AANA Journal Course

Perioperative Management of the Direct-Acting Oral Anticoagulants

Terri D. Kane, DNAP, CRNA
Tito D. Tubog, DNAP, CRNA

Since the 1950s, warfarin has been the most commonly prescribed anticoagulant in the prevention of stroke-related thromboembolism. Beginning in 2008, direct-acting oral anticoagulants (DOACs) began to replace warfarin. Although the DOACs had a greater safety profile, approved reversal agents *for use in emergent/excessive hemorrhage did not exist. This course reviews the perioperative management of the DOACs.*

Keywords: *Direct-acting oral anticoagulants, reversal agents, warfarin.*

Objectives

At the completion of this course, the reader will be able to:

1. Describe the history of warfarin as an anticoagulant.
2. Compare and contrast warfarin with the modern oral anticoagulants.
3. Describe the sequencing of the coagulation cascade.
4. List effective monitoring strategies for dabigatran, rivaroxaban, apixaban, and edoxaban.
5. Discuss nonurgent and urgent reversal techniques for the most commonly prescribed oral anticoagulants.

Introduction

Warfarin, first identified in the 1930s, achieved approval for human use in the 1950s. Since then, warfarin has been the most commonly used anticoagulant[1] in the prevention of stroke from nonvalvular atrial fibrillation (AF) and in the treatment of venous thromboembolism (VTE).[2] Antagonizing vitamin K, warfarin decreases vitamin K–dependent coagulation factors produced in the liver by 50% to 70%. These factors include factors II, VII, IX, and X and the anticoagulant proteins C and S.[3] Although effective, warfarin has a narrow therapeutic range and food interactions, and it requires laboratory monitoring, all of which make its use difficult to manage. One study, published in 2006, of more than 6,400 patients showed a lack of therapeutic level in nearly 50% of the patients.[4] In a prospective analysis of more than 1,800 patients, warfarin's adverse effects were identified as the third most common cause of hospital admission, mainly due to major and fatal bleeding events.[5]

Beginning in 2008, direct-acting oral anticoagulants (DOACs) began to replace warfarin. These DOACs eliminated the need for laboratory monitoring, were more therapeutically predictable, and were equally effective in the prevention of VTE compared with warfarin.[2,6-10] In addition, DOACs decreased the risk of serious bleeding, including intracerebral hemorrhage.[9-13] The first available DOAC was dabigatran (Pradaxa), which functions as a direct thrombin inhibitor. Subsequently, inhibitors of activated factor Xa, including rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa), have been approved for human use.[2,6]

Warfarin is rapidly reversible with the use of vitamin K and fresh frozen plasma or prothrombin complex concentrates. Antidotes have not been as readily available for the DOACs, causing concern in the event of hemorrhage, trauma, or need for emergent surgical intervention. This article will discuss the DOACs, focusing on their perioperative management and newly emerging reversal strategies.

Overview of Coagulation and Fibrinolysis

For homeostasis to occur, there is a delicate balance between clot formation and clot dissolution. As the coagulation cascade is activated because of blood vessel injury, fibrinolysis occurs to prevent excessive deposition of fibrin.

• *Coagulation.* There are 3 major stages of clot formation.[14-16] First, damaged blood vessels stimulate the

release of endothelins, a primary hormone involved in the vascular phase of the clotting process. Endothelins causes smooth muscle contraction, which aids in the repair of the damaged site. The smooth muscle contraction may slow down the bleeding and helps localize the injured area.

Second, as the smooth muscle in the vessel wall contracts, platelet formation is initiated. Often referred to as the primary hemostasis phase, injured blood vessels attract platelets to begin the formation of the primary plug. The initial step in platelet formation is adherence of platelets to the endothelial lining of the blood vessel. Glycoprotein Ib receptors emerge from the surface of the platelet and attract von Willebrand factor, allowing the platelet to adhere to the endothelial lining at the injured site. Other platelets in the surrounding areas are activated and form a complex that links and aggregates other platelets together. This primary plug is only suitable for minute and minor injury. If the vascular injury is large, secondary hemostasis through initiation of the coagulation cascade is stimulated.

Third, a series of sequential enzymatic reactions lead to the activation of prothrombin to thrombin. The formation of thrombin is vital in the formation of fibrin, which boosts the platelet plug.

• *Fibrinolysis.* Clots (in the form of a platelet plug) can be detrimental because they can be dislodged or develop uncontrollably in other areas of the vasculature. To avoid this concern, the body simultaneously activates fibrinolysis during the coagulation process. Circulating activators such as tissue plasminogen activator, urokinase, kallikrein, and neutrophil elastase convert plasminogen to plasmin, a product that breaks down fibrin.[14]

• *Mechanism of Action of Direct-Acting Oral Anticoagulants.* Two types of DOACs are currently used in the clinical setting: (1) direct thrombin inhibitors and (2) factor Xa inhibitors. Dabigatran is a direct thrombin inhibitor; rivaroxaban, apixaban, edoxaban, and betrixaban are factor Xa inhibitors.[15,16] Direct thrombin inhibitors act on the final stages of the clotting cascade. Thrombin is the last enzyme activated in the series of enzymatic activities. Thrombin cleaves fibrinogen (factor I) to fibrin. Antagonizing the function of thrombin prevents fibrin from forming (Figure).

On the other hand, factor Xa is responsible for conversion of prothrombin to thrombin as illustrated in the Figure. The conversion of prothrombin to thrombin occurs at the end of the intrinsic and extrinsic pathways. By preventing the cleavage of prothrombin to thrombin, factor Xa inhibitors interrupt clot formation.

Dabigatran

Dabigatran is a competitive direct univalent thrombin inhibitor administered orally as the prodrug dabigatran etexilate. Clinical studies of dabigatran were focused on the prevention of VTE in patients undergoing knee and hip replace-

Figure. Mechanism of Action of Direct-Acting Oral Anticoagulants[a]
[a]Roman numerals refer to coagulation factors.

ment and on prevention of stroke in patients with chronic AF not caused by a heart valve problem (RE-LY trial).[17] When data from noninferiority studies (RE-NOVATE, RE-MODEL, and RE-MOBILIZE) were pooled, oral dabigatran was noninferior to subcutaneous enoxaparin in reducing the major incidence of VTE and VTE-related mortality.[18-21] These outcomes resulted in a delay in the approval of dabigatran for use in the United States.

In the RE-LY study,[17] 2 doses of dabigatran (110 mg and 150 mg) were compared with open-label warfarin in patients with nonvalvular, persistent, paroxysmal, or permanent AF. The use of dabigatran at the 150-mg dose (not 110 mg) lowered the incidence of stroke and systemic embolism compared with warfarin, which led to the approval of dabigatran in the United States. Dabigatran is currently approved to reduce the risk of stroke and systemic blood clots in patients with nonvalvular AF and VTE.

• *Clinical Pharmacology.* Dabigatran is a prodrug that is absorbed in both its esterified (prodrug) form and in its hydrolyzed active form from the intestinal tract after oral administration. It is hydrolyzed to its active form by nonspecific esterases in the gut, plasma, and liver. Plasma concentration peaks 2 to 3 hours after administration, and elimination half-life is 12 to 17 hours. Eighty percent of the drug is eliminated in the kidney, and the remaining 20% is eliminated via the bile.[16] Dabigatran

should not be concurrently administered with known P-glycoprotein–modulating drugs because its predicted effectiveness will be altered. Examples of P-glycoprotein inhibitors are quinidine, ketoconazole, and immunosuppressive agents. Examples of P-glycoprotein inducers to avoid during dabigatran therapy are rifampin, phenytoin, and St-John's-wort. Dabigatran must also be used with caution if the patient is using antacids or proton pump inhibitors because the consequent decrease of stomach acidity has the potential to decrease absorption by as much as 25%.

• *Dosing.* In the United States, the regular dabigatran dose for patients with AF is 150 mg twice daily with a recommended dose of 75 mg twice daily for patients with severe renal insufficiency (creatinine clearance, 15-30 mL/min/1.73 m^2). For the prophylactic treatment of deep vein thrombosis (DVT), the regular dose is 150 mg twice daily.[11] After oral administration, the bioavailability of dabigatran is 6% to 7%.

• *Monitoring Strategies.* The best qualitative assessment of dabigatran efficacy is the activated partial thromboplastin time. This test is cost efficient and provides rapidly accessible information in emergency situations. However, it is less accurate in higher dabigatran concentrations, and a normal activated partial thromboplastin time does not exclude clinically relevant plasma drug levels. Although thrombin time provides excessive sensitivity, the test is useful as a diluted thrombin time. A normal diluted thrombin time excludes clinically relevant concentrations of dabigatran. Commercially, the diluted thrombin time is available as the Hemoclot thrombin inhibitor assay (Hyphen BioMed) and is simple and rapid. Prothrombin time and international normalized ratio (INR) are not reliable in assessing dabigatran activity. The most practical method for assessing residual drug effect (in patients with normal renal function) may simply be to ask when they last took the DOAC.[9,10,22-24] Because of the twice daily dosing schedule and 12- to 17-hour half-life elimination, discontinuing the drug may be sufficient in quickly limiting the drug effect.[2]

Rivaroxaban

Rivaroxaban is the first factor Xa inhibitor approved by the Food and Drug Administration (FDA). Rivaroxaban reduces the risks of stroke, systemic embolism in patients with nonvalvular AF, and recurrence of DVT and pulmonary embolism (PE). Rivaroxaban is also used to prevent DVT in patients undergoing knee or hip replacement surgery. In a noninferiority study comparing rivaroxaban to warfarin, Patel and colleagues[25] investigated rivaroxaban with the primary end point of stroke or systemic embolism in 14,264 patients with nonvalvular AF who were at moderate to high risk of stroke. In this ROCKET AF clinical trial, rivaroxaban was noninferior to warfarin in reducing stroke or systemic embolism, with a 12%

relative risk reduction.[25] In addition, there was no difference in the frequency of major and nonmajor bleeding between rivaroxaban and warfarin. However, the rate of intracranial and fatal bleeding was lower in the rivaroxaban group than the warfarin group.

Rivaroxaban is also effective in treating DVT and PE. In a clinical study conducted by the EINSTEIN investigators, administration of rivaroxaban was efficacious in the treatment and reoccurrence of DVT and PE. Rivaroxaban also reduced the risk of blood clots and PE after hip or knee surgery.

The clinical pharmacology, dosing, and monitoring strategies for rivaroxaban and the remaining anticoagulants described here are discussed in the section "Factor Xa Inhibitors" and in the Table.

Apixaban

Like rivaroxaban, apixaban binds to and inhibits factor Xa, the first clotting factor in the common clotting pathway.[2] In the ARISTOTLE Study, 18,201 patients with a history of nonvalvular AF with 1 or more risks factors for stroke were investigated.[26] Compared with warfarin, apixaban demonstrated superiority as a result of significant reduction in hemorrhagic and ischemic strokes. More patients treated with apixaban, however, experienced bleeding vs warfarin (2.5% vs 1.7%). Similarly, the AVERROES study[17] reported higher rates of bleeding in apaxiban compared with warfarin (1.5% vs 1.3%). However, apixaban is the only anticoagulant that demonstrated superiority in the prevention of both stroke and systemic embolism compared with warfarin.

Apixaban is also used to treat DVT and PE. In a randomized, double-blind, phase 3 noninferiority trial, 5,400 patients with DVT or PE were evaluated using apixaban vs enoxaparin and warfarin therapy.[27] The incidence of recurrent symptomatic VTE was lower in the apixaban group than the enoxaparin/warfarin group (2.3% vs 2.7%).

Like the other DOACs, apixaban is also used for the prophylaxis of DVT, which may lead to PE, following hip or total knee replacement. Three large phase 3 clinical trials demonstrated decreased incidence of DVT in patients with apixaban following hip or knee replacement surgery.

Edoxaban

A DOAC approved by the FDA in 2015, edoxaban is used to prevent stroke, to prevent systemic embolism in patients with nonvalvular AF, and to treat DVT and PE. Similar to rivaroxaban and apixaban, edoxaban is a highly specific inhibitor of factor Xa. In the ENGAGE AF-TIMI (Thrombolysis in Myocardial Infarction) 48 trial,[28] a study that evaluated the safety of edoxaban vs warfarin, 21,105 patients were randomly assigned into 3 groups: a warfarin group dosed to an INR between 2 and 3, low-dose edoxaban (30 mg), and high-dose edoxaban (60 mg). The

Drug	Half-life (h)	Dosing	Monitoring	Reversal	Interval between discontinuation and procedure	Interval (h) between procedure and resumption of anticoagulant
Warfarin	25-60	2.5-10 mg daily	PT INR	Vitamin K, fresh frozen plasma	5 d before intermediate or high risk; normal INR	24
Dabigatran	12-17	150 mg bid (AF or DVT) 75 mg bid (CRI)	Diluted thrombin time	Idarucizumab	4-5 d; 6 d with renal disease	24
Rivaroxaban	7-13	20 mg daily 15 mg daily (CRI)	Anti-X chromogenic assays	Andexanet	3 d	24
Apixaban	8-15	5 mg bid after 10 mg bid for 1 wk	Anti-X chromogenic assays	Andexanet	3-5 d	24
Edoxaban	5.8-10.7	60 mg daily	Anti-X chromogenic assays	Andexanet	1 d	After procedure with sufficient hemostasis
Betrixaban	19-27	80 mg daily 40 mg daily (CRI)	Anti-X chromogenic assays	Andexanet	3 d	24-72

Table. Drug Half-Life, Dosing, Monitoring, and Reversal

Abbreviations: AF, atrial fibrillation; bid, twice daily; CRI, continuous rate infusion; DVT, deep vein thrombosis; INR, international normalized ratio; PT, prothrombin time

rate of stroke or systemic embolism event was higher in the warfarin group compared with the low-dose or high-dose edoxaban groups. In addition, major bleeding was decreased in the edoxaban group compared with warfarin (hazard ratio [HR], 0.80; 95% CI, 0.70 to 0.91; $P < .001$).

In the Hokusai VTE study,[29] a total of 8,092 patients were evaluated to determine the efficacy and safety of edoxaban compared with warfarin in the treatment of VTE. The recurrence of VTE was more frequent in the warfarin group (3.5%) vs the edoxaban group (3.2%). Also, data from the Hokusai VTE study showed similar results in major bleeding rates in the edoxaban group compared with warfarin (HR, 0.81; 95% CI, 0.71 to 0.94; $P = .004$).

Betrixaban

Approved in June 2017, this factor Xa inhibitor is indicated for not only acute VTE prophylaxis but also long-term prophylaxis. This makes betrixaban unique among the factor Xa inhibitors and allows a smooth pharmacologic transition from hospital to home.

In the APEX study, oral betrixaban was compared with injectable enoxaparin in more than 7,400 high-risk medical patients. Betrixaban decreased the occurrence of DVT and PE (4.4% vs 6.0%) without increased drug related hemorrhage (0.67% vs 0.57%).[30]

Factor Xa Inhibitors

• *Clinical Pharmacology.* Factor Xa inhibitors, in contrast to dabigatran, are highly protein bound. Rivaroxaban, apixaban, and edoxaban are metabolized through the CYP3A4 pathway and they are also both substrates for P-glycoprotein. Similar to dabigatran, these medications interact with drugs such as ketoconazole, quinidine, fluconazole, and erythromycin to increase bleeding. Decreased drug effectiveness is noted with concomitant use of CYP3A4 inducers such as phenytoin, St-John's-wort, and rifampin.[6] Whereas rivaroxaban is approximately 70% eliminated through the kidneys, only 25% of apixaban is renally excreted.[16] Betrixaban is cleared primary through biliary excretion and does not require dosing adjustment in patients with renal insufficiency. In addition, betrixaban does not interact with CYP3A4 inducers, making it safe for use with certain antiseizure and antibiotic medications.[16] Of concern, betrixaban's elimination half-life is approximately twice that of the other factor Xa inhibitors. [31]

• *Dosing.* Dosing for rivaroxaban in the treatment of VTE or the prevention of stroke in nonvalvular AF is 20 mg once daily. The dosing for apixaban is 5 mg twice daily after a 10 mg twice daily dosing for the first week. For edoxaban, the dosing is 60 mg daily in patients with a creatinine clearance between 50 to 95 mL/min/1/73 m^2. A lower dose of 30 mg daily is recommended in patients with moderate to severe renal impairment with a creatinine clearance of 15 to 50 mL/min/1.73 m^2.[32] Because of the long elimination half-life, betrixaban may be dosed once daily from 40 to 80 mg.[31]

• *Monitoring Strategies.* Prothombin time prolongs at higher drug concentrations for factor Xa inhibitors but is of little practical use because of wide interreagent variability. Activated partial thromboplastin time increases in a dose-dependent fashion but demonstrates poor sen-

sitivity. Specific anti-Xa chromogenic assays have been developed but are not yet widely available in clinical practice. The chromogenic anti-Xa assays that traditionally monitor heparin and low-molecular-weight heparin (LMWH) cannot be substituted because the assay must be calibrated to the specific anti-Xa inhibitor.[2,6,24]

Management of Bleeding Associated With DOACs

• *Mild/Moderate Bleeding.* Preoperatively, DOACs should be discontinued 24 hours before procedures with low to moderate risk of bleeding. A 48-hour interruption is recommended for procedures with a moderate to high risk of bleeding.[6,11,33] In the event of bleeding, management should be individualized based on the severity and location of the hemorrhage. Traditional hemostatic measures such as direct pressure on the wound and elevation can be useful. In many cases, withholding of the DOAC for 1 or more doses is sufficient. Fluid resuscitation and the administration of packed red blood cells may be necessary for volume/clotting component replacement.

• *Life-threatening Bleeding.* Because of low protein binding, some evidence exists that hemodialysis may rapidly reverse the anticoagulant effect of dabigatran[2,8,9,34] but is not effective for reversing effects of rivaroxaban, apixaban, or edoxaban (these drugs are highly protein bound). Dialysis is most useful in patients with renal insufficiency. Oral activated charcoal has been suggested by a number of authors with acute dabigatran overdose of less than 1 to 2 hours. The activated charcoal works through absorption of the drug while in the gut and has been shown in vitro to be highly effective.[2] Fresh frozen plasma has been suggested as a useful intervention because of its variety of coagulation factors. It is a viable option for fluid resuscitation, but the volume needed to adequately reverse life-threatening hemorrhage could cause transfusion-related lung injury or circulatory overload.[2,7]

Other options include the use of human prothrombin complex concentrates (PCCs), recombinant factor VIIa, and antifibrinolytic agents. Prothrombin complex concentrate is supplied as either a 3-factor (factors II, IX, and X) or 4-factor (factor II, VII, IX, and X) complex.[2,7,8,24] A type of 3-factor PCC known as activated PCC (aPCC or factor VIII inhibitor bypassing activity) also contains protein C and activated factor VII.[2] The administration of PCC in animals and human studies has exhibited conflicting results in both the reversal of bleeding and in the correction of abnormal coagulation studies. Some PCC studies were carried out in animal models or healthy volunteers and may not correlate to patients with acute hemorrhage or trauma.[2,7-10,13] However, if reversal agents are unavailable, aPCC is the recommended treatment of life-threatening bleeding.[9] In a number of studies, recombinant factor VIIa has demonstrated varying effectiveness in the reversibility of elevated co-agulation parameters.[2,9,24,33] Factor VIIa affects hemostasis through the extrinsic pathway by producing factors Xa and IXa. Importantly, causing hemostasis via the use of factor VIIa increases the risk of arterial thrombosis.[2] Antifibrinolytics, such as tranexamic acid, have been suggested for the treatment of life-threatening hemorrhage. Although they prevent plasmins' degradation of fibrin, their efficacy in the treatment of hemorrhage related to DOACs is unknown.

Reversal of Direct-Acting Oral Anticoagulants

• *Idarucizumab (Praxbind).* Beginning in 2013, a specific antidote for dabigatran, idarucizumab, was successfully identified through animal studies.[33-35] Idarucizumab is a monoclonal antibody fragment that binds both free and thrombin-bound dabigatran. The binding affinity is 350 times greater than that seen between dabigatran and thrombin.[12,33] Early phase 1 clinical trials demonstrated no significant adverse effects[36,37] and showed complete reversal of dabigatran-associated anticoagulant effects within minutes of the drug infusion.[12,36,37] However, this small trial occurred in young, healthy volunteers. A phase 3 trial was conducted in patients who had severe hemorrhage or who required an urgent intervention. In these patients, a 5-g IV dose of idarucizumab normalized diluted thrombin time or ecarin clotting time in 88% to 98% of patients within minutes, and these values remained normal for 24 hours. In patients requiring urgent intervention, only 3 of the 36 patients subjectively reported mild to moderate bleeding during surgery. One patient had a thrombotic event within 72 hours of idarucizumab administration.[12,36,37] Because of these successes, FDA approval was obtained in October 2015 for the use of idarucizumab in *life-threatening hemorrhage or emergent surgery*.[12,37]

• *Andexanet alfa (Andexxa).* Andexanet is a modified recombinant factor Xa. By binding to Xa inhibitors such as rivaroxaban, apixaban, and edoxaban, it prevents attachment with the endogenous factor Xa,[12,37] inactivating anticoagulation. Although it has been shown safe and effective in early animal and human trials (demonstrating effect 2-5 minutes after bolus),[36] anticoagulation effects returned within 1 hour of a bolus dose related to a short drug half-life. Continuous infusion was required to maintain a sustained reversal of anticoagulation effects. In addition, elevations of D-dimer, prothrombin fragments, and elevated thrombin levels have raised concern about prothrombotic potential in patients with a prior thrombotic history.[37] Andexanet received FDA approval in May 2018 for the treatment of anticoagulation with rivaroxaban and apixaban for life-threatening or uncontrolled bleeding.[38]

Other Anesthesia Implications

The American Society of Regional Anesthesia and Pain

Medicine, in partnership with other pain societies, issued practice guidelines on patients treated with antiplatelet and anticoagulant medications for interventional spine and pain procedures.[39] The guidelines outlined perioperative strategies for patients requiring interruption of anticoagulation. Although Narouze and colleagues[39] cited lack of evidence for grading the quality of these recommendations, these practice guidelines were met with both enthusiasm and apathy. Those who agreed with the guidelines praised the monumental efforts of the authors to outline each of the recommendations of this groundbreaking document. However, critics have argued that the article was not clear on the recommendations for regional anesthesia in the acute setting or in obstetrics.

Despite the current debate on whether such guidelines can be used, Narouze and colleagues cited several suggestions. First, a 5-half-life period between discontinuation of DOACs for medium- to high-risk bleeding procedures, while shared decision making and risk stratification is warranted for low-risk bleeding procedures. Second, if the risk of VTE is high, bridging with LMWH and discontinuation of LMWH 24 hours before the pain procedure is warranted. Third, DOAC can be resumed 24 hours after the pain procedure. Last, if the risk of VTE is very high, DOAC can be resumed *12 hours* after the pain intervention.

Conclusion

Because of the short half-lives of the DOACs, discontinuation appears to be the most cost-effective and simplest approach preoperatively. Although idarucizumab and andexanet are approved for use in life-threatening/emergent situations in the United States, no cost-effective studies have been done for nonurgent use. Although these medications are seemingly safe in human subjects, most studies have been carried out in healthy humans and cohort sizes were extremely small. This certainly cautions extrapolation of the data to a wider population of emergent cases, elderly patients, and patients with multiple comorbidities.

REFERENCES

1. Pirmohamed M. Warfarin: almost 60 years old and still causing problems. *Br J Clin Pharmacol.* 2006;62(5):509-511. doi:10.1111/j.1365-2125.2006.02806.x

2. Vanden Daelen S, Peetermans M, Vanassche T, Verhamme P, Vandermeulen E. Monitoring and reversal strategies for new oral anticoagulants. *Expert Rev Cardiovasc Ther.* 2014;13(1):95-103. doi:10.1586/14779072.2015.987126

3. Kharasch E, Maze M, Evers A. *Anesthetic Pharmacology.* Cambridge, UK: Cambridge University Press; 2011.

4. Boulanger L, Kim J, Friedman M, Hauch O, Foster T, Menzin J. Patterns of use of antithrombotic therapy and quality of anticoagulation among patients with non-valvular atrial fibrillation in clinical practice. *Int J Clin Pract.* 2006;60(3):258-264. doi:10.1111/j.1368-5031.2006.00790.x

5. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ.* 2004;329(7456):15-19. doi:10.1136/bmj.329.7456.15

6. Lai A, Davidson N, Galloway SW, Thachil J. Perioperative management of patients on new oral anticoagulants [published correction appears at *Br J Surg.* 2014 Nov;101(12):1624]. *Br J Surg.* 2014;101(7):742-749. doi:10.1002/bjs.9485

7. McMahon BJ, Kwaan HC. The new or non-vitamin K antagonist oral anticoagulants: what have we learned since their debut. *Semin Thromb Hemost.* 2015;41(2):188-194. doi:10.1055/s-0035-1544159

8. Marano G, Vaglio S, Pupella S, Liumbruno G, Franchini M. How we treat bleeding associated with direct oral anticoagulants. *Blood Transfus.* 2016;14(5):465-473. doi:10.2450/2016.0180-15

9. Ruff CT, Giugliano RP, Antman EM. Management of bleeding with non-vitamin K antagonist oral anticoagulants in the era of specific reversal agents. *Circulation.* 2016;134(3):248-261. doi:10.1161/CIRCULATIONAHA.116.021831

10. Gehrie E, Tormey C. Novel oral anticoagulants: efficacy, laboratory measurement, and approaches to emergent reversal. *Arch Pathol Lab Med.* 2015;139(5):687-692. doi:10.5858/arpa.2013-0677-RS

11. Urooj F, Kulkarni A, Stapleton D, Kaluski E. New oral anticoagulants in nonvalvular atrial fibrillation. *Clin Cardiol.* 2016;39(12):739-746. doi:10.1002/clc.22582

12. Dalal J, Bhave A, Chaudhry G, Rana P. Reversal agents for NOACs: connecting the dots. *Indian Heart J.* 2016;68(4):559-563. doi:10.1016/j.ihj.2015.11.023

13. Eikelboom J, Merli G. Bleeding with direct oral anticoagulants vs warfarin: clinical experience. *Am J Emerg Med.* 2016;34(11 suppl):3-8. doi:10.1016/j.ajem.2016.09.046

14. Sagripanti A, Carpi A. Antithrombotic and prothrombotic activities of the vascular endothelium. *Biomed Pharmacother.* 2000;54(2):107-111. doi:10.1016/S0753-3322(00)88861-7

15. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost.* 2014;12(3):320-328. doi:10.1111/jth.12485

16. Davis EM, Packard KA, Knezevich JT, Campbell JA. New and emerging anticoagulant therapy for atrial fibrillation and acute coronary syndrome. *Pharmacotherapy.* 2011;31(10):975-1016. doi:10.1592/phco.31.10.975

17. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation [published correction appears at *N Engl J Med.* 2010;363(19):1875-1876]. *N Engl J Med.* 2018;361(12):1139-1151. doi:10.1056/NEJMoa0905561

18. Eriksson BI, Dahl OE, Rosencher N, et al; RE-NOVATE II Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial [published correction appears at *Lancet.* 2007 Dec 15;370(9604):2004]. *Lancet.* 2007;370(9591):949-956. doi:10.1016/S0140-6736(07)61445-7

19. Eriksson BI, Dahl OE, Huo MH, et al; RE-NOVATE II Study Group. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty. *Thromb Haemost.* 2011;105(4):721-729. doi:10.1160/TH10-10-0679

20. Eriksson B,I Dahl OE, Rosencher N, et al; RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost.* 2007;5(11):2178-2185. doi:10.1111/j.1538-7836.2007.02748.x

21. RE-MOBILIZE Writing Committee; Ginsberg JS, Davidson BL, Comp PC, et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty.* 2009;24(1):1-9. doi:10.1016/j.arth.2008.01.132

22. Douxfils J, Mullier F, Robert S, Chatelain C, Chatelain B, Dogna J. Impact of dabigatran on a large panel of routine or specific coagula-

tion assays. Laboratory recommendations for monitoring of dabigatran etexilate. *J Thromb Haemost.* 2012;107(5):985-997. doi:10.1160/TH11-11-0804

23. Stangier J, Feuring M. Using the HEMOCLOT direct thrombin inhibitor assay to determine plasma concentrations of dabigatran. *Blood Coagul Fibrinolysis.* 2012;23(2):138-143. doi:10.1097/MBC.0b013e32834f1b0c

24. Dager W, Hellwig T. Current knowledge on assessing the effects of and managing bleeding and urgent procedures with direct oral anticoagulants. *Am J Health Syst Pharm.* 2016;73(10 suppl 2):S14-S26. doi:10.2146/ajhp150960

25. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-893. doi:10.1056/NEJMoa1009638

26. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2012;365(11):981-992. doi:10.1056/NEJMoa1107039

27. Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808. doi:10.1056/NEJMoa1302507

28. Giugliano RP, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369(22):2093-2104. doi:10.1056/NEJMoa1310907

29. The Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism [published correction appears at *N Engl J Med.* 2014;370:390]. *N Engl J Med.* 2013;369(15):1406-1415. doi:10.1056/NEJMoa1306638

30. Portola Pharmaceuticals Inc. Portola.com. https://www.portola.com/. Published 2017. Accessed August 23, 2018.

31. Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: an overview of current developments. *Thromb Haemost.* 2015;112(5):931-942. doi:10.1160/TH14-11-0982

32. Fontana P, Robert-Ebadi H, Bounameaux H, Boehlen F, Righini M. Direct oral anticoagulants: a guide for daily practice. *Swiss Med Wkly.* 2016;146:w14286. doi:10.4414/smw.2016.14286

33. Shamoun F, Obeid H, Ramakrishna H. Novel anticoagulants in atrial fibrillation: monitoring, reversal and perioperative management. *Biomed Res Int.* 2015;2015:424031. doi:10.1155/2015/424031

34. Khadzhynov D, Wagner F, Formella S, et al. Effective elimination of dabigatran by haemodialysis. A phase I single-centre study in patients with end-stage renal disease. *Thromb Haemost.* 2013;109(4):596-605. doi:10.1160/TH12-08-0573

35. Schiele F, van Ryn J, Canada K, et al. A specific antidote for dabigatran: functional and structural characterization. *Blood.* 2013;121(18):3554-3562. doi:10.1182/blood-2012-11-468207

36. Tummala R, Kavtaradze A, Gupta A, Ghosh RK. Specific antidotes against direct oral anticoagulants: a comprehensive review of clinical trials data. *Int J Cardiol.* 2016;214:292-298. doi:10.1016/j.ijcard.2016.03.056

37. Ansell JE. Reversing the effect of oral anticoagulant drugs: established and newer options. *Am J Cardiovasc Drugs.* 2016;16(3):163-170. doi:10.1007/s40256-016-0162-7

38. Portola Pharmaceuticals Inc. Portola.com. https://www.portola.com/. Published 2018. Accessed July 18, 2018.

39. Narouze S, Benzon HT, Provenzano D, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications (second edition). *Reg Anesth Pain Med.* 2018;43(3):225-262. doi:10.1097/AAP.0000000000000700

AUTHORS

Terri D. Kane, DNAP, CRNA, is associate professor at Texas Wesleyan University, Fort Worth, Texas.

Tito D. Tubog, DNAP, CRNA, is assistant professor at Texas Wesleyan University.

DISCLOSURES