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 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. 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. 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.

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. Recent evidence suggests that platelets also have a new and previously unsuspected role in tissue repair and vascular remodelling.

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 A2 (TxA2), 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, TxA2), neighbouring platelet activation and recruitment occurs, rapidly forming a platelet aggregate. This interacts with fibrin and thrombin and promotes thrombus formation. 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.
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 TXA2 formation, newer drugs protect against thrombosis by interfering with GP IIb/IIIa and ADP receptors10 (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 PGH2 formation from arachidonic acid. PGH2 is the precursor for TxA2 formation by platelets (platelet aggregator and vascular vasoconstrictor), and PGI2 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 IIb/IIIa, glycoprotein IIb/IIIa; GP Ib–IX–V, glycoprotein Ib–IX–V; ADP, adenosine diphosphate; GP IIb/IIIa, glycoprotein IIb/IIIa.
AAS is rapidly absorbed through the enteric mucosa, with peak plasma level attained within 30–60 min for regular preparations and a half-life of 20 min.14 (Table 1). While antiplatelet effects can usually be detected within an hour, enteric-coated preparations slow the rate of absorption that can lead to sub-optimal antiplatelet effects in obese patients.15–19 The irreversible inhibition of COX1 maintains the antiplatelet effects of ASA for the lifespan of the platelet (7–10 days), with slow recovery of overall platelet function of 10% per day due to new platelet formation.

**Indications and efficacy**

**Coronary artery disease**

*Primary prevention.* In several trials, ASA therapy in doses of 75–325 mg daily demonstrated a 36–44% reduction in the rates of subsequent myocardial infarction (MI) with no increase in mortality. Newer data are not as convincing for the use of ASA in primary prevention.20–23 The United States Preventive Services Task Force recommends ASA 75 mg daily in patients <80 yr of age and in whom the cardiovascular benefit is greater than the risk of gastrointestinal (GI) bleeding.24 ASA 81 mg daily or 100 mg every other day is recommended in women at high risk of cardiovascular disease or women ≥65 yr of age with a similar risk/benefit profile.25

*Secondary prevention.* Patients with stable or unstable angina receiving ASA 75–1200 mg daily derive a survival benefit up to 1 yr.26 For patients with acute coronary syndromes (ACS), current guidelines recommend ASA 162–325 mg given before primary percutaneous coronary intervention (PCI) or thrombolysis and continued indefinitely (class I).27 28 This strategy leads to overall reduced mortality. For the PCI patient population, ASA significantly reduces early and late stent thrombosis (ST) rates.29 30 As part of a dual antiplatelet therapy (DAPT) regimen, ASA doses of 75–100 mg daily are considered as effective as higher doses in reducing major adverse cardiac events (MACE) but are associated with less bleeding.31 32 After coronary artery bypass grafting (CABG) surgery, ASA decreases saphenous vein graft occlusion and significantly decreases in-hospital mortality, MI, stroke, and renal failure rates.33 34

**Cerebrovascular disease**

While it is unclear if there is benefit derived from ASA therapy for primary prevention of stroke, earlier data showed a 25% reduction in recurrent cerebrovascular ischaemic events when used for secondary prevention.35 36 The indications for ASA therapy for secondary prevention of stroke are the same as discussed in detail above. In patients undergoing carotid endarterectomy, current guidelines recommend ASA 81–325 mg before the procedure and continued indefinitely if no contraindications exist.37

**Atrial fibrillation**

Compared with warfarin, ASA is less effective in preventing stroke in patients with non-valvular atrial fibrillation (AF), but can be considered an option in patients who cannot receive anticoagulation.17

**Risks**

In a review including 22 trials, low-dose ASA (75–325 mg daily) increased the risk of major GI and intracranial bleeding up to two times compared with placebo.38 A meta-analysis of 16

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
<th>Half-life</th>
<th>Time to recover platelet function after drug withdrawal</th>
<th>Platelet inhibition</th>
<th>Administration route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>COX-1 inhibition</td>
<td>325 mg</td>
<td>75–325 mg daily</td>
<td>15–20 min</td>
<td>30% at 48 h</td>
<td>Irreversible inhibition</td>
<td>Oral</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>P2Y12 receptor inhibition</td>
<td>300–600 mg</td>
<td>75 mg daily</td>
<td>7–9 h</td>
<td>40% at 3 days</td>
<td>Irreversible inhibition</td>
<td>Oral</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>P2Y12 receptor inhibition</td>
<td>60 mg</td>
<td>10 mg daily</td>
<td>7 h</td>
<td>2–3 days</td>
<td>Irreversible inhibition</td>
<td>Oral</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>P2Y12 and (partly) P2Y1 receptor inhibition</td>
<td>180 mg</td>
<td>90 mg twice a day</td>
<td>7–9 h</td>
<td>57% at 24 h</td>
<td>Reversible inhibition</td>
<td>Oral</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Adenosine triphosphate analogue with a high affinity for the P2Y12 receptor</td>
<td>30 μg kg⁻¹</td>
<td>2–4 μg kg⁻¹ min⁻¹</td>
<td>3–6 min</td>
<td>Rapid (minutes to hours)</td>
<td>Reversible inhibition</td>
<td>I.V.</td>
</tr>
<tr>
<td>Abciximab</td>
<td>Glycoprotein IIb/IIIa receptor inhibitor</td>
<td>0.25 mg kg⁻¹</td>
<td>0.125 mg kg⁻¹ min⁻¹</td>
<td>10–15 min</td>
<td>12 h</td>
<td>Reversible inhibition</td>
<td>I.V.</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>Glycoprotein IIb/IIIa receptor inhibitor</td>
<td>180 μg kg⁻¹</td>
<td>2 μg kg⁻¹ min⁻¹</td>
<td>2.5 h</td>
<td>2–4 h</td>
<td>Reversible inhibition</td>
<td>I.V.</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>Glycoprotein IIb/IIIa receptor inhibitor</td>
<td>0.4 μg kg⁻¹</td>
<td>0.1 μg kg⁻¹ min⁻¹</td>
<td>2 h</td>
<td>2–4 h</td>
<td>Reversible inhibition</td>
<td>I.V.</td>
</tr>
</tbody>
</table>
trials demonstrated that ASA therapy increases the rate of haemorrhagic stroke, despite decreasing ischaemic stroke, total stroke, and MI.39

A study including patients undergoing intermediate/high-risk non-cardiac procedures found that patients taking ASA have no significant difference in bleeding events compared with those in whom ASA was stopped.40 However, cardiac surgery patients on ASA have an increased risk for post-operative bleeding (as measured by chest tube drainage) that does not require reoperation.41

While ASA is prescribed routinely in doses up to 325 mg daily, newer evidence does not support this practice. Doses of 75–81 mg daily have a similar efficacy as higher doses with a decreased risk of GI bleeding.42

ADP receptor inhibitors

The ADP receptor blockers inhibit platelet aggregation by preventing the binding of ADP to its specific platelet receptor. While the first ADP receptor blocker, ticlopidine, is rarely used now, due to side-effects such as thrombocytopenia, newer agents (clopidogrel, prasugrel, and ticagrelor) are routinely prescribed as part of a DAPT regimen in patients with ischaemic heart disease. Cangrelor, an investigational ADP receptor antagonist, is currently in development.

Pharmacology

Clopidogrel is a thienopyridine that requires conversion to an active metabolite that irreversibly binds the ADP receptor. It is usually recommended in doses of 150–600 mg for loading and 75 mg daily for maintenance. Clopidogrel is eliminated both in faeces and urine. The dose does not have to be adjusted for patients with moderate renal and hepatic disease.43 44 At regular doses (75 mg daily), clopidogrel achieves a peak plasma level 2 h after oral ingestion and a plateau of inhibition of platelet aggregation (IPA) of 40–60% after 3–7 days.3

Similar to clopidogrel, prasugrel is a newer thienopyridine prodrug that irreversibly inhibits the ADP receptor for the lifespan of the platelet (Table 1). Prasugrel's active metabolite reaches a peak plasma concentration in 30 min, and has a 7 h elimination half-life.4 5 As with clopidogrel, dose adjustment is not required for moderate hepatic or renal impairment.46 The maximum IPA (75–85%) occurs 2–4 h after a loading dose. Prasugrel is more effective and faster than clopidogrel in achieving platelet inhibition.47 48 The recommended dose of prasugrel is 60 mg for loading and 10 mg daily for maintenance. Owing to the higher risk of bleeding incurred with prasugrel, the FDA recommends that smaller doses be used in patients ≥75 yr of age, weighing <60 kg, or with a previous history of stroke or transient ischaemic attacks (TIAs).47

Ticagrelor is a non-thienopyridine, reversible, non-competitive antagonist of the ADP receptor. Compared with clopidogrel and prasugrel, it has a more rapid onset of action and is more potent, achieving 80% IPA at 2 h after oral ingestion.49 Ticagrelor is eliminated in the faeces. Unlike its predecessors, it needs a dose adjustment in patients with liver dysfunction, but not with renal disease.50 Ticagrelor has a half-life of 7–8.5 h. The recommended loading dose is 180 mg, with 90 mg twice a day recommended for maintenance.50 51

Unlike clopidogrel, ticagrelor’s effect is independent of genetic polymorphism, making it less prone to response variability. It also has a better safety profile than prasugrel. These two considerations, including its efficacy, led to ticagrelor virtually replacing clopidogrel as the preferred ADP receptor antagonist in patients with ACS.52

Cangrelor is an i.v., direct-acting, reversible ADP antagonist currently in development. It has a fast onset of action, and infusion rates of 2–4 μg kg⁻¹ min⁻¹ result in 80% IPA. Its major advantage is its short half-life (~2.6 min). Cangrelor clearance is not affected by renal disease. Platelet function recovers within 5 min of infusion discontinuation.53

Indications and efficacy

Coronary artery disease

Patients with ACS. The 2011 European Society of Cardiology Guidelines for the Management of Acute Coronary Syndrome recommend ticagrelor as first-line therapy in patients at moderate-to-high risk of ischaemic events irrespective of initial treatment strategy (level of evidence IB). However, in ADP-inhibitor-naive patients (especially diabetics) undergoing PCI, prasugrel is the recommended drug of choice (level of evidence IB). Clopidogrel is reserved only for patients with contraindications to prasugrel or ticagrelor (level of evidence IA).54

Current American guidelines recommend clopidogrel or ticagrelor upon presentation in patients with unstable angina and non-ST-elevation MI (NSTEMI) in whom medical management is chosen. For patients presenting with ACS and undergoing PCI with stenting, a loading dose of ADP receptor inhibitor should be administered, followed by a maintenance daily dose for at least 1 yr.5 27 Current evidence strongly suggests that the use of ADP receptor inhibitors in the management of ST-elevation MI (STEMI), treated with or without fibrinolytic therapy, improves outcomes.28

Patients undergoing PCI not for ACS. The 2011 ACCF/AHA/Society for Cardiovascular Angiography and Interventions Guideline for Percutaneous Coronary Intervention recommend a pre-procedure loading dose of an ADP-receptor inhibitor in patients undergoing PCI with stenting. In patients receiving drug-eluting stents (DES) who are not at high risk of bleeding, DAPT should be maintained for at least 1 yr. Similarly, in patients receiving bare metal stents (BMS), DAPT should be maintained for at least 1 month and ideally up to 12 months. However, newer guidelines from the American College of Chest Physicians and European Society of Cardiology recommend 4–6 weeks of DAPT for patients with BMS and 6 months for patients with DES at low risk of ST.55 56 In patients with increased risk of ST, a thorough risk–benefit analysis of maintaining DAPT for more than 12 months should be performed.57

Peripheral arterial disease

Current guidelines recommend clopidogrel as an alternative to ASA therapy as secondary prevention in patients undergoing lower-extremity revascularization or amputation.58
Carotid and vertebral artery disease
The most recent guidelines recommend clopidogrel for a period of 3–6 months in patients with carotid or vertebral artery dissection associated with TIA or stroke. Patients with a history of an ischaemic cerebrovascular accident and presenting with extracranial carotid or vertebral atherosclerosis should receive either clopidogrel monotherapy or ASA and extended-release dipyridamole.59 Patients who have undergone carotid endarterectomy should receive therapy with ASA (75–325 mg daily) or clopidogrel for long-term prophylaxis against ischaemic stroke. In patients undergoing carotid stenting, DAPT is recommended for 30 days before and after the procedure.37

Atrial fibrillation
The 2011 ACCF/AHA/Heart Rhythm Society Focused Update on the Management of Patients with Atrial Fibrillation recommends the use of ADP receptor inhibitors in situations where warfarin therapy is contraindicated (class IIb).60 The CURE trial established that combination therapy with ASA and clopidogrel is superior to ASA alone by significantly reducing the rate of MACE in patients with ACS.61 Similar results were demonstrated in patients undergoing PCI.62–64 The newly developed oral antiplatelet agents, prasugrel and ticagrelor, were identified to be superior to clopidogrel when used in combination with ASA in reducing the risk of MACE in patients with ACS undergoing PCI.55–59 The efficacy of clopidogrel is still a subject of debate and thus this drug has not yet received FDA approval. Initially, clopidogrel was not found to be superior to clopidogrel when treating patients with ACS undergoing PCI.70 71 However, more recent studies show that clopidogrel significantly reduces the rate of ischaemic events, including ST, in patients undergoing PCI, with no significant increase in severe bleeding.72 73

Risks
Bleeding is the most significant side-effect associated with ADP receptor-blocker therapy. When compared with patients receiving ASA therapy alone for ACS, patients receiving DAPT with clopidogrel and ASA had an increase in major, minor, and GI bleeding. However, no increase in the incidence of fatal bleeding was noted.61 A high loading dose of clopidogrel (600 mg) leads to increased rates of major bleeding events when compared with doses of 300 mg.74

A large meta-analysis concluded that patients receiving clopidogrel within 7 days before CABG had a higher risk of major bleeding and related complications (reoperation and transfusions).75 In patients with ACS, prasugrel was found to have a higher incidence of major, life-threatening, and fatal bleeding when compared with clopidogrel.76 Despite increased chest tube drainage after CABG, patients on prasugrel did not require more red blood cell transfusions compared with clopidogrel.77 Maintenance with prasugrel is frequently associated with minor or minimal bleeding, but major bleeding is rare.78 Ticagrelor was associated with a higher rate of major bleeding unrelated to CABG surgery including higher rates of fatal intracranial bleeding compared with clopidogrel.66 Compared with ticagrelor, clopidogrel is safer with regard to GI-related risks, including fewer overall and spontaneous GI bleeding events, but data regarding prasugrel are inconclusive.79 Cangrelor was not associated with increased risk of serious bleeding.80

Glycoprotein IIb/IIIa receptor inhibitors
Glycoprotein IIb/IIIa inhibitors antagonize platelet function by inhibiting cross-linking of platelets and subsequent aggregation. Abciximab, eptifibatide, and tirofiban have been approved by the US FDA to be used as adjuncts for patients with ACS or undergoing PCI.81

Pharmacology
Abciximab rapidly binds to platelets, achieving almost immediate 80% IPA when given as a bolus dose of 0.25 mg kg⁻¹ or as an infusion of 0.125 μg kg⁻¹ min⁻¹. Most of the drug binds to platelets and is not excreted in the urine. Its metabolism appears to correlate with platelet degradation.82 Consequently, thrombocytosis requires increased dosing of the drug. Since very little drug is available in the blood, its effects can be rapidly reversed by platelet transfusion.83 Abciximab has a plasma half-life of 10 min and platelet function recovers over 48 h, although inhibition of platelet GP IIb/IIIa receptors can be documented up to 15 days after drug discontinuation.84 Eptifibatide given as a single 180 mg kg⁻¹ min⁻¹ bolus and 2 mg kg⁻¹ min⁻¹ infusion produces rapid and sustained high-grade IPA (80% within 15 min). It is renally excreted (75%) and, unlike abciximab, there is unbound drug available in the plasma.82 Therefore, platelet transfusions are unlikely to reverse its antiplatelet effects since circulating drug would most likely rapidly inhibit newly transfused platelets. Thus reversal relies primarily on stopping the medication, requiring ~4 h to achieve ~50% of normal platelet aggregation.85 Tirofiban has an onset of action within 5 min after the initiation of infusion. The ACS dosage of tirofiban includes a 30 min loading dose of 0.4 μg kg⁻¹ min⁻¹ followed by an infusion of 0.1–0.15 μg kg⁻¹ min⁻¹. Return of platelet aggregation to >80% of pre-treatment value occurs at ~4 h after stopping drug infusion. Tirofiban has a plasma half-life of 1.5–2 h. It is removed by both renal and biliary excretion. Patients with renal insufficiency require dose adjustment of tirofiban86 (Table 1).

The main difference between abciximab and the smaller molecules tirofiban and eptifibatide is the rate at which they dissociate from GP IIb/IIIa receptors (hours for abciximab vs seconds for tirofiban and eptifibatide). In addition, the lower affinity of eptifibatide for GP IIb/IIIa receptors compared with tirofiban means that a greater concentration of the former is required to achieve the same degree ofIPA.87

Indications and efficacy
The 2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction recommend the use of i.v. GP
IIb/IIIa inhibitors in combination with ASA and heparin, both in patients treated medically and interventionaliy. The 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction recommends, as a reasonable approach, initiation of therapy with heparin and an i.v. GP IIb/IIIa receptor antagonist such as abciximab (Level of Evidence: A), high-bolus-dose tirofiban (Level of Evidence: B), or double-bolus eptifibatide (Level of Evidence: B) at the time of PCI.

Many studies have evaluated the efficacy of i.v. GP IIb/IIIa inhibitors in ACS. A meta-analysis involving 21 trials concluded that GP IIb/IIIa inhibitors significantly reduce the combined endpoint of death, non-fatal MI, or urgent revascularization at 30 days in patients undergoing PCI. Similar outcomes were identified in patients with medically treated NSTEMI and in patients with STEMI treated with angioplasty.

Risks

The rates of bleeding encountered with GP IIb/IIIa inhibitor therapy have been higher than those seen with placebo. A pooled analysis of 14 randomized studies including a total of 28,000 patients treated with heparin and a GP IIb/IIIa inhibitor or placebo found that the incidence of intracerebral hemorrhage was similar between the two groups. Moreover, no difference was identified when treatment with a GP IIb/IIIa inhibitor alone was compared with heparin alone.

Perioperative management of antiplatelet agents

Perioperative management of antiplatelet agents is complex, so the team of perioperative clinicians (anaesthesiologist, surgeon, and prescribing physician—either neurologist or cardiologist) should participate in decision-making. Several factors need to be considered before a decision to continue or stop antiplatelet agents perioperatively. An important factor is the initial indication for antiplatelet therapy and, most importantly, the consequences of stopping the drug before the operation. Premature discontinuation of antiplatelet agents including GP IIb/IIIa inhibitors is associated with an increase in thrombotic events due to a rebound effect on platelet activation. The other important factor to consider is the inherent bleeding risk of certain procedures and the impact of bleeding on overall patient outcome (Table 2).

Based on the role of platelets in the coagulation cascade, various point-of-care testing devices have been developed. However, there are differences in the sensitivity of these tests in assessing recovery of platelet function after discontinuation of ADP receptor inhibitors and significant interindividual variability in results. Therefore, the role of these tests in strategies for perioperative management of antiplatelet agents is evolving.

Aspirin

In patients on ASA for AF or for primary prevention of MI and stroke, the drug can be stopped 7–10 days before operation without major consequences. In patients on ASA for secondary prevention, discontinuation is associated with increased risk of cardiovascular complications [odds ratio (OR) = 3.1], peaking at 8–10 days for coronary thrombosis and 14 days for cerebrovascular events. For patients who have undergone PCI with stenting, the likelihood of ST is much higher (OR = 90) when ASA is discontinued.

Bleeding risk has been assessed in a meta-analysis involving 49,590 patients on low-dose ASA, with results ranging from very little bleeding for dermatological, ophthalmological, visceral, minor abdominal, endoscopic, dialysis catheter insertions, and minor dental procedures to 75% in patients undergoing transurethral prostate biopsy. A large trial on patients undergoing orthopaedic surgery (hip replacement) reported an increase in GI bleeding and a decrease in postoperative haemoglobin (average of 2 g litre\(^{-1}\)), and also an increased need for blood transfusions (53 ml on average). Despite that, there was no increase in mortality. Orthopaedic patients undergoing spinal fusion or femoral neck fractures had no increase in bleeding. Patients undergoing tonsillectomy have a 7.2-fold increase in rates of reoperation for haematoma compared with those not on ASA. Vascular surgery patients have a small increase in bleeding complications. Newer studies, in high-risk patients on low-dose ASA undergoing non-cardiac surgery, show a decrease in MACE, but no overall increase in bleeding complications.

Table 2

<table>
<thead>
<tr>
<th>Surgical haemorrhagic risk</th>
<th>Blood transfusion requirement</th>
<th>Type of surgery</th>
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<tbody>
<tr>
<td>Low</td>
<td>Usually not required</td>
<td>Peripheral, plastic, and general surgery biopsies</td>
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<tr>
<td></td>
<td></td>
<td>Minor orthopaedic, otolaryngology, and general surgery</td>
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<td></td>
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<td>Endoscopy</td>
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<td></td>
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<td>Eye anterior chamber</td>
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<td></td>
<td></td>
<td>Dental extraction and surgery</td>
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<tr>
<td>Intermediate</td>
<td>Frequently required</td>
<td>Visceral surgery</td>
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<td></td>
<td></td>
<td>Cardiovascular surgery</td>
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<td></td>
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<td>Major orthopaedic surgery</td>
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<td></td>
<td></td>
<td>Otolaryngology</td>
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<td></td>
<td></td>
<td>Urological surgery</td>
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<tr>
<td></td>
<td></td>
<td>Reconstructive surgery</td>
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<tr>
<td>High</td>
<td>Possible bleeding in a closed space</td>
<td>Intracranial neurosurgery</td>
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<td></td>
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<td>Spinal canal surgery</td>
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<td>Eye posterior chamber surgery</td>
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</table>
In patients undergoing cardiac surgery, preoperative ASA administration increases postoperative bleeding and red blood cell requirements with no effect on mortality, re-exploration rate, and perioperative MI. A new meta-analysis concluded that ASA was associated with increased chest tube drainage in this patient population and might be associated with a greater requirement for blood products. Patients on ASA have a 2.7-fold increase in blood transfusion rates during transurethral prostatectomy compared with placebo. In neurosurgical procedures, ASA use has led to increased mortality.

In conclusion, with the exception of high-risk bleeding procedures (intracranial and medullary canal surgery, posterior chamber of the eye surgery, and transurethral prostate resection), ASA continuation perioperatively is not associated with significant bleeding events or with increased mortality. Therefore, the 2012 ACCP guidelines on Perioperative Management of Antithrombotic Therapy recommend continuing ASA in the perioperative period for patients at high cardiovascular risk (Fig. 2).

ADP receptor inhibitors
As with ASA, when the ADP receptor inhibitors are recommended for treatment of AF or primary prevention of cardiac or cerebrovascular events, these agents can be stopped before operation without major consequences. On the other hand, ADP receptor inhibitors are a major component of the DAPT recommended pre- and post-PCI with stenting. Several aspects need to be considered in patients with stents undergoing surgery: the appropriate time frame after stent placement before surgery can be safely performed, the potential consequences of stopping DAPT, the urgency of the intervention, and the bleeding risk associated with the intervention.

Recommended duration of DAPT after PCI
Many studies have revealed that premature discontinuation of DAPT before the recommended interval necessary for complete endothelialization of the stent can lead to fatal consequences. Studies in DES patients demonstrated that premature discontinuation of clopidogrel was the most important factor leading to early ST (hazard ratio of 57) and fatal outcomes (mortality 45% for patients developing ST). Late ST has also been linked to discontinuation of clopidogrel after 1 yr of DAPT.

The perioperative period is marked by a prothrombotic state due to increased levels of circulating fibrinogen and C-reactive protein. This hypercoagulable state leads to

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**Fig 2** Algorithm for perioperative management of antiplatelet therapy. Adapted from Di Minno and colleagues, with permission. ADP, adenosine diphosphate; ASA, aspirin; PTCA, percutaneous transluminal coronary angioplasty; BMS, bare metal stent; DES, drug-eluting stent; MI, myocardial infarction; ST, stent thrombosis.
increased atheromatous plaque instability, which, in association with premature discontinuation of the ADP receptor inhibitor, can have dire consequences (mortality varying from 30% to 86%). These effects are augmented by an ADP receptor inhibitor discontinuation rebound phenomenon, clearly demonstrated for clopidogrel and also well described with ASA cessation, which is responsible for a cluster of thrombotic events.

The recommended duration for continuing DAPT in patients receiving PCI varies with different guidelines. While there is no controversy regarding the minimum duration of DAPT after balloon angioplasty only (2 weeks) and after BMS placement (4–6 weeks), the optimal duration after DES placement is uncertain. The 2007 ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac surgery recommend a minimum of 12 months of uninterrupted DAPT after DES placement, whereas the 2010 ESC guidelines on myocardial revascularization and the 2012 ACCP guidelines on perioperative management of antithrombotic therapy endorse a minimum of 6 months. Initial data showed that discontinuation of clopidogrel 6 months after placement of a DES is associated with a 2–3 times higher incidence of late ST compared with patients receiving BMS. However, more recent literature suggests that prolonging DAPT for a period longer than 12 months in DES patients is not significantly more effective than ASA monotherapy in reducing the rate of MACCE.

The question of 6 or 12 months of DAPT after DES placement was recently addressed in several trials. A prospective trial involving 1443 DES patients receiving either 6 or 12 months of DAPT showed that the risk of target vessel failure at 12 months is similar. Another randomized trial including 2013 patients with BMS and DES demonstrated that a regimen of 24 months compared with 6 months of clopidogrel therapy was not more effective in reducing the composite endpoint of death due to any cause, MI, or stroke. Newer data evaluate the safety of discontinuing DAPT after 3 months after placement of a zotarolimus-eluting stent (second-generation DES). In a randomized study of 2117 patients, 3 months of DAPT were non-inferior compared with the standard 12 months therapy in the occurrence of the primary endpoint at 1 yr (cardiovascular death, MI, ST, target vessel revascularization, or bleeding). This was confirmed in a smaller study of 128 patients.

While the above data were obtained outside the periprocedural area, similar outcomes have also been recorded perioperatively. A population cohort study of 8000 patients undergoing major elective procedures who had BMS or DES placed up to 10 yr prior concluded that the fewest complications occurred when the patient underwent surgery between 6 months and 1 yr after DES placement.

As a result, it is still unclear what is the optimal duration of DAPT and timing of surgery. The key to these questions is the individual risk for delayed stent endothelialization. Several clinical predictors for delayed endothelialization and thrombosis of DES have been identified: presence of ACS, treatment of bifurcating lesions, presence of multiple and overlapping stents, left ventricular ejection fraction <30%, renal insufficiency, and diabetes mellitus. Newer data suggest that for low-risk patients undergoing low- to intermediate-risk procedures, a delay of surgery for 6 months after DES placement might be sufficient. However, in high-risk patients, it might be prudent to wait 12 months after DES implantation before proceeding with elective procedures.

Management of DAPT in relation to the surgical bleeding risk

In patients with coronary stents, in addition to the risk of MACE, the clinician needs to take into account the bleeding risk incurred in the perioperative period. Patients undergoing low bleeding risk procedures (endoscopy, dental extraction, plastics procedures, minor orthopaedic, vitreoretinal, and minor general surgeries) can proceed without DAPT discontinuation.

The complication rate varies in intermediate bleeding risk procedures in patients on DAPT with ASA and clopidogrel. Severe complications are eight times more likely after Mohs procedures in patients on DAPT than in control subjects taking ASA monotherapy. A study of 647 patients undergoing vascular surgery and receiving DAPT with clopidogrel and ASA up to the day of surgery concluded that maintenance of DAPT is not associated with increased bleeding complications or transfusion requirements. Prior data had reported increased hematomata associated with carotid endarterectomy. Another registry of 10 406 patients undergoing vascular procedures (carotid endarterectomy, lower extremity bypass, endovascular aneurysm repair, or open abdominal aortic aneurysm repair) found that bleeding, transfusion requirements, and reoperation rates for bleeding were similar among the four patient groups based on an antiplatelet regimen (ASA vs ASA plus clopidogrel vs clopidogrel vs no antiplatelet therapy). The average transfusion requirement was 500–700 ml in all groups.

Patients undergoing thoracic surgery do not seem to experience increased bleeding while on clopidogrel, but the incidence of perioperative MI is significantly higher among patients with stents discontinuing DAPT in the perioperative period. Retrospective data from patients undergoing major lung resection while on clopidogrel showed no differences in transfusion requirements, reoperations for bleeding, or MACE compared with patients who stopped clopidogrel. Similarly, more recent data from a study of 165 patients undergoing 182 general thoracic surgery procedures while on DAPT showed that these patients exhibited an increased rate of transfusion with no increase in mortality compared with patients off DAPT.

Patients on DAPT undergoing orthopaedic surgery (especially patients undergoing hip and knee replacement) have an increase in bleeding complications and increased risk of transfusion in the operating theatre or in the first 24 h after operation. Another study concluded that stopping clopidogrel 5 days before operation might decrease the risk of complications, although mortality is not influenced. These findings are in contrast with data from patients undergoing hip fracture surgeries, who demonstrate no increase in transfusion requirements when taking clopidogrel.
Urological surgery, with the exception of transurethral resection of prostate, can be safely performed while on DAPT.\textsuperscript{149–151} However, customary practice among urologists is to stop DAPT before cystoprostatectomy or nephrectomy due to concerns of increased bleeding.\textsuperscript{152}

In patients undergoing \textit{intra-abdominal} surgery, data suggest that these operations can be safely performed while continuing DAPT.\textsuperscript{153}

A comprehensive meta-analysis including 99 randomized, double-blind, placebo-controlled trials, prospective observational studies, review articles, and clinical registry data reported a 10% risk of vascular events after premature withdrawal of DAPT due to the life-threatening risk of ST. The study concluded that clopidogrel cannot be stopped in those patients with a recently implanted DES.\textsuperscript{154}

As noted above, all available evidence to date addresses patients undergoing non-cardiac procedures while on DAPT with ASA and clopidogrel. Perioperative data for patients on prasugrel and ticagrelor are lacking, probably due to their recent availability on the market.

On the other hand, for patients on DAPT undergoing \textit{cardiac} surgery, available evidence suggests that increased bleeding occurs if the ADP inhibitor is continued before operation. Therefore, current guidelines recommend stopping the ADP receptor inhibitor 5 days prior for clopidogrel and ticagrelor and 7 days prior for prasugrel.\textsuperscript{55 56 155} Similar to ASA, patients at \textit{high risk of bleeding} should have their DAPT therapy stopped before operation, if an appropriate amount of time has passed after stent insertion.\textsuperscript{110}

Management of DAPT in relation to the urgency of the surgical procedure

While it is advisable to wait at least 4–6 weeks after BMS placement and 6–12 months after DES placement, the urgency of certain procedures sometimes takes priority. In emergent procedures, there is not sufficient time to discontinue DAPT. Platelet transfusion can be given to counteract the effect of the antiplatelet agents. Despite the theoretical efficacy of such a measure, newer evidence from the trauma literature suggests that platelet transfusions reverse the effect of ASA on thrombocytes but not that of clopidogrel.\textsuperscript{156} This can be explained by the plasma half-life of each drug. ASA has a short half-life and therefore has a low likelihood of affecting the transfused platelets even if the drug was ingested within an hour of the surgical procedure. On the other hand, clopidogrel has a half-life of 7–9 h so if the transfusion is administered within that time frame, the new platelets will be affected by the available circulating drug. Moreover, platelet transfusions can put the patient at risk for ST. Therefore, the clinician should perform a risk–benefit analysis before making this decision.

In patients at low risk of cardiovascular complications undergoing surgeries of low or intermediate bleeding risk (urgent or elective), ASA should be continued while discontinuing the ADP inhibitor. If the same patient population is undergoing surgeries of high bleeding risk, then both the ADP inhibitor and ASA should be discontinued (Fig. 2). In patients at high risk of cardiovascular complications undergoing elective surgeries, the procedure should be postponed until the required period of DAPT has been fulfilled.

In urgent cases that cannot be postponed until the recommended period of DAPT has been completed, different therapeutic strategies have been proposed. If the bleeding risk is low, the surgical procedure can be performed while the patient continues DAPT. If the bleeding risk is intermediate, the ADP inhibitor should be discontinued before operation and ASA continued. When patients at high risk of cardiovascular events undergo procedures with a high risk of bleeding, DAPT needs to be discontinued. Consideration should be given to replacing DAPT with a short-acting agent whose effect on platelet function rapidly dissipates upon discontinuation, known as bridging therapy (Fig. 2).

Bridging therapy

Bridging therapy with unfractionated or low molecular weight heparin, similar to what is recommended for patients on warfarin, has been considered. However, heparin has relatively minor effects on platelets, and thus does not prevent a thrombotic event.\textsuperscript{157} Therefore, despite being recommended as an alternative therapy by several societies, it does not seem to be an appropriate choice.\textsuperscript{157}

Alternatively, bridging with short-acting GP IIb/IIIa inhibitors (tirofiban and eptifibatide) can be considered. While available data are scarce and the ACC/AHA guidelines do not mention bridging with GP IIb/IIIa inhibitors, the Society of Thoracic Surgeons, ESC and Australia/New Zealand guidelines recommend such an approach in patients at high risk of cardiovascular events.\textsuperscript{56 110 158 159} Several case reports and series have described bridging therapy, and reported no increase in thrombotic or haemorrhagic events.\textsuperscript{160–163} Other studies on patients undergoing non-cardiac surgery showed adequate protection against ST (at 30 days) with no cases of death or MI and no increase in reoperation for bleeding.\textsuperscript{164 165} However, a study of 67 patients who underwent non-cardiac or cardiac surgery after DES implantation with preoperative bridging with a GP IIb/IIIa inhibitor showed that ST can still occur.\textsuperscript{166}

The bridging protocols require discontinuing clopidogrel 5 days before the surgical procedure. Patients are started on an i.v. infusion of either tirofiban (0.4 \(\mu\)g kg\(^{-1}\) bolus followed by a maintenance infusion of 0.1 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) or eptifibatide (2 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)). Tirofiban is stopped 3–6 h and eptifibatide 4–12 h before the planned procedure.\textsuperscript{167} For patients undergoing cardiac surgery, a small study of 19 patients on bridging therapy with GP IIb/IIIa antagonists reported increased incidence of bleeding during revascularization surgery but no increase in ST.\textsuperscript{168}

Another drug that appears useful as a bridging agent is cangrelor, studied in a prospective, randomized, double-blind, placebo-controlled, multicentre (BRIDGE) trial. While the trial was not powered to assess for MACE, it showed promising results for patients undergoing CABG. These patients did not demonstrate an increased rate of major bleeding before
CABG surgery, but exhibited more minor postoperative bleeding episodes. Cangrelor is not yet FDA approved.169

**Glycoprotein IIb/IIIa inhibitors**

Data for perioperative management of GP IIb/IIIa inhibitors in non-cardiac surgery are derived mostly from small case series. In patients undergoing emergency or urgent CABG after treatment with a GP IIb/IIIa inhibitor, abciximab was associated with increased risk of haemorrhage and requirement of platelet transfusions if surgery is performed within 12 h of infusion discontinuation. Eptifibatide was associated with a similar risk as placebo, even when surgery was performed within 2 h of drug cessation. Limited data available for tirofiban show that bleeding is not increased compared with ASA or heparin.170 Cessation of eptifibatide 4 h before surgery results in less bleeding and fewer transfusion requirements compared with stopping the infusion 2 h before surgery.171

Intraoperatively, antiplatelet agents represent a particular challenge for the anaesthesiologist when regional anaesthetic techniques are considered (see Banzon and colleagues, this issue). According to the 2010 American Society of Regional Anesthesia practice advisory on Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy and the 2010 Guidelines of the European Society of Anaesthesiology, neuraxial and peripheral blocks can be safely performed while on ASA therapy. In contrast, due to concerns of spinal/epidural haematoma for neuraxial blocks or bleeding in non-compressible spaces for certain peripheral nerve blocks, such anaesthetic procedures should be avoided in patients on ADP inhibitors.172 In order to diminish this risk, the European Society of Anaesthesiology guidelines recommend a drug-free period of 7–10 days for clopidogrel and prasugrel and at least a 5 day cessation of ticagrelor.173 Several case reports comment on the safe placement of epidural catheters or spinal nerve stimulators in patients at high risk of cardiovascular events. In these patients bridging with eptifibatide replaced the ADP inhibitor and normal platelet function was documented 8 h after GP IIb/IIIa inhibitor infusion discontinuation and before the regional technique.174 175 For patients at high risk of cardiovascular events who have stopped antiplatelet agents for the recommended period of time before operation, single-shot techniques might be preferable as opposed to catheter-based modalities.176

**Conclusions**

Antiplatelet agents represent a quintessential therapy in preventing and treating cardiovascular events. Currently, with an increasing patient population requiring antiplatelet therapy in conjunction with an increase in the number of interventional procedures, the anaesthesia community is frequently faced with the need to manage various antiplatelet regimens perioperatively.

In general, antiplatelet agents used for primary prevention or for AF can be safely discontinued before surgery. On the other hand, recent data suggest that, with few exceptions, proceeding with surgery on DAPT is a relatively safe alternative. In situations of life-threatening bleeding, anaesthetists can consider platelet transfusions. The more challenging cases are those patients at high risk of cardiovascular events who are undergoing procedures with a high risk of bleeding, and thus are required to completely stop their antiplatelet medications. In these situations, the perioperative team can consider using bridging therapies. Each patient has to be stratified according to individual thrombotic and surgical bleeding risk. The perioperative team should all participate in the decision-making process by performing a thorough risk–benefit analysis of stopping or continuing each type of antiplatelet agent.

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