Anticoagulation is a key component in the management of many critically ill patients. Common indications for anticoagulation in critical care include deep venous thrombosis (DVT) and pulmonary embolism (PE) treatment, thromboembolism prophylaxis following orthopedic surgery, stroke prevention in atrial fibrillation, and hypercoagulable conditions. Warfarin has been the mainstay in oral anticoagulation therapy since its first medicinal use in the 1950s. The most significant drawback of warfarin therapy is the need for careful monitoring of anticoagulant effects and individualized dosage titration. In recent years, several new oral anticoagulants have been approved and marketed in the United States; these agents include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban. The major benefit of these new agents compared with warfarin is that close monitoring of anticoagulation intensity and individualized dose titration are not necessary. However, these benefits are countered by the lack of a specific reversal agent in the event of major bleeding.

The most common and serious adverse effects of anticoagulation are bleeding complications. Major bleeding caused by anticoagulation is associated with significant morbidity and mortality. The risk of death from anticoagulation-related major bleeding is nearly 30%, and long-term morbidity among survivors is as high as 15%. Outcomes of anticoagulation-related bleeding may be significantly affected by the ability to emergently reverse anticoagulation in cases of severe, life-threatening bleeding.

Several strategies are available to antagonize the effects of oral anticoagulant therapy. Although warfarin has a reversal agent, vitamin K, which targets its mechanism, the new oral anticoagulants lack a specific antidote. Additional strategies for reversal of anticoagulation include facilitated drug elimination, transfusion of coagulation factors, and pharmacological hemostatic products.

Normal Coagulation Pathways

Figure 1 outlines the normal coagulation cascade as well as the site of activity of oral anticoagulants. This cascade consists of 2 pathways, intrinsic and extrinsic, by which coagulation can be initiated. Both of these pathways consist of progressive
activation of coagulation factors that converge with factor X and culminate in the generation of cross-linked fibrin polymers, leading to clot formation. The various oral anticoagulants target different coagulation factors within this cascade; understanding their mechanisms can be important in providing effective reversal when needed.

**Review of Oral Anticoagulant Agents**

**Warfarin**

Warfarin is the most commonly prescribed anticoagulant medication in the world. It is used for anticoagulation in a multitude of situations, most commonly for stroke prevention in atrial fibrillation, in treatment of DVT and PE, and for patients with artificial heart valves. Warfarin targets the vitamin K-dependent coagulation factors, factors II, VII, IX, and X, through inhibition of vitamin K epoxide reductase. This inhibition results in the synthesis of factors with significantly reduced biological activity and dysfunction in the coagulation cascade. Aside from its effects on vitamin K-dependent factors, warfarin also inhibits the effects of proteins C and S, the body’s endogenous anticoagulants. The antithrombotic effects of warfarin are believed to be largely due to its effects on factor II (prothrombin).

The full antithrombotic effects of warfarin are not seen for several days following initiation, which is due to the long half-life of factor II of nearly 3 days. Similarly, because warfarin depletes functioning coagulation factors, the return of normal coagulation requires the regeneration of new factors. Thus, the restoration of normal coagulation following cessation of warfarin can take several days.

The international normalized ratio (INR) is used to monitor the degree of anticoagulation with warfarin use. The therapeutic range of warfarin has been well established, and the relative risk of bleeding with warfarin anticoagulation...
has been strongly correlated with the degree of elevation in INR. An INR range of 2 to 3 is the most commonly used therapeutic range and is associated with an annual risk of major bleeding of approximately 3% to 6%. Above this INR, the annual risk of major bleeding increases dramatically to approximately 20% to 25% at an INR range of 3 to 4.5 and approximately 45% at an INR range of 7.5 to 11.

Many factors can considerably affect the degree of anticoagulation with warfarin therapy. The INR can vary widely as a result of a multitude of drug interactions, variations in vitamin K intake, alcohol consumption, and patient comorbidities. These characteristics of warfarin therapy, as well as the need for close monitoring, have generated much interest in the development of oral anticoagulants with wider safety margins and less-intensive monitoring requirements.

**Novel Oral Anticoagulants**

**Direct Thrombin Inhibitors**

Dabigatran (Pradaxa) was first released in the United States in 2010 and currently has 1 indication labeled by the Food and Drug Administration (FDA): stroke prevention in atrial fibrillation. Key characteristics of dabigatran are summarized in Table 1. Its anticoagulant activity is a result of direct inhibition of factor IIa. Although dabigatran does not permanently bind to thrombin, its anticoagulant effects are irreversible until the drug is eliminated, because no reversal agent is available that specifically antagonizes its effects.

Of commonly used coagulation assays, the activated partial thromboplastin time (aPTT) is most sensitive to the anticoagulant effects of dabigatran. Dabigatran also affects the prothrombin time (PT) at supratherapeutic levels; however, this effect is variable and unreliable. Several other coagulation tests may be more sensitive to dabigatran, including the thrombin time and the ecarin clotting time. However, the utility of these tests may be hindered by institution-specific practices. Note that although these coagulation tests may be elevated with dabigatran, the degree of anticoagulation does not correlate with the degree of increase. In other words, these assays can be useful in detecting the presence but not the degree of anticoagulation with dabigatran.

**Factor Xa Inhibitors**

Two oral factor Xa inhibitors, rivaroxaban (Xarelto) and apixaban (Eliquis), became available for use in the United States in 2011 and 2013, respectively. Rivaroxaban is currently FDA approved for use in postoperative DVT prophylaxis following knee and hip surgery, stroke prevention in atrial fibrillation, and treatment of DVT and PE. Apixaban is currently FDA approved only for use in stroke prevention in atrial fibrillation; however, additional indications are being investigated. These agents exert their anticoagulant effects through direct inhibition of factor Xa.

### Table 1: Key Characteristics of the New Oral Anticoagulants*

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechnism of</td>
<td>Direct thrombin inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td>anticoagulation</td>
<td>1-3</td>
<td>2-4</td>
<td>1-3</td>
</tr>
<tr>
<td>Time to peak effects, h</td>
<td>14-17</td>
<td>5-9</td>
<td>8-15</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>Prolonged in renal impairment</td>
<td>Prolonged in renal impairment</td>
<td>Prolonged in renal impairment</td>
</tr>
<tr>
<td>Dialyzable</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Metabolism/excretion</td>
<td>80% renally excreted</td>
<td>30% hepatic</td>
<td>15% hepatic</td>
</tr>
<tr>
<td>Coagulation tests affected</td>
<td>aPTT</td>
<td>PT</td>
<td>PT</td>
</tr>
<tr>
<td>Ecarin clotting time</td>
<td>Antifactor Xa levels</td>
<td>Antifactor Xa levels</td>
<td>Antifactor Xa levels</td>
</tr>
<tr>
<td>Thrombin time</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aPTT, activated partial thromboplastin time; PT, prothrombin time.

*Data from Pradaxa, Xarelto, and Eliquis.

Tests do not correlate with the degree of anticoagulation but can be useful to detect the presence of anticoagulation.
summarizes the key characteristics of rivaroxaban and apixaban. Similar to dabigatran, although rivaroxaban and apixaban exhibit a nonpermanent binding to factor Xa, their anticoagulant effects are irreversible until the drug is eliminated, because no specific reversal agent is available.

Of commonly used coagulation assays, the PT is the most sensitive to the anticoagulant effects of rivaroxaban and apixaban, particularly at supratherapeutic concentrations. The aPTT also may be elevated at supratherapeutic drug levels; however, this response is less reliable compared with the PT. In addition, antifactor Xa levels may be more sensitive for rivaroxaban and apixaban, especially at usual therapeutic concentrations. However, the use of this test may be limited by institution-specific practices. Again, clinicians must understand that these coagulation assays can be useful in detecting the presence but not the degree of anticoagulation with these agents.

Risk of Major Bleeding Events With the New Oral Anticoagulants

Aside from the anticoagulant agent itself, several factors affect an individual’s risk of major bleeding. These risk factors include advanced age, uncontrolled hypertension, cardiovascular disease, anemia, history of major bleeding events, and concurrent antithrombotic therapy.9 In major clinical trials of dabigatran and rivaroxaban, the overall incidence of major bleeding was similar when compared with warfarin.10,11 Apixaban is the only new oral anticoagulant to demonstrate a significantly lower incidence in the rate of overall major bleeding.12 Although the rate of major bleeding events with oral anticoagulation is relatively low (~2%-4% annually), these events can have serious consequences and require rapid management to achieve hemostasis and minimize further bleeding.

 Strategies to Reverse Anticoagulation

An ideal strategy for reversal of oral anticoagulation would directly target and neutralize the mechanism of anticoagulation, rapidly correct coagulopathy, and not increase the risk of thrombotic events. Several strategies, including facilitated removal of the drug and administration of vitamin K, blood products, and pharmacological hemostatic products, can be attempted to attenuate bleeding, depending on the anticoagulant requiring reversal. Table 2 summarizes the use of these reversal strategies for the currently available oral anticoagulants.

Facilitated Removal

Activated Charcoal

Activated charcoal is designed to bind certain drugs and toxins, facilitating elimination prior to absorption from the gastrointestinal (GI) tract. Activated charcoal has been found to extensively bind dabigatran and may be effective in decreasing drug absorption following recent administration.13 Although no data demonstrate that activated charcoal binds rivaroxaban and apixaban, this strategy is a reasonable option to attempt to decrease absorption in cases of recent administrations.

To be effective, activated charcoal must be administered prior to medication absorption. Therefore, it is indicated only in situations in which ingestion of the anticoagulant occurred within the previous 1 to 2 hours. This strategy

Table 2: Relative Efficacy of Strategies for Reversal of Oral Anticoagulation a

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral activated charcoal</td>
<td>No</td>
<td>Yes</td>
<td>Likely</td>
<td>Likely</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fresh-frozen plasma</td>
<td>Yes</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
</tr>
<tr>
<td>Recombinant factor VIIa</td>
<td>Yes</td>
<td>Possible b</td>
<td>Possible b</td>
<td>Possible b</td>
</tr>
<tr>
<td>3-Factor PCC</td>
<td>Likely</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>4-Factor PCC</td>
<td>Yes</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Abbreviation: PCC, prothrombin complex concentrate.

aData from Holbrook et al,16 Kaatz et al,21 and Siegal and Crowther.28

bFactor VIIa may attenuate the anticoagulant effects of the new oral anticoagulants but the risks of adverse events likely outweigh any potential benefit.

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will not affect anticoagulant effects already present but may decrease the absorption of recently administered drug, shortening the duration of anticoagulation.

Activated charcoal has a single dose of 25 to 100 g, which is available as an oral suspension in a concentration of 25 g/120 mL and can be administered via oral or nasogastric route. Contraindications include patients with absent bowel sounds, GI perforation, bowel obstruction, recent GI surgery, and an increased risk of GI hemorrhage. In addition, activated charcoal should not be administered to patients who are unable to protect their airway to minimize the risk of aspiration. Patients who have received activated charcoal should be monitored for nausea, vomiting, aspiration, constipation, and bowel obstruction.

Hemodialysis
Hemodialysis is another option that can be used to enhance elimination of several medications and toxins. Unfortunately, the only oral anticoagulant removed by hemodialysis is dabigatran, decreasing drug levels by approximately 65%. Because of pharmacokinetic differences, hemodialysis is unlikely to be effective in the removal of rivaroxaban and apixaban and is not indicated to reverse these agents.

Despite its efficacy in the removal of dabigatran, hemodialysis poses serious risks for patients receiving anticoagulation therapy, with the primary risk being bleeding with the insertion of a dialysis catheter. However, hemodialysis may be considered to decrease the duration of the anticoagulant effects of dabigatran in patients with renal dysfunction and an impaired ability to eliminate the drug.

Pharmacological Hemostatic Products and Transfusion of Coagulation Factors

Vitamin K
Vitamin K is indicated only for reversal of warfarin anticoagulation. Vitamin K reverses the effects of warfarin by facilitating synthesis of new and functional coagulation factors. Because these new factors take time to be synthesized, the effects of vitamin K are delayed. Oral administration results in increased coagulation factors after 8 hours, with full effects seen in 24 to 48 hours. Intravenous administration results in increased coagulation factors in 1 to 2 hours, with full effects seen in 12 to 14 hours. Table 3 outlines the indications and appropriate dosing for vitamin K use in warfarin reversal according to the 2012 Chest guidelines. Oral vitamin K should be used in patients requiring anticoagulation reversal as a result of a significantly elevated INR in the absence of major bleeding. However, because of its faster onset, injectable vitamin K is the preferred route of administration in patients experiencing major bleeding associated with warfarin.

Injectable vitamin K can be administered via a subcutaneous, intramuscular, or intravenous route. The subcutaneous route is not preferred as it results in variable absorption, delayed effects, and decreased efficacy. Intravenous administration has been associated with a rare, but potentially fatal, risk of hypersensitivity and anaphylactoid reactions. This risk can be greatly minimized by dilution of vitamin K to a minimum volume of 50 mL and intravenous administration over at least 20 minutes.

Table 3: Reversal of Warfarin Anticoagulation

<table>
<thead>
<tr>
<th>INR</th>
<th>Treatment Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratherapeutic but below 4.5</td>
<td>1. Hold warfarin or lower dose until INR is within therapeutic range</td>
</tr>
</tbody>
</table>
| 4.5–10 | 1. Hold warfarin until INR is within therapeutic range  
2. Routine use of vitamin K is not recommended  
Vitamin K 2.5 mg PO × 1 can be considered for patients with a high risk of bleeding |
| Above 10 | 1. Hold warfarin until INR is within therapeutic range  
2. Vitamin K 2.5 mg PO × 1 |
| Major bleeding at any INR level | 1. Administer vitamin K 10 mg IV × 1  
2. Administer 4-factor PCC  
INR 2-4: 25 units/kg  
INR 4-6: 35 units/kg  
INR above 6: 50 units/kg  
3. FFP 10-15 mL/kg can be considered if PCC is unavailable |

Abbreviations: FFP, fresh-frozen plasma; INR, international normalized ratio; PCC, prothrombin complex concentrate; PO, by mouth.

Data from Holbrook et al.

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Fresh-Frozen Plasma

Fresh-frozen plasma (FFP) is the plasma component separated from a unit of whole blood, contains all vitamin K-dependent coagulation factors, and is the most commonly used factor product in the reversal of warfarin anticoagulation.18 To date, no studies have evaluated the effect of FFP in patients receiving the new oral anticoagulants. The mechanism of anticoagulation reversal with FFP is replacement of effective coagulation factors. As such, FFP is a viable strategy for warfarin reversal in patients for whom anticoagulation is due to a depletion of functional coagulation factors. However, in the setting of the new anticoagulants, FFP is unlikely to be of significant benefit when used alone because anticoagulation is due to a direct inhibition of existing coagulation factors. To overcome this direct inhibition, clinicians would need to use prohibitive volumes of FFP.

The typical volume of FFP administered for the reversal of warfarin is 10 to 15 mL/kg, or approximately 1 L in a 70-kg adult, and it is generally infused over 30 to 60 minutes.19 The duration of effect with FFP is temporary; when used for warfarin reversal, vitamin K should be administered in addition to FFP to effectively reverse anticoagulation. Major limitations and potential adverse effects are associated with FFP. These include fluid overload, pulmonary edema, and hypersensitivity reactions. Other logistical concerns with FFP include the need for thawing prior to administration and prolonged infusion duration, limiting its benefit in the setting of acute major bleeding.

Recombinant Factor VIIa

Recombinant factor VIIa (NovoSeven RT) is an activated coagulation factor approved by the FDA for use in patients with hemophilia or certain congenital coagulation disorders.20 It has been used extensively off-label in various clinical settings, including intracranial hemorrhage and bleeding caused by major trauma, surgery, or anticoagulation. The use of recombinant factor VIIa is effective in normalization of INR in patients receiving warfarin.16 Factor VIIa also decreases bleeding duration associated with dabigatran and rivaroxaban in animal models.21 Although reductions may be seen in bleeding duration, factor VIIa does not have a uniform effect on coagulation assays sensitive to the new oral anticoagulants. Factor VIIa is effective in normalization of the PT but does not significantly correct the aPTT.

Doses ranging from 5 to 100 mcg/kg have been shown to reverse warfarin anticoagulation.22 Appropriate dose ranges in humans have not been established for reversal of the new oral anticoagulants. Limited evidence suggests that doses of 100 to 200 mcg/kg may decrease bleeding associated with dabigatran, rivaroxaban, and apixaban.21 Factor VIIa should be reconstituted immediately prior to use and must be given within 3 hours of reconstitution20 and should be administered as a single dose intravenously over at least 2 minutes. The immediate increase in factor VIIa levels results in a rapid onset of hemostasis lasting approximately 6 hours.

The primary adverse effect associated with factor VIIa is an increased risk of thrombotic events, particularly arterial thrombosis such as ischemic stroke and myocardial infarction.23 Patients who receive factor VIIa should be monitored closely for decreases in bleeding as well as thrombotic events. Because of the increased risk of thrombosis along with very limited evidence supporting its use, factor VIIa should be used with extreme caution for reversal of new oral anticoagulants.

Prothrombin Complex Concentrates

Prothrombin complex concentrates (PCCs), also known as factor IX complex, are a class of medications that are purified blood products derived from human plasma initially developed for prevention and treatment of bleeding associated with congenital factor deficiencies. Later, they became a favorable option for the reversal of bleeding associated with warfarin anticoagulation. These products contain the vitamin K-dependent coagulation factors (factors II, VII, IX, and X) as well as proteins C and S. Note that some PCC products contain small concentrations of heparin and are contraindicated in patients with a history of heparin-induced thrombocytopenia. Although all PCCs contain similar amounts of vitamin K-dependent factors, subtle differences are present in the factor content between products. Prothrombin complex concentrates are labeled as 3-factor or 4-factor PCCs on the basis of their factor content. Three-factor PCCs have little to no factor VII, whereas 4-factor PCCs contain all of the vitamin K-dependent coagulation factors in equal amounts. Until recently, only 3-factor PCC products were available in the United States (Profilnine SD, Bebulin VH). Feiba NF is a 4-factor activated PCC available in the United States.
States. Kcentra, a 4-factor PCC containing inactive factors, is approved as Beriplex in 25 countries and was recently approved (as Kcentra) by the FDA for use in patients with major bleeding caused by warfarin anticoagulation.

Prothrombin complex concentrates have been shown to correct the INR within minutes in patients receiving warfarin. The 2012 Chest guidelines recommend 4-factor PCC, in conjunction with vitamin K, over FFP for the rapid reversal of warfarin. In animal models of anticoagulation with dabigatran, 4-factor PCC has been associated with significant reductions in bleeding time. In human studies, 4-factor PCC demonstrated no impact on the elevation of aPTT associated with dabigatran but did normalize the elevated PT due to rivaroxaban, which suggests that 4-factor PCC may be effective in the reversal of the oral factor Xa inhibitors, rivaroxaban and apixaban. However, because it failed to correct the prolonged aPTT, whether 4-factor PCC would decrease bleeding duration and severity as a result of dabigatran is unclear.

A wide range of doses of PCCs have been evaluated for reversal of anticoagulation. The recommended dose for reversal of warfarin depends on the degree of elevation in INR and ranges from 25 to 50 units/kg (Table 3). An optimal dose of PCC in the setting of anticoagulation with the new oral agents has not been established. Although the efficacy of PCCs for reversal of dabigatran, rivaroxaban, and apixaban is unclear, the most commonly used doses are similar to the range used in warfarin reversal. Prothrombin complex concentrates should be reconstituted immediately prior to administration. These products can then be given intravenously without further dilution, although the maximum rate of administration varies depending on the specific PCC product being used. Once administered, PCCs provide an increase in coagulation factors that lasts for approximately 12 hours.

Prothrombin complex concentrates offer significant benefits over other reversal strategies. Compared with FFP, 4-factor PCC provides a similar mix of coagulation factors but with significantly less volume, which allows for more rapid administration and hemostasis without the risk of volume overload. In addition, PCCs do not require the blood-type matching needed for FFP.

Similar to other coagulation factor products, the primary adverse event with PCCs is the risk of both venous and arterial thrombotic events, including DVT and PE, ischemic stroke, and myocardial infarction. This risk depends on the relative concentration of coagulation factors in the product, whether it contains active or inactive coagulation factors, and the concentrations of the anticoagulant proteins C and S. Prothrombin complex concentrates that contain inactive factors and proteins C and S are thought to carry a lower thrombotic risk compared with products with active coagulation factors or that do not contain proteins C and S. All patients who receive PCCs should be closely monitored for resolution of bleeding and the development of thrombotic complications.

Alternative Hemostatic Products
Other hemostatic agents such as desmopressin, aminocaproic acid, and tranexamic acid have not been studied in the setting of reversal of anticoagulation due to dabigatran, rivaroxaban, and apixaban. These agents should not be used routinely but may be considered as adjunctive hemostatic strategies in patients with severe, life-threatening hemorrhage unresponsive to initial resuscitation and reversal efforts.

Applications to Practice
All patients with life-threatening bleeding require general supportive care in addition to active reversal of anticoagulation. Fluid resuscitation, source identification, and treatment at the bleeding site are key components in the care of the bleeding patient. In patients receiving warfarin, rapid reversal of anticoagulation is indicated in the setting of major bleeding or the need for emergent procedures with an increased risk of bleeding. These patients should receive rapid reversal with the combination of intravenous vitamin K as well as 4-factor PCC. Fresh-frozen plasma can be used if PCC is unavailable. Patients who are not experiencing major bleeding can be managed less aggressively, either with lower doses of oral vitamin K alone or by simply discontinuing further warfarin doses until the INR normalizes (Table 3).

In patients receiving dabigatran, rivaroxaban, or apixaban, attempts at rapid reversal should be reserved for patients with major, life-threatening bleeding. The reversal of these agents is limited as a result of the lack of specific antidotes targeting their anticoagulant effects and the paucity of clinical experience in this setting. Nonspecific reversal strategies, such as facilitated removal of the medication and treatment with PCCs, are reasonable...
strategies to attenuate these agents’ anticoagulant activity. Fresh-frozen plasma and factor VIIa can be considered in refractory cases but may be of limited value and carry significant risks. Table 2 outlines the utility of each method for use in oral anticoagulation reversal. Clinicians must be aware of the potential risks when determining an appropriate reversal algorithm. Invariably, patients who require urgent reversal of anticoagulation need to be closely monitored for resolution of bleeding and the development of adverse effects resulting from treatments.

REFERENCES