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GUIDELINES

Management of antiplatelet therapy in patients undergoing elective invasive procedures: Proposals from the French Working Group on perioperative hemostasis (GIHP) and the French Study Group on thrombosis and hemostasis (GFHT). In collaboration with the French Society for Anesthesia and Intensive Care (SFAR)

Gestion des agents antiplaquettaires pour une procédure invasive programmée : propositions du groupe d'intérêt en hémostase périopératoire (GIHP) et du groupe français d'études sur l'hémostase et la thrombose (GFHT) en collaboration avec la Société française d'anesthésie-réanimation (SFAR)

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Abbreviations: ADP, adenosine diphosphate; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; ESA, European Society of Anaesthesiology; ESC, European Society of Cardiology; GFHT, French Study Group on Hemostasis and Thrombosis; GIHP, French Working Group on Perioperative Hemostasis; GP, glycoprotein; HAS, French Haute Autorité de la Santé; SFAR, French Society for Anesthesia and Intensive Care.

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<https://doi.org/10.1016/j.acvd.2017.12.004>

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Please cite this article in press as: Godier A, et al. Management of antiplatelet therapy in patients undergoing elective invasive procedures: Proposals from the French Working Group on perioperative hemostasis (GIHP) and the French Study Group on thrombosis and hemostasis (GFHT). In collaboration with the French Society for Anesthesia and Intensive Care (SFAR). Arch Cardiovasc Dis (2018), <https://doi.org/10.1016/j.acvd.2017.12.004>

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Received 19 December 2017; accepted 21 December 2017

KEYWORDS

Antiplatelet therapy;
Surgery;
Haemorrhage;
Thrombosis;
Local anaesthesia

MOTS CLÉS

Agent
antiplaquettaire ;
Chirurgie ;
Hémorragie ;
Thrombose ;
Anesthésie
loco-régionale

Introduction

Antiplatelet drugs are prescribed to prevent arterial thrombosis and especially the recurrence of thrombotic events. The four main oral antiplatelets have two distinct pharmacological targets: aspirin inhibits the enzyme cyclooxygenase 1 and therefore thromboxane A₂ synthesis; whereas clopidogrel, prasugrel and ticagrelor inhibit the adenosine diphosphate (ADP) pathway via the platelet receptor P2Y₁₂.

Many patients receiving long-term antiplatelet therapy will at some time require an elective invasive procedure. This setting requires specific management of antiplatelet therapy. The discontinuation of antiplatelet therapy to perform an invasive procedure increases the risk of thrombotic events, whereas continuation increases the bleeding risk during the procedure. These two risks must be assessed sequentially to determine the optimal management for the planned invasive procedure, and to choose between continuation, discontinuation or modification of antiplatelet therapy, or postponement of the procedure.

The perioperative management of antiplatelet therapy has been the subject of a few national and international guidelines, but they are piecemeal or old, and do not take into account recent work [1–3]. The French Working Group on Perioperative Hemostasis (GIHP) and the French Study Group on Hemostasis and Thrombosis (GFHT) have been working together to draft up-to-date proposals for the management of antiplatelet therapy in patients undergoing elective invasive procedures.

The methodology for establishing these proposals was as follows. The different parts of this text were assigned to five working groups, consisting of members of the GIHP or the GFHT. Each of the groups made proposals based on data from the literature. The other groups then re-read, discussed and modified these proposals, which were then subjected

to critical analysis by all GIHP and GFHT members. Finally, these proposals were validated by a vote (37 voters), thereby determining the strength of each of the proposals, as follows. To make a proposal on an item, at least 50% of the members had to express their agreement (for an agreement to be strong, the threshold was set at 70%), whereas disagreement was when fewer than 20% agreed. In the absence of agreement, the proposals were reformulated and voted upon again to achieve a better consensus. The proposals were made in collaboration with the French Society for Anesthesia and Intensive Care (SFAR).

Bleeding risk due to continuation of antiplatelet therapy during an invasive procedure

Continuing antiplatelet therapy in the periprocedural period is likely to increase the risk of bleeding intra- and postoperatively depending on the invasive procedure and the type of antiplatelet. The main issue is to determine the situations where the increased bleeding risk is not acceptable, thereby needing perioperative changes in antiplatelet therapy. Studies evaluating the risk of bleeding associated with the perioperative continuation of one or more antiplatelets have methodological drawbacks. Nevertheless, as a general rule, the bleeding risk due to clopidogrel is lower than that with the new P2Y₁₂ receptor inhibitors prasugrel and ticagrelor, and is greater with dual therapy (aspirin + P2Y₁₂ inhibitor) than with monotherapy (most often aspirin). The aspirin-induced bleeding risk could be lower than that with clopidogrel, as thromboxane A₂ plays a lesser role in platelet activation than ADP [4].

The risk of bleeding due to antiplatelet therapy varies from one invasive procedure to another and includes not only the volume of bleeding and transfusion requirement but also the onset of a haematoma in the event of functional surgery or the need for surgical revision. The risk of bleeding during invasive procedures is usually classified pragmatically, depending on the possibility of performing the procedure in antiplatelet-treated patients [5–11]. Several classifications have been proposed by various scientific societies and globally by the “Stent after Surgery” group [12]. These classifications may vary depending on the surgical teams and patients considered.

Proposals

- the risk of bleeding related to the invasive procedure can be divided into high, moderate and low risk (Strong agreement) (Fig. 1);
- procedures carrying a high risk of bleeding are defined as not feasible in patients on antiplatelet therapy, even aspirin monotherapy. For such procedures, the aspirin-induced bleeding risk is either unknown but considered as potentially worrying, or unacceptable or deemed as such, with a lethal or functional risk. They are infrequent and include certain procedures in urology when alternative techniques cannot be used, numerous procedures in intracranial neurosurgery, surgery with major tissue resection or wide dissections, and certain procedures of liver or thoracic surgery (Strong agreement);

- procedures carrying a moderate risk of bleeding are defined as feasible in patients on aspirin alone. This is the case with the majority of invasive procedures (Strong agreement);
- procedures carrying a low risk of bleeding are defined as feasible in patients on dual antiplatelet therapy (DAPT). They include cataract surgery, most dental procedures, certain urological procedures such as urethrocytostomy, certain vascular surgery procedures, certain bronchoscopies, certain gastro-intestinal endoscopy procedures including all diagnostic endoscopies with or without biopsies, endoscopic retrograde cholangiopancreatography without sphincterotomy, and colonic polypectomies <1 cm. However, experience with ticagrelor or prasugrel is limited. In addition, the co-administration of other drugs interfering with haemostasis or the presence of comorbidities increasing the risk of bleeding may necessitate the discontinuation of the P2Y₁₂ inhibitor (strong agreement);
- when there is no consensus or standard to classify a procedure in one of these categories, it is proposed that a referent team (surgeon, anaesthetist, cardiologist, pulmonologist, vascular specialist or specialist in haemostasis) in the hospital defines a care plan on a case-by-case basis or for a given profile of patient or procedure. Such decisions are to be recorded in the patient's file or in the hospital's procedures (strong agreement);
- regarding gastrointestinal endoscopies, it is proposed that management strategies for antiplatelet therapy be defined in each hospital according to the profile of the patients and therefore the invasive procedure that may be potentially performed during the endoscopy. Thus, if the probability of an invasive procedure requiring discontinuation of antiplatelet therapy for a given patient profile is considered high, the appropriate strategy is adopted (e.g. sphincterotomy, gastrostomy). On the other hand, if the probability is low, the antiplatelet therapy is continued (e.g. chronic inflammatory diseases of the intestine, dyspepsia). When the probability and the nature of the lesions to be resected is not known a priori, each hospital decides on its policy (e.g. endoscopy for polyp detection) (strong agreement).

Duration of antiplatelet discontinuation and substitutes

The optimal duration of discontinuation of an antiplatelet drug before an invasive procedure is the shortest duration that can reduce the excess risk of bleeding associated with it. It depends on the pharmacokinetic and pharmacodynamic characteristics of the antiplatelet and on published clinical studies evaluating antiplatelet-related bleeding based on their duration of discontinuation for various invasive procedures, including surgeries that may be considered as models, especially cardiac surgery, but also total hip or knee replacement, hip fracture surgery, etc.

The basic points to be considered for determining the duration of a possible discontinuation of an antiplatelet drug, if deemed necessary, are as follows:

- the main platelet functions involved in hemostasis are adhesion to the subendothelium, aggregation, secretion

			Procedure-associated bleeding risk <i>To assess with the surgeon or the operator</i>		
			Low	Moderate	High
Thrombotic risk of the patient	Aspirin for primary prevention		Stop or continue	Stop	Stop
	AP for secondary prevention (cardiovascular prevention, lower extremity artery disease, history of ischaemic stroke)	Aspirin monotherapy	Continue	Continue	Stop
		Clopidogrel monotherapy	Continue	Stop and bridge with aspirin	Stop
	DAPT for coronary artery disease <i>Postpone until completion of the full course of DAPT if no major life-threatening or functional risk</i>	• Stent <1 month • Stent <6 months with high thrombotic risk ^a • MI <6 months	Postpone Non-deferrable surgery: continue both APs	Postpone Non-deferrable surgery: continue aspirin and stop P2Y ₁₂ inhibitor	Postpone Non-deferrable surgery: stop both APs ^b
		None of the previous criteria	Continue both APs	Continue aspirin and stop P2Y ₁₂ inhibitor	Stop both APs

Procedure-associated bleeding risk Low: feasible in patients on DAPT (ex: cataract) Moderate: feasible in patients on aspirin alone (ex: colectomy) High: not feasible in patients on APs (ex: ampulectomy)	^a Stent with high thrombotic risk • Chronic kidney disease (i.e. CrCl < 60 mL/min) • Diffuse multivessel disease especially in diabetic patients • Prior stent thrombosis on adequate antiplatelet therapy • Stenting of the last remaining patent coronary artery • At least 3 stents implanted • At least 3 lesions treated • Bifurcation with 2 stents implanted • Total stent length >60 mm • Treatment of a chronic total occlusion
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Duration of AP discontinuation: last intake of: • Aspirin on day -3 (day 0 = day of procedure) • Clopidogrel and ticagrelor on day -5 • Prasugrel on day -7 (Add 2 more days for intracranial neurosurgery)	^b For stent <1 month, discuss bridging with intravenous APs
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Resume postoperatively as soon as possible according to the postoperative bleeding risk

Figure 1. Management of antiplatelet drugs in patients undergoing elective invasive procedures. AP: antiplatelet; CrCl: creatinine clearance; DAPT: dual antiplatelet therapy; EX: excluding; MI: myocardial infarction.

and procoagulant activities. They variably depend on the self-amplification systems of activation supported by thromboxane A₂ and ADP, and on the platelet stimulus. Their exploration in the laboratory or at the bedside remains imperfect;

- the basic effect of an antiplatelet is the inhibition of its target: aspirin irreversibly inhibits the enzyme cyclooxygenase 1 and thus the synthesis of thromboxane A₂, whereas the P2Y₁₂ inhibitors, clopidogrel, prasugrel and ticagrelor, inhibit the P2Y₁₂ platelet receptor for ADP;
- full recovery of the target's functioning is not required for the complete recovery of the platelet functions that depend on it;
- complete recovery of platelet functions dependent on thromboxane A₂ or ADP is not always necessary to achieve the sufficient haemostatic competence required for a safe invasive procedure;
- recovery of the target's functionality varies from one patient to another; but there is a well-established time interval after which recovery is achieved in all patients;
- no haemostatic safety threshold guaranteeing the absence of the perioperative risk of bleeding related to any residual effects of antiplatelet treatment has been established, whatever the platelet function test used, be it in the laboratory or at the bedside;

- standardized and anticipated durations of antiplatelet discontinuation are more convenient than decisions taken on a day-to-day basis after functional testing for elective procedure scheduling.

The differences between antiplatelets in the duration of discontinuation are explained by a combination of factors: thromboxane A₂ plays a lesser role in platelet activation than ADP; thromboxane A₂ produced by the fraction of naive platelets can stimulate all platelets in the vicinity, whether or not their cyclooxygenase-1 enzymes are inhibited; the level of inhibition before discontinuation, which classifies P2Y₁₂ inhibitors according to their potency (prasugrel and ticagrelor being more potent than clopidogrel); for ticagrelor, the reversibility of its inhibitory effect.

For the three antiplatelets with an irreversible effect, i.e. aspirin, clopidogrel and prasugrel, recovery after discontinuation depends on the turnover of circulating platelets, senescent inhibited platelets being removed from the circulation and replaced by newly produced platelets, unexposed to the drug ("naïve"). Finally, in the absence of a loading dose, the full inhibitory effect that the antiplatelets can induce in a patient takes several days to be obtained.

Aspirin

The French Haute Autorité de la Santé (HAS) recommends that aspirin should not be given for three days before the procedure [2]. However, this recommended duration may be adjusted. Aspirin irreversibly inhibits the synthesis of thromboxane A₂. The time required for the full recovery of thromboxane A₂ synthesis is that of the total turnover of circulating platelets, i.e. platelet lifetime, which is normally about 10 days, but may be shorter in some circumstances. However, recovery does not need to be total for the complete correction of the platelet functions that depend on thromboxane A₂ synthesis [13–15], nor for haemostatic competence to be sufficient to safely undergo an invasive procedure. Interindividual variability in correction of platelet function explains why not all subjects have complete correction after 4 days [16]. The association between results of platelet function tests and bleeding risk is not straightforward. For instance, in a randomized trial investigating six durations of aspirin discontinuation, from 0 to 5 days, in 258 patients treated with 100mg aspirin and requiring tooth extraction [15] (also with 212 patients not taking aspirin), the effects of aspirin on platelet aggregation induced by arachidonic acid assessed with the Multiplate[®] disappeared 96 hours after aspirin withdrawal. However, the incidence of haemorrhagic complications was similar regardless of the duration of discontinuation, including < 96 hours. Finally, faster recovery of aspirin-inhibited platelet function may occur in some patients, e.g. due to accelerated platelet turnover, such as diabetic patients, patients with high weight [17] and those with thrombocytosis in a setting of myeloproliferative neoplasia.

The haemostatic safety threshold guaranteeing the absence of perioperative risk of bleeding associated with aspirin treatment has not been established. Moreover, the functional platelet tests used in studies addressing this issue have yielded inconsistent results [18]. The data are therefore too preliminary to use those tests in clinical practice for the management of aspirin before an elective invasive procedure.

In conclusion, a 3-day washout of aspirin leads to an improvement in platelet functions that is often but not always sufficient for full correction of platelet functions. However, for procedures with a high risk of bleeding, i.e. the only procedures for which discontinuation of aspirin is essential, the goal is to completely correct the platelet functions inhibited by aspirin. This must be achieved in all patients undergoing these procedures. It is therefore proposed that invasive procedures carrying a high risk of bleeding, such as neurosurgery, should be performed only after 5 days of aspirin washout.

Although in most patients the maximal effect on platelets is achieved with 75 mg/day, for various reasons a higher dose may be given. Since the bleeding risk is not greater with 300 mg than 75–100 mg (but for gastrointestinal bleeding), there is no reason to change the chosen regimen perioperatively.

P2Y₁₂ inhibitors

The HAS recommends that clopidogrel, prasugrel and ticagrelor should not be given for 5, 7 and 5 days before the procedure, respectively [2]. The European Society of

Cardiology (ESC)/European Society of Anaesthesiology (ESA) recommendations are similar [1].

Usefulness of platelet functional tests to adjust the duration of P2Y₁₂ inhibitor washout before an invasive procedure

Given the variability of platelet response to P2Y₁₂ inhibitors in terms of both intensity and changes over time, the suggestion to guide duration of their discontinuation according to the results of a platelet functional test is attractive [19]. However, whereas there is consensus on the existence of a relationship between the level of the impairment of platelet functions and the risk of spontaneous haemorrhage after insertion of an endovascular prosthesis [20], the relationship between this level and the associated perioperative risk of bleeding have received little attention. Several tests may be used to evaluate platelet functions while on antiplatelet therapy with a P2Y₁₂ inhibitor, but sometimes inconsistent results have been found [21,22]. Moreover, definitions of perioperative bleeding events differ widely. Nevertheless, studies to date tend to show that the intensity of inhibition of platelet functions that depend on ADP is associated with an increased risk of perioperative bleeding. A meta-analysis showed that late discontinuation of P2Y₁₂ inhibitors was associated with an increased risk of death and reoperations due to bleeding compared with earlier discontinuation in patients undergoing coronary artery surgery [23]. Patients allocated to prasugrel treatment in the TRITON-TIMI 38 study and requiring coronary artery surgery had a fourfold greater risk of major bleeding than those treated with clopidogrel [24]. Furthermore, in the PLATO study, patients who had taken ticagrelor in the 24 hours before coronary artery surgery tended to have larger chest tube drainage than those treated with clopidogrel [25].

It has therefore been proposed that evaluation of platelet function might improve the prediction of the perioperative bleeding risk over standard discontinuation durations based on the type of P2Y₁₂ inhibitor, such as clopidogrel [26]. An early study used TEG[®] Platelet Mapping for clopidogrel-treated patients undergoing coronary artery surgery. It showed that being in the higher tertile of platelet function inhibition measured with this test was the only factor independently associated with increased blood loss and transfusion requirement [26]. Another study showed that a strategy based on preoperative testing of platelet functions with the same test (TEG Platelet Mapping) to determine the timing of coronary artery bypass graft (CABG) surgery in clopidogrel-treated patients was associated with the same amount of bleeding as that observed in clopidogrel-naïve patients and a 50% shorter waiting time than the standard 5 days [27].

Emerging evidence based on functional platelet testing challenges the 5-day duration of ticagrelor discontinuation before surgery that carries a high bleeding risk. A Swedish cardiac surgery registry compared perioperative bleeding in the setting of emergency or semi-emergency coronary artery surgery in patients treated with DAPT consisting of aspirin and clopidogrel ($n = 978$) or ticagrelor ($n = 1266$) [28]. The incidence of major bleeding was high when ticagrelor or clopidogrel were discontinued less than 24 hours before

surgery. In the ticagrelor group, there was no significant difference between discontinuation 72–120 hours or more than 120 hours before surgery, as opposed to what was observed in the clopidogrel group. The overall incidence of major bleeding complications was lower with ticagrelor than with clopidogrel.

An analysis of a Dutch registry also showed that a 3-day washout of ticagrelor could be considered [29]. Between 2012 and 2014, 626 antiplatelet-treated patients underwent coronary artery surgery with cardiopulmonary bypass, including 222 with DAPT. They were stratified according to the duration of discontinuation of the P2Y₁₂ inhibitor before surgery: ticagrelor discontinued ≤ 72 hours before surgery (Group Ti ≤ 72 , $n = 61$); ticagrelor discontinued 72 to 120 hours before surgery (Group Ti 72–120, $n = 23$); clopidogrel discontinued ≤ 120 hours (Clo group ≤ 120 , $n = 125$) or between 120–168 hours before surgery (Group Clo 120–168, $n = 13$). The standard duration of discontinuation of P2Y₁₂ inhibitors in the centre before scheduled surgery was 120 hours. Transfusion requirements were higher in the Ti group ≤ 72 and the Clo group ≤ 120 than in the aspirin-alone group (72.1% and 71.2%, respectively, vs 41.3%, $P < 0.001$ for both comparisons), but surgical re-exploration rates were not different. Multivariable analysis comparing the Clo groups ≤ 120 , C 120–168, Ti ≤ 72 and Ti 72–120 with the aspirin-alone group revealed Clo group ≤ 120 and Ti group ≤ 72 as predictors of bleeding-related complications. No increased incidence in bleeding-related complications was seen when ticagrelor was discontinued > 72 hours or clopidogrel > 120 hours before surgery. Although these data relate to cardiac surgery, they could probably be extrapolated to non-cardiac invasive procedures as the correction of platelet functions does not depend on the procedure. However, the correction of platelet functions that depend on ADP 72 to 120 hours after discontinuing ticagrelor showed significant interindividual variability. ADP-induced aggregation was assessed with the Multiplate® after ticagrelor discontinuation in 25 patients undergoing urgent coronary artery surgery [30]. Whereas most patients had recovered a platelet response deemed sufficient after 72 hours of discontinuation (threshold at 22 aggregation units), 25% of patients remained below this threshold. However, in another prospective study that also included patients treated with ticagrelor and requiring cardiac surgery, preoperative ADP-induced platelet aggregation assessed by Multiplate® predicted the risk for severe bleeding complications [31]. Importantly, more patients with ADP-induced aggregation below the 22-unit threshold developed severe bleeding than those above (61% vs 14%, $P < 0.001$).

Altogether, these data suggest that a 72-to-120-hour ticagrelor discontinuation is sufficient for most patients. However, within this window, the correction of platelet functions inhibited by ticagrelor is variable from one patient to another. Platelet inhibition persists in about one-quarter of patients after a 72-hour discontinuation and is associated with the risk of perioperative bleeding. It is therefore proposed that invasive procedures should be performed only after 5 days of ticagrelor discontinuation.

Based on these data, both the European Societies of Cardiovascular and Cardio-Thoracic Surgery and the Society of Thoracic Surgeons used to recommend assessing the level

of inhibition of platelet functions to determine the interval between the last intake of P2Y₁₂ inhibitors and the invasive procedure [11,32]. However, studies supporting these recommendations are few and underpowered to accurately assess bleeding events, and involved patients treated with clopidogrel or ticagrelor and not those treated with prasugrel. Therefore, the most appropriate assessment of platelet function remains debated. Finally, the type of surgery studied in this context is almost always coronary artery surgery, and the safety of the determination of the optimal duration of P2Y₁₂ inhibitor discontinuation based on a laboratory test before another type of intervention such as neurosurgery is not established. Thus, it seems premature to recommend the routine use of such an attitude, which is no longer proposed in the recent guidelines of the ESC [1]. Available data suggest at most the use of a platelet functional test to reduce the duration of discontinuation of P2Y₁₂ inhibitors in urgent coronary artery surgery.

Proposals

- if discontinuation of antiplatelet therapy is indicated before an invasive procedure, it should be as follows (Strong agreement) (Fig. 1):
 - last intake of aspirin on D-3 (D0 corresponds to day of procedure)¹,
 - last intake of clopidogrel and ticagrelor on D-5²,
 - last intake of prasugrel on D-7,
 - last intake of aspirin on D-5,
 - last intake of clopidogrel and ticagrelor on D-7,
 - last intake of prasugrel on D-9 (Strong agreement),
- it is recommended not to bridge antiplatelet agents either heparin (unfractionated or low-molecular-weight heparin) or non-steroidal anti-inflammatory drugs (Strong agreement);
- in patients treated with aspirin at doses up to 300 mg/day in the long term, it is proposed not to reduce the dosage for surgery (Strong agreement).

Management of antiplatelets based on their indication and the elective invasive procedure

The discontinuation of long-term antiplatelet therapy is associated with the occurrence of cardioneurovascular events, the frequency of which varies with the indication for antiplatelet therapy [8,33]. The thrombotic risk associated with discontinuing treatment should therefore be assessed according to each of its indications.

Antiplatelet monotherapy

Cardiovascular prevention

The perioperative effect of aspirin prescribed for primary or secondary cardiovascular prevention has been evaluated

¹ For intracranial neurosurgery.

² Recent data suggest that urgent coronary artery surgery can be performed after a shorter ticagrelor discontinuation, of 3 to 5 days, with no excess risk of bleeding in most patients. However, in this setting, patients without recovery deemed sufficient of ticagrelor-induced platelet inhibition are at increased risk of bleeding.

in only a few randomized trials in non-cardiac surgery. The PEP trial compared preoperative 160 mg/day aspirin continued for 35 days with placebo in 13,356 patients undergoing surgery for hip fracture [34]. Aspirin increased bleeding, red blood cell transfusion was more frequent and larger, and there was more gastrointestinal bleeding. In addition, although it reduced venous thromboembolic events, aspirin did not reduce the incidence of myocardial infarction or stroke.

The POISE-2 trial evaluated the benefit of aspirin versus placebo in 10,010 patients undergoing non-cardiac surgery [35]. Patients were stratified according to whether they were treated with long-term aspirin before surgery. Aspirin did not decrease the composite endpoint of myocardial infarction or mortality but increased the risk of major bleeding. The authors concluded that the risk of continuing aspirin perioperatively was greater than the risk of discontinuing it. However, fewer than one-third of the patients had a cerebrovascular or cardiovascular history. In addition, patients with recent stents and those scheduled for carotid surgery were excluded, as it is recommended to continue aspirin for carotid endarterectomy [36]. At most, POISE-2 suggests that aspirin has no perioperative benefit for patients at low cardiovascular risk. No conclusion can be drawn for high-risk patients.

The STRATAGEM trial compared placebo with aspirin prescribed for secondary prevention (coronary artery disease, ischaemic stroke or transient ischaemic attack, peripheral artery disease) in 291 patients undergoing intermediate- or high-risk non-cardiac surgery [37]; 41% of the patients had a history of acute coronary syndrome. The trial, which was interrupted prematurely for inclusion difficulties, showed no difference in the occurrence of major thrombotic or haemorrhagic events.

Finally, the ASINC trial compared aspirin with placebo in patients with cardiac risk factors undergoing elective, high- or intermediate-risk non-cardiac surgery [38]. More than two-thirds of patients had coronary artery disease and one-fifth had cerebrovascular disease. The trial showed that aspirin reduced major cardiac events by 80% compared with placebo. There was no excess risk of bleeding but the trial was unpowered due to its premature termination.

History of ischaemic stroke

For patients receiving antiplatelet therapy for secondary stroke prevention, published data, which are scarce, suggest that its discontinuation is associated with the occurrence of thrombotic events. Thus, the risk of recurrent ischaemic stroke or major cardiovascular events following antiplatelet discontinuation was investigated during the follow-up of PROFESS, a randomized, double-blind, factorial study that included 20,332 patients with recent ischaemic stroke (4 months before inclusion) [39]. The aim of the trial was to evaluate the efficacy of the combination of extended-release dipyridamole with aspirin versus clopidogrel monotherapy and the efficacy of telmisartan versus placebo [40]. The secondary analysis of the trial showed that patients who discontinued antiplatelet therapy for any reason had an absolute risk increase in stroke recurrence or a cardiovascular event of 2.02% and 1.83% within 30 days of discontinuation of dipyridamole/aspirin and clopidogrel, respectively, compared with patients who continued

treatment [39]. These results may have been biased because the authors did not perform a multivariable adjustment to account for the characteristics of patients who discontinued treatment. Cohort and case-control studies have also reported an increased risk of recurrent stroke following discontinuation of antiplatelet therapy [41–44].

Lower extremity artery disease

Patients receiving antiplatelet therapy for lower extremity artery disease are at high risk of cardiovascular events, particularly during the postoperative period [45,46], but the incidence of cardiovascular events related to discontinuation in such patients is not known. A cohort study involving 181 consecutive patients admitted to hospital for acute lower limb ischaemia showed that a thrombotic event occurred in 11 patients (6.1%) after discontinuing aspirin, four of whom stopped before a surgical procedure [47].

Proposals

- for patients not receiving antiplatelet therapy, aspirin should not be initiated to reduce the risk of perioperative cardiovascular events before non-cardiac surgery, with the exception of carotid endarterectomy (strong agreement) (Fig. 1);
- aspirin should be discontinued preoperatively when prescribed for primary prevention (strong agreement);
- aspirin should not be discontinued preoperatively when prescribed for secondary prevention (cardiovascular prevention, history of ischaemic stroke, lower extremity artery disease), except for procedures with a high risk of bleeding (Strong agreement);
- for patients treated with monotherapy with a P2Y₁₂ inhibitor and scheduled for intermediate-risk surgery, the P2Y₁₂ inhibitor should be replaced by aspirin with a daily dose of 75 to 100 mg (strong agreement). This change could be made more than 7 days before surgery to allow complete correction of platelet inhibition induced by P2Y₁₂ inhibitors (strong agreement);
- antiplatelet therapy, if discontinued, should be resumed as soon as possible, according to the risk of postoperative bleeding, in patients who have an indication for long-term antiplatelet monotherapy (strong agreement).

Dual antiplatelet therapy for coronary artery disease

Four to 15% of patients with coronary stents require non-cardiac surgery within 1 year after stent implantation [48]. The management of those patients while still on DAPT involves consideration of:

- the increased perioperative bleeding risk, especially when DAPT is continued;
- the risk of stent thrombosis, especially if DAPT has to be discontinued;
- the consequences of delaying the invasive procedure [49–51]. A multidisciplinary approach involving the anaesthetist, the interventional cardiologist, the cardiologist, the surgeon, the haematologist and the oncologist, if any, could be used to assess the risks, weigh them up and determine the best management accordingly.

The perioperative period is a period of risk for ischaemic events. Regardless of the continuation or discontinuation of antiplatelet therapy, invasive procedures induce a proinflammatory and prothrombotic state thereby increasing the risk of coronary thrombosis at the level of the stented vascular segment as well as throughout the coronary vasculature [52,53]. An increased risk of ischaemic events following non-cardiac surgery has been demonstrated with first-generation drug-eluting stents [54] but also in the first weeks after stent implantation [55,56]. Thus, the benefit-risk ratio of an invasive procedure programmed after stent implantation and/or myocardial infarction should be systematically assessed in a multidisciplinary manner, especially in the case of high-risk procedures such as malignant tumour surgery or vascular aneurysm repair. To reduce the ischaemic risk and the risk of bleeding and transfusion related to the continuation of antiplatelet therapy, the invasive procedure should be postponed when possible until the end of the recommended duration of DAPT.

Previous recommendations on the duration of antiplatelet discontinuation and resumption for non-cardiac surgery [57,58] were based on registries of patients treated with first-generation drug-eluting stents [50,59].

Compared with first-generation drug-eluting stents or bare-metal stents, the new-generation drug-eluting stents are more effective and safer, with a lower risk of stent thrombosis and a shorter minimum duration of DAPT [60–63]. In addition, the PARIS registry has shown that DAPT discontinuation grounded on physician judgment in patients requiring an invasive procedure is not associated with an increased risk of ischaemic events, unlike discontinuation for poor compliance or bleeding [64].

Most registries agree that the risk of the recurrence of the ischaemic event reaches a stable level 3 to 6 months after active stent implantation [8,9,42]. However, the absence of a control group of non-operated patients exposes results to biases related to the type or urgency of invasive procedure. This makes it difficult to establish an optimal duration allowing an invasive procedure with a minimal risk of an ischaemic event after stenting or acute coronary syndrome. A North American registry circumvented those limitations by pairing two cohorts of stented patients, one undergoing an invasive procedure, the other not. The results confirmed that the increased risk of cardiovascular events related to surgery is greater during the first 6 months after stenting, and stabilizes at 1% thereafter [65]. A Danish registry also offset those limitations by comparing two cohorts of patients treated invasively, one with active stent implantation in the previous 12 months ($n=4003$) and the other without known history of coronary artery disease and undergoing the same type of procedure ($n=20,232$) [45]. It showed an increased risk of myocardial infarction and cardiac death in the group with previous stenting. Interestingly, this increased risk was limited to the first month after stent implantation, suggesting that the invasive procedure should be postponed for at least 1 month, if possible, after stent implantation.

Analysis of a registry of 26,661 US veterans undergoing non-cardiac surgery within 24 months of stent implantation showed that major cardiac events were more common in patients with a stent implanted for myocardial infarction (7.5%) compared with other indications, including unstable angina (2.7%) or revascularization not associated with acute

Table 1 Characteristics of high-thrombotic risk after stent implantation [1].

Chronic kidney disease (i.e. creatinine clearance < 60 mL/min)
Diffuse multivessel disease especially in diabetic patients
Previous stent thrombosis on adequate antiplatelet therapy
Stenting of the last remaining patent coronary artery
At least three lesions treated
At least three stents implanted
Bifurcation with two stents implanted
Total stent length > 60 mm
Treatment of a chronic total occlusion

coronary syndrome (2.6%) [66]. The risk of events was much higher when the invasive procedure was performed within 3 months after stent implantation for myocardial infarction compared with the third group (odds ratio 5.25, 95% confidence interval 4.08–6.75). The risk decreased over time but remained higher even 12–24 months after stenting. The authors proposed that invasive procedures in patients with a stent implanted for myocardial infarction should be postponed for 6 months. The same postponement was proposed for patients with myocardial infarction without stent implantation, as well as for patients who had stent implantation associated with a high thrombotic risk (Table 1).

For patients whose invasive procedure cannot be deferred until the end of the recommended duration of DAPT, the durations of P2Y₁₂ inhibitor discontinuation are those mentioned above. For patients at very high risk of stent thrombosis, particularly those requiring discontinuation of both antiplatelets in the first month, a bridging with a reversible intravenous antiplatelet was considered [67]. However, for rapidly reversible glycoprotein (GP) IIb/IIIa inhibitors such as eptifibatide and tirofiban, the meta-analysis of the eight studies that included 280 patients concluded that there was a possible risk of bleeding associated with a persistent risk of stent thrombosis [68]. Cangrelor, a parenteral and reversible inhibitor of the P2Y₁₂ receptor, is another option in the perioperative setting, with a well-established antithrombotic effect [69] and a faster reversibility than glycoprotein (GP) IIb/IIIa inhibitors [70]. However, none of these parenteral antiplatelets have marketing authorization for this indication. The use of concomitant parenteral anticoagulation is not recommended given the potential increase in the risk of bleeding.

Proposals for patients on dual antiplatelet therapy

- preoperative antiplatelet management and postoperative restarting may be discussed with the patient's cardiologist or a referent cardiologist and traced in the patient's file for elective procedures carrying an intermediate or high risk of bleeding (strong agreement) (Fig. 1);
- non-cardiac elective procedures should be postponed until completion of the full course of DAPT when it does

not pose a major life-threatening or functional risk to the patient (strong agreement);

- if this postponement is not possible, non-cardiac elective procedures should be postponed beyond the first month following stent implantation, regardless of the type of stent or indication (myocardial infarction or stable coronary artery disease). If the procedure cannot be postponed beyond the first month, it should be undertaken in hospitals where catheterization laboratories are available 24/7 (strong agreement)
- non-cardiac elective procedures should be postponed for up to 6 months in patients with recent myocardial infarction or with a stent associated with a high thrombotic risk (Table 1) (strong agreement);
- aspirin should be continued perioperatively. If it has to be discontinued, it should be resumed as early as possible after the invasive procedure, if possible the same day, according to the risk of postoperative bleeding (strong agreement);
- if P2Y₁₂ inhibitors have to be discontinued perioperatively, they should be resumed early, if possible within 24 to 72 hours after surgery, given the increased thrombotic risk. Resumption is performed with the same P2Y₁₂ inhibitor as preoperatively (strong agreement). No recommendation can be made regarding the use or not of a loading dose;
- if both antiplatelets have to be discontinued within 1 month after stent implantation, a bridging strategy with an intravenous antiplatelet agent such as tirofiban or cangrelor can be considered on a case-by-case basis after multidisciplinary discussion (off-label use). In these exceptional situations associated with a high risk of bleeding and thrombosis, bridging must be performed in an intensive care unit and surgery must be performed in hospitals where catheterization laboratories are available 24/7 (strong agreement);
- non-steroidal anti-inflammatory drugs should not be administered perioperatively in patients treated with DAPT (strong agreement). Perioperative use of coxibs is possible.

Regional anaesthesia

Antiplatelets and central neuraxial anaesthesia

Spinal epidural hematoma is a very rare but potentially catastrophic complication of central neuraxial anaesthesia, which includes spinal anaesthesia and epidurals with or without catheters [71]. Risk factors include haemostatic disorders, traumatic punctures and female sex [3,71]. The risk is greater for epidural anaesthesia, especially with a catheter, than for spinal anaesthesia [3].

The risk of spinal epidural hematoma related to aspirin seems very low. It has only been reported anecdotally after many years of practice in a very large number of patients undergoing spinal anaesthesia [3]. No spinal epidural haematoma attributed to aspirin has been reported in the large studies that evaluated this risk in orthopaedics and obstetrics. In the few case reports of spinal haematoma involving aspirin therapy, additional complicating factors were present, particularly injections of

low-molecular-weight heparin close to a neuraxial procedure or catheter ablation [3,72].

The P2Y₁₂ inhibitors carry a greater risk of bleeding than aspirin. Cases of perimedullary haematoma have been reported with clopidogrel. Spinal anaesthesia is not advisable with these antiplatelets [3,71].

Proposals

- aspirin is not a contraindication to central neuraxial anaesthesia if the benefit–risk ratio is favourable, if there is no associated abnormality of haemostasis, including anticoagulant therapy. If possible, single-puncture spinal anaesthesia is preferable to epidural anaesthesia (strong agreement) (Fig. 1);
- central neuraxial anaesthesia is contraindicated in patients on P2Y₁₂ inhibitors (clopidogrel, prasugrel, ticagrelor), unless those antiplatelets were discontinued five, seven and five days, respectively, before the procedure (strong agreement);
- the insertion of an epidural catheter can make the management of antiplatelets more complex. Catheter manipulation and removal carry similar risks to insertion and the same criteria should apply. Catheter removal follows the same rules as those for its insertion. Use of an epidural catheter should not compromise the post-operative resumption of antiplatelets, especially P2Y₁₂ inhibitors (strong agreement).

Antiplatelets and peripheral nerve blocks

Wound haematoma is a rare complication of peripheral nerve blocks [73]. Haematoma carries three risks: surgical revision for evacuation, transfusion and nerve damage by compression. Treatment with antiplatelets, especially P2Y₁₂ inhibitors, is a risk factor for haematoma [3]. However, aspirin probably carries a very low risk. The risk of haematoma is greater during deep punctures, in the absence of compression, and when antiplatelet and anticoagulant therapies are combined [3]. Ultrasound guidance reduces the risk of vascular puncture [74].

Peripheral nerve blocks can be divided into two groups according to the degree of bleeding risk:

- low bleeding risk peripheral blocks where, if bleeding occurs, it is easily controllable, and the area of bleeding can be compressed [75]. These include superficial blocks such as the femoral nerve block, the axillary plexus block and the popliteal sciatic nerve block. These blocks could be performed in patients on antiplatelet treatment if the benefit–risk ratio is favourable and justified [3].
- high bleeding risk blocks where, in the event of bleeding, the area cannot be compressed or the consequences of the bleeding are potentially serious [75]. These include deep blocks such as the infraclavicular brachial block, the para-sacral sciatic block, and the posterior lumbar plexus block. These blocks are contraindicated in patients on P2Y₁₂ inhibitors [3]. These blocks could be performed in patients on aspirin if the benefit – risk ratio is favourable and justified [3].

While peribulbar anaesthesia has been performed in ophthalmology without any complications in large series of aspirin-treated patients, few data are available in patients treated with clopidogrel and even less with ticagrelor or prasugrel [76]. The risk of bleeding with peribulbar anaesthesia is low. Nevertheless, if bleeding occurs, compression is not possible. While the SFAR and the French Society of Ophthalmology recommend performing peribulbar anaesthesia with a single puncture in patients treated with a direct oral anticoagulant, they have not adopted a position for patients treated with P2Y₁₂ inhibitors (<http://www.attitude.sfo.asso.fr/professionnels>). Topical or subtenonial anaesthesia may be preferred if they are sufficient.

Proposals

- peripheral nerve blocks with low risk of bleeding could be performed in patients on monotherapy or DAPT according to the benefit – risk ratio. Those blocks include superficial blocks such as the femoral block, axillary block, popliteal sciatic block, etc (strong agreement) (Fig. 1);
- peripheral nerve blocks with a high risk of bleeding could be performed in patients on aspirin monotherapy if the benefit – risk ratio is favourable. These blocks are contraindicated in patients on P2Y₁₂ inhibitors (clopidogrel, prasugrel, ticagrelor), unless they were discontinued five, seven and five days, respectively, before the procedure. These blocks include deep blocks such as the infraclavicular block, parasacral sciatic block, posterior lumbar plexus block, etc. (strong agreement);
- those blocks (superficial or deep) should be performed using ultrasound guidance by an operator with experience in the technique. (strong agreement);
- the insertion of a perineural catheter should not compromise the postoperative resumption of antiplatelets, especially P2Y₁₂ inhibitors. Catheter removal follows the same rules as catheter insertion (strong agreement).

Coronary artery surgery

Most patients requiring coronary revascularization by coronary artery surgery are treated with one or two antiplatelets. It is important to assess the risk of cardiovascular complications at preoperative discontinuation of these treatments and to determine whether this risk is greater than the risk of bleeding associated with their continuation during surgical revascularization, especially in the event of cardiopulmonary bypass.

Management of aspirin for coronary artery surgery

The aim of continued perioperative administration of aspirin is to reduce the likelihood of perioperative cardiovascular events. A meta-analysis of 13 randomized trials ($n=2399$ patients) involving patients undergoing coronary artery surgery assigned to preoperative aspirin therapy or no aspirin/placebo concluded that aspirin reduces perioperative myocardial infarction without reducing mortality, but

at the cost of increased bleeding, blood transfusion and surgical re-exploration [77]. The ATACAS randomized trial, with 2100 patients undergoing coronary artery surgery, concluded differently as the administration of preoperative aspirin resulted in neither a lower risk of death or thrombotic complications nor a higher risk of bleeding, including reoperation for haemorrhage, than that with placebo [78]. Finally, as in non-cardiac surgery, low-molecular-weight heparins should not be used for aspirin bridging. They promote bleeding, are difficult to antagonize and are less effective [79].

Management of P2Y₁₂ inhibitors for coronary artery surgery

In elective coronary artery surgery, the continuation of P2Y₁₂ inhibitors led to an increase in the risk of bleeding without any clear antithrombotic benefit. The meta-analysis of the three randomized trials CLARITY, CURE and CREDO concluded that the risk of immediate complications after coronary artery surgery (death, myocardial infarction and stroke) is the same whether patients are treated preoperatively with aspirin and clopidogrel or with aspirin alone, but that the risk of bleeding is increased by clopidogrel [80]. Above all, the risk of major bleeding and reoperation is increased if clopidogrel is discontinued less than 5 days before CABG surgery [81].

The new P2Y₁₂ inhibitors also carry an increased risk of perioperative bleeding. In the randomized TRITON-TIMI 38 trial, in which patients with acute coronary syndrome were randomized to treatment with aspirin and either clopidogrel or prasugrel, 3646 patients underwent coronary artery surgery. Patients treated with prasugrel had more major bleeding, platelet transfusions and surgical re-explorations compared with those on clopidogrel, and a lower rate of death [82]. Similarly, continuation of ticagrelor before coronary artery surgery increases the incidence of major bleeding complications [28].

The usefulness of platelet functional tests to adjust the discontinuation duration of P2Y₁₂ inhibitor discontinuation before coronary artery surgery has been discussed above. Recent data suggest that a platelet functional assessment test could be used to reduce discontinuation time of P2Y₁₂ inhibitors in semiurgent CABG surgery. Studies showing the benefit of platelet function evaluation were performed with the Multiplate® and TEG® Platelet Mapping. These tests could be used for their negative predictive value regarding bleeding.

Proposals

- a multidisciplinary approach is proposed to choose the best management strategy for antiplatelet agents before coronary artery surgery, according to the patient's risk of bleeding and thrombosis (strong agreement) (Fig. 1);
- it is proposed to continue aspirin throughout the perioperative period;
- in patients treated with DAPT, discontinuation of the P2Y₁₂ inhibitor is proposed, with a last intake five days before surgery for clopidogrel and ticagrelor, and seven days for prasugrel (strong agreement);
- emerging evidence suggests that urgent surgery could be performed after a shorter duration of ticagrelor

discontinuation, with a last intake three to five days before surgery. However, patients with no recovery of platelet function dependent on ADP after ticagrelor discontinuation are exposed to a risk of major postoperative bleeding (strong agreement).

Disclosure of interest

AG: Honoraria and travel fees from Bayer-Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer and Sanofi.

PF: travel grant from Bayer.

SM: honoraria from Bayer-Healthcare, Boehringer Ingelheim, Pfizer, Daiichi-Sankyo and Bristol-Myers Squibb.

AS: grants and personal fees from Sanofi-Aventis, Leo-pharma, Boehringer Ingelheim, Bayer, Daiichi Sankyo, Takeda and Bristol-Myers Squibb.

SS: Research support: LFB, Stago, Carmat, CoreWave and CSL-Behring; Travel support: Novo, LFB, Shire, CSL-Behring, Roche and Sobi.

PA: Honoraria and travel fees from Sanofi, Bayer, Bristol-Myers Squibb-Pfizer, Pfizer, Sandoz, Boehringer Ingelheim, Portola and B-Braun.

JPC: research grants from BMS and Medtronic; consulting/lecture fees from Astra-Zeneca, Bristol-Myers Squibb and Sanofi-Aventis.

The other authors declare that they have no competing interest.

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