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Eberli, D; Chassot, P-G; Sulser, T; Samama, C M; Mantz, J; Delabays, A; Spahn, D R


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UROLOGIC SURGERY AND ANTI-PLATELET DRUGS
AFTER CARDIAC AND CEREBROVASCULAR ACCIDENTS

Daniel Eberli, MD, PhD*
Urology Clinic
University Hospital Zürich (USZ)
CH - 8091 Zürich / Switzerland
Phone: +41.44.255.9616
Fax: +41.44.255.4566
daniel.eberli@usz.ch

Pierre-Guy Chassot, MD
Faculty of Biology and Medicine University of Lausanne
CH - 1005 Lausanne / Switzerland
Phone: + 41.79.204.3455
Fax: + 41.22.361.2472
pierre-guy.chassot@chuv.ch

Tullio Sulser, MD
Urology Clinic
University Hospital Zürich (USZ)
CH - 8091 Zürich / Switzerland
Phone: +41.44.255.5401
Fax: +41.44.255.4566
tullio.sulser@usz.ch

Charles Marc Samama, MD, PhD, FCCP
Department of Anaesthesiology and Intensive Care
Hotel-Dieu University Hospital
F – 75181 Paris Cedex 04 / France
Phone: + 33.1.42.34.8551
Fax: +33.1.42.34.8960
marc.samama@htd.aphp.fr

Jean Mantz, MD, PhD
Department of Anaesthesiology and Critical Care
Beaujon & Louis Mourier University Hospitals
F – 02110 Clichy / France
Phone: +33.1.40.87.5911
Fax: +33.1.47.37.0703
jean.mantz@bjn.aphp.fr

Alain Delabays, MD
Department of Cardiology
University Hospital Lausanne (CHUV)
CH 1011 Lausanne / Switzerland
Phone: +41.21.314.0103
Fax: +41.21.804.2347
alain.delabays@ehc.vd.ch

Donat R. Spahn, MD, FRCA
Institute of Anaesthesiology
University Hospital Zürich (USZ)
CH - 8091 Zürich / Switzerland
Phone: +41.44.255.2695
Fax: +41.44.255.4409
donat.spahn@usz.ch

* Corresponding author
Word Count: 3920
ABSTRACT

Context: The perioperative management of patients under dual antiplatelet therapy after myocardial infarction, cerebrovascular event or coronary stent implantation represents an increasingly frequent issue for urologists and anaesthesiologists.

Objective: To assess the current scientific evidence and propose strategies concerning the management of urologic patients under antiplatelet therapy. A Medline & PubMed search was conducted for articles related to antiplatelet therapy after myocardial infarction, coronary stents and cerebrovascular events, and to the management of aspirin and/or clopidogrel in the context of surgery.

Results: Early discontinuation of antiplatelet therapy in secondary prevention is associated with a high risk of coronary thrombosis, further increased by the hypercoagulable state induced by surgery. Aspirin has recently been recommended to be a lifelong therapy. Clopidogrel is mandatory for 6 weeks after myocardial infarction and bare-metal stents, and for 12 months after drug-eluting stents. Surgery must be postponed beyond these waiting periods, or be performed under dual antiplatelet therapy, because withdrawal therapy increases 5-10 times the risk of postoperative myocardial infarction, stent thrombosis or death. The shorter the waiting periods between revascularisation and surgery, the higher is the risk of adverse cardiac events. The risk of surgical haemorrhage is increased approximately 20% by aspirin and 50% by clopidogrel.

Conclusions: The present review of the literature demonstrates that the risk of coronary thrombosis when antiplatelet agents are withdrawn before surgery is generally higher than the risk of surgical haemorrhage when antiplatelet agents are upheld. However, this issue has not yet been sufficiently evaluated in urologic patients and in many instances during urologic surgery the risk of bleeding might be exceedingly dangerous. In this problematic situation, a thorough dialogue between surgeon, cardiologist and anaesthesiologist is essential to determine all risk factors and to define the best possible strategy for each individual patient.
INTRODUCTION

More than 2 million patients undergo percutaneous coronary intervention (PCI) with stents each year. Since 5% of them present for surgery within the following 12 months, the perioperative management of patients with coronary stents and dual antiplatelet therapy represents an increasingly frequent issue for urologists and anesthesiologists. Most of the time, the urologist is the first physician to inform the patient about his future operation. However, surgeons are often not sufficiently aware of the high risk of withdrawing antiplatelet agents before surgery in patients after myocardial infarction (MI) or implantation of coronary stents [1,2]. Long-term dual antiplatelet therapy (aspirin and clopidogrel) is particularly important in the perioperative period because it represents the basis of the secondary prevention after acute coronary syndrome (ACS) and MI and the cornerstone of the treatment following PCI with placement of bare-metal (BMS) or drug-eluting (DES) stents.

In this review we assess the current scientific evidence and evaluate whether it is possible to propose recommendations concerning the management of urologic patients under antiplatelet therapy.

ANTIPLATELET AGENTS

Antiplatelet agents (AP) are classified into three categories: acetylsalicylic acid (aspirin), thienopyridines (clopidogrel and prasugrel) and platelet GP-IIb-IIIa inhibitors (eptifibatide, tirofiban, abciximab). This review deals mainly with aspirin and clopidogrel, since there is no perioperative experience with prasugrel, and GP-IIb-IIIa inhibitors are only used in ACS and immediately after PCI.

Aspirin inhibits irreversibly thromboxane A2 and prostacyclin (PGI2) synthesis. It is effective in doses ranging between 50 and 160 mg/day. There is no evidence that doses greater than 160 mg/day are more efficacious in reducing the cardiovascular risk, but they increase the risk of gastric bleeding. After cessation of aspirin, platelet aggregation returns to baseline in 5 days. The long-term benefit of aspirin is a relative risk reduction (RRR) of recurrent vascular events of 38% after MI and 25% after stroke [3].

Clopidogrel is a pro-drug oxidized by hepatic cytochromes into an active metabolite which has a plasma elimination half-life of 8 hours and inhibits irreversibly platelet aggregation in a dose-dependant fashion (daily dosage: 75 mg). Seven days after cessation, 80% of platelets have
recovered normal aggregation. There are no major differences in terms of bleeding between aspirin and clopidogrel when administered alone. The benefit of dual therapy (aspirin and clopidogrel) over aspirin alone has been clearly demonstrated: the 1-year RRR is 31% after PCI and stent; beyond 1 year, the benefit of dual therapy is less pronounced (RRR 23%) [4], but keeps its efficiency over aspirin alone after PCI and DES: the rate of MI and death is 3.1% in patients still on clopidogrel at 2 years, but 7.2% when stopped at 6 months [5].

EVIDENCE ACQUISITION

A PubMed search was conducted for articles published during the last 10 years using the following key words: antiplatelet agents withdrawal, perioperative antiplatelet agents and coronary stents, perioperative antiplatelet agents after cerebrovascular accidents, antiplatelet agents and management of surgical bleeding, antiplatelet agents substitution and surgery. In total, 778 papers were produced by the search, and 167 original articles matching the focus of this review were selected, including controlled trials, observational series, meta-analyses and guidelines from major medical associations.

Evidence indicates that early discontinuation of antiplatelet therapy is associated with a worsened outcome in patients after cardiac or cerebrovascular accidents [5,6,7,8,9]. However, most of the data supporting maintenance of antiplatelet therapy in the perioperative period arise from case-series and nonrandomized retrospective or prospective studies, because of the obvious ethical difficulties to perform a placebo-controlled randomized trial when the tested substance is possibly a matter of safety. The recent recommendations formulated by panels of experts [10,11,12] are essentially based on precautionary principles and on an empirical balance between the risks of vessel thrombosis when antiplatelet agents are stopped and the risk of surgical hemorrhage when they are maintained. The present review aims at demonstrating whether the risk of coronary thrombosis outweighs the risk of surgical hemorrhage when antiplatelet agents are withdrawn before surgery.

ANTIPLATELET AGENTS AND CORONARY REvascularisation

As long as coronary stents are not fully covered by a cellular layer, they behave like unstable plaques and require a dual antiplatelet therapy. The metal frame of BMS is covered by smooth
muscle cells within 6 weeks and by a normal endothelial layer within 3 months, but only 13% of DES are completely covered by endothelium at 3 months and no more than 56% at 3 years [13].

Several retrospective series have disclosed very high complication rates when surgery is performed early after PCI: the combined rate of MI and death is 10-38% within 4 weeks after BMS, but decreases to 3.8% and 2.8% when surgery is performed at 2 and 3 months respectively [14,15,16] (Figure 1). After DES, the rate of adverse cardiac events is more continuous (5.9% up to 12 months) and drops to 3.3% beyond 1 year, but the mortality is high (average 35%) [17].

BMS are threatened by an overgrowth of the neo-endothelium, which leads to a restenosis rate of 12-25% at 6-12 months. To prevent this phenomenon, DES are slowly eluting anti-proliferative agents; their rate of restenosis is lowered to 6.5% at 4 years, but the slow re-endothelialization necessitates a longer duration of dual antiplatelet therapy. The recommended duration of clopidogrel treatment of 4-6 weeks after BMS must be extended to at least 12 months after DES according to recent guidelines [10,11,12] based on the rate of re-endothelialisation [13] and on the data of clinical trials [5,6]. This duration should be considered as a minimal safety measure. Although rare (0.6%/year increase compared to BMS), late DES thrombosis is a catastrophic event with a dramatic mortality (19% to 45%), because it corresponds to the acute interruption of flow in a previously normal-throughout vessel. In all studies, the major independent predictor of stent thrombosis is antiplatelet therapy cessation.

ANTIPLATELET AGENTS AND CEREBROVASCULAR DISEASE

The combination of aspirin and clopidogrel is no more efficacious than each medication alone to prevent recurrent stroke, MI or death, but increases the risk of bleeding (2.6% versus 1.3%) [18]. The addition of extended-release dipyridamole (400 mg) to aspirin (50-150 mg) presents a RRR of 20% over aspirin alone without increasing the risk of hemorrhage [19]. Whereas aggressive antiplatelet therapy is beneficial in coronary artery disease, where most acute events are caused by unstable plaque rupture, intense platelet inhibition seems not efficacious for secondary stroke protection, where the incidence of unstable atheromatous plaque is smaller and where the rate of major bleeding, particularly intracranial, is dangerously increased [18].
EVIDENCE FOR THROMBOTIC RISKS AT WITHDRAWAL OF ANTIPLATELET AGENTS

Antiplatelet drugs withdrawal outside surgery
In a prospective study, patients who stopped aspirin within two weeks preceding an ACS have a doubled incidence (OR 2.05) of MI and death compared to those still on continuous aspirin [7]. In a meta-analysis on 50'279 patients under secondary prevention for coronary artery disease, aspirin cessation increased cardiac complication rate three times (OR 3.14), but in patients with coronary stents, the cardiac risk increased ninety times (OR 89.78) [8]. Cases of acute DES thrombosis with MI have been reported at aspirin withdrawal up to 4 years after stent implantation. After a cerebrovascular accident, discontinuing aspirin increases three times (OR 3.4) the risk of recurrent stroke within 20 days [9]. Therefore, aspirin is recommended as a lifelong therapy, and its interruption is extremely dangerous.

Clopidogrel cessation is the most significant independent predictor for stent thrombosis, with an OR of 13.74 to 57.13 [6]. Compared to patients who have taken the drug without interruption, patients who stopped clopidogrel during the first month after PCI and DES are 10 times more likely to have a fatal outcome (7.5% versus 0.7%) during the next 11 months. The 2-year rate of MI and death is increased 2.3-fold in patients with DES who stopped clopidogrel at 6 months compared to those on clopidogrel for 2 years [5].

Antiplatelet discontinuation in the surgical setting
The situation is even more risky in the perioperative period which is characterized by increased platelet aggregability and a decreased fibrinolysis. The early interruption of dual antiplatelet therapy to allow major non cardiac surgery during the first month after PCI with BMS leads to a cardiac mortality up to 86%, whereas it is 5% when the treatment is maintained perioperatively [14]. In an observational study (192 patients), the incidence of DES thrombosis after early non cardiac surgery (13% urologic operations) was 31% among patients who stopped clopidogrel before the required delay, but 0% among those who continued dual antiplatelet therapy [20]; all patients with stent thrombosis died. Pooling the data of different observational studies in non cardiac surgery among patients with coronary stents demonstrates that mortality is directly related to the delay between coronary revascularisation and noncardiac surgery in patients taken off their antiplatelet therapy before surgery (Figure 2): the shorter the delay, the higher the mortality. Maintaining the antiplatelet drugs lowers dramatically the mortality: 5% instead of 85% and 0% instead of 31% [14,20].
EVIDENCE FOR SURGICAL HAEMORRHAGE UNDER ANTIPLATELET THERAPY

Hemorrhagic risks in urologic surgery
The three best investigated interventions regarding antiplatelet therapy are transrectal biopsy of the prostate (P-Bx), transurethral resection of the prostate (TUR-P) and ureteroscopy (UE). A study following 1810 Patients after P-Bx found no statistical increase in bleeding complications when aspirin was maintained (3.7% vs 2.5%) [21]. Two prospective, randomized trials found no significant difference in the incidence of hematuria, hematospermia or rectal bleeding in patients maintained on aspirin during P-Bx, although the duration of bleeding was significantly prolonged [22,23]. A study including 387 patients found an increase in minor bleeding complications with a higher incidence and duration of hematuria and rectorrhagia, but no difference in severe bleeding [24].

Flexible UE with stone disintegration (Holmium:YAG Laser) appears to be safe under clopidogrel or aspirin [25]. None of the procedures had to be terminated due to poor visibility from bleeding. There was no difference in stone-free rate, intraoperative and postoperative complications or hemorrhagic adverse events. Although the haemoglobin decrease was greater when antiplatelet agents were maintained (0.6 g/dl vs. 0.2 g/dl, p>0.0001), the difference was clinically not relevant.

For conventional TUR-P the relationship between increased postoperative haemorrhage and use of aspirin was first documented in 1993 [26] and underlined by a retrospective analysis showing that more blood units were administered in patients taking aspirin [27]. These early studies therefore recommended the withdrawal of non-steroidal anti-inflammatory drugs one week before TUR-P. This recommendation was challenged by studies showing no significant increase in blood loss if patients were taking aspirin [28,29]. However, a higher incidence of late bleeding with tamponade of the urinary bladder requiring emptying in the operating room was found [29]. A randomized controlled study found that patients taking 150 mg aspirin showed no difference in intraoperative hemorrhage, operation time and amount of tissue resected, but an increase in postoperative blood loss of 51% (284 ml versus 144 ml) [30]. There was no difference in time to catheter removal and hospital stay. The number of patients requiring blood transfusion was higher in the aspirin group, although only three patients (11%) received three or more units of blood. The early re-initiation of aspirin if stopped 5 days prior to TUR-P was investigated in a cohort of 120 patients [31]. Starting aspirin 24h after discontinuation of the bladder irrigation or 3 weeks after surgery did not influence the time to catheter removal or persistent hematuria.
Holmium laser enucleation and vaporization of the prostate (KTP Laser) offer new methods to reduce bleeding during TUR-P in patients under antiplatelet therapy [31,32]. The published reports show no significant increase in postoperative complications if aspirin and/or clopidogrel are continued throughout surgery. Furthermore, the long-term functional results are comparable. In summary, there are evidences that P-Bx, flexible nephroscopy and TUR-P can be performed under antiplatelet agents.

The fact that many urologic procedures have not been investigated prevents from making meaningful recommendations for larger urologic surgeries including nephrectomy, cystectomy or prostatectomy. In radical prostatectomy, the technique of robotic assistance, combining the increased abdominal pressure with a more intuitive handling of surgical instruments, shows a trend towards lower blood loss during surgery [33]. The average blood loss in patients without antiplatelet therapy using robotic assistance is 100-200 ml [34] compared to 800 ml for conventional radical prostatectomy [35]. Whether this holds true for patients under antiplatelet therapy remains to be studied.

When taking other noncardiac surgeries into account to try to define a strategy for urologic patients, we realized that large randomized trials comparing the effects of antiplatelet agents with placebo in surgical settings are also lacking. Most data are provided by retrospective or observational studies, usually of low level of evidence and underpowered to answer the question of the increase in operative morbidity and mortality due to aspirin or dual antiplatelet therapy. A meta-analysis of non-urologic surgeries including 474 studies comparing surgical bleeding of patients operated with or without aspirin reports an average intraoperative hemorrhagic risk increased 1.5-fold under aspirin, but no change in the mortality and complication rates [36]. Transfusion rate is increased by 20% in some orthopedic operations. Surgical data comparing aspirin and clopidogrel alone are lacking, but in nonsurgical trials the rate of spontaneous hemorrhage is similar with both drugs [4]. Dual antiplatelet therapy, however, is associated with an average 50% increase in surgical hemorrhage, but the clinical evidence is limited to some observational series in vascular [37], visceral [38] and transbronchial [39] surgery. There is an increase in oozing and diffuse bleeding, but no increase in major blood loss [16,20] in major non urologic surgeries. There is no clear increase in morbidity and mortality outside intracranial neurosurgery. Three studies have compared the rate of perioperative transfusion during non urologic surgeries for patients with and without dual antiplatelet therapy. It was not found to be statistically different, although there is a slight trend towards an increased rate under dual antiplatelet therapy: 43% versus 38% [15], 24% versus 20% [20], and 15.4% versus 15.0% [17].
EVIDENCE SYNTHESIS

The available reports indicate that the increase in blood loss related to the perioperative upholding of aspirin and clopidogrel does not appear as a cause of potential increase in surgical complications or mortality, except in two conditions: 1) when bleeding occurs in a closed space like the skull, the spinal canal or the posterior chamber of the eye, and 2) when surgery is accompanied by massive hemorrhage and difficult hemostasis [40]. Many of the urologic operations have to be placed into the difficult hemostasis group, including partial nephrectomy, prostate surgery and cystectomy. From the survey of the current literature, we estimate that the average increase in bleeding during noncardiac surgery is about 20% with aspirin and up to 50% with dual antiplatelet therapy; the transfusion rate is inconsistently affected [15,17,20]. The global disadvantage of being transfused (short-term complications 0.4% [41], long-term survival reduced by 16% [42]) is far less than the 35% average mortality when the drugs are withdrawn before surgery. Nevertheless, blood transfusions should be avoided as far as possible by treating preoperative anemia and resorting to a highly trained surgical team familiar with modern blood sparing techniques and strategies.

The risk of MI and the mortality of patients operated on adequate antiplatelet therapy should be the same as in stable coronary artery disease: MI rate of 2-6% and mortality 1-5% depending on the surgical procedure [40]. However, the risk of withdrawing antiplatelet therapy is associated with a MI rate of 20-40% and a mortality of 19-85%, depending on the delay between revascularisation and surgery. Therefore, the risk of coronary thrombosis appears higher than the risk of surgical hemorrhage. Pending high level of evidence data on the risk / benefit balance of stopping versus continuing antiplatelet therapy, preoperative cessation of aspirin and/or clopidogrel should be avoided as far as possible.

CURRENT RECOMMENDATIONS AND PROPOSALS

It is challenging to define clear-cut recommendations for urologic patients because this population hat not been sufficiently studied. However, the most recently published guidelines [10,11,12] have all concluded that premature discontinuation of antiplatelet therapy before surgery is exceedingly dangerous due to the dramatic increase in MI and death.
Aspirin has recently been recommended to be a lifelong therapy which should be continued perioperatively when prescribed in secondary prevention after ACS, MI, stroke, vascular surgery or PCI with any type of stent, whatever is the delay since the procedure [11,40]. In primary prevention, there are no studies showing that interruption of aspirin carries an increased perioperative risk except in diabetic patients.

Dual antiplatelet therapy is recommended during 2 weeks after simple angioplasty, 4-6 weeks after BMS and at least 12 months after DES (Table 1) [10,40]. All elective surgical procedures should be postponed beyond these delays. Only vital surgery should be performed when the patients are still on aspirin and clopidogrel [11]. Unless the hemorrhagic risk is excessive, dual therapy should not be interrupted for surgery during the first 6 weeks after BMS and at least 12 months after DES. In secondary prevention of stroke, clopidogrel or dual therapy have not been proven more efficacious than aspirin alone or aspirin and dipyridamole; therefore, it seems safe to stop clopidogrel, but not aspirin, 5 days before surgery [9,18].

If clopidogrel must be interrupted 5 days preoperatively for surgical reasons in high-cardiac risk situations, aspirin should be continued without interruption [43]. Clopidogrel could be substituted with a short-acting equivalent drug. Although not proven by any controlled trial, a bridge with an anti-GP IIb/IIIa agent like eptifibatide or tirofiban (half-life 2 hours) has been described as a possible substitution for clopidogrel [44,45]. The substance is administered in continuous infusion for 3-5 days before the operation and stopped 6 hours preoperatively. There is no scientific evidence to support the use of heparin in preventing intraoperative stent thrombosis [10,11]. Preoperative low molecular weight heparin has been demonstrated to be without effect, because an antithrombin has no antiplatelet activity [7]. Although somewhat arbitrary, few authors have designed working algorithms based on expert opinions. The algorithm proposed here (Figure 3) is adapted with minor modifications from previous publications [40,46].

Since there is no antidote to antiplatelet agents, the termination of the inhibitory effect of aspirin and clopidogrel relies on the renewal of platelets (10%/day). It is usually estimated that the plasma level of a substance is negligible after 3 half-lives. Therefore, 24 hours after the last intake of clopidogrel (half-life of active metabolite: 8 hours) and 6 hours after the perfusion of eptifibatide or tirofiban (half-life: 2 hours) there is no residual antiplatelet activity in the plasma. During surgery, the platelets transfused after these delays will thus function normally. In this situation, the risk is to trigger thrombus formation inside the stents because of platelet overtransfusion. In order to prevent this potentially catastrophic event, it is necessary to accept some degree of platelet dysfunction.
After the operation, clopidogrel therapy needs to be restarted within the first 24 hours because of concerns about stent thrombosis during the postoperative phase of hypercoagulability [11]. It might be safer to re-initiate clopidogrel with a 300 mg loading dose which reduces the time to achieve maximal platelet inhibition to 4 hours and decreases the risk of hyporesponsiveness linked to the competition of other drugs with the hepatic cytochromes oxidizing clopidogrel into its active metabolite. Postoperative stent thrombosis, usually manifested as an acute MI and cardiogenic shock, is best treated with immediate PCI and dilatation; however, the survival rate with this strategy is only 65% [47]. The use of stent is questionable because the patients are at the peak of the acute inflammatory reaction and platelet hyperactivity.

**STRATEGIES TO PREVENT STENT THROMBOSIS**

In most cases, urologic surgery can be postponed by weeks or even months after the high risk period. This strategy alone will move most patients to the low risk group requiring a continued single agent antiplatelet therapy (either aspirin or clopidogel). Furthermore, the operation can possibly be deferred by offering active surveillance strategies instead of surgery or by closely following small renal masses by CT instead of an acute intervention. These might be valuable options in patients with recent cardiovascular events. Nevertheless, many patients will still require continued antiplatelet therapy during their surgery. Since clear guidelines have not been established yet, the surgeon must base his decision on some sparse reports [2,45].

A second possible strategy to prevent postoperative stent thrombosis is to avoid preoperative revascularisation whenever possible, because it does not benefit patients with stable [48] or even severe [49] coronary artery disease compared to an adequate medical therapy with tight heart rate control. In case of urgent or semi-urgent surgery, the risk of operating under maximal medical protection (β-blocker, aspirin, clopidogrel, statin) is less than operating in the early phase after coronary revascularization.

Some patients, however, may require coronary revascularisation because they suffer from an unstable coronary syndrome or a severe ischemia on stress testing, and present a surgical pathology necessitating a mandatory operation. The strategy consists of adapting the type of revascularization to the possible delays for noncardiac surgery (Figure 4). If the operation can be delayed for 6-8 weeks, the best option is a PCI with BMS or a surgical revascularization (CABG). If an operation is required within 2-4 weeks, the only possibility is to perform a balloon
angioplasty without stenting or refrain from any revascularization [11,40]. In case of emergency, surgery must be performed under pharmacologic cardioprotection, except in the rare cases where vascular surgery can be combined with simultaneous CABG. DES implantation is out of question because the optimal delay after DES is more than 1 year.

The third strategy is to maintain dual antiplatelet therapy in the preoperative period and to resume the treatment as soon as possible after surgery. This applies to high cardiac risk situations (< 6 weeks after ACS, MI, BMS or stroke, < 12 months after DES). In intermediate cardiac risk situations (6-24 weeks after ACS, MI or BMS, > 12 months after high-risk DES), it is advisable to maintain dual therapy if the risk of surgical bleeding is low, but it is possible to stop clopidogrel and maintain only aspirin in operations with very high hemorrhagic risk [43].

FUTURE TRENDS

Among new agents, prasugrel is a thienopyridine which acts like clopidogrel but is more potent and presents a much lower rate of nonresponders. It is 2-fold more efficacious than clopidogrel for preventing thrombosis after PCI and stenting, but it increases the non-surgical bleeding rate by 32% compared to clopidogrel (2.4% versus 1.8%) [50], which might raise problems in the surgical setting. All the data mentioned about DES concern the first-generation stents coated with sirolimus or paclitaxel. New devices have been introduced recently in cardiology: everolimus- or zotarolimus-eluting stents, and bioabsorbable stents. To date however, data on long-term outcome of these stents are insufficient to justify a modification of the recommendations published for first-generation DES.

CONCLUSIONS

Recent data on perioperative use of antiplatelet agents are a warning signal against their withdrawal before surgery when prescribed in secondary prevention after ACS, MI, coronary stents or stroke. In general the risk of coronary thrombosis largely outweighs the risk of surgical hemorrhage. However, this issue has not yet been clearly evaluated in urologic patients and in many instances during urologic surgery the risk of bleeding might be exceedingly dangerous. In
this problematic situation, a thorough dialogue between surgeon, cardiologist and anesthesiologist is essential to determine all risk factors and to define the best possible strategy for each individual patient. Although ethical difficulties prevent to perform placebo-controlled randomized trials, we need further prospective clinical studies to define the urologic surgeries which can safely be performed under continued antiplatelet therapy.

KEYWORDS

Antiplatelet agents, coronary revascularization, coronary stents, surgical bleeding
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Table 1
Recommendation on the duration of dual antiplatelet therapy after a coronary event

Figure 1
Incidence of major adverse cardiac events (MACE) according to the delay (months) between stent implantation and noncardiac surgery: MACE (major adverse cardiac event): myocardial infarction, in-stent thrombosis, target vessel revascularisation and death. Data from references 16 and 17. BMS: bare-metal stents. DES: drug-eluting stents.

Figure 2
Mortality of patients with coronary stents taken off antiplatelet drugs for noncardiac surgery, according to the delay since coronary revascularization: The curve is constructed with the pooled data from 6 observational studies (references below), and represents the postoperative mortality of patients taken off their antiplatelet (AP) therapy for noncardiac surgery, according to the delay since the coronary revascularization with bare-metal stents and/or drug-eluting stents. Two studies [14,20] have comparative data of mortality for patients who were operated without cessation of AP drugs (5% and 0%, respectively).
Figure 3
Algorithm for the preoperative management of patients under antiplatelet therapy: (adapted and updated from ref 40). 1) Secondary prevention: aspirin given after a previous event (myocardial infarction, acute coronary syndrome, PCI & stent, CABG, PAD and stroke) or in documented cardiovascular disease. High-risk patients: diabetics and patients with multiple risk factors. 2) High-risk stents: multiple stents, long stent, proximal location (left main) and bifurcation lesions, patients with previous stent thrombosis. 3) Vital surgery: operations which are mandatory for the long-term survival of the patient. The recommended delay between drug interruption and surgery is 5 days for aspirin and for clopidogrel. 4) Excessive risk of bleeding: invasive surgery associated with severe bleeding and difficult hemostasis, including extensive urologic operations, or bleeding in closed spaces. In these situations, the risk/benefit ratio of upholding vs. withdrawing aspirin & clopidogrel must be evaluated for each case individually; in case of withdrawing, postoperative re-institution (with a clopidogrel loading dose of 300 mg) within 24 hours is important. These remarks apply also to prasugrel. 5) Substitution for clopidogrel (stop 5 days) is 3-5 days iv perfusion of eptifibatide or tirofiban. ACS: acute coronary syndrome. MI: myocardial infarction. PCI: percutaneous coronary intervention. PAD: peripheral arterial disease. CABG: coronary artery bypass graft surgery.

Figure 4
Algorithm of the strategies to decrease the risk of stent thrombosis in case of coronary revascularization and urgent or semi-urgent noncardiac surgery

* Except in closed-space surgery (intracranial neurosurgery, surgery of the medullary canal, surgery of the posterior chamber of the eye) and invasive surgery with severe bleeding and difficult hemostasis. PCI: percutaneous coronary intervention. BMS: bare-metal stents. CABG: coronary artery bypass graft surgery.