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Guidelines

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

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ABSTRACT

The French Working Group on Perioperative Haemostasis (GIHP) and the French Study Group on Haemostasis and Thrombosis (GFHT) in collaboration with the French Society for Anaesthesia and Intensive Care Medicine (SFAR) drafted up-to-date proposals for the management of antiplatelet therapy in patients undergoing elective invasive procedures. The proposals were discussed and validated by a vote; all proposals but one could be assigned with a high strength. The management of antiplatelet therapy is based on their indication and the procedure. The risk of bleeding related to the procedure can be divided into high, moderate and low categories depending on the possibility of performing the procedure in patients receiving antiplatelet agents (none, monotherapy and dual antiplatelet therapy respectively). If discontinuation of antiplatelet therapy is indicated before the procedure, a last intake of aspirin, clopidogrel, ticagrelor and prasugrel 3, 5, 5 and 7 days before surgery respectively is proposed. The thrombotic risk associated with discontinuation should be assessed according to each specific indication of antiplatelet therapy and is higher for patients receiving dual therapy for coronary artery disease (with further refinements based on a few well-accepted items) than for those receiving monotherapy for cardiovascular prevention, for secondary stroke prevention or for lower extremity arterial disease. These proposals also address the issue of the potential role of platelet functional tests and consider management of antiplatelet therapy for regional anaesthesia, including central neuraxial anaesthesia and peripheral nerve blocks, and for coronary artery surgery.

1. Introduction

Antiplatelet agents (APAs) are prescribed to prevent arterial thrombosis and especially the recurrence of thrombotic events. The four main oral APAs have two distinct pharmacological targets: aspirin inhibits the enzyme cyclooxygenase 1 and therefore thromboxane A_2 synthesis, while clopidogrel, prasugrel and ticagrelor inhibit the adenosine diphosphate (ADP) pathway via the platelet receptor $P2Y_{12}$.

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 while the 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 recent work into account [1–3]. The French Working Group on Perioperative Haemostasis (GIHP) and the French Study Group on Haemostasis 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%), while disagreement was when fewer than 20% of them 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 Anaesthesia and Intensive Care Medicine (SFAR).

2. 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 APA. 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 APAs have methodological drawbacks. Nevertheless, as a general rule, the bleeding risk due to clopidogrel is lower than that with the new $P2Y_{12}$ receptor inhibitors, prasugrel and ticagrelor, and is greater with dual therapy (aspirin + $P2Y_{12}$ inhibitor) than with monotherapy (most often aspirin). The aspirin-induced bleeding risk could be lower than that with clopidogrel, since thromboxane A_2 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 APA-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).
- 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 majority of invasive procedures (strong agreement).
- Procedures carrying a low risk of bleeding are defined as feasible in patients on dual antiplatelet therapy. They include cataract surgery, most dental procedures, certain urologic procedures such as urethrocystoscopy, certain vascular surgery procedures, certain bronchoscopies, certain gastrointestinal 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 $P2Y_{12}$ 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).

3. Duration of APA discontinuation and substitutes

The optimal duration of discontinuation of an APA 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 APA and on published clinical studies evaluating APA-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 APA, if deemed necessary, are as follows:

- the main platelet functions involved in haemostasis are adhesion to the sub-endothelium, aggregation, secretion, and procoagulant activities. They variably depend on the self-amplification systems of activation supported by thromboxane

A_2 and ADP, and on the platelet stimulus. Their exploration in the laboratory or at the bedside remains imperfect;
- the basic effect of an APA is the inhibition of its target: aspirin irreversibly inhibits the enzyme cyclooxygenase 1 and thus the synthesis of thromboxane A_2, while the $P2Y_{12}$ inhibitors, clopidogrel, prasugrel and ticagrelor, inhibit the $P2Y_{12}$ 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 A_2 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 APA treatment has been established, whatever the platelet function test used, be it in the laboratory or at the bedside;
- standardised and anticipated durations of APA discontinuation are more convenient than decisions taken on a day-to-day basis after functional testing for elective procedure scheduling.

The differences between APAs in the duration of discontinuation are explained by a combination of factors: thromboxane A_2 plays a lesser role in platelet activation than ADP; thromboxane A_2 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 $P2Y_{12}$ inhibitors according to their potency (prasugrel and ticagrelor being more potent than clopidogrel); for ticagrelor, the reversibility of its inhibitory effect.

For the three APAs 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 APAs can induce in a patient takes several days to be obtained.

3.1. 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 inhibits the synthesis of thromboxane A_2 irreversibly. The time required for the full recovery of thromboxane A_2 synthesis is that of the total turnover of circulating platelets, i.e. platelet lifetime, which is normally about 10 days but may in some circumstances be shorter. However, recovery does not need to be total for the complete correction of the platelet functions that depend on thromboxane A_2 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 four days [16]. The association between results of platelet function tests and bleeding risk is not straightforward. For instance, in a randomised trial investigating six durations of aspirin discontinuation, from 0 to five days, in 258 patients treated with 100 mg 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 comparable 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 diabetics, 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 is therefore too preliminary to use those tests in clinical practice for the management of aspirin before an elective invasive procedure.

In conclusion, a three-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 five days of aspirin washout.

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

3.2. $P2Y_{12}$ inhibitors

The HAS recommends that clopidogrel, prasugrel and ticagrelor should not be given for five, seven and five days before the procedure, respectively [2]. The ESC/ESA recommendations are comparable [1].

3.3. Usefulness of platelet functional tests to adjust the duration of $P2Y_{12}$ inhibitor washout before an invasive procedure

Given the variability of platelet response to $P2Y_{12}$ 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, while there is a 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 $P2Y_{12}$ inhibitor, but sometimes inconsistent results have been found [21,22]. Moreover, definitions of perioperative bleeding events widely differ. 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 $P2Y_{12}$ inhibitors was associated with an increased risk of death and reoperations due to bleeding compared to 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 four-fold greater risk of major bleeding than those treated with clopidogrel [24]. Furthermore, 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 in the PLATO study [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 $P2Y_{12}$ 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 CABG in clopidogrel-treated patients was associated with the same amount of bleeding as that observed in clopidogrel-naive patients and a 50% shorter waiting time than the standard five days [27].

Emerging evidence based on functional platelet testing challenges the five-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 dual antiplatelet therapy 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 three-day washout of ticagrelor could be considered [29]. Between 2012 and 2014, 626 APA-treated patients underwent coronary artery surgery with cardiopulmonary bypass, including 222 with dual antiplatelet therapy. They were stratified according to the duration of discontinuation of the $P2Y_{12}$ 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 $P2Y_{12}$ inhibitors in the center 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. Multivariate 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 prior to surgery. Although these data relate to cardiac surgery, they could probably be extrapolated to non-cardiac invasive procedures since 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]. While 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 five 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 European Society of Cardiology [1]. Available data suggest at most the use of a platelet functional test to reduce the duration of discontinuation of $P2Y_{12}$ 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):
  - last intake of aspirin on D-3 (D0 corresponds to day of procedure)*,
  - last intake of clopidogrel and ticagrelor on D-5***,
  - last intake of prasugrel on D-7*,
- (*) For intracranial neurosurgery:
  - 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);
- (**) Recent data suggest that urgent coronary artery surgery can be performed after a shorter ticagrelor discontinuation, of three to five 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.
- It is recommended not to bridge antiplatelet agents either heparin (UFH or LMWH) or NSAIDs (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).

4. Management of APAs based on their indication and the elective invasive procedure

The discontinuation of long-term antiplatelet therapy is associated with the occurrence of cardio-neurovascular 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.

4.1. APA monotherapy

4.1.1. Cardiovascular prevention

The perioperative effect of aspirin prescribed for primary or secondary cardiovascular prevention has been evaluated only in a few randomised trials in non-cardiac surgery. The PEP trial compared preoperative 160 mg aspirin continued for 35 days with placebo in 13,356 patients undergoing surgery for hip fracture [34]. Aspirin increased bleeding, RBC transfusion was more frequent and larger, and there was more digestive 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 and 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 1/3 of the included patients had a cerebrovascular or cardiovascular history. In addition, patients with recent stents and those scheduled for carotid surgery were excluded, since it is recommended to continue aspirin for carotid endarterectomy [36]. At most, POISE-2 suggests that aspirin has no perioperative benefit for patients with low cardiovascular risk. No conclusion can be drawn for high-risk patients.

The STRATAGEM trial compared placebo to aspirin prescribed for secondary prevention (coronary artery disease, ischaemic stroke or transient ischaemic attack, peripheral arterial disease) in 291 patients undergoing intermediate- or high-risk non-cardiac surgery [37]. For 41% of them, there was 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 2/3 of patients had coronary artery disease and 1/5 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.

4.1.2. 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 APA discontinuation was investigated during the follow-up of PRoFESS, a randomised, double-blind, factorial study that included 20,332 patients with recent ischaemic stroke (4 months prior to 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 to patients who continued treatment [39]. These results may have been biased because the authors did not perform a multivariate 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].

4.1.3. Lower extremity artery disease

Patients receiving antiplatelet therapy for lower extremity artery disease are at high risk of cardiovascular events, particularly in 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 ischemia 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 APA monotherapy

- For patients not receiving antiplatelet therapy, aspirin therapy should not be initiated in order to reduce the risk of perioperative cardiovascular events before non-cardiac surgery, with the exception of carotid endarterectomy (strong agreement).
- 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 $P2Y_{12}$ inhibitor and scheduled for intermediate-risk surgery, the $P2Y_{12}$ inhibitor should be replaced by aspirin with a daily dose of 75 to 100 mg (strong agreement). This change could be made more than seven days prior to surgery to allow complete correction of platelet inhibition induced by $P2Y_{12}$ 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 APA monotherapy (strong agreement).

4.2. Dual antiplatelet therapy for coronary artery disease

Four to 15% of patients with coronary stents require non-cardiac surgery within one year after stent implantation [48]. The management of those patients while still on dual antiplatelet therapy (DAPT) involves consideration of: (1) the increased perioperative bleeding risk, especially when DAPT is continued; (2) the risk of stent thrombosis, especially if DAPT has to be discontinued; and (3) 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 tumor 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 APA 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 to first-generation drug-eluting stents or to 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 event, 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 three to six 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. It confirmed that the increased risk of cardiovascular events related to surgery is greater during the first six months after stenting, and stabilises 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 ($n = 20{,}232$) [48]. It showed an increased risk of myocardial infarction and cardiac death in the group with a 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 one 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 revascularisation not associated with acute coronary syndrome (2.6%) [66]. The risk of events was much higher when the invasive procedure was performed within three months after stent implantation for myocardial infarction compared to the third group (OR: 5.25, 95% CI: 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 six 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).

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
Prior stent thrombosis on adequate antiplatelet therapy
Stenting of the last remaining patent coronary artery
At least 3 lesions treated
At least 3 stents implanted
Bifurcation with 2 stents implanted
Total stent length > 60 mm
Treatment of a chronic total occlusion

For patients whose invasive procedure cannot be deferred until the end of the recommended duration of DAPT, the durations of $P2Y_{12}$ inhibitor discontinuation are those mentioned above. For patients at very high risk of stent thrombosis, particularly those requiring discontinuation of both APAs in the first month, a bridging with a reversible intravenous APA was considered [67]. However, for rapidly reversible anti-GPIIb-IIIa agents 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 $P2Y_{12}$ receptor, is another option in the perioperative setting, with a well-established antithrombotic effect [69] and a faster reversibility than anti-GPIIb-IIIa agents [70]. However, none of these parenteral APAs have marketing authorisation 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 APA 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).
- 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 catheterisation 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 (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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor as preoperatively (strong agreement). No recommendation can be made regarding the use or not of a loading dose.
- If both APAs have to be discontinued within one 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 catheterisation laboratories are available 24/7 (strong agreement).
- NSAIDs should not be administered perioperatively in patients treated with DAPT (strong agreement). Perioperative use of coxibs is possible.

5. Regional anaesthesia

5.1. APAs and central neuraxial anaesthesia

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

The risk of spinal epidural haematoma 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 $P2Y_{12}$ inhibitors carry a greater risk of bleeding than aspirin. Cases of peri-medullary haematoma have been reported with clopidogrel. Spinal anaesthesia is not advisable with these APAs [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).
- Central neuraxial anaesthesia is contraindicated in patients on $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, ticagrelor), unless those AAPs were discontinued respectively 5, 7 and 5 days before the procedure (strong agreement).
- The insertion of an epidural catheter can complexify management of APAs. 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 postoperative resumption of APAs, especially $P2Y_{12}$ inhibitors (strong agreement).

5.2. APAs 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 APAs, especially $P2Y_{12}$ 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 APA 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitors (http://attitude.sfo.asso.fr/professionnels). Topical or sub-tenonial anaesthesia may be preferred if they are sufficient.

Proposals

- Peripheral nerve blocks with low risk of bleeding could be performed in patients on mono or dual antiplatelet therapy according to the benefit/risk ratio. Those blocks include superficial blocks such as the femoral block, axillary block, popliteal sciatic block, etc. (strong agreement).

- 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 $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, ticagrelor), unless they were discontinued respectively 5, 7 and 5 days before the procedure. These blocks include deep blocks such as the infraclavicular block, para-sacral 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 APAs, especially $P2Y_{12}$ inhibitors. Catheter removal follows the same rules as catheter insertion (strong agreement).

6. Coronary artery surgery

Most patients requiring coronary revascularisation by coronary artery surgery are treated with one or two APAs. 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 revascularisation, especially in the event of cardiopulmonary bypass.

6.1. 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 randomised 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 randomised 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 antagonise and are less effective [79].

6.2. Management of $P2Y_{12}$ inhibitors for coronary artery surgery

In elective coronary artery surgery, the continuation of $P2Y_{12}$ inhibitors led to an increase in the risk of bleeding without any clear antithrombotic benefit. The meta-analysis of the three randomised 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 five days before CABG surgery [81].

The new $P2Y_{12}$ inhibitors also carry an increased risk of perioperative bleeding. In the randomised TRITON-TIMI-38 trial, in which patients with acute coronary syndrome were randomised 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 to 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitors in semi-urgent 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).
- It is proposed to continue aspirin throughout the perioperative period.
- In patients treated with DAPT, discontinuation of the $P2Y_{12}$ 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).

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TL, NR and YG declare that they have no competing interest.

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