Perioperative Management of Patients With Coronary Stents: Considerations for the Anesthesiologist

PRIYA A. KUMAR, MD, FASA
Professor, Anesthesiology
Director, Clinical Research
University of North Carolina School of Medicine
Chapel Hill

Dr. Kumar reported no relevant financial disclosures.

In order to prevent major adverse cardiovascular events and safely manage these patients, it is imperative for perioperative physicians to be familiar with stent dynamics.

Introduction

From its humble beginnings over four decades ago, percutaneous coronary intervention (PCI) has evolved into one of the most commonly performed standard medical procedures in the United States.1 Technological advances combined with evidence from large clinical trials have resulted in a modern era for PCI, which continues to rapidly progress. About 480,000 PCI procedures are being performed annually, which includes balloon angioplasties with or without the placement of a coronary stent.1 Contemporary data suggest that approximately one in five patients with coronary stent implantation will require noncardiac surgery within two years of their coronary intervention.2

It’s no surprise that anesthesiologists must consistently stay current with rapidly evolving guidelines for the perioperative management of these patients. Some of the clinical questions that arise include the following:

• How soon can a stented patient undergo surgery?
• Should a patient continue antiplatelet therapy (APT) during the perioperative period?
• What is the risk for surgical bleeding versus coronary thrombosis in this population?
Stent thrombosis, a potentially fatal complication, is likely with premature discontinuation of APT due to the perioperative prothrombotic pro-inflammatory state.

In order to prevent major adverse cardiovascular events (MACE) and safely manage these patients, it is imperative for perioperative physicians to be familiar with stent dynamics. They should have a clear understanding of the indications, duration and importance of APT for the prevention of stent thrombosis. Each individual patient’s risk for bleeding must be counterbalanced against the risk for life-threatening stent thrombosis in patients on APT.

It’s essential for the entire perioperative team to have a clear understanding and agreement so that early identification, vigilant care and rapid triage can prevent catastrophic outcomes in patients who develop stent thrombosis.

**History**

Since the pioneering success at percutaneous transluminal coronary angioplasty in 1977 by Grüntzig et al, stent technology has undergone tremendous evolution. Plain balloon angioplasty was met with much initial enthusiasm; however, its limitations soon came to light. The use of stand-alone angioplasty without stenting was associated with high complication rates, ranging between 15% and 60%, including the risks for early vessel closure due to elastic recoil as well as late inflammatory restenosis.

Bare metal stents (BMSs) were introduced in the 1980s to help avoid the shortcomings of balloon dilation. They were approved by the FDA in 1993. These devices functioned as vascular scaffolds and were regarded as a major advance in the nonsurgical management of coronary artery disease. Although BMSs reduced the rates of restenosis, coronary artery recoil and dissection, they presented several areas of clinical concern. Stent implantation induced trauma to the vessel wall and initiated complex interactions between the vessel wall, stent surface and blood components, leading to thrombogenesis and neointimal hyperplasia, much like the formation of scar tissue. Neointimal hyperplasia in turn resulted in in-stent restenosis (ISR), affecting 10% to 30% of patients with BMS implantations over the course of three to six months. In coronary arteries, even a small amount of hyperplastic tissue can significantly reduce the luminal diameter, resulting in gradual stent occlusion and ischemia. Numerous pharmacotherapy trials attempted to address the issue of ISR, but none was successful in reducing its incidence. Compared with drug-eluting stents (DESs), only about 25% of all stents implanted during PCI are BMSs.

In the early 2000s, DESs were introduced as a concept and a potential solution for the prevention of ISR. The metallic scaffold was coated with a drug delivery polymer embedded with a pharmacologic agent to discourage scar tissue formation. The antiproliferative drugs used to coat the stents (of the taxus and limus families) were successful in preventing the proliferation of smooth muscle and markedly reduced the rates of restenosis to a range of 5% to 8%; however, the success of DESs came with a price.

The coating of immunosuppressive and antiproliferative pharmacologic agents found on first-generation DESs interfered with and delayed the disrupted vascular endothelium from regenerating. This left the subendothelial substrate exposed for prolonged periods to circulating platelets and inflammatory mediators. Collagen in the exposed subendothelium, being a potent stimulus for platelet activation, made these patients susceptible to stent thrombosis. Whereas reendothelialization after a BMS implantation occurred within the first six to seven months after the procedure, the first-generation DESs were not fully endothelialized, even after three years of implantation. As a result, late stent thrombosis was an alarming problem in patients with first-generation DESs, especially in the hyperthrombotic perioperative period. While ISR is a pathology that evolves gradually over a period of six to nine months, stent thrombosis is an abrupt thrombotic vessel occlusion that can lead to an acute myocardial infarction (MI) with a high mortality rate of 10% to 30%.

Stent architecture, flexibility, apposition to the coronary vessel wall, its polymer coating, and the choice of pharmacologic agent may all play a significant role in the reendothelialization process to create an improved safety profile.

**First-Generation DESs**

First-generation DESs, approved by the FDA in 2003, consist of a stainless steel metallic stent platform coated with a polymer that elutes the antiproliferative pharmacologic agent. Sirolimus is an immunosuppressive compound that reduces neointimal hyperplasia. Elution off the sirolimus platform is complete in about six weeks. Paclitaxel is an agent that has antiproliferative and cytotoxic properties; 10% of the drug is released in the first 10 days, and the remainder elutes indefinitely. The Cypher (Cordis) and Taxus (Boston Scientific) stents proved superior to BMSs and successfully lowered the incidence of ISR.

**Second-Generation DESs**

Second-generation DESs differ from first-generation stents in all three components: metal frame, polymer coating and drug. They consist of thinner, more radiopaque and flexible cobalt–chromium or platinum–chromium alloy struts coated with a biocompatible polymer with superior reendothelialization kinetics. Zotarolimus inhibits smooth muscle cell proliferation and completely disappears after full elution. Everolimus, similar to sirolimus in its antiproliferative and immunosuppressive properties, is more lipophilic, allowing rapid absorption into the arterial wall.

**Polymer-Free and Bioabsorbable Polymer DESs**

The polymer coating and the metal frame have been implicated as potential causes of inflammation
and disruption of coronary vasomotor tone. As a consequence, DESs with the elimination of the polymeric carrier have been developed. Drug-filled hollow frames made with newer metal alloys allow the drug to be released from the frame itself. As a result, improved healing may allow a shorter duration of APT. Trials of these stents have suggested noninferiority compared with contemporary DESs.

Bioabsorbable polymer DESs are coated with a polymer that is absorbed over six to 12 months, eliminating the source of inflammation. Synergy (Boston Scientific) was the first of this type to receive FDA approval, in 2015. Both the drug, everolimus, and the polymer are absorbed shortly after drug elution is completed at three months. European registry data have suggested the safety and efficacy of this technology compared with contemporary DESs. Synergy has a CE mark (European equivalent of an FDA approval) for one month of dual APT, which is similar to that of BMSs.

Bioabsorbable Stents

Bioabsorbable vascular scaffolds are designed to be fully absorbed over a period of two to three years, eliminating the presence of foreign material in the vessel. Absorb (Abbott Vascular) consists of a poly-L-lactide backbone coated with everolimus. The stent received FDA approval in 2016 based on initial results, which were promising and theoretically attractive. However, the ABSORB III trial unveiled some concerns around late-developing stent thrombosis. This, along with other troubling reports, resulted in a withdrawal of the stent from the U.S. commercial market, other than for research purposes.

Additionally, a warning was issued by the FDA regarding the risk for late stent thrombosis with bioabsorbable vascular scaffolds. Long-term data collection is ongoing (i.e., the ABSORB IV trial), and additional studies may be needed to demonstrate long-term benefits. Further refinement of bioabsorbable stent design will likely continue until the hurdle of its first-generation design has been overcome.

Next-Generation Stents

Stent technology is undergoing an explosion of research and refinement with the evolution of next-generation stents with increased safety and biocompatibility. The development of antibody-coated stents, which attract circulating endothelial progenitor cells with prohealing properties to enhance the repair of endothelial cells, is now being explored. A further evolution of design combines the above endothelial progenitor cells technology with a bioabsorbable polymer matrix, which has also shown initial promise.

Evolution of Guidelines

With the rapid evolution and advancement in stent technology, perioperative management guidelines also have evolved. A lack of uniformity in American and European guidelines is a reflection of constant updates caused by the brisk pace of clinical advancement and discovery in this area. Most studies agree that there is an inverse relationship between the time from stent surgery and cardiac risk. However, with the advent of new-generation stents, the safety duration of APT is getting shortened.

At the time BMSs were approved in 1993, no formalized guidelines existed regarding the perioperative management of these patients. Several reports of adverse events and deaths from stent thrombosis began to emerge, especially in patients whose APT was held up for surgery. As a result, guidelines in 2002 recommended delaying surgery for six weeks after BMS placement. Soon after, DESs were approved by the FDA in 2003. Similar reports of acute stent thrombosis after noncardiac surgery began to appear, particularly in patients with recently implanted DESs. This was associated with significant preventable and alarming perioperative morbidity and death.

Patient compliance with APT became crucial for lowering this risk. Consequently, in 2007, the American College of Cardiology/American Heart Association (ACC/AHA) modified the guidelines for perioperative cardiovascular evaluation and care for noncardiac surgery. The group recommended that APT should be continued and elective surgery postponed for four to six weeks after placement of a BMS and for one year after DES implantation. They also stated that whenever possible, urgent surgeries in recently stented patients should be performed with the continuation of APT, although doing so may increase the risk for surgical bleeding. It was generally agreed that the risk for stent thrombosis outweighed the risk for bleeding in patients with recently implanted stents.

In 2009, the American Society of Anesthesiologists (ASA) issued a practice alert in accordance with the ACC/AHA recommendations. The ASA supported the 2007 ACC/AHA recommendations and agreed that selected patients at high risk for stent thrombosis should continue APT beyond the recommended time periods.

Long-term safety data from second-generation DESs were encouraging and led to the liberalization of the ACC/AHA guidelines in 2014. The guidelines recommended delaying noncardiac surgery for 14 days after balloon angioplasty, 30 days after BMS implantation, and one year after DES implantation. However, if the risk for delaying surgery for a year was greater than the risk for ischemia, elective surgery could be considered at six months as a class IIb recommendation.

Safety data continued to be encouraging on newer-generation stents, and the guidelines were liberalized yet again in 2016 to recommend delaying noncardiac surgery for 30 days after BMS and six months after DES implantation. However, if the risk for delay of six months was greater than the risk for ischemia, elective surgery could be considered at three months as a class IIb recommendation (Figure 1).

American and European guidelines agree that a multidisciplinary risk-benefit individualized approach is
warranted when considering timing of surgery after stenting. European guidelines are, however, more liberal, and in selective cases they recommend considering surgery as soon as one month after stenting. Additionally, although there is no recommendation on “bridging therapy” with IV antiplatelet agents in the American guidelines, the European guidelines support this concept in high-risk patients.21

**Risk for Stent Thrombosis**

As previously mentioned, stent thrombosis is a sudden, devastating complication that can lead to MI or death. It may result from stent malposition, coronary dissection or incomplete endothelial healing in the face of withdrawal of APT. According to the Academic Research Consortium, for the purposes of consistency with reporting, stent thrombosis can be classified according to its timing of occurrence as22:

- acute ST, which occurs within 24 hours of stenting;
- subacute ST, which occurs from 24 hours to 30 days of stenting;
- late ST, which occurs from 31 days to one year of stenting; or
- very late ST, which occurs one year after stenting.

The FDA’s policy outlining patients suitable for stent insertion considers those whose three-year risk for thrombosis is below 2%.23 Approved indications include stable patients without comorbid conditions (e.g., diabetes, renal insufficiency, MI, <30% ejection fraction, left main coronary lesion) with short lesions (28-30 mm), noncomplex lesions or native coronary lesions. In reality, only a minority (25%-40%) of patients meet these criteria, and the majority of coronary stents are placed in “off-label” patients, which automatically places them in the high-risk category. Although most patients in this high-risk category have good long-term outcomes, it’s important to ensure that APT is not terminated prematurely in these patients. An informed, multidisciplinary, thorough risk–benefit analysis should be undertaken for this patient population, especially in the thrombogenic, vulnerable perioperative setting.

**Figure 1. Treatment and timing algorithm for elective noncardiac surgery in patients with coronary stents.**

BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; PCI, percutaneous coronary intervention

Based on reference 20.
Antiplatelet Therapy

Activation of platelets is recognized as the primary source of stent thrombosis. Multiple pathways must be blocked in order to achieve effective APT. It is well known that there is significant crossover between the various receptors on the surface of the platelets; hence, dual antiplatelet therapy (DAPT) is recommended as the cornerstone of antithrombotic prophylaxis.

The antiplatelet agents most frequently used are a combination of aspirin and clopidogrel, both of which are irreversible platelet inhibitors, have been extensively studied and have the most favorable risk–benefit profile. However, both aspirin and clopidogrel may be partially ineffective in as many as 30% of patients. Pharmacogenomic and genetic polymorphism mechanisms play a major role in this drug resistance. With a half-life of six hours, clopidogrel is a prodrug that must be metabolized to the active drug in the liver by cytochrome P450 (CYP). Genetic variability and interaction with other drugs metabolized by this mechanism may interfere with the effectiveness of clopidogrel. Pharmacogenetic testing (CYP2C19 genotyping) for drug resistance is routine in some institutions to tailor the choice of APT in high-risk patients. Fortunately, many other safe and efficacious antiplatelet agents with reduced risks for pharmacogenetic drug resistance are now available to us. It’s helpful to be familiar with the various antiplatelet agents that are being used.

The currently available antiplatelet drugs fall into four main categories:

- **Thromboxane inhibitors (including aspirin):** According to the guidelines, aspirin is recommended as a lifelong therapy that should never be interrupted for patients with coronary stents unless the bleeding risk far exceeds the risk for stent thrombosis.
- **Glycoprotein IIb/IIIa inhibitors (including tirofiban [Aggrastat, Mediceure International], epifibatide and abciximab [Reopro, Janssen]):** Interventional cardiologists generally use these IV medications in the cardiac catheterization suite during the placement of coronary stents. As an off-label indication, these drugs also can be used to bridge the gap between discontinuation of DAPT and surgery in selected high-risk patients. Tirofiban and epifibatide have a half-life of two hours, and bleeding times return to normal about four hours after stopping infusions. However, bleeding risks with these agents are higher than with oral drugs, and their effects cannot be reversed with platelet transfusions.
- **P2Y12 or adenosine diphosphate receptor blockers (including clopidogrel, prasugrel, ticagrelor and cangrelor [Kengreal, Chiesi]):** Prasugrel, a third-generation thienopyridine, was approved by the FDA in 2000. It’s more potent than clopidogrel and has a lower rate of drug resistance with a more predictable antiplatelet response. These effects come at the cost of a higher risk for bleeding and greater expense. Ticagrelor is an orally active reversible P2Y12 receptor antagonist that was approved by the FDA in 2011. It does not require metabolic activation for its clinical effect. Cangrelor, an ultra-short-acting, reversible IV platelet inhibitor, was approved by the FDA in 2015 and has been evaluated as a bridging APT in the perioperative setting. The protease-activated receptor 1 antagonist vorapaxar (Zontivity, Aralez) was approved by the FDA in 2011, and is used as an oral reversible agent with a peak effect attained in one to two hours and a terminal half-life of eight days.

High-risk patients or patients with resistance to aspirin or clopidogrel may be placed on the above-mentioned alternate drugs. Heparins possess an insignificant antiplatelet effect and are therefore unsuitable as “bridge therapy” when DAPT is discontinued in the perioperative setting. However, other innovative and effective bridging strategies have been proposed for selective high-risk situations (Figure 2).

Perioperative Considerations

Patients with freshly placed coronary stents presenting for noncardiac surgery pose a significant challenge to anesthesiologists. It is important to manage these patients using a multidisciplinary team approach with open communication and accept input from the anesthesiologist, surgeon and interventional cardiologist.

The perioperative period is particularly risky for patients with coronary stents because of the stress response to surgery, which activates the sympathetic system. It results in the release of inflammatory mediators and stress hormones, and causes platelet activation, vasospasm and decreased fibrinolysis. Together, these effects lead to the development of a hypercoagulable state in a patient who may already have a disrupted coronary endothelial lining and is predisposed to stent thrombosis. Pain and anxiety may result in tachycardia and hypertension leading to an increased cardiac demand–supply ratio, which can add additional shear stress to the coronary plaques.

Fearful of the risk for surgical bleeding, well-meaning surgeons or other medical providers may inappropriately advise patients to discontinue their DAPT while they are still within the high-risk period after coronary stenting. There is evidence to show that an abrupt discontinuation of DAPT not only reverses the antiplatelet effect but also leads to an exaggerated rebound thrombogenic effect. These patients are susceptible to MACE in the perioperative period, with some studies reporting high mortality rates.

Sharma et al evaluated outcomes in patients with BMS undergoing noncardiac surgery. They found that patients in whom DAPT was discontinued prematurely had a mortality rate of approximately 85%, compared with 5% for patients in whom therapy was continued. Retrospective studies that evaluated the risk for perioperative MACE in patients presenting for noncardiac
surgery showed that the risk decreases 90 days after PCI in patients who receive a BMS but remains high even after one year in patients who receive a DES. Similar reviews of second-generation DESs show a higher risk of MACE during the first six months of stent implantation.

Successful management of DAPT must evaluate the patient’s risk for bleeding against that for stent thrombosis. During the vulnerable period, the risk for stent thrombosis in patients with recent PCI outweighs that of surgical bleeding. Ideally, DAPT should be continued throughout the perioperative period in freshly stented patients. If DAPT must be discontinued due to a high risk for surgical bleeding, all efforts should be made to at least continue aspirin. Procedures with a high risk for bleeding include intracranial, intramedullary spinal, prostate, middle ear, ophthalmologic and aortic surgeries.

DAPT should be reinstituted as soon as possible after surgery if it has been held for the procedure. The four-quadrant approach suggested by Metzler et al is still valid, where the risk for thrombosis is plotted against the risk for bleeding. The subset of patients who fall into the quadrant with a high risk for bleeding and stent thrombosis may benefit from extra caution. Metzler et al suggest that DAPT should be stopped in this subset with the institution of pharmacologic bridge therapy. More recently, Rossini et al created a multidisciplinary task force and published a consensus document as well as a mobile phone app (“Stent & Surgery”) to provide recommendations for patients with coronary stents undergoing surgery.

A fundamental trade-off occurs between reduced coronary ischemic risk and increased risk for surgical bleeding with the perioperative continuation of DAPT. This multidisciplinary decision must be made on an individual basis, thoughtfully weighing the coronary risk factors and bleeding risks for each patient. Patients who remain on APT intraoperatively may experience excessive bleeding. Adequate preparation with large-bore IV access and the availability of blood must be planned beforehand. If a platelet transfusion is necessary, it can be safely performed approximately four hours after the discontinuation of clopidogrel. The short half-life of clopidogrel and its metabolites will not interfere with the function of transfused platelets.

Optimal intraoperative management of these patients requires tight hemodynamic control to balance the cardiac demand–supply ratio and minimize the shear stress on coronary arteries. When considering regional or neuraxial anesthesia in patients with coronary stents, a risk–benefit analysis must be performed.

**Figure 2.** Bridging protocol for patients referred to surgery on dual antiplatelet therapy with aspirin plus a P2Y12 receptor inhibitor who are taking (top) small-molecule GPIs or (bottom) cangrelor (Kengreal, Chiesi USA).

GPI, glycoprotein inhibitor
carefully undertaken, keeping in mind that the patient may require an emergency perioperative PCI intervention with the administration of additional highly potent APT.

As with any high-risk cardiac patient, the anesthesiologist must remain vigilant for signs of cardiac ischemia and stent thrombosis. Surgical procedures in patients with coronary stents should be performed at institutions with prompt access to around-the-clock interventional cardiology services.

Intraoperative stent thrombosis, a true medical emergency, may present as hemodynamic instability with dysrhythmias and ECG changes. The recommended treatment for an MI is acute reperfusion therapy with fibrinolytic agents, depending on the risk for bleeding, or an urgent PCI (i.e., within 90 minutes). In the setting of stent thrombosis, it is imperative to immediately reperfuse the myocardium to avert a transmural MI. Thrombolytic therapy may be prohibitive in the perioperative period because of the risk for bleeding. PCI along with hemodynamic support is therefore the definitive treatment in this setting, requiring emergent action.

**Conclusion**

The 2016 ACC/AHA guidelines recommend postponing elective surgery for four weeks after implantation of a BMS, and three to six months after implantation of a DES. These periods may be extended in high-risk patients or those in whom unapproved stents were used, such as multiple overlapping stents in bifurcating vessels. Aspirin therapy should be continued indefinitely in patients with PCI, particularly in the perioperative period. Whenever possible, APT should be continued for urgent surgeries that must be performed within the high-risk period. If DAPT must be stopped for urgent procedures, clinicians could consider bridging therapy with a short-acting IV antiplatelet agent and restart the DAPT as soon as possible after surgery.

The anesthesiologist, as a perioperative physician, is uniquely poised to play a pivotal role in ensuring patient safety. Vigilant care and rapid triage to the interventional cardiology suite in case of myocardial ischemia can prevent catastrophic outcomes. Early perioperative identification and use of a multidisciplinary team approach, along with well-publicized institutional policies and management guidelines, ensure patient safety.

**References**


