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GUIDELINES

Management of antiplatelet therapy for non-elective invasive procedures or bleeding complications: 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 (SFAR)

Gestion des agents antiplaquettaires en cas de procédure invasive non programmée ou d'hémorragie : 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; APA, Antiplatelet Agent; APT, Antiplatelet Therapy; DAPT, Dual Antiplatelet Therapy; GHIP, French Working Group on Perioperative Haemostasis; GFHT, French Study Group on Thrombosis and Haemostasis; PFA, Platelet Function Analyzer; rFVIIa, Recombinant Activated Factor VII; TEG, Thromboelastography.

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Summary 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 (SFAR), drafted up-to-date proposals on the management of antiplatelet therapy for non-elective invasive procedures or bleeding complications. The proposals were discussed and validated by a vote; all proposals could be assigned with a high strength. Management of oral antiplatelet agents in emergency settings requires knowledge of their pharmacokinetic and pharmacodynamic parameters, evaluation of the degree of alteration of haemostatic competence and the associated bleeding risk. Platelet function testing may be considered. When antiplatelet agent-induced bleeding risk may worsen the prognosis, measures should be taken to neutralize antiplatelet therapy, by considering not only the efficacy of available means (which can be limited for prasugrel and even more for ticagrelor), but also the risks that these means expose the patient to. The measures include platelet transfusion at the appropriate dose and haemostatic agents (tranexamic acid; recombinant activated factor VII for ticagrelor). When possible, postponing non-elective invasive procedures at least for a few hours until the elimination of the active compound (which could compromise the effect of transfused platelets) or, if possible, for a few days (reduction of the effect of antiplatelet agents) should be considered.

MOTS CLÉS
Agents antiplaquettaires ;
Chirurgie ;

Résumé Le Groupe d'intérêt en hémostase périopératoire (GIHP) et le Groupe français d'études sur l'hémostase et la thrombose (GFHT) en collaboration avec la Société française d'anesthésie-réanimation (SFAR) ont fait des propositions sur la gestion des agents antiplaquettaires (AAP) en cas de procédure invasive non programmée ou d'hémorragie. Ces propositions ont été discutées puis validées par un vote, elles font toutes l'objet d'un accord fort. La gestion

Hémorragie ;
Thrombose ;
Transfusion plaquettaire ;
Facteur VII activé recombinant

des AAP en urgence nécessite de prendre en compte leurs caractéristiques pharmacocinétiques et pharmacodynamiques, d'évaluer l'affaiblissement de la compétence hémostatique liée aux AAP et le risque hémorragique qu'il entraîne. Les tests fonctionnels plaquettaires peuvent aider à cette évaluation. Lorsque le risque hémorragique lié aux AAP est susceptible d'aggraver le pronostic, la neutralisation des AAPdoit être envisagée, en prenant en compte l'efficacité des moyens de neutralisation (qui sont limités pour le prasugrel et le ticagrelor) mais aussi les risques associés à ces moyens. Ceux-ci incluent la transfusion plaquettaire, à des doses adaptées à l'AAP considéré, et les agents hémostatiques (facteur VII activé recombinant et acide tranexamique). Pour les procédures invasives non programmées, le report de quelques jours, voire de quelques heures, doit être envisagé lorsqu'il ne compromet pas le pronostic vital ou fonctionnel du patient, jusqu'à élimination ou diminution suffisante de l'effet de l'AAP ou de son métabolite actif.

Background

Oral antiplatelet therapy (APT) is one of the pillars of treatment of atherosclerosis, particularly for the prevention of recurrence of acute atherothrombotic events. However, non-elective invasive procedures or bleeding events during APT are frequent; their management requires evaluation of the level of haemostatic competence linked to APT and the bleeding risk it can induce. When this risk may worsen the prognosis, measures should be taken to neutralize (as defined below) APT by considering not only the efficacy of the means available, but also the risks that these means expose the patient to. For non-elective invasive procedures, the possibility of postponing them for a few days or even a few hours until the elimination or sufficient reduction of the effect of the antiplatelet agent (APA) or its active metabolite should be considered.

The management of patients treated with APAs in emergency settings is poorly codified. The French Working Group on Perioperative Haemostasis (GIHP) and the French Study Group on Thrombosis and Haemostasis (GFHT) have worked together to draft proposals for the management of APAs in case of non-elective invasive procedures or bleeding events. This work is a follow-up of the guidelines published in 2018 on the management of APT in patients undergoing elective invasive procedures.

The different parts of this text were assigned to working groups consisting of members of the GIHP and/or the GFHT. Each group performed a literature search via PubMed with the appropriate keywords. Then, each group drafted a text and made proposals based on data from the literature. Next, other groups read, debated and modified these proposals, which were then submitted for critical analysis by GFHT members and all the GIHP members. Finally, these proposals were validated by a vote ($n = 38$) that determined the strength of each proposal. In order to retain a proposal on a criterion, at least 50% of the members had to agree (for a proposal to be considered as strongly accepted, the threshold was placed at 70%), whereas disagreement was when fewer than 20% agreed. In the absence of agreement, proposals were reformulated and submitted for a new vote, with the aim of obtaining better agreement. These proposals were made in collaboration with the French Society for Anaesthesia and Intensive Care Medicine (SFAR).

APAs

The four main oral APAs have two distinct molecular targets: aspirin inhibits the enzyme cyclooxygenase 1 (COX-1), and therefore thromboxane A_2 synthesis, whereas clopidogrel, prasugrel (two thienopyridines) and ticagrelor inhibit one of the platelet receptors of adenosine diphosphate (ADP), the $P2Y_{12}$ receptor (Table 1) [1]. Thromboxane A_2 and ADP are platelet activators with specific receptors that essentially come from platelets activated by subendothelial collagen exposed after a vascular injury and the first traces of thrombin; they make up amplification pathways of platelet activation and aggregation.

Under certain conditions (a combination of activators or high concentrations of strong activators, such as thrombin and collagen), platelet responses (in particular, aggregation) rely less or even not at all on the amplification system provided by thromboxane A_2 or that provided by ADP. Consequently, these responses are only partially (or not at all) inhibited by aspirin or by a $P2Y_{12}$ inhibitor, even if it is potent, or by the combination of both.

Inhibition of thromboxane A_2 synthesis by aspirin and inhibition of the $P2Y_{12}$ receptor by a thienopyridine (but not by ticagrelor) are irreversible, but in different ways, having an impact on management with platelet transfusion. Inhibition is almost total with aspirin, whereas inhibition induced by thienopyridines is always partial (especially as platelet activation by ADP also goes through another receptor — $P2Y_1$; the inhibition of the $P2Y_{12}$ receptor being partial). In the first situation, partial recovery of thromboxane A_2 synthesis by a fraction of non-inhibited platelets (endogenous and new or provided by transfusion), can fully stimulate platelets in the vicinity (endogenous, older and irreversibly inhibited by aspirin), whereas in the second situation, only the fraction of new platelets non-inhibited by thienopyridines can be fully activated by ADP.

Table 1 Pharmacological properties of the principal oral antiplatelet agents [122,123].

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Class	NSAID	Thienopyridine	Thienopyridine	Cyclopentyl triazolopyrimidine
Mechanism of action	COX-1 irreversible inhibitor	ADP $P2Y_{12}$ platelet receptor irreversible inhibitor	ADP $P2Y_{12}$ platelet receptor irreversible inhibitor	ADP $P2Y_{12}$ platelet receptor reversible inhibitor
Maintenance dose	75 to 300 mg once daily	75 mg once daily	10 mg once daily	90 mg twice daily
Time of active compound peak concentration	15 to 40 min	30 to 60 minutes	30 min	1.5 to 3 hours
Half-life of the principal active compound[a]	15 to 20 min	30 min	3.7 hours	Ticagrelor: 6.7 to 9.1 hours; first metabolite: 8.5 to 12.4 hours

ADP: adenosine diphosphate; COX: cyclooxygenase; NSAID: non-steroidal anti-inflammatory agent.
[a] See the text for the time intervals to be taken into account after administration of the antiplatelet agent during which the transfused platelets can be inhibited, which would compromise the efficacy of platelet transfusion [124].

Finally, it is important to note that in order to stop bleeding, platelets must be recruited with the constitution of an aggregate with sufficient volume to seal the breach within a reasonable time, which does not require that all of the platelets in circulation be fully functional.

The role of platelet function testing

What platelet function tests are available?

Several platelet function tests (Table 2) are used to study APA effects. There are major differences between them — thus, they are not interchangeable [2]. In different studies that used several platelet function tests, some were associated with the occurrence of clinical events and others not, partly because the platelet function tests did not explore the same aspects of platelet function. Platelet function tests can be classified according to the nature of their approach (integrative or centred on the effect on the molecular target) and according to their ability to estimate the effect of treatment by aspirin or by ADP inhibitors or the combination of both.

Platelet function tests have preanalytical constraints that are more or less well defined, and their analytical performances have not always been well evaluated. Certain platelet function tests using whole blood can be influenced by variables such as platelet count and haematocrit. It remains unknown whether these influences correctly reflect the role that these variables play in primary haemostasis in vivo. Finally, exploration in flowing blood (and with relevant shear stress) can provide data that are markedly different from those obtained in a closed system with very low shear stress [3,4]. The only flow device that is clinically available is the Platelet Function Analyzer (PFA®; Siemens Healthcare, Marberg, Germany), which has very particular characteristics that separate it from reference devices based on blood flow that is parallel to the reactive surface.

The crucial question is the clinical significance of the test. Evaluation of platelet function is relevant if a clear objective has been defined and if the limits of each test are known, as well as the complementarity of these approaches. What platelet function tests have in common is the ability to document the degree of inhibition of the molecular target or overall function, as well as the speed and extent of recuperation. For most platelet function tests, the precise assessment of the degree of inhibition with APT requires knowledge of baseline functioning, which is rarely the case in practice. However, observation of a certain level of platelet response can reasonably lead one to consider that a return to full competence primary haemostasis has occurred — meaning that it cannot be differentiated from the competence of a subject not on APT and whose haemostasis is intrinsically normal.

The absence of a detectable effect with a platelet function test centred on a molecular target of a drug is consistent with non-observance or distant last intake, which therefore excludes the role of APAs in case of a bleeding event, or in the bleeding risk. A platelet function test with a well-established haemostatic competence threshold would make it possible to individually determine the shortest time to reach this threshold and perform a procedure after discontinuation of the APA. It could also assess the gap at this threshold and therefore the bleeding risk, the prediction of platelet transfusion requirement and the way to perform transfusion (initial dose to obtain a proportion of transfused platelets in circulation required for haemostatic competence, and the potential value of a new transfusion to maintain this proportion). Unfortunately, there is little clinical information to document that desired haemostatic competence threshold. Moreover, non-detection by an integrative platelet function test, which is possible despite a certain effect on the target, cannot be considered as a guarantee of absence of altered haemostatic competence. The practical limits of platelet function tests also include often-limited availability, user-friendliness and costs. Finally, as

Table 2 Succinct description of the main platelet function tests used for in vitro evaluation of the effect of antiplatelet therapy.

Test	Principle and interpretation
Conventional photometric aggregation	Changes in light transmission in platelet-rich plasma Activators: arachidonic acid for aspirin, ADP for $P2Y_{12}$ inhibitors or another activator (collagen, TRAP) that more or less uses activation amplification by both systems
Serum thromboxane B_2	Coagulation of whole blood at 37 °C and measurement of thromboxane B_2 (stable metabolite of thromboxane A_2) in the serum obtained Close evaluation of the aspirin target (COX-1) (but it can also be diminished by an NSAID other than aspirin or poor blood coagulation)
VASP test	ADP-induced inhibition, via its interaction with the $P2Y_{12}$ receptor, of the elevation of intraplatelet levels of cAMP (second messenger inhibiting platelet activation) induced by PGE_1 (platelet activation inhibitor); then detection by quantification of the degree of phosphorylation of the VASP protein by flow cytometry or ELISA Whole blood test that closely evaluates the target (the ADP $P2Y_{12}$ receptor) of this receptor's inhibitors (but can be influenced by other factors)
VerifyNow®[a]	Automated measurement in whole blood of the consequence of the interaction between fibrinogen and activated GP IIb/IIIa complex (artificial microbeads covered with fibrinogen) Dedicated cartridges for treatment by aspirin, $P2Y_{12}$ (or anti GP IIb/IIIa inhibitors)
Aggregation detected by changes in impedance	Whole blood (diluted), two devices: Multiplate® and ROTEM® platelet
Multiplate®[a]	Multiple electrode impedance platelet aggregometer Five channels with computer-assisted control Platelet activators to evaluate the effect of aspirin or that of $P2Y_{12}$ inhibitors (arachidonic acid and ADP, respectively)
ROTEM® platelet[a]	New module of the ROTEM® device
PFA®[a]	PFA-100® (now PFA-200®); whole blood under flow, with (very) high shear stress Occlusion by a platelet plug of an orifice in a membrane soaked with collagen and ADP, or collagen and epinephrine Sensitive to aspirin with a collagen and epinephrine cartridge, but not very sensitive to $P2Y_{12}$ inhibitors; there is a sensitized cartridge dedicated to $P2Y_{12}$ inhibitors (INNOVANCE® PFA P2Y)
TEG® PlateletMapping™[a]	Gradual modification of the viscoelastic properties of whole blood along with its coagulation and clot organization (its mechanical properties) Sensitized evaluation of platelet involvement in maximal amplitude[b]

Some tests that have been used in certain studies, but are not widely available, have not been included in this table. It is important to note that activator concentrations can differ from one test to another. ADP: adenosine diphosphate; cAMP: cyclic adenosine monophosphate; COX: cyclooxygenase; ELISA: enzyme-linked immunosorbent assay; GP: glycoprotein; NSAID: non-steroidal anti-inflammatory agent; PFA: Platelet Function Analyzer; PGE: prostaglandin E; ROTEM: rotational elastometry; TEG: Thromboelastograph; VASP: vasodilator-stimulated phosphoprotein.

[a] Tests that can be used near the patient and with whole blood are point-of-care tests; PFA® is often located in haemostasis laboratories.

[b] Three conditions are used to determine maximal amplitude: (1) the reference: citrated blood with kaolin and recalcification; (2) the contribution of fibrin(ogen): heparinized blood with a mixture of reptilase and coagulation factor XIIIa; (3) the contribution of platelets: by comparing the result obtained in condition (2) with the addition of a platelet activator that corresponds to the antiplatelet agent being evaluated (arachidonic acid and ADP for aspirin and $P2Y_{12}$ inhibitors, respectively), with the fibrin contribution and with the reference.

platelet function tests are performed with fresh blood, quality control is difficult [5].

In the perioperative context, the studied tests are mostly Multiplate® (Roche Diagnostics, Risch-Rotkreuz, Switzerland), Thromboelastograph (TEG®) PlateletMapping™ (Haemoscope Corporation, Niles, IL, USA) and, to a lesser extent, VerifyNow® (Instrumentation Laboratory Co., Bedford, MA, USA). The time required for a result with these point-of-care tests is 10 min or less, except for viscoelastometry (30 min) — to which must be added the incompressible time preceding the analysis, which even without transport to the laboratory includes ''rest'' time for the platelets between sampling and testing, and preincubation to obtain an homogeneous temperature of 37 °C [6].

If a platelet function test is used outside of a laboratory (point-of-care test), it must be performed: in coordination with the haemostasis team and the local medical laboratory; in agreement with existing regulations; and within a codified organization of patient management, including locally implemented transfusion algorithms.

As clinical validation is currently insufficient, if a platelet function test is used, it is advisable that rigorous and multidisciplinary prospective observation of its use and clinical events be performed. Participation in clinical studies is encouraged.

What is the value of platelet function testing in predicting bleeding before a non-elective invasive procedure when APT has not been discontinued?

The European Society of Anaesthesiology suggests preoperative platelet function testing in case of bleeding history to identify platelet function disorders, linked or not to APAs [7]. The grade of the recommendation (grade 2B), however, reflects the lack of solid data on the association between the degree of platelet dysfunction and the bleeding risk.

The first observational studies (with small cohorts) suggested that the degree of platelet inhibition (if determined before-after) or residual functioning is associated with perioperative or spontaneous bleeding events in patients treated with thienopyridines for percutaneous coronary intervention, but this association was not confirmed by three studies with larger cohorts [8—10].

Studies dedicated specifically to perioperative bleeding risk have mostly been performed in cardiac surgery, and the association between the degree of APA-induced platelet inhibition and bleeding was not consistently observed [2,11]. TEG® PlateletMapping™ predicted excessive bleeding in two studies [12,13], but not in a third study that compared several tests and showed that only the VerifyNow® test predicted the bleeding risk [14]. Two small observational studies reported that Multiplate® could identify patients at risk of bleeding [15,16]. Agreement was modest between the results of aggregation measured by impedance changes (Multiplate®) and those obtained with the PlateletMapping™ cartridge and the new viscoelastometric testing device TEG® 6S [17].

In non-cardiac surgery, one study including 197 patients treated with clopidogrel until the last preoperative days, with or without aspirin, found an association between perioperative bleeding and platelet inhibition evaluated by photometric aggregation, whereas such an association was not found with the other tests used (vasodilator-stimulated phosphoprotein [VASP] test, Multiplate® and INNOVANCE® PFA-200 [Siemens Healthcare, Marberg, Germany]) [18].

A consensus on the platelet function test to use has not yet been obtained, and the threshold values beyond which procedure-associated bleeding risk becomes worrisome remain to be defined (and probably to be adapted to the procedures). It would therefore appear premature to recommend platelet function testing to evaluate bleeding risk for any patient on APT. In agreement with the European Society of Anaesthesiology, it is suggested that platelet function testing be performed preoperatively in order to identify a platelet dysfunction, whatever the causes (APAs and others), when it is suspected on a clinical basis, in teams trained in and accustomed to the use of the tests.

What is the value of platelet function testing in adjusting the duration of APA discontinuation time before a non-elective invasive procedure?

When an invasive procedure can be postponed for a few days, the question is to determine whether it is possible to shorten the duration of APA discontinuation recommended for scheduled procedures [19]. The aim is to determine the shortest duration possible with an additional bleeding risk that is considered as acceptable.

While the vast majority of invasive procedures can be performed in patients on aspirin alone, dual APT (DAPT) combining aspirin and a $P2Y_{12}$ inhibitor can significantly increase the risk of bleeding. In that case, discontinuation of $P2Y_{12}$ inhibitors is recommended before procedures with moderate or high bleeding risk [7,19,20]. GIHP recommends the last intake of clopidogrel or ticagrelor at day −5, and day −7 for prasugrel [19].

There is significant variability in the response to $P2Y_{12}$ inhibitors evaluated with platelet function testing, particularly for clopidogrel and, to a lesser degree, for prasugrel and ticagrelor [21,22]. Two opposing situations can occur: low platelet function alteration noted with partial recovery, but deemed sufficient after a period of discontinuation that is shorter than that generally recommended, as recovery can be accelerated (increase in platelet turnover in cardiovascular settings, with an increased proportion of young and very reactive platelets [23]); or a longer duration of discontinuation required to reach the same degree of recovery, given a strong alteration (high sensitivity to APT). There is some degree of variability in the speed of recovery after aspirin, essentially related to accelerated platelet turnover [24], while the obtained inhibition of the molecular target is always maximal, except in case of poor compliance with treatment or interference by another non-steroidal anti-inflammatory agent (NSAID). If possible, shortening the discontinuation of this type of APA according to the results of a platelet function test is therefore attractive [25—27].

Even if there is agreement on the existence of a relationship between the level of platelet function alteration

and the risk of spontaneous haemorrhage after placement of a coronary stent [28], there have been few studies with specific interest in the level of platelet function alteration and associated peri-interventional bleeding risk. As already stated, the results of the tests are not interchangeable [29,30]. Moreover, the definitions of perioperative bleeding are very heterogeneous. Nevertheless, the available data tend to show that the intensity of platelet function alteration is associated with an increased perioperative bleeding risk. A meta-analysis of 19 studies (totalling 14,046 patients) revealed that a short interval between the last intake of APA and surgery compared with a longer interval was associated with a doubling of reoperations resulting from bleeding, and an increase of 50% in mortality in patients undergoing coronary bypass surgery [31]. Patients on prasugrel in the TRITON-TIMI 38 study undergoing coronary bypass surgery had four times more major bleeding events than patients on clopidogrel [32], and the patients who had taken ticagrelor within 24 hours of coronary bypass surgery tended to have greater chest tube drainage than those treated with clopidogrel in the PLATO study [33].

It has been logically proposed that platelet function testing could be a better means of predicting perioperative bleeding risk than duration of APA discontinuation. A few observational studies support this concept. A first study used TEG® PlateletMapping™, and reported that being in the upper tertile of platelet dysfunction measured with this test predicted transfusion requirements after coronary artery bypass surgery in a cohort of 99 patients [12]. In addition, another study with 180 patients reported that platelet function testing with the same test (TEG® PlateletMapping™) in order to decide the duration of clopidogrel discontinuation before coronary bypass surgery was associated with a mean discontinuation duration < 50% compared with 5-day discontinuation, without increased bleeding risk [34]. Lastly, a study with 90 patients receiving DAPT with ticagrelor undergoing coronary bypass surgery reported that the level of platelet function alteration measured by the Multiplate® ADP test predicted the risk of bleeding complications [15]. Another study suggested that adjustment of the discontinuation duration before cardiac surgery, based on the results of the VerifyNow® test, was cost effective, particularly in terms of shortening the duration of hospitalization [35].

The European Society of Cardiology (ESC), the European Association for Cardio-Thoracic Surgery (EACTS) and the Society of Thoracic Surgeons have drafted a grade IIb recommendation on the value of measuring the degree of platelet dysfunction to determine the time interval between last medication intake and cardiac surgery [36,37]. However, as noted above, the studies supporting these recommendations are not numerous; they dealt with small cohorts of patients treated with clopidogrel or ticagrelor, and not those treated with prasugrel. The most appropriate platelet function test in such cases has not been determined. Lastly, the type of surgery studied is almost always coronary bypass. The benefit of determining the discontinuation duration of the $P2Y_{12}$ inhibitor based on platelet function testing before another type of surgery, such as neurosurgery or urologic surgery, has not been assessed. Therefore, it would appear premature to recommend a generalized attitude. However, in case of expedited coronary artery bypass surgery, it is proposed that platelet function testing be used to shorten the duration of discontinuation of APAs, particularly $P2Y_{12}$ inhibitors, for teams who have such tests available and are accustomed to using them.

Is platelet function testing useful to guide platelet transfusion when facing a haemorrhage?

Bleeding linked to an invasive procedure

Regarding management of procedure-associated bleeding, a few studies restricted to cardiac surgery have attempted to rationalize platelet transfusion based on platelet function testing combined with the implementation of a transfusion algorithm, with varied and sometimes opposing results [38]. These studies did not all specifically address the question of preprocedural APT.

In cardiac surgery, the implementation of a transfusion algorithm (including a preoperative photometric platelet aggregation test and a test with PFA-100® [Siemens Healthcare, Marberg, Germany]) reduced the quantity of transfused blood products, especially platelet concentrates, whether the patients were treated with clopidogrel or not [39]. This prospective study was one of the rare studies to specifically consider the aspect of APT [39]. However, in a second study in cardiac surgery, this one retrospective, the implementation of another protocol using both viscoelastometric evaluation and the Multiplate® test was associated with a reduction in the transfusion of red blood cell and plasma units, but also with an increase in platelet transfusion [40]. In a prospective study by the same group, the use of the two above-mentioned tests in a modified algorithm reduced patient exposure to allogenic blood products and platelet transfusion doses [41].

The authors of a systematic review, with meta-analysis of 30 observational studies (3044 patients) and nine randomized trials (1057 patients) in cardiac surgery, which were not all centred on the question of preoperative APT, concluded that incorporating platelet function testing (often a viscoelastometric test) in a transfusion management algorithm is associated with a reduction in bleeding and transfusion requirement (red blood cells) [42]. However, it is not possible to favour one of the proposed transfusion algorithms that uses one or several of these tests. Moreover, the tests were essentially studied in cardiac surgery. A study performed in the context of intracerebral haemorrhage reported that patients considered by a platelet function test as being little affected by aspirin and not transfused, had the same evolution as patients who were not treated with aspirin [43]. Extrapolation of these results to other situations must be considered with caution. Overall, the real place of these algorithms and platelet function testing in guiding platelet transfusion remains to be validated, whether it be in cardiac surgery or other types of surgery.

Moreover, several scores have been established to predict perioperative bleeding and transfusion requirements [44,45], but none includes platelet function testing, and no study on platelet function testing has compared its results with the scores. At most, the scores include platelet count.

Non-periprocedural bleeding

In the case of non-periprocedural bleeding, platelet function testing may assess APA impact on primary haemostasis, which could guide bleeding management. The absence of a detectable effect with a test centred on the molecular target of the APA suggests poor observance of treatment or distant last intake, which could justify not performing neutralization, as it would be deemed unnecessary. However, there are still doubts about the ability of certain point-of-care tests to detect subtle, but clinically relevant, platelet function alterations in the specific setting of bleeding.

Is platelet function testing useful in guiding postoperative APT?

There is a rational basis for the postoperative evaluation of primary haemostasis: some procedures cause alterations in haemostasis that can predispose a patient to bleeding (such as cardiac surgery with extracorporeal circulation), with significant interindividual variability in the intensity of these alterations and in the speed of recovery. The post-procedural inflammatory phase also modifies haemostasis, but in the other direction (with prothrombotic effects) [46]. Similar phenomena can occur after an episode of severe haemorrhage. To our knowledge, no studies have assessed the use of platelet function testing to guide resumption of APT (time, dose, loading dose or not, etc.); their use cannot be proposed outside of research protocols.

The role of platelet function testing: proposals

Preoperative platelet function testing is proposed to identify platelet dysfunctions, regardless of the causes (APAs or others), when they are suspected on a clinical basis, in teams trained in and accustomed to the use of the tests.

In case of expedited coronary bypass surgery, platelet function testing is proposed to shorten the duration of discontinuation of $P2Y_{12}$ inhibitors in teams trained in and accustomed to the use of the tests.

If a platelet function test is used outside a laboratory (point-of-care test), it is recommended to perform it in coordination with the haemostasis team, within the framework of so-called delocalized biology; in agreement with current regulations; by including it in the management with local transfusion algorithms; and by personnel trained in and accustomed to the use of the tests.

(*) definition in section entitled ''Means of neutralizing the effect of APAs''.

Means of neutralizing the effect of APAs

The dictionary definition of the word ''neutralize'' used here is to reduce, alleviate or even cancel out the effect of something — to prevent it from acting through a contrary action. Thus, the means that can neutralize APAs are those that can reduce the increase in bleeding risk that they induce. They include not only the means to restore platelet functions inhibited by APAs, but also the means to more broadly improve primary haemostasis or even coagulation, as the aim is to improve haemostasis to reduce bleeding. The antidote for ticagrelor, if made available, will be one of these means.

A distinction must be made between the effect of a means of neutralization on platelet function testing performed in vitro (and more rarely on bleeding time in vivo) and the clinical efficacy, addressed mainly in the sections entitled ''Does neutralization of APAs improve patient prognosis?'' and ''Management of bleeding associated with APAs''.

Does platelet transfusion neutralize the effect of APAs?

Platelet products and doses

Platelet concentrates are either collected from a single donor via apheresis or are produced by pooling platelet suspensions prepared from whole blood donations from several donors. Platelet concentrates have variable platelet contents (1 to 4×10^{11} platelets) [47], but this varies depending on the country. In the international literature, the term ''unit'' often, but not always, means what can be obtained from a single donation of whole blood (around 0.5×10^{11} platelets). A platelet concentrate generally corresponds to at least 5 or 6 such units. The term ''platelet unit'' is no longer used in France, where the prescription must be based on the desired number of platelets. A transfusion of 0.5×10^{11} platelets (i.e. 50 G, or 1 unit as defined above) for 7 kg of body weight, or 0.7×10^{11} platelets for 10 kg of body weight, will increase the platelet count by approximately 50 G/L.

The dose that is usually recommended for a platelet transfusion, whatever the indication, is 0.5 to 0.7×10^{11} platelets per 10 kg of body weight (i.e. 1 to 1.5 units) [47].

Platelet transfusion and neutralization of APAs

Platelet transfusion is often recommended to neutralize the effects of APAs, and the dose is 0.5×10^{11} to 0.7×10^{11} for 10 kg of body weight [7,48,49]. The rationale for transfusion in this context is to provide platelets that have not been exposed to APAs (which can be called ''non-inhibited'') and that can sufficiently restore primary haemostasis, despite the presence in the patient's circulating blood of platelets inhibited by APA(s), and therefore correct the APA-induced bleeding risk. Three situations can be distinguished:

- irreversible platelet inhibitor, active metabolite still present in blood;
- irreversible inhibitor, no more active metabolite in blood;
- reversible inhibitor.

In the first and last cases, the transfused platelets are inhibited when circulating in the patient's blood, which compromises the efficacy of the platelet transfusion.

The ability of platelet transfusion to correct the effects of aspirin evaluated in vitro by platelet function testing has been well documented. In vitro supplementation by non-inhibited platelets in a proportion of 30 to 40% restored platelet aggregation studied by light transmission and induced with arachidonic acid [50,51]. Preoperative transfusion of a mean dose of 0.5 to 0.75×10^{11} platelets (1 to 1.5 units) per 10 kg of body weight in patients on aspirin

and requiring urgent neurosurgery corrected the platelet functions evaluated with VerifyNow® aspirin [52]. The time during which aspirin resides in the blood is brief when it is not a sustained-release formulation (half-life of around 20 min).

The effect of platelet transfusion to correct the effects of thienopyridines evaluated in vitro by platelet function testing is less documented, but higher doses of platelets than for aspirin would appear to be necessary. Correction of clopidogrel-induced platelet inhibition studied by light transmission aggregometry and induced with ADP occurs gradually with the increase in the proportion of non-inhibited platelets — thus with the lengthening of time elapsed since the last intake. Correction is partial, but significant, when there are more than 40% non-inhibited platelets. However, there are several arguments suggesting that the total correction of platelet dysfunction related to exposure to a thienopyridine, studied with such tools, is difficult to achieve, in contrast to aspirin. Neutralizing prasugrel appears to require a greater proportion of platelets than for clopidogrel [53,54]. In vitro supplementation by 60% non-inhibited platelets only provides partial correction of the ADP-induced platelet aggregation inhibited by prasugrel [55,56]. The time elapsed between thienopyridine intake and transfusion is decisive. In fact, platelet transfusion is rendered ineffective by the active metabolite of prasugrel, the concentration of which is maximal for the first 2 hours, and remains significant up to 6 hours after intake [56,57]. The half-life of the active metabolite of clopidogrel is reported to be shorter than that of prasugrel (Table 1), but in the absence of solid data, and in order to reduce the risk of ineffective transfusion, a duration of 6 hours can also be retained for clopidogrel.

Finally, platelet transfusion probably cannot neutralize the effect of ticagrelor. This directly active APA and its first metabolite, which is also a platelet inhibitor, are present in plasma at high concentrations. Their effect is reversible, but their half-lives are long: 7 hours for ticagrelor and 8.5 hours for its active metabolite [58,59]. Thus, ticagrelor present in plasma can inhibit platelets provided by transfusion [55,60,61] for up to 24 hours after the last intake [62]. Such ineffectiveness of platelet transfusion has been observed with several models. In vitro or in vivo administration of non-inhibited platelets did not restore ADP-induced platelet aggregation inhibited by ticagrelor [55,61]. ADP-induced platelet aggregation of samples from healthy volunteers was dramatically reduced even by a low (10%) proportion of plasma from patients treated with ticagrelor [57]. Likewise, transfusion of 8.5×10^{11} platelets (17 units) to a patient treated with aspirin and ticagrelor and requiring urgent neurosurgery increased platelet count, but did not improve ADP-induced aggregation evaluated with VerifyNow® [60].

Finally, 52 patients were transfused (about 3.5×10^{11} platelets; 7 units) before coronary artery bypass surgery, because they had been treated with aspirin and clopidogrel ($n = 45$), prasugrel ($n = 6$) or ticagrelor ($n = 3$), and presented active bleeding. Platelet function testing did not reveal platelet function improvement after transfusion in patients treated with ticagrelor (or prasugrel), whereas the improvement was statistically significant in those treated with clopidogrel [53].

Does desmopressin neutralize the effect of APAs?

Although desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) is often mentioned among the therapeutic options for prevention or treatment of APA-associated bleeding (doses of 0.3 to 0.4 μg/kg, perfused in 100 mL of saline solution for 30 minutes), its efficacy is very uncertain [63—65]. This synthetic drug acts by increasing the concentration of von Willebrand factor and factor VIII, and is used for certain forms of von Willebrand disease and haemophilia A. Moreover, it may have direct effects on platelets, which are still incompletely characterized [66]. Desmopressin is used for certain inherited [67] or acquired [68] platelet dysfunctions, but clinical demonstration of its efficacy has been inadequate. Studies with platelet function testing suggest a certain efficacy on the platelet dysfunctions induced by APAs [69—71].

In cardiac surgery, a meta-analysis of 10 randomized trials suggests that desmopressin can reduce red blood cell transfusion, blood loss and, more interestingly, reoperations resulting from bleeding [72]. However, half of the trials included were undertaken more than 20 years ago, and only six trials included patients treated with APAs ($n = 284$ in all), mostly aspirin, and none of the trials except for one concerned non-elective surgery. The percentage of patients transfused in the control groups was very heterogeneous. In a randomized trial including patients on DAPT undergoing coronary artery bypass surgery, desmopressin was not associated with a reduction in blood loss, but the cohort was small [73]. The use of desmopressin with the most recent APAs has been disappointing; it did not reduce bleeding in rabbits treated with prasugrel [74], and its administration to 21 healthy volunteers treated with ticagrelor did not reduce the bleeding time and did not correct platelet functions [75].

Not only has the efficacy of desmopressin not been established, but also its safety has not been submitted to much evaluation. Desmopressin exerts a systemic vasodilator effect that induces arterial hypotension, reactive tachycardia and facial flush; it also exposes patients to oliguria, hypervolaemia and hyponatremia. Rare cases of thromboembolic events after administration of desmopressin have led to recommending caution for patients at risk [76,77].

Does recombinant activated factor VII neutralize the effects of APAs?

Recombinant activated factor VII (rFVIIa) is an option proposed by the Summary of Product Characteristics for ticagrelor in case of severe bleeding. In fact, rFVIIa accelerates thrombin generation and, consequently, could improve haemostasis when platelet functions are compromised. rFVIIa is used during bleeding resulting from major inherited platelet function defects (e.g. Glanzmann's thrombasthaenia) [78].

For $P2Y_{12}$ inhibitors, there are in vitro studies and in vivo data from animal models and healthy volunteers. In platelet-rich plasma from healthy volunteers on aspirin-clopidogrel, rFVIIa still accelerated thrombin generation after platelet activation with arachidonic acid, ADP and collagen [79].

rFVIIa corrected all of the variables of thrombin generation and a viscoelastometric test, both altered by prasugrel [80]. In healthy volunteers, rFVIIa reduced blood loss volume induced by punch biopsy compared with a placebo [81]. Data with ticagrelor are limited to one animal study: the injection of 1 mg/kg of rFVIIa in mice that had received ticagrelor reduced bleeding duration and blood loss after tail section [82]. The data in favour of rFVIIa support the propositions of the Summary of Product Characteristics [83], but are very preliminary. Moreover, for thienopyridines, the target of which ($P2Y_{12}$) is shared with ticagrelor, no haemostatic effect of rFVIIa was observed. rFVIIa did not reduce bleeding in rabbits treated with clopidogrel [84] or prasugrel, whereas it induced arterial thrombosis [74].

The specific antidote for ticagrelor could combine efficacy and safety; this is a monoclonal antibody in advanced development [85].

Tranexamic acid

Although tranexamic acid probably has no direct effect on APA-induced platelet dysfunctions, it reduces surgical bleeding [86]. Thus, whether a patient is on an APA or not, tranexamic acid is recommended in case of periprocedural or traumatic severe haemorrhages [7]. In case of traumatic haemorrhage, it must be administered within the first 3 hours after trauma [87].

Means of neutralizing the effect of APAs: proposals

The type of APA and the time of the last intake should be noted (in order to take the presence or not of circulating active metabolites into account).

In situations requiring neutralization of aspirin, platelet transfusion is proposed. A dose of 0.5 to 0.7×10^{11} per 10 kg of body weight is proposed. With formulations of aspirin other than sustained-release ones, the active product will disappear from circulation in less than 2 hours (strong agreement).

In situations requiring neutralization of clopidogrel or prasugrel, platelet transfusion is proposed. A higher dose than that used to neutralize aspirin is proposed; it could be at least double and higher for prasugrel than for clopidogrel. The efficacy of platelet transfusion can be reduced if the last intake of clopidogrel or prasugrel was less than 6 hours ago. It is proposed not to administer rFVIIa to neutralize clopidogrel or prasugrel (strong agreement).

In situations requiring neutralization of ticagrelor, and if the last intake was less than 24 hours ago, no specific treatment can be proposed, because platelet transfusion at the doses used to neutralize other APAs will be ineffective. The clinical efficacy of higher doses of transfused platelets has not been evaluated. The clinical efficacy of rFVIIa, proposed in the Summary of Product Characteristics for ticagrelor, has not been evaluated. If the last intake of ticagrelor was more than 24 hours ago, platelet transfusion could provide partial neutralization (strong agreement).

It is proposed that tranexamic acid be administered because of its ability to reduce bleeding, whether the patient has received an APA or not (strong agreement).

Administration of desmopressin to neutralize APAs is not proposed (strong agreement).

Management of patients on APT facing non-elective invasive procedures

Non-elective invasive procedures are subject to the NCEPOD classification (National Confidential Enquiry into Patient Outcome and Death), which defines the degree of urgency [88]. Three types of procedures can be distinguished: immediate, urgent and expedited.

The aim of immediate procedures is to save a life, organ or limb; they are carried out within minutes of the decision to perform the procedure, and include, for example, ruptured aortic aneurysm, compartment syndrome and traumatic rupture of the spleen.

Urgent procedures are indicated in cases of conditions that could threaten a life, organ or limb; they are carried out within the hours that follow the decision to perform the procedure, and include, for example, peritonitis after perforated bowel, limb ischaemia and compound fracture.

Expedited procedures are for patients who are stable, but require a procedure for a condition that does not immediately threaten a life, organ or limb; they are carried out within the days that follow the decision to perform the procedure, and include, for example, retinal detachment and tumour obstruction syndrome.

These invasive procedures involve diverse techniques, including surgery, but also punctures, biopsies, endoscopies, endovascular procedures, etc. The vascular breach generated by these procedures has very different consequences for bleeding risk depending on the situation. The main question is to determine the non-elective invasive procedures for which an increased bleeding risk linked to APT will significantly worsen the clinical prognosis. The next question is to determine if the bleeding risk can be reduced by a specific treatment, including APA neutralization or the potential postponing of the procedure. Finally, a balance between the benefit of this specific treatment and its associated risk must be found.

Bleeding risk induced by APT

The bleeding risk induced by APAs, as monotherapy or DAPT, has been evaluated for various non-elective invasive procedures in a broad yet incomplete manner. Several points should be noted.

Most procedures can be performed on patients on aspirin as monotherapy (generally doses of ≤ 300 mg/day), which does not significantly increase the periprocedural bleeding risk [89—91]. Various evaluations or classifications are available. The procedures that can be performed on patients on aspirin include cholecystectomy, appendectomy, intestinal resections, hip fracture surgery, dislocation reductions, pleural drainage, etc. [92,93].

As for clopidogrel as monotherapy, there are no data showing an excess bleeding risk with clopidogrel versus aspirin. In a non-surgical setting, the CAPRIE trial compared the two APAs as monotherapies in 19,185 patients presenting recent ischaemic stroke, myocardial infarction

or symptomatic peripheral arterial disease [94]. Severe bleeding complications were similar with clopidogrel and aspirin (1.38% vs. 1.55%). However, digestive bleeding was less frequent with clopidogrel (1.99% vs. 2.66%). Only one randomized trial in scheduled surgery has compared the pursuit of clopidogrel to its discontinuation before 43 general abdominal surgery procedures (hernioplasty, cholecystectomy) [95]. No cases of bleeding requiring transfusion or reoperation were reported. A meta-analysis of 11 studies comparing clopidogrel with controls before surgery (397 clopidogrel-treated patients) concluded that clopidogrel did not increase reoperations resulting from bleeding (relative risk 1.84, 95% confidence interval 0.87 to 3.87; $P = 0.11$) [96]. Few data are available for non-elective procedures. For hip fracture, a meta-analysis of 14 case-control studies did not show a significant increase in transfusions in clopidogrel-treated patients [97]. Moreover, in a study of patients treated with clopidogrel and operated on for hip fracture, while transfusions were more numerous when the patients were operated on within 48 hours of admission rather than after 5 days, complications and mortality at 3 months were reduced [98]. In a small series of renal transplantations, the patients treated with clopidogrel or ticlopidine did not present major bleeding complications compared with those not treated with APAs [99]. Overall, the data suggest managing patients on clopidogrel as monotherapy in the same manner as those treated with aspirin as monotherapy — and, in particular, operating without delay in cases of hip fracture.

DAPT increases bleeding risk and transfusion exposure in non-elective invasive procedures [96]. However, the increase in bleeding risk does not always appear to be clinically significant in procedures with moderate bleeding risk. For example, DAPT with aspirin-clopidogrel during laparoscopic appendectomy was associated with neither an increase in blood loss nor more frequent transfusion requirement compared with no APAs in matched patients [100]. On the contrary, an increase in bleeding risk is clinically significant in major surgery. Thus, in a series of 171 acute aortic dissections, bleeding was significantly more pronounced in patients receiving DAPT compared with those on aspirin alone [101]. Moreover, DAPT with ticagrelor increased intraoperative bleeding compared with DAPT with clopidogrel, underscoring that the increase in bleeding risk depends on the type of APA. However, in that series, while APAs increased transfusion requirements, they did not increase mortality. Finally, while the procedure-associated bleeding risk is increased by DAPT, it presents significant interindividual variability. Thus, not all of the patients on DAPT will require transfusion. Such variability suggests evaluating intraoperative bleeding and adapting treatment according to the intensity of bleeding.

For invasive procedures that cannot be performed in patients on APT, the optimal duration of antiplatelet discontinuation to reduce the excess bleeding risk associated with APAs can be taken into account when possible (essentially for expedited procedures) [19]. It should be noted that recovery that is only partial (threshold not reached) would probably be associated with a reduction in bleeding risk. However, for different reasons, recovery in the first 24 hours is negligible (active compound still in the circulation; effect on the most mature megakaryocytes for APAs with irreversible action — therefore, the first platelets released by the hematopoietic bone marrow into the circulation are inhibited).

Does neutralization of APAs improve patient prognosis?

There have been few evaluations of the clinical benefit of platelet transfusion in the context of non-elective invasive procedures. The available data essentially concern neurosurgery. The most rigorous demonstration of the value of platelet transfusion (but with a very particular product, i.e. frozen platelets, which are not commonly used in Europe) comes from a Chinese randomized trial that included 366 patients treated with aspirin and considered as responders to the treatment, who required emergency craniotomy for haematoma removal [43]. Platelet transfusion reduced postoperative complications, disability and mortality compared with patients who were not transfused. These data have led various international guidelines to recommend platelet transfusion for patients on APT who present intracranial haemorrhage that requires neurosurgery [76,87].

A retrospective analysis of a cohort of 171 patients aged > 65 years undergoing emergency neurosurgery for traumatic intracranial haemorrhage reported that the patients on aspirin had a prognosis that was similar to that of patients not on APT, but had more platelet transfusions [102]. Above all, among the patients on aspirin, those who had platelet transfusion ($n = 38$, 44%) had perioperative bleeding and hospital mortality rates that were similar to those in patients who had not been transfused. However, treatment was heterogeneous, the response to aspirin was not evaluated preoperatively and the analysis was retrospective—limiting the significance of the results.

The results of standardized treatment with preoperative platelet transfusion (two platelet concentrates from a German transfusion centre for a little over 4×10^{11} platelets) in 72 consecutive patients on APT (DAPT, $n = 14$; aspirin, $n = 53$; clopidogrel alone, $n = 5$) presenting intracranial haemorrhage requiring decompression neurosurgery have been reported [103]. Recurrence of bleeding was observed in 26% of the patients, and clopidogrel was one of the risk factors, suggesting that the dose of transfused platelets was insufficient to neutralize clopidogrel.

Very few data have been published for general surgery. The same team reported its experience with standardized treatment of patients on DAPT requiring non-elective surgery with bleeding risk [104]. The aim was to reduce the perioperative bleeding risk over a short period in order to avoid increasing the thrombotic risk for a longer period in patients at high thrombotic risk. The protocol combined postponing the procedure for 12 to 24 hours after the last intake of APA when possible, transfusion of two PCs ($2.8 \pm 0.6 \times 10^{11}$ platelets per concentrate) 1 to 2 hours before surgery, and resumption of aspirin 6 to 9 hours and clopidogrel 24 to 48 hours after surgery. Fourteen patients were included. Only one patient developed prolonged bleeding after renal excision, without the need for further transfusion. This management strategy appears to be attractive, but the very small cohort and the absence of a control group limit its generalization.

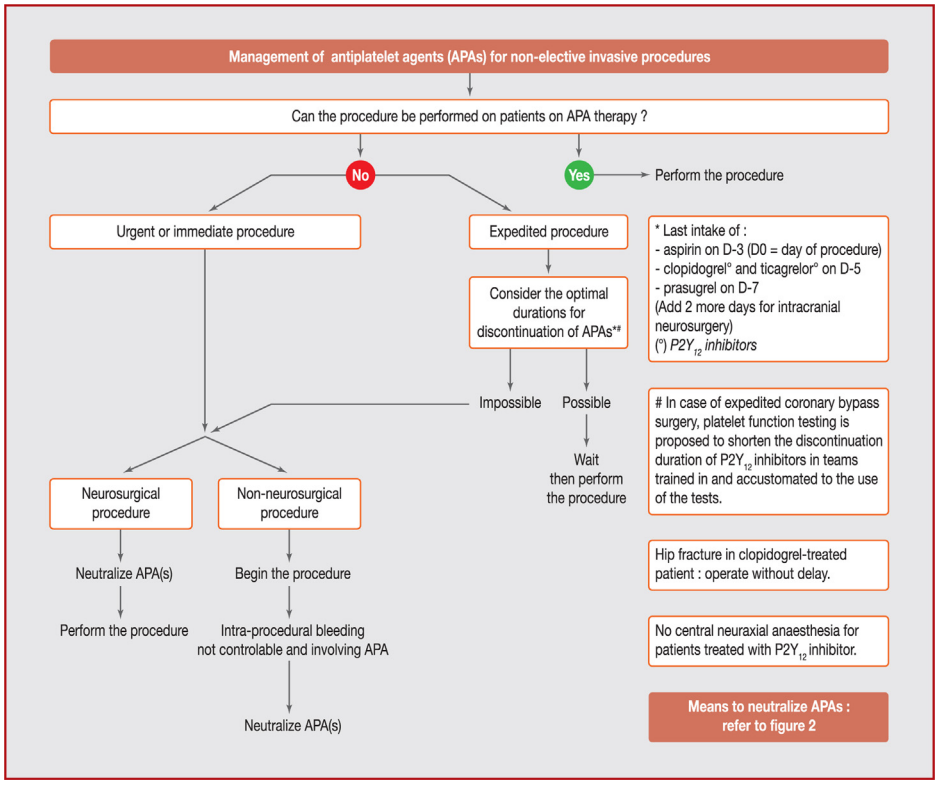


Figure 1. Management of antiplatelet agents (APAs) for non-elective invasive procedures.

There are no clinical studies in the literature confirming the (very probable) ineffectiveness of platelet transfusion in reducing the risk of haemorrhage in patients on ticagrelor.

Does neutralization of APAs induce thrombotic risk?

There is a risk of thrombotic events during the periprocedural period. Invasive procedures, irrespective of the continuation or neutralization of APAs, can induce a proinflammatory and procoagulant state that favours thrombotic phenomena. An increased risk of major cardiac events has been shown after non-elective invasive procedures [105]. Intuitively, this risk is the greater when the basal thrombotic risk of the patient is high, irrespective of the emergency situation, which includes, in particular, the first month after stent placement.

There have been few evaluations of the thrombotic risk of platelet transfusion. The transfusion of 72 consecutive patients on APT who presented intracranial haemorrhage requiring decompression neurosurgery was accompanied by no acute coronary syndrome [103]. In a cohort of 14 patients on DAPT for coronary stent, platelet transfusion before surgery did not induce stent thrombosis [104]. One patient developed acute coronary syndrome 4 days after surgery, although DAPT had been resumed. Three cases of stent thrombosis occurring 6 to 18 hours after platelet transfusion have been reported [106]: transfusion had been performed within 10 days after stent placement for acute coronary syndrome — in two cases to control bleeding for haemorrhages, and in the third case before surgery.

Management of APAs for non-elective invasive procedures: proposals (Fig. 1)

It is proposed to separate non-elective invasive procedures into immediate procedures to be carried out within minutes of the decision to perform the procedure (e.g. ruptured aortic aneurysm, compartment syndrome, etc.), urgent procedures to be carried out within the hours that follow the decision to perform the procedure (e.g. peritonitis, limb ischaemia, etc.) and expedited procedures to be carried out within the days that follow the decision to perform the procedure (e.g. retinal detachment, tumour obstruction syndrome, etc.) (strong agreement).

For invasive procedures that cannot be performed on patients on APT, it is proposed that the optimal durations for discontinuation of APAs to reduce the excess bleeding risk linked to APAs be considered whenever it is possible (essentially expedited procedures). It is therefore proposed to discontinue them as follows (with day 0 corresponding to the day of the procedure): last aspirin intake at day−3; last intake of clopidogrel and ticagrelor at day −5; last intake of prasugrel at day −7 (with the addition of two days for intracranial surgery, regardless of the APA) (strong agreement).

When it is impossible to respect these durations of discontinuation, the following proposals have been made. In patients on aspirin or clopidogrel as monotherapy: to begin non-neurosurgical non-elective invasive procedures without neutralization (strong agreement); to neutralize APT before urgent or immediate intracranial surgery (strong agreement). In patients on DAPT: to begin non-neurosurgical

non-elective invasive procedures without neutralization. If intraprocedural bleeding is not controllable by the senior surgeon and is attributable to APT, it is proposed that it be neutralized (strong agreement); to neutralize APT before urgent or immediate intracranial surgery (strong agreement); to perform expedited procedures more than 24 hours after the last intake of prasugrel or ticagrelor (strong agreement).

In patients treated with $P2Y_{12}$ inhibitor as monotherapy or combined with aspirin, it is recommended to not perform central neuraxial anaesthesia (spinal, epidural) (strong agreement).

Management of bleeding associated with APAs

Bleeding complications associated with APAs form a heterogeneous group with variable characteristics: location and intensity of bleeding, type of APT, date of last intake, patient thrombotic risk, etc.

In all cases, aetiological treatment of bleeding is essential, including haemostatic procedures, i.e. all mechanical means to control bleeding (surgery, endoscopy, embolization, tamponade, etc.), combined with symptomatic treatment of haemorrhage, including vascular filling, vasopressors, red blood cell transfusion, measures taken to fight hypothermia and early administration of tranexamic acid. This antifibrinolytic agent, which is inexpensive and safe, is recommended in cases of severe bleeding [7]. Assessed in large trials in traumatology or in cardiac surgery (for APA-treated patients), tranexamic acid was not associated with an increased thrombotic risk [107,108].

However, the occurrence of haemorrhage in APA-treated patients is a thrombotic risk factor. This excess risk of major cardiac events or myocardial infarction has been reported for perioperative patients [109], stented or not [110].

Four types of haemorrhage can be identified: intracranial haemorrhages, haemorrhagic shock, other severe haemorrhages and non-severe haemorrhages.

Intracranial haemorrhages

Intracranial haemorrhages occur in 10 to 30% of cases in patients on long-term APT [111]. APAs worsen the prognosis of intracranial haemorrhages. The mortality of patients on DAPT is superior to that of those treated with aspirin as monotherapy [112], which is also superior to that of untreated patients [113]. Clopidogrel is also an independent risk factor for mortality [113]. Early transfusion of platelets has been proposed, based on the hypothesis that neutralization of APAs will reduce both risk and volume of haematoma expansion, and thereby improve prognosis. In an observational study of patients presenting intracranial haemorrhage during treatment with aspirin confirmed by platelet function testing, early platelet transfusion within 12 hours of symptom onset was associated with less haematoma expansion and more limited disability at 3 months, compared with late platelet transfusion after the 12th hour [114]. A meta-analysis of studies evaluating platelet transfusion in patients on APT concluded that transfusion reduced mortality [115]. However, the authors underscored the limits of this work that relied on three observational studies.

The benefit of platelet transfusion has been cast in doubt by the PATCH trial [116]: in 190 patients on aspirin as monotherapy and presenting supratentorial intracerebral haemorrhage, with Glasgow Coma Scores ≥ 8 on admission and not requiring emergency neurosurgery, platelet transfusion induced an increase in mortality and dependence at 3 months compared with the control group. These results have called transfusion into question in this specific population. Likewise, negative results were obtained by analysis of a retrospective cohort of 97 patients on APT and presenting non-traumatic intracerebral haemorrhage, with 39 of the patients having received platelet transfusions [117]. In the unmatched cohort, the transfused patients had a higher risk of recourse to surgery, disability and death. After matching with a prognostic intracerebral haemorrhage score, transfusion was not a significant predictor for any poor outcome, but was not associated with any improvement.

No study has assessed the value of transfusion in patients presenting intracerebral haemorrhage with altered consciousness or in cases of treatment by $P2Y_{12}$ receptor inhibitors. In all such cases, APT must be discontinued.

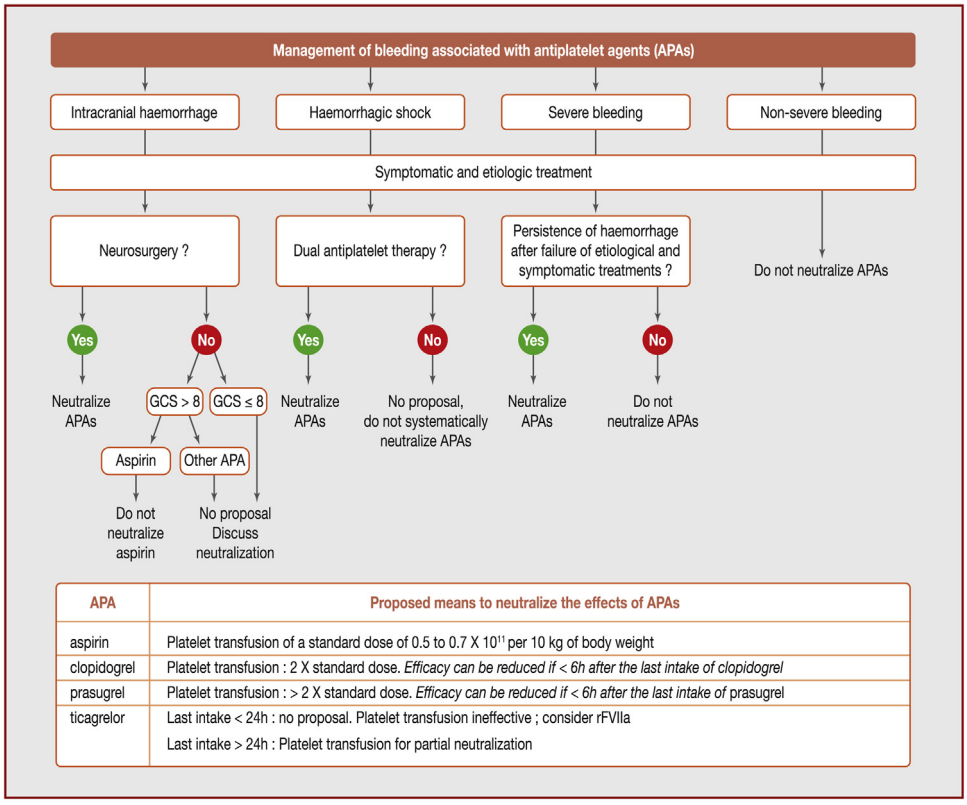
Haemorrhagic shock

We usually consider that APAs, in particular DAPT and the new $P2Y_{12}$ inhibitors, increase bleeding, and that by neutralizing APAs, platelet transfusion enables a return to the usual situation—that of haemorrhagic shock treatment in a patient not on an APA. However, the ability of platelet transfusion to neutralize APAs in this situation has not been evaluated. Nevertheless, in patients not on APT, early platelet transfusion is part of the recommended haemorrhagic shock treatment, particularly in protocols based on high ratios [87]. It would therefore appear to be reasonable to neutralize APT, especially DAPT.

Other severe haemorrhages

Other severe haemorrhages correspond to the definition proposed in the HAS 2008 recommendations concerning haemorrhages while on anticoagulation with a vitamin K antagonist (excluding intracranial haemorrhage and haemorrhagic shock): ''severe, or potentially severe bleeding is defined by the presence of at least one of the following criteria: externalized haemorrhage that is not controllable by the usual means; haemodynamic instability defined by systolic blood pressure < 90 mmHg or 40 mmHg lower than usual or mean arterial pressure < 65 mmHg or signs of shock; the need for an urgent haemostatic procedure (surgery, interventional radiology, endoscopy); the need for red blood cell transfusion; location threatening the vital or functional prognosis (e.g. intracranial or intraspinal haemorrhage, intraocular or retroocular haemorrhage, haemothorax, haemoretroperitoneum, haemopericardium, deep muscular haematoma or compartment syndrome, acute gastrointestinal bleeding or haemarthrosis).''.

In these situations, the value of APA neutralization is open to debate as, on the one hand, general haemostatic measures can be enough to control the haemorrhage and, on the other hand, there persists uncertainty as to the efficacy of



APA	Proposed means to neutralize the effects of APAs
aspirin	Platelet transfusion of a standard dose of 0.5 to 0.7 X 10^{11} per 10 kg of body weight
clopidogrel	Platelet transfusion : 2 X standard dose. *Efficacy can be reduced if < 6h after the last intake of clopidogrel*
prasugrel	Platelet transfusion : > 2 X standard dose. *Efficacy can be reduced if < 6h after the last intake of* prasugrel
ticagrelor	Last intake < 24h : no proposal. Platelet transfusion ineffective ; consider rFVIIa Last intake > 24h : Platelet transfusion for partial neutralization

Figure 2. Management of bleeding associated with antiplatelet agents (APAs). GCS: Glasgow Coma Scale.

transfusion. In cases of gastrointestinal bleeding (the most frequent location for haemorrhage associated with APAs), while it appears to be established that APAs favour the recurrence of bleeding [118], the benefit of platelet transfusion has not been well evaluated. The rare available data, essentially retrospective, did not demonstrate a benefit of transfusion in cases of gastrointestinal bleeding, but there were major methodological limits [119,120]. Guidelines propose to transfuse platelets to help stop bleeding and to prevent its recurrence, but platelet transfusion should probably only be performed in case of persistent haemorrhage after initial attempts to stop it [121].

Non-severe haemorrhages

Non-severe haemorrhages are the most frequent, and only require symptomatic treatment without neutralizing or discontinuing APT. Management of non-severe haemorrhages also includes systematic re-evaluation of the indication for APT.

Management of bleeding associated with APAs: proposals (Fig. 2)

The benefit/risk ratio of APT neutralization must consider the type of haemorrhage, the mechanical means available to manage it, the features of the APT, including the type of APA and the time of the last intake of APA, and patient thrombotic risk.

In case of intracranial haemorrhage requiring urgent neurosurgery, preoperative neutralization of APT is proposed. In case of intracranial haemorrhage that does not require urgent neurosurgery, it is proposed to not transfuse platelets if the patient is on aspirin as monotherapy and presents a Glasgow Coma Score ≥ 8 on admission. In other cases, it is not possible to favour or not neutralization of APT. It is proposed to discontinue APT.

In case of haemorrhagic shock in patients on DAPT, neutralization is proposed.

For other severe haemorrhages, neutralization of APT is proposed in case of persistence of haemorrhage after failure of aetiological and symptomatic treatments.

For non-severe haemorrhages, symptomatic treatment is proposed, without neutralization of APT.

Disclosure of interest

JP Collet has received research honorarium for talks or proctoring from AstraZeneca, Bayer, Bristol-Myers Squibb, Sanofi-Aventis, WebMD, Lead-Up, Medtronic and research grants from Fédération Française de Cardiologie, BMS and Pfizer.M Mazighi has received honorarium from Acticor. The other authors declare that they have no competing interest.

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