Management of bleeding and reversal strategies for oral anticoagulants: Clinical practice considerations

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Oral anticoagulants are used to manage a variety of common age-related conditions (e.g., atrial fibrillation), and the frequency of their use will likely rise significantly in the United States as the population ages. The number of elderly Americans 65 years of age or older is expected to increase markedly over the next two decades, from 39.6 million in 2009 to 72.1 million by 2030. Nearly one in five Americans will be elderly in 2030.

Warfarin has been widely used since it was introduced more than 50 years ago, but it is a less-than-ideal anticoagulant because of its narrow therapeutic range, interactions with numerous drugs and foods, and need for routine laboratory monitoring. Warfarin is a common cause of emergency hospitalization in elderly patients and of serious, disabling, or fatal injury from bleeding in patients of all ages.

The recent introduction of the oral direct thrombin (factor IIa) inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban and apixaban was eagerly anticipated because these agents do not require routine coagulation monitoring and are associated with a lower number

Purpose. Currently available clinical data and optimal strategies for reversing oral anticoagulants in patients who are bleeding or need an urgent invasive procedure or operation are reviewed.

Summary. Bleeding from oral anticoagulants, including new target-specific oral agents (TSOAs), is a common cause of morbidity and mortality, especially in elderly patients. Limited clinical data are available to guide the reversal of warfarin or TSOAs in patients who are bleeding or need an urgent invasive procedure or operation. A panel of five experts with diverse backgrounds in anticoagulation therapy, cardiology, critical care, and emergency medicine and with experience in managing complications of anticoagulation therapy was convened to develop practical strategies for managing patients receiving oral anticoagulants who are bleeding or have an urgent need for an invasive procedure. The strategies were designed to guide clinicians in the acute care setting by providing efficient and potentially effective management concepts to avoid delays in initiating treatment that could adversely affect patient outcomes. The consensus of this expert panel is summarized herein. Recommendations are based on currently available evidence from a comprehensive review of the literature and other pertinent data, along with the experience and expert opinion of the panelists.

Conclusion. Bleeding is a serious complication of the use of oral anticoagulants, and limited information is available to guide the reversal of warfarin or TSOAs in patients who are bleeding or are in need of an urgent invasive procedure. Use of a systematic approach to assessing and treating these patients based on available evidence and expert opinion can help avoid delays that could adversely affect patient outcomes.

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of clinically significant drug interactions. Also, unlike warfarin, which inhibits hepatic production of the vitamin K-dependent clotting factors II, VII, IX, and X, these new oral anticoagulants act on specific components in the coagulation cascade.

In separate clinical trials comparing dabigatran, rivaroxaban, or apixaban with warfarin for stroke prevention in patients with atrial fibrillation, the risk for major bleeding was significantly lower with apixaban compared with warfarin, and there was no significant difference in the risk of major bleeding between dabigatran (the larger of the two dosages evaluated) or rivaroxaban when compared with warfarin.3-7 The rate of intracranial hemorrhage was significantly lower with all three target-specific oral anticoagulants (TSOAs) when compared with warfarin. However, the rate of major gastrointestinal bleeding was significantly higher with dabigatran (the larger of two dosages evaluated) and rivaroxaban compared with warfarin, though there was no significant difference in gastrointestinal bleeding between apixaban and warfarin.

Whether the safety profile of the TSOAs in clinical practice will mirror event rates reported in large clinical trials remains to be determined. It is also unclear if outcomes may be different between agents once major bleeding occurs. Observational studies and postmarketing surveillance will assist in further clarifying the real-world safety profile of these agents. Elderly patients with renal impairment are particularly vulnerable to bleeding during treatment with dabigatran.8 During 2011, the FDA MedWatch adverse-event-reporting program received more reports of dabigatran-associated serious, disabling, or fatal injury due to bleeding compared with warfarin.4 For the second quarter of 2012, reports to the MedWatch program indicated that dabigatran was associated with a fivefold higher risk of death than warfarin after adjusting for age, sex, and the type and source of the report.5 However, in a subsequent FDA analysis of insurance claims and administrative data, gastrointestinal and intracranial bleeding rates associated with newly initiated dabigatran did not appear to be higher than bleeding rates associated with newly initiated warfarin.9-11 Therefore, the differences between dabigatran and warfarin in the MedWatch data may reflect reporting biases, such as a greater tendency to report problems with the newer drug.10 Interestingly, in the second quarter of 2012, rivaroxaban was also associated with a larger number of serious injury reports to the FDA MedWatch program and a nearly twofold higher risk of death in cases of bleeding compared with warfarin.9 Data on apixaban were not collected because the drug did not have FDA-approved labeling at that time. Regardless, the use of any anticoagulant carries a risk of bleeding, so it is vital to have a strategy to manage or prevent bleeding complications.

Guidelines developed by the American College of Chest Physicians (ACCP) address options for reversing the anticoagulant effects of warfarin and mitigating the risk of warfarin-associated bleeding.12 These guidelines involve withholding warfarin and, because of the time needed for the depletion of vitamin K-dependent clotting factors, administration of exogenous vitamin K (phytonadione) and clotting factor concentrates when urgent reversal is needed. Because clinical trials exploring the emergent reversal of warfarin and TSOAs in patients who are bleeding or need an urgent invasive procedure are limited or nonexistent, there is a certain degree of subjectivity involved in the available guidelines, leaving knowledge gaps in how to best manage these patients.

In light of these knowledge and management gaps, a panel of five experts (the authors of this article) with diverse backgrounds in anticoagulation therapy, cardiology, critical care, and emergency medicine and with experience in managing complications of anticoagulation therapy was convened during the ASHP Midyear Clinical Meeting in Las Vegas, Nevada, on December 5, 2012, for the purpose of developing practical strategies for managing patients receiving oral anticoagulants who are bleeding or have an urgent need for an invasive procedure. The strategies were designed to guide clinicians in the acute care setting by providing efficient and potentially effective management concepts to avoid delays in initiating treatment that could adversely affect patient outcomes.

This article summarizes the consensus of this expert panel. Recommendations are based on currently available evidence from a comprehensive review of the literature and other pertinent data, along with the experience and expert opinion of the assistance of Carla J. Brink, M.S., B.S.Pharm., and Susan R. Dombrowski, M.S., B.S.Pharm., in manuscript development is acknowledged.

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the panelists. Tools and strategies for patient assessment are provided for use with a user-friendly algorithm and tables for patient assessment and treatment as part of paper-based or electronic systems. These materials can be readily updated to reflect emerging data and adapted to meet the unique needs of individual institutions and the patient populations they serve. The lists, algorithm, and tables can be hyperlinked as part of a clinical decision-support system. These materials provide only a framework for clinical decision-making; applying them to the care of individual patients requires clinical judgment.

This article does not represent consensus guidelines of the American Society of Health-System Pharmacists or any other organization, and the recommendations are not graded on level of evidence.

**Pharmacokinetics and pharmacodynamics of oral anticoagulants**

The pharmacokinetics and pharmacodynamics of warfarin are well characterized and described elsewhere. The pharmacokinetics of TSOAs are summarized in Table 1. The kidneys play a more important role in the elimination of dabigatran compared with rivaroxaban and apixaban. Therefore, the potential for drug accumulation and bleeding in patients with impaired renal function, a common condition in elderly patients, is of greater concern with the direct thrombin inhibitor dabigatran than the other two TSOAs. The plasma protein binding of dabigatran is low, enabling removal by hemodialysis (e.g., at least half of the dabigatran in plasma was removed over a four-hour hemodialysis session in experimental models). By contrast, rivaroxaban and apixaban are highly protein bound and unlikely to be dialyzable.

Dabigatran is a substrate for the efflux transporter P-glycoprotein and can interact with P-glycoprotein inhibitors and inducers. Concomitant use with potent P-glycoprotein inhibitors can increase the bioavailability of dabigatran and the risk of bleeding. In renally impaired patients who are receiving dabigatran and a P-glycoprotein inhibitor, the enhanced dabigatran bioavailability and reduced clearance are likely to lead to even greater systemic exposure and risk of bleeding.

Rivaroxaban and apixaban are substrates for P-glycoprotein and cytochrome P-450 (CYP) isoenzyme 3A4 and can interact with inhibitors and inducers of P-glycoprotein and CYP3A4. Concomitant use of these TSOAs with potent inhibitors of P-glycoprotein or CYP3A4 can increase the risk of bleeding, especially when doses are given closely together or at the same time. Additional details about drug interactions involving TSOAs are available in the product labeling and published literature.

As with warfarin, the anticoagulant effects of TSOAs are highly influenced by their pharmacokinetics. The pharmacodynamic effects of these drugs, however, also reflect their effects on the clotting cascade, resulting in changes in coagulability not predicted by pharmacokinetics alone. For example, there is evidence to suggest that discontinuation of rivaroxaban could be followed by a rebound increase in coagulation (i.e., a procoagulable state) mediated by prothrombin and clotting factors V and X. The clinical significance of this phenomenon is unclear.

![Table 1. Pharmacokinetics of Target-Specific Oral Anticoagulants](image_url)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal elimination of unchanged drug, %</td>
<td>80</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td>Half-life by age, hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young, healthy adults</td>
<td>12–14</td>
<td>5–9</td>
<td>8–15</td>
</tr>
<tr>
<td>Elderly</td>
<td>12–14</td>
<td>11–13</td>
<td></td>
</tr>
<tr>
<td>Half-life by renal function, hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL&lt;sub&gt;r&lt;/sub&gt; &gt;80 mL/min</td>
<td>14</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>CL&lt;sub&gt;r&lt;/sub&gt; 50–79 mL/min</td>
<td>17</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>CL&lt;sub&gt;r&lt;/sub&gt; 30–49 mL/min</td>
<td>19</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>CL&lt;sub&gt;r&lt;/sub&gt; &lt;30 mL/min</td>
<td>28</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Protein binding, %</td>
<td>35</td>
<td>92–95</td>
<td>87</td>
</tr>
<tr>
<td>Dialyzable?</td>
<td>Yes</td>
<td>Unlikely</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

Key drug interactions

- Potent inhibitors and inducers of P-glycoprotein
- Potent inhibitors of P-glycoprotein or CYP3A4

<sup>a</sup>CL<sub>r</sub> = creatinine clearance, CYP = cytochrome P-450 isoenzyme.

<sup>b</sup>Data not available.
Laboratory assessment of anticoagulation effects

The prothrombin time (PT) and International Normalized Ratio (INR) are common assays used to assess the anticoagulation effects of warfarin therapy. Although routine anticoagulant monitoring is not required during treatment with TSOAs, laboratory assessment could provide valuable insight into the level of anticoagulation during treatment with these agents or after interruption of therapy in patients with bleeding. Laboratory assays may be used to assist in decisions about when it is safe for a patient to undergo surgery or restart anticoagulant therapy. The response to therapeutic interventions to reverse anticoagulation (e.g., hemodialysis) also may be monitored using laboratory tests, though most tests are of limited value, and care must be taken in interpreting these results.

The usefulness of laboratory tests varies with the anticoagulant being used (Table 2). The availability of certain tests in clinical practice is limited. For example, the ecarin clotting time (ECT) test is the most useful for assessing dabigatran anticoagulation because it is sensitive to the drug at all concentrations, but the ECT test is not widely available.22 The commercially available nondiluted thrombin time (TT) test is very sensitive to the level of dabigatran, making the test useful at low concentrations but not higher concentrations of dabigatran.24 The activated partial thromboplastin time (aPTT) and PT tests are widely available but are not ideal for quantifying the amount of dabigatran present.24 The PT test is less sensitive than the aPTT test at usual concentrations of dabigatran.22

Limited data are available for laboratory assessment of coagulation during treatment with the factor Xa inhibitors rivaroxaban and apixaban. Chromogenic antifactor Xa assays are useful for monitoring coagulation during therapy with these agents. However, the need to calibrate the assay for the specific factor Xa inhibitor and the contribution of variables that can influence results present notable challenges in using these assays.27 Given that such calibrators are becoming available,28 some laboratories are now bringing this test onsite. As with any test, it is important to know the reliability of the assay and assess the clinical presentation when incorporating results into management decisions.

Several newer coagulation assays have been developed and may be used in certain specialized situations, though data are not currently available to determine the clinical usefulness of these tests. These newer tests include thromboelastography, thrombin generation curve, plasma-diluted TT, chromogenic ECT, and diluted PT.22 Thromboelastography has been used as a tool to guide transfusions in the presence of bleeding, and it may be used during surgery or in trauma centers to provide insight into the possible causes of and ways to mitigate bleeding. The usefulness of thromboelastography in the presence of TSOAs, however, has not been established.

As noted, interpretation of laboratory coagulation test values and therapeutic decision-making require consideration of each patient’s specific scenario and clinical status. For example, administration of hemostatic agents may stem bleeding without affecting laboratory coagulation test results in a patient needing an urgent invasive procedure.29 In addition, the timing of the last anticoagulant dose should be considered when scheduling and interpreting coagulation test values. Turnaround time is also a critical point in the practical applicability of these assays, particularly in the hemorrhaging patient. Frequent reassessment of the patient’s clinical status and laboratory tests may be needed to accommodate acute changes in unstable patients.

Reversal agents

Various interventions may be used to reverse the effects of warfarin, including oral and i.v. phytonadione, fresh frozen plasma (FFP), and clotting factor concentrates. Concentrated clotting factor products, FFP, activated charcoal, and hemodialysis also have been considered for reversing the effects of TSOAs. Various antidotes for reversal of TSOAs are in development, but they are not yet available.30-32 FFP is obtained from human blood and contains all of the vitamin K-dependent clotting factors in plasma. The large volume of fluid administered is a potential disadvantage of using FFP.31 The limited data from FFP use for reversing TSOAs to date have not been encouraging.24

Concentrated clotting factor products include three- and four-factor prothrombin complex concentrate (PCC) products, recombinant factor VIIa (rFVIIa), and activated PCC (aPCC, also known as antihemophilia factor complex, factor VIII inhibitor bypassing activity, or FEIBA). The PCC products vary in their clotting factor content, but all three-factor PCC (PCC3) products contain inactivated clotting factors II, IX, and X and only small amounts of factor VII in an inactivated form. Four-factor PCC (PCC4) products contain a larger amount of inactivated clotting factor VII than PCC3 products as well as clotting factors II, IX, and X in an inactivated form. Activated PCC contains clotting factor VII in an activated form and clotting factors II, IX, and X primarily in an inactivated form. The risk for thrombosis is a concern with clotting factor concentrates, especially activated products. This risk must be weighed against the potential benefit of using these products for anticoagulant reversal.

Some PCC4 products and aPCC contain the natural regulatory anticoagulant protein C, protein S, or both.22,35,36 Some PCC3 and PCC4 products (but not aPCC or rFVIIa) contain heparin, which is a concern...
Table 2. Various Laboratory Tests To Consider When Concerned About Bleeding With Warfarin and Target-Specific Oral Anticoagulants (TSOAs)\textsuperscript{22-26,a}

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCr and CBC with platelets</td>
<td>Potentially useful</td>
<td>Potentially useful</td>
<td>Potentially useful</td>
<td>Potentially useful</td>
<td>Monitor serum calcium concentration if transfusing blood</td>
</tr>
<tr>
<td>INR or PT</td>
<td>Potentially useful; value increased</td>
<td>Potentially useful; value increased; use central laboratory because point-of-care test can give much higher values</td>
<td>Potentially useful; value increased</td>
<td>Potentially useful; value increased</td>
<td>PT may be considered because INR may not be calibrated for the TSOAs; PT more responsive to factor Xa inhibitors than to dabigatran; limited ability to quantify amount of drug</td>
</tr>
<tr>
<td>aPTT</td>
<td>Potentially useful; value somewhat increased</td>
<td>Potentially useful; value increased, but aPTT response flattens at higher serum drug concentration</td>
<td>Potentially useful; value increased</td>
<td>Potentially useful; value increased</td>
<td>aPTT more responsive to dabigatran than to factor Xa inhibitors; limited ability to quantify amount of drug</td>
</tr>
<tr>
<td>TT</td>
<td>Clinical use limited</td>
<td>Potentially useful; very sensitive at low concentration but not useful at higher concentration</td>
<td>Inadequate measure</td>
<td>Inadequate measure</td>
<td>Limited ability to quantify amount of dabigatran</td>
</tr>
<tr>
<td>ECT</td>
<td>Clinical use limited</td>
<td>Potentially useful if available; potential ability to quantify amount of drug present</td>
<td>Inadequate measure</td>
<td>Inadequate measure</td>
<td>Limited availability; potential quantitative test</td>
</tr>
<tr>
<td>Diluted TT</td>
<td>Clinical use limited</td>
<td>Potentially useful if available; potential ability to quantify amount of drug present</td>
<td>Inadequate measure</td>
<td>Inadequate measure</td>
<td>Lack of standardization and potential differences in measured results among laboratories; may have limitations at low dabigatran concentration</td>
</tr>
<tr>
<td>Chromogenic antifactor Xa assay</td>
<td>Inadequate measure</td>
<td>Inadequate measure</td>
<td>Potentially useful; value increased</td>
<td>Potentially useful; value increased</td>
<td>Limited availability; nonstandardized; results may vary among laboratories where available</td>
</tr>
</tbody>
</table>

\textsuperscript{a}SCr = serum creatinine, CBC = complete blood count, INR = International Normalized Ratio, PT = prothrombin time, aPTT = activated partial thromboplastin time, TT = thrombin time, ECT = ecarin clotting time.
The effects of a PCC4 product had no effect on aPTT, ECT, or TT in dabigatran-treated volunteers. The PCC4 product normalized the PT and endogenous thrombin potential within 15 minutes in rivaroxaban-treated participants. A measure of thrombin generation (Cofact, Sanquin Blood Supply, Amsterdam, Netherlands) on the anticoagulant effects of dabigatran and rivaroxaban were also evaluated in vitro. Blood samples from healthy volunteers were spiked with rivaroxaban to simulate the composition of blood samples during clinical testing. The effects of a PCC4 product or placebo followed by the PCC4 product had no effect on aPTT, ECT, or TT in dabigatran-treated volunteers. The PCC4 product normalized the PT and endogenous thrombin potential within 15 minutes in rivaroxaban-treated participants.

### Table 3. Recommended Dosing of Concentrated Clotting Factor Products for Oral Anticoagulant Reversal

<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Clotting Factor(s) Replaced</th>
<th>Dose(s) for Reversal of Specific Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Warfarin</td>
</tr>
<tr>
<td>PCC3</td>
<td>II, IX, and X (inactivated)</td>
<td>25–50 units/kg</td>
</tr>
<tr>
<td>PCC4</td>
<td>II, VII, IX, and X (inactivated)</td>
<td>25–50 units/kg</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>VII (activated)</td>
<td>17.7–53.4 µg/kg</td>
</tr>
<tr>
<td>aPCC</td>
<td>II, IX, X (inactivated) and VII (activated)</td>
<td>500 units for INR of &lt;5 and 1000 units for INR of ≥5</td>
</tr>
<tr>
<td>Building of PCC4</td>
<td>PCC3: II, IX, and X (inactivated); rFVIIa: VII (activated)</td>
<td>PCC3 30 units/kg (or a fixed dose of 4000 units/kg for an 80-kg patient) + rFVIIa 1 mg if rFVIIa is not available, the addition of a small dose of FFP (1–2 units) to PCC3 could be considered</td>
</tr>
</tbody>
</table>

*PCC3 = three-factor prothrombin complex concentrate, PCC4 = four-factor prothrombin complex concentrate, rFVIIa = recombinant factor VIIa, aPCC = activated prothrombin complex concentrate, INR = International Normalized Ratio, FFP = fresh frozen plasma.

Experience with the doses listed in this table for reversal of oral anticoagulants is limited. Aside from one abstract at the time of writing, there are insufficient data to make specific dosing recommendations for apixaban. Current references and the product labeling should be consulted for the most recent information about appropriate dosing of concentrated clotting factor products. Depending on the urgency of bleeding and estimated anticoagulant effect, lower doses can be used initially and increased as necessary to achieve the desired effect. Doses of PCC and aPCC products are expressed as units of the factor IX component and FEIBA units, respectively. The composition of PCC products varies, so doses of different products may not be equivalent.

Data are not available on PCC3 use for target-specific oral anticoagulant reversal. Doses of 25–50 units/kg can be considered if a PCC4 product or aPCC is not available.

Higher doses of rFVIIa have been associated with increased thrombosis risk. If this option is selected, a lower dose of approximately 20 µg/kg is suggested.

Limited effects noted in vitro or ex vivo even at higher doses; usefulness unclear.

Based on limited case reports.

Larger aPCC doses corresponding to 80 units/kg were evaluated in an ex vivo study of dabigatran and rivaroxaban. The initial aPCC dose should be based on the severity of bleeding, keeping in mind that additional doses can be given. Lower doses (e.g., 1 vial or ~5–10 units/kg) can be considered initially for emergent procedures, such as vascular line placement; however, limited supportive evidence is currently available.

Limited data are available regarding the benefits of concentrating clotting factor products for reversing TSOAs in humans. In addition, the dosages of these reversing agents used experimentally are not considered in this table. The composition of PCC products varies among manufacturers. Dosages of PCC and aPCC are expressed as units of the factor IX component and FEIBA units, respectively.

Information about the composition of clotting factor products is available in the product labeling and additional sources.22-38 Relevant literature is summarized elsewhere.18,33,53-56 Dosages are expressed as FEIBA units. The composition of prothrombin complex concentrates can be considered.

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(upto 800 µg/L), and PCC4 was added to these samples in concentrations used clinically to reverse the effects of vitamin K antagonists. PT (Innovin, Dade Behring, Liederbach, Germany), endogenous thrombin potential, and calibrated automated thrombo- 
graphy assays were performed with varying tissue factor concentrations. The PCC4 product did not neutralize the increase in PT and lag time of rivaroxaban-anticoagulated blood in vitro, suggesting that the Innovin PT may not be applicable for the in vitro assessment of rivaroxaban reversal by PCC4. However, the total thrombin potential was normalized, and the response of the different thrombin generation tests was found to be dependent on assay conditions. In contrast to these findings, the ex vivo study by Eerenberg et al. found that the PT of healthy human volunteers receiving rivaroxaban could be normalized using PCC4.

In the in vitro study evaluated the impact of different clotting factor concentrates in reversing the actions of apixaban. Whole-blood samples from healthy volunteers were mixed with apixaban (200 ng/mL), and various clotting factor concentrates were added to these samples. The clotting factor concentrates PCC4 (50 units/kg; Beriplex, CSL Behring, Marburg, Germany), aPCC (75 units/kg; Feiba, Baxter, Westlake Village, CA), and rFVIIa (270 µg/kg; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) compensated for or reversed apixaban’s anticoagulant action with varying degrees of efficacy. Thrombin generation improved most with the administration of PCC4, followed by aPCC and then rFVIIa. Correction of clotting time responded best to rFVIIa, followed by aPCC and then PCC4.

The effects of another PCC4 product (Kanokad, LFB-Biomedicaments, Paris, France), rFVIIa, and aPCC on the anticoagulant effects of dabigatran and rivaroxaban were evaluated by Marlu and colleagues in an ex vivo, crossover study of 10 healthy male volunteers. Venous blood samples were obtained immediately before and two hours after single 150-mg doses of dabigatran etexilate or 20-mg doses of rivaroxaban and exposed to several concentrations of PCC4 (0.25, 0.5, and 1 unit/mL, with the intermediate concentration corresponding to a dose of 25 units per kilogram of body weight), rFVIIa (0.5, 1.5, and 3 µg/mL, with the highest concentration corresponding to a dose of 120 µg/kg), and aPCC (0.25, 0.5, 1, and 2 units/mL, with the 1-unit/mL concentration corresponding to a dose of 80 units per kilogram of body weight). After a two-week washout period, blood samples were obtained immediately before and two hours after the volunteers received the other anticoagulant. The PCC4 product and rFVIIa had inconsistent effects on laboratory values of thrombin generation in dabigatran- and rivaroxaban-treated blood samples. However, aPCC had a consistent impact on thrombin generation in rivaroxaban-treated blood. The impact of aPCC on thrombin generation in dabigatran-treated blood was less consistent than the effect on rivaroxaban-treated blood, though the impact of aPCC on dabigatran-treated blood was greater than that of PCC4 and rFVIIa. These findings suggest that aPCC may play a role in reversing the anticoagulant effects of rivaroxaban and perhaps dabigatran.

Levi et al. evaluated the effects of PCC4 (Beriplex) and PCC3 (Profilnine, Grifols Biologicals, Los Angeles, CA) products on PT and thrombin generation in an open-label, parallel-group study in 35 healthy adult volunteers treated with rivaroxaban 20 mg twice daily for four days to attain steady-state concentrations. On day 5, four hours after rivaroxaban administration, participants were randomized to receive a single bolus dose of PCC3 50 units/kg, PCC4 50 units/kg, or 100 mL of 0.9% sodium chloride injection (control). The PT and endogenous thrombin potential were measured before and serially after the administration of PCC or the control. While PCC4 reduced the mean PT by 2.5–3.5 seconds, PCC3 resulted in a mean reduction of only 0.6–1.0 second. In contrast to its effect on the PT, PCC3 more effectively reversed rivaroxaban-induced changes in endogenous thrombin generation (area under the concentration–time curve, peak, and time-to-peak values) than did PCC4. Changes in lag time values did not differ greatly. The discrepancy in these results on PT and thrombin generation may reflect the absence of factor VII in PCC3 (Profilnine) and the presence of heparin in PCC4 (Beriplex). Additional studies are needed to further clarify these issues. The administration of the PCC products in this study was deemed safe and well tolerated, with no signs of prothrombotic response reported.

The limited availability of data in humans requiring reversal of the anticoagulant effects of TSOAs using the reversal agents listed in Table 3 leaves large gaps in knowledge about the best approach to use in clinical practice. Further research is underway to fill these gaps. Examples include the REVNEWANTICO study, a randomized, open-label, controlled, crossover, Phase IV study examining the use of PCC, rFVIIa, and aPCC after the administration of single 150-mg dabigatran etexilate doses and the use of a specific rivaroxaban decoy (Gla-domainless activated factor X) after the administration of a single 20-mg rivaroxaban dose in 10 young, healthy, male volunteers.

The antifibrinolytic agentsaminocaproic acid and tranexamic acid have been used to minimize blood loss during surgery. However, data are not available to characterize the role of these agents in managing serious bleeding in patients receiving oral anticoagulants.
Clinical management of bleeding
The management of patients receiving oral anticoagulants who are bleeding or need an urgent invasive procedure requires weighing the risks for thrombosis and bleeding and consideration of short- and long-term treatment goals. Individualization of therapy is needed, taking into consideration these goals, age, renal function, clinical status, and laboratory test results.

If a patient has bleeding or needs an urgent invasive procedure, a medication history should be obtained (Figure 1). If the medication history reveals the use of an anticoagulant, therapy should immediately be discontinued and the patient’s risk for thrombosis should be assessed (Table 4). The time since the last anticoagulant dose should be determined. Institutional or published tools (e.g., CHADS2 or CHA2DS2-Vasc risk scoring system for atrial fibrillation) should be used to determine the risk for thrombosis.59,60 The reasons for anticoagulation therapy (e.g., atrial fibrillation, venous thromboembolism prophylaxis or treatment, cardiac valve) and the use of antiplatelet therapy or other medications that contribute to bleeding or excessive anticoagulation effects (e.g., drug interactions) should be taken into consideration.

If the patient is bleeding, the considerations listed in Table 5 should be used to further evaluate the patient. The bleeding location, bleeding severity (i.e., volume of blood loss), and accessibility of the bleeding site should be assessed. The feasibility of surgical intervention, including mechanical procedures and the ability to drain or remove blood, can affect patient outcomes. Bleeding in enclosed spaces, especially the central nervous system (e.g., intracranial hemorrhage), eyes, and pericardium, can have devastating consequences. Imaging and other diagnostic test results (e.g., endoscopy), physical examination findings, overt evidence of bleeding, and vital signs provide insight about the bleeding location and its severity. Laboratory test results, including a complete blood count, and the patient’s clinical status also must be considered when evalu-

Figure 1. Management of patients with bleeding or needing an urgent invasive procedure.
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ating and managing a patient with bleeding.

If the anticoagulated patient is not bleeding and requires an invasive procedure, the considerations and strategies listed in Table 6 should be used to further evaluate the patient. The risk for bleeding and thrombosis from the procedure must be balanced with the risk of thrombosis from the interruption of anticoagulant therapy, taking into consideration the indication for the anticoagulant before an invasive procedure is planned. Institutional or published guidelines (e.g., ACCP guidelines) can be consulted to guide the risk assessment.61-65 The urgency and timing of the planned procedure in relation to the last dose of anticoagulant, the pharmacokinetics and pharmacodynamics of the anticoagulant therapy in use, concurrent drug interactions, and laboratory test results (e.g., level of anticoagulation, renal impairment) should be considered.61

The actions taken after completing the assessments in Tables 4–6 depend on the type of oral anticoagulant and the urgency of the need for intervention (Table 7). Patients may be stratified based on the urgency of the need for intervention in one of three categories: (1) patients for whom no action is needed within 24 hours (i.e., when there is no rush to make a decision), (2) patients for whom an expedited decision is needed within 1–24 hours, and (3) patients with an emergent need for intervention within 1 hour (i.e., patients with life-threatening bleeding or an urgent need for a procedure). The clinical status and laboratory test results of anticoagulated patients with or at risk for bleeding are subject to change, so these classifications are not fixed. For example, a patient with an expedited need for intervention may need to be reclassified as having an emergent need for intervention if his or her condition deteriorates and becomes life threatening.

The choice of therapeutic options

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Table 4.

Considerations in Assessing Risk of Thrombosis in Patients Receiving Oral Anticoagulantsa

<table>
<thead>
<tr>
<th>Oral anticoagulant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug and dosing regimen</td>
</tr>
<tr>
<td>• Time since last dose</td>
</tr>
</tbody>
</table>

| History of or current hypercoagulable condition |
| Nonvalvular atrial fibrillation (use CHADS2 or CHA2DS2-Vasc risk scoring systemb) |
| Presence of cardiac thrombus on recent echocardiogram |
| VTE prophylaxis (use institutional or published guidelines for risk assessment) |
| • Positive history of recent VTE (within past 6–12 mo) (assess time since last event and number of events) |
| • Negative history of VTE but at high risk for VTE |

| Cardiac valve |
| • Type (mechanical valve has higher thrombotic risk compared with tissue valve) |
| • Position (mitral valve has higher thrombotic risk compared with aortic valve) |

| Other |
| • Mechanical device or vascular hardware, arterial thromboembolic disease (individualize risk assessment) |
| • Recent administration of concentrated clotting factors |

| Use of medications that contribute to thrombosis |
| • Indication for use |
| • Type of therapy |
| • Risk associated with withholding therapy |

aVTE = venous thromboembolism.

bCHADS2 score estimates stroke risk based on the following factors: congestive heart failure, hypertension, age of ≥75 years, diabetes mellitus, and history of embolic stroke or transient ischemic attack. CHA2DS2-Vasc score is a modification of the CHADS2 score that aims to improve stroke risk prediction in patients with atrial fibrillation by adding three risk factors: age of 65–74 years, female sex, and history of vascular disease.

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Table 5.

Considerations in Assessing Bleeding in Patients Receiving Oral Anticoagulantsa

| Vital signs |
| Physical examination for external evidence of hemorrhage (e.g., epistaxis, open fracture, scalp laceration) |

| Diagnosis of internal hemorrhage (e.g., endoscopy, CT scan, ultrasound) |

| Access to bleeding site and feasibility of intervention |

| Bleeding severity (i.e., assessment of significance of blood loss) |

| Laboratory test results (see Table 2) |
| • Level of anticoagulation |
| • Markers for blood loss (e.g., CBC, serum lactate concentration, arterial blood gas and basic metabolic panel to evaluate for presence of acidosis) |
| • Organ function (e.g., LFT values, SCr) |
| • Additional test considerations (e.g., serum calcium concentration if transfusing with blood products, fibrinogen, thromboelastogram) |

| Clinical status |
| Need for emergent procedures |
| Rebound anticoagulant effect after administering concentrated clotting factors |
| Allergies and any recent concern for heparin-induced thrombocytopenia |

aBecause the clinical and laboratory status of patients with bleeding is subject to change, frequent monitoring is needed. CT = computed tomography, CBC = complete blood count, LFT = liver function test, SCr = serum creatinine.
may be limited by the resources and agents available at each institution. Follow-up clinical decision-making should address whether and when to reinitiate oral anticoagulant therapy to reduce the risk of thrombosis and the use of alternative shorter-acting agents.

Warfarin. In all patients who are bleeding or need an urgent invasive procedure, warfarin should be withheld and laboratory test values (i.e., INR or PT) should be used to assess the level of anticoagulation (Table 7). In patients for whom an intervention is not needed for more than 24 hours, oral phytonadione should be

### Table 6.
Considerations in Assessing Nonbleeding Patients Receiving Oral Anticoagulants Who Require Invasive Procedures

<table>
<thead>
<tr>
<th>Indication for oral anticoagulant use</th>
<th>Risk for thromboembolic events associated with interruption of oral anticoagulant therapy for invasive procedure</th>
<th>Need for bridging with alternative anticoagulant</th>
<th>Planned procedure or surgery</th>
<th>Laboratory test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk for bleeding and thrombosis from intervention (use published or institutional guidelines for risk assessment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Because the clinical and laboratory status and risk for bleeding and thrombosis in patients with indications for oral anticoagulant therapy who undergo invasive procedures are subject to change, frequent clinical and laboratory monitoring and risk assessment are needed. LFT = liver function test, SCr = serum creatinine.

### Table 7.
Therapeutic Interventions for Reversal of Oral Anticoagulants Based on Urgency

<table>
<thead>
<tr>
<th>Level of Urgency</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban or Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>No rush (&gt;24 hr)*</td>
<td>Withhold warfarin and consider oral phytonadione, with dose based on INR</td>
<td>Withhold drug and monitor clinical status and pertinent laboratory tests</td>
<td>Withhold drug and monitor clinical status and pertinent laboratory tests</td>
</tr>
<tr>
<td>Expedited (1–24 hr)*</td>
<td>Withhold drug and give oral phytonadione (1–5 mg) or low-dose i.v. phytonadione (0.25–5 mg), with dose based on initial INR and postreversal INR (checked 24 hr after dose)</td>
<td>Withhold drug, give activated charcoal* if last dose was taken within past 2 hr, and use prolonged hemodialysis (&gt;2 hr)</td>
<td>Withhold drug and give activated charcoal* if last dose was taken within past 2 hr and repeat 6 hr after the last dose</td>
</tr>
<tr>
<td>Emergent (&lt;1 hr)</td>
<td>Withhold drug, consider high-dose i.v. phytonadione (depending on anticipated need to restart warfarin), and consider clotting factor supplement (listed in order of preference):</td>
<td>Withhold drug, give activated charcoal* if last dose was taken within past 2 hr, use prolonged hemodialysis (&gt;2 hr), and consider clotting factor supplement (listed in order of preference):</td>
<td>Withhold drug, give activated charcoal* if last dose was taken within past 2 hr and repeat 6 hr after the last dose and consider clotting factor supplement (listed in order of preference):</td>
</tr>
<tr>
<td></td>
<td>• PCC4</td>
<td>• aPCC</td>
<td>• PCC3</td>
</tr>
<tr>
<td></td>
<td>• Build PCC4 with PCC3 plus rFVIIa</td>
<td>• PCC4</td>
<td>• Build PCC4 with PCC3 plus rFVIIa</td>
</tr>
<tr>
<td></td>
<td>• aPCC</td>
<td>• rFVIIa</td>
<td>• PCC3</td>
</tr>
<tr>
<td></td>
<td>• FFP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The intervention may need to be modified based on changes in the patient’s clinical status (e.g., if status worsens, expedited or emergent treatment options should be considered). INR = International Normalized Ratio, PCC4 = four-factor prothrombin complex concentrate, PCC3 = three-factor prothrombin complex concentrate, rFVIIa = recombinant factor VIIa, aPCC = activated prothrombin complex concentrate, FFP = fresh frozen plasma.

*Contraindicated in the setting of gastrointestinal bleeding.

*IV, phytonadione doses exceeding 2 mg may not increase the rate or extent of INR reversal after 24–48 hours compared with 2-mg doses. Large doses (i.e., 5–10 mg) could be considered if there is no plan to restart warfarin in the near future.

*In some health systems, rFVIIa is used in combination with PCC3 to enhance the factor VII effects of the reversal strategy. If rFVIIa is not available, the addition of a small dose of FFP (1–2 units) to PCC3 could be considered.

*While FFP is currently the most widely used option for warfarin reversal in the United States, the expert panel ranked the other options higher than FFP based on current evidence and existing guidelines.5–7

*The order of PCC3 in this listing was based on the availability of a single abstract at the time of writing.6 Pending release of the full study data, clinician preference for these listed options may change.
considered, with the dose based on the initial INR and postreversal target INR. In patients for whom an intervention is needed within 1–24 hours, oral or low-dose i.v. phytonadione should be administered, with the dose depending on the INR.

Warfarin-treated patients with an emergent need for intervention (e.g., life-threatening bleeding) or no plans to subsequently restart warfarin can receive high-dose (5–10 mg) i.v. phytonadione along with concentrated clotting factor products or FFP. Phytonadione 5–10 mg by slow i.v. injection plus PCC4 is recommended for emergent warfarin reversal by ACCP. There is increasing evidence suggesting that i.v. phytonadione doses exceeding 2–3 mg are no more effective for reversing the INR in acutely ill patients treated with warfarin, and higher doses may increase the need for and duration of bridging therapy (i.e., dual anticoagulation with another anticoagulant plus warfarin to prevent thrombosis once bleeding has resolved) compared with smaller doses. These phenomena may reflect the fat-soluble nature of vitamin K (i.e., storage of excess vitamin K in adipose tissues) and warfarin refractoriness (i.e., resistance to the effects of warfarin when the drug is restarted). The lower-dose phytonadione strategy may be attractive in situations without life-threatening bleeding and where warfarin may be reinitiated within one to two weeks.

Given the paucity of comparative trials, a definitive strategy for reversal of the INR in warfarin-treated patients is not clear, and the expert panel’s suggested therapeutic interventions are based on the available evidence and clinical experience (Table 7). The expert panelists’ first choice for reversal of the INR in a warfarin-treated patient with serious bleeding or an emergent need for intervention is PCC4, which has been shown to promptly— but only partially—reverse the INR. If premade PCC4 is not available, the expert panelists suggest that a better option than using PCC3 alone is building a PCC4 product by using low-dose rFVIIa in combination with PCC3 to enhance the factor VII effects of the reversal strategy. Using FFP with PCC3 may also be considered as an alternative method for providing factor VII. Use of PCC3 plus FFP appears more effective for reducing the INR than PCC3 alone or FFP alone. There is evidence that PCC3 plus rFVIIa is more effective for reducing the INR than PCC3 plus FFP, though it may carry an increased risk of thromboembolism if the dose of factor VIIa is high.

The use of aPCC is an alternative to building a PCC4 product, with evidence suggesting that aPCC appears to be more effective for INR reversal than FFP alone. In addition, use of small doses (11–25 µg/kg) of rFVIIa has been shown to completely reverse the INR, though the impact of this intervention on bleeding outcomes is unclear.

Dabigatran. The approach to reversing dabigatran in a patient with bleeding or the need for an invasive procedure depends on the urgency of the need for intervention. Guidance is available for how much time should elapse between the last dose of dabigatran and an invasive procedure based on renal function and the risk of bleeding, which varies by surgery type (Table 8). TT, aPTT, and INR/PT are commonly available tests for detection of the presence of dabigatran, but the results are not quantitative (Table 2). Diluted TT and ECT may be more useful for quantifying the amount of dabigatran present, but these tests are not commonly available in practice. Thromboelastography and activated clotting time may be considered, depending on the availability of the test and the clinical situation. However, one trauma group reported that the only abnormal thromboelastographic value in a patient who died from a dabigatran-related

### Table 8.

**Interuption of Target-Specific Oral Anticoagulant Therapy for Invasive Procedures and Surgery**

<table>
<thead>
<tr>
<th>Drug (Renal Function)</th>
<th>Time of Last Dose Before Minor Procedure</th>
<th>Time of Last Dose Before Major Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL &gt; 50 mL/min</td>
<td>1 day (24 hr)</td>
<td>2 days</td>
</tr>
<tr>
<td>CL 30–50 mL/min</td>
<td>2 days</td>
<td>4 days</td>
</tr>
<tr>
<td>CL ≤30 mL/min</td>
<td>4 days</td>
<td>6 days</td>
</tr>
<tr>
<td>Rivaroxaban or apixaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL &gt; 50 mL/min</td>
<td>1 day (24 hr)</td>
<td>2 days</td>
</tr>
<tr>
<td>CL 30–50 mL/min</td>
<td>1–2 days</td>
<td>3–4 days</td>
</tr>
<tr>
<td>CL ≤30 mL/min</td>
<td>2 days</td>
<td>4 days</td>
</tr>
</tbody>
</table>

*Therapy should generally be resumed 24–48 hours after a minor procedure and 48–72 hours after major surgery. If unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) is used as bridging therapy in patients with atrial fibrillation or with venous thromboembolism who are at high risk for thromboembolism, oral anticoagulant therapy with a target-specific agent should be resumed when the UFH infusion is discontinued and when the next scheduled dose of LMWH would have been given. CL₆ = creatinine clearance.
massive subdural hemorrhage was a prolonged activated clotting time. The remainder of the values, which measured clot kinetics, clot strength, and clot stability, were within the normal ranges.81

In patients who need an expedited intervention within 1–24 hours, dabigatran should be withheld. If the last dose was taken within the past 2 hours, activated charcoal should be given to reduce drug absorption unless contraindicated (e.g., gastrointestinal source of bleeding).18 Hemodialysis should be initiated and continued until sufficient dabigatran removal occurs. The mode and duration of dialysis and blood flow rates may depend on the level of anticoagulation and follow-up laboratory coagulation test results. Case reports suggest that prolonged dialysis (more than 2 hours) is needed to remove substantial amounts of the drug. In addition, a rebound in plasma drug concentrations after stopping dialysis has been observed.19,66,67,82,83 The actual duration of dialysis will depend on the assessed anticoagulation state using available tests to guide decision-making (Table 2). Laboratory coagulation tests should be repeated 1 hour after the completion of dialysis because of the risk of a rebound increase in plasma dabigatran concentration due to redistribution of the drug from tissues into the plasma.67 If the clinical situation is such that waiting for dialysis to reverse the effects of dabigatran is not an option, the reversal strategies listed for emergent reversal in Table 7 should be considered.

The expert panelists’ first choice for reversal of dabigatran in a patient with serious bleeding or an emergent need for intervention is aPCC (in addition to withholding dabigatran and using activated charcoal and prolonged hemodialysis).8 This suggestion is based on limited available evidence (ex vivo studies in healthy volunteers) and case reports.29,45,46 The optimal aPCC dose is unclear and may be lower than that explored by Marlu et al.45 or used in the management of hemophilia. Although the evidence is very limited, low doses of aPCC (i.e., ≤25 units/kg) may suffice.29 Since additional aPCC doses can be given and the onset of effect is rapid, therapy can be initiated with a low dose, and additional doses can be given based on an assessment of bleeding. The initial and any subsequent doses may depend in part on the vial size to avoid unnecessary wastage. An additional vial may need to be readily available for use if bleeding persists.29

The expert panelists suggest PCC4 as the next option for the reversal of dabigatran. An alternative would be using PCC3 plus rFVIIa to build a PCC4 product or using PCC3 plus FFP, though currently available data are limited and do not support the use of these combinations for dabigatran reversal. While acknowledging the lack of supporting data, the expert panelists prefer a combination of PCC3 plus rFVIIa over PCC3 plus FFP in a life-threatening bleeding event based on limited clinical experience. Since no studies have evaluated the impact of PCC3 plus rFVIIa for dabigatran reversal, dose selection is difficult. It may be reasonable to consider doses that have been used with relative safety for warfarin reversal (Table 3).22 If rFVIIa is the only therapeutic option available, it may be considered, but case reports and an animal model suggest that rFVIIa has a limited ability to reverse the effects of dabigatran.5,53,84 If rFVIIa is used, the panelists recommend an initial dose of approximately 20 μg/kg, extrapolated from lower doses shown effective with warfarin.48 Currently, no data are available to support the use of a PCC3 product alone for the reversal of dabigatran.

It is important to be aware of the potential for a rebound anticoagulation effect after an attempt at dabigatran reversal because of the relatively short half-life of the clotting factors used for reversal compared with the half-life of dabigatran. A rebound increase in the INR has been observed with the use of rFVIIa in patients taking warfarin who have traumatic hemorrhage.85 Follow-up laboratory coagulation tests should be considered 10–15 minutes after completing the infusion of concentrated clotting factor products to monitor for the desired reversal effect. However, clinical judgment about whether the bleeding has stopped or improved may be more useful, especially given the limited availability of assays as well as their limitations in measuring the effects of dabigatran.

Clinicians could consider administering small doses of aPCC (e.g., 8–10 units/kg) immediately before the insertion of dialysis catheters or other invasive procedures in patients receiving dabigatran, as life-threatening bleeding could develop. This suggestion is based on two case reports in which hemostasis was rapidly achieved with aPCC at these doses in patients receiving dabigatran who developed bleeding while undergoing cardiac ablation or the placement of a dialysis catheter for emergent hemodialysis.29,67 Minimally invasive procedures (e.g., use of the right femoral vein to establish dialysis access) are preferred to reduce the risk of bleeding in patients receiving dabigatran.

Rivaroxaban and apixaban. In patients receiving factor Xa inhibitors for whom there is no need to reverse the anticoagulant effects within 24 hours, withholding the drug and monitoring laboratory coagulation test values should suffice (Table 7). Guidance is available for how much time should elapse between the last dose of rivaroxaban or apixaban and an invasive procedure based on the risk of bleeding, which varies with the type of procedure being performed (Table 8).77,78,80

In patients receiving factor Xa inhibitors with an emergent need for intervention, most of the anticoagul-
lant effects should be absent ideally within 24 hours after discontinuation of the drug. If the last dose of the factor Xa inhibitor was taken within 2 hours, activated charcoal may be administered unless contraindicated (e.g., gastrointestinal source of bleeding) and repeated approximately 6 hours after the last dose of factor Xa inhibitor, though it should be noted that this recommendation is extrapolated from existing data for apixaban; data supporting the effectiveness of this intervention are lacking for rivaroxaban.\textsuperscript{13,16} Hemodialysis probably does not have a role in removing factor Xa inhibitors because they are highly protein bound (Table 1).

In patients with an emergent need for intervention, PCC4 is preferred by the expert panel based on currently available, albeit very limited, data and clinical experience.\textsuperscript{39,42,45-47} Limited data suggest that aPCC might be an alternative to PCC4, but the expert panelists prefer PCC4 because of the potential for thrombosis with aPCC.\textsuperscript{45,51} Alternatively, a combination of PCC3 plus rFVIIa could be used to build a PCC4. If rFVIIa is not available, using FFP in combination with PCC3 may be considered as an alternative option for providing factor VII. While no data are available in the literature to support the approach of combining clotting factor products to build a PCC4 for reversal of factor Xa antagonists, this approach may be considered because it has been studied in the setting of warfarin reversal. If building a PCC4 is considered for reversal of factor Xa antagonists, extrapolation of doses used safely for reversing the effects of warfarin may be considered (Table 3).\textsuperscript{52} If PCC4 is not available, PCC3 may also be considered as a potential reversal option.\textsuperscript{42}

**Systematic approach**

A plan for managing patients receiving oral anticoagulants who are bleeding or need an urgent invasive procedure should be developed using a systematic approach to ensure that appropriate laboratory tests and therapeutic interventions for anticoagulant reversal are promptly ordered when needed. The anticoagulant reversal plan must be readily accessible so that it can be promptly implemented in emergent situations at any time of day. Implementation of such a plan should be facilitated by information technology (e.g., clinical decision-support system). A pragmatic approach is needed to ensure that the plan is user-friendly. The plan should be sufficiently flexible to address other patient care needs.

The anticoagulant reversal plan should contain provisions to gain access to reversal agents and other therapeutic interventions that are not available in the institution (e.g., small or rural health care facilities lacking hemodialysis services). Clinicians need timely access to these therapies in emergent situations to avoid compromising patient outcomes. The plan should ensure that policies and procedures are established to avoid delays in obtaining reversal therapies or transferring the patient to another institution where the necessary therapy is available. The plan should address transporting the patient and communicating about the patient’s status (e.g., time since last oral anticoagulant dose, laboratory results, use of activated charcoal and reversal agents) with health care providers at the facility receiving the patient. Patient transfer agreements should be established before an emergent need arises. Such provisions will ensure a smooth transition of care.

The anticoagulant reversal plan may be communicated with local emergency medical services personnel (especially first responders) so that they are aware of institutional capabilities to manage bleeding from oral anticoagulants. Valuable time can be saved in addressing life-threatening bleeding events if patients are taken to a health care facility where the necessary interventions are available.

In devising the anticoagulant reversal plan, interprofessional input should be obtained from key clinical decision-makers and stakeholders involved in the use of reversal agents in the institution. These include emergency and trauma physicians, hematologists, nephrologists, pharmacists, intensivists (including neurointensivists), neurosurgeons and other surgeons, nurses, clinical laboratory personnel, blood bank representatives, risk managers, and health informatics professionals. This input could be obtained in conjunction with the formulary decision-making process for reversal agents or through the formation of institutional committees responsible for issues related to anticoagulation. The cost of these agents is a consideration in formulary decisions and the anticoagulant reversal plan. Volume discounts and manufacturer rebates vary widely among institutions and can have a substantial effect on product acquisition cost. The acquisition cost may also reflect local practice and physician preference. For example, the acquisition cost may be higher when PCC3 plus rFVIIa is used to build a PCC4 product instead of using aPCC.\textsuperscript{33} The clinical situation and therapeutic goals (e.g., need for multiple doses instead of a single dose to achieve management goals) can also affect the cost of treatment.

Reversal agents placed on the formulary may be subject to prescribing restrictions or requirements for approval by key individuals who are knowledgeable about anticoagulant reversal due to safety and economic concerns. Although prescribing restrictions can ensure that reversal agents are used only by personnel who are aware of their risks and benefits and prevent inappropriate use, restrictions have the potential to delay treatment. Provisions should be made to ensure that prescribing restrictions do not cause an undue
delay in treatment. Ideally, persons charged with approving the use of reversal agents should be available at any hour. In addition, a method for some flexibility in reversal agent use beyond what is formally outlined in institutional protocols should be devised because of the uncertainty about the optimal approach for using reversal agents.

Many clinicians may be unfamiliar with and ill equipped to handle questions that arise regarding the use of anticoagulant reversal agents, as many of these agents are new, the use of these agents is infrequent, and guidelines and supporting literature are limited. Many tertiary references for concentrated clotting factor products provide information on dosing and monitoring recommendations that are appropriate for treating hematology issues (e.g., hemophilia), not for reversing anticoagulation. Confusion may arise among staff about which department or location in the institution stores and dispenses reversal agents (e.g., blood bank, pharmacy department), because it varies among health care facilities. Knowledgeable individuals in the institution who can respond to questions about the use of anticoagulant reversal agents should be identified. Policies and procedures for promptly referring questions to these individuals should be established as part of the anticoagulant reversal plan to expedite the resolution of questions. Emergency department or intensive care unit clinicians, neurointensivists, hematologists, or designated pharmacists often have this expertise and can serve in this capacity. To minimize delays in providing treatment in emergent situations, contact information (e.g., pager number) for these individuals should be made available to personnel who may have questions and concerns.

Education of pharmacists and other clinicians is needed to increase their knowledge of the oral anticoagulants and available reversal strategies. Although reversal agents are not often used, their use is accompanied by a high risk of harm if used inappropriately. In education departments at some health care systems, case studies with simulated clinical scenarios involving reversal agents have been developed to train emergency medicine residents, and these simulations would be helpful for pharmacists, nurses, and other staff. Continuing education about anticoagulant reversal is needed to maintain competence due to the continually evolving and limited information currently available to guide the use of reversal agents and the rapid emergence of new data.

The anticoagulant reversal plan should be periodically revised to accommodate institutional needs. A mechanism should be established to update the plan as new reversal agents are introduced and new information about the use of established reversal agents becomes available. In revising the anticoagulant reversal plan, an assessment of past patient cases should be performed. This assessment can provide valuable insight into pitfalls encountered in managing bleeding associated with oral anticoagulants and strategies to avoid these pitfalls in the future. In addition, clinical scenario simulations with key stakeholders may be useful for understanding the clinical process and preparing staff to respond to the need for an emergency anticoagulant reversal around-the-clock.

Conclusion

Bleeding is a serious complication of the use of oral anticoagulants. Limited information is available to guide the reversal of warfarin or TSOAs in patients who are bleeding or are in need of an urgent invasive procedure. Use of a systematic approach to assessing and treating these patients based on available evidence and expert opinion can help avoid delays that could adversely affect patient outcomes.

References

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