Antiplatelet Agents in the Perioperative Period

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Objective: To determine the use of the 3 major classes of antiplatelet drugs (aspirin, thienopyridines, and glycoprotein IIb/IIIa inhibitors), their management in the perioperative period, and the risks associated with premature withdrawal.

Data Sources: We reviewed the PubMed, EMBASE, and Cochrane databases using the terms antiplatelet agents in the perioperative period, antiplatelet agents and management of bleeding, drug-eluting stents and stent thrombosis, substitutes for antiplatelet agents, and premature withdrawal of antiplatelet agents.

Study Selection: Randomized, double-blind, placebo-controlled trials; prospective observational studies; review articles; clinical registry data; and guidelines of professional bodies pertaining to antiplatelet agents were included.

Data Extraction and Synthesis: Two researchers independently read the selected abstracts and selected the studies that matched the inclusion criteria. Any discordance between the 2 researchers was resolved by discussion so that 99 articles were finally included.

Conclusions: Aspirin use should not be stopped in the perioperative period unless the risk of bleeding exceeds the thrombotic risk from withholding the drug. With the exception of recent drug-eluting stent implantation, clopidogrel bisulfate use should be stopped at least 5 days prior to most elective surgery. Use of glycoprotein IIb/IIIa inhibitors must be discontinued preoperatively for more than 12 hours to allow normal hemostasis. Premature withdrawal of antiplatelet agents is associated with a 10% risk of all vascular events. Following drug-eluting stent implantation, withdrawal is associated with stent thrombosis and potentially fatal consequences. No definitive guidelines exist to manage patients who are actively bleeding while taking these drugs.

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PLATELETS PLAY A CENTRAL role in atherosclerotic plaque disruption and subsequent thrombus formation. Understanding the processes of platelet activation and aggregation has led to the widespread use of antiplatelet therapies in cardiovascular disease.

Aspirin is the most widely prescribed antiplatelet drug. More powerful new antiplatelet agents are superior in patients with recent myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease. Coadministration of 2 antiplatelet agents, such as aspirin and clopidogrel bisulfate, enhances platelet inhibition, as each binds to a different receptor.

See Invited Critique at end of article

Advances in interventional cardiology have resulted in a growing population of patients taking antiplatelet agents following percutaneous coronary intervention (PCI). New technologies, such as drug-eluting stents (DESs) and drug-coated balloon angioplasty, have increased patency rates at 1 year and reduced the levels of neointimal hyperplasia and stent restenosis compared with balloon angioplasty alone and bare-metal stenting (BMS). Drug-eluting stents are currently used in the majority of patients undergoing PCI. Glycoprotein (Gp) IIb/IIIa inhibitors, such as ReoPro (Eli Lilly and Company, Indianapolis, Indiana, and Centocor, Horsham, Pennsylvania) (abciximab), are used as an adjunct to PCI for the prevention of cardiac ischemic complications.

Most general surgeons are familiar with warfarin as an anticoagulant and perioperative management in terms of elective heparin bridging or reversal. However, many are unfamiliar with newer antiplatelet agents, the guidelines for antiplatelet therapy following PCI and acute coronary syndrome (ACS), and the serious consequences associated with premature withdrawal of these agents. A recent audit among vascular surgeons in the United Kingdom showed wide variation in practice with no consensus with regard to thienopyridine use and major vascular surgical procedures. Similarly, Joseph et al showed a lack of consensus with regard to stopping clopidogrel use in the perioperative period among orthopedic surgeons.
The decision to stop antiplatelet medication administration in the perioperative period may be simple if the thrombotic risk is overwhelming and the bleeding risk negligible. The situation is however frequently more complex and a risk-benefit assessment must be undertaken. The aims of this article were to review the pharmacokinetics of the 3 major classes of antiplatelet drugs (aspirin, thienopyridines, and Gp IIb/IIIa inhibitors), the current indications for their use, the management of bleeding while taking these antiplatelet agents, and the consequences of premature withdrawal of antiplatelet therapy.

### METHODS

PubMed, EMBASE, and the Cochrane medical databases were searched using the broad terms antiplatelet agents in the perioperative period, antiplatelet agents and management of bleeding, drug-eluting stents and stent thrombosis, substitutes for antiplatelet agents, and premature withdrawal of antiplatelet agents. Other search strategies included using key words such as “aspirin or clopidogrel or abciximab or Gp IIb/IIIa inhibitors” and “bleeding, guidelines, reversal,” and “drug-eluting stents, drug-coated balloon angioplasty.” In addition, the references of articles retrieved were searched for relevant articles not already identified. Studies were included if they were randomized, double-blind, placebo-controlled trials; prospective observational studies; review articles; clinical registry data; or if they represented guidelines of professional bodies pertaining to antiplatelet agents. Case reports and data derived from abstracts were excluded and the search was limited from 1978 onward when coronary angioplasty and stenting were introduced.

From the initial search results, 121 studies were identified from the title as being of relevance to the study. Two researchers (J.M.O.R. and R.J.M.) independently read the abstracts and selected studies that matched the inclusion criteria. Any discordance between the 2 researchers was resolved by discussion. A total of 99 articles were finally included.

### RESULTS

The current uses of oral antiplatelet agents are presented in Table 1, derived from the recommendations of the American College of Chest Physicians.17

#### ASPIRIN

Aspirin or acetylsalicylic acid is the most widely prescribed antiplatelet drug since the first randomized trial showed a link between aspirin and reduced risk of myocardial infarction.19 Aspirin works by irreversibly acetylating serine 329 of cyclooxygenase (COX) 1, resulting in inhibition of thromboxane A2 release from platelets and prostacyclin from endothelial cells.20 Thromboxane A2 stimulates platelet activation, whereas prostacyclin inhibits platelet activation. Because platelets are unable to generate significant amounts of new COX, the effects of aspirin-induced COX-1 inhibition last for the lifetime of the platelet. In contrast, endothelial cells recover normal function shortly after exposure to aspirin; therefore, aspirin is an antithrombotic agent.

The benefits of aspirin were first recognized in the ISIS-2 trial.21 In high-risk patients, aspirin reduced the risk of a serious thrombotic event by approximately 25%. However, 10% to 20% of patients treated with aspirin following an arterial thrombotic event subsequently have a further arterial thrombotic event.22,23 Aspirin alone is not sufficient to prevent stent thrombosis in the initial phase poststenting. This prompted development of adjunctive antithrombotic therapy.

#### THIENOPYRIDINES

Thienopyridines act by covalently binding to a cysteine residue of the P2Y12 platelet receptor (Figure 1). Con-
sequently, platelets are affected for the remainder of their life span (7-10 days).14 Ticlopidine hydrochloride has been superseded by clopidogrel because clopidogrel has a faster onset of action and fewer adverse effects.25,26 The role of clopidogrel in relation to PCI has now been defined.7,27-32 The CURE33 study was the first major trial that demonstrated the benefit of adding clopidogrel to aspirin (up to 10%) have higher rates of cardiovascular events. It is these patients who benefit most from combination therapy. Clopidogrel use must be continued postinsertion of BMS for at least 4 weeks. Among patients presenting with an ACS, patients receiving thrombolytic therapy for acute myocardial infarction, and patients undergoing PCI.14,36 Aspirin and heparin have always been administered in addition to GP IIb/IIIa inhibitors in these settings. There are 2 categories of GP IIb/IIIa inhibitors. The first (eg, tirofiban hydrochloride and epifibatide) are competitive inhibitors of the GP IIb/IIIa receptor, with a short half-life of up to 2 hours. The second group (eg, abciximab) are monoclonal antibodies directed against the GP IIb/IIIa receptor. Abciximab, a chimeric (human/murine) IgG Fab fragment, produces almost irreversible inhibition. It takes more than 12 hours after stopping an infusion for the relative occupancy of the GP IIb/IIIa receptors to decrease by 50%.37 Five major randomized trials38-42 have demonstrated the efficacy of GP IIb/IIIa inhibitors in the setting of PCI and ACS and they are increasingly used as an adjunct for the prevention of cardiac ischemic complications. Table 2 summarizes the characteristics of the main antiplatelet agents.

**GP IIb/IIIa INHIBITORS**

The GP IIb/IIIa inhibitors form the third major class of antiplatelet agents. The GP IIb/IIIa receptors are present on resting platelets and undergo a conformational change on activation. They link to fibrinogen to form bridges between activated platelets (Figure 1), leading to the formation of platelet thrombi. Direct inhibitors of the GP IIb/IIIa receptor have been tested in patients admitted with an ACS, patients receiving thrombolytic therapy for acute myocardial infarction, and patients undergoing PCI.14,36 Aspirin and heparin have always been administered in addition to GP IIb/IIIa inhibitors in these settings. There are 2 categories of GP IIb/IIIa inhibitors. The first (eg, tirofiban hydrochloride and epifibatide) are competitive inhibitors of the GP IIb/IIIa receptor, with a short half-life of up to 2 hours. The second group (eg, abciximab) are monoclonal antibodies directed against the GP IIb/IIIa receptor. Abciximab, a chimeric (human/murine) IgG Fab fragment, produces almost irreversible inhibition. It takes more than 12 hours after stopping an infusion for the relative occupancy of the GP IIb/IIIa receptors to decrease by 50%.37 Five major randomized trials38-42 have demonstrated the efficacy of GP IIb/IIIa inhibitors in the setting of PCI and ACS and they are increasingly used as an adjunct for the prevention of cardiac ischemic complications. Table 2 summarizes the characteristics of the main antiplatelet agents.

**DUAL ANTIPLATELET/ TRIPLE ANTIPLATELET THERAPY**

The current European and American guidelines33,44 recommend dual antiplatelet therapy (aspirin plus clopidogrel) for all patients who present with non-ST-segment elevation ACS. High-risk patients (with recurrent ischemia, ST-segment depression, elevated troponin levels, and diabetes mellitus) may also in addition receive a GP IIb/IIIa receptor inhibitor.

**BLEEDING AND ANTIPLATELET THERAPIES**

Antiplatelet drugs predispose to bleeding.16 Coadministration of different antiplatelet therapies with different modes of action increases the risk of bleeding. The most common site of spontaneous bleeding in patients treated with clopidogrel or aspirin is the gastrointestinal tract. Bleeding is also common at arterial puncture sites in patients un-
whereas intracerebral bleeding is uncommon but is associated with its propensity to cause bleeding. Retroperitoneal bleeding is not uncommon with clopidogrel in reference to its propensity to cause bleeding.51 Retroperoxidogrel has been referred to as the “surgeon’s headache” etate,65,66 and recombinant factor VIIa.67 It is unclear whether these agents should be given prophylactically during urgent surgery or only be administered when bleeding arises. In a randomized trial of patients undergoing urgent coronary artery bypass graft, Akowuah et al84 found that continuing aspirin and clopidogrel therapy with intraprooperative aprotinin administration was associated with reduced postoperative blood loss and transfusion requirements compared with stopping the antiplatelet treatment 5 days preoperatively but without giving intraprooperative aprotinin.

**PREMATURE WITHDRAWAL OF ANTIPLATELET AGENTS**

Oral antiplatelet agent compliance and premature interruption are of great concern to cardiologists; however, there is little evidence to guide management in the perioperative period. Premature or inappropriate discontinuation of antiplatelet therapy can have serious and sometimes fatal outcomes.68 Collet et al86 found that oral antiplatelet withdrawal was an independent risk factor for death among 1358 consecutive patients admitted with an ACS. A recent meta-analysis by Burger et al70 found that single oral antiplatelet interruption may account for 10% of all vascular events whatever the arterial bed.

Interruption of oral antiplatelet therapy within the first month following DES insertion has been reported to be associated with death rates of 25% to 50%. 71 In patients who have had a DES inserted, 8 studies have reported premature interruption of oral antiplatelet therapy as one of the highest risk factors for delayed stent thrombosis.72-79 Daemen et al86 have recently suggested that late stent thrombosis is also encountered, with no evidence of diminution up to 3 years postinsertion of a DES.

Withdrawal of antiplatelet agents may induce a rebound or prothrombotic effect.70,81 In perioperative patients, this added risk as well as the underlying risk of thromboembolism associated with surgery could be responsible for the high rates of thrombosis seen in patients who stop taking antiplatelet agents before major surgical procedures, particularly after PCI. Recent American guidelines identify the risk of stent thrombosis from premature antiplatelet drug discontinuation in patients receiving DES at up to 29% with resultant risk of acute myocardial infarction or death.82

**SUBSTITUTES TO ORAL ANTIPLATELET AGENTS**

There are no clinically useful alternatives to oral antiplatelet agents whereby a drug with a shorter half-life could be substituted prior to surgery.83,84 There is also no literature to support the use of therapeutic heparin as an alternative.71 Therapeutic doses of heparin given preoperatively in patients undergoing cardiac surgery have been found to significantly increase the rate of bleeding and need for reexploration.85

**ASPIRIN IN THE PERIOPERATIVE PERIOD**

Most surgeons advise patients to stop taking aspirin at least 7 to 10 days preoperatively. The French Society of Anesthesiology and Intensive Care in 2001 questioned this policy because of a reported increased incidence of myocardial infarction86 and recommended that aspirin use should not be stopped in the perioperative period unless the risk of hemorrhagic complications related to a specific procedure appeared to be greater than the increase in thrombotic/cardiovascular risk from withhold-
ing the drug. The same group also estimated the bleeding risks associated with perioperative antiplatelet therapy with regard to specific surgical procedures based on the available evidence87 (Table 3). Belisle and Hardy,88 in a review of 50 articles that included more than 10 000 patients undergoing cardiac surgery from 70 centers, found that postoperative blood loss increased by only 300 mL on average for patients taking aspirin, with no associated increase in transfusion requirements.

Evaluation of the bleeding risk is sometimes difficult depending on the type of surgery. There are confounding factors (eg, being elderly or obese, having heart failure or renal failure) that are associated with both bleeding factors (eg, being elderly or obese, having heart failure or renal failure). Depending on the type of surgery, there are confounding factors (eg, being elderly or obese, having heart failure or renal failure) that are associated with both bleeding factors. The timing of surgery is often dictated by the clinical circumstances in which clopidogrel has been prescribed. Clopidogrel therapy is advised for at least 4 weeks after placement of a BMS. If early surgery is undertaken with premature discontinuation of clopidogrel, the incidence of thrombotic complications and/or hemorrhagic events is extremely high.89,90 As a result, elective surgery should be postponed for a period of 1 to 3 months following placement of a BMS.89

A recent Science Advisory from the American Heart Association, American College of Cardiology, and the American College of Surgeons82 emphasizes the importance of 12 months of dual antiplatelet therapy postinsertion of DES because of the risk of late stent stenosis due to delayed endothelialization. Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be postponed until patients have completed an appropriate course of thienopyridine therapy. Howard-Alpe et al92 and Brilakis et al93 have highlighted the increased risk of stent thrombosis after noncardiac surgery post-DES insertion. This risk is increased if surgery is performed early after stenting and particularly if dual antiplatelet therapy is discontinued.

Collet and Montalescot,71 based on guidelines from the French Society of Anesthesiology and Intensive Care, have suggested an algorithm for patients receiving dual antiplatelet therapy after insertion of a DES who require surgery. This involves the surgeon and anesthesiologist assessing the bleeding risk, the cardiologist evaluating the risk of stent thrombosis, and all 3 devising an individual management plan. For example, if there is a major risk of both stent thrombosis and bleeding, surgery should be postponed for at least 6 to 12 months post-DES. If this is not possible, aspirin use should be continued and clopidogrel therapy stopped 5 days before surgery. If the bleeding risk is small and there is a major risk of stent thrombosis, then antiplatelet agents should be continued in the perioperative period.

Full recovery of platelet function requires complete replacement of exposed platelets. However, hemostatic competence does not require 100% of all circulating platelets to be functioning normally. The CURE trial33 found that clopidogrel therapy could be discontinued at least 5 days prior to coronary artery bypass graft with no increased bleeding complications. Hence, for the majority of cases, stopping clopidogrel therapy at least 5 days preoperatively will allow adequate hemostatic function prior to most surgical procedures.88

Table 3. Bleeding Risk Associated With Different Surgical Procedures With Regard to Antiplatelet Therapies87,a

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Drug Therapy</th>
<th>Situation</th>
<th>Hemorrhagic Risk</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac surgery</td>
<td>Aspirin and NSAIDS</td>
<td>Preoperative</td>
<td>Modest increase in risk with few changes in transfusion rates</td>
<td>2-4</td>
</tr>
<tr>
<td></td>
<td>Thienopyridines</td>
<td>Preoperative</td>
<td>Possible increase in risk and exposure to transfusion</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Ticlopidine hydrochloride</td>
<td>Preoperative or postoperative</td>
<td>No increased risk of cervical hematoma or intracranial bleeding</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal and general surgery</td>
<td>Aspirin and other NSAIDS if patient is &lt; 75 y</td>
<td>Preoperative by &lt; 5 d</td>
<td>Contradictory findings</td>
<td>2-3</td>
</tr>
<tr>
<td>General surgery</td>
<td>Ticlopidine</td>
<td>Preoperative</td>
<td>Increased risk and transfusion requirements</td>
<td>2</td>
</tr>
<tr>
<td>Intracranial surgery</td>
<td>Ticlopidine</td>
<td>Preoperative</td>
<td>Increased risk</td>
<td>3-4</td>
</tr>
</tbody>
</table>

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

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inhibitor abciximab compared with placebo. However, the numbers of patients were small and those undergoing coronary artery bypass graft were operated on more than 12 hours after the administration of abciximab. Gammie et al showed that if abciximab was given within 12 hours of surgery, the rate of transfusion and hemorrhagic risk increased. With regard to the other Gp IIb/IIIa inhibitors (e.g., epifibatide and tirofiban), their half-lives are shorter than abciximab; hence, stopping the infusion of the drug just before surgery will allow the drug effect to disappear when the surgery is finished. Until further studies are performed, the recommendations for patients treated with Gp IIb/IIIa inhibitors undergoing cardiac surgery should also apply to patients undergoing noncardiac surgery.

Surgeons are increasingly confronted by patients prescribed antiplatelet drugs. There is a delicate balance between ischemic risk from stopping use of these drugs and bleeding risk from continuing use. No randomized data exist in noncardiac surgery patients. The ischemic risk needs to be evaluated by a cardiologist and consensus reached as to the appropriate timing of surgery and when or if the antiplatelet medication should be stopped. There is little evidence-based guidance on restarting therapy; however, it would appear prudent to limit the interruption of antiplatelet therapy to as short a time as possible.

Communication with the cardiologist in the perioperative period is important in evaluating the risk associated with stopping the antiplatelet drug therapy but also in influencing the type of stent inserted into a patient for a particular surgical procedure. Insertion of a BMS that requires 4 weeks’ minimum antiplatelet treatment may stabilize the patient from a cardiac viewpoint and allow surgery to proceed within a reasonable time frame.

Premature withdrawal of antiplatelet medications must be understood as being a significant cause of morbidity and mortality. A perceived risk of bleeding events often leads to antiplatelet medications being stopped, but in many cases, the interruption is unjustified. Management of a patient who is bleeding while taking antiplatelet agents, such as clopidogrel, depends on the site and extent of bleeding. Multidisciplinary consultation should be considered with regard to discontinuation of antiplatelet agents, platelet transfusion, and the use of other agents, such as desmopressin acetate, recombinant factor VIIa, and aprotinin.

Elective surgery after coronary stenting should be deferred until use of antiplatelet agents can be safely stopped. The literature supports the view that emergency surgery soon after coronary stenting is associated with adverse outcomes with increased rates of stent thrombosis. If emergency surgery is necessary, the actions of antiplatelet agents, such as clopidogrel, can be reversed with platelet transfusions. Close liaison between surgery and cardiology is essential to minimize both the adverse cardiac risk and surgical risk in this group of patients.

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The recent surge in the development and use of antiplatelet agents has underscored their central role in the management of vascular disease. As the number of vascular interventional procedures continues to increase, it is anticipated that more research will be done to further refine antiplatelet agents and discover new medications as well as find new uses for them. The information in this article is especially useful to surgeons as they are most likely to encounter a patient who is taking antiplatelet agents and is in need of an urgent or emergent surgical procedure. But, as practice boundaries continue to blur, surgeons as well as our colleagues in radiology, neurology, neurosurgery, orthopedics, emergency medicine, and other specialties will continue to prescribe antiplatelet medications and/or take care of patients whose medication regimen includes them. To that end, O’Riordan and colleagues have opened a door for surgeons to lead the way on enhancing patient safety relative to the use of these medications. To start, this article allows essential information about these medications to be at the fingertips of those specialists using them. That information provides a common language so that care can be delivered in a safe and efficient manner. Incorporating such essential information into a protocol is a key step toward placing patient safety at the forefront. Best practices and practice guidelines are already an integral part of medical and surgical practice and trends are showing improved care with this approach. We can no longer deliver the best care to patients by operating in silos. A central repository of information can be the beginning of providing efficient and safe patient care in a multidisciplinary environment. This should not be an opportunity missed to improve patient care and safety.

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