in thrombus formation and their activation via multiple receptors (ADP, GP IIb/IIIa) and pathways (thromboxane formation), a variety of agents targeting different steps in this process have been developed. While aspirin (ASA) is a well-established antiplatelet agent targeting TXA_2 formation, newer drugs protect against thrombosis by interfering with GP IIb/IIIa and ADP receptors[10] (Fig. 1). In addition, newer agents targeting pathways responsible for thrombin formation (direct thrombin inhibitors or factor Xa inhibitors) are being investigated as potential adjuncts to antiplatelet drugs.[11]

This review focuses on both old and novel antiplatelet drugs, including their pharmacology, indications, and possible perioperative management strategies.

Specific drugs

Aspirin

Pharmacology

ASA is an anti-inflammatory and antiplatelet agent whose effect is mediated through irreversible inhibition of cyclooxygenase 1 and 2 (COX1 and COX2). Its antithrombotic effect is primarily due to the inhibition of COX1, which is responsible for inhibiting PGH_2 formation from arachidonic acid. PGH_2 is the precursor for TxA_2 formation by platelets (platelet aggregant and vascular vasoconstrictor), and PGI_2 by endothelial cells (vascular vasodilator and antithrombotic).[12] The doses required for its anti-inflammatory effects (mediated by COX2

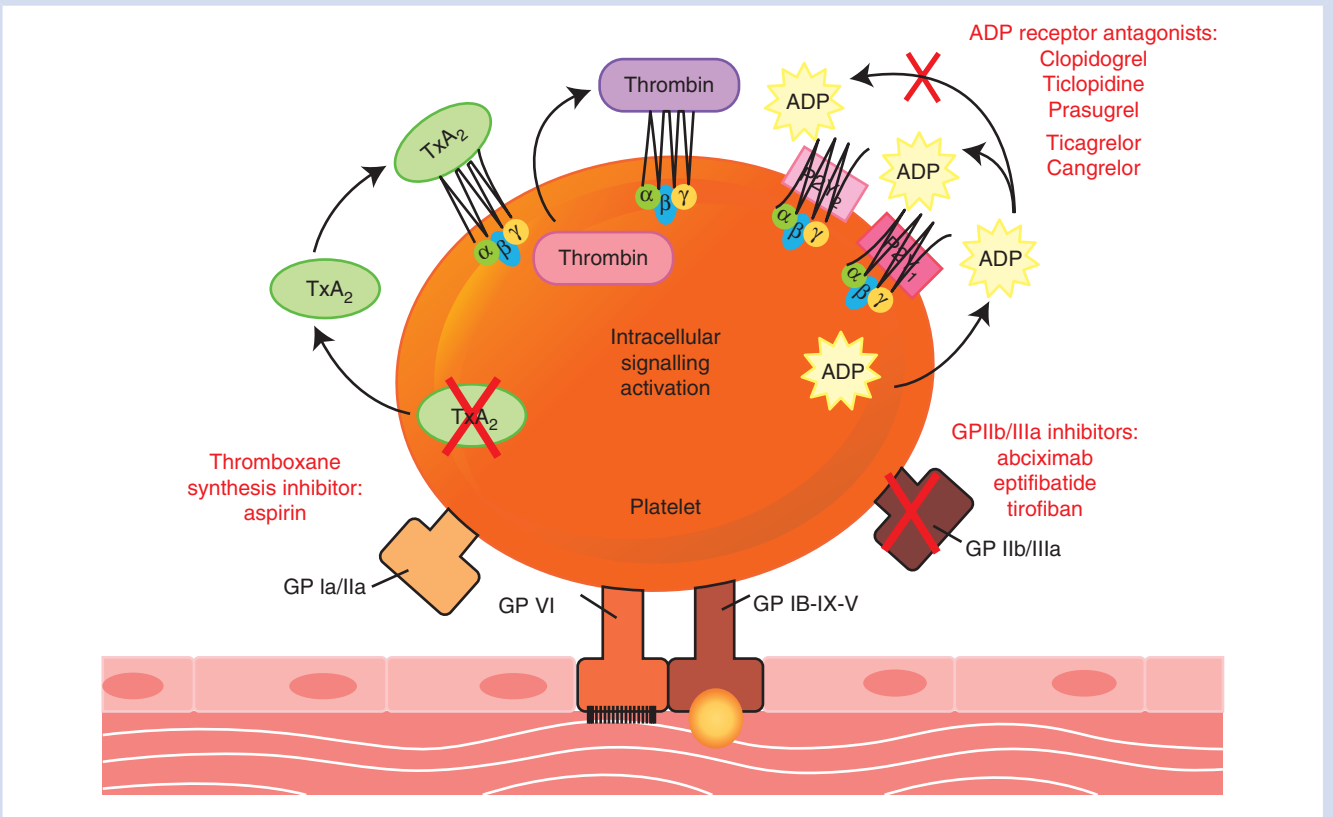

Fig 1 Therapies targeted at inhibiting various platelet receptors. These include the thromboxane inhibitors, ADP receptor antagonists, and GPIIb/IIIa inhibitors. Adapted from Meadows and Bhatt,[4] with permission. TxA2, thromboxane A2; GP Ia/IIa, glycoprotein Ia/IIa; GP VI, glycoprotein VI; GP Ib-IX-V, glycoprotein Ib-IX-V; ADP, adenosine diphosphate; GP IIb/IIIa, glycoprotein IIb/IIIa.