Quantification of the anticoagulatory effect of novel anticoagulants and management of emergencies

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Summary
Novel oral anticoagulants such as dabigatran which specifically target thrombin, and rivaroxaban and apixaban which are activated factor X inhibitors are in the process of being approved for use in Switzerland to lower the risk of stroke in patients with atrial fibrillation. Although there is currently no evidence relevant to the clinical benefit for monitoring anticoagulant intensity of these drugs in routine clinical practice, the need for measuring the anticoagulant effect of the novel anticoagulants may arise in some clinical situations such as: haemorrhage and thrombosis occurring under anticoagulation, an emergency surgery, drug interaction, overdose, impaired renal or liver function compliance monitoring. Furthermore, the effect of novel anticoagulants on routine coagulation tests must be known by the clinician. To date, clinical experience is insufficient to definitively guide the management of emergencies including major bleeding in patients receiving these drugs. Indeed, there is currently no specific antidote available. Fortunately, the half-life of these agents is short, hence treatment interruption is most of the time sufficient to reverse the anticoagulant and clinical effect. In case of life-threatening bleeding, dabigatran can be removed by haemodialysis, and rivaroxaban and apixaban can be antagonised by non-activated prothrombin complex concentrates. More importantly, preventive attitudes should be placed upfront, before the administration of the novel oral anticoagulant. The prescriber has the responsibility to carefully review possible drug interactions as well as to check renal and liver functions and to provide the patient with an identification card containing personal information, the name of the anticoagulant and treatment indication. In addition, blood cell counts, prothrombin and activated partial thromboplastin times measurements need to be performed before the introduction of the anticoagulation, at least in elderly patients.

Key words: monitoring; anticoagulation; bleeding; rivaroxaban; dabigatran; apixaban

Introduction
Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting about 1% of the general population and up to 10% of people older than 80 years [1, 2]. AF has adverse consequences related to a reduction in cardiac output, cardioembolic stroke and systemic thromboembolism, resulting in an increased risk of mortality. In patients with AF, the estimated risk of stroke is increased four- to fivefold [3, 4]. For decades, vitamin K antagonists (oral anticoagulants) are highly effective for stroke prevention and recommended for most patients with AF according to risk stratification schema [5]. They can decrease the risk for stroke by about 70% [2, 5]. However, multiple food and drug interactions, inter-individual variability and a narrow therapeutic window require regular monitoring with dose adjustment and constitute major clinical challenges [6]. Consequently, only about half of the patients who would benefit from this therapy actually receive the drug [7], and among those receiving the treatment, international normalised ratio (INR) is in the therapeutic range for less than two thirds of the time [8]. Suboptimal anticoagulation constitutes a clinically significant risk for thromboembolism, especially major bleeding [9].

We are now on the verge of an exciting new era as classes of oral anticoagulant specifically targeting thrombin, activated factor II, called factor IIa direct inhibitor (dabigatran etexilate, Pradaxa®), or activated factor X, factor Xa, called factor Xa direct inhibitors (rivaroxaban, Xarelto®; apixaban, Eliquis®), emerge. With a rapid onset of action, the need for an overlap with an-
other anticoagulant such as (low-molecular-weight) heparins vanishes. Their low propensity for food and drug interaction produces a predictable anticoagulant effect after a fixed dose administration and coagulation monitoring is unnecessary. However, the knowledge on the pharmacology of these products mainly comes from animal experiments and studies in young Caucasian subjects. Prescribing these compounds to a wider patient population may lead to unknown side-effect. There is today no antidote and standardised monitoring methods are still lacking. Rivaroxaban (Xarelto®) and apixaban (Eliquis®) are approved in Switzerland for thromboembolic prophylaxis after major orthopedic surgery, such as hip and knee arthroplasty [10]. These drugs and dabigatran etexilate (Pradaxa®) are in the process of being approved for use in Switzerland to lower the risk for stroke in patients with AF. This current review will provide a short overview of the pharmacology of these novel anticoagulants and will then focus on their impact on coagulation tests, the quantification of their anticoagulant effect and the management of bleeding in patients receiving these drugs.

### Pharmacology overview

Clinicians who prescribe the novel anticoagulants need to have a basic understanding of the pharmacology of these agents. Indeed, elimination process and drug interactions are important information for the prescriber in order to prevent major side effects. In addition, knowing time to peak concentration and half-life is necessary for monitoring and reversal processes.

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**Dabigatran etexilate (Pradaxa®)**

Dabigatran is a selective, competitive, reversible, direct thrombin (factor IIa) inhibitor that is not absorbed from the intestine because it is a strongly polar and hydrophobic molecule. It is given as an absorbable prodrug, dabigatran etexilate [6]. It has a low oral bioavailability (5 to 7%) [11]. In order to optimise the intestinal absorption capsules contain tartric acid [12]. This inactive prodrug is rapidly and completely converted to the active compound by plasma esterases. Peak plasma concentration is reached 1 to 2 hours after intake and terminal half-life is 12 to 17 hours with repeated dosing, whereas the terminal half-life following a single dose is ~9 hours in healthy volunteers [6, 11]. It takes 2–3 days to reach steady-state levels [6]. About one third of the circulating drug is bound to plasma protein. The drug is predominantly cleared by the kidney (about 80% of the drug is excreted unchanged in the urine). Absorption of dabigatran etexilate is influenced by gastric pH. Therefore, food, proton pump inhibitors, postoperative state and drugs modifying the activity of the efflux transporter P-glycoprotein (dabigatran is a substrate for P-glycoprotein), such as amiodarone, quinidine, ketoconazole, clarithromycin, verapamil (inhibitors), rifampicin and St John’s wort (inducers) interfere with dabigatran etexilate absorption (table 1) [13]. In clinical studies, dabigatran was not administered to patients with a creatinine clearance <30 ml/min and the same limitation should be applied in clinical practice. A study involving patients with moderate hepatic impairment (Child-Pugh B) showed similar pharmacological profile; however, it should not be used in

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**Table 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>VKA</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Dose based on INR value</td>
<td>150 mg twice daily</td>
<td>20 mg once daily¹</td>
<td>5 mg twice daily²</td>
</tr>
<tr>
<td>Potential drug interactions</td>
<td>Multiple interactions (see involvement of CYP)</td>
<td>Drugs modifying the activity of P-gp</td>
<td>Potent inhibitors of CYP 3A4 and/or P-gp (十足 rivaroxaban plasma level)</td>
<td>Potent inhibitors of CYP 3A4 and/or P-gp (十足 apixaban plasma level)</td>
</tr>
<tr>
<td>Inhibitors (CYP 2C9, 3A4, 1A2)</td>
<td>No</td>
<td>CYP 3A4</td>
<td>CYP 3A4</td>
<td></td>
</tr>
</tbody>
</table>

VKA, vitamin K antagonists; CYP, cytochrome P450; P-gp, P-glycoprotein

¹ A reduced dose of apixaban (2.5 mg instead of 5 mg twice daily) was used for patients who met two of the following criteria: age ≥80 years, body weight ≤60 kg or creatinine ≥133 μmol/l [21, 22].

² A reduced dose of apixaban (2.5 mg instead of 5 mg twice daily) was used for patients who met two of the following criteria: age ≥80 years, body weight ≤60 kg or creatinine ≥133 μmol/l [21, 22].

References [6, 10, 14]
**Table 2**

Effects of anticoagulants on coagulation test.

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Target</th>
<th>aPTT</th>
<th>PT</th>
<th>INR</th>
<th>TT</th>
<th>Fibrinogen</th>
<th>D-dimers</th>
<th>anti-Xa</th>
<th>anti-IIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K antagonists</td>
<td>II, VII, IX, X, protein C and S</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>IIa and Xa (AT-dependant)</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Low molecular weight heparin</td>
<td>Xa (AT-dependant)</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Xa1</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Xa1</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Xa1</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
</tr>
</tbody>
</table>

AT, antithrombin; coagulation factors are indicated by roman numbers, the "a" suffix is for "activated".

1 free and bound form; 2 PT (Quick) is expressed in %

References: [6, 24, 26, 32, 35, 46]
patients with more severe liver dysfunction [6, 11, 14]. Animal studies suggest fetal toxicity therefore dabigatran should be avoided in pregnant and lactating women [6, 11, 14].

**Rivaroxaban (Xarelto®)**

Rivaroxaban competitively and specifically binds to the active site of factor Xa and blocks its interaction with prothrombin. It has a high bioavailability (80 to 100%). Peak plasma concentration is reached after 2 to 4 hours and terminal half-life is 5 to 13 hours, increasing with subject’s age [6, 15, 16]. One third of the drug is excreted unchanged by the kidney, and two thirds are converted to inactive metabolites by hepatic metabolism involving cytochrome P450 family member CYP3A4. In addition, rivaroxaban is a substrate of the transporter protein P-glycoprotein. Hence potent inhibitors of both CYP3A4 and P-glycoprotein such as azole antifungal drugs (i.e. ketoconazole and itraconazole) and proteases inhibitors used in HIV therapy (such as ritonavir) could lead to clinically relevant drug interaction (table 1). Plasma protein binding is 92 to 95%. In the clinical trial involving stroke prophylaxis in AF patients, rivaroxaban was not used in patients with a creatinine clearance <30 ml/min [17]; the same limitation should be applied in clinical practice [10]. Importantly, in this trial, a lower dose of rivaroxaban (15 mg instead of 20 mg daily) was used for patients with a creatinine clearance 30–49 ml/min [17]. Severe hepatic dysfunction (Child-Pugh C) was an exclusion criteria in clinical studies and should be a contra-indication for rivaroxaban use [10, 18]. In milder dysfunction, plasma concentration and anticoagulant effect are increased [19]. In animal models, rivaroxaban passes the placenta and is secreted into breastfeeding milk prohibiting its use for pregnant or lactating women until further notice [10, 18].

**Apixaban (Eliquis®)**

Apixaban is a highly selective, reversible, direct factor Xa inhibitor. It is an active drug with a mean bioavailability of 52.3%. Plasma concentration peaks 3 to 4 hours after drug intake and elimination half-life is 9 to 14 hours [6, 16, 20]. Plasma protein binding is about 87%. Apixaban is eliminated via multiple pathways including oxidative metabolism, renal (27%) and intestinal (56%) routes [20]. Similar to rivaroxaban, potent CYP3A4 and p-glycoprotein inhibitors such as ketoconazole and ritonavir, or inducers such as phenytoin, carbamazepin, phenobarbital and St John’s wort, should be avoided (table 1). Patients with mild to moderate renal impairment require no dosage adjustment, however apixaban should not be prescribed in patients with severe renal impairment (creatinine clearance <15 ml/min). It is worth noticing that, in clinical studies, a reduced dose of apixaban (2.5 mg instead of 5 mg twice daily) was used for patients who met two of the following criteria: age ≥80 years, body weight ≤60 kg or creatinine ≥133 µmol/l [21, 22]. Apixaban should be used with caution by patients with mild to moderate hepatic dysfunction (Child-Pugh A and B) and avoided by those with most severe (Child-Pugh C) stage [10]. Apixaban should not be used for pregnant or lactating women [10].

**Effects of novel anticoagulants on coagulation and laboratory monitoring**

Unlike vitamin K antagonists and unfractionated heparin, the novel anticoagulants do not require routine anticoagulation monitoring because they have predictable pharmacokinetics and -dynamics, as well as a wide therapeutic window. Indeed, in the various large scale phase 3 trials no routine monitoring of the treatment was performed and clinical outcomes in relation to drug levels and to coagulation tests results were not examined [6]. However, the need for monitoring or measuring the anticoagulant effect of these agents might arise in some clinical situations such as haemorrhage or thrombosis occurring under anticoagulation, an emergency surgery, suspicion or known interaction with other drugs, suspected overdose, severely impaired hepatic or renal functions, compliance monitoring and eventually bridging from one anticoagulant to another [6, 23]. The coagulation cascade model is a useful tool to integrate the effects of these novel drugs on routine coagulation tests (fig. 1). These effects are detailed in table 2.

Thrombin (factor IIa) represents the last step of the common coagulation pathway responsible for fibrin formation. In addition, it activates platelets leading to platelet aggregation and favours constriction of endothelium-denuded vessels. Dabigatran is a direct competitive thrombin inhibitor, thus independent of antithrombin activity, that interacts specifically with the active site of thrombin. It also inactivates fibrin or platelet-bound thrombin [6]. The effects of dabigatran on blood coagulation tests are proportional to plasma dabigatran concentration [6, 11, 14]. Dabigatran prolongs both the prothrombin time (PT) and the activated partial thromboplastin time (aPTT) in vitro and ex vivo in a concentration-dependant manner [24] (table 2). However, the linear relationship with the plasma concentration is lost at high concentrations and neither PT nor aPTT are recommended for measuring the precise quantitative effect of dabigatran. aPTT might be useful when no other method is available in determining excessive anticoagulation in presence of bleeding [14].

In a dose escalation study in healthy subjects, the thrombin time (TT) increases in direct proportion to plasma concentration [11]. However, since the maximum measurement time is regularly exceeded, TT appears to be too sensitive to monitor dabigatran. In addition, TT lacks standardisation across laboratories. The diluted TT might be practically applicable for monitor-
tivation products is inhibited by dabigatran. Thus, the generation of para-nitroanilide (pNA) is inversely proportional to the plasma concentration of dabigatran. The ECA dose response results are linear and do not plateau at elevated concentrations. Results are independent of coagulation factors and inhibitors within the sample. In addition, it is not influenced by lupus anticoagulant, (low-molecular-weight) heparins, danaparoid, fondaparinux and direct anti-factor Xa anticoagulants. This test might therefore also be useful for bridging and transition to other anticoagulants. The prothrombinase-induced clotting time (PiCT) assay (Pentapharm, Basel, Switzerland; http://www.pentapharm.com/files/PiCT_Flyer.pdf) is under study for dabigatran quantification [27] (fig. 4).

Factor Xa mediated activation of prothrombin is the first step of the common pathway. Rivaroxaban binds to the active site of factor Xa and blocks the interaction with its substrates. Rivaroxaban prolongs PT in a concentration-dependent manner, increases the INR and prolongs aPTT [28] (table 2). The PT seems to be more sensitive than the aPTT which is also known for the other direct factor Xa inhibitors but is not seen with indirect inhibitors. A possible explanation is that indirect factor Xa inhibitors only inhibit free factor Xa whereas direct inhibitors also bind to factor Xa in the prothrombinase complex, which is a more efficient process to reduce thrombin generation [6, 24]. Rivaroxaban exposure could therefore be determined by using the PT, preferably expressed in INR [29]. However, it is important to note that the thromboplastins used for PT measurement have various sensitivity to factor Xa direct inhibitors and the INR introduced to correct for PT sensitivity when monitoring the vitamin K antagonists does not adequately correct for differences in assay sensitivity to direct factor Xa inhibitors [30]. In a recent study, it has been shown that INR, when calibrated for rivaroxaban,
standards in determining rivaroxaban and apixaban anti-Xa activities [29, 32, 35, 36] (fig. 5).

Reversal of novel anticoagulants

There is currently no specific antidote available to antagonise the effects of the novel anticoagulants. In addition, clinical experience is insufficient to definitively guide the management of major bleeding, suspected overdose, urgently needed surgery, urgent invasive diagnostic and therapeutic procedures in patients receiving the novel anticoagulants [6, 26].

Reversal of dabigatran prior to elective surgery

Dabigatran has a relatively short half-life (13 hours) in patients with normal renal function [14]. This means that, for most patients with minor bleeding, interruption of anticoagulation is sufficient to reverse the anticoagulant effect. It is worth noticing the half-life of dabigatran increases in the case of renal dysfunction. This

allows PT normalisation. However, it is worth noticing that this is an in-vitro study [31]. TT, assessing the last step of the common pathway, downstream of thrombin, will remain largely unaffected by specific factor Xa inhibitors [28, 32]. Rivaroxaban induces underestimation of clotting factor activity measured with PT- and aPTT-clotting-based assay [32, 33]. In a recent study, this interference was overcome in vitro by diluting plasma samples prior to the analysis [33]. Rivaroxaban also causes a dose-dependent increase of the diluted Russell viper venom ratio [29]. The PiCT assay is under study for anti-IIa inhibitor quantification [27, 34] (fig. 4). Direct quantification of anti-Xa activity can be obtained by the use of colorimetric tests. First generation tests were developed for (low-molecular-weight) heparins monitoring and now largely available but not specific for direct factor Xa inhibitors. New highly sensitive tests are being developed. In absence of confounding anticoagulant, they give results very comparable to the direct concentration measurements and will likely represent the standards in determining rivaroxaban and apixaban anti-Xa activities [29, 32, 35, 36] (fig. 5).

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has to be taken into account for the reversal strategy (table 3). Creatinine needs to be checked several days before elective surgery and the clearance calculated. In patients with normal renal function and a standard bleeding risk, dabigatran has to be interrupted 24 hours prior to elective surgery. In patients at high risk of bleeding or in whom a major surgery is planned, dabigatran should be discontinued 2 to 4 days prior to surgery (table 3). TT should be measured 6–12 hours before surgery in patients at high risk of bleeding or if a major surgery is planned, and a normal result should be obtained [14]. If TT is prolonged, assessment of dabigatran’s concentration by specific tests should be performed. In patients with severe renal dysfunction and persistently elevated dabigatran plasma concentration, haemodialysis might be considered [14].

**Reversal of dabigatran in emergency**

There is no evidence-based strategy when immediate reversal is required [6, 26]. In the case of major haemorrhage, general measures [14] comprise the discontinuation of dabigatran, the initiation of an appropriate clinical support comprising mechanical compression and local as well as surgical haemostasis, blood product transfusion, volume substitution, inotropic drugs and the maintenance of an adequate diuresis. Transfusion of platelet concentrates might be considered in case of thrombocytopenia or if antplatelet drugs have been administered. The infusion of fresh-frozen plasma is limited for reversing the anticoagulation because of its small content in thrombin and the lack of evidence for its use in this indication [37]. Also, administration of prothrombin complex concentrates (PCCs) did not cause any reversal of the anticoagulant effect of dabigatran in a controlled trial in healthy human subjects [38]. However, based on in-vitro studies and animal models, PCCs or recombinant activated factor VII (rFVIIa) might be infused empirically to bypass the anticoagulant effect of dabigatran in case of life-threatening bleeding (table 4) [6, 14]. The decision for administering these drugs has to be based on the clinical state and not on the laboratory tests. In addition, it is important to be aware that

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**Table 3**

Dabigatran, renal function and elective procedure.

<table>
<thead>
<tr>
<th>Renal function creatinine clearance (ml/min)</th>
<th>Dabigatran half-life (hours)</th>
<th>Timing of discontinuation after last dose of dabigatran prior to surgery</th>
<th>High risk of bleeding/major surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>13 (11–22)</td>
<td>24 hours</td>
<td>2–4 days</td>
</tr>
<tr>
<td>&gt;50 to ≤80</td>
<td>15 (12–34)</td>
<td>24 hours</td>
<td>2–4 days</td>
</tr>
<tr>
<td>&gt;30 to ≤50</td>
<td>18 (13–23)</td>
<td>At least 2 days (48 hours)</td>
<td>4 days</td>
</tr>
<tr>
<td>≤30</td>
<td>27 (22–35)</td>
<td>2–5 days</td>
<td>&gt;5 days</td>
</tr>
</tbody>
</table>

1 Data from renal impairment study in healthy volunteers, geometric mean (range) [47].

2 Surgery associated with a high risk of bleeding (or in major surgery where complete haemostasis may be required) includes but is not restricted to neurosurgery, cardiac surgery, abdominal surgery or those involving a major organ. Procedures such as spinal anesthesia also require complete haemostatic function. Additional determinants of bleeding risk include advancing age, co-morbidities (e.g., major cardiac, respiratory or liver disease) and concomitant use of antiplatelet therapy.

3 Dabigatran etexilate is contraindicated in these patients.

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**Figure 5**

Quantification of anti-activated factor X (anti-Xa) activity – chromogenic method. These assays measure changes in color (optical density or light absorbance) after cleavage of a synthetic substrate tagged with a chromophore, para-nitroanilide (pNA), by a constant amount of exogenously added excess-activated factor X (FXa). This process is inhibited by anti-Xa anticoagulants (rivaroxaban or apixaban) present in the plasma sample to be tested. The generation of pNA is inversely proportional to the plasma concentration of dabigatran. Using dabigatran standards (S1–S4), a calibration curve is established and dabigatran plasma level back-calculated from the amount of chromophore.
PCCs and rFVIIa administration might be complicated by thrombotic events reinforcing the importance of limiting their prescription to only life-threatening haemorrhages. Dabigatran could be absorbed via haemoperfusion over a charcoal filter. In case of major life-threatening bleeding, haemodialysis is a therapeutic option (table 4) [26]. It may take 6–8 hours to clear dabigatran by dialysis. Monitoring of the reversal of the anticoagulant effect of dabigatran can be simply done by measuring TT. A normal TT would exclude a residual anticoagulant effect of dabigatran. Nevertheless, because of the extremely high sensitivity of TT, assessment of dabigatran’s concentration by specific tests would be more appropriate. The availability of these tests is however limited as they are currently only performed by specialised haemostasis laboratories and not always on a 24 hour-based schedule.

The situation of trauma patients who were under dabigatran for AF and presenting in the emergency room with life-threatening bleeding was recently debated. According to ref. [39], the fact that no antidote exists is a crucial problem. The authors expose that, in sharp contrast, VKA can be rapidly reversed, thereby reducing morbidity and mortality. In addition, these authors mention that the effect of dabigatran in these patients was not picked up by conventional haemostasis tests such as aPTT, but by thrombelastography. The RELY investigators [40] replied that there is no evidence that the lack of antidote contributed to the death of the reported trauma patients and that the current lack of antidote should not prevent the prescription of dabigatran are required. If these measures are insufficient, aPCC or rFVIIa might be administered. This current situation does not prevent the prescription of low-molecular-weight heparins.

**Reversal of novel direct factor Xa inhibitors**

For the direct factor Xa inhibitors, in view of their short half-life, cessation of medication may be sufficient to reverse the anticoagulant effect in the case of mild bleeding (table 4) [6, 26]. However, if immediate reversal of anticoagulation is required, there is no solid evidence for any reversing agent for the anticoagulant effect of any of these orally available factor Xa inhibitors so far [6, 26]. Recently it was shown that the administration of PCCs resulted in a correction of the prolonged PT and restored depressed thrombin generation after rivaroxaban treatment in a controlled trial in healthy human subjects [38]. Importantly, in a rabbit model, rFVIIa and PCCs both partially improved in-vitro coagulation tests but did not reduce rivaroxaban-induced bleeding [42]. However, it is worth noticing that the dose of rivaroxaban used in the model would be considered an overdose in the clinical setting [43]. The inefficacy of the treatment may therefore reflect a relative underdosing of rFVIIa and PCCs [43]. In view of the relatively wide availability of PCCs, this remains an interesting option for reversal, if PCCs clinical effect can be demonstrated in patients on oral factor Xa inhibitors who present with bleeding complications. For the time being, we propose to empirically antagonise direct factor Xa inhibitors by nonactivated PCCs (50 IU/kg by one shot administration) (table 4) [6, 26]. rFVIIa could represent an alternative [6, 18]. Monitoring of the reversal of the anticoagulant effect of factor Xa inhibitors is most simply done by measuring the PT. However, antifactor Xa assays are more reliable [35, 36].

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Emergency</th>
<th>Elective procedure/surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>PCCs 50 IU/kg or rFVIIa 90 µg/kg</td>
<td>Normal renal function: Stop the drug on day –1</td>
</tr>
<tr>
<td></td>
<td>Haemodialysis</td>
<td>Stop the drug on day –1</td>
</tr>
<tr>
<td></td>
<td>Haemoperfusion over a charcoal filter</td>
<td>Stop the drug on day –2</td>
</tr>
<tr>
<td></td>
<td>Overdose: activated charcoal to reduce absorption (ingestion &lt;2 hours before)</td>
<td>Control laboratory tests on day 0</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>PCCs 50 IU/kg or rFVIIa 90 µg/kg</td>
<td>Stop the drug on day –2</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>PCCs, prothrombin complex concentrate (contains factor II, VII, IX, X); rFVIIa, activated recombinant factor VIII</td>
<td>Stop the drug on day –1</td>
</tr>
</tbody>
</table>

References: [6, 10, 18, 26, 38]
Clues to prevention of bleeding complications

A well organised follow-up after the introduction of one of the novel anticoagulants is essential. Prevention of complications starts before the prescription. First, the indication to the treatment has to be confirmed and a careful review of potential drug interactions has to be conducted. Second, renal and liver functions need to be checked. In subjects over 75 years old, blood cell count, PT and aPTT measurements have to be performed prior to the administration of the novel anticoagulants [26]. The HAS-BLED score may constitute an useful tool [44]. Monitoring after 2–3 months from the introduction of the anticoagulation in order to have a steady-state laboratory value (clotting times and, when available, specific anti-IIa/anti-Xa assessment) that may be useful in the future if adverse events occur [26]. A follow-up visit at least every 6 months to check for adverse events, renal function, dyspepsia for dabigatran has to be organised [26]. Evaluation of renal function has to be performed every year in case of mild renal failure and every 6 months in case of moderate renal failure [26]. The patient should receive an identification card containing personal information, the type of anticoagulation prescribed and treatment indication. Finally, the patient her/himself should be aware of the potential side-effects and drug interactions.

Conclusion and perspectives

Although there is currently no evidence relevant to the clinical benefit for monitoring anticoagulant intensity of the novel anticoagulants in routine clinical practice, the need for measuring the anticoagulant effect of the novel anticoagulants may arise in some clinical situations such as haemorrhage and thrombosis occurring under anticoagulation, an emergency surgery, drug interaction, overdose, impaired renal or liver function, compliance monitoring.

The novel anticoagulants influence clotting times and their anticoagulant effect can be quantified by specific assays. Although these assays are not yet widely used, they are performed by most routine laboratories specialised in haemostasis.

Conventional oral anticoagulation can be reversed by specific interventions when the clinical situation requires immediate correction of haemostasis. For the novel anticoagulants, no specific antidotes or reversing agents are currently available. Although some reversal treatment can be proposed in emergencies, they need further evaluation.

Perspectives comprise the administration of novel antidotes such as antibodies directed against the anticoagulant (dabigatran, rivaroxaban or apixaban) or recombinant antidote proteins. Portola Pharmaceuticals developed a novel recombinant protein acting as a universal factor Xa inhibitor antidote (r-Antidote, PRT064445) that was shown to reverse rivaroxaban mediated anticoagulation in animal models [45].

References


