Novel Oral Anticoagulants

Efficacy, Laboratory Measurement, and Approaches to Emergent Reversal

Eric Gehrie, MD; Christopher Tormey, MD

Warfarin, the most commonly used vitamin K antagonist (VKA) in the United States, is approved by the US Food and Drug Administration (FDA) for treatment and prophylaxis of venous thromboembolism, thrombotic events in patients with atrial fibrillation and/or cardiac valve replacement, and for the reduction in risk of thromboembolic events after myocardial infarction.1 Unfortunately, owing to a narrow therapeutic window and known interaction with various foods, bleeding events are frequently reported in patients taking warfarin.2,3 This has led to the search for novel oral anticoagulants (NOACs) that offer equivalent or improved therapeutic profiles compared to warfarin, ideally with less bleeding risk, no interactions with food, and no FDA requirements for routine laboratory monitoring. At present, there are 3 NOACs available in the United States: dabigatran etexilate (dabigatran; Pradaxa, Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut); rivaroxaban, (Xarelto, Janssen Pharmaceuticals, Titusville, New Jersey); and apixaban (Eliquis, Bristol-Myers Squibb, Princeton, New Jersey). Dabigatran is a direct thrombin inhibitor that is currently FDA approved to reduce stroke and systemic embolism risk for patients with nonvalvular atrial fibrillation.4 Rivaroxaban and apixaban are direct factor Xa inhibitors that are currently FDA approved to reduce stroke and systemic embolism risk for patients with nonvalvular atrial fibrillation.5,6 Rivaroxaban is also currently FDA approved for the treatment of deep vein thrombosis (DVT) and pulmonary embolism and to reduce recurrence of DVT and pulmonary embolism and for DVT prophylaxis in patients undergoing knee or hip replacement surgery.7 It is estimated that the cost of NOACs may exceed 60 times the cost of warfarin.8 However, the NOACs have no known interactions with food, nor do they require routine laboratory draws. Table 1 offers a summary of the properties of NOACs in comparison to warfarin.

EFFICACY OF NOVEL ORAL ANTICOAGULANTS

Several studies have been performed to compare the effect of NOACs to established therapies.5 The findings of the major studies that led to the FDA approval for dabigatran, rivaroxaban, and apixaban are summarized below.

Dabigatran etexilate

One large, randomized trial (the Randomization Evaluation of Long-Term Anticoagulation Therapy [RE-LY]) compared 2 doses of dabigatran therapy (110 mg and 150 mg) to warfarin therapy in patients with atrial fibrillation and an increased stroke risk.8 Both doses of dabigatran were found to be noninferior to warfarin therapy for the prevention of stroke or systemic embolism.8 Treatment with 150 mg of dabigatran was superior to warfarin for the prevention of stroke or systemic embolism.8 However, the rate of myocardial infarction was higher among patients taking either dose of dabigatran than patients taking warfarin.8 While both doses of dabigatran had lower rates of intracranial hemorrhage and life-threatening bleeding than warfarin therapy, the 150 mg dose of dabigatran was more likely than warfarin to cause major gastrointestinal bleeding.8 Interestingly, the FDA did not approve the 110-mg dose of dabigatran, but did approve a 75-mg dose for use in patients with impaired renal function without an additional clinical trial.9 A subsequent phase 2 dose-validation study found that dabigatran therapy was associ-
Table 1. Properties of Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (Coumadin, Bristol-Meyers Squibb, Princeton, New Jersey)</th>
<th>Dabigatran (Pradaxa, Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut)</th>
<th>Rivaroxaban (Xarelto, Janssen Pharmaceuticals Inc, Titusville, New Jersey)</th>
<th>Apixaban (Eliquis, Bristol-Meyers Squibb, Princeton, New Jersey)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Oral VKA</td>
<td>Oral DTI</td>
<td>Oral factor Xa inhibitor</td>
<td>Oral factor Xa inhibitor</td>
</tr>
<tr>
<td>FDA-approved</td>
<td>Prophylaxis and treatment of VTE/PE; prophylaxis and treatment of thromboembolism associated with aFib or heart valve; reduction in death risk or recurrent MI or thromboembolic events after MI.</td>
<td>To reduce stroke and systemic embolism risk for patients with nonvalvular aFib.</td>
<td>To reduce stroke and systemic embolism risk for patients with nonvalvular aFib.</td>
<td>To reduce stroke and systemic embolism risk for patients with nonvalvular aFib.</td>
</tr>
<tr>
<td>indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boxed label warning</td>
<td>Can cause major or fatal bleeding; perform regular monitoring (INR) on patients receiving treatment; drugs, dietary changes, and other factors affect INR levels; instruct patients how to prevent bleeding and to report signs or symptoms of bleeding.</td>
<td>Increased risk of stroke if discontinued without adequate continuous anticoagulation.</td>
<td>Increased risk of stroke if discontinued without adequate continuous anticoagulation.</td>
<td>Increased risk of stroke if discontinued without adequate continuous anticoagulation.</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>~40</td>
<td>12–17</td>
<td>5–9</td>
<td>6 h with single dose, 12 h repeated dosing</td>
</tr>
<tr>
<td>Dose</td>
<td>Adjusted to achieve target INR</td>
<td>75- or 150-mg tablets twice daily, depending on CrCl</td>
<td>10-, 15-, 20-mg tablets dosing depends on CrCl and indication</td>
<td>2.5 or 5 mg twice daily, depending on age, weight, and serum Cr</td>
</tr>
<tr>
<td>Discontinue before surgery?</td>
<td>Consider benefits and risks</td>
<td>Yes: CrCl &gt; 50 mL/min, 1–2 d CrCl &lt; 50 mL/min, 3–5 d</td>
<td>Yes: at least 24 h</td>
<td>Yes: moderate or high risk: &gt;48 h Low risk: &gt;24 h</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Category D if heart valve, otherwise X</td>
<td>Category C</td>
<td>Category C</td>
<td>Category B</td>
</tr>
<tr>
<td>CYP450 inhibitor, inducer, or substrate?</td>
<td>Urine and feces</td>
<td>Urine and feces</td>
<td>Substrate of CYP3A4 and CYP 2J2</td>
<td>Urine and feces</td>
</tr>
<tr>
<td></td>
<td>Substrate of CYP2C9, 2C19, 2C8, 2C18, 1A2, 3A4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aFib, atrial fibrillation; Cr, creatinine; CrCl, creatinine clearance; CYP, cytochrome P; DTI, direct thrombin inhibitor; DVT, deep vein thrombosis; FDA, US Food and Drug Administration; INR, international normalized ratio; MI, myocardial infarction; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

* For a detailed discussion of dabigatran discontinuation before surgery, please see van Ryn et al.14

A large, double-blind clinical trial (ROCKET AF) comparing rivaroxaban (15 or 20 mg daily dose) to dose-adjusted warfarin (target international normalized ratio [INR]: 2–3) concluded that rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation and an increased risk of stroke.11 ROCKET AF also found that rivaroxaban therapy was associated with less intracranial hemorrhage and fewer fatal bleeds, but more major gastrointestinal bleeds, compared to warfarin therapy.11 An open-label, randomized noninferiority study (EINSTEIN) compared rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg daily for 3, 6, or 12 months) to the low-molecular-weight heparin enoxaparin (1 mg/kg body weight, dosed twice daily) followed by either warfarin or acenocoumarol (to achieve an INR of 2–3) for patients with acute, symptomatic DVT.12 This study found that rivaroxaban was noninferior to enoxaparin followed by warfarin, with equivalent rates of major bleeding; however, the patients receiving VKA therapy were only found to be within the INR therapeutic range approximately 57.7% of the time.12 A randomized, double-blind, placebo-controlled continued treatment study (EINSTEIN – extension) compared rivaroxaban 20 mg daily to placebo for 6 to 12 months in patients with a history of symptomatic DVT or pulmonary embolism who had already completed 6 or 12 months of VKA or rivaroxaban therapy.13 This trial found that rivaroxaban therapy reduced the rate of recurrent venous thromboembolism compared to placebo without increasing the risk of fatal bleeding.13 Finally, a randomized, double-blind clinical trial (RECORD3) comparing oral rivaroxaban (10 mg daily) to subcutaneous enoxaparin (40 mg once...
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Table 2. Laboratory Monitoring of US Food and Drug Administration–Approved Oral Anticoagulants

<table>
<thead>
<tr>
<th>Property/Drug</th>
<th>Warfarin (Coumadin, Bristol-Meyers Squibb, Princeton, New Jersey)</th>
<th>Dabigatran (Pradaxa, Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut)</th>
<th>Rivaroxaban (Xarelto, Janssen Pharmaceuticals Inc, Titusville, New Jersey)</th>
<th>Apixaban (Eliquis, Bristol-Meyers Squibb, Princeton, New Jersey)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine monitoring required?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Qualitative assessment of NOAC levels</td>
<td>N/A</td>
<td>aPTT, PT, TT</td>
<td>PT</td>
<td>PT</td>
</tr>
<tr>
<td>Quantitative assessment of NOAC levels</td>
<td>PT/INR</td>
<td>dTT, ECA, ECT</td>
<td>Chromogenic anti-factor Xa</td>
<td>Chromogenic anti-factor Xa</td>
</tr>
</tbody>
</table>

Abbreviations: aPTT, activated partial thromboplastin time; dTT, dilute thrombin time; ECA, ecarin chromogenic assay; ECT, ecarin clotting time; FDA, US Food and Drug Administration; INR, international normalized ratio; N/A, not applicable; NOAC, novel oral anticoagulant; PT, prothrombin time; TT, thrombin time.

a Therapeutic range has not been determined.
b These assays are not FDA approved and are not routinely available.
c Care must be taken to use appropriate calibrator (see text for details).

daily) in patients undergoing total knee arthroplasty found that treatment with rivaroxaban provided more effective thromboprophylaxis than treatment with enoxaparin.13 Rivaroxaban and enoxaparin therapy were associated with similar instances of major bleeding.13

Apixaban

A large, double-blind clinical trial (ARISTOTLE) comparing apixaban (5 mg twice daily) to dose-adjusted warfarin (target INR: 2–3) found that apixaban was superior to warfarin for the prevention of ischemic or hemorrhagic stroke or systemic embolism among patients at risk for stroke and with atrial fibrillation.14 The ARISTOTLE trial also found that patients taking apixaban were less likely to suffer major or nonmajor bleeding or to die than patients taking warfarin.14

LABORATORY MEASUREMENT OF NOVEL ORAL ANTICOAGULANTS

Because VKAs have a narrow therapeutic index and various factors (including diet and genetics) influence response to therapy, patients taking VKAs are routinely monitored by using the INR. In contrast, NOACs have predictable pharmacokinetics, eliminating the need for routine laboratory assessment. As a result, NOAC-specific laboratory assays are not widely available at present.3–6 While the lack of routine monitoring is convenient and may help to mitigate some of the costs associated with NOACs, it may be informative to measure NOAC levels in patients presenting with relatively high or low body weight, renal insufficiency (dabigatran), patients taking other medications that alter P-glycoprotein and cytochrome P3A4 metabolism, or in patient populations that were not included in NOAC clinical trials.15 In addition, the lack of a well-characterized NOAC laboratory assay may complicate the management of cases of NOAC overdose, NOAC-associated life-threatening bleeding, or the scheduling of urgent surgery in patients taking NOACs.16 Therefore, it is recommended that clinical laboratories have a strategy for the assessment of NOAC-induced changes in coagulation.15 In addition, clinical laboratories should be aware that—depending on the drug and the methodology—NOAC therapy may alter clotting factor, protein C, antithrombin, and/or fibrinogen assays performed in clinical laboratories.15 Approaches for laboratory assessment of NOACs are discussed below and summarized in Table 2.

Dabigatran etexilate

Dabigatran therapy is known to prolong numerous routine laboratory assessments of hemostasis, including the activated partial thromboplastin time (aPTT), the prothrombin time (PT), and the thrombin time (TT). Of these, the aPTT is suggested in the dabigatran package insert.4 However, there is no defined aPTT therapeutic range for dabigatran,4,16 and the aPTT assay is relatively insensitive to different plasma concentrations of some direct thrombin inhibitors.16,17 In addition, the aPTT may not be used to assess dabigatran therapy if the patient has a lupus anticoagulant or an intrinsic clotting factor deficiency, as the aPTT prolongation from these conditions will mask the effect of dabigatran on the aPTT.18 In comparison to the aPTT, the TT is far more sensitive and the PT is less sensitive to dabigatran therapy.15 Therefore, a normal aPTT or TT most likely excludes therapeutic levels of dabigatran, while a normal PT may not.15

Quantitative assessment of dabigatran levels can be obtained with the dilute thrombin time (dTT), the ecarin clotting time, or the ecarin chromogenic assay.16 Unfortunately, at present, these assays are not generally available and do not yet have FDA approval for measuring levels of dabigatran or other direct thrombin inhibitors.16–18 Some laboratories may elect to make these assays available as laboratory-developed tests.16

Rivaroxaban and Apixaban

As with dabigatran, routine assessment is not required for patients taking rivaroxaban or apixaban owing to their predictable pharmacokinetics.5,6 At present, no assays or calibration reagents are FDA approved for the measurement of the direct oral factor Xa inhibitors, although such reagents may be available to clinical laboratories on a research use only basis. While rivaroxaban and apixaban have been shown to affect routine coagulation tests, including the aPTT, activated clotting time, PT, and chromogenic anti-factor Xa assay,15,19 no therapeutic ranges exist, complicating the interpretation of the results of these tests.19,20 Overall, studies using spiked plasma samples suggest using either the PT (for a qualitative assessment of direct oral factor Xa inhibitors) or the chromogenic anti-factor Xa assay (for a quantitative assessment of direct oral factor Xa inhibitors).15,19–21 The PT provides a relatively more sensitive assessment of rivaroxaban and apixaban than the aPTT or the activated clotting time.15,19 Authors of a study performed
by the manufacturer of apixaban recommended the chromogenic anti–factor Xa assay for assessment of apixaban.\(^1\) If the chromogenic anti–factor Xa assay is used, it is important to use the appropriate calibrator (and specifically not to use heparin calibrators).\(^2\) If the PT assay is used, the performing laboratory should be aware that PT prolongation is sensitive to the thromboplastin reagent and conversion to the INR increases measurement variability.\(^3\)

**POTENTIAL REVERSAL OF NOVEL ORAL ANTICOAGULANTS**

Vitamin K antagonists mediate their anticoagulant effect by inducing a deficiency of coagulation factors II, VII, IX, and X. Therefore, VKA reversal can be accomplished by stopping the VKA, replacing vitamin K and providing an exogenous source of vitamin K–dependent clotting factors.\(^2\) In contrast, NOACs mediate their anticoagulant effect by directly inhibiting their target coagulation factors. Accordingly, a successful strategy to reverse NOACs would require either removing the drugs from circulation or overwhelming their inhibitory effects. While a 4-factor prothrombin complex concentrate (PCC) was recently FDA approved for the reversal of warfarin in patients with acute, major bleeding,\(^4\) no specific NOAC reversal agent (or “antidote”) is available for clinical use to date. In addition, no clinical trials have been conducted to assess the efficacy of PCCs or recombinant factor VIIa (rFVIIa) in bleeding patients taking NOACs.\(^5\) While NOACs have shorter half-lives than warfarin\(^6\) and are not associated with a higher risk of bleeding, it may be necessary to attempt to reverse the effect of NOACs in cases of life-threatening bleeding, or in cases where other clinical factors are preventing timely clearance of a NOAC. Although there is insufficient evidence to formulate clear clinical guidelines, considerations in the treatment of NOACs (accumulated from case reports/series and the authors’ experiences) are discussed below and summarized in Table 3.

**Dabigatran etexilate**

There is no FDA-approved specific reversal agent for dabigatran and there are no clinical trials that have studied the efficacy of various interventions in bleeding patients taking dabigatran.\(^6\) In cases where intervention beyond supportive care is deemed to be necessary (eg, life-threatening bleeding or suspected overdose), there is limited evidence to support the use of activated charcoal therapy if the dabigatran was ingested within 1 to 2 hours.\(^6\) In certain clinical situations, hemodialysis may be considered, as dabigatran is only 35% bound to plasma proteins and, according to the manufacturer, hemodialysis may remove 49% to 57% of dabigatran within 4 hours.\(^7\) Several studies have been published investigating the efficacy of PCCs, rFVIIa, and/or fresh frozen plasma (FFP) in animal models of bleeding.\(^8\) A murine model of dabigatran-associated bleeding found that rFVIIa and combinations of rFVIIa plus a 4-factor PCC improved the aPTT, but not blood loss volume.\(^9\) Treatment with either the combination of rFVIIa plus a 4-factor PCC or treatment with factor eight inhibitor bypass activity (FEIBA, an activated PCC) improved the bleeding time but had an insignificant effect on blood loss.\(^9\) Another murine model reported that 4-factor PCC, but not rFVIIa, reduced expansion of intracranial hematomas.\(^9\) In contrast, a study of dabigatran-associated bleeding in a rabbit model showed that treatment with the 4-factor PCC reduced blood loss and improved bleeding time.\(^9\)

### Table 3. Considerations in the Emergent Reversal of Oral Anticoagulants in the Setting of Moderate to Severe Hemorrhage

<table>
<thead>
<tr>
<th>Property/Drug</th>
<th>Warfarin (Coumadin, Bristol-Myers Squibb, Princeton, New Jersey)</th>
<th>Dabigatran (Pradaxa, Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut)</th>
<th>Rivaroxaban (Xarelto, Janssen Pharmaceuticals Inc, Titusville, New Jersey)</th>
<th>Apixaban (Eliquis, Bristol-Myers Squibb, Princeton, New Jersey)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Product</strong></td>
<td>Platelets</td>
<td>No(^a)</td>
<td>No(^a)</td>
<td>No(^a)</td>
</tr>
<tr>
<td></td>
<td>FFP</td>
<td>Yes(^b)</td>
<td>No(^a)</td>
<td>No(^a)</td>
</tr>
<tr>
<td></td>
<td>Cryoprecipitate</td>
<td>No(^a)</td>
<td>No(^a)</td>
<td>No(^a)</td>
</tr>
<tr>
<td></td>
<td>3-Factor PCC</td>
<td>Yes(^b,c)</td>
<td>Consider(^c,d)</td>
<td>Consider(^c,d)</td>
</tr>
<tr>
<td></td>
<td>4-Factor PCC</td>
<td>Yes(^b,e)</td>
<td>Consider(^c)</td>
<td>Consider(^c)</td>
</tr>
<tr>
<td></td>
<td>FEIBA</td>
<td>No</td>
<td>Consider(^c,d)</td>
<td>Consider(^c,d)</td>
</tr>
<tr>
<td></td>
<td>rFVIIa</td>
<td>No</td>
<td>Consider(^c,d)</td>
<td>Consider(^c,d)</td>
</tr>
<tr>
<td></td>
<td>Antifibrinolytics</td>
<td>No</td>
<td>No(^d)</td>
<td>No(^d)</td>
</tr>
<tr>
<td><strong>Drug Removal</strong></td>
<td>Activated charcoal</td>
<td>No</td>
<td>Recommend(^d)</td>
<td>Recommend(^d)</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis</td>
<td>No</td>
<td>Recommend</td>
<td>No</td>
</tr>
<tr>
<td><strong>Other Therapy</strong></td>
<td>Vitamin K</td>
<td>Yes(^b,c)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: FEIBA, factor eight inhibitor bypass activity; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa.

\(^a\) The use of FFP, platelets, or cryoprecipitate may be indicated owing to blood loss, but these therapies would not be expected to be helpful as monotherapy in the reversal of the novel oral anticoagulants.

\(^b\) Consult Guyatt et al\(^2\) for specific recommendations.

\(^c\) At hospitals where 4-factor PCC is not available, the blood bank may consider using a 3-factor PCC or an activated product (FEIBA or rFVIIa). For details, see Winkler and Tormey.\(^6\) Activated factors may be more thrombogenic than the 4-factor PCC.

\(^d\) To date, no clinical trial has been performed to assess the efficacy of this approach.

\(^e\) A 4-factor PCC that is intended to be administered with vitamin K was recently approved by the US Food and Drug Administration for the purpose of treating major bleeding in patients taking vitamin K antagonists.\(^6\)

\(^f\) Only thought to be effective if the last dose was within 1 to 2 hours (eg, in an overdose).
The applicability of these animal models to patients receiving dabigatran who experience major bleeding is uncertain. One randomized, placebo-controlled trial in healthy males treated with dabigatran showed that treatment with a 4-factor PCC did not reverse the dabigatran effect on aPTT, endogenous thrombin potential lag time, TT, or the ecarin clotting time.30

There are several case reports of patients with life-threatening bleeding associated with dabigatran therapy with variable reported responses to intervention.31–38 Many of the reports seem to indicate that treatment with FFP, rFVIIa, PCCs, fibrinogen, and/or platelets were not helpful in achieving clinically relevant levels of hemostasis,33,35,36 with a few reports suggesting a benefit from rFVIIa, hemodialysis, or PCC therapy.33,34,36 There is 1 report of what appears to be a dramatic response to FEIBA, but this outcome has not been confirmed by other published case reports.38

Overall, the available information from animal models, a clinical trial in healthy young volunteers, and a series of case reports does not identify a generalizable, evidence-based strategy to achieve hemostasis in dabigatran-associated bleeding. It seems that activated charcoal therapy within 1 to 2 hours of a dose and hemodialysis are the most effective strategies, in the proper clinical context. Other therapies, such as PCCs and rFVIIa, may be considered in cases of life-threatening bleeding, but the potential benefits, as well as the potential inefficacy of the therapy, should be weighed against the possibility of thrombosis on a patient-by-patient basis.

At our institutions, we are consulted several times per month for recommendations to achieve “reversal” of dabigatran in bleeding patients. Our approach at present is to recommend drawing pretreatment laboratory tests (PT/INR, PTT, TT, and a complete blood count) and, in the event of an overdose within the past 2 hours, the administration of activated charcoal. If the patient has mild bleeding (defined as World Health Organization [WHO] grade 1–2), we recommend supportive care and careful observation. If the patient has life-threatening bleeding (WHO grade 3–4), we recommend hemodialysis if (1) the patient’s creatinine clearance is below 30 mL/min, (2) the patient has acute kidney injury, and (3) the last dose of dabigatran was more than 2 but less than 12 hours before presentation. If criteria for hemodialysis are not met, we recommend delaying/discontinuing dabigatran, fluid support (including blood product support) as needed, and the consideration of off-label use of 4-factor PCC (25 units/kg, dose not to exceed 2500 units). We do not recommend redosing the 4-factor PCC, nor do we recommend providing rFVIIa or FEIBA within 24 hours of a dose of the 4-factor PCC owing to our concern for possible thromboembolic complications.

**Rivaroxaban and Apixaban**

Similar to dabigatran, activated charcoal may prevent absorption of rivaroxaban and apixaban if administered 1 to 2 hours after ingestion.5,6 Rivaroxaban and apixaban are highly bound to plasma proteins and therefore, unlike dabigatran, there is no role for hemodialysis in the management of bleeding associated with their use.5,6 There is no currently available “antidote” for rivaroxaban or apixaban.5,6 Notably, a promising factor Xa inhibitor reversal agent (andexanet-α) has been reported in the medical literature, tested in an animal model, and is currently undergoing clinical trials.39 At present, however, andexanet-α is not available for clinical use.

Animal models have been used to study the effect of various interventions on rivaroxaban-related bleeding. One study of rivaroxaban-induced bleeding in a rabbit model reported that a 4-factor PCC and recombinant factor VIIa (rFVIIa) improved coagulation laboratory studies but did not significantly reduce bleeding.40 Another study41 showed that a 4-factor PCC, FEIBA, and rFVIIa improved laboratory assessments of coagulation and reduced bleeding times in rats treated with rivaroxaban. A baboon model of rivaroxaban-associated bleeding also showed potential utility of FEIBA and rFVIIa in rivaroxaban reversal.41

No human clinical trials have been performed to assess the efficacy of various interventions on rivaroxaban-related bleeding. However, a randomized, placebo-controlled study of young, healthy volunteers treated with 20 mg of rivaroxaban, dosed twice daily, found that administration of a 4-factor PCC led to normalization of the PT and the endogenous thrombin potential (apixaban was not evaluated).30 In contrast, an in vitro study using human plasma obtained from healthy donors found that rFVIIa was superior to a 4-factor PCC at normalizing laboratory coagulation studies.42

Animal studies of apixaban-related bleeding are sparse.43 One rabbit model of apixaban-related bleeding found that treatment with rFVIIa, 4-factor PCC, or a fibrinogen concentrate failed to reduce hepatosplenic blood loss, with fibrinogen concentrate treatment actually increasing blood loss and bleeding time.44 At present, we are not aware of any case reports of emergent apixaban reversal.43

Similar to dabigatran, we are periodically consulted for recommendations to achieve reversal of rivaroxaban or apixaban in bleeding patients. As with dabigatran reversal, we always recommend drawing pretreatment laboratory tests (PT/INR, PTT, and a complete blood count) and, in the event of an overdose within the past 2 hours, the administration of activated charcoal. If the patient has mild bleeding (defined as WHO grade 1–2), we recommend supportive care and careful observation. If the patient has life-threatening bleeding (WHO grade 3–4), we recommend delaying/discontinuing the drug in question, fluid support (including blood product support) as needed, and the consideration of off-label use of a one-time dose of the 4-factor PCC (25 units/kg, dose not to exceed 2500 units). As with dabigatran reversal, we do not recommend redosing the 4-factor PCC, nor do we recommend providing rFVIIa or FEIBA within 24 hours of a dose of the 4-factor PCC.

**CONCLUSION**

Based on data from recent clinical trials, there is reason to believe that NOACs may offer some benefits over warfarin in certain clinical circumstances. In particular, it is believed that patients may reduce the risk of thrombotic events as well as the risk of treatment-related bleeding events while avoiding therapeutic monitoring by taking NOACs instead of warfarin for certain indications. However, warfarin has been in use for decades and has the benefit of a widely available monitoring test (PT/INR) as well as several treatment options for reversal. Although it is currently believed that patients taking NOACs have fewer life-threatening bleeding events than patients taking warfarin, the safety of NOAC therapy is undermined by a lack of informative coagulation tests for NOAC measurement and the lack of specific NOAC reversal agents. At present, it is prudent for clinical laboratories to be aware of the effect of...
NOACs on routine coagulation assays and to develop an approach to guide testing in circumstances where there is a clinical need to measure NOAC levels. Ideally, the clinical laboratory would act as a diagnostic consultant in NOAC-associated bleeding and, together with the blood bank, guide rational (if not evidence-based) treatment for patients with NOAC-associated bleeding. Clinical trials assessing various interventions in bleeding patients (such as hemodialysis, 3- or 4-factor PCCs, rFVIIa, anti fibrinolytic therapies, or, potentially, an antidote such as andexanet-a) would be very helpful toward the development of evidence-based guidelines for NOAC reversal.

References