

Perioperative Antiplatelet Therapy: A New Approach

BY CHARLES-MARC SAMAMA, MD

Antiplatelet agents (APA) are familiar to anesthesiologists, but their perioperative management is a subject of controversy. The advent of drug-eluting coronary stents requiring extended antiplatelet therapy makes this issue more complicated. However, a number of simple recommendations can be made.

ANTIPLATELET THERAPY CAN OFTEN BE CONTINUED DURING SURGERY

Many clinical situations require the continuation of antiplatelet therapy. The 7th Consensus Conference of the American College of Chest Physicians (ACCP) recommends not to stop aspirin therapy before carotid endarterectomy or peripheral vascular surgery.¹ Similarly, during cardiac surgery, current studies indicate that patients who continue taking aspirin until the time of their operation do not require more transfusions, although they were found to have a slight increase in blood loss. As well, the 2001 SFAR (Société française d'anesthésie et de réanimation) Experts Conference reported that a large number of surgical situations are compatible with continuing aspirin therapy.² However, it has also been reported that there are more hemorrhagic complications when antiplatelet therapy is continued before tonsillectomy or prostate surgery although, according to a general review by Burger, the risk is minimal.³ The presence of aspirin augments bleeding by 50%, but not the severity of hemorrhagic complications except in intracranial surgery, tonsillectomy, and possibly transurethral prostatectomy.³ The data are more equivocal for the thienopyridines (eg, ticlopidine [Ticlid®] and clopidogrel [Plavix®]), which are associated with more bleeding and transfusion requirements, particularly during heart surgery.⁴ Even without evidence-based data, extra care is advised in surgical procedures where major bleeding is likely, as well as during cases where even slight peri- or postoperative hemorrhaging can negatively alter the outcome of the operation (eg, tympanoplasty).

Concerning local and regional anesthesia, spinal anesthesia can be administered to patients who are being treated with aspirin alone (without additional heparin prophylaxis) without increased risk.⁵ However, epidural anesthesia may be associated with an important theoretical risk. These two methods are contraindicated in patients being treated with thienopyridines (ticlopidine, clopidogrel). Finally, a peripheral block can be performed safely in a patient taking antiplatelet therapy, although caution is advised with deep blocks such as a posterior-approach lumbar plexus block.⁵

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STOPPING ANTIPLATELET THERAPY CARRIES A RISK

An early retrospective study by Collet et al revealed the risk associated with the sudden interruption in antiplatelet therapy; there were 11 myocardial infarctions (MIs) and one case of unstable angina managed by emergency bypass surgery associated with the cessation of aspirin prior to scheduled surgery among 475 patients with past acute MI.⁶ These patients had been taking aspirin for an average of 4 ± 2 years for stable angina. On average, the symptoms appeared 9 ± 3 days following cessation of aspirin treatment.

A number of studies have confirmed these data. The same authors tracked a cohort of 1,358 consecutive admissions for acute coronary syndrome.⁷ In this cohort, 930 patients were not taking antiplatelet therapy, 355 were being treated with aspirin or a thienopyridine (clopidogrel or ticlopidine), and 73 had recently stopped their therapy. Among the 73 patients who had stopped their therapy, 47 had done so before surgery, including 31 who substituted aspirin with flurbiprofene or a low-molecular-weight heparin. These patients were admitted on average 11.9 ± 0.8 days after cessation of therapy. When compared to the group who did not stop treatment, there was a significantly higher risk of death or MI (21.9% vs. 12.4%) and hemorrhagic complications (13.7% vs. 5.9%) in those who stopped their antiplatelet therapy.

Using multivariate analysis, cessation of antiplatelet therapy was found to be a risk factor that was predictive of mortality and bleeding. In this series, 5% of the patients stopped taking their antiplatelet agents in the 3 weeks prior to admission. Another French series focused on antiplatelet cessation in a group of 1,236 patients hospitalized for acute coronary syndrome, 51 of whom stopped taking antiplatelets ≤ 1 month prior to admission.⁸ They represented 4% of the coronary episodes concerned, but close to 13% of recurrences. The incidence of ST-segment elevation was 39% in the patients who interrupted their antiplatelet agents compared with 18% in those who continued it. Again, the coronary event occurred on average 10.0 ± 1.9 days after antiplatelet therapy cessation.

Many clinical cases have also been reported, revealing the growing awareness of this problem.^{9,10} A Swiss case-control series studied how often

aspirin was stopped in the 4 weeks preceding a cerebrovascular accident or a transient ischemic attack. In this study, 309 controls were compared with 309 subjects with a neurological history being treated with aspirin, but who had been free of symptoms in the previous 6 months.¹¹ Aspirin therapy was interrupted in 13 patients in the group with symptoms compared with 4 patients in the control group (relative risk [RR] = 3.4, 95% confidence interval [CI], 1.08-10.63, $p < 0.005$). Using multivariate analysis, aspirin cessation was found to be predictive of cerebrovascular events. Finally, Albaladejo et al noted the occurrence of lower limb ischemic episodes in a retrospective cohort of 181 vascular patients, 11 of whom had interrupted their aspirin therapy 23 days earlier (7-60 days).¹²

Thus, in practice, an array of arguments based on large retrospective cohorts, isolated clinical studies, and a case-control study indicates that the decision to stop antiplatelet agents in at-risk patients cannot be taken lightly. The risk associated with the cessation of therapy is not the same as the potentially greater risk of perioperative bleeding. When antiplatelet agents are prescribed for a recognized indication, interruption cannot be considered risk-free. When the indication for antiplatelets is compelling (for recurring transient ischemic attacks [TIAs] or severe angina), treatment must continue.

A large ($n = 35$) multicentre study – the STRATAGEM study, supported by a national research grant – is now underway in France. It compares preoperative continuation versus cessation (10 days) of aspirin therapy in terms of efficacy and tolerance. It will include 1,500 patients and should determine whether the trends indicated by the various clinical cases and series cited above are valid.

INACTIVE (BARE METAL) STENTS (BMS)

Stents to improve the patency of stenotic coronary arteries have been in use since the early 1990s. The advances in coronary angioplasty associated with these new devices have substantially improved the prognosis for patients and have resulted in a modification of the perioperative management of antiplatelets. Following reports of bleeding incidents in several series, it was recommended that a period of 4 to 6 weeks of dual therapy (aspirin + thienopyridine) was necessary for

stent reendothelialization. In an series by Kaluza, 40 patients underwent noncardiac surgery soon (< 39 days) after stent placement.¹³ Seven suffered an MI, 11 had a major bleeding episode, and 8 died. Stent thrombosis was found in most of the deceased patients. These events occurred in patients who underwent surgery within 14 days of stent implantation. The authors, therefore, suggest postponing surgery for 2 to 4 weeks after stent placement.

A similar study was performed by Wilson in 207 patients who had stents implanted at the Mayo Clinic 1 to 60 days prior to an operation. This study reports the same type of complications¹⁴: 8 major cardiac complications (including 6 deaths) occurred within 6 weeks post-stent implantation. No complications were found beyond that period. However, antiplatelet therapy had been continued in most cases, with only 13 patients (6.3%) stopping antiplatelet therapy. In the Ferrari series cited above,⁸ bare-metal stent thrombosis constituted a non-negligible portion (19%) of the coronary incidents following aspirin cessation. The stents had been implanted 15.5 ± 6.5 months earlier.

In practice, the recommendation is to schedule surgery requiring a brief interruption in antiplatelet agents between 6 weeks and three months after stent implantation. But extreme caution is advised, as indicated by the incidents in the Ferrari series.⁸

ACTIVE (DRUG-ELUTING) STENTS (DES)

The new so-called “active” stents are based on a simple idea: coat the inner wall of the stent with a pharmacologically active substance that slows neointimal hyperplasia and more effectively prevents rethrombosis. This concept has proven its effectiveness,¹⁵ reducing the rethrombosis rate by a factor of 3 to 4. However, these stents require the continuation of antiplatelet dual therapy (aspirin + clopidogrel) for a much longer period than conventional bare metal stents. Interruption of therapy carries a high risk of rethrombosis for the vascular wall because reendothelialization has been postponed. At present, currently available DESs are classified into two broad categories:

- stents using a cytostatic agent (paclitaxel, rapamycin etc.),
- stents using an immunosuppressive agent (sirolimus, tacrolimus, verolimus etc.).

In the autumn 2005, Cypher (sirolimus) and Taxus (paclitaxel) were the most commonly used DESs, although others are arriving on the market. With DES implantation ranging from 50% to 100%, depending on the country, the ratio of DES versus bare metal stents is now shifting towards the former.

Since 2003, reports of acute DES thrombosis upon interruption of antiplatelet therapy provoked debate on this issue. Fléron et al reported the first case of an MI with cardiogenic shock in a patient following implantation of two sirolimus-rapamycin (Cypher®) stents. Three months post-implantation, clopidogrel and aspirin therapy had been stopped 9 days before a mastectomy.¹⁶ Since then, other cases have been reported. McFadden describes 4 cases of late thrombosis with MIs occurring 343 and 442 days following paclitaxel-eluting stent implantation, and 335 and 375 days following sirolimus stent implant.¹⁷ In all 4 cases, the MIs were clearly related to the interruption in antiplatelet therapy (4 to 14 days earlier). Another case of late thrombosis was reported by Decoene et al. In this case, a 57-year-old patient had received a paclitaxel-eluting stent implant 19 months earlier¹⁸; 7 days after cessation of dual therapy, an extensive anterior MI, complicated by cardiogenic shock, occurred, requiring a biventricular assist device. Interestingly, Murphy reports thrombosis even when only a single dose of dual therapy was skipped prior to a hysterectomy in a patient who had a sirolimus-eluting stent implanted two weeks previously.¹⁹ In this case, it would appear that the thrombosis cannot be related to the short interruption in therapy, because it is likely that the patient's platelets were still under the influence of treatment. However, the hypothesis cannot be ruled out.

Iakovou was the first to provide an epidemiological dimension to the problem with his data on a prospective cohort of 2,229 patients, half of whom were treated with paclitaxel-eluting stents and half with sirolimus-eluting stents.²⁰ Aspirin was continued throughout, while ticlopidine or clopidogrel was stopped after 3 months in the group with sirolimus stents and after 6 months in the group with paclitaxel stents. After 9 months, 1.3% (n = 29) of the stents were occluded (0.8% of the sirolimus stents and 1.7% of the paclitaxel stents [NS]). Among these patients, 13 died after an MI (45%), which represents an extremely high

rate of stent thrombosis. The independent factors predictive of stent thrombosis were, in order:

- early cessation of antiplatelets (RR = 89.78; 95% CI, 29.90-269.60)
- and, to a lesser extent, kidney failure (RR = 6.49; 95% CI, 2.60-16.15)
- bifurcation lesions (RR = 6.42, 95% CI, 2.93-14.07)
- diabetes (RR = 3.71, 95% CI, 1.74-7.89).

It is, therefore, clear that cessation of antiplatelet dual therapy should be avoided and, if interruption is planned, it should only be done after prolonged treatment (the duration of this treatment is uncertain) and in close collaboration with cardiology teams.

SUMMARY (TABLE 1)

More often than not, the effects of the continuation aspirin therapy on bleeding risk during surgery are unremarkable. Thus, the usual decision is not to interrupt therapy except in a few specific cases (eg, during intracranial or prostate surgery, tonsillectomy). Thienopyridines are associated with an increase in bleeding and transfusion requirements during cardiac surgery. When bleeding does occur in the operating room, only platelet transfusions are relatively effective, but these should be administered only for therapeutic purposes.

Although a bridge to surgery with a flurbiprofen (Cebutid[®]) type non-steroidal anti-inflammatory drug (NSAID) has been recommended, it must be considered on a case-by-case basis. However, in a study by Collet,⁶ a number of incidents occurred with flurbiprofen. Low molecular weight heparins at a therapeutic dose falls into the same category.

There appears to be a window for surgery in patients implanted with bare metal stents that extends from the 6th week to the third month post-implant, but extreme caution is required and continuation of aspirin therapy is advisable.

Little is known about how long dual therapy should be continued following a DES implant. While 3 months has been suggested for sirolimus and 6 months for paclitaxel stents, cases of late thrombosis contradict these suggestions. It is wise to suggest that cardiology teams consider the implantation of bare metal stents in patients who are likely to undergo surgery within a year. In all cases, input from multidisciplinary teams is advised.

CONCLUSION

The severity of a patient's condition does not make decisions easy. Often, anti-thrombotic therapy is interrupted in an untimely manner, resulting in thrombotic incidents with disastrous consequences. The most suitable approach has to be multidisciplinary, involving surgeons, cardiologists or internists, neurologists and, of course, anesthesiologists.

SUMMARY

The perioperative management of antiplatelet agents is controversial and the introduction of drug-eluting stents into the market has made therapeutic decisions more complicated. However, some recommendations can be made. Because the continuation of aspirin therapy has little effect on operative hemostasis, it is recommended that aspirin treatment not be discontinued except in a few specific situations. However, the thienopy-

TABLE 1: Perioperative risk of hemorrhage and thrombosis with antiplatelet agents

	Risk of hemorrhage	Risk of thrombosis with perioperative cessation (no stent)	Risk of thrombosis with perioperative cessation (active stent)
Aspirin alone	+ to -	? to +	+ to ++
Ticlopidine or clopidogrel alone	+	? to +	++ especially if less than 1 year
Aspirin and clopidogrel dual therapy	++	? to ++	+++ especially if less than 1 year

-: no increased risk; +: low risk; ++: moderate risk; +++: high risk; ?: unknown risk.

ridines (ticlopidine [Ticlid®] and clopidogrel [Plavix®]) are associated with an increase in bleeding and the requirement for transfusions during cardiac surgery. When bleeding occurs in the operating room, only platelet transfusions are relatively effective and should be prescribed only for established bleeding.

Stopping antiplatelet therapy, followed by replacement with a flurbiprofen-type NSAID, is logical, but this approach has not been tested and must be considered on a case-by-case basis. The same advice applies to substitution with a therapeutic dose of low-molecular-weight heparin. When surgery is planned for a patient with a bare metal stent who is being treated with aspirin and clopidogrel, it is recommended that clopidogrel be discontinued between the 6th week and 3rd month following stent implantation. However, caution is required and continuation of aspirin is advisable.

The ideal duration of dual therapy following implantation of a DES has not been ascertained. It may be suggested that cardiology teams give preference to the implantation of bare metal stents in patients likely to undergo surgery within a year. In all cases, decisions must be multidisciplinary.

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Abstracts of Interest

Major noncardiac surgery following coronary stenting: when is it safe to operate?

SHARMA AK, AJANI AE, HAMWI SM, ET AL.
WASHINGTON, DC.

The optimal timing for elective noncardiac surgery (NCS) after coronary stenting is uncertain. We identified 47 patients who underwent elective NCS within 90 days of coronary stent placement between January 1995 and December 2000. Twenty-seven patients had NCS within 3 weeks of coronary stenting. Six of the seven in whom thienopyridine antiplatelet therapy was discontinued died postoperatively in a manner suggestive of stent thrombosis. In contrast, only 1 of the 20 patients in whom the thienopyridine was continued through the NCS died. The frequency of perioperative hemorrhage was similar whether or not the antiplatelet agent was continued. Only 1 perioperative death occurred in the 20 patients with NCS more than 3 weeks following stenting.

Catheter Cardiovasc Interv 2004;63(2):141-5.

The efficacy and safety of perioperative antiplatelet therapy.

MERRITT JC, BHATT DL. CLEVELAND, OHIO

Widespread adoption of the antiplatelet agents into everyday clinical practice has revolutionized contemporary care of the cardiovascular patient. Major adverse cardiovascular events including death, myocardial infarction, stroke, and recurrent angina have all been shown to be significantly decreased when these agents are employed in the treatment of coronary atherosclerosis, acute coronary syndromes, myocardial infarction, and in the setting of percutaneous coronary intervention. As a growing number of patients on antiplatelet therapy are undergoing various surgical procedures, the potential risks and benefits these drugs pose perioperatively will become increasingly important. Available data indicate that, when used appropriately, these drugs can be used safely prior to surgery. Efficacy in improving surgical outcomes and in preventing adverse cardiovascular events postoperatively has also been demonstrated. The purpose of this review is to examine the perioperative safety and efficacy of the most widely used antiplatelet agents: aspirin; the thienopyridine clopidogrel; and the glycoprotein (GP) IIb/IIIa inhibitors abciximab, eptifibatid, and tirofiban. This information, coupled with emerging platelet monitoring techniques,

may help provide additional assistance to the clinician to manage therapy and guide appropriate timing of both cardiac and noncardiac surgery.

J Thromb Thrombolysis 2004;17(1):21-7.

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CONTACT : www.cas.ca

27-30 August 2006

**10th International Congress of Cardiothoracic
and Vascular Anesthesia**
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CONTACT : www.iccva2006.cz

Dr. Samama has stated that he has no conflicts of interest to announce in association with the contents of this issue.

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This publication is made possible by an educational grant from
Organon Canada Limited