Optimizing the safety of treatment for venous thromboembolism in the era of direct oral anticoagulants

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ABSTRACT
Direct oral anticoagulants (DOACs) are rapidly replacing vitamin K antagonists (VKAs) for treatment of venous thromboembolism (VTE). The DOACs include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa. When compared with conventional VTE treatment consisting of a parenteral anticoagulant followed by a VKA, the DOACs were equally effective for prevention of recurrence, but were associated with less bleeding. With similar efficacy, better safety, and the convenience of fixed dosing without the need for routine coagulation monitoring, guidelines now recommend DOACs over VKAs for VTE treatment in patients without active cancer. Nonetheless, measures are needed to optimize the safety of DOACs. Focusing on these measures, this paper summarizes the results of phase III trials evaluating DOACs for VTE treatment; identifies which VTE patients are or are not candidates for DOACs; provides guidance on how to choose among DOACs; lists the licensed dosing information for DOACs; discusses the optimal treatment duration for VTE; describes periprocedural management of DOACs in patients requiring surgery or intervention; and finally, reviews the management of bleeding, including the role for specific reversal agents.

Introduction
Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common condition that occurs for the first time in about 1 in 1000 persons each year and the incidence rises with age. About one-third of patients with symptomatic VTE present with PE, while the remainder manifest as DVT. Within 1 month of diagnosis, death occurs in approximately 6% of patients with DVT and 12% of those with PE. Although VTE often occurs after surgery, with immobilization, or in patients with cancer, up to 50% of patients with VTE have no identifiable risk factors and are classified as having unprovoked VTE. If anticoagulant therapy is stopped in patients with unprovoked VTE, the risk of recurrence is about 10% at 1 year and 30% at 5 years. Recurrent DVT in the ipsilateral leg increases the risk of postthrombotic syndrome, a chronic disorder characterized by leg swelling and discomfort that occurs in 20% to 50% of DVT patients and can lead to venous ulcers in severe cases. Chronic thromboembolic pulmonary hypertension occurs in 2% to 4% of patients with PE and can be fatal. Therefore, VTE is a common disorder associated with significant morbidity and mortality.

Anticoagulants are the cornerstone of VTE treatment. The goal of therapy is to prevent thrombus extension or embolization, and to prevent new thrombi from forming. Conventional treatment starts with a rapidly acting parenteral anticoagulant, usually low-molecular-weight heparin (LMWH), which is overlapped with a vitamin K antagonist (VKA), such as warfarin. The parenteral anticoagulant is given for at least 5 days and is stopped when a therapeutic response to warfarin has been achieved as evidenced by an international normalized ratio (INR) between 2 and 3. Warfarin is then continued as long-term therapy for a minimum of 3 months. At this point, the decision to stop or continue treatment depends on the balance between the risk of recurrence if...
warfarin is stopped and the risk of bleeding if it is continued. Patients with VTE in the setting of transient and reversible risk factors, such as surgery, have a low risk of recurrence if anticoagulant therapy is stopped at 3 months provided that they are fully mobile. In contrast, those with ongoing risk factors, such as active cancer, and patients with unprovoked VTE are often prescribed extended anticoagulation therapy provided that the bleeding risk is not excessive. Therefore, anticoagulant treatment of VTE has been divided into 3 stages: initial therapy, long-term treatment, and extended anticoagulation.

Although conventional therapy is effective and safe, it is cumbersome because LMWH must be administered by subcutaneous injection, which is difficult for some patients, and warfarin requires frequent coagulation monitoring and dose adjustments to ensure that the INR is therapeutic. Such monitoring is cumbersome for patients and physicians and costly for health care systems. The limitations of warfarin prompted the development of direct oral anticoagulants (DOACs), which can be given in fixed doses and produce such a predictable anticoagulant response that routine coagulation monitoring is unnecessary. Because of their rapid onset of action, the DOACs enable all-oral regimens, which can replace parenteral anticoagulants and warfarin for initial, long-term, and extended VTE treatment.

Four DOACs are licensed for VTE treatment; these include dabigatran, which is an oral thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban, which are oral factor Xa inhibitors. Their approvals were based on data from phase III trials demonstrating that the DOACs were as effective as conventional therapy for prevention of recurrence, but were associated with less bleeding. With similar efficacy, better safety, and the convenience of fixed dosing without the need for routine coagulation monitoring, guidelines now recommend the DOACs over VKAs for VTE treatment in patients without active cancer. Nonetheless, measures are needed to optimize the safety of the DOACs. Focusing on these measures, this paper summarizes the results of phase III trials evaluating DOACs for VTE treatment; identifies which VTE patients are or are not candidates for DOACs; provides guidance on how to choose among DOACs; lists the licensed dosing information for DOACs; discusses the optimal treatment duration for VTE; describes periprocedural management of DOACs in patients requiring surgery or intervention; and finally, reviews the management of bleeding, including the role for specific reversal agents.

Clinical trials of direct oral anticoagulants for venous thromboembolism treatment DOACs were compared with conventional anticoagulation therapy in 27,023 patients with acute VTE in 6 phase III randomized trials; RECOVER I and II with dabigatran, EINSTEIN DVT and PE with rivaroxaban, AMPLIFY with apixaban, and HOKUSAI VTE with edoxaban. The primary efficacy endpoint in these trials was recurrent VTE or VTE-related death, while the primary safety outcome was either major bleeding or the composite of major and clinically relevant nonmajor bleeding. In a pooled analysis of the 6 trials, recurrent VTE and VTE-related deaths occurred in 2.0% of DOAC recipients compared with 2.2% of those given a VKA (relative risk [RR], 0.90; 95% confidence interval [CI], 0.77–1.06). Compared with VKAs, DOACs were associated with a 39% reduction in the risk of major bleeding (RR, 0.61; 95% CI, 0.45–0.83), a 63% reduction in intracranial bleeding (RR, 0.37; 95% CI, 0.21–0.68), and a 64% reduction in fatal bleeding (RR, 0.36; 95% CI, 0.15–0.84). In addition, clinically relevant nonmajor bleeding was reduced by 27% with the DOACs compared with VKAs (RR, 0.73; 95% CI, 0.58–0.93). Therefore, for acute VTE treatment, the DOACs are noninferior to well-managed VKA therapy, but are associated with significantly less bleeding.

The design of the phase III trials with dabigatran and edoxaban differed from those with rivaroxaban and apixaban. Whereas dabigatran and edoxaban were started after a minimum of a 5-day course of parenteral anticoagulant therapy, rivaroxaban and apixaban were administered in all-oral regimens starting with a higher dose for 21 days and 7 days, respectively. When used in this all-oral fashion, both agents were noninferior to conventional therapy and were associated with significantly less major bleeding. Therefore, DOACs simplify VTE treatment and facilitate out-of-hospital management of most patients with DVT and many with PE, thereby reducing health care costs.

Rivaroxaban, apixaban, and dabigatran have been compared with placebo for secondary VTE prevention in patients who received at least 6 months of anticoagulant therapy for their index event in the EINSTEIN-extension, AMPLIFY-EXT, and RE-SONATE trials, respectively, and dabigatran was compared with warfarin for extended therapy in the RE-MEDY trial. Pooled analyses of the 3 placebo-controlled trials revealed a significant reduction in the rate of recurrent VTE and VTE-related mortality with the DOACs compared with placebo, but an increased rate of major and clinically relevant nonmajor bleeding.

Unlike the other 2 trials, the AMPLIFY-EXT trial compared 2 dosing regimens of apixaban (2.5 mg and 5 mg twice daily) with placebo to identify the dose providing the best balance of efficacy and safety. The risk of recurrent VTE with the lower-dose apixaban regimen was similar to that with the higher-dose regimen (RR, 0.97; 95% CI, 0.46–2.02), and neither regimen was associated with a significant increase in major bleeding compared with placebo, but there was a trend for less clinically relevant bleeding with the lower-dose regimen than with the higher-dose regimen (RR, 0.74; 95% CI, 0.46–1.22). These findings suggest a superior benefit-to-risk profile with the lower-dose apixaban regimen than with the high-dose
DOACs should probably not be used in patients with a body weight over 120 kg because data on their efficacy in such patients are lacking. Patients who cannot afford the DOACs should receive conventional anticoagulant treatment because VKAs cost less than DOACs. Finally, if compliance is a concern, or if the patient is taking multiple medications that may interact with the DOACs, a VKA such as warfarin may be a better choice because INR monitoring will ensure therapeutic dosing.

Patients already on a VKA for VTE treatment should be switched to a DOAC if their INR is erratic. Switching can also be considered for patients who find INR testing and VKA dose adjustment burdensome, such as those with limited mobility or with active lifestyles. For extended treatment, the risk of bleeding is likely to be lower with DOACs than with VKAs, particularly if the dose intensity can be reduced, as was investigated with apixaban. Therefore, for patients who have already completed at least 6 months of anticoagulant treatment for their index VTE event, apixaban at a dose of 2.5 mg twice daily is a good choice. It remains to be established whether reduced dose regimens are effective for extended therapy with the other DOACs, and whether such regimens can be used in patients with a history of recurrent VTE.

Choosing a direct oral anticoagulant for venous thromboembolism treatment
In VTE patients eligible for DOACs, there is no evidence to recommend one agent over another because head-to-head data are lacking. Nonetheless, guidance can be provided based on the distinct pharmacological profiles of the DOACs, the designs of the trials in which they were investigated, and patient characteristics (Table 1). Thus, for patients with a creatinine clearance between 15 and 50 ml/min, an oral factor Xa inhibitor may be a better choice than dabigatran because factor Xa inhibitors are less dependent on renal excretion. All-oral regimens streamline the transition of care from the clinic or the emergency department to home, and rivaroxaban and apixaban are the only agents that were evaluated in this manner. Selection between the two may depend on the ease of switching from the higher initial dose to the maintenance dose at 3 weeks and 1 week, respectively, and patient preference for a once- or twice-daily regimen thereafter. In contrast, dabigatran and edoxaban should only be prescribed after patients have received a minimum of a 5-day course of therapeutic doses of heparin or LMWH treatment. Rivaroxaban or apixaban may be good choices for patients over the age of 75 with reduced renal function (creatinine clearance of 30 to 50 ml/min), particularly females with low body weight, because the benefit-to-risk profile of these agents in such patients is superior to that of conventional therapy. Dabigatran may not be the best choice in patients with a history of coronary artery disease because of its higher risk of myocardial infarction.

Maximizing the benefits of direct oral anticoagulants in clinical practice
Optimizing the efficacy and safety of DOACs depends on choosing the right drug for the right patient at the right dose and for the right duration. Proper periprocedural management of DOACs is also important to reduce the risk of bleeding.

Choosing the right anticoagulant for the right patient with venous thromboembolism
When faced with a patient with acute VTE, the first question to ask is whether the patient is suitable for treatment with a DOAC. Patients requiring thrombolytic therapy for massive PE or extensive DVT are usually treated with unfractionated heparin to start, but can be switched to a DOAC when their condition stabilizes. DOACs should be avoided in patients with planned thrombolysis, antiphospholipid syndrome with a history of arterial thrombosis, in those with renal impairment (creatinine clearance <15 ml/min for rivaroxaban, apixaban and edoxaban and <30 ml/min for dabigatran), in those with severe hepatic impairment associated with coagulopathy, in patients who are younger than 18 years old, or in women who are pregnant or breast feeding.

VKAs remain the treatment of choice for VTE patients with a creatinine clearance of less than 15 ml/min and for those with antiphospholipid syndrome, particularly when it is associated with arterial thrombosis. Although the data with DOACs in patients with cancer-associated VTE are promising, few such patients were included in randomized trials. Consequently, guidelines continue to recommend LMWH as the first-line therapy in patients with cancer-associated thrombosis. However, ongoing trials are comparing DOACs with LMWH in such patients.
TABLE 1 Choosing a direct oral anticoagulant

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Drug choice</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl, 15–50 ml/min</td>
<td>rivaroxaban, apixaban, or edoxaban</td>
<td>less affected by renal impairment than dabigatran</td>
</tr>
<tr>
<td>all-oral therapy</td>
<td>rivaroxaban or apixaban</td>
<td>dabigatran and edoxaban require heparin bridging</td>
</tr>
<tr>
<td>dyspepsia or upper GI complaints</td>
<td>rivaroxaban, apixaban, or edoxaban</td>
<td>dyspepsia with dabigatran in up to 10% of patients</td>
</tr>
<tr>
<td>recent GI bleed</td>
<td>apixaban</td>
<td>more GI bleeding with dabigatran, rivaroxaban, and high-dose edoxaban than with warfarin</td>
</tr>
<tr>
<td>significant CAD</td>
<td>rivaroxaban, apixaban, or edoxaban</td>
<td>small MI signal with dabigatran</td>
</tr>
<tr>
<td>poor compliance with twice-daily dosing</td>
<td>rivaroxaban or edoxaban</td>
<td>only agents given once daily</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CrCl, creatinine clearance; GI, gastrointestinal; MI, myocardial infarction

TABLE 2 Licensed direct oral anticoagulant dosing regimens for treatment of venous thromboembolism

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>run-in period</td>
<td>LMWH for at least 5 days</td>
<td>15 mg BID for 21 days</td>
<td>10 mg BID for 7 days</td>
<td>LMWH for at least 5 days</td>
</tr>
<tr>
<td>subsequent dosing</td>
<td>150 mg BID</td>
<td>20 mg OD</td>
<td>5 mg BID</td>
<td>60 mg OD</td>
</tr>
<tr>
<td>renal adjustment</td>
<td>110 mg BID if ≥80 years old or moderate renal impairment</td>
<td>N/A</td>
<td>N/A</td>
<td>30 mg OD if CrCl 15–50 ml/min; weight &lt;60 kg or potent P-gp inhibitors</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily; LMWH, low-molecular-weight heparin; OD, once daily; P-gp, P-glycoprotein; others, see TABLE 2

Compared with warfarin.26,27 Dabigatran should also be avoided in patients with upper gastrointestinal complaints because dyspepsia can occur in up to 10% of patients treated with this agent—a problem that tends to subside over time and can often resolve when the drug is taken with food. Except for apixaban and the 30-mg dose of edoxaban, the rate of gastrointestinal bleeding with the DOACs was higher than that with warfarin, particularly in the elderly.27 Consequently, apixaban or low-dose edoxaban may be the best choice for patients with a recent history of gastrointestinal bleeding.

The risk of bleeding with DOACs is increased with concomitant use of antiplatelet agents, such as aspirin and nonsteroidal anti-inflammatory drugs, and these agents should be avoided if possible. For patients who must use aspirin, the daily dose of aspirin should not exceed 100 mg.

Choosing the right dose of direct oral anticoagulants To maximize efficacy, it is critical that the DOACs be used in the right dose (TABLE 2). Depending on the agent, regulators have provided clinicians with dosing recommendations defined by patient characteristics including advanced age, reduced renal function, low body weight, and concomitant administration of potent P-glycoprotein inhibitors—the factors associated with increased drug exposure and increased bleeding risk (TABLE 2). Despite clear dosing recommendations, however, observational data suggest that the lower doses of DOACs are overprescribed, potentially compromising their efficacy in clinical practice.28 Education is needed to reverse this trend.

Optimal duration of venous thromboembolism treatment Optimizing the duration of anticoagulant therapy for VTE is important to minimize the risk of bleeding. All VTE patients require a minimum of 3 months of anticoagulant treatment. For patients with VTE provoked by a transient and reversible risk factor such as surgery, 3 months of anticoagulation is usually sufficient.22 In contrast, patients with ongoing risk factors, such as active cancer, or those with unprovoked VTE are often given extended anticoagulation therapy because their risk of recurrence is high if treatment is stopped.23 Therefore, many VTE patients require long-term anticoagulant therapy.

Periprocedural management in patients receiving direct oral anticoagulants Patients receiving long-term anticoagulant therapy often require elective surgery or invasive procedures, and appropriate perioperative management is important to minimize the bleeding hazard. To reduce the risk of bleeding complications, patients receiving a DOAC who require surgery associated with a moderate risk of bleeding should have the drug withheld for at least 24 hours. If the surgery is associated with a high risk of bleeding or if spinal anesthesia is planned, DOAC therapy should be stopped at least 48 hours before surgery.29 Specific guidance is provided in the product labels regarding when to stop and restart DOACs before and after surgery,20,21 as well as in practical guidelines.23,24 Assessment of the anticoagulant effect of the DOACs or quantification of drug levels can help guide the timing of surgery (TABLE 3). These assessments depend on knowing which DOAC the patient was taking, and the results must be interpreted in relation to the timing of intake of the last dose of the DOAC and consideration of the impact of renal function on the half-life of the drug. Unfortunately, drug-specific tests are not widely or rapidly available in many hospitals.
Therefore, regulators and hospitals need to work together to address this gap.

**Bleeding management in patients receiving direct oral anticoagulants**  Management of bleeding with DOACs is broadly similar to that with VKAs, but the mechanism of action and pharmacokinetic/pharmacodynamic profile of the specific drug must also be taken into account. When a bleeding event occurs, it is important to first assess its severity (ie, mild, moderate to severe, or severe and life-threatening) and location (critical or noncritical site). Mild bleeding (such as epistaxis) can usually be managed with local measures, but delaying the next dose or temporarily discontinuing treatment may be necessary for persistent bleeds. Because of their short half-lives, discontinuation of DOAC therapy usually leads to rapid normalization of coagulation tests, provided that renal function is normal. The decision to temporarily or permanently discontinue anticoagulation should always be taken with a view to balance the risk of bleeding against the risk of thrombosis.

In patients with moderate to severe bleeding events, supportive therapy is the mainstay of management. Because of the short half-life of the DOACs, most cases of bleeding will resolve within 12 hours provided that renal function is not severely compromised. The DOAC should be temporarily stopped as should concomitant long-acting antiplatelet agents (eg, clopidogrel, ticagrelor, or prasugrel) if possible. Renal function should be assessed by measuring the serum creatinine level and calculating the creatinine clearance. The anticoagulant effects or plasma levels of DOACs can be determined using commercially available and validated assays to assess the contribution of the DOAC to the bleeding event.

Routine supportive measures should be applied. This includes hemodynamic support with fluid replacement and administration of blood products, such as packed red blood cells, fresh-frozen plasma and platelets if the patient has thrombocytopenia or if they were on long-acting antiplatelet agents.

**FIGURE 1** Management of bleeding in patients taking direct oral anticoagulants (DOACs). With minor bleeding, local measures and delaying or holding 1 to 2 doses is sufficient. With moderate to severe bleeding, the DOAC should be held, and supportive therapy should be administered. Reversal is indicated with severe or life-threatening bleeding; dabigatran can be reversed with idarucizumab and prothrombin complex concentrate (PCC) can be used for reversal of rivaroxaban, apixaban, and edoxaban until specific reversal agents, such as andexanet alfa and ciraparantag, are available.
Indications for reversal of direct oral anticoagulants

Abbreviations: aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; FXa, factor Xa; PT, prothrombin time

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Assays to determine anticoagulant activity of direct oral anticoagulants</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Dabigatran</td>
</tr>
<tr>
<td>PT</td>
<td>X</td>
</tr>
<tr>
<td>aPTT</td>
<td>✓</td>
</tr>
<tr>
<td>dTT</td>
<td>✓</td>
</tr>
<tr>
<td>ECT</td>
<td>✓</td>
</tr>
<tr>
<td>anti-FXa assays</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Indications for reversal of direct oral anticoagulants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• need for urgent surgery or intervention that cannot be delayed for at least 8 hours</td>
</tr>
<tr>
<td></td>
<td>• life-threatening bleeding (eg, intracranial bleed)</td>
</tr>
<tr>
<td></td>
<td>• bleed into a critical organ (eg, intraocular bleed) or closed space (eg, pericardial or retroperitoneal bleed)</td>
</tr>
<tr>
<td></td>
<td>• ongoing bleeding</td>
</tr>
<tr>
<td></td>
<td>• expected long delay in restoration of hemostasis (eg, overanticoagulation with dabigatran in the setting of acute kidney injury)</td>
</tr>
</tbody>
</table>

Reversal agents for direct oral anticoagulant agents

Specific reversal agents include idarucizumab, which is specific for dabigatran, andexanet alfa, which reverses rivaroxaban, apixaban, edoxaban, and heparin, as well as ciraparantag, which reverses all of the DOACs and heparin (TABLE 5). Of these, idarucizumab is licensed and widely available in many hospitals, andexanet is under regulatory consideration, and ciraparantag has not yet been evaluated in patients. Until specific reversal agents for oral factor Xa inhibitors are available, PCC can be considered if specific agents are unavailable.27

Idarucizumab

A Fab fragment of a humanized antibody against dabigatran, idarucizumab (Praxbind), binds dabigatran with a 350-fold higher affinity than thrombin to form a 1:1 stoichiometric complex that is cleared by the kidneys.39 In healthy volunteers with normal or moderately impaired renal function, idarucizumab rapidly and completely reversed the anticoagulant effects of dabigatran.28

Re-administration of dabigatran 24 hours after idarucizumab administration produced full anticoagulation, and idarucizumab has been given more than once to some volunteers without any loss of its activity. The ongoing RE-VERSE AD study39 is enrolling dabigatran-treated patients with life-threatening or uncontrolled bleeding (Group A) or patients requiring emergency surgery or urgent procedures that cannot be delayed for at least 8 hours (Group B). All patients receive 5 grams of intravenous idarucizumab given as 2 boluses each of 2.5 grams no more than 15 minutes apart. Results in the first 90 patients (51 in Group A and 39 in Group B) were reported.39 Idarucizumab rapidly reverses the anticoagulant effects of dabigatran in the 81 patients with abnormal coagulation tests at baseline. In the 35 patients in Group A where the time to cessation of bleeding could be assessed, hemostasis was restored at a mean of 11.4 hours. Of the 36 Group B patients who underwent an intervention, 92% had normal hemostasis at the time of the procedure. One thrombotic event occurred within 72 hours of idarucizumab administration and 4 occurred later; anticoagulants had not been reinitiated in any of these patients.39

Andexanet alfa

Andexanet alfa (AndexXa®) is a recombinant variant of human factor Xa that has its active site serine residue replaced with an arginine residue to eliminate catalytic activity and its membrane binding γ-carboxyglutamic acid domain removed to prevent incorporation in the prothrombinase complex.40 Andexanet acts as a competitive inhibitor by binding rivaroxaban, apixaban, and edoxaban with affinities similar to that of native factor Xa, thereby serving as a decoy that sequesters the drugs until they can be cleared.40 Andexanet also reverses the anticoagulant effects of heparin, LMWH, and fondaparinux by competing with factor Xa and thrombin for binding by the heparin-antithrombin complex.41

Because it also binds tissue factor pathway inhibitor (TFPI) to form a nonproductive complex, andexanet administration is associated with a reduction in TFPI activity and transient increases in the levels of prothrombin fragment 1.2, thrombin-antithrombin complexes, and D-dimer.41 These changes are attenuated in subjects receiving oral factor Xa inhibitors because these agents compete with TFPI for andexanet binding. The clinical significance of these changes is uncertain; no thrombotic complications with andexanet have been reported to date.

In volunteers aged from 50 to 75 years, an intravenous andexanet bolus of 400 or 800 mg rapidly, but only transiently, reversed over 90% of the anti-factor Xa activity of apixaban and rivaroxaban.42 More sustained reversal was achieved when the bolus was followed by a 2-hour intravenous infusion of andexanet at a dose of 4 and 8 mg/min, respectively.42 Higher doses of andexanet are needed to reverse rivaroxaban than apixaban because the once-daily dosing of rivaroxaban results in higher drug concentrations and...
TABLE 5 Features of specific reversal agents for direct oral anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Idarucizumab</th>
<th>Andexanet α</th>
<th>Ciraparantag</th>
</tr>
</thead>
<tbody>
<tr>
<td>structure</td>
<td>recombinant humanized Fab fragment</td>
<td>recombinant human factor Xa variant</td>
<td>synthetic small molecule</td>
</tr>
<tr>
<td>molecular mass, Da</td>
<td>48000</td>
<td>39000</td>
<td>513</td>
</tr>
<tr>
<td>synthesis</td>
<td>expressed in Chinese hamster ovary cells</td>
<td>expressed in Chinese hamster ovary cells</td>
<td>chemical synthesis</td>
</tr>
<tr>
<td>mechanism of action</td>
<td>binds dabigatran with high affinity</td>
<td>competes with factor Xa for binding rivaroxaban, apixaban or edoxaban</td>
<td>binds DOACs via hydrogen bond formation</td>
</tr>
<tr>
<td>target</td>
<td>dabigatran</td>
<td>rivaroxaban, apixaban, and edoxaban</td>
<td>dabigatran, rivaroxaban, apixaban, and edoxaban</td>
</tr>
<tr>
<td>administration</td>
<td>intravenous bolus</td>
<td>intravenous bolus followed by 2-hour infusion</td>
<td>intravenous bolus</td>
</tr>
<tr>
<td>cost</td>
<td>$3500 per dose in the United States</td>
<td>unknown; likely to cost more than idarucizumab</td>
<td>unknown; likely to cost less than idarucizumab and andexanet</td>
</tr>
</tbody>
</table>

because the volume of distribution of rivaroxaban is greater than that of apixaban.

The ongoing ANNEXA-4 study is evaluating the efficacy and safety of andexanet reversal in patients taking rivaroxaban, apixaban, edoxaban, or enoxaparin who present with major bleeding.43 More recently, the study has been extended to include patients requiring urgent surgery. The initial results in the first 67 patients were reported.43 The mean age was 77 years and most presented with intracranial or gastrointestinal bleeding. Of these, 32 were taking rivaroxaban, 31 were taking apixaban and the remaining 4 were taking enoxaparin. In patients with baseline plasma rivaroxaban or apixaban concentrations over 75 ng/ml, andexanet decreased anti-factor Xa activity by 89% and 93% in those taking rivaroxaban and apixaban, respectively, after the bolus and during the infusion.43 Four hours after the infusion stopped, there was a relative decrease of 39% and 30%, respectively, indicating a rebound increase in anti-factor Xa activity. Clinical hemostasis was good to excellent in 37 of the 47 patients in the efficacy analysis. Thrombotic events occurred in 12 of 67 patients (18%) during the 30-day follow-up. Therefore, although promising, additional safety information regarding thrombotic events is needed as is information on the use of andexanet in patients requiring urgent surgery.43

Ciraparantag Ciraparantag (PER977) is a synthetic, water-soluble, cationic small molecule that was initially designed to bind to unfractionated heparin and LMWH via noncovalent hydrogen bonding and charge–charge interactions.44 Later, dynamic light scattering studies revealed that the drug also binds dabigatran, rivaroxaban, apixaban, and edoxaban.44 In rats given dabigatran, edoxaban, or enoxaparin, ciraparantag attenuated tail bleeding in this animal model and normalized the time to clot formation, as measured by thromboelastography.44

In healthy volunteers given one-time doses of edoxaban (60 mg) or enoxaparin (1.5 mg/kg), a single bolus of ciraparantag shortened the prolonged whole blood clotting time in a concentration-dependent manner.45,46 The effect persisted for 24 hours, and there was no increase in the levels of D-dimer or thrombin–antithrombin complexes suggestive of a procoagulant state. The whole blood clotting time was used to monitor the effect of ciraparantag in these studies because ciraparantag binds citrate, the reagent into which blood is collected for coagulation testing. This phenomenon precludes measurement of routine tests of coagulation or anti-factor Xa activity in subjects given ciraparantag.45,46 Unfortunately, the whole blood clotting time is not available in most hospitals. To overcome this problem, a point-of-care microfluidic device has been developed to measure the whole blood clotting time. However, this device has not yet received regulatory approval. Phase III studies with ciraparantag have not been initiated so the development of this agent lags behind that of andexanet alfa.

Prothrombin complex concentrate Several studies have shown that 3- or 4-factor PCC at least partially reverses the prothrombin time and enhances thrombin generation in volunteers given rivaroxaban or apixaban.47 Furthermore, in volunteers given edoxaban, 4-factor PCC attenuated bleeding from punch biopsy sites in a concentration-dependent manner.48 With 50 U/kg, PCC restored bleeding duration to background levels and enhanced thrombin generation. Although these findings are promising, the efficacy of PCC in patients taking oral factor Xa inhibitors who present with serious bleeding is unknown. Nonetheless, until specific reversal agents for rivaroxaban, apixaban, and edoxaban are available, PCC is a reasonable choice for such patients.

Conclusions and future directions DOACs are at least as effective as VKAs, while being safer and more convenient. As such, they are revolutionizing our approach to VTE treatment. Postmarketing studies suggest that the favorable results of clinical trials can readily be translated into practice. Nonetheless, to optimize safety there remains a need for selection of the appropriate patient, drug, and dose, as well as a careful follow-up.
The fear of uncontrolled bleeding has been lifted with the introduction of idarucizumab for dabigatran reversal. Licensing of reversal agents for oral factor Xa inhibitors will provide additional reassurance. Although DOACs represent a major advance in VTE treatment, gaps persist. For example, more information is needed about their utility in VTE patients with active cancer, their efficacy and safety in patients with a creatinine clearance between 15 and 30 ml/min, and optimal dosing in obese and pediatric patients. Such information is important because the DOACs are now being evaluated for multiple new indications. Therefore, as the use of DOACs continues to increase, ongoing efforts are needed to maximize safety.

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ARTYKUŁ POGLĄDOWY

Optymalizacja bezpieczeństwa leczenia żylnej choroby zakrzepowo-zatorowej w dobie doustnych antykoagulantów niebędących antagonistami witaminy K

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STRESZCZEŃ

Antykoagulanty niebędące antagonistami witaminy K (non-vitamin K oral anticoagulants – NOAC) coraz częściej zastępują antagonistów witaminy K (vitamin K antagonists – VKA) w leczeniu żylnej choroby zakrzepowo-zatorowej (ŻChZZ). Do NOAC zalicza się dabigatran (inhibitor trombiny) oraz rzywaroksablan, apiksaban i edoksaban, które hamują aktywność czynnika Xa. W porównaniu z konwencjonalną metodą leczenia ŻChZZ najpierw antykoagulantem podawanym pozajelitowo, a potem VKA, terapia NOAC równie skutecznie zapobiega nawrotom tej choroby i wiąże się z mniejszym ryzykiem krwawienia. Ponadto zapewnia podobną efektywność, jest bezpieczniejsza i pozwala na dogodne ustalenie dawkowania bez potrzeby rutynowego monitorowania procesu koagulacji. Według wytycznych, w leczeniu pacjentów z ŻChZZ bez aktywnego procesu nowotworowego zaleca się stosowanie NOAC zamiast VKA. Niemniej jednak, potrzebne są narzędzia do optymalizacji bezpieczeństwa terapii w trakcie leczenia NOAC. Artykuł podsumowuje wyniki badań klinicznych fazy III określające skuteczność leczenia ŽChZZ za pomocą NOAC, wskazuje, którzy pacjenci z ŻChZZ nie powinni być poddani terapii NOAC, i udziela wskazówek w zakresie wyboru odpowiedniego NOAC. Praca zawiera również informacje na temat zalecanego dawkowania, a także optymalnego czasu leczenia ŽChZZ, opis okołozabiegowej terapii NOAC przeprowadzonej wśród pacjentów, którzy wymagają zabiegu operacyjnego lub interwencji chirurgicznej, i zarys postępowania w przypadku krwawienia z uwzględnieniem roli poszczególnych środków odwracających efekt terapii.