Perioperative Antiplatelet Therapy

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Aspirin is recommended as a lifelong therapy that should never be interrupted for patients with cardiovascular disease. Clopidogrel therapy is mandatory for six weeks after placement of bare-metal stents, three to six months after myocardial infarction, and at least 12 months after placement of drug-eluting stents. Because of the hypercoagulable state induced by surgery, early withdrawal of antiplatelet therapy for secondary prevention of cardiovascular disease increases the risk of postoperative myocardial infarction and death five- to 10-fold in stented patients who are on continuous dual antiplatelet therapy. The shorter the time between revascularization and surgery, the higher the risk of adverse cardiac events. Elective surgery should be postponed beyond these periods, whereas vital, semiurgent, or urgent operations should be performed under continued dual antiplatelet therapy. The risk of surgical hemorrhage is increased approximately 20 percent by aspirin or clopidogrel alone, and 50 percent by dual antiplatelet therapy. The present clinical data suggest that the risk of a cardiovascular event when stopping antiplatelet agents preoperatively is higher than the risk of surgical bleeding when continuing these drugs, except during surgery in a closed space (e.g., intracranial, posterior eye chamber) or surgeries associated with massive bleeding and difficult hemostasis. (*Am Fam Physician.* 2010;82(12):1484-1489. Copyright © 2010 American Academy of Family Physicians.)

Long-term antiplatelet therapy is an important component of secondary prevention after a stroke, myocardial infarction (MI), myocardial revascularization, or a diagnosis of peripheral arterial disease or acute coronary syndrome. Dual antiplatelet therapy (aspirin and clopidogrel [Plavix]) prevents stent thrombosis following percutaneous coronary intervention with placement of bare-metal or drug-eluting stents. In the perioperative period, the indication for antiplatelet agents is reinforced by the increased platelet activity following surgery; however, they also increase the risk of surgical bleeding. Whether the risk of hemorrhage with antiplatelet therapy is lower than the risk of thrombosis when antiplatelet agents are withdrawn is the key question.

Preoperative coronary revascularization is recommended for patients with unstable coronary syndrome and refractory angina, but it offers no benefit compared with optimal medical therapy and adequate heart rate control in patients with stable (even severe) coronary artery disease.[1,2] In cases of semiurgent surgery, the risk of operating under maximal medical protection (beta blockers, antiplatelet agents, statins) is less than operating within six weeks of coronary revascularization.[3,4] This review proposes recommendations for the perioperative management of antiplatelet therapy based on the current scientific evidence. However, there have been no large prospective randomized controlled trials (RCTs) in perioperative patients to guide decision-making; most of the current data arise from nonrandomized observational or quasi-experimental studies.

Antiplatelet Therapy

Aspirin is effective in dosages ranging between 75 and 325 mg per day.[5] Clopidogrel (75 mg per day) is a prodrug oxidized by hepatic cytochromes into an active metabolite. Some lipophilic statins and proton pump inhibitors (except perhaps pantoprazole [Protonix]), and midazolam compete with clopidogrel for the same cytochromes and may reduce its level of active metabolite by up to 30 percent.[6,7] After cessation of aspirin or clopidogrel, platelet aggregation returns to baseline in five days.[8] There are no major differences in bleeding risk between aspirin and clopidogrel when administered alone.[9]

Compared with clopidogrel, the new drug prasugrel (Effient) is more effective at prevention of stent thrombosis, but it increases hemorrhagic risk by 30 percent.[10] Three new drugs that are inhibitors of the platelet adenosine

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Aspirin must be continued preoperatively when prescribed as secondary prevention of cardiovascular disease or stroke.	A	20, 23	Meta-analyses of high-quality trials[20] and stent thrombosis studies[23]
Early clopidogrel (Plavix) withdrawal (i.e., less than six weeks after bare-metal stents, less than six months after acute coronary syndrome, less than 12 months after drug-eluting stents) should be avoided because it is the main predictor of coronary thrombosis.	B	18, 19, 24	Large prospective observational studies
Antiplatelet agents should not be interrupted preoperatively because the risk of cardiovascular events when withdrawing them is generally higher than the risk of surgical bleeding when upholding them.	B	3, 4, 14, 15, 17, 30	Body of observational and quasi-experimental evidence favors this recommendation, but randomized controlled trials are needed to ascertain it
Elective operations should be delayed beyond dual antiplatelet therapy; operations during dual antiplatelet therapy must be performed without drug interruption.	B	3, 15, 25, 28	American College of Cardiology and American Heart Association recommendations,[3,15] comparative clinical studies[25,28]

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

diphosphate receptor are under clinical testing: cangrelor (an intravenous short-acting reversible inhibitor) and oral direct reversible inhibitors ticagrelor and elinogrel.[11] Compared with clopidogrel, these drugs present less variability, faster onset, and shorter duration of action; however, their effect on clinical outcomes in direct comparison with clopidogrel is unknown.

Dual antiplatelet therapy (i.e., aspirin and clopidogrel) is mandatory after acute coronary syndrome or stent implantation because coronary lesions and stents behave like unstable plaques as long as they are not fully covered by a cellular layer. The metal frame of a bare-metal stent is covered by smooth muscle cells within six weeks and by a normal endothelium within three months.[12] Drug-eluting stents have a slower endothelialization rate: 13 percent at three months and 56 percent at three years.[13] Therefore, the recommended duration of clopidogrel treatment is six weeks after bare-metal stents and at least 12 months after drug-eluting stents *(Table 1[14])*.[3,15-17] These minimal durations can be prolonged beyond one year in high-risk situations (e.g., drug-eluting stents implanted in dominant, proximal, ostial, or bifurcated positions) and high-risk patients (e.g., advanced age, diabetes mellitus, low ejection fraction, renal failure). Late thrombosis from drug-eluting stents is a rare (incidence of 0.6 percent per year) but catastrophic event, with a mortality of 19 to 45 percent.[18] It is analogous to the acute interruption of flow in a previously normal-throughout vessel devoid of collaterals and without tissue preconditioning.[18,19]

WITHDRAWAL

Aspirin cessation is associated with an increased risk of cardiac complications (odds ratio [OR] = 3.1), which peaks at 10 days; this risk is much higher after coronary stent placement (OR = 90).[20] Cases of acute

Table 1. Recommended Duration of Antiplatelet Therapy After a Coronary Event

Therapy type and indication	*Duration*
Aspirin (75 to 325 mg per day)	Lifelong, without interruption
Clopidogrel (Plavix; 75 mg per day; dual therapy)	
Simple angioplasty without stenting	Two to four weeks
PCI and bare-metal stents	Six weeks
Myocardial infarction	Three to six months
Acute coronary syndrome (unstable)	Six to 12 months
PCI and drug-eluting stents	Minimum of 12 months

PCI = percutaneous coronary intervention.

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Table 2. Complication Rates From Premature Discontinuation of Antiplatelet Agents During the First Six Weeks After Angioplasty and Stenting

Setting	Cardiovascular events* (percent)	Cardiovascular mortality (percent)	All-cause mortality (percent)
Nonsurgical[18,19,24,29]	25 to 60	19 to 65	20
Perioperative[25-29]	42	71	30

*—Acute coronary syndrome, nonfatal myocardial infarction, cardiogenic shock.

Information from references 18, 19, and 24 through 29.

thrombosis from drug-eluting stents have been reported with aspirin withdrawal beyond two years after stent implantation.[21,22] The mean delay between aspirin withdrawal and late thrombosis from drug-eluting stents is seven days.[23] Therefore, aspirin is a lifelong therapy that should never be interrupted.[3,15-17]

Clopidogrel cessation is the most significant independent predictor of stent thrombosis, with an OR of 14 to 57 during the first 18 months after drug-eluting stent implantation.[19,24] Although the optimal duration of clopidogrel therapy after implantation remains unsettled, there is good clinical evidence that its cessation during the first year is dangerous.[18,19]

Interruption of antiplatelet therapy is more hazardous in the perioperative period, which is characterized by increased platelet aggregability. Stopping dual antiplatelet therapy to allow major surgery during the first six weeks after angioplasty and stenting (bare-metal or drug-eluting) leads to a cardiovascular mortality of up to 71 percent, whereas it is no more than 5 percent when the treatment is maintained perioperatively[25-28] *(Table 2[18,19,24-29])*. Mortality is inversely related to the delay between revascularization and surgery.[25,26,28]

HEMORRHAGIC VERSUS THROMBOTIC RISKS

Although there is a lack of RCTs comparing the effects of withdrawing versus continuing antiplatelet agents in the perioperative period, it appears that the average relative increase in bleeding during noncardiac surgery is 20 percent with aspirin or clopidogrel alone.[9,30] Some operations, such as tonsillectomy or transurethral prostatectomy, might show a significant increase in postoperative hemorrhage.[31-33] Life-threatening hemorrhage has been reported only in intracranial neurosurgery.[34]

A meta-analysis including 474 studies comparing surgical bleeding of patients operated on with or without aspirin reported no change in the mortality and complication rates.[30] The relative risk of hemorrhage increased up to 50 percent with aspirin and clopidogrel together, but data are limited to vascular, visceral, and transbronchial surgeries.[35-37] Although hemostasis is longer and more difficult, particularly because of the increased oozing from bones and raw tissues, the surgical mortality and long-term morbidity are not increased.[35-37] The transfusion rate was inconsistently affected in three studies comparing general surgery with and without dual antiplatelet therapy (nonsignificant relative increase of 4, 12, and 16 percent in antiplatelet groups).[27,28,38] Moreover, the short-term complication rate (0.4 percent)[39] and the long-term relative survival reduction (16 percent)[40] from transfusion are far less than the 30 percent average mortality when antiplatelet drugs are withdrawn before surgery.[19,24-26,28] Aspirin and clopidogrel do not appear to increase the likelihood of other surgical complications, except for with surgery in a closed space (e.g., intracranial neurosurgery, surgery of the spinal canal, surgery of the posterior ocular chamber) or surgery associated with massive hemorrhage and difficult hemostasis.[4,14]

In patients with stents who are on continuous dual antiplatelet therapy, the combined rate of perioperative MI and mortality is the same as in stable coronary artery disease (1 to 6 percent, depending on the type of surgery), whereas withdrawing antiplatelet therapy is associated with a five- to 10-fold increase in the risk of MI (20 to 40 percent) and mortality (20 to 85 percent), depending on the delay between revascularization and surgery.[19,24-28] Therefore, the risk of coronary thrombosis appears higher than the risk of surgical hemorrhage, and preoperative cessation of aspirin and/or clopidogrel should be avoided when possible.[3,15-17] The decision must be made on a case-by-case basis

Table 3. Preoperative Management of Patients on Antiplatelet Therapy According to Cardiac and Bleeding Risk Levels

Surgical bleeding risk level	*Cardiac risk level*		
	*Low risk**	*Intermediate risk†*	*High risk‡*
Low risk§	Maintain aspirin or clopidogrel (Plavix)	Elective surgery: okay Maintain aspirin Maintain clopidogrel, if prescribed	Elective surgery: postponement Vital or urgent surgery: possible under aspirin and clopidogrel
Intermediate risk‖	Maintain aspirin or clopidogrel	Elective surgery: according to risk balance Vital surgery: okay Maintain aspirin Maintain clopidogrel, if prescribed	Elective surgery: postponement Vital or urgent surgery: possible under aspirin and clopidogrel
High risk¶	Stop aspirin or clopidogrel if necessary (five days before surgery) Restart within 24 hours after surgery	Elective surgery: postponement Vital surgery: okay Maintain aspirin Stop clopidogrel five days before surgery, if prescribed; restart within 24 hours after surgery	Elective surgery: postponement Vital or urgent surgery: okay Maintain aspirin Stop clopidogrel five days before surgery; possible substitution three to five days before surgery with intravenous tirofiban (Aggrastat) or eptifibatide (Integrilin)**

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; ENT = ear, nose, and throat; MI = myocardial infarction; PCI = percutaneous coronary intervention.

**—More than three months after PCI, bare-metal stenting, or CABG; more than six months after ACS or MI; more than 12 months after regular drug-eluting stenting.*

†—Six to 12 weeks after PCI, bare-metal stenting, or CABG; six to 24 weeks after ACS or MI; more than 12 months after high-risk drug-eluting stenting.

‡—Less than six weeks after PCI, bare-metal stenting, CABG, ACS, or MI (less than three months if complications); less than 12 months after drug-eluting stenting—may be longer in cases of high-risk drug-eluting stenting. These delays can be modified according to the amount of myocardium at risk, the instability of the coronary situation, or the risk of spontaneous hemorrhage. The same recommendations apply to newer second-generation drug-eluting stenting.

§—Peripheral and wall surgery, minor ENT and orthopedics, endoscopy without biopsy or resection, eye anterior chamber, or dentistry; transfusion not required.

‖—Visceral and vascular surgery, major ENT and orthopedics, urology, endoscopy with biopsy or resection; transfusion may be required.

¶—Cardiac surgery, surgery with massive bleeding, surgery in closed space (intracranial, intramedullary canal, posterior eye chamber); transfusion required.

***—Off-label use of platelet glycoprotein IIb/IIIa inhibitors may be considered, although there are no data regarding effectiveness and safety.*

Adapted with permission from 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(3):322.*

among the cardiologist, anesthesiologist, and surgeon, after weighing all of the risk factors, including coronary status (e.g., high-risk or low-risk stent, amount of myocardium threatened), patient conditions (e.g., age, coagulopathy, comorbidities), and type of surgery. *Table 3* outlines perioperative management based on patients' cardiovascular and surgical bleeding risks.[4]

Current Guideline Recommendations

In the absence of clinical trials, the current recommendations from specialty society guidelines are based on observational data and attempt to provide the safest possible management given the high risk of premature discontinuation of antiplatelet agents.[3,15-17] Aspirin is a lifelong therapy that should not be interrupted for surgery when prescribed for secondary prevention after stroke, acute coronary syndrome, MI, or coronary revascularization, regardless of the time since the event that led to the recommendation of aspirin.[20,23] Interruption of aspirin in primary prevention does not increase the perioperative risk, except in patients with diabetes.[41]

Dual antiplatelet therapy is recommended during the two weeks after simple dilatation, six weeks after bare-metal stents, and at least 12 months after drug-eluting stents.[3,15-17] All elective operations should be postponed

beyond these delays. Only vital surgery should be performed when the patients are still taking aspirin and clopidogrel; unless the hemorrhagic risk is excessive, dual antiplatelet therapy should not be interrupted before surgery. During the first six weeks after bare-metal stents or surgical revascularization, the operative risk is higher than without revascularization. The full benefit of revascularization is manifested only after three months, when mortality becomes identical to the postoperative mortality of patients without coronary artery disease.[25] Therefore, the recommended delay for elective surgery is longer than the delay for vital operations.

Even if clopidogrel treatment must be interrupted in high-risk surgical situations, aspirin must be continued without interruption.[3,15,17,23] Heparin has no antiplatelet activity and therefore is not an adequate substitution for aspirin or clopidogrel treatment because stent thrombosis is a platelet-mediated phenomenon.[15] Although not proven by any RCTs, bridging therapy with a short-acting platelet glycoprotein IIb/IIIa inhibitor (i.e., eptifibatide [Integrilin], tirofiban [Aggrastat]) is a possible substitution for clopidogrel while aspirin is being maintained.[42,43] After the operation, antiplatelet therapy is resumed within the first 12 to 24 hours; clopidogrel therapy is reinitiated with a 300-mg loading dose, which reduces the time to achieve maximal platelet inhibition to four to six hours and decreases the risk of hyporesponsiveness from competition of other drugs with hepatic cytochromes.

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