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Perioperative Management of the Patient with a Coronary Artery Stent

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WITH the advent of percutaneous coronary intervention (PCI), specifically the bare-metal stent (BMS) and subsequently, the drug-eluting stent (DES), the role of interventional cardiology in coronary revascularization has greatly increased.[1] An estimated 600,000 coronary artery stents are placed annually in the United States for the management of acute and chronic coronary artery disease.[1] Given the aging US population and its increasing prevalence of coronary artery disease, the use of stents will likely continue to grow. The cumulative incidence of noncardiac surgery after coronary stenting is more than 10% at 1 yr and more than 20% at 2 yr.[2] Both the safe timing of noncardiac surgery and the need for continuing chronic antiplatelet therapy for coronary artery stents to mitigate a perioperative major adverse cardiac event (MACE) remains controversial.[3]

The Pharmacology and Personalized Medicine of Antiplatelet Drugs

Aspirin, typically in combination with a thienopyridine (table 1), is the current mainstay of oral antiplatelet therapy for the prevention of arterial thrombosis that can result in acute or delayed occlusion within a BMS or DES.[4,5] Such oral antiplatelet therapy is imperative during the critical but often prolonged period of reendothelialization of the coronary artery stent lumen.[5]

Aspirin irreversibly inhibits platelet cyclooxygenase (COX)-1 activity and in turn the synthesis of thromboxane A_2.[4,5] The thienopyridines [the most commonly used being clopidogrel (Plavix®; Bristol-Myers Squibb, New York, NY)] (table 1) typically irreversibly bind to the platelet $P2Y_{12}$ receptor and inhibit adenosine diphosphate receptor-mediated platelet activation and aggregation.[4,5] Because they act *via* different platelet receptors, the coadministration of aspirin and a thienopyridine results in enhanced platelet inhibition.[4,5] However, it has been hypothesized (but unproven) that after abrupt cessation of these antiplatelet drugs, there is a "rebound hypercoagulability" lasting upwards of 90 days, which may result from an inflammatory prothrombotic state, increased platelet adhesion and aggregation, and excessive thromboxane A_2 activity.[6]

A question that commonly arises is the concurrent use of aspirin and a nonsteroidal antiinflammatory drug (NSAID) in patients with a coronary artery stent. It has been reported that in patients with a history of stroke, taking aspirin concomitantly with ibuprofen or naproxen, the platelet inhibition effect of aspirin was lost.[7] Furthermore, 72% of patients had a recurrent ischemic event while on both drugs. The US Food and Drug Administration (FDA) has thus recommended that patients on aspirin (except if enteric coated) and an NSAID should take the NSAID more than 8 h before aspirin or at least 30 min after the aspirin. This timing reduces the risk that the NSAID will prevent the inhibitory effect of aspirin on the platelet COX pathway. The US FDA has also issued a black box warning on the use of an NSAID in the immediate postoperative period after coronary artery bypass graft surgery.[8] The American Heart Association has also broadly discouraged the use of both selective (COX-2) and nonselective (COX-1 and COX-2) inhibiting NSAIDs in patients with risk factors for coronary heart disease.[9] While the concomitant use of an NSAID and aspirin may increase the risk of a myocardial infarction (MI), the effect on in-stent thrombosis remains unknown.[10]

This article is featured in "This Month in Anesthesiology," page 1A. The figure was created by Annemarie B. Johnson, C.M.I., Medical Illustrator, Vivo Visuals, Winston-Salem, North Carolina.

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Table 1. Current Most Widely Used United States Food and Drug Administration Approved Antiplatelet Drugs[4,5]

Class of Drug	Cyclooxygenase Inhibitor	Thienopyridine		
Drug	Aspirin	Clopidogrel (Plavix®)	Prasugrel (Effient®)	Ticagrelor (Brilinta®)
Prodrug?	No	Yes	Yes	No
Platelet effect reversible?	No	No	No	Yes
Loading dose	160–325 mg	300 mg (600 mg)	60 mg	180 mg
Peak onset of action	30 min	4 h (2 h)	1 h	2 h
Maintenance dose	81 mg daily	75 mg daily	10 mg daily	90 mg twice daily
Metabolism pathway	Hepatic conjugation	CYP2C19	CYP3A4, CYP2B6	CYP3A4/5
Elimination half-life (mean)	3 h	6 h	7 h	9 h
How long to hold before procedure?	5 days	5 days	7 days	5 days
Generic available?	Yes	Yes	No	No

Clopidogrel (Plavix®; Bristol-Myers Squibb, New York, NY); prasugrel (Effient®; Eli Lilly and Company, Indianapolis, IN); ticagrelor (Brilinta®; AstraZeneca, London, United Kingdom).
CYP = cytochrome P450.

Personalized medicine (precision medicine) includes targeting clinical therapies to a patient's individual pharmacogenetics.[11] Pharmacogenomics is applicable to antiplatelet therapy, because clopidogrel is a prodrug, which must be transformed by the hepatic CYP2C19 isoenzyme into its active metabolite to become clinically effective.[4,5] Reportedly, 1–6% of Caucasians, 1–8% of African-Americans, and 12–23% of Asians are CYP2C19-deficient (polymorphic "poor metabolizers") and, thus, at increased risk of treatment failure and a thrombotic event on clopidogrel—including, presumably, in the perioperative period.[12] While there is no readily available, reliable laboratory assay to test platelet response to clopidogrel, CYP2C19 clinical genotyping is commercially available and can yield results in a few hours.[12]

Two other thienopyridines are currently available and in use (table 1).[4,5] Although prasugrel (Effient®; Eli Lilly and Company, Indianapolis, IN) is also a prodrug, it is more efficiently converted into its active thiolactone form during absorption, *via* intestinal CYP3A and carboxylesterase 2 hydrolysis, resulting in more predictable and effective platelet inhibition.[4,5] A more recently available agent, ticagrelor (Brilinta®; AstraZeneca, London, United Kingdom) is a distinct cyclo-pentyl-triazolo-pyrimidine, which binds *reversibly* and directly, without any biotransformation, to the $P2Y_{12}$ receptor.[4,5] Compared with clopidogrel, ticagrelor has a more rapid onset of action and greater inhibition of platelet aggregation—significant advantages during an acute MI and emergent PCI.[4,5]

In June 2009, the European Medicines Agency authorized generic clopidogrel, and in May 2012, the US FDA approved generic clopidogrel. The net effect of these now available generics on the previous dominant worldwide market share of proprietary Plavix® remains to be determined. Ultimately, the clinical benefits associated with prasugrel (Effient®) and ticagrelor (Brilinta®) should be offset against their now greater cost, promoting the need for an evidence-based algorithm for the rational pharmacogenomic and prudent pharmacoeconomic use of these newer drugs with a PCI.[13]

The Continued Evolution of the Coronary Artery Stent

The anesthesiologist needs to be aware of a patient's type(s) of coronary artery stent(s). This often requires some clinical detective work. Since being first approved by the US FDA in 1993, the structure of coronary artery stents, and the chemotherapeutic or immunomodulatory drug eluted to inhibit adverse neointimal proliferation, have continued to evolve (fig. 1).[14] Of note, the first DES (Cypher®; Cordis, Bridgewater, NJ) was approved by the US FDA in April 2003; thus, any stent placed before this date in the United States was very likely a BMS.

Compared with a contemporary BMS, the first generation DES significantly reduced the need for repeat coronary revascularization due to in-stent restenosis.[15] However, concerns subsequently emerged with the first generation DES regarding late and very late stent thrombosis—especially after discontinuation of dual antiplatelet therapy (DAPT)—with an associated high rate of MI and death.[15] On the basis of their efficacy and safety data, the third generation, durable polymer everolimus-DES (Promus Element®; Boston Scientific, Natick, MA) and zotarolimus-DES (Endeavor® and Resolute®; Medtronic, Minneapolis, MN) have thus emerged as the optimal DES to date.[15] Anesthesiologists and surgeons can thus expect to prospectively see an increasing frequency of patients with such a third generation DES.

Pathophysiology and Epidemiology of Perioperative MACEs with Coronary Artery Stents

The Academic Research Consortium has provided standardized criteria for the definition of stent thrombosis according to the time of occurrence: (1) acute, within 24 h; (2) early, 2–30 days; (3) late, more than 1 month to less than 1 yr; and (4) very late, more than 1 yr.[14,16] Subacute stent thrombosis, a platelet-mediated intraluminal phenomenon, occurs most frequently in the first few weeks to months after coronary artery stent deployment but before endothelialization—the

US FDA approval	Stent	Manufacturer	Generation	Type of stent: Platform	Drug eluted
2000	Bx Velocity	Cordis, Bridgewater, NJ	First	BMS: 316L Stainless steel	N/A
2002	Liberté→VeriFLEX*	Boston Scientific, Natick, MA	First	BMS: 316L Stainless steel	N/A
2003	Vision	Guidant/Abbott, Indianapolis, IN	Second	BMS: Cobalt chromium	N/A
2003	Driver/Integrity	Medtronic, Minneapolis, MN	Second	BMS: Cobalt chromium	N/A
Trials underway	Omega	Boston Scientific, Natick, MA	Third	BMS: Platinum chromium	N/A
2003†	Cypher	Cordis, Bridgewater, NJ	First	DES: 316L Stainless steel	Sirolimus
2004	Taxus Express	Boston Scientific, Natick, MA	First	DES: 316L Stainless steel	Paclitaxel
2008	Taxus Liberté	Boston Scientific, Natick, MA	First	DES: 316L Stainless steel	Paclitaxel
2008	Endeavor	Medtronic, Minneapolis, MN	Second	DES: Cobalt chromium	Zotarolimus
2008	Xience V/Prime	Guidant/Abbott, Indianapolis, IN	Second	DES: Cobalt chromium	Everolimus
2008	Promus	Boston Scientific, Natick, MA	Second	DES: Cobalt chromium	Everolimus
2011	Promus Element	Boston Scientific, Natick, MA	Third	DES: Platinum chromium	Everolimus
2012	Taxus Element	Boston Scientific, Natick, MA	Third	DES: Platinum chromium	Paclitaxel
2013	Resolute Integrity	Medtronic, Minneapolis, MN	Third	DES: Cobalt chromium	Zotarolimus

Fig. 1. Currently and previously United States Food and Drug Administration (FDA)-approved bare-metal stents (BMS) and drug-eluting stents (DES).[14] N/A = not applicable.

process by which endothelial cells coat the inner surface of the deployed stent.[14] The primary advantage of stent drug elution is that it reduces vascular smooth muscle (neointimal) proliferation that causes the medium to long-term complication of in-stent restenosis. The disadvantage of drug elution is that it slows endothelialization—thus prolonging the risk period for the formation of platelet thrombi and the requirement for antiplatelet therapy.[14]

This delayed endothelialization, especially with a first generation DES, has been associated with late (between 1 month and 1 yr) and possibly very late (>1 yr) stent thrombosis and a MACE (composite outcome of MI, revascularization or death).[14,17] To avoid such complications, it has been recommended that patients receiving a DES continue DAPT for *at least* 1 yr after stent implantation, which poses a major challenge for such patients requiring surgery earlier in the poststent period.[18]

Surgery rates in patients with a DES have been reported to be as high as 9% within 1 yr, 18% at 2 yr, 22% at 3 yr, and 26% at 5 yr after stent placement.[2] Initial reports suggested that MACE rates are reduced when surgery is delayed between 21 and 90 days after BMS placement and for 1 yr after a DES.[19,20] However, the purported difference in postoperative MACE rates for DES and BMS, based on timing of noncardiac surgery, is grounded on limited and conflicting evidence.[21,22]

In patients undergoing surgery within 24 months of coronary stenting, the MACE rate was 5.1% for BMS and 4.3% for DES.[3] Furthermore, the BMS MACE rate was higher in a time-window (45–180 days after stenting) considered to be safe to proceed with surgery in patients with BMS, but not with DES.[3] In this study, a history of a recent MI, the revised cardiac risk index score, and nonelective surgical admission were most strongly associated with postoperative MACE. When surgery occurred beyond 6 months after stent implantation, there was no increased MACE risk for either stent type.[3]

Two other observations are noteworthy about the first 30 days after coronary artery stent placement.[2] The surgery is usually nonelective. Secondly, cardiologists attribute any MI up to 14 days poststent to the original disease and not a poststent MI; thus, we may be over attributing early events to poststent complications.[2]

Currently, the role of antiplatelet therapy cessation in mediating a perioperative MACE is also unclear, given there is minimal evidence to support this supposition in cohort studies of surgery in coronary stented patients.[3,19] The duration of risk of a MACE and the relationship of this risk to withdrawal of antiplatelet therapy in surgical patients with a coronary artery stent is thus controversial.[2,3]

A recent multicenter study reported the incidence and outcome of DAPT cessation after coronary artery stent

implantation.[23] Three categories of cessation were assessed: (1) physician-recommended discontinuation; (2) brief interruption (for surgery); and (3) disruption due to patient noncompliance or complication (bleeding). The overall incidence of DAPT cessation in the 24-month follow-up was 57%, and a brief interruption occurred in 10% of patients. There was no association between brief DAPT interruption for surgery and a MACE. Moreover, 74% of MACE occurred when patients were on DAPT. This result is consistent with others' findings that higher risk patients are more likely to have DAPT continued and such practice is not completely protective against MACE. In addition, this landmark analysis found that the highest risk for all MACE after DAPT cessation occurred in the first 6 months after coronary stent placement.[23] A landmark analysis is a well-established observational method used for comparing time-to-event outcome between groups that are determined during the study follow-up period.[24]

Thus, the emphasis on stent type to define the safe timing of noncardiac surgery after PCI and the effectiveness of antiplatelet therapy in mitigating untoward events appear far less important than previously thought.

Risk of Intraoperative and Postoperative Surgical Bleeding with Antiplatelet Drugs

Antiplatelet therapy should generally be continued throughout the perioperative period, except in cases where the risk of morbidity or mortality from bleeding significantly outweighs the risk of acute stent thrombosis, as in procedures (1) likely to be associated with "major" blood loss or (2) to be performed in a closed space.[25–27] While the latter circumstance is well defined, the former is more subjective and often ambiguous.

In two studies on the optimal timing of noncardiac surgery after BMS and DES placement, the continuation of DAPT at the time of surgery did not increase the risk of major surgical bleeding.[28,29] However, in another study of the optimal timing of noncardiac surgery *versus* coronary artery stent placement, the risk of severe, "life-threatening" bleeding (defined as fatal bleeding, intracranial bleeding, or bleeding requiring surgical intervention or transfusion of ≥4 units of blood products) was reported to be 4% with single antiplatelet therapy and 21% with DAPT.[20] Of note, the PeriOperative ISchemic Evaluation 2 trial, involving a total of 10,010 patients (4.3% of whom had undergone previous coronary artery stenting), observed that prophylactic administration of aspirin before surgery and throughout the early postsurgical period, in noncardiac surgery patients, had no significant effect on the rate of a composite of death or nonfatal MI but was associated with an increase in the risk of major bleeding.[30] However, the PeriOperative ISchemic Evaluation 2 trial excluded patients who received a BMS less than 6 weeks before surgery or a DES less than 1 yr before surgery.[30]

Based upon an extensive review of the available literature, after excluding cardiac surgery (with full intraoperative heparinization for cardiopulmonary bypass), surgical blood loss is increased 2.5–20% by aspirin alone, and 30–50% by aspirin and clopidogrel—but with no increased risk of bleeding-related mortality, except during intracranial surgery.[31] However, transfusion rates are reportedly increased by 30% with continuation of DAPT at the time of surgery.[31]

Existing Guidelines for the Perioperative Management of Antiplatelet Therapy in Patients with a Coronary Artery Stent

A recent systematic review identified 11 clinical practice guidelines for the perioperative management of antiplatelet therapy in patients with a coronary artery stent who need noncardiac surgery.[25] The included guidelines vary regarding delaying nonemergent surgery after stent placement, appropriate preoperative management of DAPT, and the role of bridging therapy with a glycoprotein IIb/IIIa inhibitor in those patients deemed at high risk for coronary artery stent thrombosis or a MACE. The discrepancies can be attributed in part to the lack of available quality evidence.

The 2009 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery comprehensively review of evidence and, based on expert opinion, propose an approach to the management of patients with previous PCI requiring noncardiac surgery.[26] The recommendations include delaying elective or nonurgent surgery for a minimum of 14 days after percutaneous transluminal coronary angioplasty; 30–45 days after BMS; and 365 days after DES.

Because of better long-term outcomes with stent implantation compared with percutaneous transluminal coronary angioplasty (balloon angioplasty) alone in patients undergoing primary PCI, stents are now routinely implanted during primary PCI.[32,33] However, in patients with an acute ST-elevation MI needing early coronary artery bypass graft surgery, primary percutaneous transluminal coronary angioplasty—without stent implantation—appears to allow for safe transition to subsequent coronary artery bypass graft.[33]

For those patients needing non-elective surgery within the above high-risk time periods, the AHA/ACC guidelines recommend considering continuing DAPT throughout the perioperative period unless contraindicated by the risk of bleeding from the procedure. Nevertheless, if discontinuation of DAPT is deemed necessary, low dose aspirin (≤100 mg per day) should be maintained, with the possible exceptions being with intracranial surgery and prostatectomy. While these most recent AHA/ACC guidelines review risk factors for stent thrombosis, their incorporation into the final algorithm for the perioperative continuation of aspirin or a $P2Y_{12}$ receptor remains incomplete.

Furthermore, current perioperative management of antiplatelet therapy needs to reflect new information on

perioperative in-stent thrombosis. The 2011 AHA/ACC Guideline for Percutaneous Coronary Intervention highlights several points regarding the relationship between coronary anatomy and stent placement.[27] Approximately 4% of patients who undergo angiography are noted to have unprotected left main coronary artery disease in which lack of collateral flow to the left anterior descending and left circumflex arteries can expose up to 75% of the myocardium to ischemia should the left main become fully occluded. While coronary artery bypass grafting has traditionally been the standard of care for this patient population, PCI revascularization in carefully selected patients appears to be a viable option. A corollary to this trend is that the risk related to in-stent thrombosis in this patient population will be considerably higher. In fact, all of the risk factors for in-stent thrombosis mirror the risks for stent restenosis, including placement for ST segment elevation MI, smaller arteries (< 2.5 mm diameter), longer lesions, and bifurcations. However, the currently available AHA/ACC guidelines regarding antiplatelet discontinuation before surgery do not clearly account for any of these increased risk factors for in-stent thrombosis.

It is expected that the forthcoming 2014 AHA/ACC perioperative management guideline will provide further, more specific evidence-based recommendations on (1) risk stratification of bleeding *versus* stent thrombosis and (2) continuation of single or dual antiplatelet therapy in patients with a BMS or a DES, undergoing various types of surgical procedures.

Summary

The need for continuing chronic antiplatelet therapy for coronary artery stents can be challenging and remains controversial in patients undergoing invasive procedures, including surgery and interventional pain treatment. These uncertainties can be best addressed with an understanding of the pharmacology and applicable pharmacogenomics of antiplatelet drugs, continued evolution of the coronary artery stent, and pathophysiology and epidemiology of perioperative MACE with such stents.

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Competing Interests

The authors declare no competing interests.

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