CLINICAL RESEARCH

Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors: Proposals of the Working Group on Perioperative Haemostasis (GIHP) — March 2013

Prise en charge des complications hémorragiques graves et de la chirurgie en urgence chez les patients recevant un anticoagulant oral anti-IIa ou anti-Xa direct : propositions du Groupe d’Intérêt en hémostase périopératoire (GIHP) — mars 2013

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Abbreviations: aPPT, Activated partial thromboplastin time; CrCl, Creatinine clearance calculated according to the formula of Cockcroft and Gault; FEIBA, Activated prothrombin complex concentrate factor VIII inhibitor bypassing activity; GIHP, Working Group on Perioperative Haemostasis (Groupe d’Intérêt en Hémostase Périopératoire); NOAC, New oral anticoagulant; PCC, Prothrombin complex concentrate; PT, Prothrombin time; VKA, Vitamin K antagonist.

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Serious bleeding and emergency surgery and direct oral anticoagulants

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Summary  Direct new oral anticoagulants (NOACs) — inhibitors of thrombin or factor Xa — are intended to be used largely in the treatment of venous thromboembolic disease or the prevention of systemic embolism in atrial fibrillation, instead of vitamin K antagonists. Like any anticoagulant treatment, they are associated with spontaneous or provoked haemorrhagic risk. Furthermore, a significant proportion of treated patients are likely to be exposed to emergency surgery or invasive procedures. Given the absence of a specific antidote, the action to be taken in these situations must be defined. The lack of data means that it is only possible to issue proposals rather than recommendations, which will evolve according to accumulated experience. The proposals presented here apply to dabigatran (Pradaxa®) and rivaroxaban (Xarelto®); data for apixaban and edoxaban are still scarce. For urgent surgery with haemorrhagic risk, the drug plasma concentration should be less or equal to 30 ng/mL for dabigatran and rivaroxaban should enable surgery associated with a high bleeding risk. Beyond that, if possible, the intervention should be postponed by monitoring the drug concentration. The course to follow is then defined according to the NOAC and its concentration. If the anticoagulant dosage is not immediately available, worse propositions, based on the usual tests (prothrombin time and activated partial thromboplastin time), are presented. However, these tests do not really assess drug concentration or the risk of bleeding that depends on it. In case of serious bleeding in a critical organ, the effect of anticoagulant therapy should be reduced using a non-specific procoagulant drug as a first-line approach: activated prothrombin complex concentrate (aPCC) (FEIBA® 30–50 U/kg) or non-activated PCC (50 U/kg). In addition, for any other type of severe haemorrhage, the administration of a procoagulant drug, which is potentially thrombogenic in these patients, is discussed according to the NOAC concentration and the possibilities of mechanical haemostasis.

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Résumé  Les nouveaux anticoagulants oraux (NACO), anti-IIa ou anti-Xa directs, sont destinés à être largement utilisés dans le traitement de la maladie thromboembolique veineuse ou dans la fibrillation atriale en remplacement des anti-vitamines K. Comme tout traitement anticoagulant, notamment aux doses dites « curatives », ils sont associés à un risque hémorragique spontané ou provoqué. De plus, une proportion non négligeable de patients traités sera confrontée à la nécessité d’un geste invasif en urgence. Compte tenu de l’absence d’antidote spécifique, les mesures à prendre doivent être définies dans ces situations. Le peu de données disponibles ne permet pas d’émettre des recommandations, mais seulement des propositions qui seront amenées à évoluer en fonction de l’expérience accumulée. Les propositions présentées dans cet article s’appliquent au dabigatran (Pradaxa®) et au rivaroxaban (Xarelto®), les données relatives à l’apixaban et à l’edoxaban étant encore trop peu nombreuses. Pour la chirurgie urgente à risque hémorragique, il est proposé de doser le taux plasmatique du médicament. Des taux inférieurs ou égales à 30 ng/mL, à la fois pour dabigatran et rivaroxaban, devraient permettre la réalisation d’une chirurgie à risque hémorragique élevé. Au-delà, il est convenu, dans la mesure du possible, de reporter l’intervention en surveillant l’évolution de la concentration du médicament. La conduite à tenir est alors définie selon le NACO et sa concentration. Si le dosage du médicament n’est pas disponible immédiatement, des propositions « dégradées » sur la base de tests usuels, TP et TCA, sont présentées. Ces tests ne permettent cependant pas d’évaluer réellement ni la concentration de médicament, ni le risque hémorragique qui en
Background

New oral anticoagulants (NOACs), directly targeting thrombin (factor IIa) or factor Xa, are currently used for the treatment of venous thromboembolic disease (rivaroxaban, Xarelto®, Bayer Schering) or for the prevention of systematic embolism in non-valvular atrial fibrillation (rivaroxaban; dabigatran, Pradaxa®, Boehringer Ingelheim). Given their ease of use, these anticoagulants are intended for widespread use in such long-term indications. Beyond the potential bleeding complications reported in phase III trials, a notable proportion of treated patients—considered to be 10 to 20% per year—are likely to be exposed to emergency surgery or invasive procedures. Elective surgeries have already been the subject of proposals by the Working Group on Perioperative Haemostasis (GIHP) [1]. The same group has also considered the management of bleeding and emergency invasive procedures in patients benefiting from treatment with NOACs in a curative scheme (except for prevention in major orthopaedic surgery).

The method used to develop these proposals was based on analysis of the literature reporting on the pharmacokinetic properties of these anticoagulants and their use in a surgical context. The text of the proposals was then submitted for several rounds of critical analysis by the members of GIHP, until a consensus was reached.

At the time when these proposals were made, there were very few data allowing recommendations to be made. The proposals are often based on extrapolations from data in the literature and cannot therefore constitute an absolute guide for prescription, but rather define the management bases that need to be evaluated.

Rationale

Rules regarding the management of new oral anticoagulant-treated patients during emergency surgery are poorly defined

At the time of the marketing of dabigatran and rivaroxaban, the rules regarding the management of patients in an emergency were not established. Summaries of Product Characteristics give no indications, except for the usual precautions and the need to postpone the emergency surgery or invasive procedure.

There are few data regarding perioperative management in an emergency of patients treated with dabigatran or rivaroxaban. Healey et al. [2] described the management of patients treated with dabigatran in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial who had an elective invasive procedure. During this trial, 4591 patients had at least one surgery or invasive procedure, more than half of which were at low haemorrhagic risk. Urgent surgery represented 7.8% of all surgeries. There was no significant difference in major bleeds between the groups treated with dabigatran or vitamin K antagonists (VKAs). However, there was no clear indication of anticoagulant management (time, use of procoagulant drugs, etc.).

Regarding rivaroxaban, to date there is no description of the patients, in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonists for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study, who underwent urgent surgery [3].

The published recommendations consist of expert opinions and are general. It is usually proposed to discontinue the anticoagulant drug, to transfer the patient to a ‘specialized’ centre, and to delay most urgent surgery in those at haemorrhagic risk. These recommendations are therefore of little use for the ‘specialized’ centres to which these patients will be sent.

New oral anticoagulant treatment at a curative dose is associated with haemorrhagic risk

In the EINSTEIN DVT trial, regarding the curative treatment of deep vein thrombosis, the rate of major bleedings with rivaroxaban (0.8%) was not significantly different from that observed in the comparator group treated with VKAs (1.2%) [4]. In the EINSTEIN PE trial, regarding the curative treatment of pulmonary embolism, the rate of major bleedings, although twice as low as that of the VKA group, was 1.1% [5]. In the treatment of venous thromboembolic disease, the rate of severe bleeding events in patients receiving dabigatran 150 mg twice daily was 1.6%, again similar to the VKA group (1.9%) [6]. In non-valvular atrial fibrillation, the rate of intracranial bleedings reported was widely decreased with NOACs, but the rate of overall serious bleedings (3.1–5.6%) remained similar to the VKA group [3,7]. Specific measures must therefore be defined in case of occurrence of such complications and the haemorrhagic risk should be considered for emergency surgery or invasive procedures.

New oral anticoagulants have no specific validated antidote

The management of serious bleedings or emergency surgery is delicate due to the current lack of a specific antidote. Antagonists of dabigatran or the xabans are in phases I and
Il of clinical development [8] and will not be available for at least 2 years.

The risk-benefit of procoagulant drugs is uncertain

Procoagulant drugs available in France are non-activated four-factor prothrombin complex concentrates (PCCs) (Kanokad®, LFB; Octaplex®, Octapharma; ConfideX®, CSL Behring), an activated PCC (activated prothrombin complex concentrate factor VIII inhibitor bypassing activity [FEIBA®], Baxter) and the recombinant human factor VIIa (Novoseven®, NovoNordisk). Their use in this indication is off label.

In the absence of a specific antidote, we can suggest trying to counteract the anticoagulant effect of NOACs empirically using these drugs. Analysis of their potential efficacy was based on animal experimental data, in vivo/ex vivo studies in healthy volunteers and occasional clinical cases. There are no experimental data regarding the neutralization of an NOAC overdose.

The effect of PCCs is difficult to analyse. When reported, the doses used were generally higher (50 U/kg) than those used to antagonize the effect of VKAs [9,10]. In this context, data on safety of doses that inhibit the action of VKAs are available. The frequency of the thrombotic complications associated with (but not necessarily attributable to) the administration of four-factor PCCs to inhibit the action of VKAs is low (1.8%) [11]. The occurrence of these thrombotic complications is readily associated with the administration of high doses (>50 U/kg) or the treatment of patients with severe liver disease [12].

The effect of FEIBA is evoked at doses of 30–50 U/kg, i.e., two times lower than those used in haemophilia [10]. Human clinical use in this indication has been reported in only one case [13]. There are no data on the safety of use of FEIBA in this targeted population with thrombotic risk factors.

Overall, recombinant factor VIIa seems to be poorly effective in the inhibition of the anticoagulant effect of dabigatran and rivaroxaban [14,15].

These procoagulant drugs do not alter the elimination of anticoagulant. There are no data on the impact of the administration of these agents on haemostasis tests in patients treated with NOACs.

Thus, the efficacy, safety and operating conditions (doses, rhythm, biological monitoring of these drugs) in this indication are not exactly known, which explains why they are discussed as second-line treatments in the proposals below, except for in cases of bleeding that are immediately life threatening or disabling.

Haemostasis tests for measuring new oral anticoagulant plasma concentration in an emergency

These haemostasis tests, which measure the plasma concentrations of these anticoagulants expressed in ng/mL, are currently deployed in few laboratories serving home emergency departments, but can be implemented easily. They are suitable for measuring concentrations between 500 and 50 ng/mL, including the maximum concentration ($C_{\text{max}}$: 2–4 h after oral administration of the drug) and the average residual concentration ($C_{\text{min}}$: just before the next dose). The tests are less accurate for low concentrations and their detection limit is usually around 25 ng/mL.

For dabigatran, several tests (Hemoclot®, Biophen; DTI®, Hyphen Biomed; ECA-T®, Diagnostica Stago) are available. These tests are used to screen patients at risk of bleeding at steady state, based on a residual concentration greater than 200 ng/mL.

Measuring the anti-Xa activity by specific methods (Biophen DiXal®, Hyphen Biomed; STA Liquid anti-Xa®, Diagnostica Stago), several tests also allow evaluation of the plasma concentration of rivaroxaban [16].

It is possible to extrapolate a clinical haemostatic safety threshold corresponding to a new oral anticoagulant plasma concentration allowing urgent surgery

There are no preclinical or clinical data with which to establish a haemostatic safety threshold. However, data can be extrapolated from protocols used in clinical trials and Summaries of Product Characteristics.

Dabigatran is administered in atrial fibrillation at a dose of 150 mg or 110 mg, twice daily. Rivaroxaban is administered in atrial fibrillation (20 mg once daily) and for the treatment of deep vein thrombosis and pulmonary embolism at a dose of 15 mg twice daily and then 20 mg once daily. For these two NOACs, plasma concentrations are relatively similar for both $C_{\text{max}}$ and $C_{\text{min}}$ (Table 1).

Regarding dabigatran, data on elective surgery are available from patients in the RE-LY study [2]. In this study, patients whose creatinine clearance was normal and who benefited from surgery at bleeding risk were operated on between 24 and 72 hours after the last dose or four half-lives. Given the half-life of dabigatran in this population (13–18 h), we can deduce that these patients were operated on while the plasma concentration was probably less or equal to 30 ng/mL.

Regarding rivaroxaban, the only data available are derived from the ROCKET-AF design study [3]. In this study, rivaroxaban was stopped 2 days before any surgical elective procedure again, four half-lives (7–13 h). Given the mean $C_{\text{max}}$ of rivaroxaban in this population, these patients were operated upon while the plasma concentration of the drug was probably less or equal to 30 ng/mL.

It appears that we can regard the same concentration of 30 ng/mL as compatible with surgical management, without increasing the risk of bleeding, especially in an emergency.

In case of unavailability of drug concentration measurements, the usual haemostasis tests (prothrombin time, activated partial thromboplastin time) may be useful

Tests dedicated to measuring the plasma concentration of NOACs 24 h/day are not available in all centres in an emergency setting. In contrast, conventional coagulation tests (prothrombin time [PT] and activated partial thromboplastin time [aPTT]) are available at any time. These common
tests are relatively insensitive to the effects of NOACs and suffer, depending on the reagent, from significant variability at high concentrations. However, provided that the patient does not have a bleeding disorder linked to an associated disease, normal PT and aPTT results indicate, with sufficient probability for most situations encountered, that the drug is present at a very low residual concentration, which is close to the safety threshold mentioned above. Therefore, these usual tests meet the objective of ensuring that emergency surgery can be performed without further delay and without a significant increase in bleeding risk. PT and aPTT can also be used to estimate the time required to reach the safety threshold, but this estimate is less precise than that based on concentrations.

PT is insensitive to dabigatran. The prolongation of PT depends on drug concentration and the sensitivity of response depends on the reagent used. PT cannot be used independently, but can be integrated into an approach combining PT and aPTT. aPTT is prolonged with dabigatran, but, for high concentrations, is poorly correlated with the concentration measured by a dedicated test. However, its negative predictive value is interesting because normal aPTT generally reflects a low concentration. Its use is therefore suggested by some experts [17]. Douxfils et al. [18] studied the impact of different concentrations of dabigatran on aPTT measured with different reagents. For concentrations of 10 ng/mL, all reagents used (Actin FS® Cephascreen®), CKPrest®, PTT-A®, Synthasil®), even taking into account some variability, gave a ratio of patient/control less or equal to 1.2.

PT is described as sensitive to the effect of rivaroxaban [19]. In treated patients, prolongation of PT is proportional to the concentration of rivaroxaban and varies according to the reagent used [20,21]. However, this variability is very low at a concentration of 25 ng/mL [22] and between 30 and 50 ng/mL the PT ratio is less or equal to 1.2 [20,22]. In contrast, a concentration of rivaroxaban of 150 ng/mL is responsible for the prolongation of PT, with a ratio between 1.2 and 1.5, depending on the reagent used [21]. Hillarp et al. [22] showed that aPTT was sensitive, with a large variability in response to high concentrations. However, for a concentration of 25 ng/mL, the aPTT ratio again remained less or equal to 1.2, regardless of the reagent (Actin FS®, PTT-A®, TriniCLOT®, APTT-DG®, APTT-SP®).

As far as possible, it is recommended that the laboratory performs the usual coagulation tests and forwards the specific measurement request, in order to acquire the necessary experience in the interpretation of the usual tests. One of the critical factors is the sensitivity of the analytical technique and its ability to detect low concentrations of each NOAC. A selection of reagents that are sensitive to the effect of NOACs could be useful in the management of emergencies.

Finally, it is important to remember that measurement of the international normalized ratio has no place in the management of critical situations in patients treated with NOACs; it is designed for patients treated with oral anticoagulants. The ratio for PT and aPTT is preferred.

Proposals

We will describe the management of urgent surgery that has to be performed within 48 hours in cases with a risk of bleeding, followed by severe bleeding occurring in patients treated with NOACs (dabigatran and rivaroxaban).

In all cases, it is important to specify age, patient weight, drug name, indication, dose, number of doses per day, time of last dose and creatinine clearance calculated according to the formula of Cockcroft and Gault (CrCl).

The proposals differ for laboratories that provide measurement of drug concentration and those that do not.

Urgent surgery at haemorrhagic risk monitored by measuring drug concentration

Having evaluated the bleeding risk of surgery and the possibility of postponing it without loss of chance for the patient, the drug concentration is required.

Patients receiving dabigatran

It is proposed to operate without delay on patients with a dabigatran concentration at admission less or equal to 30 ng/mL, as this is the threshold that is compatible with surgery without an increased risk of bleeding (Fig. 1). However, given that patients take dabigatran twice daily and considering the population pharmacokinetic data [23], it is unlikely that a patient taking the treatment on the same day will have a concentration less or equal to 30 ng/mL. Twelve hours after taking 150 mg of dabigatran (in a scheme of 150 mg twice daily), the plasma concentration of the drug varies between 40 and 180 ng/mL in 90% of patients with a CrCl greater than 30 mL/min (median value of about 100 ng/mL) [23]. There are no pharmacokinetic data beyond 12 hours and simulations at 24 and 48 hours can only be

Table 1 Main new oral anticoagulant pharmacokinetic data.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>220 mg once daily</td>
<td>[28] 183 (5–95 percentiles: 64–447)</td>
<td>37 (5–95 percentiles: 10–96; 24 hours)</td>
</tr>
<tr>
<td></td>
<td>150 mg twice daily</td>
<td>[29] 254 ± 70.5</td>
<td>80.3 ± 18.7 (12 hours)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>10 mg once daily</td>
<td>[30] 125 (5–95 percentiles: 91–195)</td>
<td>9 (5–95 percentiles: 1–38; 24 hours)</td>
</tr>
<tr>
<td></td>
<td>20 mg once daily</td>
<td>215 (5–95 percentiles: 22–535)</td>
<td>32 (5–95 percentiles: 6–239; 24 hours)</td>
</tr>
</tbody>
</table>

<sup>a</sup> There are no data for rivaroxaban 15 mg twice daily; 10 mg data are indicative here.
Serious dabigatran needed

12 to 24 hours after the last dose, the threshold of 30 ng/mL should be achieved, depending on the patient’s renal function. It is therefore proposed to delay the intervention by 12 hours if the patient’s condition allows it and to repeat the assay 12 hours after the first measurement before allowing surgery. The time period before assay repetition may be eventually extended depending on the availability of a technical platform for the assay.

If the concentration is between 200 and 400 ng/mL and in the absence of renal impairment, a minimum of 24 hours is needed to reach the threshold concentration of haemostatic safety. In this case, it is proposed to wait for 24 hours and repeat the assay.

If the concentration is greater than 200 ng/mL and there is impaired renal function (CrCl < 50 mL/min), it is highly unlikely that the acceptable threshold concentration will be achieved between 24 and 48 hours. Therefore, haemodialysis should be discussed before surgery. Indeed, only 35% of dabigatran is bound to circulating albumin and haemodialysis may allow a reduction of 40 to 60% concentration in 4 hours [25]. In this case, it is proposed to delay surgery for as long as possible.

Concentrations greater than 400 ng/mL correspond to an overdose and expose the patient to major bleeding. Interventional and optimized intensive perioperative procedures must be implemented. Haemodialysis should be systematically discussed. However, a long time is required for dialysis to reach the threshold of 30 ng/mL following an overdose. This delay must therefore be taken into account during the decision to postpone the surgery.

Patients receiving rivaroxaban

Based on the data from the ROCKET-AF study [3], it is also estimated that the concentration of 30 ng/mL is a haemostatically acceptable safety threshold for surgical treatment in an emergency (Fig. 2). It is therefore proposed to operate without delay on patients with a rivaroxaban concentration less or equal to 30 ng/mL at admission. The pharmacokinetics of rivaroxaban (once daily) are available at 24 hours [26]. Therefore, an approach similar to that for dabigatran is proposed.

For rivaroxaban plasma concentrations between 30 and 200 ng/mL, it is proposed to delay the operation, if possible, until 12 hours after the first drug concentration measurement and to repeat the assay 12 hours before allowing surgery.

For rivaroxaban plasma concentrations between 200 and 400 ng/mL, it is proposed to wait for 24 hours and repeat the assay.
Concentrations greater than 400 ng/mL corresponding to an overdose expose the patient to major bleeding. Interventional and optimized intensive perioperative procedures must be implemented. Dialysis is not possible with this medication. The probability of reaching the haemostatic safety threshold is low. In this case, it is proposed to delay surgery for as long as possible if the patient’s condition permits.

**Urgent surgery at haemorrhagic risk monitored by the usual haemostasis tests**

The proposals below, which are very similar for both drugs, can be considered in the context of emergency in the case of unavailability of drug dosage. However, this is a worse proposition. The usual tests have several limitations. They cannot determine an absolute haemostatic safety threshold value for NOACs, which is required or surgery with a very high risk of bleeding (e.g. neurosurgery). The tests can be prolonged for reasons other than the presence of the anticoagulant, which would be responsible for an unnecessary delay in surgery. Finally, administration of certain procoagulant drugs (recombinant factor VIIa and PT) can shorten coagulation times without guaranteeing a haemostatic effect in vivo.

Patients receiving dabigatran

The combination of normal aPTT and PT indicates, with relative reliability, that a dabigatran plasma concentration less than 30 ng/mL is consistent with emergency surgery (Fig. 3). The proposed ratios are less or equal to 1.2 for both tests. Each laboratory must validate this information, as described above. The thrombin time is extremely sensitive to dabigatran. A normal thrombin time value allows the presence of the drug to be excluded, which is probably unnecessary for most situations and delays the decision about the intervention. Therefore, this test is not very useful in emergency situations.

If either test indicates a ratio greater than 1.2, the time of surgery can be estimated as follows, based on the aPTT alone.

An aPTT ratio less or equal to 1.5 but greater than 1.2 corresponds to concentrations from 30 to 200 ng/mL [18]. For these concentrations, a delay of up to 12 to 24 hours, depending on renal function, should achieve concentrations close to 30 ng/mL. Under these conditions, it is proposed to repeat the aPTT test and, during this time (if still compatible with the surgical emergency), to obtain a measurement of concentration. Indeed, it is not possible, on the basis of an aPTT ratio between 1.2 and 1.5, to accurately determine the time required to reach a threshold ratio less or equal to 1.2.

An aPTT ratio greater than 1.5 corresponds to concentrations greater than 200 ng/mL, i.e. Cmax. In the absence of renal failure, a minimum of 24 hours is necessary to reach the haemostatic safety threshold concentration. Concentration measurements must be obtained within this period to detect a possible overdose. If CrCl is less than 50 mL/min and the aPTT ratio is greater than 1.5, it is highly unlikely that an acceptable haemostatic safety threshold concentration will be obtained within 24 to 48 hours. It is imperative to obtain a measure of concentration in order to detect an overdose and consider dialysis.

**Figure 2.** Support for emergency surgery in a patient treated with rivaroxaban (curative scheme), based on the determination of plasma concentrations. FEIBA: activated prothrombin complex concentrate factor VIII inhibitor bypassing activity; GIHP: Working Group on Perioperative Haemostasis; PCC: prothrombin complex concentrate; rFVIIa: recombinant factor VIIa.
Patients receiving rivaroxaban

The combination of normal aPTT and PT indicates, with relative reliability, a rivaroxaban plasma concentration less than 30 ng/mL, which is consistent with emergency surgery (Fig. 4).

The proposed ratios are less or equal to 1.2 for both tests, but must be validated by each laboratory, as described above. Measurement of the anti-Xa activity by the usual technique that is suitable for heparins is very sensitive to rivaroxaban. Activity less or equal to 0.1 U/mL guarantees the absence of the drug, which is probably not necessary for most situations and delays the decision regarding the intervention. This test is not very useful in emergency situations.

If the ratio is greater than 1.2 with either test, an approach similar to that for dabigatran is proposed. An aPTT ratio between 1.2 and 1.5 corresponds to concentrations of rivaroxaban of 30–200 ng/mL [22,26] and a delay until 12 hours should achieve a rate less than 30 ng/mL. It is proposed to repeat the aPTT test and, during this time (if it is compatible with emergency surgery), to obtain a drug concentration measurement. Indeed, it is not possible, on the basis of an aPTT ratio between 1.2 and 1.5, to accurately determine the time to reach a threshold less or equal to 1.2.

An aPTT ratio greater than 1.5 corresponds to concentrations of rivaroxaban greater than 200 ng/mL. A minimum of 24 hours is necessary to reach the haemostatic safety threshold value. The drug concentration must be obtained within this period. In these cases, it is proposed to delay surgery for as long as possible.

What to do if surgery cannot be delayed and haemostatic safety thresholds are not met?

In this situation, it is proposed to operate without the prophylactic administration of procoagulant drugs and to use them (PCC 25–50 U/kg or FEIBA 30–50 U/kg; eventually readministered once in case of failure) in cases of abnormal intraoperative or postoperative bleeding. It is advisable to use the lowest dose proposed as a first-line approach.

What to do in case of severe bleeding (spontaneous or surgical)?

Recommendations for clinical practice published by the French Health Authority (HAS, 2008) regarding haemorrhages related to VKA use, defined severe bleeding as shown on Fig. 1 [27] (Table 2). This definition, including serious bleeding, put intracerebral haemorrhage and deep muscle haematoma on the same level. This was due on the one hand to the long half-life of VKAs and on the other hand to the existence of a specific well-controlled
Urgent surgery and RIVAROXABAN (XARELTO®)
There is a worse proposal in case of unavailability of immediate dosage.
It does not guarantee the absence of formal haemorrhagic complications

| Ratio aPTT ≤ 1.2 and ratio PT ≤ 1.2 | • Operate |
| Ratio 1.2 < aPTT ≤ 1.5 or ratio PT > 1.2 | • Wait up to 12 h³ and obtain specific dosage / new aPTT - PT or (if time is not compatible with emergency) • Operate, if abnormal bleeding: antagonise the anticoagulant effect** |
| Ratio aPTT > 1.5 | • Wait up to 12-24 h and obtain specific dosage or (if time is not compatible with emergency) • Maximum delay surgery • Operate, if abnormal bleeding: antagonise ** |

In case of renal insufficiency, half-life of rivaroxaban is clearly increased
* It is not possible to accurately determine the time to reach a threshold of 30 ng/ml, so the sentence "until 12h" ** This proposal applies primarily to emergency situations where you cannot wait:
  • PCC 25-50 U/kg or FEIBA = 30-50 U/kg depending on the availability
  • No data are available on the thrombotic risk of high doses of PCC or FEIBA in these patients
  • Reversal by CCP or FEIBA does not fully correct the abnormalities of haemostasis tests
  • rFVIIa is not considered first-line

Note: PT and aPTT can be disrupted for reasons other than the anticoagulant effect. We can use in a second time the anti-Xa activity analysis, if available, and if it is normal, consider rivaroxaban concentration <30 ng/ml.

Figure 4. Support for emergency surgery in a patient treated with rivaroxaban (curative scheme), based on the determination of prothrombin time (PT)/activated partial thromboplastin time (aPTT). FEIBA: activated prothrombin complex concentrate factor VIII inhibitor bypassing activity; GIHP: Working Group on Perioperative Haemostasis; PCC: prothrombin complex concentrate; rFVIIa: recombinant factor VIIa.

Table 2 Definition of serious or potentially serious bleeding with vitamin K antagonists, according to the French Health Authority [27].

| Serious or potentially serious bleeding in the context of treatment with a VKA is defined by the presence of at least one of the following criteria |
| Externalized bleeding uncontrollable by conventional procedure |
| Haemodynamic instability |
| SBP < 90 mmHg or |
| 40 mmHg decrease in SBP compared with usual or |
| Mean arterial pressure < 65 mmHg or |
| Signs of shock |
| Need for urgent haemostatic surgery, interventional radiology, endoscopy |
| Need for blood transfusion |
| Threatening or functional location |
| Intracranial or intraspinal haemorrhage |
| Retro-orbital and intraocular bleeding |
| Haemothorax, haemoperitoneum and |
| retroperitoneum, haemopericardium |
| Deep muscular haematoma and/or compartment syndrome |
| Acute gastrointestinal bleeding |
| Haemarthrosis |

SBP: systolic blood pressure; VKA: vitamin K antagonist.

antidote (PCC). The present context is different in every respect: NOACs have a short half-life with large interindividual variability and the possibility of available reversion is poorly known, especially the efficacy/tolerance profiles of non-specific procoagulant drugs. Therefore, we propose to distinguish between two serious bleeding situations.

Intracerebral haemorrhage or haemorrhage in a critical organ (e.g. the eye) warrants immediate attempts to neutralize the anticoagulant effect of the NOAC, by either FEIBA 30—50 U/kg or PCC 50 U/kg, possibly readministered once at an 8-hour interval (Fig. 5). Monitoring the concentration of the drug as described above will be useful for further surgical decisions.

For other serious bleeding meeting the definition of HAS, three situations must be considered. If the drug concentration is less or equal to 30 ng/mL, haemorrhage is unlikely to be only due to the drug; this does not require the administration of a haemostatic agent (FEIBA or PCC). If a haemostatic procedure is feasible (endoscopic, intravascular), it should be preferred regardless of the drug concentration. If the drug concentration is greater than 30 ng/mL and no haemostatic procedure is appropriate, it is proposed to optimize the resuscitation measure and, if necessary, to try to inhibit the anticoagulant effect (PCC 25—50 U/kg or FEIBA 30—50 U/kg, eventually readministered once). In the case of dabigatran, haemodialysis treatment guided by measuring the drug concentrations must be considered.
Serious bleeding and emergency surgery and direct oral anticoagulants

**Haemorrage and DABIGATRAN (PRADAXA®) or RIVAROXABAN (XARELTO®)**

Bleeding into a critical organ (intracranial, acute subdural, intraocular) → 1) FEIBA® 30-50 UI / kg* or 2) PCC 50 UI / kg*

- If [ ]* ≤ 30 ng/ml: no reversal
- Prefer haemostatic procedure if feasible
- If no haemostatic procedure is appropriate and [ ]* > 30ng/ml
- Discuss reversal*** (not always necessary)

* Depending on availability. No data available on the thrombotic risk of high doses of PCC or FEIBA in these patients
** [ ]* means concentration
*** PCC≥25-50 UI/kg or FEIBA≥30-50 UI/Kg
rFVIIa is not considered first-line

Figure 5. Support for severe bleeding in a patient treated with dabigatran or rivaroxaban (curative scheme), on the basis of the determination of the drug concentration. FEIBA: activated prothrombin complex concentrate factor VIII inhibitor bypassing activity; GIHP: Working Group on Perioperative Haemostasis; PCC: prothrombin complex concentrate; rFVIIa: recombinant factor VIIa.

**Haemorrage and DABIGATRAN (PRADAXA®) or RIVAROXABAN (XARELTO®)**

Bleeding into a critical organ (intracranial, acute subdural, intraocular) → 1) FEIBA® 30-50 UI / kg* or 2) PCC 50 UI / kg*

- If ratio aPTT ≤ 1.2 and ratio PT ≤ 1.2: no reversal
- Prefer haemostatic procedure if feasible
- If no haemostatic procedure is appropriate and if ratio aPTT > 1.2 (isolated) or ratio PT > 1.2
- Discuss reversal** (not always necessary) and obtain specific dosage

* Depending on availability. No data available on the thrombotic risk of high doses of PCC or FEIBA in these patients
** PCC≥25-50 UI/kg or FEIBA≥30-50 UI/Kg
rFVIIa is not considered first-line

Figure 6. Management of severe bleeding in a patient treated with dabigatran or rivaroxaban (curative scheme), based on the determination of prothrombin time/activated partial thromboplastin time. FEIBA: activated prothrombin complex concentrate factor VIII inhibitor bypassing activity; GIHP: Working Group on Perioperative Haemostasis; PCC: prothrombin complex concentrate; rFVIIa: recombinant factor VIIa.

If the determination of NOAC plasma concentration is not possible, the rationale and corrective measures can be based on aPTT and PT, but with a high level of uncertainty (Fig. 6).

**Conclusion**

The management of emergency surgery and severe bleeding in patients treated with NOACs requires specific measures that must be fully codified. Unfortunately, available data are scarce in 2013 and a prospective evaluation is needed to quickly consolidate these proposals.

**Disclosure of interest**

The authors declare the following conflicts of interest: Bayer, Boehringer, Baxter and LFB.
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References

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