Q: When is it appropriate to stop antiplatelet therapy in a patient with a drug-eluting stent prior to noncardiac surgery?

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A: The US Food and Drug Administration recommends that combined antiplatelet therapy (aspirin plus clopidogrel) be continued for at least 3 months after placement of a sirolimus-eluting stent and at least 6 months after placement of a paclitaxel-eluting stent. Current guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and from the American College of Chest Physicians recommend 9 to 12 months of dual-antiplatelet therapy after placement of either stent. Multidisciplinary discussions are necessary if surgery is considered prior to completion of 1 year of combined antiplatelet therapy. Antiplatelet therapy must also be reinstituted as soon as possible after surgery in suitable patients.

Drug-eluting stents: Less restenosis, more late thrombosis

In the first decade of interventional cardiology practice (1977–1987), the restenosis rate at 6 months after balloon angioplasty was 32% to 40%.[1] This was in addition to a high acute closure rate that often required repeat interventions. This led to the introduction of bare-metal stents (BMS) in 1986, but the 6-month restenosis rate with these stents remained as high as 17% to 32%.[1]

Drug-eluting stents (DES) were designed to address the high rates of in-stent restenosis associated with BMS. DES, which now constitute about 90% of all stents placed in the United States, have reduced the restenosis rate to less than 10%.[1] However, late stent thrombosis, which occurs more than 30 days after stent placement, is thought to occur more frequently with DES than with BMS, and results in death or infarction in 60% of patients.[2]

Extended dual-antiplatelet therapy is recommended in patients with DES because of the delayed endothelial regeneration caused by drug elution within the stent's local environment. This creates a microenvironment conducive to platelet thrombus formation.

With adequate antiplatelet therapy, however, the rate of stent thrombosis is less than 1% with DES.[3] A pooled analysis of 10 randomized trials showed no difference in rates of stent thrombosis between DES and BMS when patients were on appropriate combined antiplatelet therapy.[3] Although another recent clinical trial found no significant difference in the incidence of late stent thrombosis between patients receiving DES or BMS, it did find higher rates of major adverse cardiovascular events with DES compared with BMS in the year following clopidogrel discontinuation and showed that late stent thrombosis occurred up to 18 months after stent placement.[4] A study of 2,006 patients who were followed for at least 1 year after stent placement found that late stent thromboses developed in patients on stable aspirin monotherapy while no thromboses occurred in patients on combined antiplatelet therapy.[5]

The recently modified ACC/AHA guidelines on percutaneous coronary intervention recommend 325 mg of aspirin and 75 mg of clopidogrel daily for at least 3 months following placement of a sirolimus-eluting stent and for at least 6 months following placement of a paclitaxel-eluting stent, followed by 75 to 162 mg of aspirin daily indefinitely.[1] These guidelines also recommend that, in the absence of excessive bleeding risks, clopidogrel 75 mg daily ideally be continued for 12 months following DES placement.

Limited data from noncardiac surgeries

In addition to the above issues, perioperative management also must take into account the "prothrombotic rebound" phenomenon upon stopping antiplatelet therapy (which has never been studied) as well as the prothrombotic state portended by the surgery itself. Noncardiac surgeries performed within 3 to 6 weeks of coronary artery stent placement were associated with an increased incidence of major adverse cardiovascular events.[6–9]

No published studies have addressed the issue of perioperative stent thrombosis in patients with DES undergoing noncardiac surgeries; the only study we know of that has done so is a retrospective analysis conducted at the Cleveland Clinic and presented in pre-

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liminary form.[10] The median time to surgery in this cohort of 114 patients was 236 days after DES placement. Eighty-eight patients (77%) had all antiplatelet agents discontinued prior to surgery. Aspirin and clopidogrel were both discontinued a median of 10 days before surgery. Clopidogrel was discontinued within 90 days of stenting in 13 patients and within 180 days of stenting in 35 patients. No patients died in this study. Two patients developed myocardial infarction (on postoperative days 3 and 7, respectively); neither of these patients had DES thrombosis by postoperative catheterization. One patient developed major bleeding.

While encouraging, these data alone are not sufficient to demonstrate that discontinuation of antiplatelet therapy in patients with DES is safe. Most patients in this study continued antiplatelet therapy for at least 4 months after stent placement. Also, the study's retrospective design and small size are major limiting factors.[10]

What should drive the decision?

Preoperative decisions about antiplatelet therapy in a patient with a DES are dictated by several factors, most importantly the date of stent implantation. Other factors are DES type, risk of postoperative bleeding, surgeon and surgical center experience, and possibly the technical details of stent deployment (eg, stent length, diameter, or underexpansion). Patient characteristics that suggest a higher risk of stent thrombosis include renal failure, diabetes, and a lower ejection fraction.[2,11] The risk of thrombosis after DES placement rises proportionally with the length of the stent and is also increased in patients undergoing treatment for in-stent restenosis and bifurcations.[3,11] Premature discontinuation of antiplatelet therapy is the most important predictor of stent thrombosis after DES implantation.[2]

Discussion with the surgeon to verify that continuing antiplatelet therapy is truly a significant risk for bleeding is imperative. Aspirin can be continued for coronary artery bypass graft and cataract surgeries, and most vascular surgeons are comfortable with continuing antiplatelet therapy perioperatively. Studies of perioperative bleeding in patients on antiplatelet therapy have yielded varied results and have been conducted mainly in cardiac surgery patients. Only a few studies address antiplatelet therapy and noncardiac surgery. One study of 40 consecutive patients reported 7 myocardial infarctions, 11 major bleeding episodes, and 8 deaths, with stent thrombosis accounting for most of the fatal events.[6] In another study of patients who had received stents within the prior year, antiplatelet therapy was not interrupted perioperatively or was interrupted only briefly; of the study's 103 patients, 46 suffered complications and 5 died.[9]

Despite uncertainties, some recommendations emerge

Several important recommendations can be drawn from the discussion above.

Coronary revascularization should be undertaken only if the patient's clinical characteristics dictate it, irrespective of the surgery. If revascularization is inevitable, consider BMS or optimized plain balloon angioplasty. There is no evidence that preoperative revascularization in an asymptomatic patient changes postoperative outcomes.[12]

All patients should be optimized with beta-blockade.[13] If surgery is required urgently, a multidisciplinary risk-benefit analysis should be done with the surgeon at the helm. Every effort should be made to continue dual-antiplatelet therapy if possible. If the surgical team has reservations about hemorrhagic risk and surgery is indicated, consider referral to a tertiary surgical center with more experience. A cardiologist should be an integral part of any decisions related to discontinuing antiplatelet therapy because high-risk patient and stent characteristics are best interpreted by a cardiologist. Wherever feasible, discontinuation of clopidogrel 5 days before surgery and aspirin 7 days before surgery appears reasonable, but this largely depends on the surgeon's preference. Multiple reports of very late stent thrombosis in patients with DES (> 1 year after placement) suggest that antiplatelet therapy must be reinstituted as soon as possible after surgery.

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