REVIEW ARTICLE

Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction

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Recent clinical data show that the risk of coronary thrombosis after antiplatelet drugs withdrawal is much higher than that of surgical bleeding if they are continued. In secondary prevention, aspirin is a lifelong therapy and should never be stopped. Clopidogrel is regarded as mandatory until the coronary stents are fully endothelialized, which takes 3 months for bare metal stents, but up to 1 yr for drug-eluting stents. Therefore, interruption of antiplatelet therapy 10 days before surgery should be revised. After reviewing the data on the use of antiplatelet drugs in cardiology and in surgery, we propose an algorithm for the management of patients, based on the risk of myocardial ischaemia and death compared with that of bleeding, for different types of surgery. Even if large prospective studies with a high degree of evidence are still lacking on different antiplatelet regimens during non-cardiac surgery, we propose that, apart from low coronary risk situations, patients on antiplatelet drugs should continue their treatment throughout surgery, except when bleeding might occur in a closed space. A therapeutic bridge with shorter-acting antiplatelet drugs may be considered.

Antiplatelet agents are prescribed very widely for primary and secondary prevention of cardiovascular disease in Western countries to decrease the incidence of acute cerebro- and cardiovascular events. These events are tightly linked to the instability of atheromatous plaques and to the thrombogenicity of blood.[77] For example, more than two-thirds of the sudden cardiac events (acute coronary syndrome or sudden cardiac death)[36 126] and half of the postoperative myocardial infarctions (MIs)[26 64 93 94] are due to the disruption and thrombosis of an unstable plaque. These plaques are characterized by a large lipid core covered by a thin cap; they are densely infiltrated by macrophages, with signs of active inflammation;[59] and they appear as moderate stenoses (<60%) on coronary angiogram. Multiple cellular, humoral, and neuro-vegetative triggers may destabilize these plaques and lead to the development of an occluding thrombus.[94] Acute coronary syndrome is linked with pro-inflammatory and pro-thrombotic conditions that involve an increase in fibrinogen, C-reactive protein, and plasminogen activator inhibitor.[45] In the postoperative setting, the risk of acute coronary syndrome is further aggravated by the augmented release of endogenous catecholamines, increased platelet adhesiveness, and decreased fibrinolysis, which are characteristic of the acute phase reaction.[15 62 93] It is, therefore, understandable that antiplatelet agents are particularly helpful when the thrombogenic risk is the highest.

Around 2 million patients undergo coronary dilatation each year in Western countries,[111] and more than 90% of these percutaneous coronary interventions (PCIs) involve the placement of intracoronary stents. This procedure requires long-term treatment with antiplatelet agents, which are mandatory for the success of coronary stents. About 5% of patients who have undergone PCI will undergo non-cardiac surgery within the first year after stenting,[121] and anaesthetists may often be confronted with such patients.

Therefore, a new problem frequently encountered in clinical anaesthesia is how to manage a patient on aspirin and clopidogrel after a recent PCI who is to undergo a potentially haemorrhagic procedure. The dilemma is between the risk of increasing blood loss when continuing the antiplatelet agents in the perioperative period and the risk of coronary thrombosis if the drugs are stopped

abruptly. Recent data suggest that the traditional attitude of stopping the medication 10 days before surgery poses considerable danger and requires revision.[23 49 53 70 76 103] This review concentrates on the perioperative use of antiplatelet agents in coronary artery disease (CAD) patients, although antiplatelet agents are used in many other conditions such as peripheral vascular disease, carotid artery stenting, prevention of recurrent stroke, and MI, or in primary prevention for patients with multiple cardiovascular risk factors, particularly in diabetes.[97] It is intended to be an additional contribution to a recent review in the *British Journal of Anaesthesia* on coronary artery stents,[48] but dealing more specifically with the use of antiplatelet drugs in the perioperative setting.

Antiplatelet agents: pharmacology

Antiplatelet agents are classified into three categories: acetylsalicylic acid, thienopyridines, and platelet glycoprotein (GP) IIb/IIIa receptor antagonists. Statins will be added to this list because one of their pleiomorphic effects is a decrease in platelet aggregability.

Acetylsalicylic acid

Acetylsalicylic acid (aspirin) achieves a complete and irreversible blockade of platelet COX-1 at the usual dosage of 50–150 mg per day. For a normal adult, a daily dose beyond 150 mg increases haemorrhagic risk without increasing protection.[87] The dose may be increased up to 325 mg in patients with increased bodyweight. The ability of platelets to aggregate is partially restored within 4–5 days after stopping aspirin.[40] In primary prevention, aspirin is indicated when the 10-yr risk of vascular events is more than 10%.[97] In secondary prevention, aspirin decreases the myocardial re-infarction rate by 30% and subsequent stroke by 25%.[6 41] Aspirin is a lifelong therapy which should never be discontinued after a coronary or cerebrovascular event.[2 3 39 91 106] In the absence of (low-molecular weight) heparin, up to 300 mg per day is not a contra-indication to regional or neuraxial blockade.[46]

Thienopyridines

Clopidogrel (Plavix®; loading dose: 300 mg, daily dose: 75 mg) is the only platelet ADP-receptor antagonist used clinically. It decreases the risk of MI in unstable angina by 18% and the risk of coronary stent thrombosis and recurrent stroke by 30%,[71 111 126] but increases the risk of spontaneous haemorrhage by 38% (incidence 1–2%).[23 71] Bleeding time increases to a maximum of 1.5- to threefold normal after 3–7 days of treatment.[40] The half-life of clopidogrel is short (4 h), but recovery from the drug is long (7 days) because of irreversible platelet inhibition.[122] As for aspirin, normalization of coagulation relies on the release of new platelets into the circulation, not on the

disappearance of the drug from the plasma. Clopidogrel is an absolute contra-indication to regional/neuraxial blockade.[34 47 96 116] If necessary, it should be stopped 5–7 days before operation.[122] Clopidogrel can be a substitute for aspirin in non-responders or in the case of allergic reactions. A new substance, prasugrel (AZD6140), is to be released shortly; it is expected to be more potent and to elicit fewer non-responders than clopidogrel.[50] Thienopyridines are often combined with aspirin (dual antiplatelet therapy) for unstable coronary plaque or during the re-endothelialization phase of coronary stents.

Unfortunately, 12–20% of patients do not respond to aspirin, particularly women and patients with diabetes, and 6–24% do not respond to clopidogrel.[66] This wide variation is due to the multiplicity of tests used to quantify aspirin effects and to the absence of an efficient and specific test for evaluating clopidogrel activity.[61] Resistance to antiplatelet agents might explain the high incidence of MI recurrence or stent thrombosis in some patients. Some studies show that patients with recurrent stent thrombosis have an impaired response to aspirin, which is not overcome by additional treatment with clopidogrel.[123] Specific gene variants implicated in thrombosis might have an impact on the efficiency of antiplatelet agent strategies. For example, the effect of aspirin on platelet function is modified by the GP-IIIa nucleotide polymorphism P1^A2. Patients who are heterozygous for this gene keep a high platelet adhesiveness under aspirin therapy, whereas adhesiveness is efficiently blunted in homozygous patients at the same dosage.[24] In the future, pharmacogenomics may be able to provide tests for differentiating responders from non-responders.

GP IIb/IIIa antagonists

Platelet GP IIb/IIIa receptor antagonists are used for the prevention of immediate thrombosis of coronary stents and are prescribed for 24–48 h after PCI.[74] Abciximab (ReoPro®) exhibits high-affinity receptor binding, whereas tirofiban (Aggrastat®) and eptifibatide (Integrilin®) have low-affinity, competitive, dose-dependent pharmacodynamics.[40] After discontinuation of an infusion of abciximab, the receptor occupancy decreases to approximately 70% in 12 h, bleeding time, which is prolonged to >30 min during infusion, decreases to 10–15 min,[30] and effective platelet aggregability is restored in 48 h, but residual receptor blockade can be observed up to 7 days. Tirofiban has a plasma half-life of only 2 h; at 4 h after stopping the infusion, platelet aggregability is already 50% of its normal value and bleeding time returns to normal.[58] The half-life of eptifibatide is 2.5 h; within 6 h after stopping the infusion, platelet function recovers to more than 50%.[114]

Statins

Statins are used widely for their ability to lower low-density lipoprotein and for their anti-inflammatory effects.

They also increase nitric oxide (NO) production and decrease vascular smooth muscle proliferation,[57] properties which, respectively, diminish platelet aggregation, and re-stenosis rate after PCI. Statins are associated with minor muscle side-effects (weakness, myalgias, or cramps in 1–5% of the cases) and slight elevation of creatine-kinase; the incidence of major rhabdomyolysis is very low (0.15 per 1 million prescriptions), but postoperative cases have been reported.[33] In a retrospective study of 2816 patients, atorvastatin was shown to decrease cardiac morbidity and mortality by 50% after non-cardiac surgery.[89] A controlled randomized trial on a small population (100 patients), with treatment for 30 days before and 6 months after vascular surgery, showed a decreased cardiac complication rate from 26% (placebo group) to 8% (atorvastatin group).[27] These results have been supported by a large retrospective analysis of 780 591 patients, where in the 77 278 patients (9.9%) who had preoperative treatment with a statin, the surgical mortality was lowered by 40%.[68] A recent meta-analysis of 15 publications (223 010 patients) suggests that statins are beneficial in cardiovascular patients, where the mortality is reduced from 3.1% to 1.9% in cardiac surgery and from 6.1% to 1.7% in vascular surgery.[43] This benefit is noticeable mainly in high-risk cases and in long-term mortality (>4 yr), but the incidence of postoperative MI is not modified. However, the evidence of benefit is largely based on observational data and not on controlled trials.[55] Therefore, patients already on statins should continue the treatment in the perioperative period, but there is insufficient evidence to recommend the routine use of statins for patients other than those with established CAD.

Percutaneous coronary revascularization

The immediate period after a PCI is a high-risk period because the stenotic lesion is transformed into an unstable area due to the rupture of its endothelial covering. When patients undergo non-cardiac surgery during this early period, the rate of MI and mortality (average 30% and 20–40%, respectively) is 5–10 times higher than that for matched patients undergoing the same operation under maximal medical therapy or after appropriate delay.[53 90 92 103] There are no high level of evidence studies on the optimal delays between revascularization and non-cardiac surgery. Therefore, recommendations are based on pathology reports,[38 60 117] expert opinion,[1 3 91 106] and manufacturer advice, to estimate the time to complete re-endothelialization of the coronary vessel. During this period, a dual antiplatelet therapy consisting of aspirin and clopidogrel is mandatory.[2 106] It is usually accepted that the duration of this dual treatment is 4–6 weeks after bare metal stents (BMS), 3 months after sirolimus drug-eluting stents (DES) (Cypher™), 6 months after paclitaxel DES (Taxus™ Achieve™, V-flex™, CoStar™), and 3–6

Table 1 Duration of antiplatelet therapy and recommended delays for non-cardiac surgery after PCI

Dilatation without stenting: 2–4 weeks
  Surgery postponed for 2–4 weeks (vital surgery only)
PCI and BMS: 4–6 weeks
  Vital surgery postponed for ≥6 weeks
  Elective surgery postponed for ≥3 months
PCI and DES: 12 months
  Elective surgery postponed for ≥12 months
Aspirin: lifelong therapy, whichever is the revascularization technique

months for the second generation DES with zotarolimus (Endeavor™) or everolimus (Xience V™).[1 2 5 91 101 106] However, recent data (discussed later) tend to indicate that DES are extremely dependent on the administration of clopidogrel and that clopidogrel should be continued for 1 yr after all types of DES, despite the increased risk of bleeding. The updated AHA/ACC Science Advisory and the Society of Cardiovascular Angiography DES Task Force recommend 12 months of dual antiplatelet therapy after DES, and postponement of all elective operations during this period[39 44 106] (Table 1). Aspirin is a lifelong treatment and should never be interrupted whichever type of stent is used.[3 5 39 91]

The usefulness of a dual antiplatelet therapy was demonstrated by the PCI-Cure study of 2658 patients with acute coronary syndrome undergoing PCI. Patients were randomly assigned to a 1 yr treatment with clopidogrel and aspirin or placebo and aspirin. In this study, an overall 31% reduction ($P=0.002$) of cardiovascular mortality or MI rate was observed in the clopidogrel group (Fig. 1).[71] The difference between both groups appears during the first 3 months, and stays constant or slightly increasing up to 12 months. This raises the question of the usefulness of clopidogrel beyond 1 yr. The CHARISMA study[13] tried to answer this question with 15 603 high-risk cardiovascular patients randomly assigned to receive clopidogrel and aspirin or placebo and aspirin, followed for a median
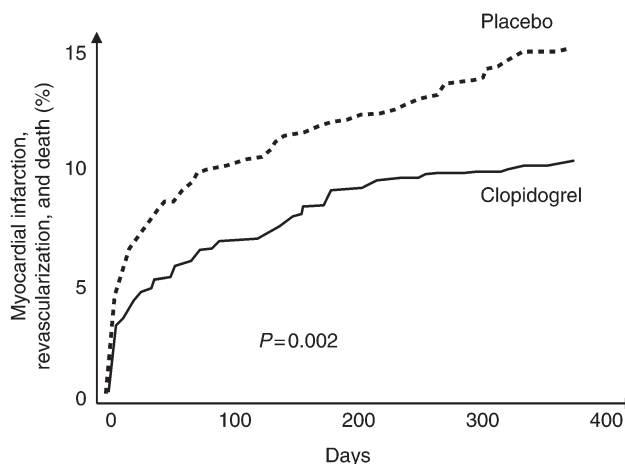

Fig 1 Twelve- month outcome of patients with stents receiving clopidogrel or not (reproduced with permission from Mehta[71]).

duration of 28 months. Similar rates of MI, stroke, or cardiovascular death in both groups indicated that clopidogrel plus aspirin was not more effective than aspirin alone as primary prevention. Moreover, the rate of severe spontaneous bleeding was increased (2.1% *vs* 1.3%). In secondary prevention, a small 12% reduction in relative risk was observed in the clopidogrel group, but also with a slight increase in the bleeding risk. These data seemed to support the use of clopidogrel for 1 yr only after PCI or a cardiovascular event, except in some particularly unstable cases.

New problems with DES

In late 2006, new findings were published concerning the possible increased rate of late thrombosis with DES. It is essential for the anaesthetist to be aware of the recent controversies in cardiology because they have a direct impact on decisions concerning the perioperative management of stented patients. In the BASKET trial,[88] 746 non-selected patients, randomly assigned to BMS or DES and surviving 6 months without major events, were followed for a further year after discontinuation of clopidogrel at 6 months. The 18-month rate of re-stenosis was lower in DES compared with BMS (4.5% *vs* 8.7%, OR 0.51), but the 18-month rate of cardiac death or MI was not different between DES and BMS patients. However, after the discontinuation of clopidogrel (between months 7 and 18), these events occurred in 4.9% after DES compared with 1.3% after BMS ($P=0.01$). The DES thrombosis-related events had a mortality rate of 19%. In addition, an observational study on 4666 patients (3165 BMS and 1501 DES) taking clopidogrel for 6 months[28] showed that the individuals with DES still taking the drug after 24 months had a composite rate of death or MI of 3.1%, whereas those who stopped clopidogrel at 6 months had a composite rate of 7.2% ($P=0.02$) (Fig. 2). In patients with BMS, there were no differences in death or MI rate with or
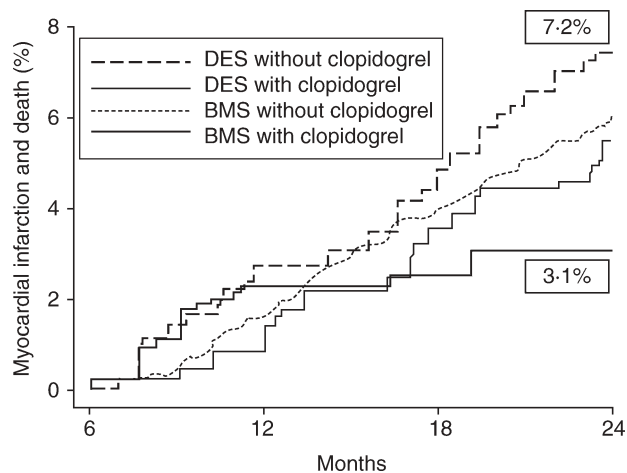

Fig 2 Twenty-four month outcome of patients with BMS and DES, with or without clopidogrel (reproduced with permission from Eisenstein[28]).

without long-term clopidogrel treatment. In the recent *Swedish Coronary Angiography and Angioplasty Registry* (6033 patients with DES and 13 738 patients with BMS), the 13.7% reduction in composite rate of death and MI among DES-treated patients in the first 6 months is offset by a 12.7% increase in events in this group during the following year,[63] giving an adjusted relative risk of death between 6 months and 3 yr 30% higher in DES patients. A meta-analysis involving 8221 patients[80] seems to indicate that not only cardiac mortality is increased among DES compared with BMS patients, but also non-cardiac mortality (OR 1.6–2.14), mainly due to an over-representation of tumours in the patients with sirolimus-eluting stents. Another intriguing observation is an impaired collateral function with DES,[72] where despite equal stenosis severity and follow-up duration, collateral flow index is diminished in DES compared with BMS patients ($P=0.005$), and the rate of collaterals insufficient to prevent ischaemia during occlusion is higher in DES compared with BMS ($P=0.001$). Whether sirolimus-DES or paclitaxel-DES are more prone to late thrombosis is still controversial,[9 25 44 105] but the mortality with both types of DES is increased, at a rate of 0.6% yr^{-1}.[19 25 51 88] Other meta-analyses of recent clinical trials have shown slightly conflicting results. Although some find a consistent trend towards more frequent death and Q-wave MI at late follow-up with DES,[19 112] others tend to show that late stent thromboses and death occur in BMS and DES,[102] but are more frequent with DES in diabetics.[108] This raises a difficult question about the replacement of BMS by DES: are we trading early re-stenosis with BMS for late thrombosis with DES?[104] In other words, are we trading a relatively benign but frequent event (12–20% at 12 months) for a rarer event (incidence 0.8–3%), but with a much higher mortality (19–45%)?[25 49 84 88] Numerically, this means that for each 100 DES implanted, five re-stenoses are prevented at 6 months, but three deaths or MIs occur by 18 months.[51 88] Part of the problem might be linked to off-label indications for DES, which are normally indicated for intermediate lesions, medium-sized vessels (<3.5 mm), and short stenosis (<30 mm).[75] Despite the manufacturer recommendations, up to 60% of DES are implanted in proximal, long, or bifurcated lesions, and some studies suggest that adverse outcomes are more frequent when DES are implanted outside the terms of the licence.[9 44 88 105]

Withdrawal of antiplatelet agents

The fear of excessive bleeding leads to the generally accepted policy of withdrawing antiplatelet agents 7–10 days before a surgical or endoscopic procedure. Knowing the efficacy of these drugs in preventing coronary stent thrombosis and MI, this raises an important question regarding the safety of interrupting antiplatelet therapy.

Acute withdrawal of antiplatelet agents produces a deleterious rebound effect; pro-thrombotic effects overcome the physiological balance. Excessive thromboxane A_2 activity and decreased fibrinolysis have been noted on stopping aspirin.[12 31 120] In a study of 2229 patients with DES and a thrombosis rate of 1.5% during the first year, premature clopidogrel discontinuation was the most significant independent predictor of stent thrombosis, with a hazard ratio of 57.13 ($P<0.001$) and a mortality rate linked to stent thrombosis of 45%.[49] Patency of DES is particularly dependent on clopidogrel during the first year. Two-thirds of the late DES thromboses were linked to stopping antiplatelet drugs.[84] Compared with patients who have taken the drug continuously, patients who stopped clopidogrel during the first month after PCI are 10 times more likely to die (7.5% and 0.7%, $P<0.0001$) or to be re-hospitalized (23% and 14%, $P=0.08$) during the next 11 months.[109] In the BASKET trial, the MI and death rates 7–18 months after cessation of clopidogrel were more than doubled with DES compared with BMS (4.9% and 1.3%, adjusted hazard ratio 2.2, $P=0.03$).[88] During the year after discontinuation of clopidogrel, patients with DES had a 38% higher rate of MI or death than with BMS ($P=0.03$).[19] Antiplatelet drug withdrawal is even more dangerous in the perioperative period. Stopping clopidogrel to allow major surgery during the first 3 weeks after PCI and stenting leads to mortalities ranging from 30%[32] up to 86%.[103] These data reinforce the need to maintain full antiplatelet therapy in the perioperative period, particularly for DES, even if the time from PCI is relatively long.

The interruption of aspirin alone is also risky and may lead to stent thrombosis even more than 1 yr after PCI and DES.[70 76] Acute coronary syndrome, leading to MI or death, in patients who have stopped aspirin within the previous 3 weeks occurs at twice the rate of that for patients who continued antiplatelet therapy.[23] A meta-analysis of 50 279 patients for secondary prevention for CAD showed that the cardiac complication rate was three times higher after aspirin withdrawal (OR 3.14, $P=0.0001$).[14] This risk was even higher in patients with coronary stents (OR 89.78). The delay between stopping aspirin and thrombotic events averages 10.6 days (8.5 days for coronary symptoms and 14.3 days for cerebral vascular accidents).[14 18] These data support the continuation of aspirin perioperatively. When aspirin is withdrawn for situations such as intracranial neurosurgery, the interruption should be for a maximum of 5–7 days, and the treatment resumed as soon as possible after surgery (within 12–24 h). However, in patients with stents, aspirin must never be stopped.[5 39 44]

The acute cessation of statins is also harmful, because it is accompanied by a rebound phenomenon and an increased platelet aggregability. Statin therapy withdrawal within 24 h of acute coronary syndrome is associated with a significant increase in cardiac risk (adjusted hazard ratio 2.93, $P=0.005$), independent of cholesterol levels.[42] It is, therefore, safer to continue statin therapy throughout the surgical period, despite the small risk of rhabdomyolysis.[43 57]

Stopping antiplatelet agents is the major independent predictor for late stent thrombosis, but other factors have a high predictive value for thrombotic events, including stenting of small vessels, multiple lesions, long stents, ostial or bifurcation lesions, suboptimal stent result, low ejection fraction, advanced age, renal failure, and diabetes.[5 39] In these situations, the advice is to maintain long-term dual antiplatelet therapy. Stent thrombosis is characterized by high mortality rates (19–45%)[32 49 51 84 88] because it corresponds to an abrupt interruption of the blood flow in a high-output vessel and the involved myocardium has poor collaterals and is not pre-conditioned by previous recurrent ischaemic episodes. DES tend to inhibit collateral growth.[72] With an average mortality of one for every three cases, stent thrombosis is an extremely dangerous event. In a surgical setting, the risk is further increased (up to 85%)[103] by the cardiac complication rate specific to the type of surgery and by the postoperative phase of platelet hyper-aggregability and decreased fibrinolysis. This clearly suggests that only exceptional situations can justify stopping antiplatelet agents in these patients.

Haemorrhagic risks

If the thrombotic risk at withdrawal of antiplatelet agents is high, what is the danger of surgery under continuous antiplatelet therapy? Apart from surgery, the rate of severe spontaneous bleeding recorded in various trials is increased in patients taking dual therapy compared with those on aspirin alone; 0.7–1.13% (37% increase in relative risk) in the ATC trial[6] and 2.7–3.7% (27% increase in relative risk) in the CURE trial.[126] Unfortunately, studies on intraoperative haemorrhagic risk of antiplatelet therapy, although numerous, are usually statistically underpowered and there are few if any large prospective randomized studies. These have been carried out mainly in orthopaedics (hip arthroplasty) and cardiac surgery (CABG). However, analysis reveals interesting facts about the impact of aspirin and clopidogrel on surgical bleeding.

Patients on aspirin

A large review and meta-analysis of 474 studies on the impact of low-dose aspirin on surgical blood loss showed that patients on aspirin alone have an average intraoperative haemorrhagic risk increased by a factor of 1.5, without an increase in surgical mortality or morbidity.[18] Despite a modest rise in bleeding rate, there were no differences in surgical complications or outcome linked to haemorrhage in most procedures such as dental, ophthalmological, visceral and minor general surgery, endoscopies, biopsies, and dialysis catheter insertion. In vascular surgery, the increase in bleeding complications was only

2.46%.[78] In orthopaedics, the data are less clear, with studies showing an increased rate of bleeding and transfusion in hip arthroplasty,[82] but not in osteosynthesis of femoral neck fractures,[69] spinal instrumentation, or multi-level fusion surgery.[81] Where there was an increased blood loss, the average transfusion rate was increased by a factor of 1.5, mainly due to oozing from bone and surrounding tissues. Bleeding threatening vision did not occur in the studies in ophthalmology.[18 52] Local haemostasis measures sufficiently controlled bleeding in oral surgery.[107 118] Although aspirin increases bleeding by approximately 20–30%, surgeons could not differentiate patients on aspirin from patients on placebo just from surgical bleeding.[67]

Aspirin seems to be associated with a rise in bleeding rate only in specific procedures. In cardiac surgery with cardiopulmonary bypass, a review of 50 studies revealed an average increase in bleeding of 300 ml per patient.[11] After tonsillectomy, the re-operation rate for postoperative haemorrhage was increased 7.2 times in an aspirin group compared with an acetaminophen group.[110] During transurethral prostatectomy, the blood transfusion rate was increased by a factor of 2.7 in patients on aspirin compared with control groups,[115] and importantly, there were two fatalities in this series. However, the new technique of photoselective vaporization with the potassium-titanyl-phosphate (KTP) laser for endoscopic prostatectomy may decrease haemorrhagic complications in these patients.[100] In intracranial neurosurgery, aspirin has been involved in an increased risk of postoperative intracerebral haematoma. In some cases, it has been a contributing factor to the fatal outcome.[85]

Patients on dual therapy (aspirin and clopidogrel)

It would be expected that the addition of clopidogrel to aspirin would increase surgical haemorrhage. Blood loss is effectively increased on average by 30–50%, but most of the studies have been conducted in cardiac surgery with full intraoperative heparinization for cardiopulmonary bypass. Clopidogrel intake during the last 4 days before CABG has been shown to be an independent predictor of re-operation for control of haemorrhage (OR 4.9, 95% Cl 2.63–8.97),[54] (OR 6.9, 95% Cl 1.6–30)[125] transfusions (OR 4.22, 95% Cl 1.79–9.95),[22] and length of stay in the intensive care unit (OR 3.14, 95% Cl 1.40–7.04).[22] Nevertheless, surgical outcomes and operative mortality were not different from usual practice.[54]

There are fewer studies of the effect of clopidogrel in non-cardiac surgery. In patients undergoing vascular, orthopaedic, and visceral surgery after coronary stent implantation, the transfusion rate was 38.5% in controls and 42.6% in patients taking dual antiplatelet therapy[124] (NS). After trans-bronchial biopsy, the bleeding rate is very high (89%) in patients taking clopidogrel compared with patients not on antiplatelet treatment (3.4%), but no patient required transfusion and each case was controlled by the endoscopic route.[29] Case reports and small clinical series in visceral and vascular surgery have shown a moderate increase in surgical blood loss and transfusion rate, but not in morbidity, mortality, or surgical outcome. However, diffuse bleeding and tissue oozing where direct surgical haemostasis is difficult may lead to delayed blood loss during the first postoperative days. In oral surgery and dentistry, there was no increased risk of haemorrhagic complications in patients taking clopidogrel.[39 107] In neurosurgery, a short communication has recently described seven patients who developed fatal intracerebral haemorrhage associated with neuro-interventional procedures and the use of clopidogrel and the anti-GP IIb/IIIa, abciximab.[95] It appears, therefore, that the continued use of clopidogrel during the perioperative period increases the surgical bleeding and the transfusion rate probably by a factor of 50% but not the morbidity or the mortality, with the exception of intracranial surgery.

Withdrawing or continuing antiplatelet agents: the risks in balance

This question was already raised in the recent review in the *British Journal of Anaesthesia*.[48] Clinicians like to receive clear-cut answers when they are confronted with difficult situations. Therefore, we would like to present the arguments balancing the risks of increased surgical blood loss by continuing the antiplatelet drugs during the perioperative period and the risks of acute coronary syndrome if they are withdrawn before the procedure.

On one hand are the risks of maintaining the antiplatelet drugs.[21]

- Average increase in surgical blood loss of 2.5–20% with aspirin, or 30–50% with aspirin and clopidogrel; no increase in surgical mortality linked to this increased bleeding, except during intracranial surgery, but occasional increase in surgical complications.
- Average increase of 30% in transfusion rate; however, complication rate of red blood cell transfusion is only 0.4% (all types of complications included),[73] and mortality linked directly to massive surgical blood loss is ≤3%.[56]
- The incidence of ischaemic events is probably similar to the rate observed in patients with stable CAD; depending on the type of procedure, the rate of non-fatal MI is 2–6% and the cardiac mortality is 1–5%.[1 20]

On the other hand are the risks of withdrawing the antiplatelet agents.

- Rebound effect with increased platelet adhesiveness;[120] simultaneously, the systemic inflammatory syndrome and the acute phase reaction to surgery increase platelet adhesiveness and decrease fibrinolysis;[48 93] also, some pathologies, such as carcinoma and diabetes, are accompanied by hyper-coagulability.
- Doubled infarction and death rates in acute coronary syndrome.[23]

- During the re-endothelialization phase of coronary stents, the average postoperative MI rate due to stent thrombosis is 35%; the average mortality of stent thrombosis is 20–40%,[32 49 53] up to 85% in one post-operative study;[103] therefore, the perioperative cardiac death rate is increased 5–10 times.
- First-generation DES are highly dependent on antiplate-let agents during the first year after PCI.[28 49 70 84 88]
- Emergency PCI for revascularization of a thrombosed coronary vessel during the early postoperative period is more difficult and associated with a greater risk than red blood cell transfusions and surgical haemostasis during the operation. Thrombolysis and abciximab are not an option in the immediate postoperative period because of the risk of catastrophic bleeding.

It appears, therefore, that the risks of withdrawing the patients from antiplatelet agents in the perioperative period are generally higher than those of maintaining this vital medication. Although each case must be managed on an individual basis by the anaesthetist together with the cardiologist and the surgeon, it is necessary to modify the approach of withdrawing patients from all antiplatelet agents 7–10 days before surgery, except when bleeding might occur in a closed cavity.

Possible approaches

Pending large prospective studies with a high degree of evidence on different antiplatelet agents regimens during non-cardiac surgery, there is a wide diversity of practice for patients on antiplatelet drugs. However, we would like to propose a general approach based on the most recent data, even if they are mainly based on research in cardiology.

Proposed algorithm

The preoperative evaluation of patients on antiplatelet therapy is presented in an algorithm we use in our insti-tutions (Table 2, Fig. 3).[21] In our opinion, this algorithm is helpful for guiding the clinician through the, frequently difficult, bedside decisions. Aspirin is a lifelong therapy and should never be stopped before surgery when pre-scribed as a secondary prevention after stroke, angina, MI, or any type of revascularization (CABG, simple coronary dilatation, PCI with any type of stent). However, when prescribed as primary prevention, there are no studies indi-cating that interruption might be harmful. Aspirin as primary prevention may, therefore, be safely withdrawn but no more than 7 days before surgery.

If clopidogrel is prescribed for an unstable angina or during the re-endothelialization of a stent, it should not be stopped before a non-cardiac procedure. This period lasts at minimum 2–4 weeks after simple dilatation, 6 weeks after BMS, 12 months after DES, and may even be pro-longed beyond 1 yr in high-risk DES, such as long (>36 mm) and proximal stents, multiple stent implantation, overlapping stents, stents in chronic total occlusions, small vessels, or bifurcated lesions.[5] High-risk situations also include patients with a history of stent thrombosis, low ejection fraction, diabetes, and carcinomas (possible

Table 2 Proposed scheme for management of patients taking antiplatelet therapy and requiring surgery. MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; BMS, bare metal stent; DES, drug-eluting stent; EF, ejection fraction

| Surgical haemorrhagic risk	Cerebro- and cardiovascular risk		
	Low	**Intermediate**	**High**
	>6 months after MI, PCI, BMS, CABG, stroke >12 months if complications	6–24 weeks after MI, PCI+BMS, CABG, or stroke (Ø complication); >12 months after DES; high-risk stents (long, proximal, multiple, overlapping, small vessels, bifurcation); low EF, diabetes	<6 weeks after MI, PCI, BMS, CABG; <6 months after same if complications; <12 months after high-risk DES; <2 weeks after stroke
Low risk Transfusion normally not required; peripheral, plastic, and general surgery, biopsies; minor orthopaedic, ENT, and general surgery; endoscopy; eye anterior chamber; dental extraction and surgery	Elective surgery: OK; maintain aspirin	Elective surgery: OK; maintain aspirin, clopidogrel (if prescribed)	Elective surgery: postpone; vital or emergency surgery: OK; maintain aspirin and clopidogrel
Intermediate risk Transfusions frequently required; visceral surgery; cardiovascular surgery; major orthopaedic, ENT, reconstructive surgery; endoscopic urology	Elective surgery: OK; maintain aspirin	Elective surgery: postpone; surgery absolutely required: OK; maintain aspirin, clopidogrel (if prescribed)	Elective surgery: postpone; vital or emergency surgery: OK; maintain aspirin and clopidogrel
High risk Possible bleeding in a closed space; intracranial neurosurgery; spinal canal surgery; eye posterior chamber surgery	Elective surgery: OK; maintain statin; withdraw aspirin (maximum 7 days)	Elective surgery: postpone; surgery absolutely required: OK; maintain aspirin, or replace aspirin by ibuprofen; stop clopidogrel	OK only for vital or emergency surgery; maintain aspirin Bridge with tirofiban/eptifibatide and heparin
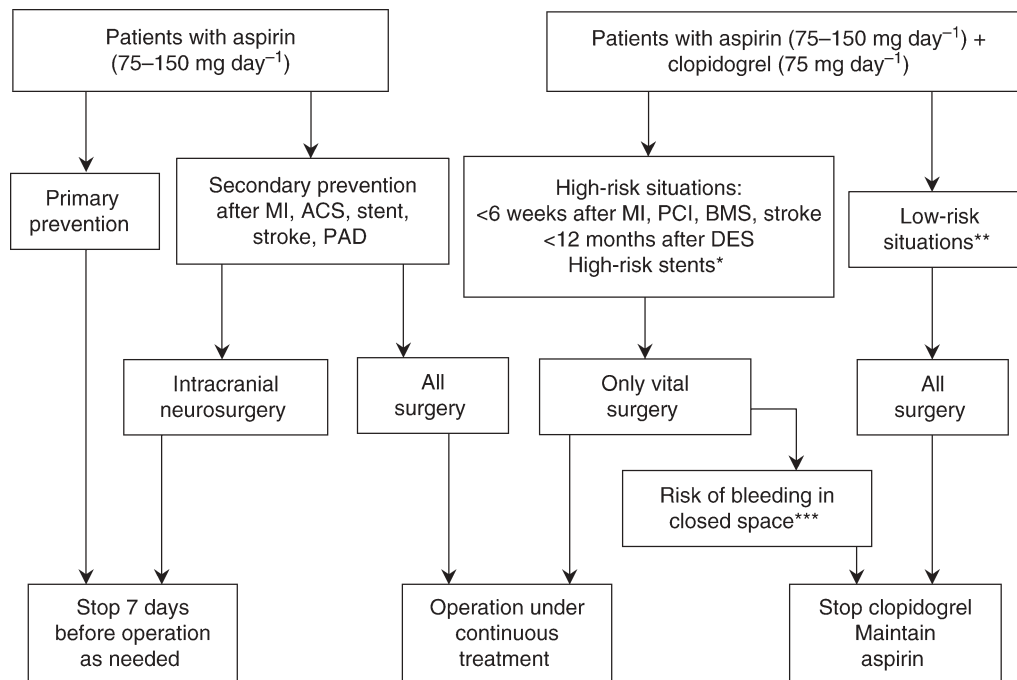
Fig 3 Algorithm for preoperative management of patients under antiplatelet therapy. MI, myocardial infarction; ACS, acute coronary syndrome; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; BMS, bare metal stent; DES, drug eluting stent. *High-risk stents: long (>36 mm), proximal, overlapping, or multiple stents implantation, stents in chronic total occlusions, stents in small vessels or bifurcated lesions. **Examples of low-risk situations: >3 months after BMS, stroke, uncomplicated MI, PCI without stenting. ***Risk of bleeding in closed space: intracranial neurosurgery, intra-medullary canal surgery, posterior eye chamber ophthalmic surgery. In these situations, the risk/benefit ratio of upholding *vs* withdrawing aspirin must be evaluated for each case individually; in case of aspirin upholding, early postoperative re-institution is important.

hypercoagulability due to paraneoplasic syndromes). In low-risk situations, it is possible to discontinue clopidogrel for 1 week, but not aspirin. Low-risk situations include patients more than 3 months after BMS, stroke, uncomplicated MI, or PCI without stenting. Present clinical data tend to suggest that DES are probably never low-risk.

There is no evidence that patients who have completed their clopidogrel treatment and are symptom-free after discontinuation should be restarted on dual therapy because of surgery. However, patients still on dual antiplatelet therapy during the re-endothelialization period after coronary stenting should be operated on without interrupting treatment. This statement applies to thoracic, abdominal, vascular, orthopaedic, and superficial general surgery, and to endoscopies and biopsies. Patients on clopidogrel planned for an endoscopic urologic procedure should be transferred to a centre equipped with the new KTP laser technology instead of discontinuing antiplatelet agents for transurethral prostatectomy. In ENT, oral surgery, and dentistry, it is possible to perform all types of procedures while on low-dose aspirin treatment. In the case of dual therapy, most of the current surgical procedures can be safely undertaken. However, operations traditionally associated with excessive blood loss should be postponed unless vital. In ophthalmology, extra-ocular and anterior chamber surgery can be conducted during dual antiplatelet therapy, but not posterior chamber procedures, which

require the cessation of clopidogrel (but not aspirin). For elective procedures, it is safer to postpone surgery until clopidogrel can be withdrawn without risk. Only vital or emergency surgery should be performed on full antiplatelet therapy. After the operation, antiplatelet agents should be resumed within the first 12–24 h.[48]

In closed spaces, such as intracranial surgery, spinal surgery in the medullary canal, and surgery of the posterior chamber of the eye, even a small postoperative haemorrhage can have disastrous consequences. Extracranial neurosurgery such as hernial disc repair can be performed without stopping antiplatelet agents. Therefore, the approach adopted in our institutions is to leave aspirin but withdraw clopidogrel 7 days[47] before intracranial surgery, medullary surgery, and posterior chamber ophthalmic surgery. In these cases, a 'bridge' with tirofiban or eptifibatide and heparin may be an option (discussed later). This approach is not based on any controlled prospective study, but may be viewed as a compromise between platelet half-life, thrombotic risk, and haemorrhagic risk, and it may be an option for operations associated with excessive blood loss. Treatment must be resumed as soon as possible after surgery with a loading dose of 300 mg clopidogrel.[5 48] In stereotaxic intracranial procedures, aspirin should also be stopped, but it is more reasonable to postpone this type of procedure until the patient can safely stop all antiplatelet medication. Thus,

the presence of DES may be a contra-indication to stereotaxic procedures, since stopping aspirin is too dangerous.

The problem of regional and neuraxial blockade

Clopidogrel with aspirin during the week preceding an operation is an accepted contra-indication to any form of regional anaesthesia (RA).[34 47 96] Spinal haematoma has been described during clopidogrel treatment,[113] but the precise risk of spinal or epidural haematoma with dual antiplatelet therapy is unknown.[116] Anaesthetists may be tempted to interrupt antiplatelet drugs on the assumption that neuraxial blockade is safer than general anaesthesia in a patient with CAD. However, only a high thoracic epidural blockade (>T6 level) can produce cardiac sympatholysis which increases coronary blood flow, decreases myocardial O_2 consumption (mVO_2),[83] and may reduce the incidence of postoperative MI linked to tight stenoses and DO_2/VO_2 imbalance.[10 96] In a meta-analysis of 11 randomized trials (1173 patients), neuraxial blockade at levels below T6, alone or in combination with general anaesthesia, did not significantly reduce the cardiac risk,[86] or mortality and infarction rate.[10] In abdominal vascular surgery, one study showed a decrease in cardiac complication rate with combined anaesthesia compared with general anaesthesia (10:18%), but only in a subgroup of high-risk patients undergoing long operations.[86] One can argue that RA might reduce the intensity of the acute phase reaction linked to surgery, and therefore decrease the risk of thrombosis on unstable plaques, but this has not yet been demonstrated.

High thoracic epidural anaesthesia decreases cardiac morbidity by 40%,[10 83] but stopping clopidogrel in the case of unstable plaques or uncovered stents increases infarction and death rates 5–10 times. To the best of our knowledge, the protective effect of antiplatelet agents is more efficacious than the effects of RA on arterial thrombosis and on the reduction of MI and cardiac death rates. Moreover, the intraoperative sympatholysis of epidural anaesthesia can be achieved with agents such as β-blockers, α2-agonists, and higher dosages of opioids given i.v. The price to pay for optimal protection against acute coronary ischaemia may be a poorer quality of postoperative analgesia and comfort for the patient without epidural. We conclude that the risk/benefit ratio of preoperative withdrawal of antiplatelet drugs in order to perform a regional or neuraxial blockade is not justified.

Platelet transfusion and antagonism

As the effects of antiplatelet agents are not reversible by other drugs, fresh platelets are the only way to re-establish a normal coagulation process. Haemostatis requires that at least 50% of the circulating platelets have a normal function. The recommendations concerning platelet transfusions have been presented in guidelines.[48 99] However, the activity of new platelets may be inhibited by drug present in the circulation. The half-life of clopidogrel is 4 h and its plasma level is close to zero after 12 h (three half-lives). Therefore, beyond 6–8 h after the last intake, the transfused platelets will not be significantly inhibited by the substance, whereas the patient's platelets are still blocked by an irreversible effect. In emergency situations or in the case of major bleeding, therefore, haemostasis can be restored by administration of fresh platelets within a few hours of the last clopidogrel intake. After discontinuation of abciximab (ReoPro®), effective platelet aggregability is restored in 48 h, when <50% of the receptors are blocked.[30 40] Platelet transfusions are mandatory within 48 h after abciximab, even if some of the fresh thrombocytes will be blocked by the residual circulating levels of the drug. The plasma half-life of tirofiban (Aggrastat®) and eptifibatid (Integrilin®) is close to 2 h. Around 6 h after administration of these drugs, platelet function returns to 60–90% of normal and bleeding time is prolonged less than 1.5 times.[35 114] Platelet transfusions are rarely required in this case.

Although aprotinin is not a specific antagonist of antiplatelet agents, it has been shown to decrease postoperative bleeding and transfusion rate in patients undergoing CABG and treated with clopidogrel during the days preceding surgery.[119]

Possible substitutes

An anti-thrombin agent such as a heparin does not mimic the effect of antiplatelet agents such as clopidogrel or aspirin. Aspirin substitution by low-molecular weight heparin does not afford a real protection against the risk of coronary or stent thrombosis. The infarction and cardiac complication rates are similar in patients substituted or not after stopping aspirin.[23 121] There are no data to support that maintenance of aspirin and replacement of clopidogrel by heparin is an efficient protection in high-risk coronary situations. Nevertheless, heparin is routinely prescribed as a substitute because it has been proven efficient in the treatment of unstable angina and non-ST-elevation MI.[7] Non-steroidal anti-inflammatory drugs (NSAIDs) as does ibuprofen or indobufen inhibit COX-1 such as aspirin,[37] but their blocking action on platelet activity is reversible. As platelet function is completely recovered within 24 h after NSAID withdrawal, these drugs can be used to maintain an efficient antiplatelet activity during the week between aspirin cessation and surgery.[98] This might be useful in situations such as intracranial surgery. Replacing a long-acting antiplatelet agent such as clopidogrel by a shorter-acting GP-IIb/IIIa inhibitor such as tirofiban[17] or eptifibatid[79] has been suggested empirically as a bridge across the period between clopidogrel discontinuation and re-initiation.

Unstable coronary syndrome and vital surgery

Antiplatelet drugs are also used in situations where the patient with unstable coronary syndrome requires vital

surgery. Depending on how long the surgery can be delayed, three situations are possible.

- The operation can be delayed for at least 6–8 weeks. This is enough to perform a PCI with a BMS and allow 4–6 weeks of dual antiplatelet agents therapy. DES is not an option in this circumstance, because the operation would be performed during the re-endothelialization phase, when the risk of stent thrombosis is the highest; after DES, the delay for elective surgery is 1 yr.[39 44]
- The surgery can only be delayed for 2–4 weeks. In cases of extremely unstable coronary flow, very proximal stenosis, and a large area of threatened myocardium, it is possible to consider a PCI without stenting,[21] because the rate of death and MI of non-cardiac surgery within 2 weeks of balloon angioplasty without stenting is the same as 3 months later.[16] When optimal 'stent-like' coronary dilatation is obtained with simple balloon angioplasty, the MI, repeat revascularization, and death rates up to 12 months are similar for PCI with or without BMS.[4] Therefore, PCI without stenting may be a safe means of revascularization for patients who need an operation with only a short delay.[8 20] However, many cardiologists are reluctant to use this approach and would rather refrain from any intracoronary intervention.
- The non-cardiac operation must be performed within 24–48 h. The patient should be put on maximal medical therapy (β-blocker, aspirin, and clopidogrel). It is useless to perform a coronary angiogram, because the results will not modify the therapeutic choice. If necessary, a simple transthoracic echocardiography will determine the ventricular function and rule out associated valvular disease.
- In all these circumstances, it is safer to operate under the continued protection of antiplatelet agents and maximal cardioprotection with β-blocker, aspirin, clopidogrel, and statin.

As yet, these suggestions are not supported by outcome data of controlled trials with a high level of evidence. They are gathered from the outcome of different studies and case reports, many of which have been conducted outside the surgical setting.

Postoperative PCI

As the greatest risk of ischaemia and infarction occurs during the first days after surgery, the treatment of chronic CAD (β-blocker, calcium antagonist, and anti-hypertensive agent) or unstable coronary syndrome (aspirin, clopidogrel, and heparin) must be restarted as soon as possible after the operation. Routine monitoring of cardiac enzymes is useful to detect silent ischaemia, which is frequent during the postoperative period, and predicts long-term mortality.[65] ST elevation on the ECG is an indication for coronary angiogragraphy and PCI. Dilatation is mandatory, but stenting may be a problem because of early postoperative acute systemic inflammatory syndrome

and blood hypercoagulability. It is not possible to use thrombolysis or GP IIb/IIIa inhibitors in the first 24–48 h after surgery, because of the risk of major bleeding. In such a case, it may therefore be safer to avoid stenting and proceed to a simple dilatation.

Conclusions

The present data demonstrate how dependent on antiplatelet drugs patients with unstable coronary perfusion and recently implanted stents are. They also demonstrate that the haemorrhagic risk is usually modest when antiplatelet therapy is continued throughout surgery. The widespread use of DES, on the other hand, has shown their risk of late thrombosis and their dependency on long-term clopidogrel. Therefore, it seems advisable to change the current practice of withdrawing antiplatelet drugs before an operation, except in situations where bleeding might occur in a closed space or where excessive blood loss is expected.

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