

Abstract

In 2013, the GIHP published guidelines for the management of severe haemorrhages and emergency surgery. This update applies to patients treated with dabigatran, with a bleeding complication or undergoing an urgent invasive procedure. It includes how to handle the available specific antidote (idarucizumab), when to measure dabigatran plasmatic concentration and when to use non-specific measures in these situations. It also includes guidelines on how to perform regional anaesthesia and analgesia procedures.

Reference


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Guidelines


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1. Introduction

In 2013, the GIHP published guidelines for the management of severe haemorrhages and emergency surgery [1,2]. These guidelines took into account:

- the clinical use of the only two direct oral anticoagulants (DOAC) available at that time (rivaroxaban and dabigatran);
- very limited access to biological tests to measure DOAC concentrations;
- incomplete knowledge of the haemorrhagic complications of these medications;
- little experience in practical strategies to neutralise their anticoagulant effect and;
- the absence of a specific antidote.

Since 2013, the situation has evolved on each of these points, but without definitive answers to all of the questions:

- three DOACs are currently available in France: dabigatran, rivaroxaban and apixaban;
- specific biological tests measuring the concentrations of DOACs are now quite widespread. However, their immediate implementation is not possible in every Emergency Room. Conventional haemostasis tests, i.e. activated partial thromboplastin time (aPTT) and prothrombin time (PT) have sensitivities that are generally low and variable depending on the DOAC and the reagent used, thereby precluding their standardisation and use in this context [3,4]. On the contrary, thrombin time (TT) and anti-Xa assay (anti-Xa ng/mL) are very sensitive to dabigatran and xabans (direct oral anti-Xa) respectively. None of these tests can therefore be used reliably as a surrogate for concentration measurement [5];
- the epidemiology of DOAC haemorrhagic complications outside of clinical trials has been reported in various publications that have generally confirmed the results obtained in pivotal trials in terms of severity [6–8];
- the use of nonspecific haemostatic agents [activated or inactivated prothrombin complex concentrates (PCCs)] is widely evaluated in biological studies, in preclinical studies [9], but the efficacy and tolerance in patients treated with DOACs in critical situations (haemorrhage or urgent invasive procedures) have not been formally demonstrated;
- a specific dabigatran antidote (idarucizumab, Praxbind®), Boehringer–Ingelheim) has been recently approved and is now available. Its biological efficacy to neutralise the anticoagulant effect of dabigatran has been demonstrated, but its clinical efficacy and tolerance are only plausible on the basis of the intermediary results of a trial with a low-grade methodology [10,11] and the clinical experience of this medication is almost absent.

This evolution justifies the updating of GIHP guidelines [1,2], primarily for dabigatran (direct oral anti-Xa). This update includes access to the dabigatran antidote. An appendix will later be proposed with the introduction of an antidote for anti-Xa medications.

1.1. Available haemostatic agents

Three nonspecific haemostatic agents are available for cases of severe bleedings associated with DOACs [1,2,12]. These are inactivated (Prothrombin Complex Concentrates [PCC] 4 factors: Kanokad®, LFB; Octaplex®, Octapharma; Conﬁdex®, CSL Behring) or activated (Factor Eight Inhibitor Bypassing Activity or FEIBA®, Baxter) PCCs and recombinant factor VIIa (rFVIIa, NovoSeven®, NovoNordisk). Activated PCCs and rFVIIa are indicated for treatment of haemophiliacs who have developed inhibitors. Non-activated PCCs are used to compensate clotting factor deficiencies and are used for bleeding or urgent surgeries in patients on vitamin K antagonists (VKA).

The use of these haemostatic agents to reverse DOAC effect is off-label. Non-activated PCCs, rFVIIa [13,14], then FEIBA® (which associates activated and inactivated coagulation factors) were initially included in national and international guidelines [12]. Conversely, rFVIIa is currently no longer included in the guidelines owing to a very uncertain benefit/risk ratio.

The efficacy of these haemostatic agents has not been formally established. They have not been assessed in clinical trials and have only been evaluated in in vitro or ex vivo studies in healthy volunteers and in various animal models of bleeding. PCCs corrected the decrease of endogenous thrombin potential induced by dabigatran or rivaroxaban in a thrombin generation test [15].

A review of the literature [9] analysed 11 animal studies and two trials in healthy volunteers that evaluated DOAC reversal with these nonspecific haemostatic agents. The authors emphasised the large heterogeneity of the results and stressed the difficulty in their interpretation. Depending on the haemostatic agent tested and the DOAC, they observed the partial or complete correction of certain parameters of haemostasis tests whereas in the animals, the results on the reduction of bleeding were not consistent. Finally, the absence of correlation between correction of biological parameters of haemostasis and bleeding control makes it difficult to conclude on the efficacy of the haemostatic agent in case of major bleeding.
Non-specific haemostatic agents expose the patient to possible thrombotic risk that has not been evaluated in these specific situations. This risk depends on the nature of the agents (activated or non-activated) and on their posology. The rate of thrombotic complications associated with the administration of PCC (4-factor) to neutralise vitamin K antagonist (VKA) is moderate (1.8%) [16]. The occurrence of thrombotic complications is probably associated with the administration of high doses (> 50 U/kg) or the treatment of patients presenting severe hepatopathy [17]. However, the doses of PCC proposed to correct the anticoagulant effects of DOACs are generally superior (50 U/kg) to those used to antagonise VKA (25 U/kg) [16,17]. Conversely, thrombotic complications with FEIBA® have been reported in patients with acquired hemophilia at high doses (> 100 U/kg), corresponding to twice the recommended doses to correct the anticoagulant effects of DOAs (30 to 50 U/kg). rfVila, when used off label in non-anticoagulated patients, is associated with thrombotic complications, especially arterial and more frequently in elderly patients [18].

1.2. Dialysis

Dabigatran can be dialysed. However, the place of dialysis has not been clearly established in the management of haemorrhages and emergency invasive procedures. The availability of idarucizumab further reduces the potential place of this strategy [19].

1.3. Activated charcoal

Activated charcoal is proposed to limit the digestive absorption of dabigatran [20]. Currently, the use of activated charcoal is only mentioned in rare clinical cases of dabigatran overdose.

1.4. The antidote for dabigatran: idarucizumab

Idarucizumab (Praxbind®) is the specific antidote for dabigatran. It is a Fab fragment of humanised and purified murine monoclonal antibody, which presents structural similarities to thrombin. It specifically binds to dabigatran with a very strong affinity that is approximately 300 times greater than the affinity of dabigatran for thrombin and thus neutralises its anticoagulant effects [19,20]. Its initial elimination half-life is estimated at 45 minutes, mainly in unaltered form in urine. According to studies in healthy volunteers, idarucizumab is well tolerated and is not immunogenic after a single administration [21,22].

In pigs that have been administered dabigatran, the antidote reduced bleeding secondary to hepatic traumatism and reduced mortality [23]. In the RE-VERSE-AD study (prospective, open, non-randomised and non-controlled), idarucizumab was administered at a dose of 5 g to patients treated with dabigatran and presenting life-threatening haemorrhage (n = 301) or requiring emergency surgery (n = 202) [11]. Efficacy was judged on biological criteria, the maximum percentage of reversion of the anticoagulant effect of dabigatran, evaluated by diluted thrombin time (dTT) or ecarin clotting time (ECT), within four hours following the administration of idarucizumab. Median reversion was 100% (IC50 100–100) for dTT or ECT in both groups. At 90 days, thrombotic events had occurred in 6.3% and 7.4% and the mortality rate was 18.8% and 18.8%, in the life-threatening haemorrhage and requiring emergency surgery, respectively.

Nevertheless, these results raise several questions. The effect of idarucizumab can be transitory, especially in case of high concentrations of dabigatran to be neutralised: the concentrations of unbound dabigatran were superior to the detection threshold in 23% of the cases 24 hours after administration of the antidote, possibly following a redistribution of dabigatran from the extravascular to the intravascular compartment. This point can be critical when the dabigatran concentration is in a high range (plasma level > 95th percentile, > 600 ng/mL), requiring normalisation of haemostasis for several days. This situation is most often associated with a low clearance of the drug (renal failure and/or strong drug interaction). Moreover, more than 25% of the patients received the antidote while their initial unbound dabigatran concentration was below 50 ng/mL.

This observation puts into question patient selection for the antidote and opposes two strategies:

- prior measurement of the concentration of dabigatran and prescription of idarucizumab to those with a significant concentration and;
- prescription of idarucizumab without previous dabigatran level evaluation, knowing that a significant proportion of patients will be unnecessarily exposed to this expensive antidote and to possible side effects and delays the implementation of other haemostatic measures that could be more appropriate.

Finally, the RE-VERSE-AD study did not make it possible to conclude on the clinical efficacy of the antidote. Indeed, the only outcome was biological. There was no control group, the majority of the 39 invasive procedures had a low or intermediate risk of hemorrhage and 18 patients (20%) died, including five of fatal haemorrhage. Overall, the first available data from studies suggest that idarucizumab immediately corrects the coagulation parameters of patients treated with dabigatran. It is indicated for adult patients treated with dabigatran when rapid reversion of the anticoagulant effect is required for an emergency invasive procedure or in case of uncontrolled bleeding or a life-threatening situation.

The recommended dose of idarucizumab is 5 g (2 x 2.5 g/50 mL) without adjustment linked to age, the plasma concentration of dabigatran, renal or haepatic function. Contraindications and drug interactions have not been reported for this antidote. It can potentially cause the patient to develop antibodies, which would limit its repeated use.

According to the European Summary of Product Characteristics (SmPC): “In a subgroup of patients, the reappearance of plasma concentrations of unbound dabigatran and the concomitant lengthening of coagulation tests was observed up to 24 hours after the administration of idarucizumab”… “The administration of a second dose of 5 g [idarucizumab] can be proposed in the following cases: the resumption of a clinically relevant bleeding associated with a lengthening of coagulation time, or when new bleeding appears to be life-threatening associated with a prolongation of coagulation tests, or in patients requiring a second surgical procedure or an urgent procedure whereas the coagulation times are lengthened. The pertinent coagulation parameters are aPTT, dTT or ECT”.

In the absence of a precise clinical evaluation of the antidote and given the absence of a comparison between the antidote and alternatives (PCC), we empirically propose to neutralise the anticoagulant effect of dabigatran with the antidote or if the antidote is not available, with active or non-activated PCCs.

1.5. Specific tests

Specific tests to determine the circulating concentration of dabigatran in clinical practice rely on haemostatic techniques.

Measurement of dabigatran concentration relies on determination of itsanti-IIa activity, expressed in ng/mL, on the basis of a (chronometric or chromogenic)dTT, or on the use of a chromogenic test using ecarin activation.

1.6. Safe haemostatic thresholds

Specific tests were initially developed to determine concentrations in the range usually found in practice (50–400 ng/mL).
Their performance is insufficient for low concentrations < 30 ng/mL. Although dabigatran plasma level should not be assessed routinely, it may be of some help for the management of haemorrhages and emergency surgery. Indeed, measurement of the concentration of a medication is useful to evaluate the causality of bleeding or potential haemorrhagic risk linked to the anticoagulant. The threshold below which a bleeding is not caused by dabigatran is not precisely identified (as for other anticoagulants). It varies between 50 ng/mL (expected mean trough concentration after 2 elimination half-lives for normal renal function) and 30 ng/mL (expected mean trough concentration after 3 to 4 elimination half-lives).

1.7. Routine haemostasis assays and dabigatran

The effects of dabigatran on routine assays vary according to the concentration of the medication and the test used (Table 1).

Normal aPTT and PT are not indicators of a circulating concentration of the medication below this safe haemostatic threshold. On the other hand, given their great sensitivity, a normal TT excludes the presence of a significant level of dabigatran.

In the text that follows, each item in Figs. 1 and 2 is discussed.

2. Management of haemorrhages in patients treated with dabigatran

2.1. Bleeding threatening vital or functional prognosis that cannot be rapidly controlled by standard measures in patients treated with dabigatran

These are settings with very severe functional or life-threatening consequences. It is principally represented by spontaneous or traumatic intracranial haemorrhages, intraspinal or ocular haemorrhages. This list can be extended to bleeding whose severe functional or lethal consequences cannot be rapidly controlled by a haemostasis procedure. This includes haemorrhagic shock. These are situations where it is essential to eliminate the bleeding that is attributable to the anticoagulant (Fig. 1).

2.1.1. “Idarucizumab or if unavailable, PCC or FEIBA”

In this situation, if idarucizumab is available, it must be administered according to the SmPC. In all cases, a blood sample to measure the concentration must be taken as soon as possible. However, administration of idarucizumab must not be delayed until the results had been received. In case of neurological symptoms with suspected intracranial bleeding, a CT scan or MRI to confirm the diagnosis is essential before administration of idarucizumab. A new concentration measurement 12 to 18 hours after the administration of idarucizumab should be considered if needed (e.g. resumption of bleeding). A secondary increase in the concentration of dabigatran beyond 30 ng/mL will indicate a

Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Dabigatran</th>
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<tr>
<td>PT</td>
<td>±</td>
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<tr>
<td>aPTT</td>
<td>+</td>
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<tr>
<td>TT</td>
<td>+++</td>
</tr>
<tr>
<td>Anti-Xa</td>
<td>–</td>
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PT: prothrombin time; aPTT: activated partial thromboplastin time; TT: Thrombin time; Anti-Xa: Anti-Xa activity; +: test sensitive to DOA; –: little sensitivity of test to dabigatran.

Fig. 1. Haemorrhage in a patient treated with dabigatran.
Fig. 2. Urgent invasive procedure in a patient treated with dabigatran.

Fig. 3. Anaesthesia, analgesia and urgent invasive procedure in a patient treated with dabigatran.

*These blocks (superficial or deep) must be carried out under ultrasound guidance by an experienced operator. Perineural catheters should not compromise postoperative resumption of anticoagulants. The catheter must be withdrawn in optimal hemostatic conditions.

**Perimedullar anesthesia must be performed by an experienced operator. The use of an epidural catheter should not compromise postoperative resumption of anticoagulants. The catheter must be withdrawn in optimal hemostatic conditions.

***Non-activated or activated PCCs have not proven their ability to neutralize dabigatran. Their administration can therefore not be recommended to realize a regional anesthesia.

Conc: plasmatic concentration
second administration of idarucizumab (at a dose of 5 g) depending on the clinical evolution.

If idarucizumab is unavailable, administration of non-activated PCC (50 U/kg) or activated PCC (FEIBA® 30 to 50 U/kg) must be performed in an attempt to overcome the anticoagulant effect of dabigatran and possibly renewed once after eight hours.

No studies have confirmed the efficacy of the administration of procoagulant agents (PCC or activated PCC) in order to reduce the morbidity-mortality of haemorrhages in critical organs in patients treated (or not treated) by VKA or DOA. Nevertheless, there are indirect arguments from observational studies that suggest that the rapid recovery of normal haemostasis could contribute to the reduction in morbidity-mortality for VKAs [24]. Given the methodology, RE-VERSE-AD study could not demonstrate clinical efficacy of idarucizumab in these situations despite the neutralisation of dabigatran.

2.1.2. Intracranial haemorrhages

Intracranial haemorrhages include cerebral haemorrhages, acute or chronic subdural haematomas, extradural haematomas, subarachnoid haemorrhages, haemorrhagic contusions, of a spontaneous or traumatic nature. These different types of intracranial bleeding have very different mechanisms, risk factors and prognoses. Regarding intracerebral haemorrhages, it is accepted that the progression of a haematoma in the first hours of evolution is accelerated in the presence of haemostatic disorders [23,25,26]. It is also admitted that a spontaneous or traumatic intracranial hemorrhage that occurs in a patient treated with an anticoagulant agent will have more severe consequences than in the absence of anticoagulation [24,25].

Two questions can be raised for these patients:

- should “normal” haemostasis be systematically and rapidly re-established by neutralising the action of medications by antidotes, procoagulant agents, or blood products, and if so, in any situation?
- is there an interest in prescribing procoagulant agents to slow down the progression of bleeding, irrespective of the presence of haemostatic disorders?

2.1.2.1. Neutralisation. The question of the interest of rapidly normalising coagulation in these circumstances remains controversial. Regarding VKAs, a large study reported a significant reduction in the size of intracranial haematomas after administration of PCC compared with plasma, but without reducing mortality [27]. Numerous observational studies have reported a positive association between morbidity-mortality and reversion of VKAs or an INR close to 1 [23,27].

As for DOACs, several sub-studies of pivotal studies have shown that the prognosis of patients presenting intracranial hemorrhage was not worse in the group of patients treated with DOACs than in the groups treated with warfarin, whereas no specific anticoagulant reversion strategy was used in these studies [28–30]. It should be noted that the PATCH study reported a negative link between the transfusion of platelets and morbidity-mortality in patients presenting intracranial hemorrhage while treated with antiplatelet agents [31]. Despite these doubts about the efficacy of reversion strategies, all of the national or international guidelines “suggest” the administration of procoagulant agents: PCC and vitamin K for VKA, inactivated or activated PCC for DOAs, without distinction between DOACs [1,2,12,32].

In the RE-VERSE-AD study, among the 51 patients included for haemorrhages, 18 presented intracranial haemorrhages. Two of these patients died after worsening of the bleeding or new intracranial bleeding. It is not possible to discriminate among the data from this study what the concentrations of dabigatran were before and after the administration of idarucizumab [10]. However, it should be noted that 1) whatever the initial concentration of dabigatran (unbound dabigatran [ng/mL]), before the administration of idarucizumab, the concentration after idarucizumab was highly inferior to 30 ng/mL in 95% of the patients, from 10 to 30 minutes, to at least 12 hours after the administration of 5 g of idarucizumab, 2) the haemostasis tests, TT, aPTT, dTT and ECT, were normalised after a period of at least 12 hours after administration of idarucizumab in almost all of the patients.

In several patients, the initial concentration of dabigatran was very high. These patients may be exposed to a rapid new increase of dabigatran concentrations after administration of idarucizumab by redistribution of dabigatran from the extravascular compartments towards the vascular compartment. It is not possible to identify these patients without measuring plasma concentration of dabigatran. It is therefore recommended to measure the concentration of dabigatran before and 12 to 18 hours after the first administration of idarucizumab in order to determine if it is advisable to subsequently administer a new dose of 5 g of idarucizumab.

2.1.2.2. Procoagulant agents when haemostatic tests are normal or normalised. The question arises whether to administer the procoagulant agent to slow down the progression of intracranial bleeding. The studies that have tested the hypothesis of an improvement in the prognosis of these patients by the administration of rFVIIa [33,34] have responded negatively to this question. As for PCC, the benefit has not been evaluated and the data on safety are not favourable. Administration of non-activated or activated PCC may be associated with thrombotic events in a patient with thrombotic risk whose biological haemostasis is normal or normalised [16]. There is therefore no reason to administer non-activated or activated PCC in addition to idarucizumab except if idarucizumab is not available.

2.2. Severe haemorrhages

National guidelines for clinical practice regarding management of bleeding in patients treated with VKA defined severe haemorrhages as follow: “Severe hemorrhage or potentially severe hemorrhage, in the context of a treatment with VKA is defined by one or more of the following: visible hemorrhage not controllable by usual means; hemodynamic instability: systolic blood pressure < 90 mmHg or a decrease by more than 40 mmHg from the usual systolic blood pressure or mean blood pressure < 65 mmHg, or any sign of shock; the need for a haemostatic procedure: surgery, embolization, endoscopy; the need for red blood cell transfusion; life-threatening bleeding site or bleeding site with severe functional consequences, such as: intracranial, intraspinal, ocular or retro-ocular hemorrhage; hemorrhaxor, peritoneal or retroperitoneal bleeding, haemopericardial bleeding, deep muscular haematoma and/or compartment syndrome, GI bleeding, haemarthrosis. If there is no such criteria, the hemorrhage is not qualified as major” [35].

This definition of severe haemorrhages puts intracerebral bleeding and muscular haematomas, for example, at the same level. This is due in part to the long half-life of VKA and to the existence of a well-mastered specific antidote (PCC). The present context is different. Dabigatran has a short half-life with great inter-individual variability. The available neutralisation possibilities are poorly codified, in particular, the efficacy/tolerance profiles of nonspecific procoagulant medications, which act by a mechanism that is poorly known and different from the simple correction of a deficit in dependent vitamin K factors.

The availability of an antidote must not lead to its excessive use. It should be only prescribed in situations where PCC is indicated.
For example, in the case of digestive hemorrhage, which is a frequently observed complication under DOAC, the same strategy should be applied and the use of an antidote should only be used for haemodynamically unstable patients with active bleeding. In those cases, management is limited to an endoscopic procedure and possibly a transfusion of packed red blood cells.

2.2.1. Haemostatic procedure

This term includes all of the mechanical and instrument strategies to reach and control bleeding (surgery, endoscopy, embolization, packing...). They are substitutes for the administration of an antidote or PCC. Conversely, the administration of an antidote or PCC does not exclude the performance of haemostatic procedures and must not delay their implementation. When haemostatic procedures are indicated, they must be performed urgently.

2.2.2. “Rapid, effective haemostatic procedure”

If a haemostatic procedure can be performed immediately (endoscopy, embolization, packing, compression), it should be carried out no matter the concentration of the medication. This situation does not require the immediate administration of an antidote or PCC. Optimal management of the hemorrhage must be obtained with appropriate nonspecific measures.

2.2.3. No indication for a haemostatic procedure or persistent bleeding despite the procedure

If an haemostatic procedure is not indicated (unfavorable technical conditions, diffuse bleeding, not accessible to an instrumental strategy) or immediately available and the clinician judges that a neutralisation can improve the clinical situation (bleeding in part due to an anticoagulant), the administration of an antidote or PCC must depend on a strategy that includes measurement of the dabigatran concentration or an estimation of the residual concentration that depends on the time since the last administration (TLA) and/or creatinine clearance according to Cockcroft-Gault formula (ClCr).

2.2.4. “Dabigatran concentration > 50 ng/mL or dabigatran concentration unknown and TLA to be defined (time from last administration ≤ 24 h or ClCr ≤ 50 mL/min)”

When the TLA of dabigatran is inferior to 24 hours, there is a high probability that the circulating concentration is participating in the bleeding.

When the Cockcroft score is inferior to 50 mL/min, there is a relatively high probability that the dabigatran concentration is participating in the bleeding given the pharmacokinetic data on this medication.

In these situations, idarucizumab can reasonably be administered. If it is unavailable, administration of non-activated or activated PCC may be effective. These reversion strategies must be performed in addition to the nonspecific measures of the management of bleeding.

2.2.5. “Concentration ≤ 50 ng/mL or dabigatran concentration unknown and (TLA > 24 h and ClCr > 50 mL/min)”

If the concentration can be measured and is ≤ 50 ng/mL, the active bleeding cannot be attributed partially or totally to the presence of an anticoagulant.

When the dabigatran concentration is unknown, a reasonable estimate can be given with TLA and ClCr.

TT is a test that is very sensitive to the presence of dabigatran but unusable to discriminate a threshold of 50 ng/mL. Consequently, if the thrombin time is normal, it ensures that the concentration is undetectable. If it is prolonged, the concentration can be sufficiently low and not contribute to the persistence of bleeding.

In this situation, we advance the hypothesis that the residual concentration is low enough to not significantly contribute to the bleeding given the pharmacokinetics of dabigatran. Non-specific measures must be sufficient to optimally manage bleeding.

2.3. Non-severe hemorrhage in patients treated with dabigatran

In the absence of signs of severity, it is not necessary to neutralise dabigatran with the administration of an antidote or PCC, no matter the concentration of dabigatran. Temporary or permanent contraindications to the use of dabigatran should be investigated (Cockcroft ≤ 30 ml/min, drug interactions). Possible strategies are a short discontinuation or a reassessment of the anticoagulation (indication, therapeutic scheme).

3. Management of patients treated with dabigatran for an emergency invasive procedure

Emergency invasive procedures include very diverse technical and clinical situations from surgery to punctures or biopsies and diagnostic or therapeutic endoscopic procedures (Fig. 2). The injury generated by these invasive procedures has very different consequences on bleeding depending on the situation. We have distinguished three situations:

Low haemorrhagic risk

These procedures are associated with bleeding that is not significant or that is easily controllable by simple means.

High haemorrhagic risk (controllable haemostasis)

The risk is high, but haemostasis is always controllable or an estimation of the situation can be made in a reasonable time to distinguish “normal” and acceptable bleeding given the procedure or bleeding attributable to the anticoagulant, which will justify a specific reversion strategy.

Very high haemorrhagic risk (uncontrollable haemostasis)

The risk is very high because the procedure is performed in tissue or an organ where the severity of the functional consequences (neurosurgery or neuraxial procedures), the induced bleeding or the uncontrollable character of bleeding by reasonable surgical manoeuvres (hepatic surgery) justifies optimal biological haemostasis.

Neuraxial procedures (lumbar puncture included).

Performance of a neuraxial procedure is contraindicated under anticoagulants. These procedures include diagnostic or therapeutic lumbar punctures (LP) [36], neuraxial anaesthesia (spinal and epidural) with or without catheter [37–39] and image-guided (or not) therapeutic spinal injections [40,41].

Performance of an emergency diagnostic LP is therefore also contraindicated [20,21]. The French Society of Infectious Diseases states that “any situation that leads to delaying a lumbar puncture requires the prescription of empiric antibiotic therapy owing to the direct link between the prognosis and early administration of the treatment” [20]. It recommends “in this situation to perform a blood culture before antibiotic therapy during initial management. The lumbar puncture will be performed as soon as possible after correction of these abnormalities” [20].

If the LP is indispensable given its diagnostic value in a patient treated with dabigatran, idarucizumab could be administered before the procedure. This strategy is based on the hypothesis that given its neutralising action, idarucizumab will provide the immediate restoration of normal coagulation. If idarucizumab is not available, administration of non-activated or activated PCC will guarantee neither normalisation of haemostasis nor a reduction in the haemorrhagic risk dominated by neuraxial haematomas and therefore cannot be recommended. In any case, an experienced operator must perform the LP with a fine needle.

Neuraxial anaesthesia is contraindicated in patients on anticoagulants [37–39] and general anaesthesia should therefore be
preferred. However, when a major contraindication to general anaesthesia is identified, perimедullar anaesthesia can be performed after administration of idarucizumab in order to neutralize the dabigatran. Perimедullar anaesthesia must be performed as a single puncture with a fine needle and by an experienced operator (Fig. 3).

An epidural catheter will expose the patient to a complex anticoagulant management. The catheter must be withdrawn in optimal haemostatic conditions. The use of an epidural catheter should not compromise postoperative resumption of anticoagulants.

Non-activated or activated PCCs have not proven their ability to neutralise dabigatran. Their administration can therefore not be recommended to perform perimедullar anaesthesia.

Peripheral nerve blocks

A peripheral nerve block procedure in a patient on anticoagulants increases the risk of haematoma. Haematomas induce three risks: reoperation for evacuation, transfusion and nerve damage by compression or neuropathy [42].

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

- peripheral blocks with a low risk of haemorrhage: in case of haemorrhage, bleeding is easily controllable or the haemorrhagic zone can be compressed [43]. They include superficial blocks such as femoral block, sciatic block in the popliteal fossa. It is suggested that these blocks be performed under dabigatran if the benefit/risk ratio is favourable and justified;
- peripheral blocks with a high risk of haemorrhage: in case of bleeding, the haemorrhagic zone cannot be compressed or the consequences of bleeding are potentially severe [43]. They include deep blocks such as infraclavicular block, parasacral sciatic block, posterior lumbar plexus block... These blocks are contraindicated under anticoagulants. These blocks can be performed if the concentration of dabigatran is ≤ 30 ng/mL. However, when a major contraindication to general anaesthesia is identified and if the concentration of dabigatran is > 30 ng/mL or unknown, administration of idarucizumab is recommended before this block is performed. Non-activated or activated PCCs have not demonstrated an ability to neutralise dabigatran. They therefore cannot be recommended for a deep peripheral nerve block.

In all cases, it is recommended that the performance of these blocks (superficial or deep) be carried out under ultrasound guidance by an experienced operator. Perineural catheters should not compromise postoperative resumption of anticoagulants. The catheter must be withdrawn in optimal haemostatic conditions (Fig. 3).

3.1. “High risk of hemorrhage and dabigatran concentration > 30 ng/mL or unknown”

The strategy depends on the urgency of the procedure (Fig. 2):

- if the procedure can be delayed (> 8 hours), it is preferable to wait for a concentration that enables the procedure under maximum safety conditions (in practice, ≤ 30 ng/mL). This delay will make it possible to measure the concentration of dabigatran. If the level is ≤ 30 ng/mL, the procedure can be performed. If the procedure is performed without this information, it is preferable to administer the antidote (idarucizumab) or if unavailable non-activated or activated PCCs;
- if the procedure cannot be delayed (< 8 hours or haemostatic surgery), prior administration of the antidote (idarucizumab) or if unavailable, activated or inactivated PCCs is suggested.

3.2. “High risk of hemorrhage and dabigatran concentration ≥ 50 ng/mL or dabigatran concentration unknown and TIA ≤ 24 h or CrCl ≤ 50 mL/min”

The strategy depends on the urgency of the procedure (Fig. 2):

- if the procedure can be delayed (> 8 hours) without negatively affecting the patient, it is preferable to wait for a concentration that enables the procedure to be performed in good conditions (in practice, ≤ 50 ng/mL). This delay will make it possible to measure the concentration of dabigatran. When the procedure is performed, if the bleeding observed per- or postoperatively can be attributed to a residual concentration of dabigatran, a neutralisation strategy by idarucizumab or if unavailable, non-activated or activated PCC could be considered;
- if the procedure cannot be delayed (< 8 hours, surgery for sepsis...), a neutralisation strategy by idarucizumab or if unavailable, non-activated or activated PCC could be considered.

Perioperative administration is preferable to preoperative prophylactic administration in cases where bleeding is not controllable by the surgeon.

3.3. “Low risk of hemorrhage” or “High risk of hemorrhage and dabigatran concentration ≤ 50 ng/mL or TIA ≥ 24 h and CrCl ≥ 50 mL/min” or “Very high risk of hemorrhage and concentration ≤ 30 ng/mL”

In these conditions, if bleeding is observed during the procedure, it cannot reasonably be attributed to dabigatran either because dabigatran concentration is low, or the probability is low (TIA ≥ 24 hours and CrCl ≥ 50 mL/min) that the concentration is superior to the haemostatic threshold (≤ 30 or ≤ 50 ng/mL depending on the type of invasive procedure) (Fig. 2).

Disclosure of interest

The authors declare that they have no competing interest.

References

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