The expanding role of direct oral anticoagulants in the management of thromboembolic disease

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Abstract
Venous thromboembolism is a leading cardiovascular disease that affects hundreds of thousands of Americans each year. For decades, the recommended treatment was a short course of intravenous anticoagulants followed by months of laboratory monitoring and adjustments of warfarin dosage. Recently, agents in the class of medications known as direct oral anticoagulants have been approved by the FDA for the treatment of acute thromboembolism and for the long-term prevention of this condition. These agents have been proven safe and effective for many patient types and have few drug-drug interactions. Additionally, agents to reverse their effects are on the horizon.

Introduction
The term venous thromboembolism (VTE) encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE) and is the third most common cardiovascular disease in the United States, trailing only myocardial infarctions and stroke. Estimates suggest that somewhere between 350,000 and 600,000 Americans develop a venous thrombosis each year, leading to as many as 100,000 deaths. Many of those who survive complications that lead to serious and negative effects on their quality of life. Additionally, VTE is estimated to cost the healthcare system $7 to $10 billion each year. In 2008, the U.S. Surgeon General issued a “Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism.” Such a call to action is intended to bring attention to a major health issue, disseminate information, stimulate research, and improve coordination of care. At the time of the Surgeon General’s call to action, and for many decades prior, the only therapy available for DVT and PE

Educational Objectives
GOAL: This educational activity for pharmacists and technicians will review the treatment of venous thromboembolism with the class of medications known as direct oral anticoagulants.

After participating in this activity, pharmacists will be able to:
increase the role of the direct oral anticoagulants in the treatment of deep vein thrombosis and pulmonary embolism
• Identify the unique dosing requirements of each agent at therapy initiation and maintenance
• Discuss the use of direct oral anticoagulants for VTE (venous thrombosis) in high-risk patient groups: pregnancy, cancer, and the elderly
• Discuss the current options available for treatment of direct oral anticoagulant-related bleeding
• Explain what the patient needs to know to ensure safe use of direct oral anticoagulants

After participating in this activity, pharmacy technicians will be able to:
• Recognize the direct oral anticoagulants for the treatment of deep vein thrombosis and pulmonary embolism
• Recognize that the direct oral anticoagulants have unique dosing requirements at therapy initiation and maintenance
• Recall the current options available for treatment of direct oral anticoagulant-related bleeding
• Explain the role of the pharmacy technician in assisting the pharmacist to ensure safe use of direct oral anticoagulants

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in the knowledge-based activity, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission.

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For questions concerning the online CPE activities, e-mail: cpehelp@advanstar.com.
was treatment with an injectable anticoagulant such as unfractionated heparin, the low-molecular-weight heparins (LMWHs) enoxaparin and dalteparin, or fondaparinux, with patients then treated with oral warfarin over the long term. With the introduction of the first oral alternative to warfarin in 2010, the door to new treatment options was finally opened.

Causes and symptoms of VTE

Venous thrombosis is the occurrence of a thrombus within a vein. A thrombus, or blood clot, can occur in a superficial or deep vein in nearly any part of the body but most commonly occurs in the deep veins of the lower extremities. A potentially life-threatening complication of DVT is PE, which occurs when a thrombus travels (embolization) into the pulmonary arteries of the lungs. German physician Rudolph Virchow is credited with describing a set of conditions associated with the formation of a thrombus in 1846. Known as Virchow’s Triad, these conditions include venous stasis, a hypercoagulable state, and vascular trauma.

Venous stasis describes the decrease in blood flow and venous pooling associated with immobility. Prolonged bed rest or immobility because of lower extremity fractures, spinal cord injury, or joint replacement surgery all increase the risk of a patient developing VTE. Decreases in cardiac output such as congestive heart failure and myocardial infarctions may also lead to venous stasis in the lower legs, and so these conditions are also associated with a high risk of DVT formation.

Hypercoagulability describes a state of increased concentration or activation of clotting factors that lead to clot formation. Physiologic stress, pregnancy, oral contraceptive use, cigarette smoking, and cancer have all been shown to increase the risk of DVT formation through alterations in clotting factors. A loss of body fluids because of injury, disease, or dehydration can also result in an increase in clotting factor concentrations and therefore an increased risk of thrombus formation. In addition, there is a wide range of hereditary disorders associated with alterations in clotting cascade homeostasis, leading to an increased risk of thrombus formation.

Vessel injury can occur from direct traumatic injury or surgical procedures. Persons undergoing joint replacement surgeries are at a particularly high risk of DVT formation because of physiologic stress, vessel injury secondary to the procedure, and decreased mobility in the postoperative period. Inflammation of vessel walls can also be caused by infections and by direct irritation from indwelling catheters.

The common signs of venous thrombosis include pain, swelling, and redness in the affected area. However, many individuals may not develop these symptoms if the vein is not totally occluded by the clot or when adequate collateral circulation is available. As many as 50% of those who develop a DVT will remain asymptomatic. A total of 10% to 30% of patients diagnosed with VTE will die within one month of their diagnosis, and one-third of survivors will have a recurrence of VTE within 10 years. Therefore, steps to prevent venous thrombosis should be taken whenever possible. Antithrombotic stockings and early ambulation after childbirth or surgical procedures assist in preventing blood pooling, and sequential pneumatic compression devices encourage blood flow through the lower extremities. Low-dose anticoagulant medications are also used to prevent those at high risk for VTE.

Treatment of VTE

The treatment goals for DVT are to prevent further growth and extension of the clot, prevent formation of additional thrombi, prevent embolization to the lungs, and limit vascular damage that leads to the development of a postthrombotic syndrome that occurs in 50% of VTE sufferers (pain, swelling, and discoloration in the affected limb). Surgical removal of the thrombosis and the use of thrombolytic medications are options when the size and location of the thrombosis are limb or life threatening. However, for most patients, anticoagulant medications are the mainstay of treatment. Depending on the patient’s presentation and comorbid risk factors, patients may need to be hospitalized for treatment initiation, or they can be treated as outpatients from start to finish with close medical monitoring for complications.

Treatment of VTE can be divided into three stages: acute, short term, and long term. The acute stage is the first five to 10 days after diagnosis when patients are traditionally treated with parenteral anticoagulants such as heparin or enoxaparin. Depending on the severity of the disease and other comorbid risk factors, patients may be hospitalized during the acute stage. The short-term stage includes the next three to six months. During this time, most patients will be treated with an oral agent. Expert guidelines recommend a minimum of three months of such treatment. The exact duration of the short-term stage is dependent on the patient’s risk for thrombosis recurrence. Patients whose initial thrombosis was caused by reversible risk factors such as surgery, limb trauma, or pregnancy may be treated for only three months. More complicated clinical situations will require at least six months of treatment.

VTE is a disease with a high rate of recurrence; 20% to 25% of patients will develop another VTE within five years.
FDA-APPROVED INDICATIONS

Interactions. Therefore, no laboratory monitoring is required. 
Prolongation of these markers indicates the relative amount of anticoagulation.

DOACs can be divided into two classes:

- Direct thrombin inhibitors (DTIs) and oral factor Xa inhibitors. Dabigatran is the lone DTI. Thrombin is a cofactor that enables the conversion of fibrinogen into fibrin, marking the final step to thrombus formation in the coagulation cascade. When the activity of thrombin is inhibited, the development of a thrombus is prevented. The oral factor Xa inhibitors rivaroxaban, apixaban, and edoxaban work further upstream in the coagulation cascade. Because factor Xa is integral to the production of thrombin itself, inhibiting factor Xa will directly decrease the production of thrombin and indirectly inhibit thrombin-induced platelet aggregation. At recommended therapeutic doses, all of the DOACs will affect common laboratory measurements of coagulation. Prolongation of these markers indicates drug activity in the body, but these markers cannot be used to predict serum levels or to gauge the relative amount of anticoagulation.

DOACs

- Dabigatran etexilate: Dabigatran etexilate was the first oral anticoagulant approved for use in the United States since warfarin was approved in 1954. Dabigatran was initially approved in 2010 to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Dabigatran has since been approved to treat DVT and PE in patients who have already been treated with a parenteral anticoagulant for five to 10 days and to reduce the risk of recurrence of DVT and PE in patients in the short- and long-term stages of therapy (Table 1). Dabigatran is a competitive DTI that reversibly binds to both clot-bound and free thrombin. Dabigatran itself is a highly polarized, hydrophilic molecule that is not orally absorbed. The drug is therefore formulated as the lipophilic prodrug dabigatran etexilate. Absorption of this drug is improved in an acidic environment, so the capsules contain dabigatran etexilate pellets with a tartaric acid core. As formulated, the absolute bioavailability is only 6.5%. If the capsule is opened, crushed, or chewed, the bioavailability increases dangerously by 75%, which could lead to excessive absorption and serum levels.

Absorption of dabigatran etexilate is subject to the effects of the P-glycoprotein (P-gp) efflux system. P-gp is a drug transporter pump found in many tissues, including those of the small intestine. Substrates of P-gp are pumped from the walls of the intestine back into the gastrointestinal tract lumen, reducing absorption of the substrate drug. P-gp-inducing drugs will further decrease absorption, and P-gp inhibitors will increase serum levels of substrates. Therefore, avoidance of the concurrent use of dabigatran and strong P-gp inducers and inhibitors is important to decrease the risk of serious side effects or treatment failure. Patients with a creatinine clearance (CrCl) <50 mL/min should avoid the concurrent use of dabigatran and any P-gp inhibitors, regardless if they are weak or strong inducers/inhibitors.

Dabigatran etexilate undergoes rapid hydrolysis to the active compound dabigatran. Dabigatran reaches peak plasma concentrations within 1.5 to 3 hours after administration, and steady state is achieved after approximately three days of continuous dosing. Renal excre-

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<tr>
<th>TABLE 1</th>
<th>FDA-approved Direct-acting Oral Anticoagulants</th>
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<td><strong>DRUG</strong></td>
<td><strong>FDA-APPROVED INDICATIONS</strong></td>
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| **Dabigatran etexilate** | • To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation  
• To treat DVT and PE in patients who have been treated with a parenteral anticoagulant for 5-10 days  
• To reduce the risk of recurrence of DVT and PE in patients who have been previously treated  
• For the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery |
| **Rivaroxaban** | • To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation  
• To treat DVT and PE and to reduce the risk of recurrence of DVT and PE  
• For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery |
| **Apixaban** | • To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation  
• For the prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery  
• To treat DVT and PE after initial therapy |
| **Edoxaban** | • To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation  
• To treat DVT and PE after 5-10 days of initial therapy with a parenteral anticoagulant |
IN THE MANAGEMENT OF THROMBOEMBOLIC DISEASE

Because the DOACs have predictable pharmacokinetics, few drug interactions, and no need for laboratory monitoring, would medication therapy management services provide a benefit?

Patients received dabigatran 150 mg twice daily or placebo for a median duration of 182 days after six to 18 months of therapy for an acute VTE. Recurrent VTE occurred in 0.4% of dabigatran-treated patients versus 5.6% of placebo-treated patients. Major or clinically relevant bleeding occurred in 5.3% of patients in the dabigatran arm versus 1.8% of patients in the placebo arm.†

Rivaroxaban

Rivaroxaban has dose-dependent bioavailability that can be influenced by the presence of food. At lower doses, the bioavailability is 80% to 100%, and the agent can be taken without regard to the timing of a meal. At doses of 15 to 20 mg, the bioavailability is reduced to 66% without food and improves to >80% in the presence of a meal. Therefore, higher doses should be taken with the largest meal of the day to ensure adequate serum levels.† Peak absorption occurs two to four hours after administration. The drug can be crushed for administration if necessary. Rivaroxaban is a substrate of P-gp as well as CYP 3A4; therefore, drugs that are dual P-gp and CYP 3A4 inhibitors may increase rivaroxaban serum levels to dangerous amounts. Concurrent use should be avoided. Likewise, concurrent use of strong dual inducers may lead to inadequate serum levels of rivaroxaban and may therefore result in treatment failure. Use of ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, conivaptan, carbamazepine, phenytoin, rifampin, and St John’s wort should be avoided in patients taking rivaroxaban. A total of 36% of a rivaroxaban dose is cleared unchanged in the urine. In young healthy volunteers, the half-life was found to be five to nine hours; the half-life increases to 11 to 13 hours in elderly patients. Rivaroxaban should be avoided for the treatment or prevention of VTE in patients with a CrCl <30 mL/min.† The recommended dose for treating VTE is 15 mg twice daily for the first 21 days, followed by 20 mg once daily for the remainder of the treatment course.†

Rivaroxaban was studied for the treatment and reduction of the occurrence of VTE in two similarly designed trials: EINSTEIN DVT and EINSTEIN PE. These studies were open-label noninferiority trials that enrolled a total of 8281 patients. The intended duration of treatment was chosen as three, six, or 12 months based on the investigators’ assessment before randomization. Subjects were randomized to receive rivaroxaban alone at a dose of 15 mg twice daily for three weeks followed by 20 mg once daily or standard care treatment with enoxaparin for a median of eight days followed by warfarin or acenocoumarol. In the two studies, rivaroxaban was found to be noninferior to traditional therapy for the composite end point of time to first recurrence of VTE. Major or clinically relevant bleeding occurred in 8.1% of patients in both treatment arms in the EINSTEIN DVT trial and in 10.3% of rivaroxaban-treated patients and 11.4% of the standard therapy group in the EINSTEIN PE trial.†

Conducted in parallel with the EINSTEIN DVT trial was a double-blind, placebo-controlled extension trial investigating the use of rivaroxaban 20 mg once daily versus placebo for an additional six or 12 months of therapy in patients who had already completed six to 12 months of treatment for an acute VTE event. A total of 1196 patients were randomized. Rivaroxaban was found to be superior to placebo for the primary end point of time to first recurrence of VTE (hazard ratio, 0.18; 95% confidence interval, 0.09-0.39). Eight events occurred in the rivaroxaban-treated group versus 42 in the placebo-treated group.†

Apixaban

Apixaban is rapidly absorbed and reaches maximum serum concentration in one to three
hours. Its bioavailability of 50% is not affected by food intake. Like rivaroxaban, apixaban is a substrate of both P-gp and CYP 3A4. If patients are taking apixaban 5 or 10 mg twice daily and concurrently taking strong dual inhibitors (ketocnazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, conivaptan), the manufacturer recommends reducing the dose of apixaban by 50%. Patients who are receiving apixaban at a dose of 2.5 mg twice daily should avoid coadministration of dual strong inhibitors. Coadministration of strong dual inducers (carbamazepine, phenytoin, rifampin, and St John’s wort) and apixaban should be avoided in all patients.12,22

Approximately 27% of an apixaban dose is eliminated via the kidneys, with a half-life of eight to 14 hours in healthy volunteers. Patients with renal dysfunction experience an increase in drug exposure; however, no dose adjustments are currently recommended for patients with renal dysfunction who are treated with apixaban for VTE. Elderly patients and those with low body weight (<60 kg) have significant increases in AUC exposure compared to young patients and those with normal body weight. Dose reductions are recommended for the treatment of atrial fibrillation in patients with a combination of low body weight, age ≥80 years, and a serum creatinine (S Cr) ≥1.5 mg/dL; but not for the treatment/prevention of VTE. The usual recommended dose for the treatment of VTE is 10 mg twice daily for the first 7 days, then 5 mg twice daily for the remainder of the treatment phase. Following initial treatment, long-term prophylaxis is treated with 2.5 mg twice daily. These doses may need to be adjusted based on the drug interactions mentioned previously.12,22

The safety and efficacy of apixaban for the treatment of DVT/PE and reduction in VTE recurrence were assessed in the AMPLIFY and AMPLIFY-EXT trials. AMPLIFY enrolled 5395 patients with an acute VTE event to receive either 1) traditional treatment with enoxaparin followed by warfarin or 2) apixaban 10 mg twice daily for seven days followed by 5 mg twice daily for six months. The primary outcome of recurrent symptomatic VTE or VTE-related death occurred in 2.3% of apixaban-treated patients and 2.7% of enoxaparin/warfarin-treated patients, demonstrating noninferiority. The composite outcome of major bleeding or clinically relevant bleeding occurred more frequently in the enoxaparin/warfarin-treated group (9.7%) than in the apixaban-treated group (4.3%; P = .001).22,23

In the AMPLIFY-EXT trial, patients who had already been treated for a VTE for six to 12 months were randomized to treatment with apixaban 2.5 mg twice daily, apixaban 5 mg twice daily, or placebo for an additional 12 months. A total of 2482 patients were enrolled and followed for a mean of 312 (apixaban group) or 330 (placebo group) days. Both apixaban treatment arms were superior to placebo in preventing symptomatic recurrent VTE or all-cause death.22,24

Edoxaban

Edoxaban has a pharmacokinetic profile similar to that of other agents in this class. Its oral bioavailability of 62% in healthy volunteers is not affected by food, and its maximum serum concentration is reached in one to two hours. The elimination half-life is 10 to 14 hours in healthy volunteers, and 70% of the drug is eliminated unchanged, mostly in the feces. Although not labeled as such for VTE treatment, edoxaban is contraindicated for the treatment of stroke prevention in patients with atrial fibrillation who have a CrCl <95 mL/min.

Edoxaban is a substrate of P-gp. Concomitant use of strong P-gp inhibitors may increase edoxaban exposure by >150%. Therefore, concomitant use of these agents and edoxaban should be avoided. Product labeling also states that patients should not concurrently use edoxaban with rifampin, a P-gp inducer.12,25 The recommended dose for treatment of VTE is 60 mg once daily. The dose should be reduced to 30 mg daily in patients with a CrCl of 15 to 50 mL/min or weigh 60 kg or less, or also taking strong P-gp inhibitors.25

A total of 8292 patients were enrolled in the Hokusai-VTE study, which assessed the use of edoxaban for the treatment of DVT and PE. All patients received initial treatment with LMWH or unfractionated heparin for a minimum of five days before randomization to edoxaban 60 mg once daily or warfarin for three to 12 months. Treatment duration was at the discretion of the investigator. The edoxaban dose was reduced to 30 mg once daily in patients who met at least one of the following criteria: CrCl of 30 to 50 mL/min, body weight ≤60 kg, and concurrent use of the P-gp inhibitors verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole. The use of other P-gp inhibitors was not allowed. Edoxaban was found to be noninferior to warfarin for the primary end point of recurrent symptomatic VTE (3.2% in edoxaban-treated patients vs 3.5% in warfarin-treated patients). Major or clinically relevant bleeding occurred in 8.5% of the edoxaban group and in 10.3% of the warfarin group (P = .004).25,26

Choosing between warfarin and a DOAC

Clinically, the current evidence suggests that warfarin and the DOACs are equally safe and effective for the treatment and prevention of VTE. Therefore, selecting the right agent for a particular patient will depend on other factors. Perhaps the most significant factor is cost. The DOACs are currently all branded medications, and so the acquisition cost is much greater than that of generic warfarin. However, a true cost comparison is not that simple. Depending on the frequency of laboratory measurements and professional monitor-

### TABLE 2

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Abbreviations: DOAC, direct-acting oral anticoagulant. Source: Refs 13,18,22,25

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**THE EXPANDING ROLE OF DIRECT ORAL ANTICOAGULANTS**

**CONTINUING EDUCATION**

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**Choosing between warfarin and a DOAC**

Clinically, the current evidence suggests that warfarin and the DOACs are equally safe and effective for the treatment and prevention of VTE. Therefore, selecting the right agent for a particular patient will depend on other factors. Perhaps the most significant factor is cost. The DOACs are currently all branded medications, and so the acquisition cost is much greater than that of generic warfarin. However, a true cost comparison is not that simple. Depending on the frequency of laboratory measurements and professional monitor-
ing required, the total cost of treatment with warfarin may far exceed that of the DOACs.

Patients with a history of poor compliance are considered poor candidates for DOAC treatment. With the relatively short half-life of each DOAC, a missed dose may leave the patient unprotected until the next dose is taken. Furthermore, the structured follow-up and serum monitoring required with warfarin provide the patient with consistent education, encouragement, and recognition of compliance issues.

Because there is a lack of data regarding patients at the extremes of body weight being treated with DOACs, warfarin remains the preferred agent in this patient population because of the assurance of a therapeutic effect with international normalized ratio (INR) monitoring.27 Patients who have barriers to appropriate warfarin monitoring may be ideal candidates for DOAC treatment. However, patients with comorbidities such as mechanical heart valves, valvular atrial fibrillation, moderate to severe hepatic disease, and severe renal impairment usually require treatment with warfarin.

Patients who presented with PE and hemodynamic instability were excluded from DOAC clinical trials; therefore, the safety and efficacy of these agents in this patient population are unknown.

**Transitioning from other anticoagulants to a DOAC**

The process of switching a patient from warfarin, heparin, or a LMWH therapy to a DOAC agent is relatively straightforward. In order to avoid full therapeutic levels of both agents, one agent must be stopped in time to allow for serum levels to fall before the DOAC agent is fully absorbed. If not, the full therapeutic dose of both agents would place the patient at a significant risk for bleeding. When converting from an unfractionated heparin infusion, the first dose of dabigatran, apixaban, or rivaroxaban is administered as soon as the heparin infusion is stopped. Edoxaban is started 4 hours after the infusion is stopped. When changing from a LMWH agent, the LMWH is discontinued, and the oral agent is administered at the time the next dose of LMWH was due. Converting from warfarin involves stopping the warfarin and waiting for the INR to fall to a level specified by the package labeling of each agent (Table 2).13, 18, 22, 25

**Choosing among the DOACs**

Once the decision to use a DOAC is made, choosing among the four available agents is often difficult because there are few distinguishing differences (Table 3). Because of the increased rate of gastrointestinal upset associated with dabigatran, patients with a history of upper gastrointestinal disturbances should likely be treated with a different agent. Dabigatran would also be a poor choice for patients who need to crush their medications or use a pill box, as dabigatran capsules are sensitive to moisture and must be kept in the manufacturer’s bottle containing a desiccant.13 If concerns exist regarding taking the medication properly with respect to timing around a meal, only rivaroxaban is labeled with a need to be administered with food.18 Patients with fluctuating renal function or with a body weight that fluctuates around 60 kg may want to avoid treatment with edoxaban. Dabigatran and edoxaban must follow an initial course of treatment with an injectable anticoagulant.13, 20 Currently, the only agent with a readily available, FDA-approved reversal agent is dabigatran, making this agent more attractive for patients with a higher risk of bleeding complications.28 Additionally, only rivaroxaban and apixaban are labeled for use during the acute phase of treatment.18, 22

**Managing DOAC therapy**

Although DOACs are generally believed to not require routine monitoring or frequent dosage adjustments, patients prescribed one of these agents should still receive follow-up. Trials in patients with atrial fibrillation have demonstrated that patients receiving dabigatran and undergoing frequent pharmacist-led monitoring had increased compliance, leading to improved outcomes.29, 30 Published guidelines now advocate for structured monitoring and follow-up for patients receiving a DOAC.27 Pharmacists in almost all settings can perform most of these tasks.

At treatment initiation, a pharmacist provider should confirm the appropriateness of the chosen therapy and prescribed dose by reviewing key laboratory parameters (liver function tests and serum creatinine) and by calculating the patient’s CrCl with the Cockcroft-Gault formula. A full medication review should be conducted to assess for any potential drug-drug interactions. Patient education should be provided, including a review of indications for therapy, proper medication administration and storage, and information about how to monitor for and react to the occurrence of side effects. All education provided should be supplemented with written materials.31 Pharmacy technicians can provide assistance by taking a thorough medication history, by identifying customers/patients who may need extensive counseling or who show signs of poor compliance based on refill history, and by bringing attention to patients with financial difficulties to ensure that they do not go without vital treatment for their condition.

One proposed DOAC follow-up monitoring plan suggests that the “ABCDEF” should be performed at each physician office visit at weeks one and three, months three and six, and then every six months thereafter.32 The “ABCDEF” consists of:

- Adherence assessment and counseling
- Bleeding risk assessment
- CrCl estimation
- Drug interaction screening
- Examination
- Final assessment and follow-up

**Treatment of VTE in special populations**

**Patients with cancer**

The presence of cancer is a strong independent risk factor for the development of VTE. The incidence of VTE in patients with cancer is widely variable and depends on the cancer type, treatment, and other patient factors.
The occurrence of VTE in these patients has a negative effect on morbidity and mortality. Patients with cancer also have increased risks of recurrent VTE and bleeding complications. Clinical trials have demonstrated the superiority of using LMWH continuously for six months after a DVT over the use of warfarin in this patient population. These results led the American Society of Clinical Oncology to recommend anticoagulation with a LMWH for six months instead of treatment with warfarin or heparin.22 Extended treatment beyond the initial six months should be considered in patients with active cancer and in those who are undergoing chemotherapy. The need for continued anticoagulant treatment must be reassessed often, as the patient’s risk of bleeding, life expectancy, and quality of life change throughout the disease process.10,34

The DOACs have been shown to be at least as effective as warfarin for the treatment of VTE in patients with cancer. However, trials directly comparing the use of DOACs with the use of LMWH have not been conducted. Therefore, the general use of these agents in cancer-related DVT cannot be recommended at this time. A trial comparing the use of edoxaban versus dalteparin in the treatment of cancer-related VTE has begun and may provide new information once completed.10,34

Pregnant patients
Not only is pregnancy associated with a doubling in the risk of developing VTE, but PE is the leading cause of death in pregnant women in Western countries. LMWHs do not cross the placenta and are the recommended drugs of choice for both treatment and prophylaxis in pregnant women, according to American College of Chest Physician guidelines.35 The dose of LMWH should be weight adjusted to 75% of the usual therapeutic dose or adjusted according to anti-factor Xa monitoring. Women in the third trimester may need dose adjustments as often as every 10 to 14 days.

Warfarin is a known teratogen. Use of warfarin therapy during the sixth to twelfth week of pregnancy is associated with a 14% to 56% risk of miscarriage and a 6% to 30% risk of congenital abnormalities in the fetus, including various types of malformations, nasal hypoplasia, cleft lip, and stippling of bones. In almost all clinical scenarios, warfarin use in pregnancy is contraindicated. However, warfarin can be used during breastfeeding.35

Dabigatran, rivaroxaban, and edoxaban are labeled as pregnancy category C drugs, indicating that animal reproduction studies have shown an adverse effect on the fetus and that no adequate and well-controlled studies have been performed in humans.13,18,25 Apixaban is labeled as a category B drug, meaning that animal reproduction studies have failed to demonstrate a risk to the fetus but that no adequate and well-controlled studies have been performed in pregnant women.22 Neither of the DOAC agent are recommended as safe for use during breastfeeding. Because of the lack of quality, safety, and efficacy data in this population, DOACs should be considered contraindicated during pregnancy.10,27

Elderly patients
VTE is an age-related disease, with incident rates for VTE and bleeding increasing with age for both men and women. The proportion of patients developing a PE as their thrombotic event also increases with age. Although practitioners may be hesitant to prescribe anticoagulant medications in the elderly, the risk of a fatal PE is 4.5 times the risk of a fatal bleeding event in patients older than 80 years. However, elderly patients do present a variety of challenges for treatment because of age-related changes such as reduced kidney function, decreased body weight, and increased fall risk.

Age is not listed in package labeling as a determining factor for changes in the recommended dose for any DOAC. In the Hokusai-VTE trial of edoxaban, 32% of patients were aged 65 years and older, and 14% of patients were aged 75 years and older. The safety and efficacy of edoxaban were similar in elderly and younger patients.21 In the EINSTEIN clinical studies, approximately 37% of patients were aged 65 years and older and approximately 16% were older than 75 years. The efficacy of rivaroxaban in elderly patients was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in older patients, but the risk-benefit profile was favorable in all age groups.18 In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of patients were aged 65 years and older and >13% were aged 75 years and older. No clinically significant differences in safety or effectiveness were observed among various age groups.22 There is naturally less experience with the use of these newer agents compared with warfarin for the treatment of VTE in elderly patients, which may lead to some hesitancy in prescribing them. However, the available clinical evidence suggests that DOACs are a reasonable choice in this patient population.

Reversal options for DOAC-associated major bleeding
Because major bleeding is the most worrisome complication of anticoagulant therapy, the ability to rapidly reverse the physiologic effect of warfarin has been considered a key advantage of this agent over the

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**TABLE 3**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ACUTE STAGE</th>
<th>SHORT-TERM STAGE (3-6 MONTHS)</th>
<th>LONG-TERM STAGE (&gt;6 MONTHS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIVAROXABAN</td>
<td>Rivaroxaban 15 mg twice daily for 21 days</td>
<td>Rivaroxaban 20 mg once daily</td>
<td>Rivaroxaban 20 mg once daily</td>
</tr>
<tr>
<td>APIXABAN</td>
<td>Apixaban 10 mg twice daily for 7 days</td>
<td>Apixaban 5 mg twice daily</td>
<td>Apixaban 2.5 mg twice daily</td>
</tr>
<tr>
<td>DABIGATRAN</td>
<td>Heparin, LMWH for 5-10 days</td>
<td>Dabigatran 150 mg twice daily</td>
<td>Dabigatran 150 mg twice daily</td>
</tr>
<tr>
<td>EDOXABAN</td>
<td>Heparin, LMWH for 5-10 days</td>
<td>Edoxaban 60 mg once daily</td>
<td>Not studied</td>
</tr>
</tbody>
</table>

Abbreviations: LMWH, low-molecular-weight heparin; VTE, venous thromboembolism. Source: Ref 13, 18, 22, 25
DOACs. However, recent advances in therapy are improving our ability to treat patients with major bleeding episodes associated with oral anticoagulant therapy.

Reversing anticoagulation is often a risky endeavor; patients taking anticoagulant medications are likely doing so because they have an underlying disease that places them at a higher than normal risk of thrombosis. Reversing antithrombotic therapy may lead to the development of a life-threatening thrombosis. Therefore, when clinically feasible, anticoagulant therapy should be restarted as soon as possible.36

Praxbind (idarucizumab) was approved in October 2015 for the reversal of the anticoagulant effect of dabigatran for emergency surgery/urgent procedures or life-threatening or uncontrolled bleeding. Idarucizumab is a humanized monoclonal antibody fragment with a high affinity for dabigatran; when bound, this agent neutralizes the clinical effect of dabigatran. Studies have demonstrated that idarucizumab administered to patients receiving dabigatran restores the laboratory measurements of anticoagulation back to normal levels. The onset of this effect is very rapid—only five minutes—and this effect lasts for 24 hours. The idarucizumab-dabigatran complex is renally cleared; however, no dose changes are necessary in patients with any degree of renal dysfunction. The approved dose is 5 g administered intravenously as two separate 2.5-g vials given sequentially. The vials come ready to administer, so there is no delay for drug preparation. Unlike reversal agents that contain coagulation factors, idarucizumab is not thrombogenic and therefore has a low risk of leading to a thrombosis after administration. However, the use of this agent to reverse the effectiveness of dabigatran will expose patients to the thrombotic risk of their underlying disease.28

Adverse effects with idarucizumab appear to be minor, with only headache occurring in >5% of healthy volunteers studied. There are no labeled contraindications. Because the formulation contains sorbitol, there is a warning about its use in patients with hereditary fructose intolerance. Parenteral administration of sorbitol may lead to serious adverse reactions including hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, and acute liver failure. Although this agent is effective with a low risk of adverse reactions, its wholesale acquisition cost is $3,500/dose, meaning that idarucizumab will likely be reserved for life-threatening situations.29,37

Four-factor prothrombin complex concentrate (PCC), marketed as Kcentra, is indicated for the urgent reversal of coagulation factor deficiency induced by warfarin in adults with acute major bleeding or a need for an urgent surgical procedure.38 It is a mixture of coagulation factors II, VII, IX, and X; proteins C and S; and heparin. Dosed according to patient weight and pretreatment INR, this agent rapidly restores vitamin K-dependent coagulation factors to near-normal levels. The dosing and potency of this product are defined by the factor IX content.29

Four-factor PCC is contraindicated in patients with disseminated intravascular coagulation. Because this agent contains heparin, PCC is also contraindicated in patients with heparin-induced thrombocytopenia. The most frequent adverse reactions in clinical trials were headache, nausea/vomiting, hypotension, and anemia. The most serious adverse reactions were thromboembolic events, including stroke, PE, and DVT.29

There are few clinical data to support the use of four-factor PCC as a reversal agent for the factor Xa inhibitors. Limited studies in healthy volunteers have demonstrated the ability of this product to normalize various measures of anticoagulation. Nonetheless, experts do recommend the off-label use of PCC at a dose of 25 to 50 units/kg to a maximum of 5000 units in severe, life-threatening situations.27,36

Andexanet alfa is a modified factor Xa molecule designated as a breakthrough therapy by the FDA. This agent, which is administered as a bolus with continuous infusion, binds to oral factor Xa inhibitors to negate their effect. Portola Pharmaceuticals has already submitted a Biologics License Application to the FDA for this agent. With potential approval in summer 2016, the company plans to launch the drug in the second half of 2016. If proven safe and effective, this agent could potentially be used to reverse the effects of rivaroxaban, apixaban, and edoxaban.39,40

PER977 (Ciraparantag) is another new agent in late development for the reversal of anticoagulation drugs. PER977 was designed to bind to heparin and LMWH but also binds to oral factor Xa inhibitors and dabigatran. Phase II trials have demonstrated the ability of PER977 to reverse the effects of enoxaparin and edoxaban. Further study is being conducted by Pverspective Inc. If eventually proven to be safe and effective, PER977 may become the first broad-spectrum reversal agent that can be used for all currently marketed anticoagulant medications.41

Conclusion
The DOACs have been shown to be a viable option for the treatment and prevention of VTE in a variety of patients. Although the DOACs do not require frequent monitoring and dose adjustments, improved outcomes may be seen with regular follow-up and frequent assessment for compliance and drug-drug interactions. Recent developments in the area of anticoagulant reversal agents may lead to an improved margin of safety for patients using these high-risk medications.

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