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ADVANCES IN SURGERY

Aspirin, Clopidogrel, and the Surgeon

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Keywords

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Key points

- Increasing numbers of patients are being placed on antiplatelet regimens, either aspirin monotherapy or dual antiplatelet therapy with aspirin and clopidogrel, for the primary and secondary prevention of cardiovascular and cerebrovascular events.
- Discontinuation of preoperative antiplatelet therapy in the patient presenting for surgery can lead to thrombotic conditions, which may result in perioperative acute coronary syndromes and stent thrombosis.
- Continuation of preoperative antiplatelet therapy into the perioperative period may result in increased major and minor bleeding episodes, depending on the complexity of the surgery.
- The risks and benefits for continuing or discontinuing preoperative antiplatelet therapy should be assessed prior to surgery. The timing of preoperative cessation, the timing of surgery, and the timing of postoperative reinstitution of therapy should be based on current guideline recommendations, along with individualized patient management.
- At a minimum, continuation of aspirin therapy should be considered in all patients.

INTRODUCTION

The use of antiplatelet agents for both the primary and secondary prevention of cerebrovascular and cardiovascular disease is a common practice that has established benefits. Long-term therapy with antiplatelet drugs has decreased the incidence of cardiovascular events, including myocardial infarction and stroke [1,2]. Furthermore, the use of dual antiplatelet therapy leads to additional benefits in patients with acute coronary syndromes (ACS) [3]. In those patients who undergo

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coronary stenting, it is crucial to maintain the appropriate antiplatelet therapy for prevention of stent thrombosis and further cardiovascular events [4–6].

As the number of patients on antiplatelet therapy continues to increase, physicians are faced with the dilemma of a growing number of patients presenting for surgery while simultaneously taking these medications. Despite the benefits noted previously, these drugs do carry a higher risk of minor and major bleeding episodes [1,3]. In the perioperative period, the surgeon must balance the benefits of continuing antiplatelet therapy with the risks associated with brief cessation of therapy [7]. The decision should be made based on initial indications for an antiplatelet regimen, the patient's preoperative physical status, and the complexity of the planned surgery. Consultation with the patient's primary physicians, as well as other perioperative physicians, is warranted.

This article aims to summarize the commonly used antiplatelet medications (aspirin and thienopyridines) and the consequences of cessation of therapy. The cardiovascular risk associated with the perioperative period, which adds to the risk of withdrawing antiplatelet therapy, is discussed. Considerations for continuing or discontinuing antiplatelet agents for a proposed surgery are evaluated for both noncardiac and cardiac surgery, as well as for patients with coronary stents. Current practice guidelines will be reviewed, with the goal of aiding the surgeon in the perioperative management of these drugs. Importantly, there are currently new guidelines on perioperative cardiovascular evaluation and management for noncardiac surgery being written; however, these guidelines have not yet been published. Additionally, a large-scale randomized clinical trial, POISE-II (PeriOperative ISchemic Evaluation), is currently being undertaken, which includes an aspirin arm (ClinicalTrials.gov: NCT01082874). Results of this trial may inform the discussion regarding the value of aspirin therapy.

ASPIRIN AND THIENOPYRIDINES

Because of its risk–benefit ratio and low cost, aspirin (acetylsalicylic acid, ASA) remains the most commonly used antiplatelet agent worldwide. Aspirin irreversibly inhibits cyclooxygenase-1 (COX-1). This leads to decreased production of thromboxane-A2, which is necessary for platelet aggregation [8]. Oral aspirin is rapidly absorbed from the stomach and upper intestine, and it begins to have an effect on platelet inhibition in as little as 60 minutes [8,9]. Despite having a plasma half-life of only 15 to 20 minutes, the platelet inhibitory effect of aspirin remains for the lifespan of the platelet (7–10 days) because of the irreversible effect on COX-1 [9].

Thienopyridines are antiplatelet agents that inhibit the $P2Y_{12}$ receptor on the platelet membrane, preventing adenosine diphosphate from binding to the receptor to augment platelet aggregation [10]. Ticlopidine, an early generation thienopyridine, has now been largely replaced in clinical practice by clopidogrel, which is not associated with the blood dyscrasias seen with ticlopidine [8]. Clopidogrel is an oral agent that is rapidly absorbed and metabolized by cytochrome P450 in the liver to an active form. Because it begins as a prodrug, a loading dose of clopidogrel is often used to achieve therapeutic levels [11]. After

loading, platelet inhibition is detected in as little as 2 hours after ingestion. Because of the irreversible nature of $P2Y_{12}$ antagonism, the effect of clopidogrel is also for the lifespan of the platelet, and therefore similar to aspirin, platelet function returns to normal after approximately 7 days [9].

A third-generation thienopyridine that has become approved clinically is prasugrel. Similar to clopidogrel, it is an indirect and irreversible $P2Y_{12}$ inhibitor. However, it offers the advantage of rapid onset and greater reliability, because it is less dependent on the cytochrome P450 system, whereas many clopidogrel patients experience antiplatelet resistance because of this pathway for metabolism [8]. Several other agents capable of platelet inhibition via the $P2Y_{12}$ receptor are also being investigated. These novel nonthienopyridine drugs include cangrelor (an intravenous direct $P2Y_{12}$ inhibitor), ticagrelor (an oral direct $P2Y_{12}$ inhibitor), and elinogrel (an oral and intravenous direct $P2Y_{12}$ inhibitor) [11,12]. These will not be discussed further here, but hopes are that they will enter clinical practice soon because of their advantage of reversible binding. The GpIIb/IIIa antagonists also offer prevention of thrombosis, but they are primarily used as infusions in the inpatient setting immediately after percutaneous coronary intervention (PCI).

INDICATIONS FOR ANTIPLATELET THERAPY

Platelets play an essential role in thrombosis and hemostasis. They serve as a first line of defense to vascular injury by forming vascular plugs via adhesion and aggregation [10]. Therefore, when an unstable atherosclerotic plaque ruptures, the development of a platelet clot at the injured site leads to acute arterial thrombotic events. The resulting cardiovascular outcomes such as myocardial infarction and stroke have led to the emphasis on platelet blockade to prevent these occlusive events. Aspirin and clopidogrel are the most commonly encountered antiplatelet agents currently in clinical practice. They are prescribed for either primary prevention (patients with certain risk factors but no cardiovascular event) or secondary prevention (patients who have experienced a cardiovascular event). Primary prevention is often recommended based on age, gender, and risk factors such as diabetes, hypertension, hyperlipidemia, and active smoking status. Net benefit over potential bleeding risk must exist for antiplatelet use in this setting [13]. However, the overall value of aspirin in primary prevention has been questioned despite task force recommendations [14].

The use of antiplatelet agents in secondary prevention is more established. They are recommended following myocardial infarction, coronary revascularization, stroke, and transient ischemic attacks, as well as after a diagnosis of ACS or peripheral arterial disease [15]. Aspirin in this particular group of patients has been shown to decrease the risk of cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) by 21% and the risk of all-cause mortality by 13% [16]. An earlier meta-analysis also found similar results with a one-fourth reduction in the rate of cardiovascular events when taking any antiplatelet agent (not limited to aspirin) [2]. Directly comparing clopidogrel with aspirin reveals that clopidogrel can be more

effective in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death ($P = .043$) [17].

Dual antiplatelet therapy with aspirin and clopidogrel is recommended in patients presenting with all types of ACS with or without PCI. For those with established cardiovascular disease, combination treatment may be of benefit without any significant increase in major bleeding [18]. Also, it is recommended in the patient who has undergone PCI without an acute event because of the added benefit of preventing stent thrombosis [19]. The duration of treatment varies depending on the initial presentation and management. Dual antiplatelet therapy, however, is not routinely recommended in patients with a history of ischemic stroke or cardioembolic stroke because of a lack of clinical benefit [20].

CONSEQUENCES OF CESSATION OF ANTIPLATELET THERAPY

Withdrawing aspirin in the patient with cardiovascular disease can lead to a three-fold higher risk of major adverse cardiac events (odds ratio [OR] 3.14) as determined by a large meta-analysis of over 50,000 patients [21]. This risk is significantly higher if the patient has a coronary stent (OR 89.78). When aspirin is stopped in the perioperative period, additional risk is added due to the nature of hypercoagulability and increased platelet activity and aggregation from the stress of surgery. Acute withdrawal also leads to a rebound effect, resulting in pro-inflammatory conditions and an increase in acute phase reactants [22,23]. The prothrombotic activity occurs because of increased thromboxane A2 production and decreased fibrinolysis [24]. A prospective study found that many patients presenting with an ACS were actually patients who had recently stopped taking aspirin. Of these, the primary reason for interruption was for elective surgery [25]. A large meta-analysis looked specifically at low-dose aspirin for secondary prevention of cardiovascular disease and found that perioperative withdrawal precedes up to 10.2% of acute cardiovascular syndromes. Additionally, the average time interval between cessation and an acute coronary event was 8.5 days, 14.3 days for an acute cerebral event, and 25.8 days for an acute peripheral vascular event [26].

In patients with coronary stents, early discontinuation of antiplatelet therapy (clopidogrel) has been shown to be an independent predictor of late stent thrombosis (>30 days). This risk factor for thrombosis was observed in patients with drug-eluting stents (DES) and was associated with a 45% mortality rate [27]. When compared with bare metal stents (BMS), cessation of antiplatelet therapy in the DES patient also leads to a significantly increased rate of myocardial infarction and death (4.9% vs 1.3%) [28]. The thrombogenic nature of the exposed DES metal struts likely contributes to these findings [29]. Maintaining aspirin as lifelong therapy is also crucial in patients who have undergone stent placement. Stent thrombosis leading to myocardial infarction can occur more than 1 year after PCI with DES, and it occurs very quickly when aspirin is stopped [30]. However, aspirin alone is not sufficient for preventing late stent thrombosis. Dual antiplatelet therapy in DES patients should be emphasized, because

thrombosis can still occur in patients who have discontinued clopidogrel and were initially considered stable on aspirin monotherapy [31].

The hyperaggregability of platelets during the perioperative period described previously also provides additional risk in the PCI patient presenting for surgery. Discontinuation of antiplatelet therapy not only leads to increased risk of stent thrombosis, but it also leads to significantly increased mortality. Reported mortality rates vary depending on the antiplatelet agent that was stopped and the timing of surgery in relation to the stent placement. One extreme is the patient undergoing major noncardiac surgery within 3 weeks of stenting and also discontinuing clopidogrel; in this population, a mortality rate as high as 86% has been described [32].

CURRENT GUIDELINE RECOMMENDATIONS REGARDING ANTIPLATELET USE AND TIMING OF SURGERY

In patients presenting with unstable angina or non-ST elevation myocardial infarction, the current guidelines recommend that aspirin be started as soon as possible and continued indefinitely [33]. Also, in those patients in whom conservative management (noninvasive) is taken, adding a thienopyridine such as clopidogrel for up to 12 months is recommended (class 1; level B evidence).

If the patient undergoes PCI with balloon angioplasty alone (no stent), then dual antiplatelet therapy is also warranted. Aspirin is recommended as lifelong therapy, with clopidogrel for 2 to 4 weeks. For the patient who has undergone PCI with stent placement, dual antiplatelet therapy is again recommended, uninterrupted aspirin use with thienopyridine duration varying depending on the indication. For the patient who underwent PCI for ACS, thienopyridine therapy should be given for at least 12 months (class 1; level B evidence). Options include clopidogrel, prasugrel, or ticagrelor. For non-ACS patients receiving a stent, clopidogrel is recommended for at least 12 months if a DES was placed (if not at high risk for bleeding) and for a minimum of 1 month if a BMS was placed (up to 12 months if not at high risk for bleeding) (class 1; level B evidence) [19]. Premature termination of clopidogrel, specifically in the DES population, has been linked to significantly increased mortality, especially when terminated within 1 month of stent placement [34].

If a patient presents for noncardiac surgery following the initiation of antiplatelet therapy, it is important to consider the timing of any prior intervention (Table 1). After balloon angioplasty, it is reasonable to proceed with surgery 2 to 4 weeks later without thienopyridine treatment. Aspirin should be continued if the bleeding risk is acceptable. It is believed that this time frame allows for sufficient healing of the vessel after angioplasty [35]. In a patient with a BMS, surgery should be delayed until at least 4 to 6 weeks after stent placement. At this time, endotheliazation of the stent is likely to have occurred and therefore decreases the risk of restenosis [6]. Following this time period, it is reasonable to discontinue the thienopyridine agent, continue aspirin, and proceed with surgery. For the patient with a DES, surgery should be delayed whenever possible for at least 12 months, especially for elective procedures

Table 1
Recommendations for timing of noncardiac surgery after PCI

PCI	Time since PCI (d)	Recommendation
Balloon angioplasty	<14	Delay for elective or nonurgent surgery
	>14	Proceed to operating room with aspirin
BMS	<30–45	Delay for elective or nonurgent surgery
	>30–45	Proceed to operating room with aspirin
DES	<365	Delay for elective or nonurgent surgery
	>365	Proceed to operating room with aspirin

Adapted from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery). J Am Coll Cardiol 2007;50:1720; with permission.

where there exists a significant risk of perioperative or postoperative bleeding [6]. At that time, thienopyridine therapy can be discontinued while aspirin is maintained. It is important to keep in mind that these are recommendations based on expert consensus panels, and that perioperative morbidity cannot simply be prevented by following guidelines. Newer registry data suggest that patients continue to be at high risk even after 12 months of dual antiplatelet therapy, with a 3.5% incidence of major adverse cardiac events still occurring when noncardiac surgery has been performed between 12 and 24 months after initial stent placement [36]. However, that study also suggested that the period of highest risk was the first 6 months, with no difference after that time period. Therefore, the risk–benefit ratio of proceeding with surgery after DES placement must be considered at each individual time point.

Table 1 does not provide a solution for all patients who present for surgery while on antiplatelet therapy after PCI. Situations where surgery cannot be delayed require a decision to be made based on patient risk factors and operative bleeding risk. If surgery must be performed sooner than the recommended time frame, and the bleeding risk is acceptable, continuing antiplatelet therapy through the perioperative period is advised. When discontinuation is necessary due to increased bleeding risk, antiplatelet therapy should be resumed as soon as possible in the postoperative period, keeping in mind that clopidogrel's maximal antiplatelet effect will not occur as quickly without a loading dose. It is also important to recognize that bridging with an anticoagulant such as heparin, either preoperatively or postoperatively, does not provide an acceptable substitute for either aspirin or clopidogrel (since heparin lacks antiplatelet activity) [4].

Further guideline recommendations provide insight into specific procedures [37]. Minor cases involving dental, ophthalmologic, and dermatologic procedures in patients taking aspirin for secondary prevention should continue aspirin around the time of procedure rather than discontinuing aspirin for 7 days before the procedure [37]. Several studies have shown a very low risk for major bleeding, with 1 retrospective study also suggesting no increase in bleeding episodes in patients maintained on dual antiplatelet therapy for dental procedures [38].

Patients presenting for other types of noncardiac surgery have to be assessed based on their risk for cardiovascular events. Moderate- to high-risk patients such as those with coronary artery disease, heart failure, diabetes, renal insufficiency, or cerebrovascular disease, as well as those undergoing major vascular surgery, would likely benefit from continued perioperative aspirin use [37]. These benefits must be balanced with the potential bleeding risk. In a large meta-analysis of over 49,000 patients, continued perioperative aspirin did increase bleeding risk by 1.5; however, it did not lead to bleeding that required medical intervention [26]. The exception was in cases known to have increased bleeding risk such as intracranial surgery or prostate surgery. Therefore, the current guidelines would recommend that aspirin be discontinued prior to noncardiac surgery in low-risk patients, while being continued in the perioperative period in patients at moderate to high risk for cardiovascular events [37,39].

In cardiac surgery, specifically coronary artery bypass grafting (CABG), it is very common to encounter patients on aspirin, since it is a mainstay in the treatment of coronary artery disease. The exact timing of preoperative discontinuation is often debated. Multiple observational studies have identified continued perioperative use of aspirin as a risk factor for increased bleeding and transfusion, however, not as a risk factor for increased reoperation [40]. For the opposite argument of continuing aspirin into the perioperative period, there are studies concluding a reduction in overall mortality when patients are exposed to aspirin within 5 days of CABG surgery [41]. Similarly, another prospective study found that perioperative aspirin use did not lead to an increased rate of reoperation or blood transfusion [42]. A slightly higher risk for bleeding without any major risk for reoperation and improved mortality results in the recommendation that aspirin be continued around the time of surgery rather than stopping use 7 days before surgery [37,43]. As for the patient also taking clopidogrel prior to surgery, it is clear that use within the immediate perioperative period (within 5 days of CABG) does result in increased bleeding and increased need for blood transfusion [44]. Therefore, it is reasonable to stop clopidogrel at least 5 days before proceeding to CABG surgery [37,43]. This recommendation applies to the newer thienopyridine agent, prasugrel, as well. If emergent surgery needs to be performed within this 5-day window, a likely increase in perioperative bleeding should be anticipated by the surgeon, but given the varying pharmacodynamics and patient responses to clopidogrel, a period of time less than 5 days (as short as 3 days) may be acceptable in some patients [45]. Although these recommendations are based on the patient presenting for isolated CABG, there exist fewer data for antiplatelet continuation in the patient presenting for isolated valve or combined CABG-valve surgery. Similarly, the guidelines leave surgeons with some ambiguity as to exact timing for discontinuing therapy, since it is often stated that antiplatelet agents may be continued "around the time of surgery" or "preoperatively" rather than stating they be continued until the day of surgery [37,43].

It is again important to keep in mind that the previously mentioned information provides only guideline recommendations and that no definitive algorithm

can be followed for decision making. It is also important to note that variation exists in the clinical practice guidelines of different societies (eg, timing of preoperative antiplatelet discontinuation) [46]. All cases must be assessed on an individual basis. It is imperative to maintain antiplatelet therapy whenever possible in the perioperative period, but given that certain patients will be at risk for bleeding and transfusion, this is not always feasible. Table 2 provides a proposed strategy for patients based on their preoperative cardiovascular risk

Table 2
Management of patients on preoperative antiplatelet therapy based on cardiovascular and bleeding risk

Bleeding risk of planned surgery	Cardiovascular risk		
	Low risk[a]	Intermediate risk[b]	High risk[c]
Low risk (transfusion usually not needed; peripheral, minor orthopedic, minor ear, nose and throat [ENT], general surgery, endoscopy without biopsies, eye anterior chamber, dental)	Continue aspirin and/or clopidogrel	Continue aspirin and/or clopidogrel for elective surgery	Postpone elective surgery; proceed with necessary surgery while continuing aspirin and/or clopidogrel
Intermediate risk (transfusion often needed; visceral; vascular; major orthopedic, major ENT, reconstructive, urology)	Continue aspirin and/or clopidogrel	Postpone elective surgery; proceed with necessary surgery while continuing aspirin and/or clopidogrel	Postpone elective surgery; proceed with necessary surgery while continuing aspirin and/or clopidogrel
High risk (transfusion needed; cardiac; surgery in closed space (eg, intracranial, eye posterior chamber, spinal canal)	Discontinue aspirin and/or clopidogrel	Postpone elective surgery; proceed with necessary surgery while continuing aspirin and discontinuing clopidogrel	Postpone elective surgery; proceed with necessary surgery while continuing aspirin and discontinuing clopidogrel (consider bridge with GpIIb/IIIa inhibitors)

[a]>3 months after PCI, bare-metal stent, CABG; greater than 6 months after ACS or myocardial infarction; greater than 12 months after drug-eluting stent.
[b]6–12 weeks after PCI, BMS, CABG; 6–24 weeks after ACS or myocardial infarction greater than 12 months after high-risk DES; diabetes; low ejection fraction.
[c]<6 weeks after PCI, BMS, CABG. Myocardial infarction (longer if complications); less than 12 months after high-risk DES.

Adapted from Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. Br J Anaesth 2007;99:322; with permission.

profile and the bleeding risk of the planned surgery [15,22]. Preoperative cardiac risk is primarily based on time since cardiovascular event, as well as other factors such as ejection fraction and diabetes. Surgical bleeding risk is based on likelihood of transfusion, as well as bleeding in an enclosed space. Note that continuing aspirin is a common suggestion for almost all combinations of cardiac and bleeding risks. When discontinuation of aspirin or clopidogrel is suggested, it should be stopped 5 days prior to the proposed surgery. When postponement of elective surgery is recommended, preoperative patient risk status should be further optimized prior to surgery.

SUMMARY

The rising use of antiplatelet therapy for primary prevention and secondary prevention of cardiovascular and cerebrovascular events poses a dilemma for physicians in the perioperative period. The proven benefits of aspirin in preventing further thrombotic events in patients with prior ACS or stroke make it difficult to withdraw this therapy. The risk of hypercoagulability associated with surgery is also independent of antiplatelet withdrawal, but adds to the rebound effect of platelet responsiveness. Therefore, aspirin should be continued whenever feasible. Similarly, the use of thienopyridines such as clopidogrel, especially for the prevention of stent thrombosis, should be maintained for at least the recommended time frame, if not longer. It is recognized that maintaining antiplatelet therapy is also not without risk, as bleeding complications have been well documented. Unfortunately, current perioperative guidelines do not often provide a simple solution for management. Therefore, the risk of bleeding has to be weighed against the risk of thrombosis, and decisions should be made with all providers caring for the patient on an individual basis.

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