Anesthesiology 2008; 109:573–5

Noncardiac Surgery for Patients with Coronary Artery Stents

Timing Is Everything

PHYSICIANS are increasingly being confronted with questions regarding the appropriate treatment of patients with recently implanted coronary stents who are in need of noncardiac surgery. Specifically, what is the optimal timing of elective procedures, and how should antiplatelet therapy be managed in these patients, especially in those in need of emergent procedures? Continued antiplatelet therapy through the perioperative period might increase the risk of surgical bleeding, while interruption of antiplatelet therapy predisposes to stent thrombosis, particularly in the setting of systemic hypercoagulation, which frequently occurs after some surgeries.[1] In this issue of ANESTHESIOLOGY, two articles from the Mayo Clinic in Rochester, Minnesota, provide further insight into these perplexing issues.[2,3]

Deployment of a stent after balloon angioplasty reduces both the acute risk of abrupt vessel closure by sealing coronary artery dissections and the long-term risk of restenosis by preventing elastic recoil and negative vessel remodeling. What bare-metal stents (BMSs) do not prevent, and may actually stimulate, is the development of neointimal hyperplasia, the other major determinant of restenosis. This provided the rationale for coating stents with substances such as sirolimus and paclitaxel, which inhibit the growth and proliferation of smooth muscle cells, the major cellular constituent of the neointima. Approved by the US Food and Drug Administration in 2003, drug-eluting stents (DESs) have had a major impact on reducing the incidence of target vessel revascularization, the most important clinical indicator of restenosis, by as much as 75% compared with BMSs.

Until adequately covered by a layer of endothelial cells, the exposed metal struts of a newly deployed stent are a potent nidus for the formation of platelet-rich microthrombi, which can propagate to cause occlusive stent thrombosis. Stent thrombosis is a catastrophic complication of percutaneous revascularization procedures that results in myocardial infarction in 40–60% and death in 15–45% of cases.[4] Administration of dual antiplatelet therapy, consisting of aspirin and a thienopyridine such as clopidogrel, during the period of stent endothelialization effectively reduces the risk of stent thrombosis to less than 1%. It is now recognized that premature discontinuation of dual antiplatelet therapy during this critical period is a major independent risk factor for stent thrombosis. This point is highlighted by data from a recent large, multicenter, prospective study indicating that the 9-month risk of cumulative stent thrombosis was nearly 90-fold higher in DES patients who prematurely discontinued dual antiplatelet therapy compared with those who did not.[5] These clinical observations are likely explained by histologic data from both animals and humans revealing that near-complete endothelialization of BMSs occurs rapidly, within 2–6 weeks of implantation, whereas endothelialization of DESs is significantly delayed for many months.[6] There is also sobering evidence from several small studies using coronary angioscopy, optical coherence tomography, and postmortem histologic analyses revealing that incomplete DES strut endothelialization/tissue coverage can be observed in some patients 2–4 yr after implantation and is often associated with the presence of microthrombi.[7–9] These findings form the basis for the most recent Science Advisory of the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, which recommends uninterrupted dual antiplatelet therapy for a minimum period of 1 month after BMS implantation and for a minimum of 1 yr after DES implantation.[10]

In this month's ANESTHESIOLOGY, Nuttall *et al.*[2] report on 899 patients identified from the Mayo Clinic percutaneous coronary intervention and surgery registries who had undergone BMS placement before noncardiac surgery over a 15-yr period, including a cohort of 207 patients whose clinical course has previously been reported. The primary outcome of the study was major adverse cardiac events (MACEs) defined as the composite of death, myocardial infarction, stent thrombosis, and repeat revascularization. MACEs occurred in 10.5, 3.8, and 2.8% of patients when surgery occurred less than 30

◆ This Editorial View accompanies the following two articles: Nuttall GA, Brown MJ, Stombaugh JW, Michon PB, Hathaway MF, Lindeen KC, Hanson AC, Schroeder DR, Oliver WC, Holmes DR, Rihal CS: Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. ANESTHESIOLOGY 2008; 109:588–95; Rabbitts JA, Nuttall GA, Brown MJ, Hanson AC, Oliver WC, Holmes DR, Rihal CS: Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. ANESTHESIOLOGY 2008; 109:596–604.

Accepted for publication July 15, 2008. Supported by grant No. R01 HL080142 (to Dr. Rade, Principal Investigator) from the National Institutes of Health, Bethesda, Maryland; grant No. 0855440E (to Dr. Hogue, Principal Investigator) from the American Heart Association, Dallas, Texas; and BMS/Sanofi Pharmaceuticals, Princeton, New Jersey (to Dr. Rade).

days, between 31 and 90 days, and more than 90 days after BMS placement, respectively. Based on multivariate regression analysis, the duration between BMS placement and surgery was significantly related to risk for MACEs (odds ratio, 3.2; 95% confidence interval, 1.5–1.9; $P = 0.006$). That is, the longer that surgery was delayed after stent placement, the lower the risk for MACEs. In an accompanying article, Rabbitts *et al.*[3] used a similar approach to evaluate the frequency of MACEs in 520 patients who underwent noncardiac surgery within 2 yr of DES placement. MACEs occurred in 6.4, 5.7, and 5.9% of patients when surgery was performed 0–90, 91–180, or 181–365 days after DES placement. The rate of MACEs was 3.3% when surgery was performed 365–730 days after DES placement. This apparent lower rate, though, was not significantly different than the MACE rates when surgery was performed less than 365 days after stent placement even when statistical adjustments were made to attempt to control for potential confounding variables. Neither study found that the risk of surgical bleeding was significantly associated with perioperative administration of antiplatelet therapy.

How should physicians interpret these results? It must first be accepted that prospectively randomized clinical trials investigating these issues would be extremely difficult to perform, so by necessity one will need to rely predominantly on retrospective observational studies with their associated inherent limitations to guide clinical judgment. Because the previous literature on this subject consists mostly of case reports and small series, the two observational studies by the Mayo group are, thus, important contributions to understanding this issue because they represent the largest series of patients reported to date even though limitations to their methods are acknowledged.

With the important caveat that the two studies differed in terms of the duration of the follow-up period, several important patient demographic features, relatively few numbers of adverse events, and the lack of a control group needed to interpret the MACE event rate for patients with a similar acuity level undergoing surgery without previous stent placement, some meaningful comparisons can be made regarding outcomes in patients with BMSs and DESs. For patients with both types of stents, the absolute event rates after noncardiac surgery seemed similar during the first 90 days after stent implantation (7.1% and 6.4% for BMS and DES groups, respectively). The event rate for the BMS group declined to 2.8% between 90 and 365 days, whereas the event rate for the DES group during the same period remained relatively constant at 5.8%. These data seem to parallel and are possibly explained by the differential rates at which BMS and DES endothelialize. As with the uncertainty about how long it takes DESs to fully endothelialize, these studies leave open the questions of when beyond 1 yr does the perioperative risk for MACEs in DES and BMS patients equalize, and how do these risks compare with those in patients with coronary artery disease without previous revascularization. Very late (>1 yr) stent thrombosis is rare with BMSs, though there is growing evidence to support a small (approximately 0.5%) but persistent incidence of very late DES thrombosis, especially in patients where stents were implanted for "off-label" indications (*i.e.*, long, bifurcational, left main or vein graft lesions).[11] Some cardiologists, therefore, advocate continuing dual antiplatelet therapy indefinitely in patients with DESs who are at low risk of bleeding until the long-term risks of stent thrombosis are further clarified. Although continuing to defer elective surgery for at minimum of 1 yr after DES implantation per current guidelines of the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association[10] should remain the standard of care, maintaining vigilance beyond that time in certain high-risk patients such as those with off-label DESs or undergoing high risk-surgical procedures also seems warranted.

These two studies also convincingly demonstrated that emergent noncardiac surgical procedures were associated with a significantly higher MACE rate compared with nonemergent procedures regardless of what type of stent was deployed (11.7% *vs.* 4.4%, $P = 0.003$, and 17.9% *vs.* 4.7%, $P = 0.006$, for emergent *vs.* nonemergent surgeries in BMS and DES groups, respectively). The limited sample size of the two studies does not permit a comparison between stent types or a parsing of the data to determine which components of the composite MACE endpoint are responsible for this effect (*e.g.*, stent thrombosis *vs.* ischemic events due to another mechanism). Nonetheless, it is fair to conclude that stent patients undergoing emergent noncardiac surgeries are at high risk for perioperative cardiac events and, therefore, need to be monitored closely and receive aggressive prophylactic therapy for the prevention of perioperative ischemia.

Most surgeons and anesthesiologists are reluctant to perform surgery while patients are taking dual antiplatelet therapy out of fear of excessive bleeding and routinely discontinue all antiplatelet agents 5–10 days before surgery. Preoperative use of clopidogrel is well recognized to increase the risk of postoperative bleeding after cardiac surgery,[12] and current American Heart Association–American College of Cardiology guidelines recommend discontinuing its use if clinically feasible at least 5 days before surgery.[13] By comparison, far less is known about the risks of perioperative bleeding with continued dual antiplatelet therapy after noncardiac surgery. In a review of the available literature, Chassot *et al.*[14] estimated that surgical blood loss increases 2.5–20% for aspirin and 30–50% for clopidogrel use in the perioperative period, with a 30% increased need for

transfusions but no increased risk of bleeding-related mortality except during intracranial surgery. Vicenzi *et al.*[15] looked at outcomes in 103 patients with coronary artery stent implantation within the preceding year (46% had stents placed within 90 days) in whom antiplatelet therapy was not interrupted or was only briefly interrupted before urgent or semiurgent noncardiac surgery. Of the 46 patients who experienced a postoperative adverse event, only 2 had significant bleeding as the only event of interest, whereas the remainder of patients experienced only adverse cardiac events. This suggests that for many patients with recently implanted coronary stents, the risks of significant surgical bleeding may be outweighed by the benefit of continued antiplatelet therapy. Findings from the two Mayo studies, especially of Nuttell *et al.*,[2] add to the validity of this concept. In patients with BMSs, bleeding events were not statistically different in patients with antiplatelet use within 7 days of surgery compared with those who discontinued it more than 7 days and more than 30 days before surgery. By multivariate analysis, the risk of experiencing an adverse cardiac event was significantly higher in the first 30 days after BMS implantation, whereas the risk of surgical bleeding was not, despite patients' receiving dual antiplatelet therapy during this time period.

The studies of Nuttell *et al.*[2] and Rabbitts *et al.*[3] add to a growing body of literature demonstrating that timing really is everything when considering the risks and management strategy of noncardiac surgery in patients with coronary stents. Their data confirm current guidelines that recommend delaying elective noncardiac surgery for at least 6 weeks after BMS implantation and 1 yr after DES implantation but cautions that some risk does extend beyond these time frames. Their data also support the use of a treatment algorithms proposed by Chassot *et al.*,[14] which recommend that all patients with cardiovascular disease be continued on aspirin throughout the perioperative period for all noncardiac surgery except intracranial neurosurgery. Patients within the 6-week and 1-yr vulnerable period after BMS and DES stent placement, as well as patients with high-risk stent procedures (*i.e.*, off-label indications) who are beyond these time points, should also continue clopidogrel therapy through the perioperative period unless at high risk for bleeding in a closed space.

Jeffrey J. Rade, M.D., Charles W. Hogue, Jr., M.D. Johns Hopkins Medical Institutions, The Johns Hopkins Hospital, Baltimore, Maryland. chogue2@jhmi.edu

References

1. Howard-Alpe GM, de Bono J, Hudsmith L, Orr WP, Foex P, Sear JW: Coronary artery stents and noncardiac surgery. Br J Anaesth 2007; 98:560–74

2. Nuttall GA, Brown MJ, Stombaugh JW, Michon PB, Hathaway MF, Lindeen KC, Hanson AC, Schroeder DR, Oliver WC, Holmes DR, Rihal CS: Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. ANESTHESIOLOGY 2008; 109:588–95

3. Rabbitts JA, Nuttall GA, Brown MJ, Hanson AC, Oliver WC, Holmes DR, Rihal CS: Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. ANESTHESIOLOGY 2008; 109:596–604

4. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza JP Jr, Chauhan MS, Rodriguez O, Kuntz RE: Stent thrombosis in the modern era: A pooled analysis of multicenter coronary stent clinical trials. Circulation 2001; 103:1967–71

5. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A: Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005; 293:2126–30

6. Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R: Vascular responses to drug eluting stents: Importance of delayed healing. Arterioscler Thromb Vasc Biol 2007; 27:1500–10

7. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R: Pathology of drug-eluting stents in humans: Delayed healing and late thrombotic risk. J Am Coll Cardiol 2006; 48:193–202

8. Chen BX, Ma FY, Luo W, Ruan JH, Xie WL, Zhao XZ, Sun SH, Guo XM, Wang F, Tian T, Chu XW: Neointimal coverage of bare-metal and sirolimus-eluting stents evaluated with optical coherence tomography. Heart 2008; 94:566–70

9. Awata M, Kotani J, Uematsu M, Morozumi T, Watanabe T, Onishi T, Iida O, Sera F, Nanto S, Hori M, Nagata S: Serial angioscopic evidence of incomplete neointimal coverage after sirolimus-eluting stent implantation: Comparison with bare-metal stents. Circulation 2007; 116:910–6

10. Grines CL, Bonow RO, Casey DE Jr, Gardner TJ, Lockhart PB, Moliterno DJ, O'Gara P, Whitlow P: Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: A science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Circulation 2007; 115:813–8

11. Mishkel GJ, Moore AL, Markwell S, Shelton ME: Correlates of late and very late thrombosis of drug eluting stents. Am Heart J 2008; 156:141–7

12. Kapetanakis EI, Medlam DA, Boyce SW, Haile E, Hill PC, Dullum MK, Bafi AS, Petro KR, Corso PJ: Clopidogrel administration prior to coronary artery bypass grafting surgery: The cardiologist's panacea or the surgeon's headache? Eur Heart J 2005; 26:576–83

13. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleishmann KE, Freeman WK, Froehlich JB, Kasper E, Kersten JR, Riegel B, Robb JF: ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2007; 116:e418–99

14. Chassot PG, Delabays A, Spahn DR: Perioperative antiplatelet therapy: The case for continuing therapy in patients at risk of myocardial infarction. Br J Anaesth 2007; 99:316–28

15. Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzler H: Coronary artery stenting and noncardiac surgery: A prospective outcome study. Br J Anaesth 2006; 96:686–93