Perioperative Antiplatelet Drugs with Coronary Stents and Dancing with Surgeons: Can We Ever Agree About Bleeding Versus Ischemic Risk?

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PHARMACOLOGY OF ANTIPLATELET DRUGS
Aspirin, usually in combination with a thienopyridine (Table 1), is the present-day cornerstone of oral antiplatelet therapy for the prevention of (a) neointimal hyperplasia, with resulting in-stent restenosis and (b) acute stent thrombosis, after placement of a bare-metal stent (BMS) or a drug-eluting stent (DES).1–4 This oral antiplatelet therapy is especially important during the initial critical but often delayed period of reendothelialization of the lumen of the BMS or DES.5,6 Aspirin irreversibly inhibits platelet cyclooxygenase (COX-1) activity and in turn the synthesis of thromboxane A₂.6 The thienopyridines [e.g., clopidogrel (Plavix®)] irreversibly bind to the platelet P2Y₁₂ receptor and inhibit adenosine diphosphate receptor-mediated platelet activation and aggregation.6 Both aspirin and clopidogrel are “selective platelet-receptor” inhibitors that are considered weaker and thus safe antiplatelet drugs. The co-administration of aspirin and clopidogrel results in enhancement of beneficial platelet inhibition, since they act via the above different platelet receptors.7

Clopidogrel is a pro-drug that must be transformed by the hepatic CYP2C19 isoenzyme into its active metabolite to become clinically effective.9 A reported 1% to 6% of Caucasians, 1% to 8% of African Americans, and 12% to 25% of Asians are CYP2C19 deficient (“poor metabolizers”) and thus at risk of treatment failure.10 A subset of patients also displays diminished or absent response to aspirin (“aspirin resistance”), likely due to a combination of clinical, biological, and genetic properties affecting platelet function.11 This has raised the concern of drug resistance, with both clopidogrel and aspirin, which has been associated with an increased risk of an acute thrombotic event.12,13 This is problematic because while there is commercially available CYP2C19 clinical genotyping,14,15 there is no readily available, reliable laboratory measure of platelet function.13,16

The proton-pump inhibitors, omeprazole (Prilosec®) and esomeprazole (Nexium®) are also hepatically metabolized by CYP2C19. Omeprazole and esomeprazole compete with clopidogrel for the CYP2C19 isoenzyme, thus decreasing the conversion of clopidogrel into its clinically active metabolite and possibly reducing its cardioprotective effect.17,18 This drug-dug interaction prompted the United States Food and Drug Administration (U.S. FDA) in November 2012 to issue a safety labeling change, warning against the concomitant use of esomeprazole or omeprazole with clopidogrel.19

While clopidogrel and ticlopidine (Ticlid®) are metabolized solely by the hepatic cytochrome P450 system, prasugrel (Effient®) is also converted to its active thiolactone by carboxylesterase 2 hydrolysis during its intestinal absorption, resulting in a reportedly more predictable antiplatelet effect with prasugrel.20–22 Ticagrelor (Brilinta®) is a distinct cyclo-pentyl-triazolo-pyrimidine, which binds reversibly, and directly without biotransformation, to the P2Y₁₂ receptor on platelets.23–25 Cangrelor is an IV-administered cyclo-pentyl-triazolo-pyrimidine, with rapid onset and return of normal platelet function within 60 minutes of discontinuation, which is currently awaiting U.S. FDA approval.22,23

Of note, given the rapid onset of action of prasugrel or ticagrelor and their potential to decrease the risk of acute stent thrombosis, current international guidelines recommend prasugrel and ticagrelor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI).24–26 However, in June 2009, the European Medicines Agency authorized six generic versions of clopidogrel, and in May 2012, the U.S. FDA approved generic clopidogrel. The net effect of these available generics on the previously dominant worldwide market share of proprietary Plavix® remains to be determined. Ultimately, the clinical benefits associated with prasugrel and ticagrelor need to be offset against their increased cost, promoting the need for an algorithm for using these new drugs in the primary PCI setting.27

PATHOPHYSIOLOGY AND EPIDEMIOLOGY OF A PERIOPERATIVE MAJOR CARDIAC ADVERSE EVENT WITH CORONARY ARTERY STENTS

With the advent of PCI, in particular, coronary artery stenting, interventional cardiology has made significant progress in the management of coronary artery disease.2 The scope of interventional cardiology has also greatly increased with the development of the BMS and DES (Table 2), and the associated use of antiplatelet drugs.2

While such strategies have reduced the need for more invasive coronary artery bypass grafting (CABG) surgery, a major adverse cardiac event (MACE) can occur after coronary artery stent placement. While the definition of a MACE has varied considerably and hence the validity of such a composite end point in cardiovascular studies has been questioned,28 in patients who have undergone a PCI, a MACE conventionally includes any of the following:

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Specifically, acute coronary artery stent thrombosis and occlusion carries a very high morbidity and mortality. In the modern era of second-generation stents, high-pressure stent deployment, and current antithrombotic regimens, angiographic-confirmed stent thrombosis has a reported 64% incidence of death or MI at the time of acute stent deployment, and current antithrombotic regimens, the modern era of second-generation stents, high-pressure finishedment) and late stent thrombosis (LST) (> 30 days after initial stent placement) have been well-defined to include:

- Premature discontinuation of antiplatelet therapy
- Advanced age (> 75 years)
- Acute coronary syndrome (at the time of initial stent placement)
- History of coronary artery stent thrombosis
- Diabetes (poorly controlled with a hemoglobin A1C > 9.0)
- Low ejection fraction (left ventricular ejection fraction < 30%)
- Anemia (with hemoglobin < 10 g/dL)

Chronic renal insufficiency (creatinine > 2.0 mg/dL)
- Prior brachytherapy for prostate or cervical cancer
- Stent in left main artery, proximal left anterior descending, proximal right coronary artery, or proximal dominant circumflex artery
- Long stents, multiple, or overlapping stents in a single vessel
- Ostial or bifurcation lesions
- Post-CABG stent(s) in saphenous vein graft(s)

A 0–19 point scoring system for risk of LST (low, medium, high, very high) has been developed. However, several studies have identified the most important risk factor for LST is the complete and premature discontinuation of dual antiplatelet therapy.

Perioperative coronary artery stent thrombosis is likewise a catastrophic, often life-threatening complication that can occur in patients with either a BMS or DES. Noncardiac surgery appears to increase the risk of acute stent thrombosis, myocardial ischemia and MI, and death, especially when patients undergo surgery soon after stent implantation. The incidence of these complications is further increased when dual-antiplatelet therapy is abruptly discontinued preoperatively. This rebound is marked by an inflammatory prothrombotic state, increased platelet adhesion and aggregation, and excessive thromboxane A2 activity. Surgery itself further promotes an inflammatory response and prothrombotic state, which, in the presence of an incompletely reendothelialized DES, can lead to an acute stent thrombosis, with likely MI and/or death.

In one Mayo Clinic study, the incidence of a MACE was reportedly lowest when noncardiac surgery was performed at least 90 days after PCI with BMS placement, but remained at 2.8% thereafter. In a concomitant Mayo Clinic study, the risk of a MACE with noncardiac surgery after DES placement was observed to not be significantly associated with time between stenting and surgery, but the observed MACE rates were lowest after 365 days, but

### Table 2. Currently U.S. Food and Drug Administration (FDA) approved bare-metal stents (BMS) and drug-eluting stents (DES)

<table>
<thead>
<tr>
<th>Stent (manufacturer, FDA approval date)</th>
<th>Generation</th>
<th>Type of stent</th>
<th>Drug eluted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberté* (Boston Scientific)</td>
<td>First</td>
<td>BMS: 316L Stainless steel</td>
<td>N/A</td>
</tr>
<tr>
<td>ZeniFlex* (Boston Scientific)</td>
<td>First</td>
<td>BMS: 316L Stainless steel</td>
<td>N/A</td>
</tr>
<tr>
<td>Bx Velocity (Cordis/J&amp;J)</td>
<td>First</td>
<td>BMS: 316L Stainless steel</td>
<td>N/A</td>
</tr>
<tr>
<td>Vision (Abbott)</td>
<td>Second</td>
<td>BMS: Cobalt chromium</td>
<td>N/A</td>
</tr>
<tr>
<td>Driver/Integrity (Medtronic)</td>
<td>Second</td>
<td>BMS: Cobalt chromium</td>
<td>N/A</td>
</tr>
<tr>
<td>Omega (Boston Scientific, trials underway)</td>
<td>Third</td>
<td>BMS: Platinum Chromium</td>
<td>N/A</td>
</tr>
<tr>
<td>Cypher (Cordis, 4/2003)</td>
<td>First</td>
<td>DES: 316L Stainless steel</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Endeavor (Medtronic, 2/2008)</td>
<td>Second</td>
<td>DES: Cobalt chromium</td>
<td>Zotarolimus</td>
</tr>
<tr>
<td>Promus (Medtronic-marketed Xience)</td>
<td>Second</td>
<td>DES: Platinum chromium</td>
<td>Everolimus</td>
</tr>
<tr>
<td>Promus Element (Medtronic, 11/2011)</td>
<td>Third</td>
<td>DES: Platinum chromium</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Taxus Ion (Boston Scientific, 2/2012)</td>
<td>Third</td>
<td>DES: Platinum chromium</td>
<td>Everolimus</td>
</tr>
<tr>
<td>Resolute (Medtronic, 2/2013)</td>
<td>Third</td>
<td>DES: Cobalt chromium</td>
<td>Zotarolimus</td>
</tr>
</tbody>
</table>

*Liberté BMS was renamed ZeniFlex BMS by Boston Scientific in late 2009, to prevent continued confusion and inadvertent implantation of Taxus Liberté DES and vice versa.*
remained at 3.3% thereafter.39 Subsequent analyses of large-scale Canadian patient registry data and population-based administrative health care databases have revealed the earliest optimal time for elective surgery is 46 to 180 days after BMS implantation and 180 days after DES implantation.41 However, in a cohort of Dutch noncardiac surgery patients who experienced a MACE, 45% were receiving single and 55% receiving dual antiplatelet therapy.42 So indeed it would appear that “timing is everything,” at least with elective noncardiac surgery in patients with a coronary artery stent.43

**RISK OF INTRAOPERATIVE AND POSTOPERATIVE SURGICAL BLEEDING WITH ANTIPLATELET DRUGS**

In the above two Mayo Clinic studies on the optimal timing of noncardiac surgery after BMS and DES placement, the continuation of dual antiplatelet therapy at the time of surgery did not increase the risk of major surgical bleeding.42,43 However, in the above Dutch study of the optimal timing of noncardiac surgery versus 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 or blood products) was reported to be 4% with single antiplatelet therapy and 21% with dual antiplatelet therapy44. 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% to 20% by aspirin alone, and 30% to 50% by aspirin and clopidogrel, but with no increased risk of bleeding-related mortality except during intracranial surgery.42,45 Of note, transfusion rates are reportedly increased by 30% with continuation of dual antiplatelet therapy at the time of surgery.42

It is generally felt that antiplatelet therapy (aspirin and/or clopidogrel) should be continued throughout the perioperative period, except in cases where the risk of morbidity and mortality from bleeding during and after surgery significantly outweighs the risk of acute stent thrombosis, as with procedures likely to be associated with major (massive) blood loss or performed in a closed space (e.g. intracranial, intraspinal, posterior eye chamber, transurethral prostatectomy).42,46–48 While the latter circumstances are frequently quite evident, the former is often more subjective and hence ambiguous.

Current Evidence and Guidelines for the Perioperative Management of Antiplatelet Drugs in Patients with a Coronary Artery Stent

The optimal perioperative management of patients with a coronary artery stent hence remains a very significant yet challenging patient safety issue for clinicians.39,37,50,51 The U.S. FDA and the American Heart Association/American College of Cardiologists have recommended continuing dual-antiplatelet therapy in patients with a DES for one year and in patients with a BMS for six weeks.3,32 Unless medically contraindicated, all patients with any type of coronary artery stent should remain on lifelong aspirin monotherapy.3,46,49,52 These therapies for the prevention of stent thrombosis have major implications for anesthesiologists and surgeons.42,49 Not surprisingly, these recommendations regarding the optimal duration of and perioperative continuation of antiplatelet therapy continue to be debated, both in the literature and in routine clinical practice. Hence the title of this paper, “Dancing with Surgeons: Can We Ever Agree about Bleeding versus Ischemic Risk?” The answer is likely yes; though despite the availability of the above published clinical practice guidelines, “all politics is local.”53

**PRINCIPLES AND USE OF CONSENSUS DECISION-MAKING**

Consensus decision-making is one form of group decision making.34,55 Consensus decision-making does not require unanimity but instead seeks the agreement of the majority of participants as well as the resolution or mitigation of minority held objections.54,56 Consensus decision-making is applicable to the management of complex clinical conditions, in particular, the development of clinical practice guidelines and clinical care pathways, involving a variety of health care providers.57–60 Specifically, the Consensus-Oriented Decision-Making (CODM) model61 has been successfully applied to arrive at a consensus among local clinical stakeholders about the management of patients with coronary artery stents.60 Offering a detailed, step-wise description of the consensus process, the CODM model can be applied in any type of decision-making process. It outlines a process in which proposals can be collaboratively built with full participation of all stakeholders.61 The CODM model allows groups to be flexible enough to make decisions when they need to, while still following a format that is based on the primary values and goals of consensus decision-making.61 The CODM model involves seven steps:

- Framing the topic
- Open Discussion
- Identifying Underlying Concerns
- Collaborative Proposal Building
- Choosing a Direction
- Synthesizing a Final Proposal
- Closure

**ACHIEVING INSTITUTIONAL STAKEHOLDER CONSENSUS ABOUT PERIOPERATIVE ANTIPLATELET DRUGS FOR CORONARY ARTERY STENTS**

Coordinated care by all clinicians involved with a coronary artery stent patient is essential to avoid a high incidence of perioperative cardiac mortality and morbidity.2 Currently, though, as noted above, there are limited published data to guide surgeons, anesthesiologists, cardiologists, and primary care physicians, on the optimal care of patients with indwelling coronary artery stents presenting for noncardiac surgery.2,60,62,63 Surgery on a patient receiving antiplatelet therapy thus creates a dilemma: Is it better to withdraw the drugs and reduce the hemorrhagic risk or to maintain them and reduce the risk of a myocardial ischemic event?64 In either case, optimal perioperative care includes prompt recognition of myocardial ischemia and/or infarction. If stent thrombosis occurs, rapid triage to an interventional catheterization laboratory is essential for restoration of coronary blood flow.1,37
From July 2011 to November 2011, the above seven-step CODM model was followed to arrive at a consensus, among the institutional clinical stakeholders at the University of Alabama at Birmingham Health System (UABHS), to develop a protocol for the perioperative management of patients with indwelling coronary artery stent(s) undergoing elective surgery at our satellite university hospital without an on-site cardiac catheterization laboratory. Subsequently, between January 2013 and March 2013, this CODM model was also reiteratively applied by a UABHS Anticoagulation Task Force to create two evidence-based and local expert opinion-supported protocols (Figure 1A and Figure 1B), which standardized the preoperative management of antiplatelet therapy in patients with an indwelling coronary BMS or DES. This small yet multidisciplinary clinical task force included representatives from anesthesiology, cardiology, critical care medicine, gynecology, hospitalist medicine, pulmonology, transfusion medicine, and surgery. The efforts of this task force were enhanced the well-established UAB Department of Anesthesiology Section on Quality and Patient Safety and the departmental electronic Anesthesiology Dashboard, which provided an online mechanism for efficient sharing of pertinent published articles and successive protocol drafts.

1. Determine whether it would have been indicated, based on the BMS protocol or DES protocol, for the patient to stop single or dual antiplatelet therapy.

2. If discontinuation of the antiplatelet drug and/or aspirin is indicated by the protocol, surgery may proceed as planned.

3. If continuation of aspirin is indicated per the protocol, and the patient has been off aspirin for more than 5 days: (a) if there is a high risk of morbidity or mortality from bleeding during and after the planned procedure, obtain cardiology consult for management recommendations; (b) if there is an intermediate risk from bleeding during and after the planned procedure, give 81 mg of aspirin before surgery; and (c) if there is low risk of morbidity or mortality from bleeding during and after the planned procedure, give 325 mg of aspirin before surgery.

4. If continuation of another antiplatelet drug (other than aspirin) is indicated by the protocol, and the patient has been off this drug for more than 5 days, options include:
   a. Give 600 mg of clopidogrel and proceed with surgery a minimum of 2 hours later.
   b. Give 300 mg of clopidogrel and proceed with surgery a minimum of 4 hours later.
   c. Reschedule surgery for a later date. In this case, give 300 mg of clopidogrel and start clopidogrel 75 mg daily.
   d. If there is a high risk of morbidity or mortality from bleeding during and after the planned procedure, obtain Cardiology consult for management recommendations.

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**Figure 1A.** Protocol for preoperative antiplatelet therapy with an indwelling bare metal stent (BMS) (See “Day of Surgery Proviso” below).
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11. Cheng X, Chen WH, Simon DI. Aspirin resistance or variable response or both? Am J Cardiol 2006;98:11N–7N

**Figure 1B.** Protocol for preoperative antiplatelet therapy with an indwelling drug-eluting stent (DES) (**See “Day of Surgery Proviso” below**)

**Day of Surgery Proviso:** For patients scheduled for elective surgery who have independently stopped antiplatelet therapy before presentation to UAB on the day of surgery, the following steps can be used to guide the joint decision making by the anesthesiologist and surgeon:


85. Servin FS. Is it time to re-evaluate the routines about stopping/keeping platelet inhibitors in conjunction to ambulatory surgery? Curr Opin Anaesthesiol 2010;23:691–6


89. Weitzel NS, Edelstein SB, Cleveland JC Jr, Cornelissen CB. Drug-eluting stents in the perioperative period: what are the key aspects in management? Semin Cardiac Companion 2011;15:44–8


