Perioperative Management of Antiplatelet Agents

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Abstract: Perioperative management of antiplatelet agents is a common challenge with the increased number of patients requiring long-term therapy following coronary stenting. Debate currently exists regarding if and when to discontinue antiplatelet therapy prior to elective surgery. The delicate balance between decreasing the risk of bleeding intraoperatively and minimizing the risk of stent thrombosis in patients who are already at a high thrombotic risk is a major concern. This article summarizes the information available for perioperative management of common antiplatelet agents, as well as antiplatelet agents in development.

Percutaneous coronary intervention is a common procedure performed for patients with coronary artery disease. More than 1 million interventions are performed each year in the United States, with more than 85% of the cases involving coronary stenting. Accompanying the increase in percutaneous coronary intervention is an increase in the use of antiplatelet medications to prevent stent thrombosis. Stent thrombosis can be classified on a temporal basis. Acute stent thrombosis occurs during percutaneous coronary intervention or within 24 hours of stent placement, subacute stent thrombosis occurs between 1 and 30 days after percutaneous coronary intervention, and late stent thrombosis occurs 1 month to 1 year after percutaneous coronary intervention.

Very late stent thrombosis occurs more than 1 year after percutaneous coronary intervention. The majority of stent thrombosis occurs in the acute phase. The current American Heart Association/American College of Cardiology Foundation (AHA/ACCF) percutaneous coronary intervention guidelines for patients after stent implantation recommend dual antiplatelet therapy with aspirin and an adenosine diphosphate (ADP)-mediated P2Y12 receptor inhibitor (eg, clopidogrel, prasugrel) for at least 1 month after bare-metal stent implantation and for 1 year after drug-eluting stent implantation. This recommendation is based on a warning from the Food and Drug Administration published in 2003 following reports of acute stent thrombosis following abrupt discontinuation of dual antiplatelet therapy 3 to 6 months after drug-eluting stent implantation. Although the Food and Drug Administration’s warning was rescinded 1 year later due to further research, the warning successfully increased awareness of perioperative management of antiplatelet medications. Clinical practice currently supports 12 months of dual antiplatelet therapy after a drug-eluting stent to avoid late thrombosis; however, observational data have shown a decreased incidence of late stent thrombosis with at least 6 months of dual antiplatelet therapy.

Antiplatelet medications are often used to decrease the risk of thrombotic events due to stroke or myocardial infarction; however, antiplatelet medications are used after stent implantation to prevent platelets from binding to the newly implanted wire mesh stent prior to endothelialization into the coronary artery. This endothelialization process takes up to 30 days after a bare-metal stent implantation and 1 year after a drug-eluting stent implantation. Acute stent thrombosis causes significant morbidity and possible mortality (up to 45%).
due to abrupt coronary artery occlusion. Patients often present with symptoms similar to ST-elevation myocardial infarction.6

Although it is important to avoid abrupt interruption of dual antiplatelet therapy, particularly following percutaneous coronary intervention with stent implantation, approximately 5% of patients who have undergone percutaneous coronary intervention with stent implantation will require noncardiac surgery within the first year.6 Although avoiding abrupt discontinuation is important in the prevention of thrombosis, continuation of dual antiplatelet therapy during surgical procedures often increases the risk of bleeding complications. Debate exists regarding if and when to discontinue therapy prior to surgical procedures. The delicate balance between decreasing the risk of bleeding intraoperatively and minimizing the risk of stent thrombosis in patients who are already at a high risk for thrombosis is a major concern.

**RISK STRATIFICATION**

Currently, no standardized approach exists to managing a patient receiving dual antiplatelet therapy after stent implantation when the patient requires a surgical procedure. Determination of the ability to use a shorter time period than recommended for dual antiplatelet therapy largely depends on the indication for the antiplatelet agent and the type of surgical intervention needed.7 When attempting to risk stratify a patient, the practitioner must determine the thrombosis risk of the patient, the bleeding risk of the procedure, and the bleeding risk of the patient based on comorbidities. Stent-specific factors must also be considered during risk stratification. Longer stent lengths and stents located in the left anterior descending artery or the left main coronary artery are associated with increased thrombosis risk.8

Low-risk patients after dual antiplatelet therapy have been discontinued include those who are being treated for secondary prevention of stroke or myocardial infarction and have not undergone percutaneous coronary intervention. Intermediate-risk patients are those who have undergone percutaneous coronary intervention and are more than 4 weeks post bare-metal stent or 1 year post drug eluting stent implantation (Table 1).3,6 High-risk patients include those who have undergone percutaneous coronary intervention with implantation of a bare-metal stent within the past 4 weeks3 or a drug-eluting stent within the past year and those who have comorbidities such as diabetes mellitus or malignancy (Table 1). Factors that must be taken into account when determining the patient’s risk of bleeding include inherent bleeding risk of the procedure and patient-specific factors and comorbidities. Diabetes mellitus and malignancy increase the risk of bleeding due to a possible acute phase reaction intraoperatively.2 Heart failure, renal failure, liver failure, obesity, and other major organ dysfunction result in a higher risk for bleeding and must be considered when a practitioner stratifies a patient into a risk category.9 Certain disease states, such as obesity, diabetes mellitus, heart failure, and renal failure, put patients at risk for both bleeding and ischemic events.9

With minor orthopedic procedures, either a low risk for bleeding exists or the bleeding can be easily stopped. Procedures with an intermediate bleeding risk, such as major orthopedic procedures (excluding hip arthroplasty), require professional judgment when deciding whether to continue antiplatelet agents periprocedurally. High-risk procedures, such as hip arthroplasty, require antiplatelet discontinuation 5 to 7 days preoperatively because the risk of bleeding outweighs the risk of thrombosis.

**ELECTIVE SURGERIES**

Patients who have had a recent bare-metal stent or drug-eluting stent present a unique situation when being evaluated for elective surgery. Elective surgery is often viewed as an unnecessary risk to a patient who is receiving dual antiplatelet therapy following stent implan-

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**Table 1**

**Thrombosis Risk**<sup>3,6,7,9</sup>

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention of stroke or myocardial infarction</td>
<td>&gt;1 year after drug-eluting stent</td>
<td>Drug-eluting stent within 1 y</td>
</tr>
<tr>
<td>6 mo after myocardial infarction or CABG without complications</td>
<td>6 mo after myocardial infarction or CABG with complications</td>
<td>Bare-metal stent within 4 wk</td>
</tr>
<tr>
<td>Stroke within 12 mo without complications</td>
<td>&gt;4 wk bare metal stent</td>
<td>2 wk after stroke</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 wk after myocardial infarction or CABG</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>High-risk stents&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Low ejection fraction</td>
<td>Diabetes mellitus; malignancy</td>
<td></td>
</tr>
</tbody>
</table>

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<sup>a</sup>History of stent thrombus, >1 stent, long stent, stent placed at bifurcation, stent in left main artery or in small arteries.<sup>2</sup>

Abbreviation: CABG, coronary artery bypass graft surgery.
tation within the past year. A 5- to 10-fold higher risk has been found for acute stent thrombosis during the early phase prior to complete endothelialization.

The current recommendation suggests that if a patient with a coronary stent is receiving dual antiplatelet therapy and requires surgery, the surgery should be deferred for at least 30 days after placement of a bare-metal stent and for at least 1 year after placement of a drug-eluting stent. In patients requiring surgery within 6 weeks of placement of a bare-metal stent or within 6 months of placement of a drug-eluting stent, dual antiplatelet therapy should be continued around the time of surgery instead of discontinuing therapy 7 to 10 days before surgery. Patients undergoing cardiac risk evaluation prior to elective surgical procedures and who require percutaneous coronary intervention preoperatively should either have a percutaneous transluminal coronary angioplasty or a bare metal stent implantation to avoid unnecessary surgical delays.

The BASKET-LATE trial evaluated the risk of late clinical events and late stent thrombosis (7 to 18 months after stent placement) in patients treated with drug eluting stents vs bare metal stents. The study concluded that after the discontinuation of clopidogrel, drug eluting stents were associated with a higher incidence of late clinical events (cardiac death and documented non-fatal myocardial infarction) and were twice as likely to thrombose compared with bare metal stents.

**ASPIRIN**

Aspirin is the most common drug used for the prevention of thromboembolic complications. Aspirin is an irreversible COX enzyme inhibitor whose effects are reversed by a generation of new platelets. Bleeding risk with aspirin is 1.7%.

For procedures with a low risk of bleeding complications, aspirin should be continued without regard to the thrombosis risk for the patient (Table 2). For procedures with a moderate to high bleeding risk (Table 2), aspirin should be discontinued in patients who are at low risk for thrombosis but continued in patients who are at a moderate or high risk for thrombosis (Table 1). Procedures with a moderate bleeding risk are the most difficult for practitioners due to the innate subjectivity of stratification.

If aspirin requires discontinuation, it should be discontinued at least 7 to 10 days preoperatively. Postoperatively, aspirin should be resumed as soon as possible, preferably within 24 hours.

**CLOPIDOGREL**

Clopidogrel is a thienopyridine that inhibits platelet aggregation through irreversible inhibition of the ADP-mediated P2Y12 receptor. Clopidogrel is commonly used in combination with aspirin for 1 to 12 months following acute coronary syndrome or percutaneous coronary intervention procedures or in place of aspirin when the patient is unable to tolerate aspirin.

For procedures with a low risk of bleeding, it is recommended to stop clopidogrel preoperatively in patients with a low risk of thrombosis (Table 1); however, in patients receiving dual antiplatelet therapy, aspirin may be continued. For patients with a moderate or high risk of thrombosis undergoing procedures with a low risk of bleeding, dual antiplatelet therapy may be continued.

For procedures with a moderate risk of bleeding (Table 1), clopidogrel should be discontinued perioperatively. Aspirin may also be discontinued in patients with a low risk of thrombosis in this category but continued in those at a moderate or high risk of thrombosis. For procedures with a high risk of bleeding (Table 1), all antiplatelet therapies should be discontinued perioperatively. In these procedures, the risk of bleeding outweighs the risk of thrombosis.

If clopidogrel requires discontinuation, the CHEST guidelines recommend discontinuing therapy at least 7 to 10 days preoperatively to completely replatelet the platelet pool. This recommendation is in contrast to the package insert and the current AHA/ACCF percutaneous coronary intervention guidelines, which recommend discontinuing clopidogrel 5 days prior to elective surgery. The risk of major bleeding complications increases when surgery is performed within 24 hours after clopidogrel discontinuation. No increase in bleeding or transfusions is noted when surgery is performed more than 5 days after clopidogrel discontinuation. The magnitude of bleeding risk when surgery is performed 1 to 4 days after discontinuation of clopidogrel is less certain.

The practitioner should weigh the patient’s risk of thrombosis (Table 1) with the risk of surgical bleeding (Table 2) to determine when dual antiplatelet therapy can safely be discontinued. Clopidogrel should be resumed as soon as possible postoperatively, preferably within 24 hours.

<table>
<thead>
<tr>
<th>Table 2: Procedural Risk of Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
</tr>
<tr>
<td>Dental</td>
</tr>
<tr>
<td>Dermatologic</td>
</tr>
<tr>
<td>Biopsies</td>
</tr>
<tr>
<td>Minor orthopedic</td>
</tr>
<tr>
<td>Eye (anterior chamber)</td>
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<tr>
<td>Eye (posterior chamber)</td>
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</tbody>
</table>
Pharmacology Update

The Bottom Line

- Aspirin should be continued in all patients undergoing low bleeding and low thrombotic risk procedures. For moderate or high bleeding risk procedures, aspirin should be discontinued 7 to 10 days preoperatively in patients at low thrombosis risk, but continued in patients at moderate or high risk for thrombosis.
- For procedures with low bleeding risk, clopidogrel and prasugrel should be discontinued 5 and 7 days preoperatively, respectively, if the patient is at a low risk for thrombosis, but continued if the patient is at a moderate or high risk of thrombosis. For procedures with moderate or high bleeding risk, clopidogrel and prasugrel should be discontinued.
- Bridging patients from maintenance dual antiplatelet therapy to surgery is not currently recommended routinely unless patients are at high risk of thrombosis and low to moderate risk of bleeding.
- In patients requiring premature dual antiplatelet therapy discontinuation perioperatively, therapy should be resumed within 24 hours postoperatively provided no bleeding complications exist.

Prasugrel

Prasugrel is an oral irreversible ADP-mediated P2Y12 inhibitor in the thienopyridine class. Prasugrel is associated with a greater degree of platelet inhibition with fewer major adverse cardiac events following acute coronary syndromes than clopidogrel. The risk of major bleeding was higher with prasugrel than clopidogrel in clinical trials. The package insert for prasugrel recommends discontinuation 7 days preoperatively when possible; however, the CHEST guideline recommendations are similar to other antiplatelets, with discontinuation of prasugrel 7 to 10 days before elective surgery.

Ticagrelor

Ticagrelor is an oral, reversible, nonthienopyridine ADP-mediated P2Y12 inhibitor. The ONSET/OFFSET trial showed 41% inhibition of platelet aggregation within 30 minutes with ticagrelor, similar to the clopidogrel inhibition of platelet aggregation at 8 hours. Ticagrelor does not require metabolic conversion to an active metabolite for therapeutic effect. The trial also demonstrated that ticagrelor had a faster offset than clopidogrel, with inhibition of platelet aggregation on day 3 following ticagrelor discontinuation equaling the inhibition of platelet aggregation of clopidogrel 5 days after discontinuation. The PLATO trial tested this strategy and stopped ticagrelor 24 to 72 hours before coronary artery bypass surgery and clopidogrel 5 days before surgery. Although the total number of bleeding episodes was statistically reduced with ticagrelor vs clopidogrel, ticagrelor was shown to have a statistically significant increase in noncoronary artery bypass surgery related major bleeding.

Due to this risk, the package insert recommends stopping ticagrelor 5 days preoperatively. However, a subset analysis evaluating only patients who underwent coronary artery bypass surgery showed a decrease in total and cardiovascular mortality without an excess risk of bleeding. Although the most recent CHEST guidelines acknowledge the fact that reversible P2Y12-receptor inhibitors such as ticagrelor may play a role in bridging due to the specific antiplatelet effects, data from the PLATO CABG trial suggest discrepant results regarding ticagrelor reversibility between phase 3 randomized trials and pharmacokinetic data.

Bridging Antiplatelets During Surgery

No beneficial data were found to support bridging a patient with anticoagulants, such as unfractionated heparin, low-molecular-weight heparin, or direct thrombin inhibitors, while dual antiplatelet therapy is discontinued pending a surgical procedure. Because the risk of acute stent thrombosis is high following stent implantation, several antiplatelet bridging strategies, including use of glycoprotein IIb/IIIa inhibitors or cangrelor, have been used.

Glycoprotein 2b/3a Inhibitors

Some case reports have demonstrated the successful use of short-acting glycoprotein 2b/3a (GP2b/3a) inhibitors as transitional agents following premature discontinuation of P2Y12 inhibitors until a surgical procedure is performed. Reversible GP2b/3a inhibitors (eg, eptifibatide and tirofiban) can be discontinued within 6 hours preoperatively. Although these agents may be an option for preventing stent thrombosis in the short term, this practice requires patients to be admitted electively 5 to 7 days preoperatively. Patients are also at risk for GP2b/3a inhibitor–induced bleeding complications, which may further delay or complicate surgery. With the risk of bleeding complications plus the necessity of elective preoperative admission, bridging with GP2b/3a inhibitors is a difficult approach in anyone except patients at the highest risk for thrombosis.

Cangrelor

Cangrelor (The Medicines Company, Parsippany, New Jersey) is an intravenous, reversible, ADP-mediated P2Y12 receptor inhibitor that is not yet commercially available. It holds many of the same advantages as ticagrelor and is the focus of a recent trial evaluating bridging patients in whom clopidogrel was discontinued in preparation for cardiac surgery. The BRIDGE trial was a prospec-
tive, randomized, double-blind, placebo-controlled multicenter trial involving 210 patients with acute coronary syndrome or coronary stent. The objective of the study was to measure platelet reactivity in patients being bridged to coronary artery bypass surgery from their maintenance thienopyridine therapy with either cangrelor or placebo. Ticlopidine and clopidogrel were discontinued at least 5 days preoperatively, whereas prasugrel was discontinued 7 days preoperatively. Cangrelor was stopped 1 to 6 hours before surgical incision. Patients treated with cangrelor had higher levels of platelet inhibition without excessive bleeding compared with the standard care group. Cangrelor may offer a viable approach for bridging patients at a high risk for thrombosis requiring premature discontinuation of P2Y12 inhibitor therapy perioperatively.

**REFERENCES**


