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Platelets for anaesthetists—Part 2: pharmacology

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Key points

- Aspirin is the most widely used antiplatelet agent.
- The thienopyridine group of antiplatelet agents block platelet activation by inhibiting the adenosine diphosphate receptors.
- Good understanding of the pharmacodynamics and pharmacokinetics of antiplatelet agents provides us an insight into the perioperative management of patients with antiplatelet agents.
- Perioperative management of patients with antiplatelet agents comprises a fine balance between the risk of cardiovascular events on stopping the medication and the bleeding complications due to the continuation of the antiplatelet agent.

Platelets play a major role in the pathogenesis of atherosclerosis and thrombotic diseases. Antiplatelet agents are widely used to prevent complications of the atherosclerotic disease process. As anaesthetists, we encounter patients on antiplatelet therapy regularly and more frequently. This review describes the pharmacokinetics and pharmacodynamics of various antiplatelet agents.

Platelet activation and aggregation occurs due to the binding of various ligands and agonists to several platelet receptors. The receptors of interest in relation to antiplatelet therapy are TP (thromboxane A_2 receptor), ADP (adenosine diphosphate) receptor, PAR (protease-activated receptor), and GP IIb/IIIa receptor. TP, PAR, and ADP receptors all belong to the G-protein family of receptors. There are two types of ADP receptors, $P2Y_1$ and $P2Y_{12}$. Both $P2Y_1$ and $P2Y_{12}$ are G-protein-coupled receptors. Thrombin activates platelets via PAR receptors. There are four types of PAR, of which PAR-1 and PAR-4 are present in humans. GP IIb/IIIa receptor (αIIb/β3) is a transmembrane receptor present in the surface of platelets and belongs to the integrin group of receptors.

Aspirin

The most commonly used antiplatelet agent is aspirin, which is a cyclooxygenase (COX) enzyme inhibitor. This enzyme converts arachidonic acid to prostaglandin H2 (PGH2), which itself is a precursor for the formation of other prostaglandins, in particular thromboxane A2 (TXA2) by thromboxane synthase and Prostacyclin (PGI2) by prostacyclin synthase. TXA2 is responsible for stimulation of platelet aggregation and localized vasoconstriction, while PGI2 is responsible for inhibition of platelet aggregation and localized vasodilatation.

Cyclooxygenase enzyme exists in two isoforms, COX-1 and COX-2. COX-1 is mainly responsible for TXA2 synthesis and COX-2 is mainly responsible for PGI2 synthesis. COX-2 enzyme is abundant in endothelium and exerts its antiplatelet actions. Aspirin at low doses (75–300 mg) selectively inhibits COX-1 enzyme and is responsible for its antiplatelet actions. However, at high doses (1 g day^{-1}), it inhibits COX-2 enzyme as well. Low-dose aspirin is preferred as high doses cause increased incidence of upper gastrointestinal bleeding without an increase in efficacy (Fig. 1).[1]

Aspirin is widely used in the secondary prevention of coronary events and stroke in patients with coronary artery disease, cerebrovascular disease, and peripheral vascular disease. The important adverse event with aspirin is bleeding complications in the gastrointestinal tract. This can be reduced by co-administration of proton pump inhibitor or a H_2 blocker. Aspirin is contraindicated in children and adolescents <16 yr due to risk

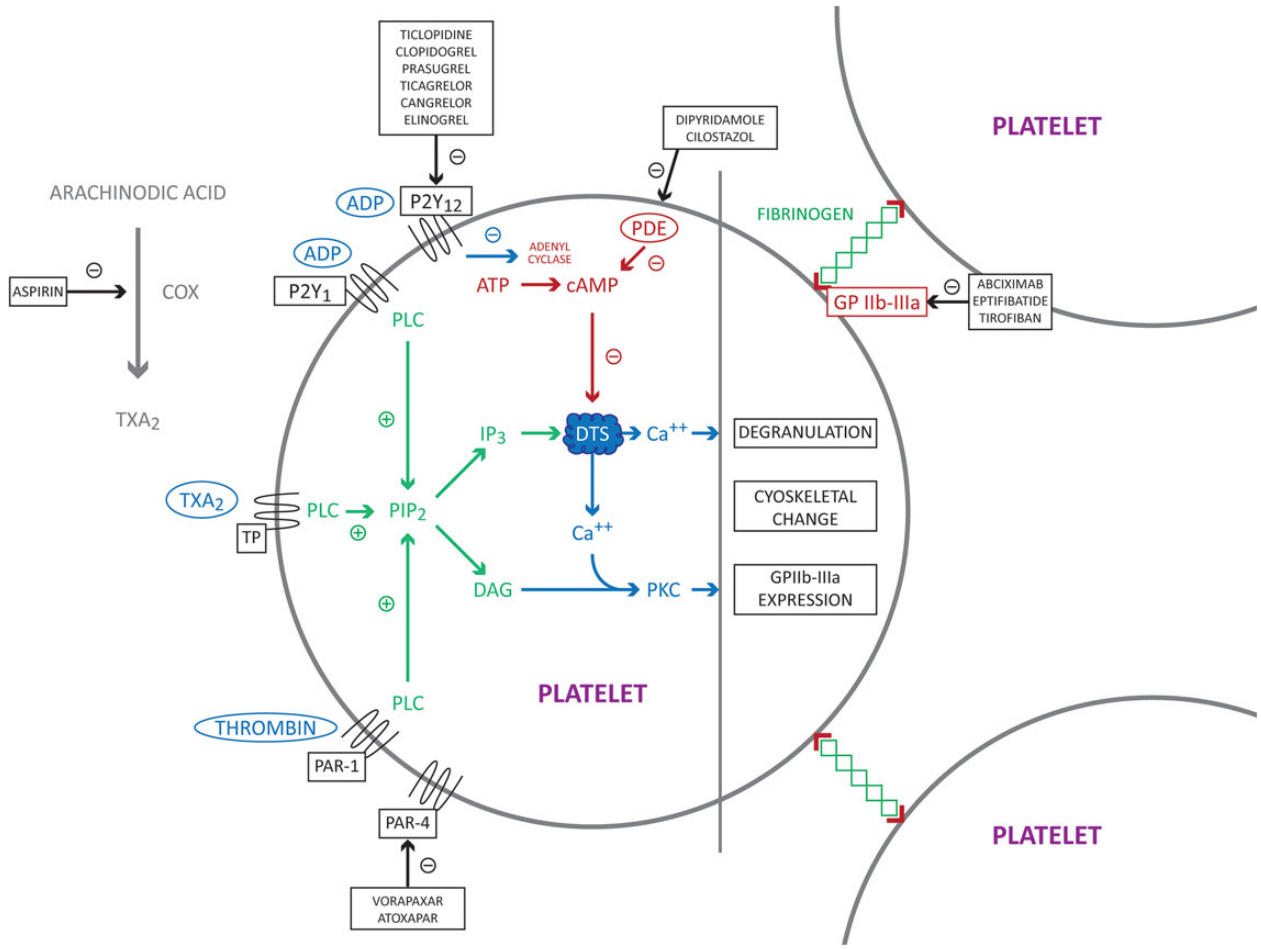

Fig 1 Mechanism of action of antiplatelet agents. ADP, adenosine diphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; DAG, diacyl glycerol; DTS, dense tubular system; IP_3, inositol triphosphate; PAR, protease activated receptor; PDE, phosphodiesterase; PIP_2, phosphatidylinositol 4,5-biphosphate; PKC, protein kinase C; PLC, phospholipase C.

of developing Reye's syndrome. It should be used with caution in elderly patients and patients with asthma.

Phosphodiesterase inhibitors

Dipyridamole is pyrimidopyrimidine derivative. It prevents the degradation of cAMP by inhibiting the phosphodiesterase (PDE) enzyme. An increase in cAMP causes inhibition of platelet activation by increasing the level of calcium ions. The antiplatelet effects are also due to inhibition of adenosine uptake by platelets and other cells. Dipyridamole also inhibits PDE-5 enzyme resulting in increased levels of cGMP (cyclic guanosine monophosphate). An increased level of cGMP causes vasodilatation similar to nitric oxide.

The absorption of the oral drug is variable, but the current modified release preparations have better bioavailability. The drug undergoes extensive enterohepatic circulation with elimination half-life of 19 h.

Current indication of dipyridamole is mainly limited to the prevention of cerebral events in patients with transient ischaemic attack (TIA) and stroke. NICE (National Institute for Health and Care Excellence) recommends modified-release dipyridamole with aspirin if clopidogrel is contraindicated or not tolerated for the prevention of occlusive vascular events in patients with TIA and as second line in patients with ischaemic stroke if clopidogrel is contraindicated.

Cilostazol

Cilostazol is a PDE 3 inhibitor. Its mechanism of action is similar to dipyridamole. It is more potent than aspirin and ticlopidine. It is metabolized through a CYP3A4 enzyme system and hence prone to interaction with other drugs. Headache and hypotension due to vasodilating properties of the drug are the main side-effects, which leads to poor patient compliance with the drug. Its use is currently limited to patients with peripheral vascular disease for its vasodilating properties.

ADP receptor blocking drugs

First-generation thienopyridine: ticlopidine

Ticlopidine irreversibly binds with the $P2Y_{12}$ ADP receptor and inhibits platelet aggregation. It is very effective in reducing thrombotic events, but its use had greatly diminished because of the serious side-effects like thrombocytopenia and most importantly, neutropenia and agranulocytosis. Normally, ticlopidine is given in a twice-daily oral dose of 250 mg. It is well absorbed after an oral dose; the oral bioavailability is 80%. It is highly protein-bound. The half-life of ticlopidine is 12 h. The IPA (inhibition of platelet aggregation) is 50% in 5 days after starting the therapy. Although ticlopidine is effective in the prevention of platelet

aggregation, it is replaced by clopidogrel because of its serious side-effects. Ticlopidine is not licensed in the UK.

Second-generation thienopyridine: clopidogrel

Clopidogrel is a prodrug that requires conversion to an active metabolite by the liver for its antiplatelet effects. Clopidogrel is six times more potent than ticlopidine.[2] The active metabolite forms a disulphide bridge with the cysteine residues on the $P2Y_{12}$ ADP receptor and inhibits binding of ADP to its receptor, thereby inhibiting ADP-mediated platelet aggregation.[3] The binding of clopidogrel to the ADP receptor is irreversible and permanent for the duration of the platelets' life span (7–10 days), despite an initial drug half-life of 6–7 h. Generation of new platelets are required to restore the normal platelet physiology.

It is given as an oral loading dose of 300–600 mg followed by an oral maintenance dose of 75 mg once a day. When given a loading dose, 50–60% of IPA is achieved in 4–6 h rather than 5 days if a loading dose is not given. The bioavailability is 50% after an oral dose and is highly protein-bound. The absorbed drug is metabolized by two different pathways. In one pathway, it is degraded by esterases into an inactive metabolite. The other pathway, in the liver, it is converted to an active form in a two-step process by the hepatic cytochrome CYP450 group of enzymes, mainly the CYP2C19. This stage of metabolism accounts for considerable interpatient difference in the efficacy of clopidogrel. The drug is excreted equally through faeces and urine. Clopidogrel should be used with caution in patients with renal impairment.

Despite being the first-line agent for ADP receptor block, there is a time lag from administration of the drug to the inhibition of platelet aggregation, which may not be ideal for patients undergoing primary percutaneous coronary intervention (PCI).[4] Secondly, genetic variations in the CYP2C19 enzyme create a subset of patients who are classified as poor metabolizers (low responders). Poor metabolizers who are treated with clopidogrel for acute coronary syndrome and primary coronary intervention have higher rate of cardiovascular events. The efficacy of clopidogrel is also affected by other medications (e.g. omeprazole) that interact with CYP2C19. Omeprazole competitively inhibits CYP2C19 and hence reduces the efficacy of clopidogrel. There is also evidence that esomeprazole has similar effects on clopidogrel. Proton pump inhibitors other than omeprazole or esomeprazole are to be considered in patients taking clopidogrel.

Adverse effects include increased risk of bleeding, particularly in the perioperative period. Other side-effects include diarrhoea and rash. Thrombotic thrombocytopenic purpura is a rare complication.[3]

Third-generation thienopyridine: prasugrel

Prasugrel, a prodrug, is a thienopyridine derivative. When taken orally, 80% of the drug is absorbed into the circulation. It is rapidly hydrolysed by esterases to a thiolactone, which is then converted to the active metabolite in the liver mainly by CYP3A4 and CYP2B6 enzyme.[4] In contrast to clopidogrel, there is no reported difference in the efficacy of prasugrel due to genetic variation of CYP enzyme systems. Ninety-eight per cent of the drug is bound to protein plasma. The oral loading dose is usually 60 mg followed by a maintenance dose of 10 mg. It achieves 50% of IPA within 1 h. The active metabolite irreversibly binds to the $P2Y_{12}$ ADP receptor and causes its antiplatelet action. The active metabolite is metabolized to two inactive compounds by S-methylation or conjugation with cysteine. Approximately two-thirds of the prasugrel dose is excreted in the urine and one-third in the faeces as inactive metabolite. No dosage adjustment is necessary for patients with renal impairment. The active metabolite has an elimination half-life of 7 h. The platelet function returns to baseline levels around 7–10 days after cessation of the drug.

The risk of bleeding complications is higher with prasugrel when compared with clopidogrel.[5] It is contraindicated in patients with history of TIA and stroke.

Ticagrelor

Ticagrelor belongs to the cyclopentyltriazolopyrimidines (CPTPs) group of compounds. It is an oral reversible $P2Y_{12}$ ADP-receptor antagonist. It binds to the receptor and inhibits platelets induced by the ADP. The mechanism of action is different from the thienopyridine group of antiplatelet agents. It binds to an allosteric modulation site and creates a conformational change in the $P2Y_{12}$ receptor. In contrast to other thienopyridines, ticagrelor does not prevent binding of ADP but inhibits ADP-induced signalling.[4]

Dose: ticagrelor is taken as an oral loading dose of 180 mg followed by 90 mg twice a day for up to 12 months. Ninety per cent of patients have an IPA of more than 70% by 2 h post-loading dose. The oral bioavailability is 30–40%. It is metabolized rapidly into a circulating active metabolite by a CYP3A4 enzyme. Avoid concomitant use of CYP3A inhibitors (ketoconazole, clarithromycin) and CYP3A inducers (phenytoin, carbamazepine, rifampicin). Both ticagrelor and its metabolite are highly protein bound (>99%). The primary route of elimination is by biliary secretion. No dosage adjustment is necessary for patients with renal impairment. The terminal half-life of the drug is 7 and 9 h for the active metabolite. Apart from bleeding complication associated with all antiplatelet agents, ticagrelor is associated with transient dyspnoea.

The PLATO[6] (Platelet Inhibition and patient outcomes) trial compared ticagrelor with clopidogrel in patients with acute coronary syndrome; 18 624 patients were enrolled of which 35% had STEMI (ST Elevation Myocardial Infarction). Ticagrelor showed significant reductions in cardiovascular events when compared with clopidogrel.

Cangrelor

Cangrelor (an ATP analogue) is a short-acting i.v. $P2Y_{12}$ ADP-receptor antagonist. It has a rapid onset of action. It is given as an i.v. loading dose of 30 $\mu g\ kg^{-1}$ followed by 2–4 $\mu g\ kg^{-1}\ min^{-1}$ i.v. The maximal inhibition occurs within 15 min and a rapid reversal after discontinuation of the drug.[7]

The elimination half-time is under 9 min and platelet function tends to come to normal in 60 min. Metabolism of the drug is through dephosphorylation and is not dependent on the liver or kidneys. Cangrelor appears as an effective drug for bridge therapy during the perioperative period or even during ACS when possibility of surgery exists. Although the drug appeared promising in bridging therapy, the FDA this year refused marketing approval citing inconclusive phase III clinical trials.[8]

Glycoprotein IIb/IIIa receptor antagonists

GP IIb/IIIa receptors play a crucial role in platelet aggregation. GP IIb/IIIa receptors are present on the surface of platelets normally in an inactive form. When the platelets are activated, they undergo a conformational change resulting in binding of fibrinogen and von Willebrand factor (vWF). These molecules function as a bridge for the platelet aggregation. GP IIb/IIIa receptor blocking

drugs bind to the GP IIb/IIIa receptor and inhibit platelet aggregation by preventing the binding of vWF and fibrinogen. Abciximab is a monoclonal antibody, while the other two are synthetic derivatives.

Abciximab, the Fab fragment of chimeric murine (humanized form) monoclonal antibody, binds with the GP IIb/IIIa receptor and prevents platelet aggregation. It also binds and inhibits vitronectin receptor found in platelets and endothelial and smooth muscle cells. Abciximab is given as an i.v. loading dose of 0.25 mg kg^{-1} followed by an i.v. infusion of 0.125 μg kg^{-1} min^{-1}. After a bolus dose, the plasma levels reduce very rapidly with a half-life of 10 min due to the rapid binding of abciximab to platelets and phase II half-life of 30 min. It takes 48 h for the platelet function to recover after cessation of the medication. Abciximab can be found in the circulation even after 15 days. It is not necessary to adjust the dose of abciximab in patients with renal impairment.

Eptifibatide is a cyclic heptapeptide. It selectively binds to GP IIb/IIIa receptors and inhibits platelet aggregation. Unlike abciximab, eptifibatide does not bind to any other receptors. It is given as an i.v. bolus dose of 180 μg kg^{-1} followed by an i.v. infusion of 2 μg kg^{-1} min^{-1}.[9] It inhibits platelet aggregation in a dose-dependent and concentration-dependent manner, resulting in 80% IPA within 15 min.[9] Eptifibatide dissociates from platelets rapidly on discontinuation of infusion and is mostly excreted unchanged in urine. The plasma elimination half-life is 2.5 h. Since the drug is eliminated unchanged in urine, the dose needs to be reduced in renal impairment. If the creatinine clearance is <60 ml min^{-1}, the dose should be reduced to 1 μg kg^{-1} min^{-1}.

Tirofiban is a reversible non-peptide antagonist of the GP IIb/IIIa receptor. It is given as an i.v. loading dose of 25 μg kg^{-1} over 3 min followed by an i.v. infusion of 0.15 μg kg^{-1} min^{-1}.[9] Ninety per cent IPA is achieved within 10 min. It is excreted unchanged in urine and faeces. The half-life of tirofiban is 2 h. Similar to eptifibatide, the dose of tirofiban should be reduced to half in patients with reduced creatinine clearance (<60 ml min^{-1}).

GP IIb/IIIa receptor antagonists were associated with increasing bleeding complications when compared with other antiplatelet agents. Thrombocytopenia has been reported to occur with all three GP IIb/IIIa receptor antagonists. GP IIb/IIIa antagonists are not effective when used as the only antiplatelet agent, with the only significant benefit obtained from infusion of these drugs being during PCI. In patients undergoing PCI, GP IIb/IIIa receptor antagonists were reserved for specific patient populations as mentioned below.

PAR-1 blocking drugs

Vorapaxar, a tricyclic himbacine-derived drug, selectively inhibits thrombin-mediated platelet aggregation. FDA recently (May 2014) approved this drug for marketing purposes after phase III trials. Although it is a reversible antagonist to PAR-1 receptor, it behaves like an irreversible drug due to its long half-life. It has no effect on ADP-mediated platelet aggregation. It is given as a 2.5 mg once-daily dose. The bioavailability of this drug is almost 100%. It achieves 80% IPA within 1 week. It is metabolized by the CYP3A4 enzyme system. The main route of elimination is through the faeces. No dosage adjustment is necessary for patients with renal impairment or for mild-to-moderate hepatic impairment, but it is contraindicated in patients with severe hepatic impairment due to increased bleeding problems. The terminal half-life of vorapaxar is 8 days. Even after weeks of stopping the drug, the IPA can be as high as 50%. It is currently approved for use with either aspirin or clopidogrel for secondary prevention in patients with history of myocardial infarction (MI) or peripheral vascular disease.

Newer antiplatelet agents

There are several antiplatelet drugs currently under various stages of development.

(i) Terutuban, a thromboxane receptor antagonist.
(ii) Elinogrel, a $P2Y_{12}$ receptor blocker, it can be administered both orally and i.v.
(iii) Atoxapar, PAR-1 antagonist.

Antiplatelet therapy

There are several reasons a patient could be on antiplatelet therapy. They may be either on a platelet monotherapy or on dual antiplatelet therapy. The following list would summarize the common indications for antiplatelet therapy.

(i) Aspirin
  (a) In patients with MI (indefinitely),[10]
  (b) peripheral vascular disease (not much evidence),
  (c) primary prevention for cerebral vascular disease (not licensed),
  (d) atrial fibrillation (no longer recommended),
  (e) vascular dementia.
(ii) Dipyridamole monotherapy[10]
  (a) Ischaemic stroke if aspirin and clopidogrel is contraindicated.
  (b) TIA if aspirin is contraindicated.
(iii) Clopidogrel monotherapy[10]
  (a) All patients with MI if aspirin is contraindicated.
  (b) To prevent occlusive vascular events in patients who have had an ischaemic stroke or who have peripheral arterial disease.
  (c) Multivascular disease.
(iv) Aspirin+dipyridamole[10]
  (a) Patients with history of TIA.
  (b) Patients with history of ischaemic stroke if clopidogrel is contraindicated.
(v) Aspirin+clopidogrel[11]
  (a) At least 12 months for patients with NSTEMI (Non-ST elevation MI).
  (b) At least 12 months for patients with STEMI (ST Elevation MI) with drug-eluting stent (DES) or bare metal stent (BMS).
  (c) At least 1 month for patients with STEMI who had medical treatment with fibrinolytic agent.
(vi) Aspirin+prasugrel[12]
  (a) Patients with ACS for PCI if
  - Immediate primary percutaneous coronary intervention (PPCI) for STEMI.
  - Stent thrombosis on patients with clopidogrel therapy.
  - Patients with diabetes mellitus.
(vii) Aspirin+ticagrelor[13]
  (a) For 12 months on patients
  - STEMI if the patients have PPCI
  - NSTEMI
  - Unstable angina
(viii) I.V. eptifibatide or i.v. tirofiban[14]
  (a) Patients with unstable angina who are undergoing angiography within 96 h of admission.

Other indications

(i) Prevention of eclampsia and its complications[15,16]
(ii) Thrombocytosis (controversial and uncertain)[17]
(iii) Anticancer therapy (animal studies)

Surgery and antiplatelet therapy

Surgery on patients with dual antiplatelet therapy poses a significant challenge to anaesthetists. On the one hand, continuing dual antiplatelet therapy increases the risk of bleeding, on the

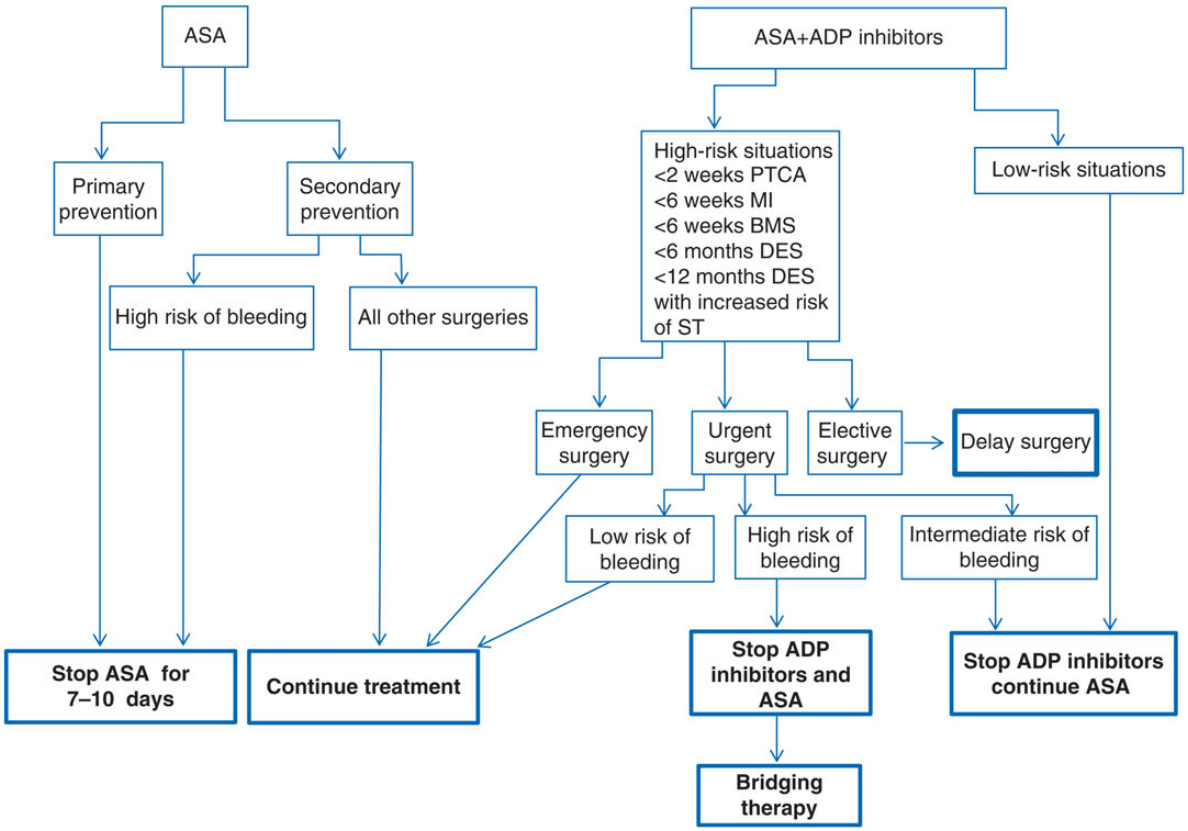

Fig 2 Antiplatelets and surgery. Reproduced with permission from Oprea and Popescu.[9]

Table 1 Antiplatelets and regional anaesthesia. Adapted (with permission) from the AAGBI guidelines on regional anaesthesia and patients with abnormalities of coagulation, 2013

Drug	Elimination half-life	Acceptable time after the drug for performing block	Administration of drug while spinal or epidural catheter in place	Acceptable time after spinal block performance or catheter removal for next drug dose
Aspirin	Not significant irreversible	No additional precautions	No additional precautions	No additional precautions
Dipyridamole	10 h	No additional precautions	No additional precautions	6 h
Ticlopidine	4–5 days	14 days	Not recommended	6 h
Clopidogrel	Not significant irreversible	7 days	Not recommended	6 h
Prasugrel	Not significant irreversible	7 days	Not recommended	6 h
Ticagrelor	8–12 h	5 days	Not recommended	6 h
Abciximab	24–48 h	48 h	Not recommended	6 h
Eptifibatide	4–8 h	8 h	Not recommended	6 h
Tirofiban	4–8 h	8 h	Not recommended	6 h
Vorapaxar	8 days	No data	Not recommended	No data

other hand, stopping the antiplatelet can lead to cardiovascular events such as stent thrombosis, MI, and death.

Each patient should be managed individually. It should be a multidisciplinary approach between surgeon, anaesthetist, cardiologist, and haematologist. The following factors should be taken into consideration.

(i) Emergency or urgent (cancer related) surgery, elective surgery.
(ii) Type of surgery: low risk, intermediate risk, or high risk for bleeding.
(iii) Time duration from the occurrence of acute coronary syndrome or PCI to the surgery and if patient had a primary PCI, type of stent, that is, DES or BMS.
(iv) Type of lesion—global coronary disease or specific coronary lesions.

Aspirin can be continued until the day of surgery in most circumstances but may need to be stopped for some specific surgeries such as intracranial surgery.

Platelet transfusions may not provide rapid reversal of the antiplatelet effects. Some antiplatelet drugs have a long half-life, so they remain in circulation for a considerable period of time. When platelets are transfused on these patients, the circulating drug will also inhibit the transfused platelets. Figure 2 illustrates the algorithm for the management of antiplatelets during surgery.

Regional anaesthesia and antiplatelet agents

There is no evidence that aspirin needs to be stopped for performing regional anaesthetic techniques. For all other antiplatelet agents, sufficient time should be allowed for the platelet function to recover. This time duration depends upon the elimination half-life and mechanism of action of the antiplatelet agents as shown in Table 1.

Conclusion

The list of antiplatelet agents in the market is growing constantly. Newer antiplatelet agents are being developed continuously to overcome the shortcomings of existing antiplatelet agents. As anaesthetists, we should continue to update ourselves with these newer antiplatelet agents to manage the patients effectively and safely during the perioperative period. A haematologist or cardiologist should be contacted in complex and difficult situations.

Declaration of interest

None declared.

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MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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