

**ANTIPLATELET AGENTS IN THE PERIOPERATIVE PERIOD : EXPERT  
RECOMMENDATIONS OF THE FRENCH SOCIETY OF ANESTHESIOLOGY  
AND INTENSIVE CARE (SFAR) 2001 – SUMMARY**

Charles Marc SAMAMA<sup>1</sup>, MD, PhD, Olivier BASTIEN<sup>2</sup>, MD, François FORESTIER<sup>3</sup>, MD, Marie-Hélène DENNINGER<sup>4</sup>, Pharm D, Christian ISETTA<sup>5</sup>, MD, Jean-Michel JULIARD<sup>6</sup>, MD, Dominique LASNE<sup>7</sup>, MD, Didier LEYS<sup>8</sup>, MD, Patrick MISMETTI<sup>9</sup>, MD and the expert group.

From : 1 - Département d'Anesthésie Réanimation, Centre Hospitalier Universitaire (CHU) Avicenne, Bobigny ; 2 - Département d'Anesthésie Réanimation - Hôpital Louis Pradel, Lyon ; 3 - Département d'Anesthésie-Réanimation, Hôpital Cardiologique Groupe Hospitalier Sud, Pessac; 4 - Service d'hématologie-immunologie Hôpital Beaujon, Clichy; 5 – Département d'Anesthésie-réanimation, Service de Chirurgie Cardiaque, Hôpital Pasteur , Nice; 6 - Service de Cardiologie, CHU Bichat, Paris; 7 – Hémostase, CHU Necker, Paris ; 8 - Service de Neurologie, CHR Roger Salengro, Lille; 9 – Pharmacologie, Hôpital Bellevue, Saint Etienne, France.

Corresponding author : Pr Charles Marc Samama: Département d'Anesthésie-Réanimation, Hôpital Avicenne-125, route de Stalingrad, 93009 Bobigny cedex, France.  
Tel : 33 1 48 95 55 91 - fax : 33 1 48 95 55 89  
e-mail: cmsamama@invivo.edu

### **Organizing Committee**

*Co-ordinator:* Charles Marc Samama (Anesthesiology, Bobigny)  
G rard Janvier (Anesthesiology, Bordeaux), Thomas Lecompte (Hemostasis, Nancy),  
Jean Franois Schved (Hemostasis, Montpellier), Brigitte Jude (Hemostasis, Lille),  
Nathalie Nathan (Anesthesiology, Limoge), Beno t Vallet (Anesthesiology, Lille), Henri  
Bricard (Anesthesiology, Caen)

### **Expert Group**

Pierre Albaladejo (Anesthesiology, Beaujon, Paris), Pierre Amarenco (Neurology,  
Lariboisi re, Paris), Olivier Bastien (Anesthesiology, Lyon), Jean-Pierre Carteaux  
(Cardiac Surgery, Nancy), Franois Charpentier (EFS\*, Paris), Isabelle Daudenthun  
(Anesthesiology, Beaujon, Clichy), Marie-H l ne Denninger (Hemostasis, Beaujon,  
Clichy), Laurent Dub  Anesthesiology, Angers), Herv  Fernandez (Obstetrics, Antoine  
B cl re, Clamart), Patrick French (Hemostasis, Lyon), Franois Forestier  
(Anesthesiology, Bordeaux), Elisabeth Gaertner (Anesthesiology, Strasbourg), Christian  
Isetta (Anesthesiology, Nice), Jean-Michel Julliard (Cardiology, Bichat, Paris), Philippe  
Lacroix (Vascular Surgery, Limoges), Dominique Lasne (Hemostasis, Necker, Paris),  
Didier Leys (Neurology, Lille), Emmanuel Marret (Anesthesiology, Tenon, Paris), Jean  
Marzelle (Vascular Surgery, Antony), Marc-Antoine May (Anesthesiology, Tours),  
Patrick Mismetti (Clinical Pharmacology, St Etienne), Philippe Nguyen (Hemostasis,  
Reims), Nadia Rosencher (Anesthesiology, Cochin, Paris), Marc Samama  
(Anesthesiology, Bobigny), Kamran Samii (Anesthesiology, Toulouse), Gabriel Steg  
(Cardiology, Bichat, Paris), Sophie Susen (Hemostasis, Lille), Claude Vielpeau  
(Orthopedic surgery, Caen), Paul Zetlaoui (Anesthesiology, Le Kremlin-Bic tre),

### **Reading Group**

Marie-Christine Alessi (Hemostasis, Marseille), Jeanne Barr  (Anesthesiology, Reims),  
Thierry B gu  (Orthopedic surgery, Bobigny), Sadek Beloucif (Anesthesiology, Amiens),  
Liliane Bodin (Surgical Intensive Care and Anesthesiology, Piti , Paris), Herv  Bouaziz  
(Anesthesiology, Nancy), Yves Cadroy (Hemostasis, Toulouse), Gilles Chain   
(Ophthalmology, Bobigny), Annie Derlon (Hemostasis, Caen), Jean-Dominique Doublet  
(Urology, Tenon, Paris), Emile Ferrari (Cardiology, Nice) Gilles Dupuy (ORL, Issy-les-  
Moulineaux), Martine Gayraud (Internal Medicine, Institut Mutualiste Montsouris,  
Paris), Olivier Genty (General Practitioner, Ch tillon), Christophe Lelaidier (Gynecology-  
Obstetrics, Montpellier), Dan Longrois (Anesthesiology, Nancy), Fabrice Michaut-  
Paterno (Anesthesiology, Le Kremlin-Bic tre), St phane Racine (Anesthesiology,  
Bobigny), Lionel Simon (Anesthesiology, Saint Vincent de Paul, Paris), Olivier Souchot  
(Anesthesiology, Bobigny), Annick Steib (Anesthesiology, Strasbourg), Patrick Tubiana  
(Gynecology-Obstetrics, Antony), Olivier Tuil (Anesthesiology, Bobigny), Michel  
Vinchon (Neurosurgery, Lille) and the organizing committee.

\* *Établissement français du sang* = French Blood Transfusion Agency

Two groups contributed to the organization of this expert meeting, namely the *Société française d'anesthésie et de réanimation* (SFAR), the French Society of Anesthesiology and Intensive Care, and the Study Group on Hemostasis and Thrombosis of the *Société française d'hématologie* (French Society of Hematology). Responses to questions formulated by the Organizing Committee were drafted by a group of experts and reviewed by a multidisciplinary reading committee in accordance with the SFAR expert committee recommendations on methodology. Recommendations were classified (grade) according to the evidence level of the studies supporting them (1)(table 1). All surgical fields could not be covered given the dearth of medical literature.

This summary text was presented at a public session of the SFAR National Congress held on September 22, 2001. Based on the response of the sizable audience (more than 300 people), improvements were made to the text.

### **Antiplatelet Agents (NSAIDs included) – Definitions**

- Antiplatelet agents (platelet inhibitors) are drugs capable of inhibiting platelet function, in particular platelet activation and aggregation (2).
- Currently available antiplatelet agents include aspirin, dipyridamole, the thienopyridines (ticlopidine and clopidogrel) and the glycoprotein IIb/IIIa (  $\text{IIb}\beta\text{3}$ ) receptor antagonists (3).
- Aspirin blocks the production of platelet-derived thromboxane  $\text{A}_2$ , a potent inducer of platelet aggregation, by irreversibly inhibiting platelet cyclo-oxygenase. Other non-steroidal anti-inflammatory agents (NSAIDs), including flurbiprofen, are reversible inhibitors of cyclo-oxygenase. There is a relationship between duration of effect and half-life, which in the case of NSAIDs varies from one drug to the next. For example, the half-life of flurbiprofen is 4 to 5 hours.
- Ticlopidine and clopidogrel, via their active metabolites, inhibit ADP-induced platelet aggregation by irreversibly changing one of the platelet receptors of ADP.
- Platelet activation on the surface of the  $\alpha\text{IIb}\beta\text{3}$  (glycoprotein IIb/IIIa) receptor site results in platelet aggregation (4). Glycoprotein (GP) receptor antagonists are monoclonal antibodies that target the platelet GP IIb/IIIa complex. Other classes of GP IIb/IIIa receptor antagonists are peptide or non-peptide (e.g. eptifibatide, tirofiban) analogues of this complex that compete with fibrinogen and von Willebrand factor (vWF) for this receptor binding site.

## Question 1a

### What are the recognized indications for antiplatelet agents in cardiology?

1 - Aspirin, when administered at a minimum dose of 160 mg for the initial management of **acute myocardial infarction**, reduces mortality by approximately 20% and must be followed by a daily dose of 75 to 325 mg (**grade A**).

2 - There is also scientific evidence to support the indication for aspirin in other clinical forms of **acute coronary syndrome** (unstable angina and/or infarction without Q wave) and in stable angina (**grade A**). The minimum recommended initial dose is 160 mg, followed by a maintenance dose of 75 to 325 mg daily.

3 - In **percutaneous transluminal coronary angioplasty (PTCA)** with stent implantation, aspirin (100 to 250 mg/day) in association with clopidogrel (75 mg/day) is prescribed for one month to prevent the risk of a stent blockage (**grade A**). This drug combination replaces the previous one of aspirin and ticlopidine (5). In coronary artery bypass (CAB), it is preferable not to discontinue treatment prior to the procedure and to continue with it during the first few hours postoperatively (**grade C**).

4 - As a **secondary preventive** measure (after myocardial infarction, cerebrovascular accident [CVA] or arteritis), clopidogrel 75 mg/day is administered to ensure slightly better vascular protection than aspirin 325 mg/day (**grade B**). After an infarction, flurbiprofen 100 mg/day as opposed to placebo comparatively reduces the risk of a recurrence (**grade B**).

5 - In patients over 50 years of age with at least one vascular risk factor (e.g., hypertension), the use of small doses of aspirin, namely 75 to 100 mg, is beneficial and is a **primary prophylactic** strategy against the risk of death and myocardial infarction (**grade B**).

6 - Aspirin 325 mg can replace anticoagulants in young patients under 65 years of age who have **atrial fibrillation** without any associated risk factor and in the absence of emboligenic cardiopathies (**grade A**). Aspirin is also indicated when anticoagulant therapy is contraindicated or cannot be monitored (**grade B**).

7 - In patients with **valvular prostheses** also receiving vitamin K antagonists, aspirin use is reserved for those who have already had an embolic accident while on appropriate anticoagulant therapy, or for cases of associated coronary disease (**grade C**). Small doses, i.e., 75 to 100 mg are recommended and there is no evidence to warrant routine prescription use.

8 - The accepted indications for intravenously administered GP IIb/IIIa receptor antagonists (12 to 48 hours) are currently as follows (4,6):

- eptifibatide and tirofiban: death and myocardial risk prevention in acute coronary syndromes without persistent ST-segment elevation (**grade B**);
- abciximab: prevention of coronary angioplasty complications (**grade A**).

### Question 1b

**What are the recognized indications for antiplatelet therapy in neurology?**

1- For patients in the acute phase of a cerebral infarction ion who cannot be treated by thrombolysis, aspirin 160 to 325 mg/day is recommended in the absence of any major contraindication and independently of the presumed cause (**grade A**) (7).

2 - In the primary prevention of CVA, patients at low risk should not receive antiplatelet therapy (**grade C**).

3 - In atrial fibrillation, aspirin 325 mg can replace anticoagulant therapy in young patients under 65 without an associated risk factor (**grade A**). Aspirin is also indicated when anticoagulant therapy is contraindicated or cannot be monitored (**grade B**).

4 - For secondary CVA prevention, a patient without emboligenic cardiomyopathy must receive first-intention treatment with aspirin at a daily dose of 75 to 325 mg (**grade A**) or, possibly, an association of aspirin and extended-release (ER) dipyridamole (50 mg and 400 mg, respectively) or with a thienopyridine derivative (**grade A**) (8). The aspirin/ER dipyridamole combination is more effective than each of the components taken separately (**grade A**). As far as the thienopyridine derivatives are concerned, clopidogrel should be the preferred choice over ticlopidine because it has fewer side effects (**grade A**). Clopidogrel is slightly more effective than aspirin in the secondary prevention of ischemic accidents of a non-cardioembolic origin (**grade A**). Because of its cost, clopidogrel is at present reserved for patients who do not tolerate aspirin, those at high risk of a recurrence and who have a recurrence on aspirin.

5 - Given the slightly inferior efficacy of dipyridamole alone compared with aspirin and its superiority versus placebo, it should be reserved for the secondary prevention of patients without emboligenic cardiopathy who cannot tolerate either aspirin or clopidogrel (**grade B**).

6 - There is no evidence that long-term combination use of aspirin and clopidogrel and of GP IIb/IIIa receptors antagonists is beneficial. These drugs should not be used for the prevention of cerebral ischemia outside the context of controlled trials (**grade E**) or, in the

case of clopidogrel combined with dipyridamole, for the month following angioplasty with carotid artery stent placement (**grade E**).

7 - Antiplatelet agents do not increase the risk of a cervical hematoma or intracranial bleeding after carotid artery surgery (**grade B**). Carotid artery surgery performed without a platelet inhibitor is associated with a higher postoperative myocardial infarction mortality rate (**grade B**), and it is recommended that patients undergoing such surgery be treated by aspirin (**grade B**).

## Question 2

### What place does aspirin have in the prophylaxis of thromboembolic venous disease?

1 - **Aspirin should not be recommended for the prevention of early postoperative thromboembolic venous disease (first two weeks) regardless of the type of surgery.** This position is in keeping with the recommendations of the sixth North American consensus conference on antithrombotic therapy (**grade A**) (9).

2 - However, the prophylactic effect of aspirin on thromboembolic venous disease is likely, with a significant decrease in the risk of deep venous thrombosis (DVT), established by the administration of labelled fibrinogen and/or phlebography, and risk of symptomatic pulmonary embolism (PE) postoperatively (**evidence level I**) (10).

3 - Nevertheless, almost 25% of patients included in various trials, notably 50% of patients in the Pulmonary Embolism Prevention (PEP) (11). Study, also received prophylactic doses of heparin as an adjunct to aspirin therapy. Under such conditions, the effect of aspirin use alone remains uncertain.

4 - Based on historic and direct comparisons, the prophylactic effect of aspirin appears to be inferior to that seen with other antithrombotic treatments such as low-molecular weight heparins (LMWH) (**evidence level II**).

5 - Aspirin use does not result in decreased postoperative mortality, notably cardiovascular deaths. At the same time, heparin products appear to decrease postoperative mortality (**evidence level II**).

6 - **Aspirin cannot be recommended when heparin is contraindicated**, in cases of heparin-induced thrombocytopenia or when there is a bleeding risk since other therapeutic substitutes (e.g., danaparoid) have clearly demonstrated their efficacy (**grade A**).

7 - In terms of effective DVT prophylaxis, there is no benefit in combining aspirin with other preventive strategies such as the administration of heparin or intermittent pneumatic compression (**grade B**).

**8 - Aspirin as an adjunct to prophylactic doses of heparin increases the risk of a peroperative and postoperative hemorrhagic accident (evidence level I).**

**9 - Aspirin should not be recommended on an extended basis as first-line prophylactic therapy after orthopedic surgery (grade A).** Based on the results of the PEP Study, however, it could be an alternative to heparin preparations and oral anticoagulants for this indication, notably when these agents are contraindicated or their use is not advisable (renal insufficiency, etc.) (**grade B**).

### Question 3

**Must treatment with antiplatelets agents be biologically assessed (efficacy, bleeding risk)?**

1 - At present, recommendations for the biological monitoring of treatment with antiplatelet agents are limited to:

- platelet counts performed 2 to 4 then 24 hours after initiation of treatment with intravenous glycoprotein IIb/IIIa antagonists;
- polynuclear neutrophil counts every 15 days during the first 3 months of treatment with ticlopidine.

2 - All patients receiving platelet inhibitors must be considered to have drug-induced altered platelet function.

3 - At present, there is no suitable bioassay test sophisticated enough to be used routinely for the monitoring of side effects associated with platelet inhibitors:

- bleeding time (**BT**) should not be used to estimate the hemorrhagic risk of a patient on platelet inhibitors because sensitivity to platelet inhibitors is inconsistent (12);
- the Platelet Function Analyzer (**PFA**) should not be used to estimate the hemorrhagic risk of a patient on platelet inhibitors. Although the PFA seems to be more sensitive than BT for aspirin and glycoprotein IIb/IIIa antagonists, no study for the time being has demonstrated that its results are predictive of hemorrhagic risk associated with platelet inhibitor use (13).

- Platelet aggregation and flow cytometry are cumbersome techniques not suited to routine use. Furthermore, the predictive value of their results with regard to clinical efficacy and hemorrhagic risk of antiplatelet agents has not been clearly demonstrated.

4 - Given the varying degree of sensitivity to certain platelet inhibitors, it could be interesting to have a bioassay test adapted to routine use for monitoring, in real time, the efficacy of antiplatelet agents and predicting their hemorrhagic risk (14).

#### Question 4

**Do antiplatelet agents increase the perioperative surgical risk of bleeding? If yes, what are the consequences?**

The perioperative risk of bleeding with antiplatelet agents varies and depends on the surgical procedure (15). Key study aspects deal with procedures for which the functional or vital consequences are well-known (ENT, ophthalmology) and with those that are often controlled pharmacologically (cardiac and orthopedic surgery), either by antithrombotic (aspirin) or analgesic (NSAIDs) agents (16). Results are presented according to evidence level and not by recommendations given the heterogeneity of the reported studies. Finally, many interventions are not even broached because of the lack of clear data on the risk of hemorrhage with antiplatelet therapy.

##### 1.1 Evidence Level I

- In *hip surgery*, low preoperative aspirin doses (160 mg in association with a LMWH) increase the risk of hemorrhage and exposure to transfusion. The postoperative combination of a NSAID and a LMWH does not, however, increase either the risk of hemorrhage or exposure to transfusion in *hip surgery*. Aspirin alone administered postoperatively does not increase the risk of hemorrhage or exposure to transfusion in *hip and knee surgery*.
- Pre- or postoperatively prescribed NSAIDs (diclofenac and the discontinued ketorolac) or aspirin for *tonsillectomy* may induce perioperative bleeding and increase the number of revision procedures for hemostasis (**evidence levels I to III**).

##### 1.2 Evidence Level II

- In *ophthalmology*, preoperatively administered aspirin only slightly increases the risk of hemorrhage during surgical procedures involving the avascular structures

(lens, cornea). In *strabismus surgery*, NSAIDs prescribed during the postoperative period do not increase the risk of hemorrhage.

- NSAIDs administered during the postoperative period only slightly increase blood loss without any impact on transfusion requirements after *prostate surgery via an abdominal approach*. Pre- and postoperative ticlopidine increases postoperative bleeding and transfusion requirements for *transurethral resection of prostate (TURP)*. However, the medical literature has contradictory accounts on the risk of bleeding and transfusion exposure in patients receiving aspirin or NSAIDs during the *TURP* preoperative period (**evidence levels II and III**).
- Aspirin use during *pregnancy* does not increase bleeding frequency or severity during delivery. NSAIDs seem to have no effect on perioperative blood loss during *cesarean* deliveries.
- NSAIDs prescribed postoperatively for *hip and knee surgery* do not increase the risk of hemorrhage or transfusion exposure.
- In cardiac surgery, NSAIDs and aspirin administered in the preoperative period moderately increase postoperative bleeding without significantly affecting transfusion requirements (**evidence levels II to IV**).

### 1.3 Evidence Level III

- Aspirin use in the preoperative period does not increase the occurrence of a cerebral hematoma or intracranial bleeding in *carotid vascular surgery*.
- The preoperative use of antiplatelet agents seems to increase the risk of perioperative bleeding in *intracranial surgery* (**evidence levels III to V**).
- In *prostate surgery via the abdominal approach*, preoperative use of aspirin may increase bleeding and transfusion requirements.

The risk of hemorrhage in *general surgery* is considered to be great in patients treated preoperatively with thienopyridines.

- In *digestive tract surgery* on patients under 75 years of age, the prescribed use of NSAIDs for at least 5 days postoperatively does not seem to increase the risk of perioperative bleeding or the incidence of repeat interventions for hemostasis.
- Use of either aspirin or NSAIDs alone in the preoperative period for *hip surgery* may increase bleeding risk and transfusion exposure.

- When used continuously or within a few hours prior to emergency *cardiac surgery*, abciximab seems to increase the risk of hemorrhage and transfusion exposure (17). The risk appears to be lower with glycoprotein IIb/IIIa antagonists that have a short half-life (tirofiban, eptifibatide), but has yet to be evaluated.

#### **1.4 Evidence Level IV**

- *In cardiac surgery*, increased risk of bleeding is a cause for serious concern in patients treated preoperatively with thienopyridines.

## Question 5a

**Is a peripheral block possible in patients treated with antiplatelet agents?**

### **Peripheral Block**

1- Induction of peripheral regional anesthesia in patients receiving antiplatelet agents becomes an issue only if their continued use is not an obstacle to the intervention.

2 - There is nothing in the medical literature on the risk of hemorrhage associated with antiplatelet agents in peripheral regional anesthesia of the limbs (limb nerve block).

Aspirin and NSAIDs likely carry a very small or negligible risk (**grade D**).

Thienopyridines are thought to constitute a more significant risk. The discontinuation of their use warrants an accurate assessment of the risk/benefit ratio on a case-by-case basis when considering regional or peripheral regional anesthesia (**grade D**).

3 - As far as regional anesthesia induction in ophthalmological procedures is concerned, the discontinuation of aspirin or NSAIDs does not appear to be either necessary or warranted prior to surgery (**grade C**) (18). On the contrary, it is preferable to discontinue thienopyridine therapy. For patients in whom thienopyridine therapy cannot be discontinued, topical anesthesia, if possible, is preferable. In other situations, if the risk/benefit ratio of general anesthesia versus regional anesthesia favours the latter, peribulbar anesthesia with a single injection into the inferior external quadrant may be recommended.

4 - Discontinuation of aspirin in carotid artery surgery is not desirable regardless of the anesthetic technique (**grade B**) (19,20). The risk of complications associated with regional anesthesia in patients receiving thienopyridines has not been documented. However, their administration is usually discontinued prior to a cervical plexus block (**grade C**). If thienopyridine therapy is maintained until the day of the intervention, it is advisable to consider another first-line anesthetic technique, in particular surgical local anesthesia. If regional anesthesia is being contemplated, superficial cervical plexus block is preferable to deep cervical plexus block (**expert opinion**) given the comparable efficacy of both techniques.

## Question 5b

**Is central neural blockade (CNB) possible in patients treated with antiplatelet agents?**

1- The risk of an epidural/spinal hematoma in patients treated with aspirin or NSAIDs seems to be very small (21). Indeed, there are only anecdotal reports of such an occurrence despite the fact that antiplatelet agents have been used for several years in a

large number of surgical patients having undergone spinal/epidural anesthesia (**evidence level IV**).

2 - There are no reported cases of spinal hematoma in large series studies on the combined use of spinal/epidural anesthesia with aspirin in either orthopedic surgery or obstetrics (**evidence level II**) (22).

These reassuring data apply to a great number of patients.

3 - No comparative study between spinal/epidural anesthesia and general anesthesia has irrefutably or patently demonstrated the superiority of either one of these anesthetic techniques except in obstetrics. A recent meta-analysis concluded that from a morbidity standpoint regional anesthesia is more advantageous (23). Since any such comparison is controversial, indications must be established on an individual case basis.

4 - Aspirin and NSAIDs should preferably be considered distinctly from other antiplatelet agents (ticlopidine, clopidogrel) whose use is far less widespread and would result in an increased risk of hemorrhage. Spinal/epidural anesthesia with these agents is inadvisable (**expert opinion**).

5 - The use of aspirin and NSAIDs is not a contraindication to spinal/epidural anesthesia on an individual basis (24) if one bears in mind that its benefits are greater than the very low risk of medullary hematoma provided that:

- the patient has not received any anticoagulant therapy prior to the injection;
- single-injection spinal anesthesia is preferable over epidural analgesia or subarachnoid anesthesia (continuous spinal anesthesia) through catheter implants;
- there are no hemostasis-associated anomalies (hence the importance of the history-taking);
- the patient's postoperative neurological status is stringently monitored (**grade E**).

6 - Preference must be given to a compound with a short half-life in the event that a NSAID is prescribed in the postoperative period (**expert opinion**).

## Question 6

**Is it possible to discontinue treatment with antiplatelet agents? If yes, for how long and under what conditions? Must replacement therapy be implemented? What type of treatment(s)?**

1- In patients who present with cerebrovascular or coronary pathology, long-term antiplatelet treatment with aspirin is recommended (**grade A**) (25), and can be discontinued in the perioperative period only when, compared with the benefits, the

specific hemorrhagic risk inherent to the intervention is definitely greater than the cardiovascular risk associated with discontinuation (notably the risk of acute coronary syndrome)(26). The precise risk associated with the discontinuation of antiplatelet agents in known coronary patients during the perioperative period is poorly elucidated, however (27). Some uncontrolled studies suggest that this risk is far from negligible (28). Prospective studies to investigate this risk are, therefore, urgently needed.

2 - In the absence of a validated study for each case scenario, some experts (ophthalmology, neurosurgery, obstetrics, etc.) have proposed a decision-making algorithm that must take into account the surgical and anesthetic technique, hemostatic potential, and specific cardiovascular risk.

3 – No single investigative test for primary hemostasis has a predictive value for hemorrhagic risk.

4 - The risk of acute stent thrombosis is more important during the first month after stenting. Studies on the maximum efficacy period for antiplatelet agents after coronary stent implantation, the natural early risk of subacute stent thrombosis, the delayed risk of restenosis, and the risk of recurrent worsening coronary artery disease have given rise to the following recommendation (**expert opinion**), namely a maximum interval of **1 to 3 months** between stent implantation and minor surgery **requiring a brief discontinuation of antiplatelet agents**.

5 - Cardiovascular risk associated with discontinuation of antiplatelet agents could depend on the duration of discontinuation. When such a discontinuation is deemed essential, one must take into consideration the mode of action (reversible or not) as well as the varying durations of action between the different agents (4 hours to 10 days). For aspirin, ticlopidine and clopidogrel, the current practice is to discontinue use for 10 days. A 50% effective platelet regeneration rate is quite common without any validation of the time period supported by high-evidence level trials. As a reference value, one considers a platelet mean lifespan of 10 days, with a daily platelet regeneration rate of 10% (29).

6 - Cardiovascular risk associated with discontinuation of antiplatelet agents must be conducive to the early resumption of treatment postoperatively, ideally between 4 and 6 hours after coronary revascularization (**evidence level IV**).

7 - Aspirin or thienopyridine replacement therapy is conceivable through the use of reversible antiplatelet or antithrombotic agents that have a short duration of action. To the best of our current knowledge, no replacement therapy (curative doses of unfractionated heparin [UFH] or LMWH, salicylate derivatives [trifusal] or NSAIDs) has been prospectively validated although some agents, flurbiprofen, for example, are licenced as platelet inhibitors in coronary disease (30). Low-molecular weight heparins administered at curative doses as an adjunct to aspirin have demonstrated their efficacy in the curative treatment of acute coronary syndrome without ST segment elevation. They

entail other specific risks, notably hemorrhagic risks, and are not always easily manageable in a perioperative context. Prospective studies are highly desirable, notably for prospective validation or comparative purposes of the most widely used strategies.

8 - Suggested dosages are as follows:

- flurbiprofen: one 50 mg-tablet twice daily, with the last dose given 24 hours prior to the intervention.
- LMWH: In the absence of renal failure, two daily injections at a curative dose.

Platelet counts are to be checked twice weekly.

9 - After a joint discussion with the prescribing physician, the patient must be advised of the conditions and risks of changing antiplatelet therapy.

### **Question 7**

#### **How can per- and postoperative bleeding complications induced by certain antiplatelet agents be avoided?**

1 - Antiplatelet agents that may cause early per- and postoperative bleeding complications are aspirin, thienopyridines, glycoprotein IIb/IIIa antagonists and, to a lesser extent, NSAIDs. Prophylaxis implementation must take into account the duration of antiplatelet agent-induced biological effects.

2 - Steroids to reduce or eliminate any possible increase in perioperative blood loss are not recommended in patients on antiplatelet therapy (**grade E**).

3 - Prophylactic platelet transfusions to reduce or eliminate any possible increase in perioperative blood loss are not recommended in patients on antiplatelet therapy. Platelets must, however, be readily available (**grade C**).

4 - Non-specific methods to decrease perioperative blood loss are recommended (**grade E**). For example, it is recommended that physicians:

- Select a surgical approach designed to achieve the most effective hemostatic control.
- Use, if possible, a controlled hypotension technique.
- Ensure normothermia.

- Restrict hemodilution and maintain hematocrit levels to allow for transfusion savings compatible with optimal oxygen transport and blood viscosity while ensuring normal biological hemostasis (usually at 30%).
- Screen early for abnormal bleeding syndrome requiring additional surgical hemostasis.
- Adhere to the strict indications for postoperative anticoagulant treatment.

5 - In cardiac surgery patients on antiplatelet therapy, prophylactic use of tranexamic acid or aprotinin reduces postoperative bleeding and, in a similar fashion, transfusion exposure (**evidence level I**) (31-33). A very low thrombotic risk has been documented with aprotinin (34). Aprotinin may be responsible for allergic reaction, even anaphylactic shock (0.3% first exposure and 2.5 to 3% after initial contact). Tranexamic acid does not involve this allergic risk and its cost-benefit ratio is more favourable (**grade A**).

6 - The lack of data in other types of surgery makes it impossible to formulate prophylaxis recommendations.

7 - In cardiac surgery, established efficacious pharmacological modalities for reducing postoperative bleeding in patients on antiplatelet agents include aprotinin (**evidence level I**) and desmopressin. Desmopressin is effective only in patients presenting with major bleeding syndrome (**evidence level III**) (35) and it is imperative that its thrombotic risk potential be taken into account.

8 - Platelet transfusions to reduce or stop postoperative blood loss in patients treated with antiplatelets are effective (**grade E**) despite the absence of **level I or II evidence**.

9- Dosage regimens for hemostatic drugs are as follows:

- *Aprotinin* - 2 million kallikrein inhibitory units (KIU) administered intravenously over 20 minutes, followed by a continuous infusion of 500,000 KIU for the entire duration of the procedure. In cardiac surgery, a “prime pump” dose, i.e., 2 million KIU, is added to the priming fluid of the bypass circuit. Half the dosage is also effective (**grade A**) and the risk of an allergic reaction must be considered.
- *Tranexamic acid* - 10 mg/kg intravenously prior to surgical incision, followed by a continuous infusion of 1 mg/kg for 10 hours, alternatively 15 mg/kg, with repeat dosing 4 to 6 hours later (**grade A**).
- *Desmopressin* - 0.3 µg/kg intravenously, possibly repeated 4 hours later (**grade C**). It is possible to reduce the dosage by half (0.15 µg/kg) in elderly patients or

patients presenting with cardiovascular disorders and in patients under 2 years of age. The thrombotic risk must be taken into account.

10 - Platelets are transfused at a dosage of  $0.5$  to  $0.7 \times 10^{11}$ , i.e., the standard concentrate, per 7 kg of body weight in adults.

### **Conclusion**

More and more patients are coming to surgery while on antiplatelet drugs.

Anesthesiologists should be aware of the indications, potential complications and means of substitution of these agents. They also should be convinced that preoperative antiplatelet withdrawal is not always the best solution and could be harmful.

Finally, the ways to control per- and postoperative bleeding complications in close relationship with antiplatelet treatments should be considered.

**References :**

- 1 – *Sackett DL* . Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1989; 95: 2S-4S
  
- 2 – *Patrono C, Collier B, Dalen JE, FitzGerald GA, Fuster V, Gent M, Hirsh J, Roth G* . Platelet-active drugs : the relationships among dose, effectiveness, and side effects. *Chest* 2001;119 :39S-63S.
  
- 3 - *Bennett JS, Mousa S*. Platelet Function Inhibitors in the year 2000. *Thromb Haemost* 2001 ; 85 : 395-400.
  
- 4 - *Topol EJ, Byzova TV, Plow EF*. Platelet GPIIb-IIIa blockers. *Lancet* 1999 ; 353 : 227-31.
  
- 5 - *Bertrand M, Rupprecht HJ, Urban Ph, Gershlik AH, for the CLASSICS Investigators*. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting. The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation* 2000; 102: 624-9.
  
- 6 - *Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, Cohen EA, Bertrand M, Neumann FJ, Stone GW, DiBattiste PM, Demopoulos L*. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001; 34: 1888-94
  
- 7 - *International Stroke Trial Collaborative Group*. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet* 1997; 349:1569-1581.
  
- 8 - *Diener H.C., Cunha L., Forbes C., Sivenius J., Smets P., Lowenthal A*. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996 143:1-13.

- 9 - *Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr, Wheeler HB.* Prevention of venous thromboembolism. *Chest* 2001 ;119 :132S-175S.
- 10 - *Collaborative overview of randomised trials of antiplatelet therapy-III.* Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *Br Med J* 1994 ;308 :235-46.
- 11 - *Pulmonary Embolism Prevention (PEP) trial.* Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin : *Lancet* 2000 ;355 :1295-302.
- 12 - *Rodgers RPC, Levin J.* A critical reappraisal of the bleeding time. *Seminars in thrombosis and hemostasis* 1990 ; 16 : 1-20
- 13 - *Lasne D, Fiemeyer A, Chatellier G, Chammas C, Baron JF, Aiach M.* A study of platelet functions with a new analyzer using high shear stress (PFA100) in patients undergoing coronary artery bypass graft. *Thromb Haemost* 2000 ; 84 : 794-9
- 14 - *Steinhubl SR, Talley D, Braden GA, Tcheng JE, Casterella PJ, Moliterno DJ et al.* Point-of-care measured platelet inhibition correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention. Results of the GOLD (AU-Assessing Ultrega) multicenter study. *Circulation.* 2001 ; 103 : 2572-8
- 15 - *Ferraris VA, Swanson E.* Aspirin usage and perioperative blood loss in patients undergoing unexpected operations. *Surg Gynecol Obstet* 1983; 156: 439-42.
- 16 - *Fauno P, Petersen KD, Husted SE:* Increased blood loss after preoperative NSAID. Retrospective study of 186 hip arthroplasties. *Acta Orthop Scand* 1993; 64: 522-4.
- 17 - *Gammie JS, Zenati M, Kormos RL, Hattler BG, et al.:* Abciximab and excessive bleeding in patients undergoing emergency cardiac operations. *Ann Thorac Surg* 1998; 65: 465-9.
- 18 - *Shuler JD, Paschal JF, Holland GN.* Antiplatelet therapy and cataract surgery. *J Cataract Refract Surg* 1992 ; 18 : 567-71.

19 - *Taylor DW, Barnett HJ, Haynes RB, Ferguson GG, Sackett DL, Thorpe KE, Simard D, Silver FL, Hachinski V, Clagett GP, Barnes R, Spence JD.* Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy. *Lancet* 1999 ; 353 : 2179-84.

20 - *Self DD, Bryson GL, Sullivan PJ.* Risk factors for post-carotid endarterectomy hematoma formation. *Can J Anaesth* 1999 ; 46 : 635-40.

21 - *Urmey WF, Rowlingson J :* Do antiplatelet agents contribute to the development of perioperative spinal hematoma ?  
*Reg Anesth Pain Med* 1998 ; 23 (S2) : 146-51

22 - CLASP : a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women  
*Lancet* 1994 ; 343 : 619-629

23 - *Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S.* Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ.* 2000;321:1493-1504

24 - *Horlocker TT, Wedel DJ, Schroeder DR, Rose SH, Elliott BA, McGregor DG, Wong GY :* Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia.. *Anesth Analg.* 1995;80:303-9

25 - *Jackson MR, Clagett GP.* Antithrombotic therapy in peripheral arterial occlusive disease. *Chest* 2001;119(1 Suppl):283S-99S.

26 - *Collet JP, Himbert D, Steg PG.* Myocardial infarction after aspirin cessation in withdrawal. *International J Cardiol* 2000 ;76 :257-8

27 - *Samama CM, Thiry D, Elamamy I, Diaby M, Guillosson JJ, Kieffer E, Coriat P.* Perioperative activation of hemostasis in vascular surgery patients. *Anesthesiology* 2001;94:74-8

28 - *Kaluza GL, Joseph J, Lee JR, Raizner ME, et al.:* Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol* 2000; 35: 1288-94.

29 - *Lecompte T, Ferrari E, Nguyen P, De Moerloose P, Samama CM.* Médicaments inhibiteurs des fonctions plaquettaires. . S T V. *Sang Thrombose Vaisseaux* 2000 ; 12 (N° spécial) : 3-11.

30 - *Brochier ML.* Evaluation of flurbiprofen for prevention of reinfarction and reocclusion after successful thrombolysis or angioplasty in acute myocardial infarction. *Eur Heart J* 1993 ; 14 : 951-7.

31 - *Murkin JM, Lux J, Shannon NA, Guiraudon GM, Menkis AH, McKenzie FN, Novick RJ .* Aprotinin significantly decreases bleeding and transfusion requirements in patients receiving aspirin and undergoing cardiac operations. *J Thorac Cardiovasc Surgery* 1994 ; 107 : 554-61

32 - *Casati V, Bellotti F, Gerli C, Franco A , Oppizzi M, Cossolini M, Calori G, Benussi S, Alfieri O, Torri G.* Tranexamic acid administration after cardiac surgery, a prospective, randomized, double-blind, placebo-controlled study. *Anesthesiology* 2001 ; 94 : 8-14

33 - *Laupacis A, Ferguson D.* Drugs to minimize perioperative blood loss in cardiac surgery: Meta analyses using perioperative blood transfusion as the outcome. The international study of peri-operative transfusion (ISPOT) investigators. *Anesth Analg* 1997 ; 85 : 1258-67

34 - *Alderman EL, Levy JH, Rich JB, Nili M, Vidne B, Schaff G, Uretzky G, Pettersson G, Thiis JJ, Hantler CB, Chaitman B, Nadel A.* Analyses of coronary graft patency after aprotinine use : results from the International Multicenter Aprotinin Graft Patency

Experience (IMAGE) trial. J Thorac Cardiovasc Surg 1998 ; 116 : 716-30

35 - *Beck KH, Mohr P, Bleckmann U, Schweer H, Kretschmer V*, Desmopressin effect on acetylsalicylic acid impaired platelet function Semin Thromb Hemost 1995 ; 21 Suppl 2 : 32-9.

**Table 1. *The Relation Between Levels of Evidence and Grades of Recommendations.***  
*Adapted from(1)*

<b>Level of Evidence</b>	<b>Grade or Recommendation</b>
Level I : Large randomized trials with clear-cut results (and low risk of error)	Grade A : Two level I studies or more Grade B : only one level I study
Level II : Small randomized trials with uncertain results (and moderate to high risk of error)	Grade C : One or several level II studies
Level III : Nonrandomized contemporaneous controls.	Grade D: One or several level III studies
Level IV : Nonrandomized, historical controls	Grade E : Level IV or V studies
Level V : No controls, case-series only.	