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GUIDELINES

Surgery and invasive procedures in patients on long-term treatment with direct oral anticoagulants: Thrombin or factor-Xa inhibitors. Recommendations of the Working Group on perioperative haemostasis and the French Study Group on thrombosis and haemostasis

Chirurgies et actes invasifs chez les patients traités au long cours par un anticoagulant oral anti-IIa ou anti-Xa direct. Recommandations du Groupe d'intérêt en hémostase périopératoire (GIHP) et du Groupe d'études sur l'hémostase et la thrombose (GEHT)

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Summary Direct oral anticoagulants (DOAs) – inhibitors of thrombin or factor-Xa – are expected to replace vitamin K antagonists in most of their indications. Patients receiving long-term treatment with DOAs are likely to be exposed to elective or emergency surgery or invasive procedures. Owing to the present lack of experience in such conditions, we cannot make recommendations, but only propose perioperative management for optimal safety regarding the risk of bleeding and thrombosis. DOAs may increase surgical bleeding, they have no validated antagonists, they cannot be monitored by simple standardized laboratory assays and their pharmacokinetics vary significantly between patients. Although DOAs differ in many respects, the proposals in the perioperative setting need not be specific to each. For procedures with low haemorrhagic risk, a therapeutic window of 48 hours (last administration 24 hours before surgery, restart 24 hours after) is proposed. For procedures with medium or high haemorrhagic risk, we suggest stopping DOAs 5 days before surgery to ensure complete elimination in all patients. Treatment should be resumed only when the risk of bleeding has been controlled. In patients at high thrombotic risk (e.g. those in atrial fibrillation with a history of stroke), bridging with heparin (low molecular-weight heparin, or unfractionated heparin, if the former is contraindicated) is proposed. In an emergency, the procedure should be postponed for as long as possible (minimum 1–2 half-lives) and non-specific antihaemorrhagic agents, such as recombinant human activated factor VIIa or prothrombin complex concentrates should not be given for prophylactic reversal due to their uncertain benefit-risk.

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MOTS CLÉS

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Résumé Les anticoagulants oraux directs (AOD), anti-IIa ou anti-Xa, sont destinés à remplacer les antagonistes de la vitamine K pour une majorité de leurs indications. Les patients traités par ces médicaments pourront bénéficier d'une chirurgie ou d'un acte invasif programmé ou urgent. L'absence d'expérience de cette situation ne permet pas d'émettre des recommandations, mais seulement des propositions pour la meilleure gestion possible vis-à-vis du double risque hémorragique et thrombotique. Les AOD sont à risque hémorragique en cas d'acte invasif, n'ont aucun agent de réversion validé, ne sont pas facilement mesurés par les tests de laboratoire et leur variabilité individuelle est importante. Bien qu'il existe des différences entre les AOD, elles n'imposent pas une prise en charge périopératoire particulière à chacun. Pour les actes programmés à risque hémorragique faible, il est proposé de réaliser une fenêtre thérapeutique de 48 h encadrant l'acte. Pour ceux à risque hémorragique modéré ou élevé, il est proposé d'interrompre le traitement à j5 pour assurer l'élimination complète du médicament chez tous les patients et de ne le reprendre que lorsque le risque hémorragique est contrôlé. Un relais par une héparine est justifié, si le risque thrombotique lié à l'indication initiale du traitement par l'AOD est élevé (patients en fibrillation atriale ayant un antécédent cardio-embolique). Dans les situations non programmées, l'acte invasif doit être retardé au maximum (1 à 2 demi-vies d'élimination du médicament si possible) et les agents hémostatiques non spécifiques (facteur VIIa recombinant, concentrés de complexe prothrombinique) ne doivent pas être utilisés à titre prophylactique.

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Background

Direct oral anticoagulants (DOAs), inhibitors of thrombin or factor-Xa (and potentially inhibitors of factor IXa), are expected to replace vitamin K antagonists (VKAs) in the majority of their current indications, such as the long-term treatment and prevention of venous thromboembolism

Abbreviations: AF, Atrial fibrillation; aPTT, Activated partial thromboplastin time; DOA, Direct oral anticoagulant; GEHT, Groupe d'études sur l'hémostase et la thrombose; GIHP, Groupe d'intérêt en hémostase périopératoire; HAS, Haute Autorité de santé; INR, International normalized ratio; LMWH, Low molecular-weight heparin; PCC, Prothrombin complex concentrate; PT, Prothrombin time; UFH, Unfractionated heparin; VKA, Vitamin K antagonist; VTE, Venous thromboembolism.

(VTE) and the prevention of thromboembolic events in patients with atrial fibrillation (AF). The target population for these different indications, once they are registered, could represent 1% of the population. These patients will be treated with a dose designated in the following text as the "curative dose", summarized in [Table 1](#). This dose corresponds to a level of treatment defined by an international normalized ratio (INR) in the range 2–3 using the VKA treatment that served as the comparator in clinical trials.

A significant proportion of patients treated with these drugs will inevitably be exposed to various critical situations: accidental or voluntary overdose; spontaneous bleeding; trauma; or the need for scheduled or emergency surgery or invasive procedures. As part of a process of "risk management" and in anticipation of marketing authorization, which may be granted in the months or years

Table 1 Principal pharmacokinetic variables for direct oral anticoagulants in phase III clinical trials for patients with atrial fibrillation (ongoing, terminated and/or published).

Target	Dose (mg)	T _{max} (hours)	Elimination route and metabolism	Elimination t _{1/2} (hours) [*]	Dialysable
Dabigatran (Pradaxa®)	110/150 bid	2	Faecal 20%; renal 80%	14–17	Yes
Rivaroxaban (Xarelto®)	20 od	2–4	Faecal 65%; renal 33%	7–13	No
Apixaban (Eliquis®)	5/2.5 bid	3–4	Faecal 75%; renal 25%	8–15	No
Edoxaban	30/60 od	1–2	Mainly renal	8–10	?

bid: twice daily; od: once daily.

* The intervals shown are not applicable to the entire patient population (see third section of Rationale).

to come for the various DOAs for the indications listed above, consultations were conducted within the Working Group on Perioperative Haemostasis (Groupe d'intérêt en hémostase périopératoire [GIHP]) and the French Study Group on Thrombosis and Haemostasis (Groupe d'études sur l'hémostase et la thrombose [GEHT]) concerning the perioperative management of patients on these new treatments. These proposals do not concern patients receiving DOAs for the prevention of VTE following major orthopaedic surgery, nor those who will receive them for other indications in the prevention of VTE currently covered by low molecular-weight heparins (LMWHs), which may represent a simple alternative that is relatively easy to control in at-risk situations. The group declined to issue proposals for the management of other critical situations (in particular, acute bleeding) pending the results of ongoing preclinical and clinical studies. The method used to develop these proposals was as follows. A first version based on the recommendations of the French Health Authority (Haute Autorité de santé [HAS]) for the perioperative management of patients treated with VKAs [1] (www.has-sante.fr) was adapted for DOAs using the published pharmacological data collected mainly during the phase I and II studies of these drugs. Some of these are included in the "Rationale" section below. This text was then submitted for several rounds of critical analysis by the members of GIHP and the pharmacology group of the GEHT, until a consensus was reached.

Rationale

Treatment with a curative dose of a DOA is associated with a risk of bleeding DOAs were developed to be used without laboratory controls and without the need for dose adjustment, which could give them an important advantage in terms of convenience over VKAs. However, the incidence of spontaneous bleeding described as "major" during the trials was still significant compared with VKAs [2–5] and remains, even at low doses, higher than that of placebo [6]. Although the therapeutic range is wider and the stability of the anticoagulant effect better than that of VKAs, the risk of bleeding at the recommended dose should be taken into consideration in the event of surgery or invasive procedures.

Direct oral anticoagulants (DOAs) have no effective antidote

Unlike VKAs, which can be antagonized by vitamin K and by prothrombin complex concentrates (PCCs) that provide the vitamin K dependent factors II, VII, IX and X, the new DOAs have no specific antidote. An antagonist that acts as a decoy with regard to factor-Xa (recombinant non-carboxylated factor-Xa without clotting activity) [7] is being tested ex vivo [8]. This strategy is not applicable to inhibitors of thrombin, as thrombin is not γ -carboxylated, but other approaches can be imagined. For example, a humanized monoclonal antibody specific to dabigatran was recently proposed as a specific antagonist [9]. Even if their clinical efficacy can be demonstrated, these agents will not be marketed for several years. Thus, the currently

available non-specific reversing agents potentially include: non-activated (Kanokad[®], Octaplex[®]) or activated (FEIBA[®]) PCCs and activated recombinant human factor VIIa (r-FVIIa, NovoSeven[®]). These were proposed on the basis of an extrapolation of experimental [10–14] and clinical [15] data on the reversal of fondaparinux or idraparinux (parenteral antithrombin-dependent inhibitors of factor-Xa) or melagatran (the first direct oral thrombin inhibitor, now withdrawn from the market). However, these data are fragmentary. The effectiveness of these drugs is controversial and their safety in terms of thrombotic risk in the target population has not been established. The arterial risk of r-FVIIa [16] and, potentially, that of the other antagonists that have not been studied as thoroughly, is a concern among vascular and often elderly patients. A venous risk has not been shown in clinical trials, but these excluded patients with a history of VTE, for whom a DOA could be prescribed. Finally, the modalities of these treatments in this indication (dose, frequency of administration, etc.) are not known. In practice, the safety of a scheduled surgical or invasive procedure is based primarily on the natural clearance of the anticoagulant after preoperative suspension of treatment. PCCs, r-FVIIa and possibly, in the case of failure of these, plasma purification techniques (dialysis or haemofiltration for DOAs such as dabigatran that bind only weakly to plasma proteins and plasmapheresis for other DOAs) could, in exceptional circumstances, provide an emergency solution when faced with refractory severe bleeding.

The interindividual pharmacokinetic variability of direct oral anticoagulants (DOAs) is large

The four drugs that are most advanced in their clinical development and regulatory proceedings (dabigatran, rivaroxaban, apixaban and edoxaban) differ in their rate and extent of digestive adsorption and in the mechanisms and rate of elimination, predominantly renal or hepatobiliary. The values reported in Table 1 for patients are similar to those reported for healthy volunteers [17]. As the blood concentration of the drug decreases exponentially beyond T_{max} , it is expected that at the suspension of treatment, about 10% of the value of C_{max} (theoretically 12.5%) is reached after 3 half-lives. It is interesting to recall that in a surgical context, the risk of bleeding appears to be more closely related to the value of C_{min} than to that of C_{max} [18]. However, the absorption, distribution, metabolism and elimination of these drugs are governed by many variables: liver and/or renal function, sex, weight, age, genetic polymorphisms of enzyme or efflux systems, drug-drug interference, etc. It follows that for a given patient, the residual concentration at a given time after halting treatment cannot be accurately calculated from the average values of the pharmacokinetics in the target population.

Thus, at steady state (i.e. 3 to 5 days on average after starting treatment), the C_{max} and C_{min} of dabigatran at a dose of 150 mg twice daily had coefficients of variation of about 70–80% in the BISTRO I study [19] and a high dispersion of C_{min} in the PETRO study [20]. Similarly, the C_{min} and C_{max} following 20 mg rivaroxaban once daily in phase II trials on hip replacement surgery [21] or 30/60 mg edoxaban in

patients with AF [18], were subject to significant variability. Finally, in daily clinical practice, for the doses approved in orthopaedic surgery, the equilibrium C_{max} measured beyond the fifth day is assigned coefficients of variation of the order of 81% and 67% for dabigatran and rivaroxaban, respectively [22].

Direct oral anticoagulants (DOAs) cannot be monitored by a simple standardized laboratory test, accessible to all non-specialized laboratories

At pharmacological doses, these drugs have an effect on routine coagulation assays (prothrombin time [PT], activated partial thromboplastin time [aPTT]). The sensitivity of these assays varies with the reagents used [13,23]. This is particularly the case for PT, whether its results are expressed as a PT ratio or an INR. The INR performed in routine practice is standardized to measure the effect of VKAs, but this is not so for DOAs [24]. Furthermore, for a given concentration, the results for PT and aPTT vary between individuals as a function of factors that have not yet been identified (G. Freyburger, personal communication). It is important to remember that the therapeutic ranges and safety thresholds of INR validated for VKAs do not apply to the new anticoagulants. For example, an INR of 1.5 corresponds to a low risk of surgical bleeding for a patient who has stopped VKA treatment. The same INR value corresponds, *in vitro*, to plasma overloaded with 0.2 $\mu\text{g}/\text{mL}$ of rivaroxaban [23,24], a concentration in the range of the C_{max} observed after oral administration of 20 mg. To avoid any confusion, the expression of results as an INR, even standardized, should not be done. To interpret the results of a coagulation test prescribed to monitor a patient's haemostasis (e.g. in the case of postoperative bleeding), the interference of DOAs with routine coagulation assays should be known. This has been reported in the course of preventive treatment with dabigatran and rivaroxaban in major orthopaedic surgery [22], but is not published for patients treated with a curative dose. Based on phase II trials, INR values varying widely around 1.5 (expression as an INR unsuitable for reasons indicated above) and aPTT patient/control ratios between 1.5 and 2 are expected at C_{max} at equilibrium. This interference should disappear after 2 half-lives, but as indicated below, the pharmacokinetic variability is large and the interference may persist beyond 24 hours. Finally, aPTT prolongation is characterized by a very pronounced plateau effect at high DOA concentrations *in vitro*, making this test unsuitable for the detection of overdoses.

Dedicated assays derived from thrombin clotting time or ecarin clotting time or factor-Xa inhibitor chromogenic testing will soon be available to measure DOA plasma concentrations using appropriate calibration. It is not clear, however, whether they will be available in the near future to non-specialized laboratories, which is a prerequisite if they are to be used in contexts of relative urgency.

The security objective that must be reached for DOAs in the context of surgery or an invasive procedure has not yet been defined.

The interpretation and use of laboratory test results, whatever they may be, implies that safety thresholds exist.

As yet, no preclinical or clinical data allow us to define a minimum plasma concentration below which the risk of bleeding during surgery is not different from that of a non-treated subject.

Proposals

As the future indications for treatment with DOAs are the same as those for VKAs and in the absence of perioperative experience with these new drugs, an adaptation of the recommendations published by the HAS for VKAs ([1] www.hassante.fr) is proposed. To avoid introducing additional complexity, the authors consider that the aspects that DOAs have in common are more important than those that differentiate them, as for LMWHs, which, although different from one another, are in practice regarded as a homogeneous class. Therefore, in the absence of information to the contrary, no distinction will be made in the proposals in terms of the drug used. In the future, the introduction of new DOAs, with pharmacokinetic profiles that may be significantly different from those presented in Table 1, could lead to drug-specific attitudes. The proposals differ depending on whether the situation is scheduled or is one of emergency. For scheduled situations, they rank the surgical or invasive procedures depending on the potential for bleeding and the thrombotic risk to which the patient would be exposed on interruption of anticoagulant therapy in the perioperative period.

Scheduled surgery or invasive procedures with low risk of bleeding

These are the procedures for which bleeding, if it occurs, will be of low abundance, non-critical in its location and/or easily controlled by simple mechanical haemostasis. These elements must be assessed according to the nature of the procedure, the type of anaesthesia, postoperative monitoring opportunities and patient-specific conditions, especially concomitant medications that might interfere with haemostasis [25]. It should be noted that the estimates of risk on which these recommendations are based are documented only for treatment with VKAs, with a low level of evidence (experts' opinion) and remain controversial for certain procedures. In the absence of a validated antagonist, the major component of risk assessment is the ability to mechanically control a possible bleed. In these patients, provided that a laboratory assessment of the absence of overdose is performed by measuring the INR, VKA treatment would not be interrupted. Owing to the lack of a validated antagonist, it is proposed to produce a short therapeutic window as follows: last administration of the DOA 24 hours before the procedure and restart 24 hours after it (Fig. 1A). Associated aspirin monotherapy does not change this highly conservative proposition.

Scheduled surgery or invasive procedures at moderate or high risk of bleeding

This includes all procedures for which the probability of clinically significant bleeding cannot be excluded or, a fortiori, any surgery that is usually haemorrhagic or for which the risk

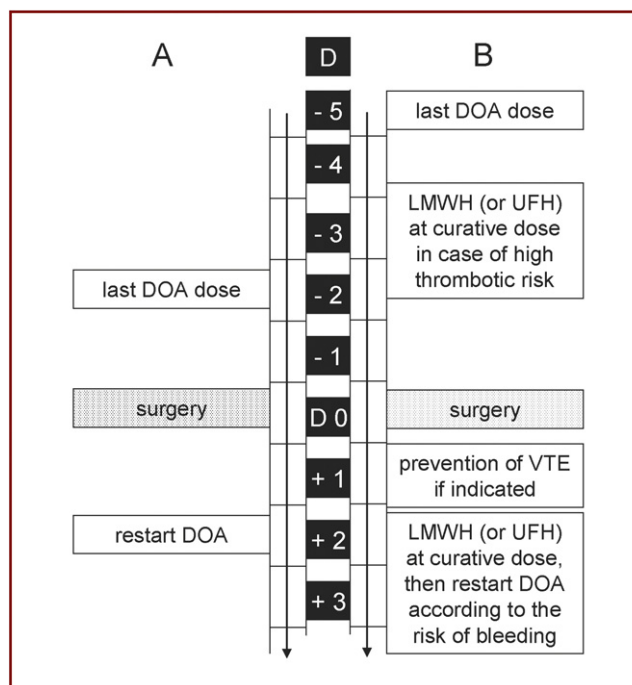


Figure 1. Example of a protocol for creating a direct oral anticoagulant therapeutic window for surgery or an invasive procedure with a low risk of bleeding (A) or a moderate or high risk of bleeding (B). In the case of bridging with a heparin (situation B), no overlap of the two anticoagulants is allowed, either preoperatively or postoperatively. Direct oral anticoagulant (DOA); low molecular-weight heparin (LMWH); unfractionated heparin (UFH); venous thromboembolism (VTE).

of bleeding would be unacceptable. In these patients, VKA treatment would be stopped early enough to perform the intervention in conditions of haemostatic safety based on preoperative monitoring of the INR. VKA treatment would be resumed postoperatively after checking the risk of bleeding. If necessary, the thrombotic risk during the VKA therapeutic window would be prevented by heparin (LMWH or unfractionated heparin [UFH]). In patients receiving a DOA, the management of thrombotic risk does not differ from that in patients who could have been on a VKA for the same indication. It is therefore necessary to set the duration of the therapeutic window and then to discuss how the risk of thrombosis, for which the long-term anticoagulant treatment with a DOA was prescribed, can be prevented during this interruption. An example of the proposed protocol is shown in Fig. 1B.

Duration of the therapeutic window

Discontinuation of treatment on day-5 (last administration 8:00 PM) for a procedure scheduled on day 0, is proposed empirically. Indeed, although using the database of average pharmacokinetic variables, it may be possible to propose 48 hours (~3 mean half-lives) as the duration of preoperative suspension of treatment suitable for the majority of patients, haemostatic safety is not guaranteed for all. Various covariates (liver and/or renal function, drug-drug interactions, genetic polymorphisms, etc.) may significantly extend the elimination half-life of the drug. Until there is proof to the contrary, in the absence of a validated

antagonist, the residual concentration must be close to 0 for safety of procedures with a high risk of bleeding. Thrombin time and anti-Xa assays configured and calibrated for measuring heparins are very sensitive to the effect of thrombin and direct oral factor-Xa inhibitors [13,23], respectively. Therefore, a thrombin time identical to the control or factor-Xa inhibitor activity less than 0.1 U/mL can, if necessary, be used to affirm that this goal has been achieved.

Restarting postoperative DOA treatment at a curative dose is determined by the possibility of oral administration and the risk of postoperative bleeding, either surgical or related to the anaesthetic technique. For the latter, the recommendations of the European Society of Anaesthesiology, applicable to the prophylaxis of VTE after surgery, have been recently updated [26]. The absence of an antagonist requires that the resumption of a curative dose is delayed until this risk has been controlled with certainty. The anticoagulant effect of DOAs is obtained within a few hours, unlike that for VKAs (Table 1). The recovery time is highly variable (a few hours to several days) depending on the nature of the procedure.

Management of thrombotic risk during the therapeutic window

During the therapeutic window, bridging with a heparin can be put in place or not, depending on the importance of the individual risk of thrombosis.

Patients at high risk of thrombosis

These are patients with a recent history (<3 months) of proximal venous thrombosis with or without pulmonary embolism, patients with recurrent idiopathic VTE and patients with AF at high risk because of a history of cardioembolic disease. For these patients, a therapeutic window of several days is risky. Bridging is imperative, using LMWH (or UFH if there is a contraindication to the former), administered at the curative dose as two subcutaneous injections per day, according to the modalities recommended for VKA bridging [1].

Treatment with heparin should be initiated 12 hours after the last dose of the DOA, if it is administered twice a day or 24 hours after the last dose of the DOA, if it is administered once a day. The treatment with heparin should be discontinued before surgery (last administration 24 and 12 hours before surgery for LMWH and subcutaneous UFH, respectively) and restarted after surgery when the risk of postoperative bleeding is considered to be under control. When the DOA can be resumed safely, the first oral dose should be administered 12 hours after the last subcutaneous administration of LMWH. Owing to the rapid action of DOAs (Table 1), they should never be given together with heparin, whatever the dose of the latter. Unlike for VKAs, there should be no overlap between treatment with heparin and a DOA, regardless of the dose.

Patients at moderate risk of thrombosis

Preoperative bridging with heparin may be considered as optional. However, the postoperative thrombotic risk may be increased by inflammation. If the DOA treatment cannot be resumed rapidly (e.g. due to the impossibility of administration by an oral route), a curative dose of heparin is advised, as soon as the bleeding risk is controlled.

Prevention of venous thromboembolism (VTE) after surgery

If the resumption of postoperative anticoagulant therapy at a curative dose (heparin or DOA) is delayed and prophylaxis of VTE after surgery is indicated, it should be performed conventionally using a heparin or by mechanical means if all types of anticoagulant are contraindicated. It should be recalled that, to date, none of the DOAs has received marketing approval as a prophylactic for postoperative VTE, with the exception of major orthopaedic surgery. As emphasized above, no overlap of heparin therapy and a DOA is allowed.

Emergency surgery or invasive procedures

The time of last dose must be known. If surgery is haemorrhagic, it should be delayed for as long as possible (at least 1 or 2 elimination half-lives of the drug or based on a sensitive laboratory assay [a normal thrombin time or absence of detectable activity for factor-Xa inhibitor for thrombin inhibitor and factor-Xa inhibitor drugs, respectively]); this is provided that the delay does not imply a loss of chance for the patient. At present, no other overall recommendation can be made.

The benefit–risk of non-specific antagonists (PCCs, r-FVIIa, etc.) should be evaluated on an individual basis. In the absence of bleeding, they cannot be recommended as preventive measures and are instead proposed for the rescue from bleeding that cannot be controlled by the usual means. To date, there is no published evidence in favour of r-FVIIa rather than a PCC (activated or not). A plasma clearance technique would probably be effective, but difficult to implement in this context. In all cases, neuraxial anaesthesia is strictly contraindicated [26].

Conclusion

The introduction of DOA treatment for patients receiving long-term anticoagulation therapy at a level equivalent to that of VKA treatment poses the problem of the perioperative management of these patients. However, this has never been well evaluated by preclinical studies or clinical trials in an unselected population. The proposals put forward here highlight the need for security regarding the risk of bleeding, without compromising the protection expected against the thrombotic risk; they are likely to evolve and become more clearly defined in the course of the practitioner's individual experience. It is important that clinical cases are published and any adverse events reported to the pharmacovigilance authorities.

Since the submission of this paper, the results of the Aristotle trial comparing apixaban with warfarin in patients with atrial fibrillation have been published [27]; the results were promising but do not fundamentally change the present proposals.

Disclosure of interest

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