Coronary Artery Stents: II. Perioperative Considerations and Management

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The management of patients with coronary artery stents during the perioperative period is one of the most important patient safety issues clinicians confront. Perioperative stent thrombosis is a life-threatening complication for patients with either bare-metal or drug-eluting stents. Noncardiac surgery appears to increase the risk of stent thrombosis, myocardial infarction, and death, particularly when patients undergo surgery early after stent implantation. The incidence of complications is further increased when dual-antiplatelet therapy is discontinued preoperatively. It is generally agreed that aspirin must be continued throughout the perioperative period, except in circumstances when the risk of bleeding significantly outweighs the benefit of continued anticoagulation, such as procedures performed in a closed space. We present considerations for regional anesthesia, as well as postoperative recommendations as the occurrence of perioperative stent thrombosis appears to be greatest during this period. Immediate percutaneous coronary intervention is the definitive treatment for perioperative stent thrombosis, and 24-h access to an interventional cardiology suite should be readily available. Algorithms for perioperative management of patients with bare-metal and drug-eluting stents are proposed.

(Nearey 23 yr after the first percutaneous coronary interventional procedures (PCIs) were performed, reports of deleterious outcomes in patients undergoing noncardiac surgery who had previously undergone PCI appeared in the literature.1 Of the more than 2 million patients undergoing PCI annually, more than 90% will receive one or more intracoronary stents.2 Approximately 5% of patients in this group will undergo noncardiac surgery within the first year after stenting, and an increasing number will continue to present for surgery thereafter.5 Because success of the stents requires long-term antiplatelet therapy, management of patients with these devices poses a dilemma to the anesthesiologist. This is Part II in a series that reviews perioperative issues and management related to coronary artery stents relevant to the anesthesiologist.

CORONARY ARTERY STENTS AND NONCARDIAC SURGERY

Discontinuation of antiplatelet therapy relatively soon after PCI with stenting confers significant morbidity and mortality during noncardiac surgery (Tables 1 and 2). Because stent endothelialization may not yet be complete at the time of surgery, abrupt discontinuation of clopidogrel and aspirin combined with the prothrombotic state induced by surgery increases the risk of acute perioperative stent thrombosis and abrupt vessel closure, leading to significant morbidity and mortality (Fig. 1). Kaluza et al. reported 7 myocardial infarctions (MIs) and 8 major bleeding episodes in patients who underwent elective noncardiac surgery <14 days after PCI with bare-metal stenting (BMS)1 (Table 1). Mortality occurred in six of the patients who suffered postoperative MIs and in two of the patients who developed major postoperative bleeding. Moreover, patients who stopped all or part of their antiplatelet regimen preoperatively died. In two patients who underwent immediate cardiac catheterization, stent thrombosis was confirmed angiographically, and was presumed to occur in the remaining patients who suffered MIs diagnosed by electrocardiographic criteria. Despite the 2002 American Heart Association/American College of Cardiology (AHA/ACC) guidelines, which recommended a 4–6 wk interval between BMS and noncardiac surgery “to allow 4 full weeks of dual-antiplatelet therapy and re-endothelialization of the stent to be completed, or nearly so,” reports of perioperative morbidity and mortality continued to be published1–9 (Table 1). Sharma et al. reported an 85.7% mortality rate among patients who stopped thienopyridine therapy and underwent surgery within 3 wk of BMS implantation.6 Wilson et al. reported 4% morbidity and 3% mortality rates among patients who stopped dual-antiplatelet therapy preoperatively and underwent surgery within 6 wk of BMS placement.7 The authors...
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<tr>
<td>Kaluza et al. 2000&lt;sup&gt;1&lt;/sup&gt;</td>
<td>CS</td>
<td>40 (1996-98)</td>
<td>BMS</td>
<td>1–39 d average 13 d</td>
<td>General 10%</td>
<td>100% patients received &gt;1 dose of ticlopidine after PCI</td>
<td>Management for patients with MI/death (n = 9)</td>
<td>Death (n = 8, 20%); MI (n = 7, 18%, 6 fatal, 1 nonfatal); 4/7 MI occurred within 24 hr postop</td>
</tr>
<tr>
<td>Vicenzi et al. 2001&lt;sup&gt;2&lt;/sup&gt;</td>
<td>CR</td>
<td>1 (2000)</td>
<td>BMS</td>
<td>32 d</td>
<td>Urologic</td>
<td>100% patients were receiving ASA before PCI</td>
<td>6/9 ticlopidine discontinued 0–2 d preop</td>
<td>MI 2 hr postop; PCI performed with successful recanalization of stent Death/MI/stent thrombosis 4% (n = 8)</td>
</tr>
<tr>
<td>Wilson et al. 2003&lt;sup&gt;3&lt;/sup&gt;</td>
<td>R</td>
<td>207 (1990-2000)</td>
<td>BMS</td>
<td>1–60 d</td>
<td>Vascular 57.8%</td>
<td>All patients started on ASA/heparin prior to procedure</td>
<td>At time of surgery: ASA/thieno 27% (n = 54)</td>
<td>All adverse cardiac events occurred in patients who underwent surgery within 6 wks of PCI</td>
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<tr>
<td>Marcucci et al. 2004&lt;sup&gt;4&lt;/sup&gt;</td>
<td>CR</td>
<td>1 (2003)</td>
<td>BMS (1-LAD; 1 LCx)</td>
<td>6 wk</td>
<td>Thoracic</td>
<td>Dual APT with ASA/clopidogrel for 4 wk</td>
<td>No APT/ACT for &gt;10 d 6% (n = 13)</td>
<td>No adverse cardiac events in patients who underwent surgery 7–9 wks after PCI</td>
</tr>
<tr>
<td>Sharma et al. 2004&lt;sup&gt;5&lt;/sup&gt;</td>
<td>R</td>
<td>47 (1995-2000)</td>
<td>BMS</td>
<td>All patients: &lt;3 wk 27 pts &lt;3 wk 20 pts ≥3 wk</td>
<td>Vascular GI Urologic Cancer Ortho No difference between groups (&lt;3 wk vs ≥3 wk)</td>
<td>Dual APT 2–4 wk 1995–98: ASA/ticlopidine 1998–2000: ASA/clopidogrel</td>
<td>No APT/ACT for &gt;3 wk 6/7 patients off thieno died (85.7% mortality); 1 patient died while on dual APT &gt;3 wk: 1/6 patients off thieno died (16.6% mortality); 2 patients suffered non-STEMI (no thieno); all deaths occurred early postop (&lt;17 d)</td>
<td>No difference in bleeding between patients on/off thieno (Continued)</td>
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Table 1. Percutaneous Coronary Intervention with Bare-Metal Stenting and Noncardiac Surgery
recommended a 6-wk course of dual-antiplatelet therapy, presuming that BMS endothelialization would be completed during this time, thereby preventing perioperative stent thrombosis and its sequelae. The most powerful predictor of acute stent thrombosis in BMS is a time delay of <14 days between implantation and interruption of dual-antiplatelet therapy. The current 2007 ACC/AHA Perioperative Guidelines state BMS thrombosis is exceedingly rare more than 4 wk after insertion. However, Doyle et al. suggest otherwise. In their retrospective study of 4503 patients, the investigators found a 2% cumulative incidence in BMS thrombosis at 10 yr, which was increased among patients considered “off-label” for drug-eluting stent (DES) use (P = 0.024). Very late (>12 mo) BMS thrombosis was also associated with increased risk of death (P < 0.001). However, the authors did not mention whether any of these cases occurred perioperatively.

Numerous publications of perioperative morbidity and mortality in patients with DES, coupled with clinical and pathology reports of incomplete stent endothelialization, suggest that acute stent thrombosis, MI, and death may be more prevalent than previously thought with these devices, particularly when dual-antiplatelet therapy is interrupted perioperatively. The current 2007 ACC/AHA Perioperative Guidelines state BMS thrombosis is exceedingly rare more than 4 wk after insertion of dual-antiplatelet therapy. The current 2007 ACC/AHA Perioperative Guidelines state BMS thrombosis is exceedingly rare more than 4 wk after insertion of dual-antiplatelet therapy.

### Table 1. Continued

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<tr>
<td>Reddy et al. 2005&lt;sup&gt;4&lt;/sup&gt;</td>
<td>R</td>
<td>56 (1993–2004)</td>
<td>BMS</td>
<td>0–14 d: 8 pts 15–42 d: 8 pts &gt;42 d: 40 pts</td>
<td>Vascular 20% Abdominal 18% Ortho 13% Ophtho 11% GYN/GU 11% ENT 7% Neuro 7% Transplant 5%</td>
<td>21-GPIIb/IIIa inhibitors 14%-heparin 98%-on ASA after PCI 96%-on clopidogrel after PCI</td>
<td>79% taking ASA; 32% clopidogrel Time to discontinuation of ASA/ clopidogrel not reported</td>
<td>0–14 d: 2 MI, 1 death, 1 major bleeding 15–42 d: 4 MI, 3 deaths, 2 major bleeding &gt;42 d: no adverse events of patients with MI/death 60% taking ASA and 60 taking clopidogrel (patients not specified)</td>
</tr>
<tr>
<td>Vicenzi et al. 2006&lt;sup&gt;5&lt;/sup&gt;</td>
<td>P/O</td>
<td>103 (2001–2004)</td>
<td>25 BMS 5 DES 79 cases: stent type not reported</td>
<td>Within 1 yr Vascular 25.2% ENT 2.9% Orthopedic 6.8%</td>
<td>General 26.2% Urologic 13.6%</td>
<td>ASA plus clopidogrel</td>
<td>ASA plus clopidogrel either continued throughout periop period or stopped &lt;3 d preop 100% patients received either UFH or LMWH in therapeutic doses</td>
<td>Cardiac complications 44%; death 5%; MI 13%; myocardial cell injury 22%; bleeding 4% All cardiac complications occurred within 60 d of PCI 21.11-fold risk of suffering cardiac event &lt;25 d after PCI v &gt;90 d after PCI 1 pt: postop MI (31 d after BMS)–no PCI 1 pt: postop MI (90 d after BMS)–no PCI 1 pt: postop MI (44 d after BMS)–PCI, then MI and death</td>
</tr>
<tr>
<td>Brichon et al. 2006&lt;sup&gt;34&lt;/sup&gt;</td>
<td>R</td>
<td>32 (1999–2004)</td>
<td>32 pts–all BMS</td>
<td>&lt;30 d 22% 30–60 d 53% 61–90 d 25%</td>
<td>Lobectomy 84% Pneumonectomy 16%</td>
<td>ASA plus clopidogrel</td>
<td>Periop heparin 34% (ASA discontinued) Periop heparin/ ASA 66% Clopidogrel stopped in all pts 7–10 d before surgery</td>
<td>1 pt: postop MI (90 d after PCI)–PCI 1 pt: postop MI (90 d after BMS)–PCI 1 pt: postop MI (44 d after BMS)–PCI, then MI and death</td>
</tr>
</tbody>
</table>

CS = case series; CR = case report; R = retrospective study; P/O = prospective/observational study; L = letter.

BMS = bare-metal stent; DES = drug-eluting stent; LAD = left anterior descending artery; LCX = left circumflex artery.

PCI = percutaneous coronary intervention; ASA = aspirin; GP = antiplatelet therapy; LMWH = low molecular weight heparin; ACT = anticoagulation therapy; MI = myocardial infarction; Thieno = thienopyridine; SES = sirolimus-eluting stent; PES = paclitaxel-eluting stent; UFH = unfractionated heparin; RCA = right coronary artery; OM = obtuse marginal artery; ENT = ear, nose, throat; GYN = gynecological; GU = genitourinary; GI = gastrointestinal.
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<tr>
<td>Fleron et al. 2003</td>
<td>CR</td>
<td>1 (2003)</td>
<td>2-SES</td>
<td>3 mo</td>
<td>Mastectomy</td>
<td>Dual APT with ASA/ clopidogrel for 3 mo–course completed 6-mo course ASA/ clopidogrel</td>
<td>Clopidogrel/ASA stopped 9 d prior to procedure</td>
<td>MI and cardiogenic shock postop</td>
</tr>
<tr>
<td>Auer et al. 2004</td>
<td>CR</td>
<td>1 (2003)</td>
<td>1 BMS (RCA)</td>
<td>12 wk</td>
<td>Orthopedic</td>
<td>Dual APT discontinued after 3 mo of therapy (length of cessation not reported)</td>
<td>MI occurred 2 hours postop–PCI performed: both PES occluded and recanalized; BMS patient–no therapy needed</td>
<td></td>
</tr>
<tr>
<td>McFadden et al. 2004</td>
<td>CS</td>
<td>4 (2004)</td>
<td>2 pts: 1 SES 2 pts: 1 PES</td>
<td>331–442 d</td>
<td>Urologic General GI endoscopy</td>
<td>ASA plus clopidogrel</td>
<td>1 patient with SES: stopped dual APT other 3 patients stopped clopidogrel, taking ASA only</td>
<td>Stent thrombosis and MI occurred in all 4 patients 4–14 d after discontinuation of ASA/ clopidogrel (4–5 d postop) PCI performed with successful recanalization in all 4 cases 1 patient also had BMS which was patent hours postop: cardiogenic shock–emergent PCI, recanalized occluded RCA–SES; patient died 4 d later 11 d postop: cardiogenic shock, PCI performed with cannalization to LAD–SES</td>
</tr>
<tr>
<td>Nassar et al. 2005</td>
<td>CR</td>
<td>2 (2004)</td>
<td>1 pt: 2 SES (RCA) 1 pt: 1 SES (LAD)</td>
<td>4 mo 21 mo</td>
<td>Excisional biopsy supraclavicular node Total hip replacement</td>
<td>Clopidogrel 1 mo; lifetime ASA Not reported</td>
<td>ASA stopped 10 d prior ASA stopped, but time not reported</td>
<td>Death due to sepsis with peak troponin ( n = 11.53 ) mcg/L (SES implanted for 6 mo; ASA only continued) Two pts with troponin leaks, but no other abnormalities No complications in 11/15 pts, no excess bleeding (Continued)</td>
</tr>
<tr>
<td>Charbuchinska et al. 2006</td>
<td>CS</td>
<td>15 (18 procedures) 2006</td>
<td>7 pts: PES 7 pts: SES</td>
<td>1–12 mo 1 pt: 2 PES + 1 SES 3 pts: not reported</td>
<td>Vascular</td>
<td>All taking ASA preop; 14 taking clopidogrel preop</td>
<td>Death due to sepsis with peak troponin ( n = 11.53 ) mcg/L (SES implanted for 6 mo; ASA only continued) Two pts with troponin leaks, but no other abnormalities No complications in 11/15 pts, no excess bleeding (Continued)</td>
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<tr>
<td>Broad et al. 2007&lt;sup&gt;145&lt;/sup&gt;</td>
<td>CS 3 (2006)</td>
<td>1 pt: PES (1st Dx), BMS (LAD)</td>
<td>49 d</td>
<td>Parathyroidectomy</td>
<td>ASA plus clopidogrel</td>
<td>Clopidogrel stopped 5 d preop</td>
<td>Tirofiban (GPIIb/IIa inhibitor) started 3 d preop</td>
<td>6 h preop: tirofiban/heparin discontinued</td>
<td>No complications in any patient</td>
</tr>
<tr>
<td></td>
<td>1 pt: PES (LAD)</td>
<td>1 yr</td>
<td></td>
<td>Microlaryngoscopy/vocal cord biopsy</td>
<td>ASA plus clopidogrel</td>
<td>ASA plus clopidogrel</td>
<td></td>
<td></td>
<td>Patient 3 previously presented for subacromial decompression 18 mo after DES–clopidogrel was stopped, and the patient suffered a preop MI 7 d after clopidogrel stopped</td>
</tr>
<tr>
<td></td>
<td>1 pt: PES (RCA)</td>
<td>33 mo</td>
<td></td>
<td>ENT/GU/Ortho</td>
<td>ASA plus clopidogrel</td>
<td></td>
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<tr>
<td>de Souza 2007&lt;sup&gt;40&lt;/sup&gt;</td>
<td>CR 1 (2006)</td>
<td>2 PES (1 LCx, 29 mo 1 LAD)</td>
<td>Nephroureterectomy</td>
<td>ASA plus clopidogrel for 1 yr, then ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70 min in PACU: ventricular tachycardia, then ST changes indicating posterior MI, then cardiogenic shock</td>
</tr>
<tr>
<td>Head et al. 2007&lt;sup&gt;23&lt;/sup&gt;</td>
<td>CR 2 (2006)</td>
<td>1 pt: PES (2-RCA, 1-OM)</td>
<td>8 mo</td>
<td>Renal transplant</td>
<td>ASA plus clopidogrel</td>
<td>ASA plus clopidogrel stopped 7 d preop</td>
<td></td>
<td></td>
<td>MI 1 hr postop–PCI recanlazed, thrombosed LCx stent</td>
</tr>
<tr>
<td></td>
<td>1 pt: 2 DES-RCA, 2DES-LCx, 1 BMS-PDA</td>
<td>6 mo</td>
<td></td>
<td>Kidney–pancreas transplant</td>
<td>Lifelong ASA/clopidogrel therapy</td>
<td>ASA plus clopidogrel stopped 1 day preop, ASA resumed POD1, clopidogrel resume POD2</td>
<td></td>
<td></td>
<td>No cardiac complications; patient suffered significant postoperative bleeding</td>
</tr>
<tr>
<td>Chung et al. 2007&lt;sup&gt;25&lt;/sup&gt;</td>
<td>L 6 mo</td>
<td>1 DES (LAD)</td>
<td>Cervical medianoscopy</td>
<td>ASA plus clopidogrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Postop: emergent PCI for LAD thrombosis with unsuccessful canalization–death ensued</td>
</tr>
<tr>
<td>Bakhru et al. 2006&lt;sup&gt;56&lt;/sup&gt;</td>
<td>R 114 (2004–2006)</td>
<td>DES</td>
<td>11.4%: 90 d 30.7%: 180 d 1 pt: 33 d 1 pt: 297 d 10%: 0–30 d 26%: 30–180 d 34%: 180–365 d 30%: &gt;365 d</td>
<td>Not specified</td>
<td>ASA plus clopidogrel</td>
<td>ASA plus clopidogrel discontinued at 10 d in 77% 78% major cases: ASA continued</td>
<td></td>
<td></td>
<td>2 MI in 2 pts: thrombosis not seen by catheterization</td>
</tr>
<tr>
<td>Compton et al. 2006&lt;sup&gt;27&lt;/sup&gt;</td>
<td>R 38 (2003–2006)</td>
<td>57% SES 43% PES</td>
<td>28 pts: 34% abdominal, 22% vascular, 17% urological, 27% other 10 pts: minor procedures</td>
<td></td>
<td>ASA plus clopidogrel</td>
<td>ASA plus clopidogrel</td>
<td></td>
<td></td>
<td>No thrombotic or bleeding complications</td>
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(Continued)
stopped clopidogrel after the recommended duration for dual-antiplatelet therapy (3 mo for sirolimus-eluting stents; 6 mo for paclitaxel-eluting stents). When clopidogrel alone was discontinued, the median time to an adverse clinical event was 30 days (range, 14–690 days). In comparison, if both aspirin and clopidogrel were stopped, the median time to an adverse clinical event was 7 days (3–150 days, \( P < 0.0001 \)). Forty-two percent of events occurred in relation to a surgical procedure in which dual-antiplatelet therapy or clopidogrel alone were discontinued. The morbidity and mortality rates were 92% and 8%, respectively. There was no difference in occurrence between sirolimus- and paclitaxel-eluting stents. The authors recommended the perioperative continuation of aspirin.

**THE PERIOPERATIVE DILEMMA**

Patients with coronary stents, particularly DES, who subsequently present for noncardiac surgery, pose a particular challenge during the perioperative period. Clinicians must balance the risks of discontinuing antithrombotic therapy and the possibility of perioperative stent thrombosis, MI, and cardiac death against continuing clopidogrel and aspirin, thus increasing the potential for surgical bleeding, which in certain cases may be life-threatening. Patients who discontinue dual-antiplatelet therapy prematurely have higher rates of rehospitalization and mortality when compared with those who continue therapy.\(^{46}\) Surgery performed early after DES implantation is associated with a significantly increased incidence of perioperative MI and death, regardless of whether clopidogrel and aspirin are continued.\(^{47,48}\) Moreover, a patient may complete the recommended 12-mo duration of antiplatelet therapy yet still be at risk for perioperative stent thrombosis, MI, and death. Some institutions treat patients with dual-antiplatelet therapy for 12–24 mo, and in cases where there are additional stent complexities and comorbidities (Table 3), clopidogrel and aspirin are continued indefinitely.\(^{4,47,49}\) This complicates management since 60%–70% of patients are receiving DES for “off-label” or unapproved use (Table 3), which further increases the risk of catastrophic stent thrombosis, MI, and death.\(^{33,50–54}\) Chassot et al. contend, based on the currently available data, that the risks of withdrawing patients from antiplatelet drugs are greater than continuing them, imposing a perioperative cardiac death rate that is increased 5- to 10-times.\(^{55}\)

Surgical intervention creates a prothrombotic and proinflammatory state conducive to development of perioperative stent thrombosis. The stress response to surgery includes sympathetic activation and cytokine
release that promote shear stress on arterial plaques, enhanced vascular reactivity conducive to vasospasm, reduced fibrinolytic activity, increased platelet activation, and hypercoagulability.\textsuperscript{56,57} Significant increases in platelet counts may still be observed a week postoperatively. \textsuperscript{58} While procoagulant clotting factors increase, fibrinolysis is impaired, producing a hypercoagulable state, which persists for several days postoperatively.\textsuperscript{8,59} This environment far exceeds the prothrombotic state observed in acute coronary syndromes (ACS) in the absence of any surgical stimulation.\textsuperscript{60} Inflammatory activation from endothelial damage, during both PCI and surgery, exacerbates the prothrombotic state, worsening the susceptibility for thromboembolic events. Autopsy results have shown this mechanism is responsible for at least half of all perioperative MIs.\textsuperscript{48,61} Despite this milieu, surgeons often stop all antiplatelet drugs preoperatively, regardless of their patients' co-morbidities, to minimize intraoperative bleeding.

Withdrawal of oral antiplatelet drugs is an independent predictor of mortality in patients with ACS and those at risk for coronary artery disease (CAD).\textsuperscript{62,63} Abrupt cessation of aspirin results in a rebound phenomenon, whereby both cyclooxygenase-1 and thromboxane B\textsubscript{2} (the product of thromboxane A\textsubscript{2} [TxA\textsubscript{2}] hydrolysis) levels increase rapidly, not returning to baseline for 3–4 days.\textsuperscript{64} Complete recovery of platelet function occurs in half of patients by day 3, and 80% of patients by day 4.\textsuperscript{65} These patients subsequently generate increased levels of thrombin and decrease fibrinolysis, further enhancing platelet aggregation and worsening the risk for perioperative stent thrombosis, MI, and death. Collet et al. prospectively studied 1358 patients admitted with ACS and found a two-fold increase in both death and death/MI among recent withdrawers compared with chronic users and nonusers.\textsuperscript{66} Recent withdrawers comprised 5% of the patients who presented with ACS, having interrupted aspirin monotherapy <3 wk of admission. Of this group, 57.5% had known CAD, and 64% had discontinued aspirin for scheduled surgery. Multivariate analysis found aspirin withdrawal to be a strong independent predictor (OR = 2.02, \( P = 0.003 \)) of mortality and death/MI at 30 days. Aspirin interruption was also found to be an independent predictor for bleeding events (OR = 2.6, \( P < 0.01 \)). Ferrari et al. found, in 383 patients with established CAD hospitalized with recurrent ACS, 13.3% of events occurred 10.9 ± 1.9 days (range, 4–17 days) after abrupt aspirin withdrawal.\textsuperscript{67} Ten (20%) patients developed thrombosis of a BMS implanted 15.5 ± 6.5 mo earlier, which accounted for 50% of the ST-segment elevation MIs (STEMIs) diagnosed. Aspirin was interrupted in 20 patients (40%) for minor surgery or dental treatment. Biondi-Zoccai et al. performed a meta-analysis of 50,279 patients at risk for CAD and found aspirin nonadherence/withdrawal was associated with a three-fold increase in the risk of death and MI (OR = 3.14, \( P = 0.0001 \)).\textsuperscript{63} The risk was significantly higher in patients with intracoronary stents (OR = 89.78, \( P < 0.001 \)). Although the data from these
studies are not specifically from perioperative patients, it is likely applicable. The loss of aspirin’s protective effect during the hypercoagulable perioperative state confers an increased risk of stent thrombosis not fully appreciated by clinicians.

Recent studies suggest that clopidogrel may provide antiinflammatory protection, further attenuating the thrombotic process. Abrupt withdrawal may result in a proinflammatory and prothrombotic state. After 12 mo of dual-antiplatelet therapy in diabetics with DES, significant increases in platelet aggregation ($P < 0.0001$) and inflammatory biomarkers ($P < 0.05$ for C-reactive protein, $P < 0.001$ for P-selectin) were measured 1 mo after clopidogrel withdrawal. This may have serious perioperative implications, particularly for surgical patients with additional risk factors for stent thrombosis.

**IMPACT OF ASPIRIN AND CLOPIDOGREL ON PERIOPERATIVE BLEEDING**

The impact of aspirin on surgical bleeding has been primarily studied in cardiac and vascular surgery. Although preoperative aspirin may increase chest tube drainage and re-exploration rates in cardiac surgery, these clinical end-points were observed with larger doses ($\geq 325$ mg), prolonged duration of cardiopulmonary bypass, lack of antifibrinolytic use, and emergent/urgent surgery without a difference in operative mortality rates. Tuman et al. evaluated the influence of preoperative aspirin versus placebo on patients undergoing reoperative coronary artery bypass graft (CABG). No significant difference was found in mediastinal drainage, re-exploration, or blood-component transfusion between the two groups. Further, the timing of the most recent aspirin ingestion did not impact blood loss. In patients undergoing “off-pump” CABG, there was no difference in blood loss between aspirin users and nonusers. Others advocate using 75–150 mg of aspirin, since these smaller doses reduce morbidity and mortality and have less risk of perioperative bleeding.

The peri- and postoperative protective effects of aspirin have been well documented in vascular surgery. Perioperative aspirin significantly improves long-term peripheral bypass graft patency. Low-dose aspirin (75 mg/d) started preoperatively appears to have a protective effect against transient ischemic attacks and stroke in patients undergoing carotid endarterectomy. Burger et al. performed a review and meta-analysis of the surgical and interventional literature to determine the risks of low-dose aspirin withdrawal versus the bleeding risks associated with aspirin continuation. Aspirin withdrawal preceded 10.2% of acute cardiovascular syndromes (MI, stroke, peripheral arterial occlusion, cardiac death). Although aspirin increased the incidence of bleeding by a factor of 1.5, it did not increase the severity or perioperative morbidity/mortality, except in intracranial surgery and, possibly, transurethral prostatectomy, where increased bleeding may be life-threatening. The authors recommended discontinuing aspirin only if the risk of bleeding complications exceeds the cardiovascular risks of aspirin withdrawal. Whether aspirin increases blood loss in noncardiovascular surgery is not well

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**Figure 2.** Time from discontinuation of clopidogrel (triangles) and of clopidogrel and aspirin (squares) to an adverse clinical event [death, myocardial infarction (MI)]. The time axis is in logarithmic scale. Bars = medians. Reproduced from Artang R, Dieter RS. Analysis of 36 reported cases of late thrombosis in drug-eluting stents placed in coronary arteries. (Reprinted with permission from Elsevier Limited. Am J Cardiol 2007;99:1039–43; Fig. 1, page 1041.)

**Table 3.** Risk Factors for Perioperative Stent Thrombosis with Drug-Eluting Stents

| Stent(s) implanted in the left main coronary artery | Stent(s) implanted in bifurcations or crossing arterial branch points |
| Greater total stent length (multiple stents and/or overlapping stents) | Heightened platelet activity (surgery, malignancies, diabetes) |
| In-stent restenosis | Left ventricular dysfunction |
| Localized hypersensitivity vasculitis (possibly to the stent polymer or antiproliferative drug) | Penetration by stent into necrotic core |
| Plaque disruption into non-stented segment | Renal failure/insufficiency |
| Diabetes | Resistance to antiplatelet medications |
| Inappropriate discontinuation of antiplatelet drug therapy | |
studied, and the data are conflicting, with increased bleeding observed only in specific procedures. 85–90 In their review, Merritt and Bhatt concluded aspirin monotherapy should be continued in elective noncardiac surgery. 91

The likelihood of increased bleeding and/or an increased requirement for blood transfusion in patients undergoing major noncardiac surgery while taking clopidogrel has largely been inferred from the cardiac surgical literature, which contains conflicting data.92 Patients who remain on clopidogrel and aspirin while undergoing CABG, particularly within days of the scheduled procedure, have a significantly higher incidence of perioperative bleeding, reexploration, blood-component transfusion, and extended intensive care/hospital stays.83,93–100 Although Yende et al. reported a higher incidence of reexploration for bleeding in patients receiving clopidogrel preoperatively (9.8% vs 1.6%, P = 0.01), no significant difference in bleeding, transfusion requirements, and perioperative mortality was found among patients receiving clopidogrel/aspirin/heparin versus aspirin/heparin alone.93,96,101,102 Of the 2072 patients who underwent CABG in the Clopidogrel in Unstable Angina to Prevent Recurrent Events study, there was an overall 1% excess of severe bleeding.103 Patients who stopped clopidogrel >5 days before CABG did not have significant bleeding, but a trend towards increased postoperative bleeding was observed among patients who stopped clopidogrel within 5 days of CABG (9.6% vs 6.3% in the placebo group, relative risk = 1.53). Additional studies of on- and off-pump CABG report significantly increased blood component-transfusion rates without increased morbidity/mortality in patients receiving clopidogrel.94,95,104 However, other studies of blood product transfusion have found transfusion itself to confer a significant long-term survival disadvantage. Koch et al. reported significant reductions in both early and long-term survival in patients receiving a perioroperative blood transfusion with CABG.105,106 The 10-yr survival rate among patients transfused with 1 U of red blood cells was 63% versus 80% in nontransfused patients (P < 0.0001). One may extrapolate that each additional unit of transfused blood products further decreases long-term survival.

There is little evidence to define the true impact of continuing thienopyridines on bleeding in noncardiac surgery, and the information available remains anecdotal and inconsistent.91,107 When compared with aspirin alone, the combination of clopidogrel and aspirin increases the absolute risk of major bleeding by 0.4%–1.0%.108–111 Chapman et al. described a case in which dual-antiplatelet therapy caused massive hemorrhage during elective abdominal aortic aneurysm repair.112 Two other cases of severe bleeding during carotid endarterectomy have been reported.113 Both patients were taking clopidogrel and aspirin. In a multicenter registry, Vichova et al. reported an 18.6% postoperative bleeding complication rate; aspirin and clopidogrel had been withheld in 26% and 24% of patients, respectively.38 After transbronchial biopsy, Ernst et al. reported an 89% bleeding rate in patients taking clopidogrel versus 3.4% in patients not receiving antiplatelet therapy.114 However, bleeding was controlled endoscopically and no transfusions were administered. A study conducted by Payne et al. in healthy volunteers found after 2 days of treatment with clopidogrel 75 mg and aspirin 150 mg that there was a significant 3.4-fold increase in bleeding time.115 The authors suggested the combination of these drugs carried a significantly increased risk of surgical bleeding. In contrast, the same authors found that neither surgical bleeding nor transfusion rates increased during carotid endarterectomy in patients pretreated with clopidogrel and aspirin.116 On the contrary, a beneficial and significant reduction in transcranial Doppler-determined incidence of emboli was demonstrated. If antiplatelet therapy is discontinued, the risk of bleeding decreases; however, if antiplatelet therapy is discontinued <10 days before surgery, there is still an increased risk, although this remains ill-defined.1,7,9 Multiple case reports and series found similar bleeding and transfusion frequencies regardless of the dual-antiplatelet regimen administered.3,6,7,42 Schouten et al. found transfusion was required in 24% of patients continuing and 20% of patients who discontinued antiplatelet therapy (P = 0.50).47 Further, there was no difference in the number of units transfused between the two groups. In their review, Chassot et al. reported that perioroperative clopidogrel use increased surgical bleeding and transfusion rates by 50% without concomitant increased morbidity and mortality, except in intracranial surgery.55 Moreover, they report a complication rate of red blood cell transfusion of only 0.4%, and mortality due to massive surgical blood loss of ≤3%. In procedures where blood loss can be controlled easily, there may be no indication to stop antiplatelet drugs.92,117

Despite concerns regarding perioroperative bleeding, data suggest postoperative clopidogrel confers a protective effect against MI, stroke, and death. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial indicates clopidogrel monotherapy was more effective than aspirin alone in reducing the combined risk of ischemic stroke, MI, and vascular death in high-risk patients with previous CABG (relative risk reduction 8.7%).118,119 Fewer gastrointestinal side effects were observed with clopidogrel than with aspirin monotherapy.

CURRENT RECOMMENDATIONS FOR PERIOPERATIVE MANAGEMENT OF PATIENTS WITH CORONARY ARTERY STENTS

At present, there is no definitive standard of care for the management of surgical patients with coronary artery stents.47 Evidence-based medicine currently
Table 4. Duration of Antiplatelet Therapy and Timing of Noncardiac Surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Duration of Antiplatelet Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilatation without stenting</td>
<td>2–4 wk of dual-antiplatelet therapy</td>
</tr>
<tr>
<td>Surgery postponed for 2–4 wk (vital surgery only)</td>
<td>PCI and BMS: 4–6 wk minimum of dual-antiplatelet therapy</td>
</tr>
<tr>
<td>Elective surgery postponed ≥6 wk, but not for more than 12 wk, when restenosis may begin to occur</td>
<td>PCI and DES: 12 mo of dual-antiplatelet therapy</td>
</tr>
<tr>
<td>Elective surgery postponed ≥12 mo In patients in whom coronary revascularization with PCI is appropriate for mitigation of cardiac symptoms and who need elective noncardiac surgery in the subsequent 12 mo, a strategy of balloon angioplasty or BMS placement followed by 4 to 6 wk of dual-antiplatelet therapy is probably indicated</td>
<td>Aspirin: lifelong therapy, whichever is the revascularization technique</td>
</tr>
</tbody>
</table>


fails to identify the optimum perioperative antiplatelet regimen in these patients, particularly those with DES. Ultimately, registries and prospectively studied protocols are critical to determine the safest management strategies and provide evidence-based recommendations. Education of surgeons and anesthesiologists, as well as development of well-publicized institutional policies and perioperative management guidelines, are paramount to understanding the perioperative risks associated with coronary stents and to preventing catastrophic stent thrombosis. In a survey of anesthesiologists, 63% were unaware of recommendations regarding the appropriate length of time between stent placement and a subsequent surgical procedure. Thirty-six percent of the respondents recommended no delay or a 1–2 wk interval between PCI and stenting, which is clearly insufficient regardless of the stent type implanted.

The 2007 AHA/ACC/Society for Cardiovascular Angiography and Interventions/American College of Surgeons/American Dental Association Science Advisory concluded that premature discontinuation of dual-antiplatelet therapy markedly increases the risk of catastrophic stent thrombosis, MI, and death. They recommend postponing all elective procedures for which there is a significant risk of bleeding until dual-antiplatelet therapy is completed (Table 4). However, if patients with DES are to undergo subsequent procedures that mandate discontinuation of thienopyridine therapy, aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure because of concerns about late stent thrombosis. Aspirin should also be continued perioperatively in patients with BMS. Additional guidelines for prophylactic PCI and stent implantation are included in Table 4.

Table 5. Preoperative Evaluation in Patients with Coronary Artery Stents

<table>
<thead>
<tr>
<th>Evaluation</th>
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</thead>
<tbody>
<tr>
<td>Determine the type of stent(s): BMS, SES, PES</td>
</tr>
<tr>
<td>When were stents(s) implanted?</td>
</tr>
<tr>
<td>Determine location of stent(s) in coronary circulation</td>
</tr>
<tr>
<td>How complicated was the revascularization (longer length, overlapping stents)</td>
</tr>
<tr>
<td>Were there any complications during the revascularization (i.e., malposition)?</td>
</tr>
<tr>
<td>Is there a previous history of stent thrombosis?</td>
</tr>
<tr>
<td>What antiplatelet regimen is being followed?</td>
</tr>
<tr>
<td>Determine patient’s comorbidities, if any, to further ascertain level of risk (ejection fraction, diabetes, renal insufficiency, see Table 3)</td>
</tr>
<tr>
<td>What is the recommended duration of dual-antiplatelet therapy for that specific patient?</td>
</tr>
<tr>
<td>Consultation with an interventional cardiologist, or preferably, patient’s cardiologist to elucidate procedural complexities, review current antiplatelet management, and discuss optimal patient management strategy</td>
</tr>
</tbody>
</table>

BMS = bare-metal stent; DES = drug-eluting stent; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

Similar recommendations have been published in multiple other publications, including the ACC/AHA 2007 Perioperative Guidelines for Noncardiac Surgery. However, Chassot et al. and others contend dual-antiplatelet therapy is the cornerstone for stent thrombosis prevention, and the risk of discontinuing clopidogrel and aspirin preoperatively outweighs the benefit of reduced hemostasis, especially in patients with procedural complexities and comorbidities, which place them at higher risk for developing stent thrombosis (Table 3). In their recent publication, the authors emphasized the importance of continuing aspirin throughout the perioperative period, except in instances when surgery is performed in a closed space (intracranial surgery, posterior chamber of the eye, spinal surgery in the medullary canal). Chassot et al. also recommend postponing elective surgery for 3 mo in patients with BMS, whereas the 2007 ACC/AHA Guidelines state elective surgery should be performed between 6 and 12 wk after BMS, when restenosis begins to occur.

Although case reports and series of perioperative management of patients with DES have been published, there are no universally accepted guidelines. The anesthesiologist, as perioperative physician, can play a pivotal role in ensuring patient safety. Early preoperative identification and use of a multidisciplinary team approach to guide perioperative management is essential. Important aspects of the preoperative assessment are included in Table 5. Many advocate simply the perioperative continuation of clopidogrel and aspirin whenever possible. In 2006, a French task force comprised of cardiologists, anesthesiologists, hematologists, and surgeons published perioperative management guidelines. Although the task force emphasized total withdrawal of dual-antiplatelet therapy exposes patients to an undue risk of stent
thrombosis and advised the continuation of aspirin, they recommended the substitution of flurbiprofen, a reversible nonsteroidal antiinflammatory drug (NSAID), and low molecular weight heparin (LMWH) in surgical procedures with excessive hemorrhagic risk. The substitution of nonselective NSAIDs and LMWH for dual-antiplatelet therapy is controversial and there is no scientific evidence to support their efficacies in preventing perioperative stent thrombosis, as ACS has been reported with this practice. The concomitant use of nonselective NSAIDs and aspirin significantly increases cardiac morbidity and mortality in patients with CAD and the incidence may be even higher in patients with coronary stents. Nonselective NSAIDs competitively inhibit aspirin binding to the serine residue at position 530 by binding to the catalytic site of cyclooxygenase-1. Collet and Montalescot contend there are no good alternatives to clopidogrel and aspirin.

Although heparin therapy is often used perioperatively for thromboembolic prophylaxis, it does not have antiplatelet properties and is not protective against stent thrombosis. Further, “heparin re-bound” occurs after abrupt cessation of an unfractionated heparin (UFH) infusion. Vicenzi et al. described an association between perioperative heparin therapy and increased cardiac morbidity and mortality among patients with coronary stents. During UFH infusion, increases in thrombin and platelet activity have been measured and persist for many hours after an infusion is discontinued, whereas any protective anticoagulant effect declines rapidly because of the short half-life of UFH. Webster et al. found that the administration of UFH significantly and transiently increases platelet aggregation despite chronic aspirin therapy (150 mg/d) in patients undergoing carotid endarterectomy or lower extremity angioplasty but before heparinization; D, 3 min after heparin was administered, before insertion of shunt; E, 3 min after shunt opening; F, at the end of surgery, after flow restoration; G, 4 h postoperatively; and H, 24 h postoperatively but before the next dose of aspirin. Reproduced from Webster SE, Payne DA, Jones CI, Hayes PD, Bell PR, Goodall AH, Naylor AR. Antiplatelet effect of aspirin is substantially reduced after administration of heparin during carotid endarterectomy. J Vasc Surg 2004;40:463–8; Fig. 1, page 465.

Figure 3. Platelet aggregation in response to arachidonic acid (5 mmol/L) in patients undergoing carotid endarterectomy at time points A, preoperative, at admission to hospital; B, after induction of anesthesia but before skin incision; C, after skin incision and soft tissue dissection but before heparinization; D, 3 min after heparin was administered; E, 3 min after shunt opening; F, at the end of surgery, after flow restoration; G, 4 h postoperatively; and H, 24 h postoperatively but before the next dose of aspirin. Reproduced from Webster SE, Payne DA, Jones CI, Hayes PD, Bell PR, Goodall AH, Naylor AR. Antiplatelet effect of aspirin is substantially reduced after administration of heparin during carotid endarterectomy. J Vasc Surg 2004;40:463–8; Fig. 1, page 465.

platelet inhibitor in the treatment of ACS, Théroux et al. reported a lower incidence of death and MI at 7 days, 30 days, and 6 mo. The authors reported major bleeding did not increase in patients receiving aspirin alone or in combination therapy. McDonald et al. reported that preoperative LMWH was associated with significantly increased postoperative bleeding and reexploration in cardiac surgery. However, the INTERACT (Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment) trial suggested enoxaparin, when compared with UFH, reduced perioperative blood loss during CABG and reduced the incidence of death and MI by 39% over a 2.5-yr period. Di Nisio et al. found abrupt cessation of enoxaparin results in rapid increases in prothrombotic activity with maximum levels measured 12 and 24 h after discontinuation. Xiao et al. found minor elevations in platelet activation associated with LMWH.

Brilakis et al. recently summarized treatment options for patients with DES: (1) continue dual antiplatelet therapy throughout the perioperative period for patients at low risk of bleeding; (2) implement “bridging therapy,” in which a short-acting GP IIb/IIIa inhibitor (tiroliban or eptifibatide) or thrombin inhibitor, or both, is substituted for clopidogrel during the perioperative period; or (3) discontinue clopidogrel preoperatively, restarting it as soon as possible postoperatively. Although empiric and without evidence-based data supporting its efficacy, multiple institutions use bridging therapy to prevent perioperative stent thrombosis. GP IIb/IIIa inhibitors have been favored since this platelet receptor is the pivotal mediator for platelet aggregation and thrombus formation (Part I, Fig. 1). Exposure to the vascular subendothelium activates the receptor, causing a marked affinity for fibrinogen and von Willebrand factor, the principal adhesive macromolecules responsible for crosslinking platelets by binding adjacent GP IIb/IIIa receptors. This facilitates platelet aggregation, the final common pathway for platelet plug and thrombus formation. The development of GP IIb/IIIa inhibitors (abciximab, eptifibatide, and
tirofiban) was integral in preventing thrombus formation and improving outcome in patients with ACS, particularly patients with non-STEMI. In addition to preventing platelet aggregation, these inhibitors (1) displace fibrinogen from GP IIb/IIIa receptors and (2) block signaling processes, which further prevents secretion, clot retraction, and prothrombotic activity. GP IIb/IIIa inhibitors are more potent than the combination of aspirin and a thienopyridine.

Broad et al. in 2007 published a series using bridging therapy in three patients undergoing elective noncardiac surgery 49 days to 33 mo after DES placement. Aspirin was continued throughout the perioperative period. All three patients stopped clopidogrel therapy 5 days preoperatively and were admitted for bridging therapy with tirofiban and heparin 2 days later. Both infusions were continued for 3 days until midnight, the day before surgery. Each surgery proceeded uneventfully, and either clopidogrel (postoperative day 1) or tirofiban (4 h postoperatively) was resumed. There were no cardiac or bleeding complications reported. More recently published protocols, including from the Cleveland Clinic, recommend bridging therapy with GP IIb/IIIa inhibitors primarily (1) in patients who have not completed dual-antiplatelet therapy and (2) in patients whose stent complexities and comorbidities significantly increase their risk for developing catastrophic stent thrombosis and its sequelae.

Reversible P2Y12 receptor antagonists are undergoing clinical trials, and may prove to be of value perioperatively (Part 1, Fig. 1). Cangrelor is a parenteral, reversible direct P2Y12 inhibitor whose half-life of 5–9 min allows 100% recovery of platelet function 1 h after the infusion is stopped. A 4 μg · kg⁻¹ · min⁻¹ infusion achieves complete platelet inhibition when measured at 4 min. Rabbat et al. suggest that cangrelor may play a role in bridging therapy. AZD6140 is an oral, reversible direct P2Y12 receptor antagonist. It provides more rapid and complete platelet inhibition than clopidogrel. AZD6140 has a half-life of 12 h, making it effective in the perioperative setting. Current trials have found similar rates of bleeding. Phase III trials are currently evaluating the efficacy of AZD6140 versus clopidogrel in patients with non-STEMI or STEMI elevation ACS.

Although success with bridging therapy has been reported, prospective studies are necessary to validate it as a viable management strategy. Opponents argue bridging therapy is (1) expensive, (2) logistically difficult, (3) exposes patients to risks associated with a prolonged hospitalization, and (4) confers no protection against intraoperative stent thrombosis. Resuming clopidogrel or a GP IIb/IIIa inhibitor as soon as possible postoperatively is paramount to protecting against stent thrombosis when the risk is greatest. Brilakis et al. recommend a postoperative 600 mg initial dose of clopidogrel, which reduces (1) the time to achieve maximal platelet inhibition (2 vs 6 h with a 300 mg initial dose), and (2) the frequency of hyporesponsiveness to clopidogrel, particularly in patients whose platelets are activated secondary to surgical intervention. However, anesthetic drugs metabolized by CYP3A4 may irreversibly inhibit this isoenzyme and prevent the conversion of clopidogrel to its active state, modulating its antiplatelet effect.

Midazolam irreversibly inactivates CYP3A4 after metabolism to 1-hydroxymidazolam. Midazolam also exerts antiplatelet activity, the mechanisms of which are not fully elucidated; whether this counteracts clopidogrel modulation is unknown. Competitive (reversible) inhibitors, drugs that may not prevent clopidogrel activation, of CYP3A4 include fentanyl, alfentanil, and propofol.

If a patient presents for surgery with aspirin and clopidogrel inadvertently stopped by their surgeon or another physician, some advocate administering 325 mg of nonenteric coated aspirin the day of surgery, and delaying the procedure until later that day. Theoretically, the patient should have antiplatelet effects within 2 h secondary to the rapid absorption of aspirin. A single dose of 160 mg has been shown to completely eliminate platelet TXA2 production; however, this may not be the case in patients with aspirin resistance. Others have suggested administering aspirin 325 mg for 3–5 days to achieve a steady-state, which may overcome issues with resistance.

**MANAGEMENT OF PATIENTS WITH CORONARY ARTERY STENT THROMBOSIS**

When stent thrombosis occurs, it acutely manifests as a STEMI or a sudden malignant dysrhythmia, and must be treated with immediate reperfusion to avoid a transmural MI due to the abrupt interruption of coronary blood flow in a myocardial region that is neither collateralized nor preconditioned by recurrent chronic ischemia. Thrombolytic therapy (IV or intracoronary) is significantly less effective than PCI in treating stent thrombosis and restoring myocardial perfusion. Administration of thrombolytic therapy is often prohibitive in the perioperative period. Therefore, primary PCI is the definitive treatment for perioperative stent thrombosis and restoration of coronary stent patency. Surgical procedures should be performed in institutions where 24-h interventional cardiology is available to provide immediate and emergent intervention. PCI carries an increased risk of bleeding when performed early.
after surgery because antiplatelet and antithrombin drugs must be administered during the procedure.\(^3,121\) However, Brilakis et al. state that the only medications necessary for patients with an acute coronary stent occlusion who have an increased bleeding risk are aspirin and at least one dose of an antithrombin (heparin or bivalirudin).\(^{121,142}\) Berger et al. performed a retrospective analysis of 48 patients with acute MI occurring within 1 wk postoperatively.\(^{187}\) All patients received aspirin and heparin with immediate PCI. Despite the high frequency of cardiogenic shock and cardiac arrest in this study population, the survival rate was 65%. Only one patient developed significant bleeding at the operative site (patient with a knee replacement). Patients who had undergone craniotomies and thoracic surgery were included in this series.

Postoperative management should include admission to a higher-acuity unit with continued electrocardiogram monitoring and cardiology surveillance.\(^{142,184}\) Routine monitoring of cardiac biomarkers would be useful in detecting myocardial injury, recurrent ischemia, and for risk stratification, and should be drawn before emergent transfer to the cardiac catheterization laboratory.\(^{35}\) Elevated perioperative troponin levels are statistically significant independent predictors of morbidity and mortality 1 yr after surgery.\(^{185}\) However, the occlusive nature of stent thrombosis, and continuing myocardial necrosis, may quickly lead to hemodynamic instability, ventricular arrhythmias, cardiogenic shock, or cardiac arrest, necessitating emergent PCI.\(^{186}\)

**CONSIDERATIONS FOR REGIONAL ANESTHESIA FOR PATIENTS WITH CORONARY ARTERY STENTS**

In patients with coronary artery stents, particularly DES, the use of regional anesthesia (RA) must be carefully considered. RA, particularly neuraxial blockade, attenuates the hypercoagulable perioperative state by blunting the sympathetic response.\(^{188–191}\) Systemic absorption of local anesthetics provides antiplatelet effects by blocking TxA\(_2\) and decreasing platelet aggregation.\(^{192–194}\) These benefits may be advantageous, and RA may seem the safest choice in certain situations.\(^3\) However, the potential for stent thrombosis with discontinuation of antiplatelet drugs and potential coagulation abnormalities must be taken into account when considering RA, particularly in patients considered higher-risk\(^{50,55}\) (Table 3).

It is generally interpreted from the 2003 American Society of Regional Anesthesia (ASRA) guidelines that the thienopyridines and dual-antiplatelet therapy are contraindications to neuraxial anesthesia or peripheral nerve blockade in noncompressible regions that cannot be observed for bleeding.\(^{195}\) The actual risk of spinal hematoma is unknown in this population, although case reports of this unfortunate complication in the presence of antiplatelet and antithrombin drugs have been described.\(^{195}\) Although the ASRA recommends discontinuing clopidogrel 7 days and ticlopidine 14 days before RA; they also state, “Variance from recommendations may be acceptable based on the judgment of the responsible anesthesiologist.”\(^{195}\) Following the guidelines confers no guarantee that neuraxial anesthesia will be free from bleeding complications.\(^{195–199}\) In fact, only about one-third of patients who developed neuraxial hematoma in a large series of spinal and epidural anesthetics had any coagulation abnormality.\(^{200}\) Aspirin alone does not appear to increase the risk of neuraxial hematoma, and does not appear to interfere with the performance of neuraxial blockade.\(^{195,199,201}\) However, the concurrent use of UFH or LMWH increases the risks of bleeding and neuraxial hematoma in the presence of aspirin monotherapy.\(^{195,202,203}\) In patients receiving LMWH prophylaxis alone, the current ASRA guidelines recommend delaying neuraxial blockade at least 10–12 h after the last LMWH dose. Patients receiving higher doses will require delays of at least 24 h to assure normal hemostasis at the time of needle placement.\(^{195}\) Although there is small or very limited risk associated with neuraxial blockade in the presence of subcutaneous UFH treatment alone, ASRA does not consider this treatment a contraindication to neuraxial blockade or catheter placement.\(^{195}\) However, in patients who have received UFH for >4 days, a platelet count should be obtained to exclude heparin-induced thrombocytopenia.\(^{195}\) For patients receiving bridging therapy with eptifibatide or tirofiban, 8 h must elapsed before a neuraxial blockade can be performed.\(^{195,202,204}\)

Although perioperative platelet transfusions have been suggested in patients on dual-antiplatelet therapy when RA is considered safest, this practice cannot be justified.\(^{31,144,184,205–207}\) Transfusions are not without risks.\(^{207}\) An adequate platelet count does not reflect function, which may still be abnormal, precluding the performance of a regional anesthetic.\(^{207}\) There are no clinically available tests, which accurately and reliably assess platelet function. Theoretically, apheresis platelets administered to patients with stents who then receive clopidogrel and aspirin may not develop antiplatelet effects to provide adequate protection from stent thrombosis for hours to days.\(^{144}\) The administration of platelets should probably be avoided, except in instances of life-threatening bleeding.\(^3\)\(^4,144\) If platelet administration is considered absolutely necessary, Doyle et al. recommend waiting for 12 h (3 half-lives) after the last dose of clopidogrel (half-life of clopidogrel is 4 h) when serum levels of the drug are no longer detectable to ensure normal platelet function.\(^3\) However, Cornet et al. published a case series of three patients with gastrointestinal bleeding or who were scheduled for emergency surgery and who received platelet transfusions shortly after BMS insertion.\(^{208}\) Dual-antiplatelet therapy was discontinued in one patient 14 h before transfusion, whereas the other
two patients remained on clopidogrel and aspirin. Stent occlusion was diagnosed 6–17 h after transfusion by electrocardiographic criteria in the two patients still receiving clopidogrel and aspirin, and by angiography in the patient whose antiplatelet therapy was discontinued. In this series, thrombus formation with donor platelets occurred in both the presence and absence of dual-antiplatelet therapy, suggesting that therapeutic serum levels of clopidogrel and aspirin may not affect transfused platelets.

Ex vivo studies have shown that transfused platelets may not be inhibited by the presence of adequate serum levels of antiplatelet drugs. Both MI and PCI can activate circulating platelets for at least 48 h, and their adhesive function may also increase. Moreover, the thrombogenic surfaces of stents may attract and activate donor platelets to a even greater extent than endogenous platelets, further increasing the risk of stent thrombosis, MI, and death.

The dilemma with RA, particularly neuraxial blockade, in patients with stents is that postoperative PCI, with concomitant administration of antithrombotic therapy plus GP IIb/IIIa inhibitors, cannot be delayed to allow for catheter removal and prevent spinal cord compromise. Performance of neuraxial instrumentation, whether a single-shot technique or involving catheter insertion, significantly increases the risk of a neuraxial hematoma in patients who must subsequently receive antithrombotic therapy with or without GP IIb/IIIa inhibitors during PCI for acute stent thrombosis. The risk of spinal cord compromise in a patient who will receive antiplatelet and anticoagulant medication must be carefully balanced against the need for immediate coronary revascularization. If a surgical patient requires PCI, catheters should be removed before antithrombotic/antiplatelet/thrombolytic therapy, and PCI must be undertaken urgently. Popescu et al. recently described the postoperative management of an indwelling thoracic epidural catheter in a patient with postoperative right coronary artery DES thrombosis after aortic surgery. After confirmation of a normal coagulation profile, the catheter was removed, and the decision was made to delay PCI 2 h to minimize the risk of an epidural hematoma. The patient received eptifibatide and bivalirudin with percutaneous transluminal coronary angioplasty,

Figure 4. Proposed algorithm for perioperative management of patients with bare-metal stents based on current literature. “The 2007 ACC/AHA perioperative guidelines state, “it appears reasonable to delay elective noncardiac surgery for 4–6 wk to allow for at least partial endothelialization of the stent, but not for more than 12 wk, when restenosis may occur.”
and did not suffer any neurologic sequelae. Vigilant and intensive monitoring of sensorimotor function should be performed to detect any evidence of spinal cord compromise. In the case described by Popescu et al., neurologic examinations were continued for 48 h (every 2 h for the first day). Current ASRA guidelines recommend removal of an epidural catheter 1 h before administration of UFH, and 2 h before LMWH. The appropriate time delay between catheter removal and clopidogrel administration remains undefined. There are no guidelines for catheter removal preceding bivalirudin or GPIIb/IIIa inhibitor administration. Douketis et al. recommend administering clopidogrel or GP IIb/IIIa inhibitors 2–3 h after epidural catheter removal. Although longer time delays have been suggested, these increase the risk and complications of postoperative stent thrombosis if clopidogrel is withheld; this must be a mutual decision between the anesthesiologist and cardiologist. There are no guidelines regarding peripheral nerve blockade and catheters. Ultrasound-guided blockade, with and without catheter placement, may be safest in preventing potential bleeding complications, particularly in the setting of dual-antiplatelet therapy. Based on the current information available, the decision to perform RA should be made case-by-case, with consideration given to all potential complications.

**CONCLUSION**

The management of patients with coronary artery stents during the perioperative period is an important patient safety issue. Figures 4 and 5 present recommendations based on the currently available literature. Communication between the patient’s cardiologist, surgeon, and anesthesiologist is essential to minimize the risk of catastrophic stent thrombosis, MI, and death. Elective surgery should be avoided until the appropriate course of dual-antiplatelet therapy is completed, as determined by the patient’s cardiologist. Clinical judgment is of the utmost importance in balancing the risk/benefit ratio of dual-antiplatelet therapy interruption versus continuation. Aspirin should never be interrupted unless the risk of bleeding far outweighs the risk of stent thrombosis. Surgical procedures should be performed where 24-h interventional cardiology is available, as perioperative stent thrombosis acutely results in cardiogenic shock/arrest requiring emergent PCI. Although RA may provide some antithrombotic protection, the potential risk of bleeding complications must be carefully weighed.

Figure 5. Proposed algorithm for perioperative management of patients with drug-eluting stents based on current literature.
in these patients. Prospective studies to determine the safest perioperative management are of paramount importance.

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